Molecular Imaging CRO Network

Micron's Viewpoint

The Development of Software as a Medical Device (SaMD)

-Clarification of Clinical Significance-

Micron, Inc.

Contents

Introduction

In recent years, medical programs and applications such as Artificial Intelligence (AI) have been actively developed. The Ministry of Health, Labour and Welfare (MHLW) of Japan has issued "Guidelines of Determining Whether Software is Classified as a Medical Device (SaMD: Software as a Medical Device)[1]" regulated by The Act on "Securing the Quality, Efficacy, and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics". According to these guidelines, software programs are considered medical devices depending on their intended use and degree of risk. Once their classification as a medical device is clear the next task is to apply for regulatory approval. Approval is dependent on the risk classification of the medical device program (risk I-IV), which then determines the pharmaceutical certification, regulatory approval and more[2]. Intended use is generally synonymous with the clinical significance of a medical device program, and risk is very closely related to clinical significance. In other words, the clinical significance of a program is an important issue when determining medical device program applicability and regulatory affairs.

What exactly is the clinical significance? According to the "Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices"[3], clinical significance is defined as an "effect obtained from an action" and clinical positioning exists in a way that embraces clinical significance. Clinical positioning is defined as "the aim to use the medical device or the effect provided by the medical device while characteristics of disease and patient or any other conventional therapies and diagnostics are considered. Also, the clinical positioning means the difference of performance, etc., the priority of the treatment to be undergone with the medical device, when the therapy using the medical device to be developed is compared with any other therapies.". With reference to this guidance, the following points to consider when organizing the clinical significance of a SaMD are:

- Target patients
- Target diseases
- Environment of use (inside/outside the hospital)
- Clinical departments to be installed and used
- Timing of use (check-up/examination)
- CADe/CADx/CADt
- Differentiating features of approved similar medical devices, additional value of medical device
- Clinical use styles (Second Reader/Concurrent Reader/First Reader)
- Effectiveness compared to existing diagnostic methods

In addition to organizing the above considerations, the identification of current issues and needs in clinical practice would help to clarify the clinical significance.

The most common category of AI-based SaMDs approved by the PMDA are disease diagnosis programs, including imaging diagnosis decision support systems. These SaMDs use imaging to assist doctors in diagnosis. The clinical significance of imaging diagnostic decision support systems can also be effectively examined through the six levels of clinical efficacy evaluation (Figure 1)[4]. The six levels of clinical efficacy evaluate how effective medical imaging diagnostic decision support systems in relation to patients, healthcare professionals, and society in general. As clinical significance and clinical efficacy evaluation exist as a pair of objectives and goals, one way of considering clinical significance is by considering which of the six levels applies to the imaging diagnosis decision support system being considered.

