1. Introduction

We have found that PET (Positron Emission Tomography) communities in the U.S. (United States) and Japan have been in a similar situation. Both of them have been intensively discussing and making efforts about the PET drug-specific regulations; developing similar PET drug products; as well as aiming for a similar goal to expand use of various PET drugs for better public health. So what is the difference? The "American Dream World" does not necessarily mean that the PET community in the U.S. is far superior in the levels of science and technology of this field or of diagnostic practices using PET. It implies that it is praiseworthy that the ways in which the U.S. PET community has implemented a well-designed regulatory system, has succeeded in consensus formation and collaboration among industry, academia, and regulators, within the clarified timelines of developing the new regulatory framework and of implementing their policies.

We previously discussed the trends concerning PET drug regulations in the U.S. in the November 2011 issue of *Rad Fan* [1]. Later on, we surveyed the actual situation in the U.S., having interviewed all concerned parties that appeared in the previous *Rad Fan* article and summarized it in our task force report [2]. So we now introduce these situations in this series of articles with the title of "PET Drug American Dream World History."

2. Historical background of the regulations of PET drugs in the U.S.

The U.S. PET drug community and regulators had discussed during the 1980s about whether the PET drug is a product of "compounding" by a pharmacy or of the "manufacturing" process. The FDA (Food and Drug Administration) Modernization Act of 1997 (a bill to amend the overall regulations concerning FDA, which includes PET drugs) required that PET drugs be prepared according to the standards and monographs in the **USP (United States Pharmacopeia)** *2 until the FDA would establish appropriate approval processes and **GMP (Good Manufacturing Practice)** regulations specific to PET drugs [3] *3.

Then the monographs of 12 well-known PET drugs were listed in the USP, which the FDA can make use of. The FDA was obligated to develop frameworks for GMP regulations specific to PET drugs and other related systems. Then, as long as these drugs were manufactured in accordance with these monographs, until the new regulations went into effect, it had been possible to use them in clinical practice, and companies were allowed to commercially market these PET drugs even though they were unapproved.

Members of the PET community in the U.S. often mention the following key words:

- "PET is special" (different from other drugs in terms of the half-life, stability, etc.)
- "Patients are the same" (since every patient's right to get the best medicine is the equal,

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

*3 This article (Reference 3) was published by the members of the Committee on Pharmacopeia, Society of Nuclear Medicine and Molecular Imaging at the time when the new regulatory framework was implemented, in which they argued that these monographs should be deleted from the list in USP. (Responding to this argument, on December 1, 2014, USP omitted unapproved 8 PET drugs from their list of monographs in the USP.)

when they undergo the examination using diagnostic drugs produced at a small facility or supplied by a big manufacturing company, the safety and reliability should be assured at the same level.)

According to such principles, GMP regulations specific to PET drugs (PET drug GMP) that do not differentiate companies from medical/research institutions were proposed, and finalized on December 10, 2009. Although the deadline for enactment of the regulations was initially December 12, 2011, people involved in this issue expressed the opinion that they would not be able to meet the target date, therefore the date of enactment was postponed until June 12, 2012.

Three sets of guidance that explained the steps from development of PET drugs through clinical studies to acquisition of FDA approval were also published in 2004 [4~6]. Furthermore, exploratory clinical research employing a certain limited usage of radioactive drugs not intended for development of diagnostic drugs nor clinical diagnosis can be carried out within the framework of the **RDRC (Radioactive Drug Research Committee)** without submitting an **IND (Investigational New Drug application)** to the FDA. The guidance explaining this framework was finalized in 2010 [7]. Please refer to our previous article [1] for these details.

3. Updates of the regulations of PET drugs in the U.S.

Since the enactment of the new system, if companies and medical/research institutions are to use PET drugs in general practice, they all have to submit an **NDA (New Drug Application)** or **ANDA (Abbreviated New Drug Application)**, and pass GMP inspections by the FDA to obtain approval. The FDA will sequentially implement inspections according to the applications and plans to complete inspections and determine whether or not to approve. For the NDAs submitted by the time of enactment of new regulations on June 12, 2012, the FDA's determination would be made by December 12, 2015. The U.S. approved medical/research institutions can prescribe the drugs not only in their institutions, but also supply and sell them to other medical institutions*4. If institutions do not submit an NDA/ANDA, they must use the drugs as part of a clinical trial or research within the framework of an IND or RDRC.

Outside these frameworks, "clinical" use of unapproved PET for routine practice is prohibited. When they have to use an unapproved drug for clinical practice for necessity, they have to submit an **Expanded Access IND**. Manufacturing regulations to be applied for NDA/ANDA status are found in **21 CFR (Code of Federal Regulations) 212 (PET drug GMP)** ; and manufacturing standards applied for clinical trials or research of an IND or RDRC status are found in **USP823** (more flexible manufacturing standard specific to PET drugs).

