Chapter 6
Ethics, Regulations, and Clinical Development of Precision Medicine: Activating with Molecular Imaging

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Abstract "Precision medicine" is becoming a keyword toward new and more effective healthcare in the twenty-first century, a concept evolved from "personalized medicine." Therefore, it is a prerequisite for the community of molecular imaging to clarify elements of ethics, regulations, and clinical development strategies to achieve the goal of precision medicine, activated with imaging technologies. Through literature review and continuous discussion with people of related communities, we identified key elements from view of regulations and clinical development strategies as follows: (1) quality assurance and standardization of methodologies and procedures of imaging technologies and (2) formulation of larger-scale global clinical trial network and imaging archives, both of which would accelerate regulatory approval of new therapeutic drugs and diagnostic technologies. Additionally, key elements of ethics are as follows: (1) view of individual ethics to protect human rights and human dignity, i.e., (i) privacy protection, (ii) right to know and right not to know, as well as (iii) presymptomatic diagnosis consultation, and (2) view of collective ethics to assure social value such as (i) clinical trial registration and data sharing, (ii) justifiable commercialization, and (iii) preventing exploitation and stigmatization. In conclusion, precision medicine can be activated with molecular imaging, through more global collaborative initiatives, which recognize and have a profound understanding of the characteristics of science, regulations, and ethics in the era of precision medicine.

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6.1 Introduction

6.1.1 Precision Medicine Initiative

Voices for "precision medicine" have been skyrocketed since the plan to launch the "Precision Medicine Initiative" was announced by the United States (US) President Barack Obama on January 2015 [1]. The definition of precision medicine by the White House is described as "an innovative approach that takes into account individual differences in people's genes, environments, and lifestyles." They expect that this strategy will overcome traditional "one-size-fits-all" approach, which has been designed for the "average patient." They unveiled "$215 million investment in the President's 2016 Budget" for research [2], which allocated $130 million to National Institutes of Health (NIH) to develop a cohort of a million or more volunteers, who agree to conditional sharing of their data with responsible researchers; $70 million to the National Cancer Institute (NCI) to accelerate genome-based cancer research; $10 million to Food and Drug Administration (FDA) to acquire additional expertise, including a new approach to evaluate next-generation sequencing technologies of DNA or even entire genomes; and $5 million to Office of the National Coordinator for Health Information Technology (ONC) to develop standards and requirements for privacy protection and security of data exchange across systems. They state that the mission is for the "development of individualized treatments" along with their "Guiding Principles for Protecting Privacy and Building Trust" [1]. These perspectives suggest their intention to strengthen ethical, regulatory foundation of research and development in the era of genome-wide association study (GWAS) and "big data" analysis.

The term "precision medicine" has emerged during 2008–2011 to give a more "complete picture" to "personalized medicine" [3]. The World Molecular Imaging Society welcomed the term, which spotlights their technology with the announcement on October 2015 of "Precision Medicine… Visualized" [4]. In this context, our discussion concerning "precision medicine" aims to clarify key elements of ethics and regulations associated with the clinical development of personalized medicine, which can be activated utilizing technologies of molecular imaging.

6.2 From Personalized Toward Precision Medicine: A Change of the Trend?

Strategic reformation of drug development beyond "one-size-fits-all" had already been called for just around the year of 2000, when the US President Bill Clinton announced the completion of the first draft of human genome that resulted from the Human Genome Project, launched in 1990. The genesis of the idea for this Project dates back to the 1984 Alta meeting, which sought new DNA analytical methods to detect mutations among Hiroshima and Nagasaki survivors of the atomic bombing [5]. The term "personalized medicine" could only be insinuated in a simple meaning of patient-centered, good medical care [6]. Then and particularly in the context

of genome science, this term came to be used to facilitate genome-targeted drug development. This covers drug seed hunting and prevention of genetic polymorphism-related adverse reactions. Several numbers of such drugs or diagnostics have been approved by regulatory agencies, and the approach to develop this kind of drugs has been called "pharmacogenomics" or "pharmacogenetics." People imagined a medical system in the near future, which aims to get whole-genome screening tests before or after the time of birth. Then, by means of an individual identifier code, people could access the best-fit medical care anytime and anywhere utilizing security-protected web system. These medical records, including individual's genome information, are followed and utilized for large-size cohort analysis without identification of personal information. Ethical, social, and legal issues are to be well discussed, and rigorous human right protection measures need to be established. Such health system has been imagined and often described with the term "personalized medicine."

So what is changing in "precision medicine?" Some argue that the term "personalized medicine" creates a misleading image of a medical practice that is tailored to each individual, while others argue that there is no difference between them [3]. A major technological breakthrough toward "a new era" is the development of the so-called next-generation sequencing which enables to decipher the whole genome of one individual in a short period of time, at a reasonable cost, and thus enhances the affordability of the "whole genome-wide association study (GWAS)." At the same time, data-sharing strategy such as the US President "big data" initiative [7] led NIH to release 1000 genome data into the Amazon Cloud [8]. This kind of increased availability of genome data caused legitimate concerns of whether such data can be actually anonymous by means of traditional de-identification procedures. This question was posed by both, the US Department of Health and Human Services [9] and the Presidential Commission for the Study of Bioethical Issue [10]. The latter stressed the value of public benefit and responsibility of investigator as well as democratic deliberation. We should explore fundamental conflicts between "individual ethics" which is to ensure individual human rights and well-being and "collective ethics" which is to achieve public benefits. This conflict between individual and collective ethics was formerly articulated by the established clinical trial statistician Pocock [11]. Precision medicine must be achieved by means of seeking higher standards of both collective and individual ethics. In keeping with this notion, International Cancer Genome Consortium (ICGC) promulgated standardization guidelines for the whole-genome sequencing analysis after benchmarking exercise among their study sites [12]. Here, we will be able to characterize "precision medicine" as follows [13]: Completion of human genome project and development of *genome sequence technology* have enabled or will enable *large-size cohort studies* and therapeutic options, which more *precisely* fit each *subgroup* of patients, beyond one-size-fits-all but *not individually personalized*. It will also enable more effective disease prevention strategies, through strengthened ethical foundation and scientific integrity, as well as regulatory reformation.

Then, is it necessary to define the role of molecular imaging in the era of precision medicine? If so, this article is an overview of the regulatory reformation in the

USA from the beginning of the enterprise to establish regulatory frameworks for positron emission tomography (PET) imaging, as a key technology of molecular imaging. We called this process "PET Drug American Dream World History" [14–16] because it suggests a "gold standard" for regulatory framework of PET imaging and it has been more or less followed or referred to by other countries in the world [17]. Secondly, in the later part of this article, we discuss ethical issues to be deliberated more in depth in the era of "precision medicine," from both perspectives of individual and collective ethics.

