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.

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 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 con-

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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Interview

Interview with Dr. Louis B. Jacques on insurance coverage policy of CMS focusing PET imaging

— Scientific evidence and social, ethical implications concerning healthcare reimbursement —*1

Louis B. Jacques*2
Senior Vice President & Chief Clinical Officer, ADVI Reimbursement & Health Policy Consultancy

Interviewer: Chieko Kurihara*3
Molecular Imaging Center, National Institute of Radiological Sciences (NIRS)
(June 13, 2014, ADVI, Washington D.C., United States)

Abstract

This is the record of an interview with Dr. Louis Jacques, M.D., Senior Vice President & Chief Clinical Officer, ADVI Reimbursement & Health Policy Consultancy, on June 13, 2014, at his office in Washington D.C., United States. He had just left CMS (Centers for Medicare & Medicaid Services) at the end of February 2014 after 11 years of contribution. He is a key-person to whom the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and Alzheimer's Association presented arguments seeking a positive decision of the CMS on Medicare coverage of beta-amyloid imaging PET (Positron Emission Tomography) scan for finding cognitive disease. He was a responsible person, as the Director, Coverage and Analysis Group, Center for Clinical Standards and Quality, at the time of final decision memo of the CMS which allowed only a 1-time scan of amyloid imaging to be covered in the CMS-approved studies under the scheme of CED (Coverage with Evidence Development).

He also talked about the profound idea of the scientific, social, and ethical implication of the diagnosis of Alzheimer's disease, as well as a rationally designed framework of the CED. We Japanese can learn much from this talk to consider future perspectives of the design of health insurance coverage of advanced medical technologies to conquer many of our incurable diseases.

Key words

CMS (Centers for Medicare & Medicaid Services), PET (Positron Emission Tomography), amyloid-beta, CED (Coverage with Evidence Development), NOPR (National Oncologic PET Registry)

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*1 Japanese translation of this interview is published in *Rinsho Hyoka (Clin Eval)*. 2015; 43(1). Forthcoming.

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Dr. Louis Jacques, M.D., Senior Vice President & Chief Clinical Officer, ADVI Reimbursement & Health Policy Consultancy

Dr. Louis Jacques leads ADVI's strategic product development initiatives by spearheading focus on a top down commitment to change, recognizing that public and private payer "pay for value constructs" will require evidencing value and tying remuneration of our client's offerings to the evidencing of that value. Dr. Jacques is a graduate of Georgetown University and The University of Maryland School of Medicine.

A Distinguished Career in Government Service and in Medicine:

- Director, Coverage & Analysis Group (CAG), Centers for Medicare and Medicaid Services (CMS) since 2009
- Division Director, Items and Devices within CAG from 2004-2009
- Led CMS collaborations with Food and Drug Administration (FDA) including Entrepreneurs in Residence Program
- Practiced medicine as an attending physician for almost 20 years, and was an Associate Dean at Georgetown University School of Medicine before coming to CMS

Passionate about Change and Innovation:

- Implemented Coverage with Evidence Development (CED) under the Medicare program
- Co-created joint parallel review pilot between CMS and FDA
- Responsible for updating Medicare coverage in FDA IDE trials
- Coauthored over 60 Medicare National Coverage Determinations
- Developed program oversight of the Local Coverage Determination process
- Invited speaker at national policy and professional society meetings nationally and abroad
- Authored or coauthored original research and commentaries in peer reviewed medical journals
- Awarded FDA Leveraging/Collaboration Award (TVT Registry Team) 2013; FDA Parallel Review Team Award 2012; CMS Leadership Awards 2006, 2010; Golden Apple (Teaching Award - Georgetown University School of Medicine)

Source: http://www.advi.com/

1. Background of PET scan coverage

Interviewer Thank you so much for your acceptance of today's interview. It is fantastic that you moved from CMS (Centers for Medicare & Medicaid Services) to this company, ADVI. I came here as you were addressed in the letter of August 1, 2013[1], from Gary Dillehay, the President of the Society of Nuclear Medicine and Molecular Imaging (SNMM) of the time, requesting the CMS for coverage of amyloid-beta (Aβ) PET imaging for dementia and neurodegenerative disease. Also I am very much interested in the scheme of CED (Coverage with Evidence Development) and how it was implemented for PET (Positron Emission Tomography) examination. First, please introduce background story about the coverage of PET in the U.S. (United States).