The enactment of the new system was scheduled during the **SNM (Society of Nuclear Medicine)** Annual Meeting. The society's name was changed to **SNMMI (Society of Nuclear Medicine and Molecular Imaging)** during the meeting period. A total of at least 16 presentations by FDA personnel (at least 3 sessions provided by the FDA and 2 sessions not provided by the FDA but containing presentations by FDA personnel) were performed,

*4 In Japan, there are two tracks to develop new PET drug from research status to general practice: medical institutions buy PET drugs supplied from companies who obtained approval for the PET drugs; or purchase a PET drug synthesizer apparatus approved as a medical device, and manufacture and use drugs only in their institution or hospital, but not permitted to supply outside.

Table 1 Comparison of authorized status of PET drugs in Japan and in the U.S., at the time of May 2013: Approval as "established techniques" (See page W52 footnote 5) in Japan and Listing USP in the U.S.; regulatory approval status in Japan and in the U.S.

Names of Drugs (Authorized as "established techniques") USP: USP listed Needs: *1	Usage ("established techniques") / Regulatory approved indications (Device/Drugs): *2	Years of authorizations as "established techniques"	Approved by Ministry of Health, Labour and Welfare (Year/Month): *3	Approved by FDA (Year/Month): *4 ( ) indicates NDA discontinuation Underlines indicate "under the new system"
[^{11}C] Carbon monoxide gas (^{11}C) USP	Blood amount, blood pool	85		
[^{13}N] Nitrogen gas ($^{13}N_2$)	Lung ventilatory performance	85		
[^{15}O] Oxygen indicator gas ($^{15}O_2$)	Oxygen metabolism, lung functions / local tissue oxygen metabolism, local lung functions	85	(Covered by insurance since 1996) Medical device (synthesizer system) SHI: 91/9 CYPRIS-G, 00/01 Supplementary application JFE: 97/3 (DAINIPPON) [^{15}O] Gas synthesis system, 05/4 Transferred from DAINIPPON, 10/2 Supplementary application (manufacturer: DAINIPPON) MIL: 12/11(manufacturer: UG) ^{15}O-labeled gas synthesis and supply device	
[^{15}O] Carbon dioxide indicator gas ($C^{15}O_2$)	Blood flow, lung functions / local tissue blood flow, local lung functions	85		
[^{15}O] Carbon monoxide indicator gas ($C^{15}O$)	Blood amount, blood pool / local tissue blood amount, blood pool	85		
[^{13}N] Ammonia injection ($^{13}NH_3$) USP	Blood flow / diagnosis of ischemic cardiac disease	85	(Covered by insurance since 2012) Medical device SHI: 10/3 N100 JFE: 12/3 (manufacturer: Kyorin) Lab-CUBE NH_3	NDA, 07/8, Feinstein Institute ANDA, 12/12, Houston Cyclotron
[^{15}O] Water injection ($H_2{}^{15}O$) USP	Blood flow, blood flow imaging	85		
2-deoxy-2-[^{18}F] fluoro-D-glucose injection *2 USP Needs *1	Glucose metabolism / assessment of abnormal glucose metabolism in diagnosing malignant tumors; evaluation of myocardial glucose metabolism; confirmation of abnormal regions for glucose metabolism focusing on epileptic fit	85	(Covered by insurance since 2002) Medical device GE: 01/12 FDG MicroLab → discontinued, 03/7 (JFE) TRACERlab MX FDG, 05/5 Supplementary application → 05/9 Transferred from JFE, 11/12 FASTlab JFE: 02/12 (DAINIPPON) [^{18}F] FDG injection synthesis system, 05/4 Transferred from DAINIPPON (manufacturer: DAINIPPON) SHI: 02/3 F100, 05/6 F200, 10/7 F300 CMI: 07/6 Explorer (FDG4) SCETI: 07/6 FDG automated synthesizer, 11/6 IBA-1 Drugs NMP: 05/7 FDG scan injection Advanced (manufacturer) / NMP (marketer): 05/07 FDG scan-MP injection	(NDA, 94/8, Downstate Clinical PET Center) NDA, 04/8, Weill Medical College NDA, 05/8, Feinstein Institute ANDA, 11/2, PETNET Solutions
L-[^{11}C] Methionine injection USP Needs *1	Amino acid uptake rate	88		
[^{11}C] Acetate injection USP	Myocardial aerobic metabolism	94		
N-[^{11}C] methyl-spiperone injection USP	Dopamine D2 receptor	94		
[^{11}C] Choline injection	Malignant tumors	01		NDA, 12/9, Mayo Clinic
[^{18}F] Sodium fluoride injection ($Na^{18}F$) USP Needs *1	Bone diseases	09		(NDA, 72/2, GE Healthcare) (NDA, 11/1, NIH-NCI) ANDA, 12/12, Houston Cyclotron

[^{11}C] Raclopride injection [USP]	Dopamine D2 receptor	09		
[^{11}C] Flumazenil injection [USP]	Central benzodiazepine receptor	09		
Name of Drugs (Listed in USP ([USP]))/ FDA approved				
Fluorodopa F 18 injection [USP]				
Rubidium chloride Rb 82 injection [USP]				NDA, 89/12, Bracco
Florbetapir F 18 injection				NDA, 12/6, Avid＊5

＊1: [Needs]: The designated medical technologies as of high needs at the "Working Group on Early Introduction of Medical Devices with High Medical Needs" of the Ministry of Health, Labour and Welfare in November 2011 in response to a request from Japanese Society of Nuclear Medicine. Based on these designations, companies are recommended to apply for approval of these medical devices, synthesizers of these PET drugs. Although the indications of FDG stated on the front have already been approved, additions of the efficacy to differentiate Alzheimer's type and to diagnose causal lesions of fever of unknown origin were requested. The requests were approved for methionine with tumors (brain tumor, etc.) as the indications, and for NaF with malignant bone tumor as the indication.