6.3 Regulatory Reformation Toward Personalized Medicine

6.3.1 Critical Path to Achieve Product Approval

6.3.1.1 Radioactive Drug Research Committee (RDRC) and Investigational New Drug (IND) Application/New Drug Approval (NDA)

It was in 1975 that the US government authorized the usefulness of "basic" research to administrate radiopharmaceutical drugs of limited dose to subjects with the aim to explore the human pathophysiology and drug metabolism. The code of federal regulations of this year established the RDRC [18], which states that basic research without the intention of diagnostic, therapeutic safety or efficacy evaluation of drugs can be exempted from IND regulations. IND requires investigators to apply for FDA authorization to initiate clinical trials. Alternatively, the investigator submits the protocol to an FDA-approved RDRC, along with ordinary process to submit to an institutional review board (IRB). While more than 70 approved RDRCs have to submit their annual reports to FDA, the agency does not review each protocol for authorization to initiate clinical trials [19]. This exemption from IND regulations is limited to the cases in which administered radioactive doses are limited in the range described below, which is known from previous experience in the literature. This means that first-in-human study without such previous experience is excluded from this RDRC framework to be followed, along with other limitations (e.g., limited to capable adults, number of study subjects, etc.).

- In whole body, active blood-forming organs, eye lens, and gonads: 3 rem (30 mSv) for single dose and 5 rem (50 mSv) for a cumulative annual dose
- In other organs: 5 rem (50 mSv) for single dose and 15 rem (150 mSv) for a cumulative annual dose

As for PET drug manufacturing, FDA Modernization Act (FDAMA) in 1997 [20], which covered whole regulations under the agency's jurisdiction, caused great change of regulations for clinical development and clinical practice of PET drugs. According to the FDAMA and related regulations, after June 2012 (half a year extended deadline responding to the voices of related community), any of

commercial, hospital, or academic institute which manufactures PET drugs for clinical use (excluding research use under IND or RDRC regulations) has come to manufacture PET drugs in compliance with PET drug-specific GMP (good manufacturing practice/"PET-GMP," hereafter) [21]. This means that they must obtain NDA, which means marketing authorization or abbreviated NDA from FDA, passing FDA's inspection. There had been monographs of 12 well-known generic PET drugs described in the US Pharmacopeia (USP) [22], among which 8 had not been approved but exceptionally included. These 12 PET drugs were exempted from the newly established PET-GMP regulations, as far as they were manufactured according to USP. However, as originally defined in FDAMA as well as in voices of PET drug specialists [23], this exemption expired, and these eight PET drugs were removed from USP at the end of 2014. Now, an increasing number of research/academic institutions or hospitals have obtained approvals of generic PET drugs such as FDG [14, 24]. In the same context, companies got approval of innovative PET drugs including amyloid imaging agents. Many of other promising PET drugs have been studied in pipelines of private companies and academic institutions.

6.3.1.2 Critical Path Initiative

Along with the above regulatory establishment, FDA's Critical Path Initiative report in 2004 [25] highlighted the importance of biomarker assessment, one of which is PET imaging, among other various drug development tools. Demand of the citizens for more "personalized," safe, and effective drugs has caused inflation of cost and stagnation of success in new and innovative drug development. FDA issued in 2005 a draft guidance entitled "Drug-Diagnostic Co-Development Concept Paper" [26] to introduce key critical steps during drug development that translated basic research into clinical applications, as a means to get regulatory approval, through several steps of validation process from biomarkers to diagnostics. It explained prospective "enrichment" stratification strategy to define subgroups of subjects in study protocol according to defined diagnosis, as well as more flexible retrospective subgroup analysis after completion of study. Description in package insert (product specification) would be different according to each strategy. This guidance is mainly for genetic diagnosis but can be directly applied for imaging diagnosis. Imaging agents can be developed through a molecular targeting probe optimization process as well as pharmacological assessment and its validation, toward some diagnostic drugs, biomarker or companion diagnostics, or radioisotope therapeutic drugs.

Simultaneously in 2004, FDA issued a set of three parts of guidance to provide instructions for development of medical imaging agents for (1) nonclinical and clinical safety data assessment [27], (2) clinical indications [28], and (3) design, analysis, and interpretation of clinical studies [29] (Fig. 6.1). This set of guidance clearly showed "critical path" of imaging drug development in IND framework and how to get through and reach to the final goal of NDA. The priority of PET drug is that you can utilize both the RDRC and IND frameworks for efficient imaging drug development as well as biomarker assessment tool validation: When you have some

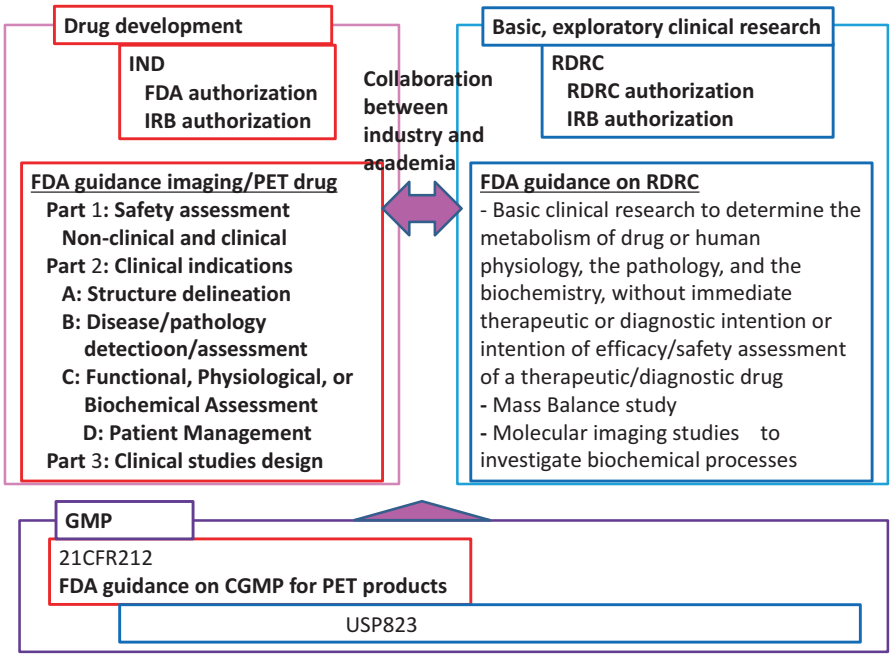

Fig. 6.1 Constructions of guidance documents by FDA concerning medical imaging drug development and radioactive drug clinical research

information of the radiation dose within the above limitation, based on first-in-human study results under IND in the USA or under other regulatory frameworks in anywhere else, you can explore this imaging tool more in depth in RDRC framework. Then, if this agent is found to be promising, you can start clinical development toward regulatory approval again in the IND framework [30, 31]. Through the efforts of related communities more recently, the concept of "drug-diagnostic co-development" was switched to concept of "in vitro companion diagnostics [32]" and can be applied in molecular imaging [33]. This reflects demands for achievements of more validated diagnostic products being approved by regulatory authority.

