Translation

Insurance coverage of PET drugs and imaging accreditation in the U.S.

— PET Drug American Dream World History: The 3rd Report —*1

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Abstract

In the U.S. (United States), for public insurance coverage of PET (Positron Emission Tomography) imaging procedures, not only FDA (Food and Drug Administration)-approval of PET drugs and PET imaging devices, but also imaging facility accreditation is required, for the public healthcare insurance coverage by the CMS (Center for Medicare & Medicaid Services). Here we introduce the policy and framework in the U.S. towards evidence-based decisions concerning public healthcare insurance coverage, including the recent situation of a new PET drug used for imaging beta amyloid plaques in adults with cognitive impairment.

Key words

CMS (Centers for Medicare & Medicaid Services), CED (Coverage with Evidence Development), NOPR (National Oncologic PET Registry), IAC (Intersocietal Accreditation Commission), ACR (American College of Radiology)

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1. New drug approval and insurance coverage

In the previous articles [1~3] we introduced the recent situation in the U.S. (United States) of clinical development and the FDA (Food and Drug Administration)'s approvals of PET (Positron Emission Tomography) drugs. Here we introduce the situation of Medicare national health insurance coverage determinations of these drugs by the **CMS (Centers for Medicare & Medicaid Services)**[*2], as shown in Table 1. In the U.S., after the new drug approval by the FDA, sometimes there is a time lag until the determination of Medicare insurance coverage by the CMS. The CMS is not obliged to approve payment for anything the FDA approves for clinical use. The requirements are different – a drug could meet the FDA requirements for safety and efficacy, but not the CMS requirements for improved health outcomes for Medicare beneficiaries. On the other hand, there is a scheme of **CED (Coverage with Evidence Development)**. In this framework clinicians-researchers can use approved drugs, including the usage for unapproved indications, being reimbursed by payers in the limited frameworks of studies under the conditions defined by the CMS. They should conduct clinical studies for evidence development towards insurance coverage determination by the CMS. This scheme was explicitly proposed in April 2005 and finalized in July 2006 [4]. There are two types of CED: the **CAD (Coverage with Appropriateness Determination)** in which "additional clinical data is needed"; and the **CSP (Coverage with Study Participation)** in which the procedures can be covered only "within a research setting".

Table 1 The situation of CMS coverage of PET drugs in the U.S.

FDA approvals	CMS coverage
Included in USP & approved by the FDA ^{13}N-ammonia injection ^{18}F-fludeoxyglucose injection ^{18}F-sodium fluoride injection ^{89}Rb rubidium chloride injection	Approved indications are covered Specific, defined indications are covered only in the scheme of CED
Included in USP* & not approved by the FDA ^{18}F-fluorodopa injection ^{11}C-flumazenil injection ^{11}C-methionine injection ^{11}C-raclopride injection ^{11}C-sodium acetate injection ^{11}C-carbon monoxide injection ^{11}C-mespiperone injection ^{15}O-water injection	Not covered
Not yet included* in USP & approved by the FDA ^{18}F-Florbetapir ^{18}F-Flutemetamol ^{18}F-Florbetaben	Decision memo on September 27, 2013 to cover only 1 time of scan in the defined type of studies within the scheme of CED.

* As described in the previous article, the monographs of PET drugs included in USP (United States Pharmacopeia) but not approved by the FDA were to be removed from USP, according to FDA Modernization Act, and the drug which was approved by the FDA is to be included in USP. Finally on December 1 of 2014, these unapproved 8 PET drugs were omitted from the USP.

*2 The terms shown in **bold letters and underlined** are explained in Box (glossary).

2. Expanded Medicare coverage of PET-FDG [5, 6]

One of the successful examples which started at the time of beginning of CED scheme is the expansion of coverage for indications of FDG (^{18}F-fludeoxyglucose). In the U.S., CT (Computer tomographie) and MRI (Magnetic Resonance Imaging) have been covered by Medicare for general oncologic applications since their introduction, but coverage of PET-FDG had been made cautiously. In 1998, the CMS decided to cover only for limited use of PET-FDG, and then according to the submissions of each of the new indications, each determination of coverage has been made one by one. When CMS released the draft guidance of CED in 2005 in which they explained the idea of a coverage scheme involving a nation-wide registry of medical records, the PET community started to develop the NOPR, the first registry in the U.S. which is compatible with the standards required by the CMS.