＊2: Since approved indications as well as coverage by insurance may vary depending on the individual product, caution is needed in actual practice.

＊3: At the times of applications noted here, no differentiations were made between the new medical device and the generic medical device as they are at present. Thus, this differentiation is not shown regarding the status of Japan. These data are as of May 2013, which have not been changed since January 2013 when we surveyed the situation in the U.S.

＊4: Data as of January 2013. Those with NDA/ANDA approval are listed, and different manufacturers are not noted. See the end of this article and the next report for NIH-NCI.

＊5: The only newly developed PET drug in this table, and is indicated for measurement of the beta-amyloid plaque buildup in patients suspected of Alzheimer's disease. Avid Radiopharmaceuticals, Inc. obtained approval, but was acquired by Eli Lilly subsequently. Whether or not it will be covered by insurance is to be determined in July 2013. (After the publication of Japanese original version of this report other two PET drugs for beta-amyloid, Florbetaben, Flutemetamol, were approved by FDA, but coverage is for only a 1 time scan under the program of Coverage for Evidence Development, according to the protocol approved by CMS (Center for Medicare and Medicaid Services. Details of this system are reported.) In Japan also these three PET drugs were applied for NDA and only Florbetapir was approved as of 2015 February.)

[Explanations for the abbreviations used in Table 1]
SHI: Sumitomo Heavy Industries, Ltd.
JFE: Nihon Kokan Kabushiki-gaisha (NKK Corporation) → (omitted) → JFE Engineering Corporation (its operation was transferred, the company name was changed, partially omitted)
DAINIPPON: DAINIPPON SEIKI Co., Ltd.
Kyorin: Kyorin Systemac Co., Ltd.
MIL: Molecular Imaging Labo Inc.
UG: UNIVERSAL GIKEN CO., LTD
GE: GE Yokokawa Medical Systems Co., Ltd. → GE Healthcare Japan Corporation (the company name was changed)
SCETI: SCETI Co., Ltd. → SCETI K.K. (the company name was changed)
CMI: CMI Inc.
NMP: Nihon Medi-Physics Co., Ltd.
Advanced: Japan Advanced Medicine and Pharmacology Research Center

In the U.S. with the new system described in this report and also in Japan with the efforts by Japanese Society of Nuclear Medicine facilitating the discussion at the Working Group of ＊1 above, various PET drugs other than FDG are expected to receive approval by authorities both in U.S. and in Japan, and become available in clinical practice in the near future. This table shows the start line for both Japan and the U.S. toward such a new trend of clinical practice using newly approved PET drugs.

which demonstrated their focus on promoting the new regulatory system. FDA has a Division of Medical Imaging Products (DMIP). In addition, PET Working Group (WG) specific to PET drug regulations has been formed, and 9 WG specialists accepted our visit to their office in February 2012 as a part of our task group survey to discuss general issues of PET drugs which are open to the public.

According to the presentations by the FDA at the SNMMI Mid-Winter Meeting (MWM) in January 2013, 3 out of 86 ANDAs for PET drugs were approved by December 2012. There were 2 approved NDAs, one of which was Florbetapir F 18 (Amyvid®) in the framework of **505(b)(1)** (based on data from clinical studies), and the other was Choline C 11 in

the framework of **505(b)(2)** (based on a retrospective review of the literature). There were 115 INDs for PET drugs between December 10, 2009 and January 4, 2013, and of those, at least 4 applications were made as Expanded Access INDs. (These numbers are from our quick short note and not confirmed.)

Table 1 shows the approval status of PET drugs in the U.S.[8], compared with Japanese situation (at the time of May 2013). In Japan, there had been so-called "Drugs of established technique" (PET drugs of established manufacturing technique) approved by the Expert Committee of the Japan Radioisotope Association, which was academic society initiative[9)*5,6]. There are also regulatory-approved PET examinations using approved PET drugs or approved synthesizer apparatus, by the Ministry of Health, Labour and Welfare.

Box Basic terms to understand the framework of the new system for PET drugs in the US

FDA
United States Food and Drug Administration

USP
United States Pharmacopeia:
A non-governmental organization called the United States Pharmacopeial Convention, founded in 1820, which was earlier than the enactment of the Federal Food and Drugs Act of 1906. They have been working with the FDA and specialists in academia and companies to establish monographs listed in the USP and the related standards. As with the Japanese Pharmacopoeia (JP) and the European Pharmacopoeia (EP), USP basically lists monographs of approved drugs. However, the USP also lists as an exception the monographs (specifications for manufacturing) of 12 approved/unapproved PET drugs (Later monographs of 8 unapproved PET drugs were omitted from the USP. See the Footnote 2 and the Reference 3).