6.3.1.3 Clinical Trial Network and Standardization

Accordingly, more and more quality assurance and validation of imaging technologies have been promoted in order to utilize them for the development of therapeutic drugs or otherwise developed for diagnostics approval in clinical practice. A number of activities of clinical trial networking and standardization of PET imaging and PET drug manufacturing have taken place. The National Cancer Institute (NCI) carried forward their "shared IND" strategy [34] to share their IND information with those who are starting clinical trial submitting INDs to FDA (Fig. 6.2). This

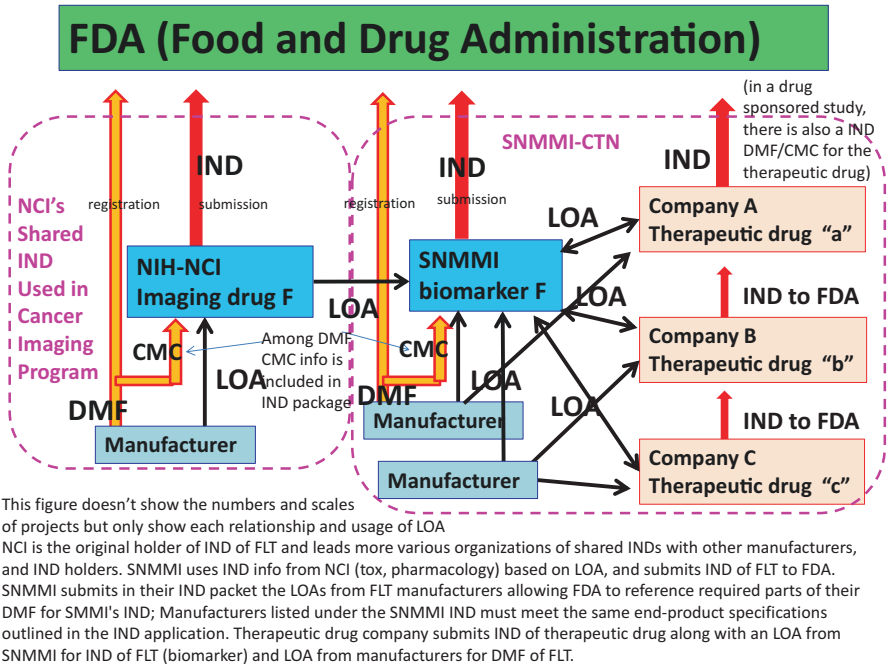

Fig. 6.2 Shared-IND strategy of NCI and centralized-IND strategy of SNMMI

means that NCI will share with others, under mutual agreement, IND information including toxicity studies and chemistry, manufacturing, and control (CMC) assessments, which were authorized by FDA as supporting information for the conduct of clinical trials. This is an ethical and efficient strategy to avoid duplication of unnecessary animal experimentation to acquire toxicity data and duplication of massive paperwork for IND submission [15]. Also, the Society of Nuclear Medicine and Molecular Imaging (SNMMI)-Clinical Trial Network (CTN) has been promoting "central IND" strategy to share their IND with therapeutic drug companies under mutual agreements [15] (Fig. 6.2). SNMMI-CTN is interested in IND of PET biomarker imaging agents, while therapeutic drug companies are interested in IND of their therapeutic drugs for which imaging agent is just a tool for their true objectives. Because the quality of this network has to be assured enough for the use of sponsor companies, SNMMI-CTN facilitates registration of manufacturing PET drugs and standardization and validation of PET imaging sites to be utilized by collaborating companies.

There are other excellent clinical trial networking activities led by academic societies and universities. One prominent example is the American College of Radiology Imaging Network (ACRIN) [35], which started earlier than SNMMI-CTN, and involves a larger number of radiological physicians and scientists. Also, the Radiological Society of North America (RSNA) organizes a standardization activity group named Quantitative Imaging Biomarker Alliance (QIBA) [36]. This initiative

by RSNA/QIBA is involving larger stakeholders and the scope of modalities and engaged in the development of standardized protocol of clinical trials, methodologies, and procedures for imaging biomarker validation of each modality. To respond to the demand for more "precise" diagnosis, it is required to achieve higher reproducibility of study data, as well as to standardize methodologies and procedures to generate these data. Reproducibility can be assured by means of quality control, documentation, and storage of the study data. Standardization of quality control procedures among variety of communities is a difficult task but necessary to achieve global, simultaneous clinical development [37].

6.3.2 Precision Medicine to Achieve Global Health

6.3.2.1 Precision Medicine Initiative in the Era of GWAS and Big Data

Clinical trial networking and standardization activities have been gaining additional features, advocated by the Precision Medicine Initiative. The attractive challenge of this Initiative is to grant NIH the formulation of million or more population cohorts, which cannot only provide medical records to research communities but also information of gene profiles and metabolites and microorganisms, environmental and lifestyle data, as well as personal device and sensor data [38]. These active participants are involved in the design of the initiative, which ensures the access to their own health data and empowers them to invest and manage their health. Patient involvement is facilitated with a symbolic campaign at the President's website, to show photos and names of individual patients who struggle with diseases [1]. They also announced their progress of 6 months to honor people of "Champions of Change," including not only researchers but also patients who contribute to this initiative [39]. The size of the cohort order is larger than the previously developed by worldwide-known biobank projects such as the United Kingdom (UK) Biobank of 0.5 million; the China Kadoorie Biobank of 0.5 million; Biobank Japan of 0.3 million; and the Taiwan Biobank of 0.2 million. Among them, the UK has launched the next phase project, named 100,000 Genome Project [40], to conduct whole-genome analyses on 100,000 genomes of 70,000 patients of the National Health Service (NHS). Genomics England, a company owned by the Department of Health, is engaged in the genetic sequencing services for this project. The stories of the first benefited family patients and other participants appear with individual names and photos, in the website of this company [41].

Another part of the $70 million grant of the USA to NCI involves large-size clinical trials of new type, such as the Molecular Analysis for Therapy Choice (NCI-MATCH) [42]. This is a nationwide 10-arm clinical trial to recruit 3000 patients of advanced solid tumors of various cancer types and lymphomas. Among these and on the basis of DNA sequence mutation analysis, about 1000 patients would be enrolled and allocated into tens arms of drugs that target distinct molecular biomarkers. This NCI-MATCH and another one called Molecular Profiling-based Assignment of

Cancer Therapeutics (NCI-MPACT) are genetic testing-based clinical trial strategies called "basket" studies, where multiple tumor types with multiple single mutations are targeted to evaluate effects of multiple drugs, in a single trial [43]. A second type of new clinical trial design is called the "umbrella" study, where single tumor type is targeted, but multiple therapeutic strategies are evaluated in a single trial. One example is the *i*nvestigation of *s*erial studies to *p*redict *y*our therapeutic response with imaging and molecular analysis 2 (I-SPY 2) [44]. This is a breast cancer trial to use tissue and magnetic resonance imaging (MRI) biomarkers to test the 12 investigational drugs. These two new types of trials are conducted in collaboration with multiple sponsor companies of these drugs and genetic sequencers.