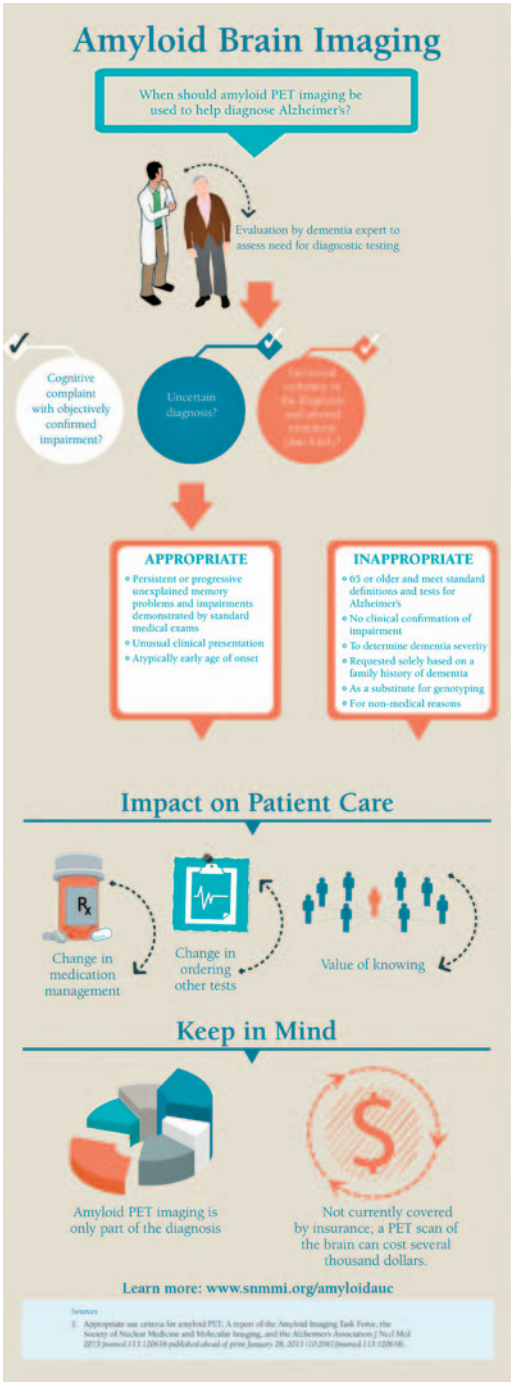
Among the more than 30,000 eligible NOPR-registered cohort data, approximately 23,000 questionnaire data were analyzed to find doctors' changes of management associated with PET examinations [5, 6] (During nearly four years of operation after the development, over 150,000 patients have undergone FDG-PET under NOPR's mechanism that allows for Medicare coverage of these scans. http://www.cancerpetregistry.org/what.htm Now total accrual should be more expanded). Further evidence development by the NOPR cohort and clinical research under insurance coverage led to the determination of CMS to end the prospective data collection requirements across oncologic indications of FDG PET. This determination also included the statement that previous "cancer-by-cancer consideration" for coverage "should be replaced by a more omnibus consideration": [7], and in June 2013, it was decided almost all the solid tumor is covered, although examination for initial treatment strategy for prostate is not covered and there are some exceptions for initial treatment strategy for cervix, breast, melanoma [8].

3. Coverage consideration of beta amyloid imaging

Among the 12 PET drugs included in USP, FDG and other 3 drugs have been approved by the FDA (as described in detail in our first report of this series, the USP monographs of non-approved drugs come to be not effective), and the FDA-approved indications of these PET drugs are covered by Medicare insurance, and some of the unapproved indications of these approved drugs are covered in the scheme of CED (Table 1). The NDA of ^{18}F-Florbetapir (Amyvid ®) was approved by the FDA in 2012 for its beta amyloid imaging "to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline". (Subsequently, ^{18}F-Flutemetamol and ^{18}F-Florbetaben were also approved.)