SNM
Society of Nuclear Medicine

SNMMI
Society of Nuclear Medicine and Molecular Imaging
(The name was changed from SNM in June 2012)

NCI
National Cancer Institute:
One of the institutes of the NIH (National Institutes of Health), focusing on cancer research.

NDA
New Drug Application

ANDA
Abbreviated NDA:
New Drug Application by a simplified procedure for an already approved drug, which is the same as the application for generic drugs.

505(b)(1), 505(b)(2)
A 505(b)(1) is the article number of the regulation for drug approval application, which requires full data package.
A 505(b)(2) is the article number of the regulation for drug approval application, which does not require a full data package but will accept an application with published literature for which the applicant does not own or has not obtained a right of reference (similar to "a public knowledge-based application" in Japan). These article numbers are of the Federal Food, Drug, and Cosmetic Act. The ANDA noted above is under 505(j).

*5 The compounds so-called "established techniques" are PET drugs with established manufacturing techniques approved by the Subcommittee on Medical Application of Positron Emitting Radionuclides, Medical Science and Pharmaceutical Committee, the Japan Radioisotopes Association. The approved drugs shown in Table 1 are based on Reference 9. This academic-initiated approval system was asked to be redesigned, and new standards were established in 2011 by the Japanese Society of Nuclear Medicine (See http://www.jsnm.org/guideline/molecule). Instead of the system to approve "established techniques", they are implementing activities to support and promote "regulatory approval" and clinical use of PET drugs and synthesizers.

*6 As shown in Table 1, 10 out of 15 drugs approved as "established techniques" in Japan match those listed in USP, and discussions about them at the drafting stage had been published prior to the finalization of specifications of the drugs listed in USP of 1997. As for the FDA approved items, we confirmed them on the FDA web site based on Reference 8.

In the U.S., the Mayo Clinic and **NCI (National Cancer Institute)** have obtained their NDA approval as medical/research institutions. At the above-mentioned SNMMI- MWM, the Mayo Clinic and PETNET Solutions Inc. presented their experiences in accepting FDA's GMP inspections as a medical institution and as a company, respectively, and discussed that the same applicable rules might be put into effect in different manners. NCI first received NDA approval with PETNET Solutions Inc. as PET drug manufacturer, and soon afterwards notified the FDA to discontinue this NDA (That is why this was not included in the 2 applications noted above). At the time of our visit to NCI, we found that this was an excellent strategy involving the collaboration among academia, industry, and regulators, which we will introduce in detail in the next (2nd) report of this series [10].

IND
Investigational New Drug application:
An application for authorization by FDA to conduct clinical trials. Although it corresponds to "Clinical Trial Notification" in Japan, unlike in the case of Japan where only the clinical trials aiming for new drug approval are covered, in the U.S. any clinical trials of a new drug investigation or comparative clinical studies of approved drugs the results of which may be used for new indication approval or for drug promotion are required to submit IND.

Expanded Access IND
A procedure for clinical use of unapproved drugs for treatment of serious or life-threatening disease for which there is no other available drug. They submit to the FDA almost the same information as in the case of an IND but in a simplified manner. They also have to obtain IRB approval.
With regard to a PET drug, the FDA seems to allow the interpretation of the above conditions in the meaning "clinical use of unapproved diagnostic drugs for examination for serious or life-threatening disease for which there is no other available diagnostic procedure." It is a framework similar to "Compassionate Use" currently being discussed in Japan.

RDRC
Radioactive Drug Research Committee:
The Radioactive Drug Research Committee (RDRC) program began when the Food and Drug Administration published a Federal Register notice in 1975 classifying all radioactive drugs as either new drugs requiring an IND for investigational use (21 CFR 312) or as generally recognized as safe and effective when administered under the conditions specified in the RDRC regulations (21 CFR 361.1). The RDRC program under 21 CFR 361.1 permits basic research using radioactive drugs in humans without an IND when the drug is administered under the following conditions: Based on other already conducted human studies in which the radiation dose from a single study can be estimated not to exceed 3 rem (5 rem for a cumulative annual dose) in the whole body; active blood-forming organs; lens of the eye; and gonads, or 5 rem (15 rem for a cumulative annual dose) in other organs. The number of subjects is limited and the study should not be intended for drug development or clinical diagnostic purposes. The FDA will approve the Committees and requires the committees to submit an annual report to the FDA, by which the FDA can monitor the contents of the protocols of research. In 2012, there were 72 approved active committees in the U.S.

IRB
Institutional Review Board

GMP
Good Manufacturing Practice:
Regulatory standards for manufacturing drug products. In Japan, we have "Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs" under the Pharmaceutical Affairs Law.