Jacques Thank you for coming here for such interesting discussion. PET in the U.S. (United States) was originated as a research tool, and it wasn't until about 20 years ago that there was significant interest in using it as a mainstream medical imaging tool. That raised some challenges to the use of PET because FDG ([18F]-fluorodeoxyglucose) isn't owned by one company. Because of that it didn't seem that there was a unique responsible party to oversee the generation of clinical evidence

to determine whether or not FDG/PET imaging is clinically valuable as opposed to just being a scientific curiosity. There was a lot of political pressure in the U.S., from Congress, to cover PET scans.

Interviewer In the Congress?

Jacques I was informed at the time that the developer of PET had influence in Congress. So the Medicare program was essentially told to find a way to cover PET. So they developed this "coverage with evidence development" which is a paradigm where the PET is covered if additional clinical information is collected. That led eventually to the NOPR (National Oncologic PET Registry) registry for cancer, in the framework of CED (Coverage with Evidence Development) [2, 3]. There are other covered uses of PET like rubidium and ammonium for cardiology but they're relatively smaller uses.

But it was not clear in the setting of cancer whether FDG/PET would actually be informative or not to help physicians make decisions that produce better outcomes for patients because there are some tumors that are not FDG avid, e.g., adenocarcinoma of prostate.

The Medicare rules from Congress are not very flexible so Medicare has to make decisions in certain ways; so Medicare did a series of national decisions to say first that most oncologic FDG PET was covered only with further study. We divided PET imaging into 2 big categories. If this is used to guide initial definitive anticancer therapy, we said there are PET scans leading up to the choice of the initial therapy and then there are PET scans afterwards for people who have failed therapy or who had therapy and you're trying to monitor them for recurrence.

Interviewer Diagnosis and management, you mean?

Jacques But there's a nuance there because Medicare originally divided PET into diagnosis, staging, re-staging and monitoring response to therapy. That was a very awkward classification because in this space before the treatment, staging information helps to inform diagnosis, and diagnostic information helps to inform staging. It's not like the doctor orders the test and says, "Well, you know, this is 30 percent for diagnosis and 70 percent for staging." That's not how it works. So instead of 4 categories, we divided it up into 2 categories. We also heard from oncologists that the concept of re-staging is not really a common paradigm in cancer because you have whatever stage you had when you were first diagnosed. Now you may be in remission but you are still stage 4 in remission. You don't become a stage zero or a stage 1 patient.

So NOPR moved forward, looking for evidence that FDG PET imaging changes physician management of the patient in a way that improves patient outcomes. In cancer, because the treatments themselves can be lethal, there are clinical utilities from avoiding unnecessary treatment. Because so much is known about the treatment side of cancer, you could say that if you have evidence, for example, that if a woman is suspected of having cervical cancer and she has a positive supraclavicular node that cure is not expected; it's more palliation and symptom control; so that patient would be able to avoid surgery, for example, and we think avoiding surgery if you don't need it is a benefit for patients.

Thus, in the cancer space, we were able to say that if there was persuasive evidence that physicians were actually going to change their management that we would cover it. What was interesting, the way that PET is paid for in the U.S., the PET imager isn't necessarily related to the cancer doctor so these people were going to be paid or not based on whether a different group of physicians were going to submit data. The oncologists, even though they didn't get paid to participate in NOPR,

nonetheless, oncologists are, I think, accustomed to working in a protocol and to reporting the information so they kindly essentially volunteered. So over the course of about 5 years, we removed the NOPR requirement, first for PET scan in this initial period [4], and then later on in PET scan for this period after completion of initial anticancer treatment, with the exception of prostate cancer [5]. PET in prostate cancer here remains non-covered.

2. Medicare Coverage concerning beta amyloid imaging

Jacques Now that is different than what happened with beta amyloid PET imaging. Because these agents are made by specific companies, there's clearly one company that's responsible for manufacturing each beta amyloid PET tracer, and they undergo formal review by the U.S. FDA (Food and Drug Administration). The reason why we covered beta amyloid PET with CED in Medicare was explained in the decision memo. One, the treatment of Alzheimer's disease is not as well developed or understood as the treatment of cancer. We had expert physicians saying even if the scan were negative they would treat the patients as if they had Alzheimer's anyway because everybody feels desperation. So there really was a lack of persuasive evidence for Medicare's purposes that beta amyloid scanning actually results in an improvement for the patients. That's why Medicare said we will only cover it in clinical study.