Three clinical studies have supported the NDA. Study 1 showed a high accuracy rate in the 35 "autopsy cohort" between image interpretation and postmortem cortical amyloid burden (truth standard); The other 2 studies showed high performance characteristics: Study 2, using an in-person tutoring type of training, showed a 92% median sensitivity; a 95% median specificity (using 59 cases from previous clinical studies with postmortem data, including 35 of study 1); and Study 3, using an electronic media-based training method, showed a 82% median sensitivity; a 95% median specificity (using imaging data of 59 cases of study 2 and the other 92 cases from previous studies without postmortem data (92 includes AD; other

Fig. 1　Infographic of Amyloid Brain Imaging by SNMMI



As described in this article, CMS proposed to cover a one time scan in the scheme of CED and the proposal may be decided in October 2013 (It was decided in September 2013). This reproduction of this figure is permitted by SNMMI.

cognitive disorders; mild cognitive impairment (MCI); and volunteers without cognitive impairment)). Study 3 also showed a high intra-reader reproducibility (overall kappa statistic: 0.83%).

Development of a training program was required as the condition of the approval and now the program has been developed and provided by the sponsor company.

The CMS advisory committee's opinion in January 2013 was that there is insufficient evidence to support the benefit of amyloid imaging examination to improve the healthcare outcome of patients, while several numbers of committee members support the coverage in the scheme of CED. The SNMMI (Society of Nuclear Medicine and Molecular Imaging) and the Alzheimer's Association published a report of appropriate use criteria of amyloid PET in January 2013 [9], and in April, collaborating with other key specialists, they submitted an opinion to CMS to seek insurance coverage. The usage criteria described in the report was summarized in "infographic" (Fig.1), which is comprehensible to practitioners in order to educate them that early stage examination for patients who have not been diagnosed by experts as AD has not been approved and the examination is expensive at this moment without insurance coverage. The sponsoring company, Eli Lilly, submitted for coverage to the CMS and in July 3 2013 CMS released their proposed decision memo to state that a 1 time scan is covered in a clinical trial program under the conditions defined by the CMS (Table 2) [10]. This proposal is to be finalized in October 2013. (It was decided in September 2013 [11]).

4. Ethical, social issues of early detection of AD

According to Eli Lilly in the news article in November 2012 [12], there are more than 300 centers

Table 2 Proposal by the CMS on the coverage of PET amyloid imaging (outline)

The evidence is insufficient to conclude that the use of PET amyloid-beta (Aβ) imaging improves health outcomes for Medicare beneficiaries with dementia or neurodegenerative disease; however, there is sufficient evidence that the use of PET Aβ imaging could be promising in the following scenarios. Therefore, we propose to cover one PET Aβ scan per patient through the CED, under clinical studies that meet the following criteria:
(1) To exclude AD in narrowly defined and clinically difficult differential diagnoses.
(2) To enrich clinical trials seeking better treatments or prevention strategies for AD, by allowing for selection of patients on the basis of biological as well as clinical and epidemiological factors.

Clinical study criteria:

Objectives:
(1) To develop better treatments or prevention strategies for AD, or, as a strategy to identify subpopulations at risk for developing AD, or
(2) To resolve clinically difficult differential diagnoses (e.g., frontotemporal dementia (FTD) versus AD) where the use of PET Aβ imaging appears to improve health outcomes.

Design: Clinical studies must be approved by the CMS, involve subjects from appropriate populations, be comparative, prospective and longitudinal, and use randomization and postmortem diagnosis as the endpoint where appropriate. Radiopharmaceuticals used in the PET Aβ scans must be FDA approved.

Research question (one or more of the following):
With cognitive impairment suspicious for AD, or who may be at risk for developing AD:
1. Do the results of PET Aβ imaging lead to improved health outcomes?
2. Are there specific subpopulations, patient characteristics or differential diagnoses that are predictive of improved health outcomes in patients whose management is guided by the PET Aβ imaging?
3. Does using PET Aβ imaging in guiding patient management, to enrich clinical trials seeking better treatments or prevention strategies for AD, by selecting patients on the basis of biological as well as clinical and epidemiological factors, lead to improved health outcomes?

that can provide amyloid imaging examination and approximately 700 doctors who completed and have been qualified with the educational program to read the scans. Concerning AD diagnosis, development of drugs for prevention and/or therapy has been strongly desired, while the following ethical issues have been raised but not yet completely resolved:

- Proxy consent issue: In California, the state law did not sufficiently cover proxy consent for research participation, so a nursing scientist led the amendment of the law to justify proxy consent for research [13].
- Incidental findings of disease or condition outside of the research purpose: a recent trend of NIH (National Institutes of Health)-funded research is to require the provision of "ancillary care" for the patients in such a situation [13, 14].
- Influence upon QOL (Quality of Life) of knowing future possibilities of disease for which therapeutic tools have not been well developed: A questionnaire survey by Harvard School of Public Health granted by Bayer found that 89% of American (respondents) say that if they were exhibiting confusion and memory loss, they would want to know if the cause of the symptoms was AD; of those aged 60 years and older, 95% say they would want to know if they had AD; more than 97% say that if they had a family member exhibiting problems with memory loss, they would want him or her to see a doctor to determine whether the cause was AD [9].
- Discrimination in insurance and employment: In the U.S. there are legislations to prohibit discrimination of disabled people and also to

prohibit discrimination based on genetic test results, but these do not cover the cases of early detection of disease factors found by the imaging procedure [12].

For resolving and managing these issues, it is important that the SNMMI created the infographic, which would limit unapproved expansion of examination and to promote appropriate use. We should learn from this kind of initiative.

5. Imaging accreditation by the IAC

For insurance coverage in the U.S., not only PET drugs and imaging devices have to be approved but also imaging site accreditation is necessary. This accreditation framework focuses on imaging clinical practice rather than quantitative validation of imaging technology.

Among various aspects of health insurance reformation in the U.S., "**MIPPA (Medicare Improvements for Patients and Providers Act)**" mandated the sites which provide "advanced" imaging technologies (PET, SPECT, CT, MRI) to acquire accreditation by January 2012, as the condition of Medicare health insurance coverage.

The authorized accreditation organizations are the **ACR (American College of Radiology)**, the **IAC (Intersocietal Accreditation Commission)** and the **JC (Joint Commission)** at this moment (Later one another organization was additionally authorized).

This Act excludes hospitals, because hospitals have been getting accreditations for the entire hospital activities. So, this Act is for the non-hospital facilities which provide imaging technology. A well-known accreditation organization for hospitals is the "Joint Commission (JC)" and the international network of the JC is "Joint Commission International (JCI)". The JCI is well-known in Japan as they grant accreditations to many hospitals in the world, especially in Asian hospitals which provide the service for "medical tourists".

Both ACR and IAC have continued voluntary initiative of imaging accreditation for more than 20 years, collaborating with specialists and they now have become the government-authorized accreditation organizations. The ACR focuses on all kinds of radiology, and is not limited to imaging but also covering radiation oncology; and the IAC focuses on nuclear medicine and PET as well as noninvasive vascular testing, echocardiography, MRI and CT. It is up to the sites being accredited which of these to choose. Kurihara visited the office of IAC Nuclear/PET (see Photo) and met the CEO, Sandra L Katanick, CAE and the director of accreditation, Mary Beth Farrell, MS, CNMT, NCT in February of 2012 and met Ms. Farrell again at the SNMMI Annual meeting in June 2012 and exchanged e-mails and the information listed in Table 3 has been provided (Later in February 2014 Inoue and other members of the Japanese Society of Nuclear

The mark of accreditation by IAC

Table 3 Imaging accreditation by the IAC (July 2013)

- At the time of July 2013, 3745 sites are accredited by the IAC in nuclear medicine and approximately 10% of those in PET imaging.
- The office of the IAC occupies the entire 5th floor of a building, where more than 50 staff are working in more than 10 rooms. Their organization is almost all managed based on accreditation fee. There are offers from other countries to apply for accreditation. (Answering the questions whether the IAC wants to be an international accreditation organization, the CEO said jokingly. "We want to accredit the whole world".)
- Accreditation is the condition of reimbursement of Medicare/Medicaid, but the decision of the CMS influences private insurance companies and the hospital list of reimbursement items.
- Now IAC is applying for ISO 9000 and 27001 (ISO for accreditation organization) (They passed ISO in September 2013).

As of 2013, at the time of original Japanese publication

Medicine visited the office of IAC Nuclear/PET).

Answering the questions whether or not some objections were raised because the sites which could not get accreditation might have to stop their operations, they said that there were several objections, but throughout the 4-year preparation period, the Government had repeatedly explained the situation to the people, so problems had been resolved at that moment.