6.3.2.2 Basket-Type Clinical Trial and Imaging Archive

Again and for the concept of precision medicine, we shall seek knowledge on how the basket-type clinical trials can incorporate additional value by means of molecular imaging. Being driven toward the era of precision medicine, the key message "Precision Medicine… Visualized" from WMIS in 2015 is a simple and comprehensible catchphrase. Moreover, the European College of Radiology provided more practical and specified concepts in 2014 to argue that "imaging genomics show great potential in precision medicine" [45]. They described "radiomics" as a "high-throughput extraction of large amounts of imaging features" (sometimes from population imaging); "imaging genomics" as a "discovery of associations between imaging phenotypes and genotypic information," to identify imaging characteristics that indicate genetic predispositions; and "theranostics" as an intriguing new field that can correlate the power of the imaging technology with genomic information, which can help to tailor precision therapy. Later on, they developed more detailed statement on this concept [46]. It is prerequisite for imaging technology to play a key role in precision medicine not only to facilitate exploration of human physiology or drug metabolism at the molecular level (in RDRC framework) but also to expand clinical trial network strategies for drug approval (in the IND framework). This expanded networking strategy should be directed toward larger amount of data sharing to facilitate partnership with patients.

The set of ongoing NCI programs to support Precision Medicine Initiative includes projects of imaging, e.g., "Quantitative Imaging Network (QIN)" and "The Cancer Imaging Archive (TCIA)" [47]. QIN is an initiative to develop quantitative therapeutic outcome measurements among networked institutes of excellence. A recent announcement focuses on "radiomics" to develop standard operating procedures (SOPs) to convert descriptive, qualitative imaging techniques into inherently quantitative mineable data to connect with patient demographic, outcome, and gene expression databases. The procedures of data acquisition, segmentation, extraction, and analysis are to be standardized by this initiative [48]. TCIA is another initiative to develop a large archive of cancer imaging data accessible to the public, which includes many study results linked to The Cancer Genome Atlas (TCGA) project. The aim of the TCIA initiative is to generate multidimensional maps of the key

genomic changes in major types and subtypes of cancer. These archived data can be used for secondary analysis and hypothesis generation, through an open-source software package [49].

6.3.2.3 Expanding the Clinical Trial and Global Standardization Networks

To facilitate precision medicine, global collaboration and standardization are key prerequisites. The rationale stems from the fact that the precise focus on one genetic variability needs to seek out a common population with the same set of characteristics all over the world. It is conceivable that a group of individuals who are fit for a specific therapeutic intervention may not be located in the same geographic region, and, hence, the search may need to be expanded beyond jurisdictional boarders. Contrary to that, there would be some kind of ethnic (intrinsic and extrinsic) factors, which may affect the response to some interventions that are globally utilized. This is the basic premise of many of the initiatives from global pharmaceutical companies to facilitate multinational clinical development, aiming at simultaneous approvals in multiple countries.

For this reason, the Japanese and Chinese Society of Nuclear Medicine agreed in April 2015 to develop an Asian-initiated clinical trial network, as a means to facilitate the participation of Asian regions into multinational clinical trial initiatives [50]. Development of the Asian network will contribute to (1) more and better participation in the already existing Western-initiated clinical trial networking and standardization activities and (2) establishment of alternative networks for the development of medical technologies that are highly needed by the Asian population. The use of a given network by a researcher or a company will depend on the purpose of each study or clinical development. We should realize precision medicine for better health in the world. This implies that precision medicine should be for the majority of the world citizens who seek for but have not yet access to their best-fit medicine. To achieve this end, clinical trial networking and data archive along with standardization should be established from various regional perspectives and initiatives.

So, what about ethics? In the latter part of this paper, we reflect upon trend of discussion of research ethics to articulate characteristics in the era of precision medicine, considering how ethics in molecular imaging science is discussed in these contexts.

6.4 Ethical Consideration for Precision Medicine (Table 6.1)

Table 6.1 Summary of characteristics of ethical consideration in the era of precision medicine

Individual ethics to assure human dignity
Rigorous privacy protection
Traditional de-identification procedures may not be effective in study settings of data sharing, including whole-genome sequencing. Advancement of information technology on anonymity and informed consent process, with the recognition of the characteristics of a given research setting, is essential prerequisites.
In some settings of brain imaging studies, we need to seek not only for valid informed consent but also for advance-directive and broad consent of study subjects, with the perspective of autopsy reports after the death of the subjects, as well as surrogate consent and permission of their family members.
Right to know and right not to know
Taking a more patient involvement strategy comes with the requirement to assure participants' right to know the results of the study by means of information sharing, which is not only among the research community but also with the participants of the study. This right also requires the ethical obligation of the researcher of managing incidental findings, e.g., a brain tumor found in the process of brain imaging.
Sometimes, patients do not want to know about the future possibility of a disease, but some of the family members or related community need to be informed. The right not to know of the people at risk of disease should be assured not to coerce diagnostic test on such people.
Presymptomatic diagnosis consultation
Needs for presymptomatic diagnosis consultation are critical when diagnosis is somewhat credible, but there are no therapeutic options.
Traditional ethical issues of diagnostic genetics are common in imaging diagnostics, particularly with regard to how the information of future disease development without therapeutic option can be ethically managed. Collaboration and integration of medical practitioners beyond disciplinary specifications are required to provide care for patients in this setting.
Collective ethics to assure social value of research
Clinical trial registration and data sharing
The initiative aims to ensure collective ethics that generate reliable research results contributing to public health and individual patient in the future. To that end, clinical trial registration has already become a regulatory requirement as well as an ethical obligation.
Data sharing is becoming an ethical obligation of investigators of clinical trial. Initiative of imaging archive is responding to this demand.
Justifiable commercialization
In the setting of clinical trials, more industry-academia collaborations are promoted, along with stricter conflict of interest management. For imaging scientists, decision of installation of costly equipment should be independent from benefit provided by the manufacturer.
In the setting of biobank and health data archive, a critical issue is the separation of the process of informed consent to donate samples or materials and the process of utilizations of these donated samples or materials.

(continued)

Table 6.1 (continued)

Avoid exploitation and stigmatization
To avoid exploitation, we should recognize the issue of distributive justice: Research participants have equal right to access the benefit generated from research. Additionally, abuse of newly developed technologies for getting return of investment should be carefully avoided.
To avoid stigmatization, more in-depth partnership with patients and an empowerment approach are needed. It is a prerequisite to protect the population at risk of a disease found by diagnostic research, from discrimination or stigmatization by their social status and access to health insurance and social security.

6.4.1 Individual Ethics to Assure Human Dignity

6.4.1.1 Rigorous Privacy Protection

As described above, the Precision Medicine Initiative needs a large amount of data sharing associated with genetic information of individuals. Of course such initiative needs more rigorous privacy protection beyond the traditional way of data protection. Patient participants have been more and more involved in this initiative in terms of the design as well as the appearance in the webpages. Whatever you achieve with their participation, it should be based on traditional ethical obligations to protect the right of privacy derived from the respect to human dignity. The US Health Insurance Portability and Accountability Act (HIPAA) [51] of 1996 and the Privacy Rule [52] of 2000 stipulated the definition of protected health information (PHI) and how it could be "de-identified" (by removing some individual identifiable information) to be exempted from the regulations. The 2012 report of President's Commission on ethics of whole-genome sequencing [10] reflected that items defined as de-identification in HIPAA regulation may not be actually enough for anonymity purposes. In such case, one option is to redefine more sophisticated ways of de-identification of the genome-sequenced data by means of information technology. Another option would be to obtain informed consent of study subjects to use their "de-identified" data, which may not be in complete anonymity. While both options may be needed in certain circumstances, more rigorous data security infrastructure is required. Additionally, some mechanisms may be needed where only a "qualified" investigator can access such information.