21 CFR 212 (PET drug GMP)
Article number of the U.S. Code of Federal Regulations (CFR) on GMP specific to PET drugs for clinical use. There is a guidance that explains the regulations. They were initially intended to apply for clinical studies as well. However, after receiving public objections just before their finalization, it was decided that USP 823 would be applied for clinical trials under an IND and exploratory clinical research within the framework of RDRC.

USP 823
USP contains not only specifications of individual drug products but also general rules for drug manufacturing. USP 823 includes manufacturing standards applied for clinical trials or research of PET drugs. USP 823 was amended so as to be consistent with 21 CFR 212, but it contains much fewer requirements than 21 CFR 212, and has little binding force and few documentation requirements.

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Translation

PET drug clinical trials and networking strategy for development

— PET Drug American Dream World History: The 2nd Report —*1

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Abstract

In the U.S. (United States), there are various activities to develop diagnostic PET drugs toward the use in medical practice being covered by healthcare insurance and also to make use of PET drugs for assessment of biomarkers for therapeutic drug development. In this second report of 3-part series, we introduce some of the strategic initiatives to promote multi-center clinical research and clinical trial network being facilitated by collaboration among academia, industry, and regulators.

Key words

NCI (National Cancer Institute), SNMMI-CTN (Society of Nuclear Medicine and Molecular Imaging-Clinical Trial Network), DMF (Drug Master File), LOA (Letter of Authorization), Shared-IND

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*1 This article is an English translation of the article originally written in Japanese and published in *Rad Fan.* 2013; 11(9): 118-21, under the permission of the publisher, Medical Eye. The information included is not completely identical with the original one and has not been updated since the time of original publication except for some of the important information subsequently added.

1. Strategy with NaF by National Cancer Institute (NCI)[1)]

In our first report[2)] of this series, we reviewed the status of PET (Positron Emission Tomography) drugs in the United States (U.S.). Various industrial and medical centers have begun to receive authorizations of **NDAs (New Drug Applications)**[*2] or **ANDA (Abbreviated NDAs)** to market and use PET drugs in routine clinical practice from the FDA (Food and Drug Administration) in compliance with the newly established PET drug regulations, including PET drug GMP (Good Manufacturing Practice regulations specific to PET drugs).

Soon after the FDA issued the new regulations of PET drug GMP, the U.S. National Cancer Institute (NCI) received approval of their NDA of NaF ([^{18}F] – Sodium Fluoride) on January 26, 2011. The NCI notified the FDA to discontinue this NDA, on May 3, 2012. The reason was as follows: NCI is a governmental agency so they are not required to pay user fees for the FDA's review of NDA or any other user fees to keep the NDA active. Once an NDA of a drug is approved, any other companies or medical institutes can submit ANDA for the drug, if the sponsor holding the NDA waives an exclusivity period, and NCI did do that. Furthermore, in the case of PET drugs (different from other general therapeutic drugs), a new regulation starting from January 2012 makes ANDA free of charge for commercial companies and academic institutes ("PET is special")[2)]. It was NCI's strategy from the beginning to gain approval of an NDA of NaF to facilitate others to submit ANDAs. Dr. Jacobs, during our interview, said, "Free is good!" and explained that it would help make these small volume drugs more readily available for patients.

According to the FDA's review report, the shortage of molybdenum-99 didn't make approval condition to be mitigated, but it supported NaF categorization for "priority review", to shorten the review time. NaF was one of the drugs established in the FDA's guidance regarding required information for NDA/ANDA using historical data (505(b)(2), "literature NDA")[3)]. Toxicological data was not reviewed, but one **DMF (Drug Master File)** owned by PETNET Solutions was approved as a manufacturer of this approved NDA for NaF. Since this time, many institutions and commercial firms have filed ANDAs based on the the NCI NDA.

2. NCI's strategy of "Shared INDs"[1)]

NCI was previously authorized INDs of various PET drugs and has conducted clinical trials and owns information of the toxicology and pharmacology of these drugs. They also have another strategy named "Shared INDs". They have a mission of the national institute to promote the development of PET drugs and under the NCI group named the "Cancer Imaging Program," they submitted INDs of various PET drugs and have conducted clinical trials. Once the FDA approved the INDs of these drugs, other institutes can submit INDs of these drugs saving duplicated procedures, if the NCI provides a **LOA (Letter of Authorization)** to other institutes. Other institutes that received a LOA from the NCI can refer to toxicology and pharmacology data of NCI and the FDA can have access to the NCI's previous IND information for their reviews of newly submitted INDs.

Another merit is to save the lives of animals and save the cost of toxicology and pharmacology stud-

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

ies. Also it is possible to shorten the time of the FDA's review and they can focus on the review of the clinical trial protocol.

The NCI lists the PET drugs which can be utilized in this "Shared INDs" strategy as shown in the Table 1. These drugs are not necessarily manufactured in the NCI. The NCI has manufacturing facilities for human use but in the case of multicenter trials, it is preferable to use commercial manufacturing sites that are more quality-assured for large-scale production. Therefore, manufacturers who are the holders of the DMF issues a LOA to the NCI and the NCI submits INDs to the FDA along with these LOAs from manufacturers, then the FDA can have access to these DMFs of the manufactures. Fig. 1 shows supplies of FLT ([^{18}F]-fluorothymidine) in U.S. in this framework of strategy.