What's happening now is that the Alzheimer's community is working on study protocols that Medicare could cover, and one study is currently in progress. One of the challenges with Alzheimer's disease is that the amyloid-beta theory is really one of several theories. Even the FDA-approved labeling for an agent says this is not diagnostic of Alzheimer's Disease. We understand that older patients tend to accumulate amyloid-beta anyway. So the challenge becomes if a patient is going to have amyloid-beta in their brain anyway, and if the amyloid-beta theory has not really been firmly conclusively established, finding amyloid-beta in an older patient is of uncertain clinical value unless there are meaningful treatments that would follow a positive scan result. If there is a patient with early signs and symptoms that might suggest a progression to Alzheimer's, those patients may be younger than Medicare age anyway; I mean if they're 55, it's not primarily a Medicare issue. It's really a private insurance issue.

Interviewer But Medicare will have impact on private companies.

Jacques It can. It depends. Some private companies seem to hide behind Medicare decisions even if the issues are different for a younger population or an older one. The other advantage that private companies have is they can do prior authorization. They can review the claim first and then decide whether to cover the scan. Medicare does in general not have prior authorization. The way the Medicare program is designed means that it doesn't have the national flexibility to say, "Well, this person can get a scan; not that person; this person can based on our review of their medical record."

Interviewer I understand. I read the final version of the decision memo by CMS [6]. Your name was at the top of it, as the Director of Coverage and Analysis Group. It was dated on September 23, 2013. Now before coming here I attended the Annual Meeting of the SNMMI in St. Louis , where people discussed that it's not just clinical trial program but a NOPR registry trial could be covered by CMS. Is that correct?

Jacques Yes, depending on the methodologic rigor of the registry. So the NOPR registry can be tied to a later use of Medicare claims data to see whether the patient had other outcomes. Thus, a

simple registry might not be sufficient for "coverage with evidence development" program because "coverage with evidence" program has to look at clinical outcomes. The Medicare program guidance on practices around "coverage with evidence" development has evolved since the original guidance document was published 2006[7] describing CED as including both Coverage with Appropriateness Determination (CAD) and Coverage with Study Participation (CSP)[3]. So coverage with evidence development initially could allow a regular registry under CAD. Later on, CAD was set apart on its own and CED reached a point where there needed to be a requirement that there be some reported outcomes about that cohort in the registry – whether it was mortality or whether it was hospitalization or something else. But fundamentally the registry worked well in the cancer imaging setting and doesn't necessarily work quite so well in other settings.

Interviewer According to the discussion in the SNMMI meeting other amyloid-beta probes, not just florbetapir, are also covered by the coverage with evidence development system.

Jacques Yes. What Medicare does (which is what many insurance companies do) is they generally don't cover based on the brand-name. They cover by the class. So for example, a surgical procedure maybe covered and the insurance company doesn't necessarily get into the details of this device or that device. So with PET scanning for amyloid-beta imaging in the context of dementia, the decision applies to any subsequently approved amyloid PET imaging agent. Whether it's flutemetamol, florbetaben or something else, they all are automatically brought into the decision. So any future FDA-approved amyloid-beta PET agent falls under the current decision and could go into coverage with evidence development.

3. CMS policy for Coverage

Interviewer The description in the decision memo is explained in such way; similar to the decision about the expanded use of FDG?

Jacques Yes. What would happen is when the clinical trials or clinical studies are completed and published, Medicare would reconsider the policy decision and consider evidence not only through NOPR or other coverage with evidence development studies but if anyone else were doing clinical trials or clinical studies, they would go ahead and do that. They would look at that evidence as well. So whether it's FDG in the past or amyloid-beta now, Medicare also covers in NIH trials. For example with FDG PET, the cancer imaging group at National Cancer Institute (NCI) had clinical trials where they also wanted to use PET in the protocol. Medicare paid for PET in that study because it was part of a clinical trial.

As for the amyloid imaging, because there really are apparently no effective treatments for Alzheimer's, the interest in PET scanning seems to be if there are patients with Pick's disease or frontotemporal dementia or something else, who should not get certain anti-cholinesterase inhibitors. There may be some benefit early in that population but not more broadly because people struggle with what to do with Alzheimer's disease anyway. The question in the U.S. is if someone has a scan and it's positive or negative, what do you do next? I mean the stakeholders acknowledge that there really is no need to progressively scan someone over and over again. If a patient has symptoms and don't have significant amyloid-beta at that point, then Alzheimer's is not the cause of their symptoms.