In case of brain imaging, there are additional issues. One issue is that MRI brain imaging data may be reconstructed to such image of face, which enable subject's acquaintances to identify whose image it is. Development of a technology to "deface" brain MRI data has been discussed, but there would be some cases, in which such procedures are not practical. In such a case, the abovementioned informed consent comes to be required. Another issue is arising, regarding studies of Alzheimer's disease, in which brain imaging is associated with pathological autopsy analysis. This type of studies not only need the "informed consent" of a subject for imaging examination but also "advance directive" of this subject during living time for future autopsy analysis, which has a nature of "broad consent"

(without complete information of future studies). Furthermore, and upon the death of this subject, "legal permission (or authorization)" for autopsy by a family member of a deceased is required by law. Similarly, a "surrogate consent" by a family member may be needed to perform association studies and enable to compare brain images with tissue pathological analysis.

6.4.1.2 Right to Know and Right Not to Know

When you take a strategy of patient involvement, expanding awareness, and empowerment to them, you need further efforts to assure their "right to know" and "right not to know." The right to know means patients' right to control, including access to, their own information. This right is derived from fundamental privacy right, a part of a personal right, a corollary of human dignity. A recent discussion on this issue goes beyond the traditional issue of informed consent at the time of inclusion of a study subject. The Declaration of Helsinki [53], international ethical principles for medical research involving human subjects by the World Medical Association, recommends to provide the research subject with an option of being informed about the study results. Also, the European Union's Clinical Trial Regulation [54], implemented in 2016, requires the investigators to provide participants with an identifier number of clinical trial registration by which the ongoing trial information and trial results are open to public. In addition to the study's information or outcome, there is an issue of "incidental findings." For example, during the process of brain imaging for neuro-imaging study, the researcher may find a brain tumor as an unintended or incidental finding [55]. In this case the ethical question is: does this neuroscientist has the obligation to provide care for this brain tumor? A priori, the immediate perception is that the investigator's ethical obligation is to deal with such incidental finding properly. Logically, if the neuroscientist does not have the expertise to provide proper treatment for the brain tumor, he or she should advise this patient to consult with an oncologist. There may be other cases in which an investigator could provide care for a disease revealed as incidental findings (e.g., comorbidity diseases), which is called "ancillary care" [56]. The issue is particularly problematic in the case of epidemiological studies in developing country, where ancillary care may not be available in the ordinary practice [57]. To what extent the investigator has to provide care, or who should pay for this additional medical expenditure, depends on how the study's protocol was designed and the nature of the particular situation. At the very least, the researchers are obliged to define at the time of protocol development how this kind of incidental findings should be managed, including who should pay for what.

Meanwhile, some patients do not want to know about the future possibility of serious incurable diseases, whereas family members or surrounding community members want and need to be informed. "Right not to know" is a right of a person who is at risk of future possibility of a disease, which is based on family history information. This "right" is argued in a book [58] by psychologist Nancy Wexler, who was at risk of Huntington's disease and one of the finders of a genetic marker

of this disease [59], causing debates on "genetic discrimination." The UK government granted insurance companies conditional access to genetic test information of their clients, while the USA established the Act to prohibit health insurance and employment discrimination, based on genetic information. While it is still controversial whether the "right not to know" is a part of privacy right, the central issue is to avoid undue influence on a person to undergo certain examination, in case this person does not want to know about their risk of future development of diseases.

6.4.1.3 Presymptomatic Diagnosis Consultation

The issue of presymptomatic diagnosis has been long discussed in the context of genetic research, which is the same in case of imaging. This issue is critical when the diagnosis is somewhat credible, but there is no therapeutic option. This topic is often discussed in the context of amyloid imaging, where it is conceivable to detect Alzheimer's disease, and there is no therapeutic option. There is the argument that such diagnosis could help the patient and family to develop a life plan. However, there is a likely possibility that the public healthcare insurance will refuse to pay for such social benefit [60]. In case the validity of diagnostics is not enough, it is justifiable not to provide the patients with such information in which the implication is still uncertain. Meanwhile, validated presymptomatic diagnostic information without therapeutic option should be provided to patients, along with careful consultation service.

Traditionally, genetic counseling has been provided for reproductive decision-making. Later on, such service has come to be provided in various settings of the medical practice. In this context, collaboration among a variety of medical professionals is needed, e.g., primary care physicians and specialists, psychologists, and social workers. Similarly, diagnostic radiologists should take a leading role to integrate various disciplines related to the imaging results of a patient. The function of a qualified diagnostic radiologist in the era of precision medicine should not be limited to reading the results but rather extend his or her skills to coordinate the necessary steps for the patient's decision-making of therapeutic options and lifestyle choices.

6.4.2 Collective Ethics to Assure Social Value of Research

6.4.2.1 Clinical Trial Registration and Data Sharing

Beyond traditional consideration on individual rights, research ethics are more and more expanding their scope to global public health. Three fundamental principles of research ethics were defined in the Belmont Report in 1979 [61]: (1) respect for persons, which means autonomy, derived from human dignity and applied to informed consent; (2) beneficence and non-maleficence, applied to risk-benefit

assessment; and (3) justice, implying fair distribution of risks and benefits. This set of principles was expanded to eight principles by Emmanuel [62], focusing on global health in developing countries and now including values of "collaborative partnership" and "social value." Social value means value generated from research and utilized in medical practice and public health. To achieve social value, a better integration of research results is needed. From this demand, ethical obligation of clinical trial registration and data sharing has been required in recent decades. Clinical trial registration is mostly facilitated by the statement of the International Committee of Medical Journal Editors (ICMJE) in 2004 [63], to set a condition of trial registration that considered the publication of trial results. Registration must be in a nonprofit, publicly available registry, and a defined set of information of the trial has to be registered prior to the first subject enrollment. This obligation is derived from reciprocity with altruism of volunteers, who trust that their participation would contribute to improvement of healthcare for others. Another related reason of this obligation is to avoid publication bias and make positive and negative trial results publicly available. This requirement is included in the legal system of the USA [64] and EU [54] and in governmental ethical guidelines of Japan [65]. In these three regions, the obligation of registration is expanding from the outline of initial trial information toward information of revisions of the protocols, as well as trial results. Furthermore, the Declaration of Helsinki [58] included this obligation of clinical trial registration in the 2008 revision and then in the 2013 revision to expand the scope of obligated study type, from only clinical trials to any study covered by the Declaration. This means that an observational study including individual-identifiable human tissue or health data initiated by physicians must be registered to some eligible registry.