Table 1 NCI's "Shared INDs"

- [^{18}F]-FLT – proliferation
  LOA with 9 companies for drug development, 34 research institutes, and SNMMI. DMF of several number of manufactures. 80 clinical trials, 1/4 of these are multicenter trials and half of these are based on a LOA from NCI. 75% is in U.S. and others are in Europe, Asia. Academic institutes: Companies= 1:4.
- [^{18}F]-FMISO – hypoxia
  DMF of 1 company. 9 LOAs, 25 clinical trials (5 multi-center).
- [^{18}F]-FES – estrogen receptor
  3 LOAs, 10 clinical trials (1 multi-center)
- [^{18}F]-Sodium Fluoride – bone seeking
  10 clinical trials (3 multi-center)
- [Zr-89]-panitumumab – EGFR directed
  (There are two other imaging drugs listed, along with the above PET drugs)

As of 2013, at the time of original Japanese publication, quoted from the reference 1

Fig. 1 Commercial FLT supply sites 5/2012

Not updated from the original Japanese publication in 2013, ©National Cancer Institute, quoted from the reference 1.

3. SNMMI's CTN (Clinical Trial Network)

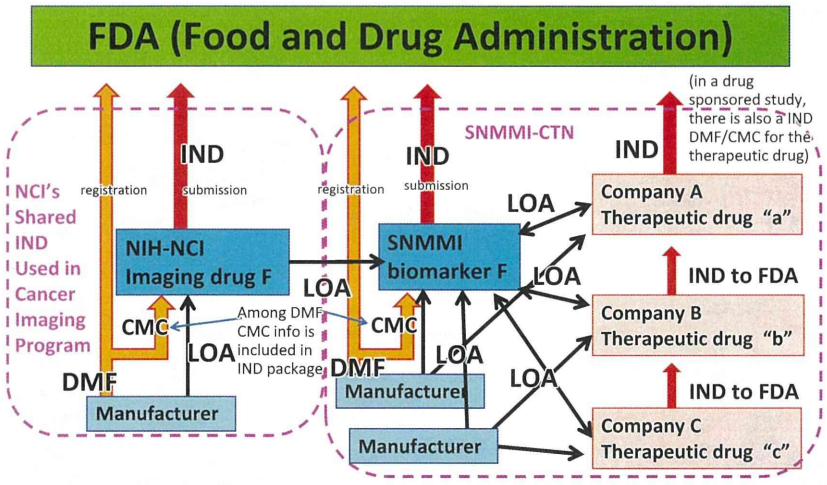
U.S. Society of Nuclear Medicine and Molecular Imaging's Clinical Trial Network promotes the initiative of manufacturing sites registration and scanner sites registration and validation for their organization of global drug development [3]. They also take "Shared IND" strategy (Fig. 2).

SNMMI submits an IND of FLT to the FDA, making use of a LOA from NCI, to conduct a clinical trial of FLT as a diagnostic drug. The SNMMI-CTN has established a collaborative clinical trial network with therapeutic and diagnostic companies and academic institutes, being funded by some of the partner companies. By using the LOA from the CTN's IND for FLT imaging in their therapeutic trials, drug companies can put their expenditure saved towards other drug development efforts, either done in-house or as part of their ongoing support to the CTN for its continued efforts in facilitating the effective use of molecular imaging biomarkers in clinical trials.

Diagnostic drug companies and academic sites manufacture and provide FLT as a biomarker for the therapeutic companies' clinical trials. These manufacturers own their DMFs and issue a LOA to the SNMMI and therapeutic drug companies. The SNMMI and therapeutic drug companies exchange LOAs of each IND and the SNMMI utilize FLT based on their IND and therapeutic drug companies utilize their therapeutic drug based on their IND. These LOAs and cross reference among SNMMI, manufacturers, therapeutic drug companies, and the FDA avoid duplication of tasks.

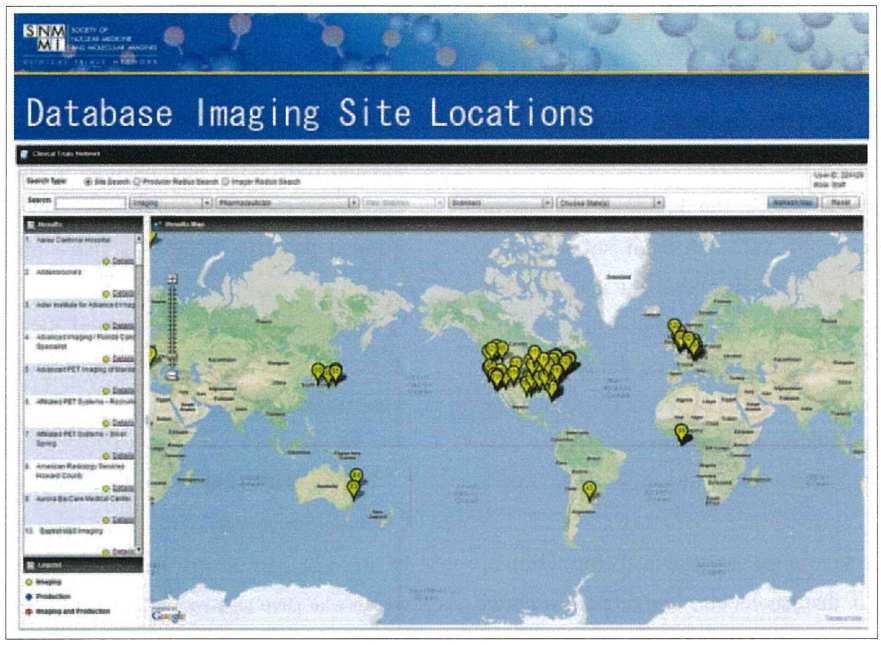
Now many of the scanners in the world have completed SNMMI-CTN's validation process (Fig. 3, provided by SNMMI) and clinical trials have been facilitated (Table 2).