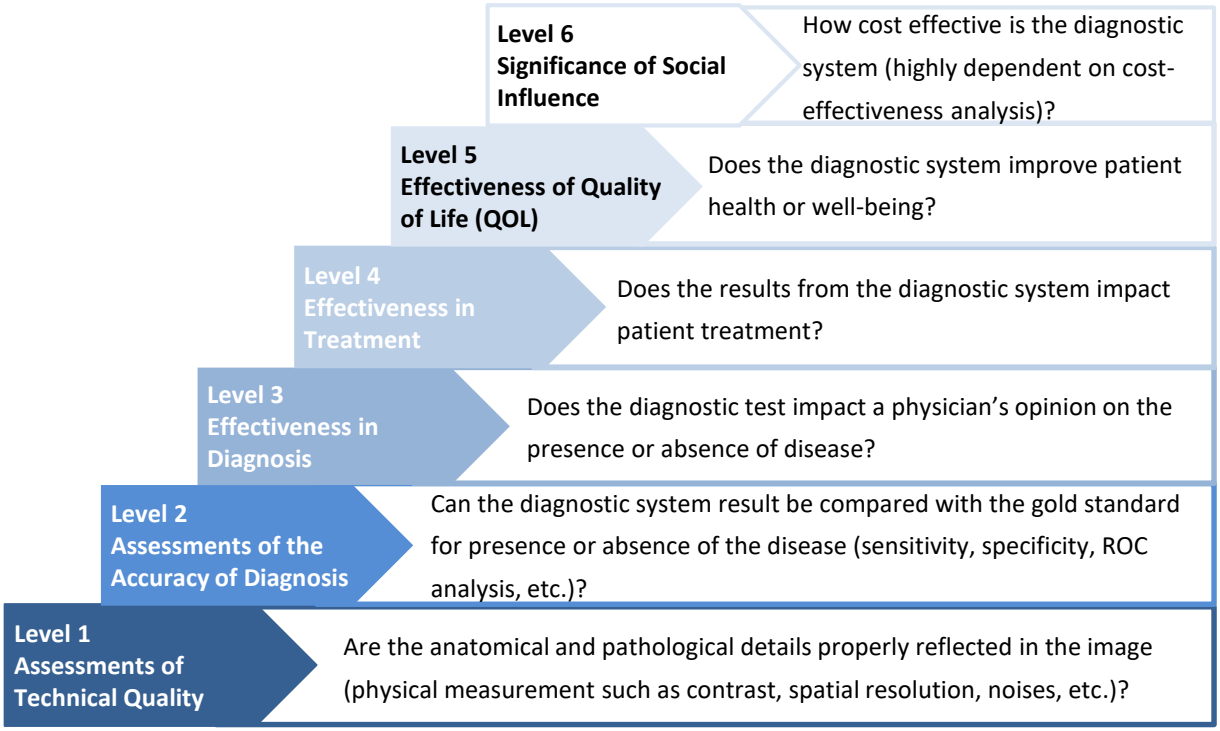

Figure 1. Six Levels of Evaluation of the Clinical Efficacy of Medical Imaging Diagnostic Decision Support System
(Reference 4 with partial modifications)

In the previous issue of Micron's ViewPoint, we discussed the importance of reference standards in imaging diagnostic decision support system clinical trials and the social implementation of medical AI. In this paper, examples of imaging diagnostic decision support system are described and the clinical significance of SaMDs is outlined.

The Classification of Imaging Diagnostic Decision Support Systems

Imaging diagnostic decision support systems for detecting and diagnosing the presence or absence of disease and conditions are also known as CAD (Computer Aided Detection/Diagnosis)[5]. There are multiple different possible functions of CAD and numerous types of applications in clinical workflow [6, 7] (Figure 2). The effectiveness of use, target patients, and clinical timing of various CADs will differ, making the clinical significance more apparent.

Functions of CAD

- CADe (Computer Aided Detection)
  The computer automatically detects suspicious lesions in the image, and displays marked candidate lesions to the physician.

- CADx (Computer Aided Diagnosis)
  In addition to detecting suspicious lesions, CADx also provides physicians with information about the nature of diagnosis, such as whether a target lesion is benign or malignant, or the stage of a disease.

- CADt (Computer Aided Triage)
  Before the images are presented to radiologists, they are analyzed by the program. The program will then alert the specialist as to whether there is a significant finding that needs to be dealt with urgently.

Clinical Application

- Second Reader Type
  Physicians interpret the images without using CAD (i.e. normal image interpretation). They then interpret the images again with added perspective of CAD.

- Concurrent Reader Type
  Physicians interpret all images while simultaneously referring to CAD results.

- First Reader Type
  CAD interprets the images in isolation and identifies potential lesions. Physicians read only the target lesions proposed by CAD.