In addition, responsible data sharing is becoming strengthened as an ethical obligation, which entails the storage of anonymous raw data from each study subject in a public repository to be shared by a responsible research community. Associations of pharmaceutical companies of the USA and Europe issued a joint policy statement [66] in 2015, based on a workshop organized in 2013 by the US Institute of Medicine (IOM). Then, IOM issued a comprehensive report in 2015 [67]. Similarly, a recent draft revision of the Ethical Guidelines of Biomedical Research by the Council for International Organizations of Medical Sciences (CIOMS) released in 2015 [68] includes the data sharing and study registration as subcategories of ethical obligation of public accountability. Finally, the ICMJE issued again a statement to set the data sharing as a condition for the publication of study results [69]. The abovementioned imaging archive initiatives are responding to this ethical requirement.

6.4.2.2 Justifiable Commercialization

Increasing demand for precision medicine and generation of "social value" of research requires approval of research products granted by a regulatory authority. This situation needs strengthened partnership between academic research institutes and profit-making companies, which raises the question what is justifiable and

unjustifiable commercialization in the context of clinical trials, human sample banking, and health data archive? In the context of clinical trials, there is skepticism that a commercial company may influence an academic researcher to generate biased results to benefit company's product. Meanwhile, involvement of industry is prerequisite to achieve quality control or acceptable research levels for product approval. In the recent trend to facilitate industry-academia collaboration, disclosure and management of conflict of interests are becoming an ordinary practice in the medical research community. In some situations, an academic researcher should decline receiving monetary incentives from industry or otherwise limit their involvement in some process of the research. In case of imaging studies, the academic researcher may be engaged in the decision-making process of the installation of costly equipment. Independence of such decisions from benefit-taking manufacturers of the equipment is strictly required by laws, and such legal framework is up to various jurisdictions.

In the context of biobanks, there is a question of morality in which the governance framework of the society can justify commercial use of human-derived materials (including samples and information). To say it simply, research use of human material by commercial companies (e.g., pharmaceutical companies or commercial research institutes) with objective of making a profit would be ethically justifiable on conditions that all the legal regulations and ethical norms are followed. On the other hand, commercial trade of human material as it is would not be ethically justifiable with the exception of some conditional cases. Then, what is the borderline between these justifiable and unjustifiable cases? Commercialization of human body and human-derived information would be an infringement of human dignity, according to the Kantian philosophy, which prohibits the utilization of human as a mere tool for other objectives. For this reason, the process of the individual's permission for the use of his/her material and the process of granting permission of each project to use these materials should be separated. In the former process, monetary inducement is prohibited to avoid moral corruption to induce an individual to sell his/her own body parts or health information. An individual will trust some nonprofit organization to store their materials, e.g., biobank institute and donate the material without intention of making a profit, by means of selling body parts. Under a strong governance framework, this biobank would permit qualified researcher or commercial entities to make use of materials trusted by individuals. This is the established scheme identified as a justifiable commercialization of human materials, discussed in the context of ethics of the biobank.

6.4.2.3 Avoid Exploitation and Stigmatization

From the abovementioned Kantian philosophy to prohibit utilization of human as a mere tool for other objectives, it is also required not to utilize a human being as a research subject, without allowing them to access the benefits generated from research. This is also a fundamental ethical dilemma, as research is conducted for the goal to generate results and contribute to public health but not for the care of

individual research subjects. The ethical principle of "justice" in the Belmont Report [61] suggested that it is not ethical if only vulnerable people participated in the research and wealthy people can have access to better care provided as the research results. This issue of exploitation has been long discussed in the process of revisions of the Declaration of Helsinki. The 2013 revision of the declaration recommend researchers and related government to make provisions to grant post-trial access to all research participants who need an intervention identified as beneficial and to provide this information to participants during the informed consent process. This is based on recognition that research participants have equal right to access the benefits generated from the research. Imaging studies can be conducted mostly in wealthy people where the majority of the research participants are able to pay for diagnosis and research status not covered by public healthcare insurance. More imaginable ethical infringement in the setting of diagnostic imaging would be abuse of diagnostic services in clinical practice to get a return of investment. To avoid this kind of abuse, health technology assessment for public and private insurance coverage is strictly demanded.

As often discussed in genetic research, diagnostic research to find mechanisms of a disease and provide some kind of prognosis but not provide care confronts the issue of stigmatization. Especially in case of utilization of the large amount of data of patients or people at risk of serious disease, we need ethical consideration to avoid collective stigmatization of some populations. To avoid stigmatization, more in-depth partnership with patients and an empowerment approach are needed. This implies that the characteristics of a patient involvement strategy must be in agreement with President Obama's Precision Medicine Initiative. Imaging studies for early diagnosis of cancer or neurodegenerative disease associated with genetic information would contribute to the development of better healthcare for these people at risk. However, it is prerequisite to protect these people from discrimination or stigmatization for their social status and access to health insurance or social security.

6.5 Conclusion

We have discussed the history and evolution of the US regulatory framework and clinical development strategies related to molecular imaging, which focuses on a critical path initiative that aims at personalized medicine and then precision medicine to achieve individual well-being and global public health. Next, we reflected upon ethics in the era of precision medicine from both perspectives of individual and collective ethics. Some of the discussions are common in various disciplines of the medical science. In some aspects, the focusing trend is in the era of GWAS and big data analysis, whereas in other parts, the main focus is on how imaging studies play the role of activating these trends.

As for regulatory reformation and initiative of clinical development, more collaborative approach is required in the era of precision medicine. This should include

the basket-type clinical trial network, large-scale cohorts associated with imaging archives, and clinical outcome information. Establishment of regulatory framework along with communities' collaboration toward quality assurance and standardization are key issues.

A reflection on ethics articulated that interests of ethical consideration are shifting from individual ethics toward collective ethics to achieve social value of research and global health. Traditionally, individual and collective ethics are regarded to be conflicting. However, to explore recent trends carefully, we can say that assurance of collective ethics could be simultaneously assurance of individual ethics in matured scientific communities. Nevertheless, both can still be seen conflicting in some immature research settings. This is also consistent with the theory of precision medicine, which should contribute to the well-being of an individual patient and the entire public health. This can be achieved through global collaborative research initiatives of sound scientific and ethically justifiable project designs, which aim at clinical development, profound understanding of the broad characteristics of science, clear regulatory definition attachment, and research and moral ethics in the era of precision medicine.

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References

1. The White House. The Precision Medicine Initiative [cited 2016 Feb 5]. Available from: https://www.whitehouse.gov/precision-medicine
2. The White House. FACT SHEET: President Obama's Precision Medicine Initiative; 2015 [cited 2016 Feb 5]. Available from: https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative
3. Katsnelson A. Momentum grows to make "personalized" medicine more "precise". Nat Med. 2013;19(3):249.
4. World Molecular Imaging Society. WMIC 2015 Highlights: Precision Medicine… Visualized [cited 2016 Feb 5]. Available from: http://www.wmis.org/meetings/archives-of-past-meetings/wmic-2015-highlights-precision-medicine-visualized/
5. Cook-Deegan RM. The Alta Summit, December 1984. Genomics. 1989;5(3):661–3.
6. Arnold RM, Forrow L. Rewarding medicine: good doctors and good behavior. Ann Intern Med. 1990;113(10):794–8.