Interviewer So at this moment, the coverage is only for 1 time of scan?

Jacques Yes. Coverage for FDG is different. So this is in the context of a cancer therapy that clearly evolves as the patient responds to treatment or undergoes second. There are 3 PETs covered nationally here; and then the local Medicare contractors can decide if they want to cover more. For amyloid scanning, only one scan is covered. But the way Medicare system is designed, there is central Medicare and then there are about 10 local Medicare contractors that are free to make any decision as long as they don't conflict with the central one.

Because there is already evidence that people accumulate amyloid in their brain as they get older, and the issue is that if the symptoms comes and the scan shows you don't already have amyloid, by current definition you don't have Alzheimer's disease. You have some other kind of dementia. And because you already have a non-Alzheimer's dementia here, no one has proven the clinical value of testing you again, let's say 5 years later or 10 years later, because you're already demented here.

Interviewer I understand very well. But how about if we say we cover the use of 2 or 3 PET scans in very limited well-designed clinical trial during some years to find something, for example, to assess development of the disease like accumulation of the amyloid beta, or to determine the clinical condition of these people being scanned?

Jacques Medicare pays the routine cost in a clinical trial as well as the investigational item or service depending on policy. But Medicare by law doesn't pay for the administrative cost in a clinical trial. Medicare primarily is an insurance agent. It's not the National Institutes of Health. The Medicare mandate really has not been around research because that is not what health insurance is primarily for. Healthcare insurance is ideally for things that are firmly established. So even if you have a clinical trial where Medicare is paying all the routine cost plus paying for one CT scan, at some point, I think the sponsor institution has to

take responsibility for some of the costs of the trial because they're the ones who are going to make the money if the trial is successful. I mean, Medicare doesn't get a share of the profit if the drug is successful.

Interviewer Do you mean that 2 or 3 additional scans would be regarded as a part of the clinical trial administrative cost?

Jacques They're clinical costs but they're non-covered clinical costs. So either the sponsoring institute (if they were NIH) or the company (if the company was the sponsor) would need to pay for those.

Interviewer Okay, I understand very well. It's very similar to the Japanese situation because in Japan all of these cannot be covered at this stage of clinical trial. However, I think there is a good policy of CMS, different from a policy in Japan. If it is according to the agent, this something investigational part can be covered depending on the situation, according to the decision It seems to lead to such strategy that early approval FDA and promotion of evidence development partially covered by CMS.

Jacques It depends on the situation, yes.

4. Ethical issues

Interviewer A little bit different point. In this letter from SNMMI [1] addressed to you, there are a number of claims not only about coverage but also there is some ethical viewpoint mentioned here that if the coverage applies only to those entering a clinical trial, it would be something like coercion to enter the trial.

Jacques In any clinical research, people voice concerns about the motivations of patients. I'm not saying that these are not legitimate concerns for discussion. I'm just saying that we've clearly managed to conduct clinical research for a long period of time, as long as the patient is adequately informed, you know. I think the issue is that maybe patients are not being told the complete story about the test. If the doctor says, "There's an Alzheimer's scan for you. We're going to help diagnose your Alzheimer's." Then the patient doesn't realize that that is a very, very shortened explanation of all the concerns around diagnosing Alzheimer's.

Interviewer This is an illustration [8] based on their very well written literature on usage criteria of amyloid-beta imaging [9]. After the publication of that literature, SNMMI developed this kind of illustration on "appropriate use" to explain how to use the amyloid-beta scan. They are saying that amyloid-beta scans should be very much carefully used to avoid abuse.

Additionally, there is some ethical standpoint in what you said about there being no treatment for Alzheimer's at this moment There should be some kind of support for such kind of people. One good point I think is that people can manage their remaining life if they can know about their situation.

5. Background culture to support elderly people

Jacques Given the differences between Japanese culture and American culture especially with regards to family and elderly people, in the U.S., it's not uncommon for the older person with Alzheimer's to live very far away from their family and from their children. They may well be living alone or living in a nursing home. Is Japanese society more cohesive so that the older family members aren't alone or is it starting to become more like Western societies where the grandparents are just alone?