Fig. 2　Shared-IND strategy of NCI and centralized-IND strategy of SNMMI



This figure doesn't show the numbers and scales of projects but only show each relationship and usage of LOA (update of ref. 3 Fig. 3).
NCI is the original holder of IND of FLT and leads more various organizations of shared INDs with other manufacturers, and IND holders. SNMMI uses IND info from NCI (tox, pharmacology) based on LOA, and submits IND of FLT to FDA. SNMMI submits in their IND packet the LOAs from FLT manufacturers allowing FDA to reference required parts of their DMF for SNMMIs IND; Manufacturers listed under the SNMMI IND must meet the same end-product specifications outlined in the IND application. Therapeutic drug company submits IND of therapeutic drug along with an LOA from SNMMI for IND of FLT (biomarker) and LOA from manufacturers for DMF of FLT.

Fig. 3 Database Imaging Site Locations



Not updated from the original Japanese publication in 2013, ©Society of Nuclear Medicine and Molecular Imaging

Table 2 Registration/validation and clinical trial in the SNMMI-CTN's initiative

- As of February 1, 2015, the CTN database has 410 sites registered in three distinct categories (the increase in numbers is based upon the information from June of 2013, at the time of previous, original Japanese publication):
  - imaging sites only: 170 sites (19 increase)
  - manufacturing only: 114 sites(commercial) (5 increase)
  - sites with both imaging and manufacturing capabilities (primarily academic): 126 sites (28 increase)
- CTN has validated 241 (27 increase) scanners at 163 (10 increase) sites using its unique oncology chest phantom. Sites with validated scanners are located in the U.S., Canada, Australia, Germany, Switzerland, Netherlands, Belgium, United Kingdom, Korea, Taiwan, Spain, and Japan (No change of the countries). The number of validated scanners broken down by country/region are: US (166); Asia (15); Australia (13); Canada (13); UK-Europe (34).
- The CTN has recently developed a new model of their chest phantom to more closely harmonize with the number and size of lesions found in the NEMA NU-2 phantom. It is expected that the new model will be available for use in multicenter clinical trials by 2Q2015. The CTN has completed scanning their unique brain phantom on PET/CT scanners currently being used in an NIH Pediatric Brain Tumor Consortium study. Analysis of the data is being performed with a report anticipated to be released by mid summer 2015. (Progress from the previous original report in 2013.)
- CTN is currently engaged with industry and investigators in projects using 7 different investigational agents and has four trials open in 24 (previously 41*) sites in U.S., Canada, and Australia. Sites in Germany and Korea have completed clinical trials with the SNMMI-CTN. Among the four studies actively recruiting patients, 1 protocol (5 sites) uses HX4, 1 protocol (10 sites) uses 18F-Choline, 1 protocol (4 sites) uses FDHT and the fourth study (7 sites) uses FLT under the SNMMI-CTN held IND for FLT. (Increase in number of PET investigational agents. Previously only FDG and FLT were used**.)

As of February 1, 2015, updated from the table in the original Japanese publication in 2013.
* This decrease of number is because one large FDG study closed because it met the recruitment goal.
** This is because large FDG study closed and they are working on studies using investigational PET agents, which can change at any time depending on what a sponsor may need.

4. Initiative of Japanese Society of Nuclear Medicine Scanner and manufacturing validation and networking

Learning from the U.S., the Japanese Society of Nuclear Medicine (JSNM) has been setting up a framework of PET drug development and also for making use of PET for therapeutic drug development. In June 2012 JSNM Molecular Imaging Strategic Committee and U.S. SNMMI-CTN agreed on the MOU (Memorandum of Understanding), for collaboration and information sharing each other (Photo).

The JSNM developed a standard for clinical research of PET drug molecular imaging and started an initiative of a manufacturing and scanner audit and authorization (http://www.jsnm.org/english/15-01-23). Also, based on collaboration with regulators, companies, and academic institutes, JSNM supports the activities of multi-center clinical trials and IND/NDA submissions to translate clinical research towards regulatory authorization and clinical practice with healthcare insurance coverage.