7. Office of Science and Technology Policy Executive Office of the President. Obama Administration unvailes "Big Data" Initiative: Announce $200 million in new R&D investments; 2012 [cited 2016 Feb 8], Available form: https://www.whitehouse.gov/sites/default/files/microsites/ostp/big_data_press_release_final_2.pdf
8. National Institutes of Health. News Releases: 1000 genomes project data available on Amazon Cloud: Project is exemplar of new White House Big Data Initiative; 2012 [cited 2016 Feb 8]. Available from: http://www.nih.gov/news-events/news-releases/1000-genomes-project-data-available-amazon-cloud
9. U.S. Department of Health and Human Services. Advance Notice of Proposed Rulemaking (ANPRM), Human subject research protections: enhancing protections for research subjects and reducing burden, delay, and ambiguity for investigators. Fed Regist. 2011;76(143):44512–31.
10. Presidential Commission for the Study of Bioethical Issues. Privacy and progress in whole genome sequencing; 2012 Oct [cited 2016 Feb 5]. Available from: http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf
11. Pocock SJ. Clinical trials: A practical approach. New York: Wiley; 1983.
12. Alioto TS, Buchhalter I, Derdak S, Hutter B, Eldridge MD, et al. A comprehensive assessment of somatic mutation detection in cancer using whole-genome sequencing. Nat Commun. 2015;6:10001. doi:10.1038/ncomms10001.
13. Kurihara C. Ethics and regulation of precision medicine in nuclear medicine: Toward more international collaboration in the world. In: Precision Medicine Forum in Nuclear Medicine. 26–27 Sept 2015; Linyi, Shan dong Province, China.
14. Kurihara C, Inoue T. New regulations of PET drugs in the U.S. and the trends in FDA approvals-PET Drug American Dream World History: The 1st Report-. Rad Fan. 2013;11(8):108–11. Japanese. [Kurihara C, English trans. Kurihara C, Inoue T. New regulations of PET drugs in the U.S. and the trends in FDA approvals-PET Drug American Dream World History: The 1st Report-. Rinsho Hyoka (Clinical Evaluation). 2015;43(1):W47–54 [cited 2016 Feb 5].Available from: http://homepage3.nifty.com/cont/43_1/w47-w54.pdf]
15. Kurihara C, Inoue T. PET drug clinical trials and networking strategy for development-PET Drug American Dream World History: The 2nd Report-. Rad Fan. 2013;11(9):118–21. Japanese. [Kurihara C, English trans. Kurihara C, Inoue T. PET drug clinical trials and networking strategy for development-PET Drug American Dream World History: The 2nd Report-. Rinsho Hyoka (Clinical Evaluation). 2015;43:W55–61 [cited 2016 Feb 5]. Available from: http://homepage3.nifty.com/cont/43_1/w55-w61.pdf]
16. Kurihara C, Inoue T. Insurance coverage of PET drugs and imaging accreditation in the U.S. -PET Drug American Dream World History: The 3rd Report-. Rad Fan.2013; 11(10): 86–9. Japanese. [Kurihara C, English trans. Kurihara C, Inoue T. Insurance coverage of PET drugs and imaging accreditation in the U.S. -PET Drug American Dream World History: The 3rd Report-. Rinsho Hyoka (Clinical Evaluation). 2015;43:W63–71 [cited 2016 Feb 5]. Available from: http://homepage3.nifty.com/cont/43_1/w63-w71.pdf]
17. Kurihara C, Inoue T. Regulatory framework for approval of PET drug in Korea: a survey report. Kakuigaku. 2015; 52(4): 341–52. [Kurihara C, English trans. Kurihara C, Inoue T. Regulatory framework for approval of PET drug in Korea: a survey report. Rinsho Hyoka (Clinical Evaluation). 2016;43(2):W107–19 [cited 2016 Feb 5]. Available from: http://homepage3.nifty.com/cont/43_2/w107-w119.pdf
18. U.S. Food and Drug Administration. Code of Federal Regulations Title 21: Food and Drugs, Volume 5, Part 361: Prescription drugs for human use generally recognized as safe and effective and not misbranded:Drugs used in research: Sec. 361. 1: Radioactive drugs for certain research uses[cited 2016 Feb 5]. (40 FR 31308, July 25, 1975) Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=361.1
19. Huleiman OH, Fejka R, Houn F, Walsh M. The Radioactive Research Committee: background and retrospective study of reported research data (1975–2004). J Nuclear Med. 2006;47(7):1220–6.

20. U.S. Food and Drug Administration. Food and Drug Administration Modernization Act of 1997: section 121: Positron Emission Tomography [cited 2016 Feb 5].. Available from: http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm#SEC. 121
21. Department of Health and Human Services, Food and Drug Administration. 21 CFR 210, 211, and 212: Federal Register. 2009;74(236):65409–36.
22. U.S. Pharmacopeial Convention. The United States Pharmacopeia and The National Formulary [cited 2016 Feb 5]. Available from: http://www.usp.org/usp-nf
23. Schwarz S, Norenberg J, Berridge M, Dragotakes S, Hung J, Link J, Mason NS, Mattmuller S, Nickel RA, Packard A, Paolino J, Petry N, Ponto J, Quinton TM, Seifert KL, Swanson D, Weiner RE, Zigler S. The future of USP monographs for PET drugs. J Nucl Med. 2013;54(3):472–5.
24. Zigler S. One Year Post-212 Commercial Inspections. Society of Nuclear Medicine and Molecular Imaging 2013 Mid-Winter Meeting; 2013 Jan 25; New Orleans.
25. U.S. Department of Health and Human Services, Food and Drug Administration:Innovation Stagnation: Challenge and opportunity on the critical path to new medical products. 2004.
26. U.S. Department of Health and Human Services, Food and Drug Administration. Drug-Diagnostic Co-Development Concept Paper [draft]. 2005.
27. U.S. Department of Health and Human Services, Food and Drug Administration: Guidance for Industry: Developing medical imaging drug and biological products. Part 1: Conducting safety assessments. 2004.
28. U.S. Department of Health and Human Services, Food and Drug Administration: Guidance for Industry: Developing medical imaging drug and biological products. Part 2: Clinical indications. 2004.
29. U.S. Department of Health and Human Services, Food and Drug Administration: Guidance for Industry: Developing medical imaging drug and biological products. Part 3. Design, analysis, and interpretation of clinical studies. 2004.
30. Yang D. Inoue T, Kurihara C, interview and supervising trans. Interview with Prof. David Yang: PET molecular imaging, drug development, and FDA guidance. Rinsho Hyoka (Clinical Evaluation). 2010;38(2):3335–52.
31. Kurihara C, Inoue T. Commentary on the interview with Prof. David Yang: PET molecular imaging in the RDRC system and drug development in United States. Rinsho Hyoka (Clinical Evaluation). 2010;38(2):353–8.
32. U.S. Department of Health and Human Services, Food and Drug Administration: Guidance for Industry: In vitro companion diagnostic devices. 2014.
33. Van Heertum RL, Scarimbolo R, Ford R, Berdougo E, O'Neal M. Companion diagnostics and molecular imaging-enhanced approaches for oncology clinical trials. Drug Des Develop Ther. 2015;9:5215–23.
34. Jacobs PM. NCI's Initiative in INDs: Update on Investigational Radiopharmaceuticals. Society of Nuclear Medicine Annual Meeting 2012. Miami; 2012.
35. American College of Radiology Imaging Network [cited 2016 Feb 5]. Available from: https://www.acrin.org/
36. Radiological Society of North America (RSNA). Quantitative Imaging Biomarker Alliance [cited 2016 Feb 5]. Available from: http://www.rsna.org/qiba/
37. Sullivan D. Objectives and current status of QIBA (Quantitative Imaging Biomarkers Alliance). Rinsho Hyoka (Clinical Evaluation). 2017; 44(4). In press. Based on the lecture at the 51th autumn clinical meeting of Japan Radiological Society, held October 2–4, 2015, Iwate, Japan. This lecture was provided on October 3.
38. The White House. Fact sheet: President Obama's Precision Medicine Initiative. 2015 Jan 30 [cited 2016 Feb 8]. Available from: https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative
39. The White House. FACT SHEET: New Patient-Focused Commitments to Advance the President's Precision Medicine Initiative. 2015 Jul 8 [cited 2016 Feb 5]. Available from: https://www.whitehouse.gov/the-press-office/2015/07/08/fact-sheet-new-patient-focused-commitments-advance-president%E2%80%99s-precision