6. Conclusion: Learning from the American Dream World

With the sub-title of "American Dream World", we have reported our survey results of the recent regulatory reformation in the U.S. concerning PET imaging research and practice. It seems to be a very hard burden for the PET community to get the FDA's approval and the CMS insurance coverage, although there is no such principle as in Japan to prohibit "mixed medical practice (see Box, item of CMS)". Our friends in the U.S. suggest that the real situation is far from a "dream world", and some said that the "FDA is mysterious". However, as we mentioned in the beginning of this series, the collaboration among academia, industry, and regulatory people toward policy development and actual realization of the policy seems brilliant for us, and we can learn much from their efforts. It is also excellent that they work together for evidence development and better healthcare of the people. The Japanese PET community are discussing to identify the direction to go forward and making efforts to develop new framework. We wish to develop the way which finally leads to the improvement of the patients' healthcare, based on an internationally standardized framework of research and development, regulatory authorization, and public healthcare insurance coverage.

We hope this series of articles could provide some insight for the Japanese PET community working towards the future world where a variety of PET imaging technologies, not only FDG-PET, is coming to be available for routine medical practice.

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Box Basic terms to understand the situation of Medicare national insurance coverage of PET drugs in the U.S.

CMS (Centers for Medicare & Medicaid Services)
The CMS is an agency under the Department of Health and Human Services and deals with national health insurance, Medicare for elderly and disabled people, Medicaid for lower income people. They make the decisions of coverage based on evidence generated from research studies, considering the expert opinions of an advisory committee. The decisions by the CMS can influence the coverage determinations of private health insurance companies. Medicare is administered by the federal government so its coverage decisions are not always the same as the coverage of Medicaid, as it is administered by individual states. In the U.S., there is not such a principle as in Japan to prohibit "mixed-medical practice (public health insurance coverage for the part of practice and not coverage for the part of not-authorized procedures in a line of patient care)".

CED (Coverage with Evidence Development)
One type of determination by the CMS to cover the procedures in some evidence development program defined by the CMS. There are two types of CED: the **CAD** and the **CSP**, explained in the following. In these schemes, medical records are gathered in compliance with the privacy rule under **HIPAA**, and research studies should be conducted under the regulations of human subject protection. After the results are published in peer-reviewed journals, CMS will analyze the evidence and make decisions whether or not to cover the submitted new indications for clinical practice.

CAD (Coverage with Appropriateness Determination)
One type of CED in which "additional clinical data is needed"; and sometimes registry of patients' data and prospective data accumulation is required as the condition of insurance coverage.

CSP (Coverage with Study Participation)
One type of CED in which the procedures can be covered only "within a research setting", under the conditions defined by CMS.

NOPR (National Oncologic PET Registry)
Nation-wide registry of patient medical records, which was sponsored by the Academy of Molecular Imaging (now the World Molecular Imaging Society) and developed and managed by the **ACR**, and started in 2006. It was designed being reviewed by multiple agencies of the Department of Health and Human Services, also to be compliant with the standards defined by the CMS

ACR (American College of Radiology)
An American professional society composed of radiologists, radiation oncologists, medical physicists, interventional radiologists, nuclear medicine physicians and allied health professionals.

IAC (Intersocietal Accreditation Commission)- **IAC Nuclear/PET**
IAC is a nonprofit organization to provide accreditation service and IAC Nuclear/PET is one division to deal with nuclear medicine/PET accreditation.

JC (Joint Commission)
Hospital accreditation organization in the U.S. The international version of the JC is the well-known JCI (Joint Commission International).

HIPAA (Health Insurance Portability and Accountability Act)
The legislation of the rules to protect privacy of individually identifiable health information and to set national standards for the security of electronic protected health information, enacted in 1996.

MIPPA (Medicare Improvements for Patients and Providers Act)
A multi-faceted piece of legislation that contains several important provisions that directly change the Medicare program, enacted in 2008.

cerning nuclear medicine diagnosis using PET drugs produced by an in-house PET drug synthesizer; and 2013, 2014 fiscal year: Regulatory science concerning clinical application of nuclear medicine diagnosis using PET drugs produced by an in-house PET drug synthesizer (including this publication of English translation of an article written in Japanese).

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