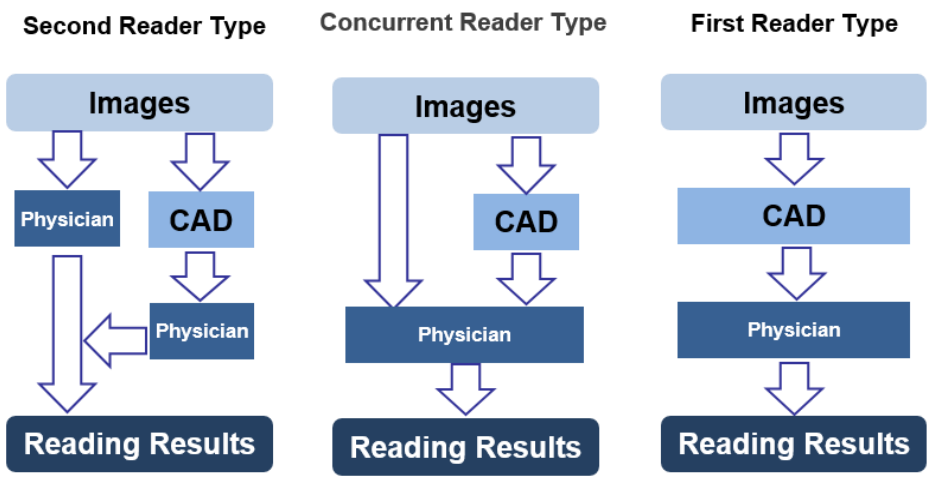

Figure 2. Clinical Application of CAD (Reference 6 with partial modifications)

Examples of Clinical Significance

The most common clinically significant function of SaMDs is to avoid lesions from going undetected. The most promising result of this is that more accurate diagnoses can be achieved through the use of SaMDs. The following is a list of items with clinical significance that have been approved by regulatory authorities.

Avoid Lesions from Going Undetected

Pulmonary nodule detection program FS-AI688 (distributed by: Fujifilm Corporation)[8], is a SaMD that assists in the detection of pulmonary nodules on CT imaging. Early detection of lung cancer can reduce mortality, with the detection of pulmonary nodules in early stage lung cancer crucial to this. However, CT imaging used to detect pulmonary nodules may depend on physician experience, and in some cases, pulmonary nodules may be missed. The use of a pulmonary nodule detection program can reduce the number of lesions being missed.

Reduction of Invasiveness

HeartFlow FFRct (distributed by HeartFlow Japan Corporation)[9], is a SaMD that assists in determining whether percutaneous coronary intervention (PCI) is applicable for coronary artery disease. Conventionally, in order to determine whether or not a patient is eligible for PCI, in addition to coronary arteriography-CT, invasive and complex operations such as myocardial stress scintigraphy and cardiac catheterization are performed. HeartFlow FFRct analyses coronary angiographic CT to obtain information on functional stenosis and responsible lesions non-invasively.

Solution for the Shortage of Specialist Doctors

IDx-DR (distributed by: Digital Diagnostics, not approved in Japan, FDA DE Novo-cleared)[10], is a conditional First Reader Type CAD that facilitates specialist diagnosis of diabetic retinopathy by analyzing fundus photographs of diabetic patients. Routine screening for early detection of diabetic retinopathy is important for primary care of diabetic patients for vision protection. The introduction of IDx-DR to primary care facilities in the USA, where there is a shortage of specialist physicians in the vast landmass of the country, will improve patient accessibility. The clinical significance of IDx-DR is particularly high in the USA, where diabetes is common.

Early Intervention

The Apple Watch ECG app (distributed by: Apple, Inc.)[11], is a SaMD that analyzes pulse rate data to detect irregular heartbeats suggestive of atrial fibrillation, notifying the user if detected. The clinical significance of this product is that asymptomatic users can be notified of the possibility of atrial fibrillation and be prompted to see a doctor and thus receive a formal diagnosis. This means that early awareness of possible onset atrial fibrillation may allow for earlier intervention by clinicians and prevent longer-term harm.

Approaches to SaMD Development

Considering the clinical significance before developing a SaMD is a fundamental aspect of medical device development. In fact, in the midst of the AI boom, development has sometimes been driven by technology first, with the needs of clinical practice taking a back seat. This is a case of so-called Technology Push Type medical device development (Figure 3)[12]. Particularly with regard to AI, the power word "AI" becomes a corporate branding, leading to AI-oriented product development. AI may be forced to pivot from its clinical significance in the early stages of development, as it is difficult to set targets for product achievement and performance is dependent on the quality of data collected and correct labels. In the development of Technology Push Type SaMDs, the planning of subsequent clinical trials and regulatory filings with regulatory authorities will proceed more smoothly if the clinical significance of the program is at least clarified by the time the program is completed.