40. Genomics England. 100,000 Genome Project [cited 2016 Mar 9]. Available from: https://www.genomicsengland.co.uk/the-100000-genomes-project/
41. Genomics England. First patients diagnosed through the 100,000 Genomes Project. Posted on March 11, 2015 [cited 2016 Mar 9]. Available from: http://www.genomicsengland.co.uk/first-patients-diagnosed-through-the-100000-genomes-project/
42. National Cancer Institute. NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trial. Updated 2016 Apr 19 [cited 2016 Apr 27]. Available from: http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match
43. Politi K, Herbst RS. Lung cancer in the era of precision medicine. Clin Cancer Res. 2015;21(10):2213–20.
44. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009;86(1):97–100.
45. European Society of Radiology, Patuzzi J, Zizka D. Press Release for European Congress of Radiology 2014. 6–10 March, Vienna, Austria [cited 2016 Feb 5]. Available from: http://www.myesr.org/html/img/pool/Sunday_NH14_Precision_Medicine_ECR2014_PR.pdf
46. European Society of Radiology (ESR). Medical imaging in personalised medicine: a white paper of the research committee of the European Society of Radiology (ESR). Insights Imaging. 2015;6:141–55.
47. National Cancer Institute. Varmus H. Precision Medicine Initiative® and Cancer Research. 2015 [cited 2016 Mar 10]. Available from: http://www.cancer.gov/news-events/cancer-currents-blog/2015/precision-medicine-initiative-2016
48. Gillies RJ, Goldgof D, Hall L, Gatenby RA, Balagurunathan Y, Eschrich S. Radiomics at Moffitt. Quantitative Imaging Network. 2012;2(3):1–2 [cited 2016 Mar 10]. Available from: http://imaging.cancer.gov/programsandresources/specializedinitiatives/qin/Newsletter_7
49. Prior F, Freymann J, Vendt B, Clark K, Kirby J, Tarbox Lawrence, Koppel P, Moore S, Pringle M, Phillips S, Maffitt D, Jaffe C. A repository of advanced imaging information correlated with TCGA samples [cited 2016 Mar 10]. Available from: http://wuerlim.wustl.edu/documents/posters/tcga2011.pdf
50. Kurihara C. Asian collaborative clinical trial network utilizing PET imaging: Toward global health and innovative medicine. Japanese and Chinese Societies of Nuclear Medicine Network Committee Meeting; 5 May 2016; Shanghai, China.
51. Health Insurance Portability and Accountability Act, Public Law 104–191. 1996.
52. Department of Health and Human Services, Office of the Secretary. Standards for Privacy of Individually Identifiable Health Information. 45 CFR Parts 160 and 45 CFR 164. Federal Register: Dec. 28, 2000. (Volume 65, Number 250).
53. World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 [cited 2016 Feb 5]. Available from: http://www.wma.net/en/30publications/10policies/b3/index.html
54. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Communities. 2014; L158:1–76.
55. National Institute of Neurological Disorders and Stroke. Detection and disclosure of incidental findings in neuroimaging research. 2005 [cited 2016 Mar 10]. Available from: http://www.ninds.nih.gov/news_and_events/proceedings/ifexecsummary.htm
56. Richardson HS. Incidental findings and ancillary-care obligations. J Law Med Ethics. 2008;36(2):256–70. 211 doi:10.1111/j.1748-720X.2008.00268.x.
57. Dickert N, DeRiemer K, Duffy PE, Garcia-Garcia L, Mutabingwa TK, Sina BJ, Tindana P, Lie R. Ancillary-care responsibilities in observational research: two cases, two issues. Lancet. 2007;369(9564):874–7.
58. Wexler A. Mapping fate: a memoir of family, risk and genetic research. University of California Press; 1995.

59. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY, et al. A polymorphic DNA marker genetically linked to Huntington's disease. Nature. 1983;306(5940):234–8.
60. Jacques LB. Kurihara C, 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. Rinsho Hyoka (Clinical Evaluation). 2015; 43(1):W73–84. Available from: http://homepage3.nifty.com/cont/43_1/w73-w84.pdf
61. The Belmont Report. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [cited 2016 Feb 5]. 1979.
62. Emanuel EJ, Wendler D, Grady C. An ethical framework for biomedical research. In: Emanuel EJ et al., editors. The Oxford textbook of clinical research ethics. New York: Oxford University Press; 2008. p. 123–35.
63. De Angelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;315(12):1250–1.
64. Food and Drug Administration Amendment Act Section 801.
65. Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare. Ethical Guidelines for Research Involving Human Subjects; 2014.
66. PhRMA (Pharmaceutical Research and Manufacturers of America), EFPIA (European Federation of Pharmaceutical Industries and Associations). Principles for responsible clinical trial data sharing: Our commitment to patients and researchers. 2013 [cited 2016 Feb 5]. Available from: http://www.phrma.org/phrmapedia/responsible-clinical-trial-data-sharing; http://transparency.efpia.eu/responsible-data-sharing
67. The National Academies of Sciences Engineering Medicine, Institute of Medicine. Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk. 2015 [cited 2016 Feb 5]. Available from: http://iom.nationalacademies.org/Reports/2015/Sharing-Clinical-Trial-Data.aspx
68. Council for International Organizations of Medical Sciences [cited 2016 Apr 24]. Available from: http://www.cioms.ch/
69. Taichman DB, Backus J, Baethge C, Bauchner H, de Leeuw PW, Drazen JM, et al. Sharing clinical trial data: a proposal from the International Committee of Medical Journal Editors. PLoS Med. 2016;13(1):e1001950. doi:10.1371/journal. pmed.1001950.