Interviewer Generally it is true that there is a conventional way of life that Japanese elderly people live with their family, if comparing with

Western society. However, recent trend in Japan is that these elderly people are coming to be in hospital or some other facilities.

How do you connect this kind of social situation of Alzheimer's people with the issue on PET scan?

Jacques One of the things that people had suggested was that PET scans could help people with their financial planning and with things like that. The challenge is that financial planning is not a health insurance issue. There may be many things that might be beneficial for a society but it's not a health insurance role to go fix it. For example, if Medicare pays for something it would increase employment in the factory but Medicare should not be concerned that if we don't pay for this, this will close the factory in some town or unemployment or things like that. There are many things that are clearly beneficial like eyeglasses. They're cheap. They're customizable or they can work in a power failure. They help you very well. But Medicare by law cannot pay for eyeglasses or hearing aids or modifications to the home. If you have an older patient who may have osteoporosis and they may fall in their home, it might make a lot of sense to modify their home so that they are less likely to fall, and if they fall they're less likely to be injured. But health insurance generally doesn't pay for modifying your home.

Interviewer I understand that CMS policy is limited to the clinical benefit, not social benefit.

Jacques Yes, and it's the clinical benefit of the patient because there are no family insurance policies in Medicare. So if doing something to the patient helps the family member but doesn't help the patient, Medicare can't deal with it.

6. Clinical benefit of beta-amyloid scan

Interviewer In your personal opinion as a physician apart from being involved in the CMS policy, how do you think is the effect of PET scanning or amyloid PET scanning in terms of social value?

Jacques I think it's unclear because right now it's based on an amyloid-beta proposition which has not been definitively proven. I have an example I use. I tell men, "I have a test that is 100 percent sensitive for prostate cancer. It's a Y-chromosome. Every person who has or is going to develop prostate cancer has a Y-chromosome. If you don't have a Y-chromosome you don't get prostate cancer." So the knowledge that every men anywhere if he lives long enough will get prostate cancer, it is not really actionable because there's no preventive strategy for prostate cancer. The treatments (whether it's surgery or anything else) have side effects that people don't want. What you end up with then is a population of people who become focused on the possibility of prostate cancer when in fact they're more likely to die of heart disease or lung cancer or something else depending on their health habits. The Kaplan-Myer curve for any trial if you study it long enough everybody dies in both arms. So if we accept in the long run that we are all going to die of something, the issue is not to identify everything that might possibly kill you but to identify the things that will cause you your early death and disability that you can actually act on and do something about. Otherwise, you simply face the reality that life is short.

Interviewer So which kind of evidence should be expected and which type of study is necessary for amyloid-beta scans?

Jacques What would be needed in amyloid beta (because the therapeutic side is unclear) would be

evidence that patients who are managed based on a amyloid-beta scan have better outcomes than patients who are not; and that, if one uses the cancer paradigm, would be either that they are targeted for early treatment of Alzheimer's and thus they have fewer symptoms, or that a significant proportion of them are able to avoid therapies that has significant burdens, whether it's adverse events or whether it's something else. That's essentially what's needed. And because the therapeutic side of Alzheimer's is so unclear, that really requires a longer term study than if the therapies were very well known. For example, with colorectal cancer and the use of *k-ras* testing, *k-ras* testing was adopted fairly quickly because so much was known about the treatment options in colorectal cancer and what the benefit would be, whereas with Alzheimer's that's just not that clear.

7. Research study for future development and ethical considerations

Jacques This is actually about genetic testing. This is a copy of Archive Biomarkers. It's a similar issue here in the sort of what do you do, especially with Alzheimer's because what you may be dealing with are archived brain. You can have this. You can keep it.

Because in Alzheimer's, patients don't realistically get a brain biopsy so many of the studies have been based on archived tissue samples which is not unlike the paradigm in certain cancer trials. This is the chief of biometry at the National Cancer Institute so he is very influential, and he proposed an evidentiary paradigm for biomarkers to acknowledge that studying a biomarker is harder than studying a therapeutic treatment.