In the next issue, we report about the imaging authorization system in U.S. which is linked to insurance coverage.

Acknowledgement

We deeply appreciate the specialists in the U.S., some of whom appear in this series of articles and those in Japan who gave us meaningful cooperation for our survey

June 12, 2012, US Society of Nuclear Medicine and Molecular Imaging Annual Meeting. In the front row, the middle is Michio Senda, the chairman of Molecular Imaging Strategic Committee, Japanese Society of Nuclear Medicine; on both of his sides are co-chairs of SNMMI-CTN, John M. Hoffman (left) and Michael M. Graham (right). In the back row, on the far right, is the president at this time of the SNMMI, Frederic H. Fahey and next is Tomio Inoue, the president of the Japanese SNM. (As of 2013, at the time of original Japanese publication)

Box Basic terms to understand PET drugs development strategy by academia, industry and regulators in the U.S.

DMF (Drug Master File)
DMF contains all the information of the drug concerning manufacturing and quality assurance, including **CMC**. A manufacturer owns its DMF and can voluntarily register it with a domestic or foreign regulatory authority.

CMC (Chemistry, Manufacturing and Controls)
Information of components, raw materials, chemical synthesis, manufacturing production, quality control and validation of the drug, which is a part of the DMF, and should be included in IND.

LOA (Letter of Authorization／Letter of Access)
A DMF holder manufacturer or another IND holder gives a Letter of Authorization (LOA) to applicants of an IND/NDA and the applicant submits the IND/NDA along with the LOA to the FDA, then the FDA can have access to DMF of the manufacturer or the IND of the other sponsor. This sharing of information among manufacturer, IND/NDA applicant and the FDA is called "cross-reference". The data does not have to be shared, but the letter authorizes the FDA to look at it when reviewing the new IND.

(The following terms are explained in the first piece of this series)[2)]
NDA (New Drug Application)
ANDA (Abbreviated NDA)
IND (investigational new drug application)

and for this manuscript. This report is based on the following task force research fund. Ministry of Health, Labor and Welfare, 2011, 2012 fiscal year: Regulatory frameworks of the United States and other countries concerning 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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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 This article is an English translation of the article originally written in Japanese and published in *Rad Fan.* 2013; 11(10): 86-9, under the permission of the publisher, Medical Eye. The information included is not completely identical with the original one and has not been updated since the time of original publication except for some of the important information subsequently added.

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.

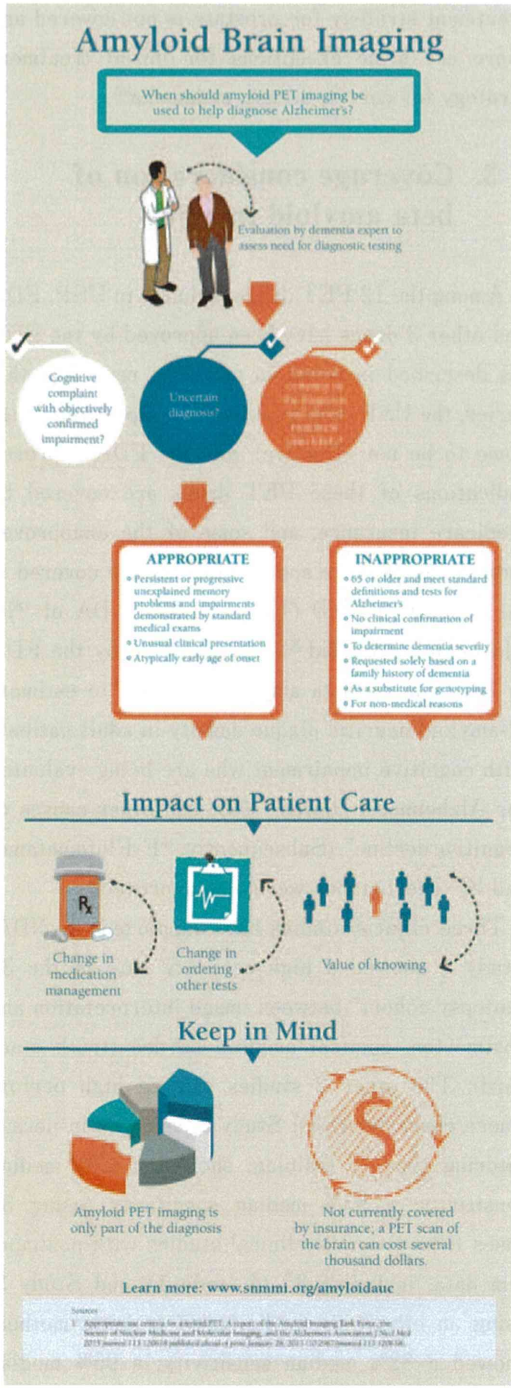
Among the more than 30,000 eligible NOPR-registered cohort data, approximately 23,000 questionnaire data were analyzed to find doctors' changes of management associated with PET examinations [5, 6] (During nearly four years of operation after the development, over 150,000 patients have undergone FDG-PET 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