The Needs Pull Type approach is an approach that considers the clinical significance of a SaMD before it is developed[12]. It is also referred to as Needs Driven Type or Design-Thinking medical device development. This approach develops medical devices with the issues and needs of the medical field as the starting point instead of technology. The development of a Needs Pull Type SaMD would be expected to clarify the clinical significance and facilitate cooperation with the medical community, in addition to facilitating smooth handling of regulatory applications. In developing a Needs Pull Type SaMD seeking a wide range of opinions from as many hospitals and physicians as possible may be more accurate than relying on the opinion of one well-informed doctor. In addition, it is also important to consult leaders in the field and related academic societies for future marketing strategies.

Whether it is a Technology Push Type or Needs Pull Type, mutual collaboration between the medical field and the industry side will result in the development of truly valuable products. In particular, AI-based SaMDs are expected to include products whose performance will change with additional learning data once being brought to market[12]. Thus, it is essential to communicate and cooperate with the medical field, as they will be asked to collect additional data, create correct labels and conduct clinical evaluations.

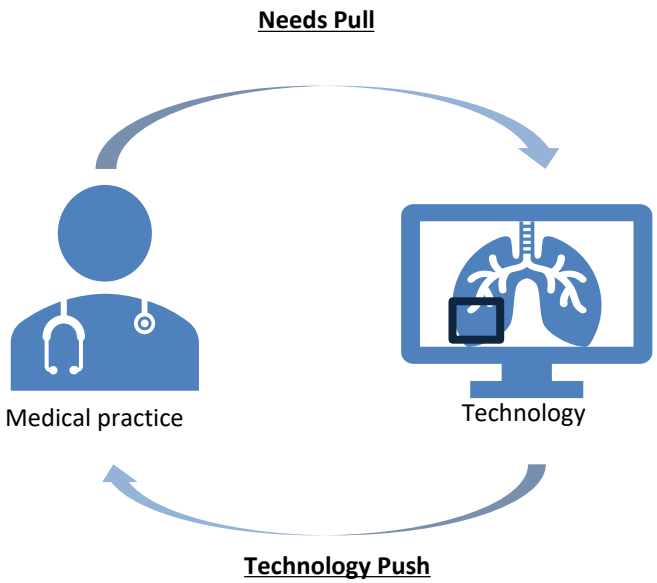

Figure 3. Needs Pull Type/Technology Push Type Medical Device Development
(Reference 12 with partial modifications)

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Clinical Significance of PMDA Approved Items

As mentioned earlier, clinical efficacy evaluation and clinical significance are paired. The clinical significance of SaMDs approved by the PMDA (the Japanese regulatory authority) is investigated from clinical trial endpoints. Our research identified 27 products approved as SaMDs. We summarized the primary and secondary endpoints of the clinical trials and clinical performance studies by referring to the accompanying documents of each product and to the supporting documents of the application for approval for which we requested disclosure (Table 1). Out of 27 products, 89% (24 products) had evaluation indicators related to diagnostic accuracy, such as sensitivity, specificity, positive predictive rate, negative predictive rate, positive diagnosis rate, ROC and FROC (Figure 4). In addition, many of the items in the development background section of approval applications clearly state “to avoid lesions from going undetected” and “improving diagnostic accuracy”, suggesting that these are the most common aspects of clinical significance of SaMDs currently approved by regulatory authorities. Furthermore, 14 of the 27 products were identified for reading tests, which evaluate how the use of additional SaMDs changes the accuracy of diagnosis compared to the accuracy of diagnosis by the physician alone. The items where no reading tests were conducted included items with conditional approval under COVID-19 and cases where no readers were envisaged, which suggests that Level 2 of the clinical efficacy assessment is the main focus of the clinical trials and efficacy evaluation of clinical performance assessment.