Interviewer Yes. One point you mentioned is about brain tissue examination. It's also a problem in Japan. Some Japanese doctors are informing study subjects of their future plan to take the patient's brain tissue after their death. But some doctors are hesitant to mention such kind of things especially to very elderly patient whose brains are okay, or their cognitive situation is okay. They hesitate to explain these things to patients in clinical trial, especially if the physical condition of the elderly patient is very bad. Such kind of patient is a good recruitment candidate for study to the compare PET imaging and brain tissue. But in Japanese culture, there is hesitancy to say to these people that after your death we would like to take your tissue. I have spoken about this with some Europeans and Americans. They say this kind of thing should be explained very clearly to the patient. (This is the separate issue from the authorization of the family after the death of this research subject.) So this is a cultural difference. How do you think about this issue? This is very much ethical question, I know.

Jacques Clearly someone would need to give permission (whether it's the patient or whether it's their family) afterwards. Even in the U.S., autopsies are no longer routine. Most patients when they die they go to a funeral home and they go from there. Studying Alzheimer's is fraught for a number of reasons. One, it's very sensitive topic that can be politicized, it's like studying certain cancer. But at the same time, if we make decisions based on insufficient evidence because we're afraid to do the definitive thing, we run the risk of mistreating an entire generation of patients because we were not brave enough to actually either acknowledge to these patients that they were being treated on scant evidence or to say, yes, we really do need to study. It's very difficult for physicians to admit that they don't know. There's tremendous pressure to give the patient an answer even if the answer is a poorly informed answer. And I think that desperation,

unfortunately, is bad motivation for good science because desperation makes one take great leaps without actually doing good science.

Interviewer So you're saying that for a researcher to conduct good science, it is also necessary to support these people by telling them what will actually happen after their death, and this is valuable for good science.

Jacques Yes. It's something like – we may not be able to help you but we might be able to help your children – because most parents already made great sacrifices for their children even while they're alive so the idea that a parent would continue to make a sacrifice for the benefit of their children later on, I think, can be a compelling one, not only a scientific one but also a financial one. In the United States, there's a lot of conversations that the grandparents' generation has all the disposal income and the grandchildren's generation is financially facing the burden of supporting their elders meanwhile the elders are the ones with all the money. Especially with declining birthrates, it becomes a greater and greater burden on a smaller and smaller number of people. So if there are things that can either help the younger generation scientifically/medically or help them financially by assuring that the things that they are responsible for are things that actually work as opposed to funding a generation of long experiments, social experiments, maybe that's persuasive.

8. Business, family, and future generation

Interviewer Thank you so much, it is very important point. Just one last question. Could you introduce your personal history. After working in a university hospital, you joined CMS. And what is the prospective of this company.

Jacques I left CMS at the end of February of this year (three months and a half before) to come and join ADVI. ADVI is a consultancy that helps

companies in the life sciences whether it's drugs, diagnostics, or devices. We also deal with health plans, drug plans, private insurance; things like that. So we're essentially a consultancy with partners and then a larger number of staff, and we work with both large companies and small companies.

Interviewer How about your joining CMS after your work in the university?

Jacques I basically went to CMS because I didn't want to miss my daughter's soccer games. My daughter played in high school, and my son also played sports. I worked at Georgetown. It was a very long drive and I was afraid I would miss some of the things with my children. And I had already been at the university then for 8 years, and I decided to work closer to home.

Interviewer Really. You are a good father.

Jacques That's why I went to Medicare – to watch my daughter's soccer games.

Interviewer Between your work in the university and this company, you only worked in CMS?

Jacques Yes. Eleven years.

Interviewer I heard that after you left CMS, next person is a lawyer.

Jacques Yes. She was my deputy. She's very good. Her name is Tamara Syrek Jensen. Here is an article written with her on the issue of reimbursement of regenerative medicine [10].

Interviewer Thank you, it is meaningful information for Japanese readers, they are deeply interested in how to reimburse for regenerative medicine, stem cell therapy, or other kinds of advanced technologies. Is it often that lawyers get appointed to CMS positions?

Jacques The job historically has been filled in recent years by physicians, although Medicare as a public governmental insurer is essentially a legal entity. Medicare is not a hospital. Medicare is a creation of Congress, which means that Medicare is really the result of a legal process rather than a medical process. So whether the head of coverage is a lawyer or a physician, I don't think ultimately matters that much because if it's run by a physician you still need legal input. If it's run by a lawyer you still need medical input. So it would be a different model but I think it could be successful with either model.

Interviewer So collaboration would be important.

Jacques Yes, because she and I had offices next to each other, so we used to talk everyday.

Interviewer So thank you very much. It was very precious experience to talk with you and heard about some parts of policy and philosophy of reimbursement in the U.S.

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