Evaluation Item	Reading Test	Standalone Performance Assessment
Sensitivity	11	21
Specificity	7	17
Positive predictive rate	4	8
Negative predictive rate	2	6
Positive diagnosis rate	2	4
False positive rate	2	0
False negative rate	2	2
Average false positive cases	3	3
FROC	6	0
ROC	2	2
Correlation coefficient	2	1
% of upturns and implosions	5	0
Reproducibility of reading	1	0
Reading time	1	1
Pass rates for similar scores	1	0

Table 1. Efficacy Evaluation for Regulatory-Approved SaMD

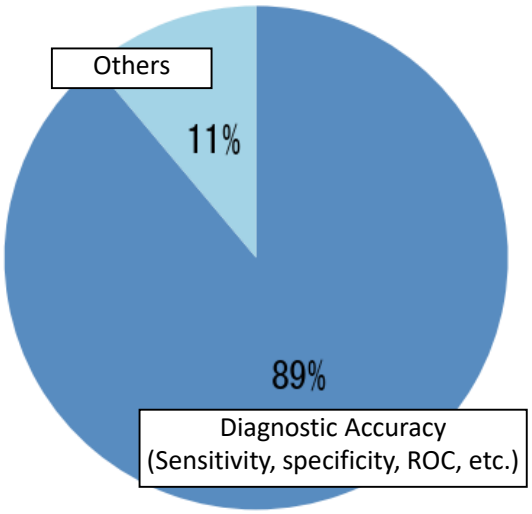

Figure 4. Applicability of diagnostic accuracy for the assessment item

Improved diagnostic accuracy (including to avoid lesions from going undetected) is the most common clinically significant aspect of SaMDs.

Conclusion

In comparison with Europe, the United States and Asia, the number of utilized SaMDs used in clinical practice in Japan is relatively low, and SaMDs need to be promoted in Japan. In 2020, MHLW published the "Drastic Reform of Review Systems for Innovative Medical Devices Including Software as a Medical Device (DASH for SaMD)"[14], which aims to establish an examination system and structure based on the characteristics of SaMDs and to promote the early commercialization of cutting edge SaMDs. The Council for Promotion of Regulatory Reform at Cabinet Office[14] has raised a number of issues from both industrial and regulatory perspectives, ranging from pharmaceutical regulation to insurance coverage and sales of SaMDs. In order to continue to promote the implementation of SaMDs into clinical practice, the clinical significance of the tools must be clarified to ensure communication between industry and regulation.

In this paper, the clinical implication of SaMDs for improving diagnostic accuracy and preventing oversights has been discussed. Furthermore, SaMDs may enable non-specialist physicians to perform medical procedures with increased confidence. As changing techniques is also an issue in the medical field, reducing the physical and mental burden on doctors is also of clinical significance and may continue to attract attention well into the future.

As mentioned earlier, the development of SaMDs requires the matching of needs and technology and the building of mutual cooperation. Micron offers a service called ''INDICATE'' to bridge the two (URL: https://micron-kobe.com/archives/works/indicate). Interested parties are welcome to access the website.

In this paper, we outlined the clinical significance of SaMDs for diagnostic purposes, and in future issues of Micron's ViewPoint, we will describe how to reduce bias in clinical trials, ROC analysis commonly used in clinical trial endpoints, etc.

Micron offers a full range of services for certification/approval of SaMDs, from consultation through to the planning and operation of trials and handling of PMDA applications for approval. We also offer a range of training services tailored to the SaMD you would like to certify/approve.

Company Overview

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Nagoya Office	7-430 Morioka-cho, Obu, Aichi, Japan Phone: +81-562-46-2105
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Website	https://micron-kobe.com/en
Linkedin	https://www.linkedin.com/company/micron-imaging/
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https://www.meti.go.jp/policy/mono_info_service/healthcare/iryou/downloadfiles/pdf/47_guideline.pdf
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