Public-Private Dialogue for the Creation of Innovative Medical Devices and In-Vitro Diagnostics

November 28, 2022

Japan Association of Clinical Reagents Industries

American Medical Devices and Diagnostics Manufacturers' Association
IVD Committee

European Business Council EBC Medical Devices and IVD Committee

Issues of the day

A) **Evaluation of innovation for clinical laboratory testing**

B) **Measures against the following infectious disease crises**

C) **Measures for stable supply in the event of price increases**

A) Evaluation of innovation for clinical laboratory testing

As stated in the Proposal* on the Proper Implementation System of Clinical Laboratory Tests, " Definition of innovation for clinical laboratory tests, and based on this definition, Introduction of Valid and Transparent Evaluation Standards " are very important for the creation of innovative in-vitro diagnostics.

* Quotation : Excerpt from Recommendation 2 on page 14 to the Minister of Health, Labour and Welfare from 3 organizations (JACRI, EBC and AMDD) of the Recommendation on the proper implementation system of clinical laboratory tests on December 15, 2021

Reference : Policy proposals regarding on Evaluation and Ideal state of Clinical Testing Based on Medical Value - Promotion of Evaluation of Clinical Tests that form the basis of Medical Care - Social Insurance Sunpo No. 2867, 2022 9 11

Current status

- Even if innovative products are developed for in-vitro diagnostics, the system for evaluating such products is not clarified. (For medical devices : Premiums for innovativeness, improvement, marketability, etc.) * * Refer to reference material : Case examples on pages 8-12
- The motivation for developing next-generation products cannot be maintained due to the difficulty in securing development costs and predictability of incentives for development to continue developing innovative in-vitro diagnostics that can contribute to patients and medical facilities in line with recent advances in science and technology.
- In the supplementary opinion to the report at the general meeting of Chuikyo on May 18, 2022 (see next page ***), the Expert Committee on Insurance-Covered Medical Materials is to consider the evaluation of innovation in clinical labolatory tests.

Proposal

- It is requested that the Expert Committee on Insurance-Covered Medical Materials consider in-vitro diagnostics **evaluating innovation and reflecting it in medical fee points**.
  - Step1 : Agree on the definition of innovation
  - Step 2 : Institutionalize additions to items that meet the definition of innovation

*** Excerpt from Chuikyo material

Chuikyo So-9
4.5.18

How to proceed with consideration of matters related to supplementary comments on the written report (Draft)

○ 2022 Report on Revision of Medical Service Fees Incidental opinions need to be investigated, verified and discussed conducted. As shown in the attachment, it may be appropriate to examine the impact of the fiscal year 2022 medical fee revision and to start investigations and necessary deliberations toward the next medical fee revision to at each of the discussion places.

Attachment

Supplementary Comments on Reported Damages	Main Places for Consideration
(Evaluation of Medical Technology) 11 From the viewpoint of perspective of promoting high-quality medical care based on clinical practice guidelines, etc., we will continue to consider the revision of clinical practice guidelines, the analysis results of world data with registries, etc., including the appropriate medical technology evaluation process based on them. matter. In addition, regarding advanced medical technology including innovative medical devices (including programmed medical devices) and innovations such as testing, from the viewpoint of perspective of prompt and stable supply and provision to patients, we should continue to consider appropriate evaluation methods based on evidence related to efficacy and safety.	Subcommittee on Evaluation of Medical Technology, Expert Subcommittee on Insurance-Covered Medical Materials

B) Measures against the Next Infectious Disease Crisis (Lessons from the COVID-19) It is extremely important to continue developing and strengthening the examination system, including the maintenance of measuring instruments and human resources that have been developed and secured in medical institutions, etc., as a measure against the next infectious disease crisis.

Current situation

In preparation for the next infectious disease crisis, the COVID-19 Response Headquarters has raised the following issues with the aim of **" Strengthening the Testing System "** *.

- Prefectures, etc. shall develop a necessary system to ensure that inspections are conducted smoothly from the initial stage of infection. In addition, the inspection system will be drastically strengthened by promoting the utilization of private inspection organizations.
- Testing reagents, test kits, and other materials necessary for examination are also produced and imported in emergencies. For these purpose, develop a framework for taking appropriate measures.

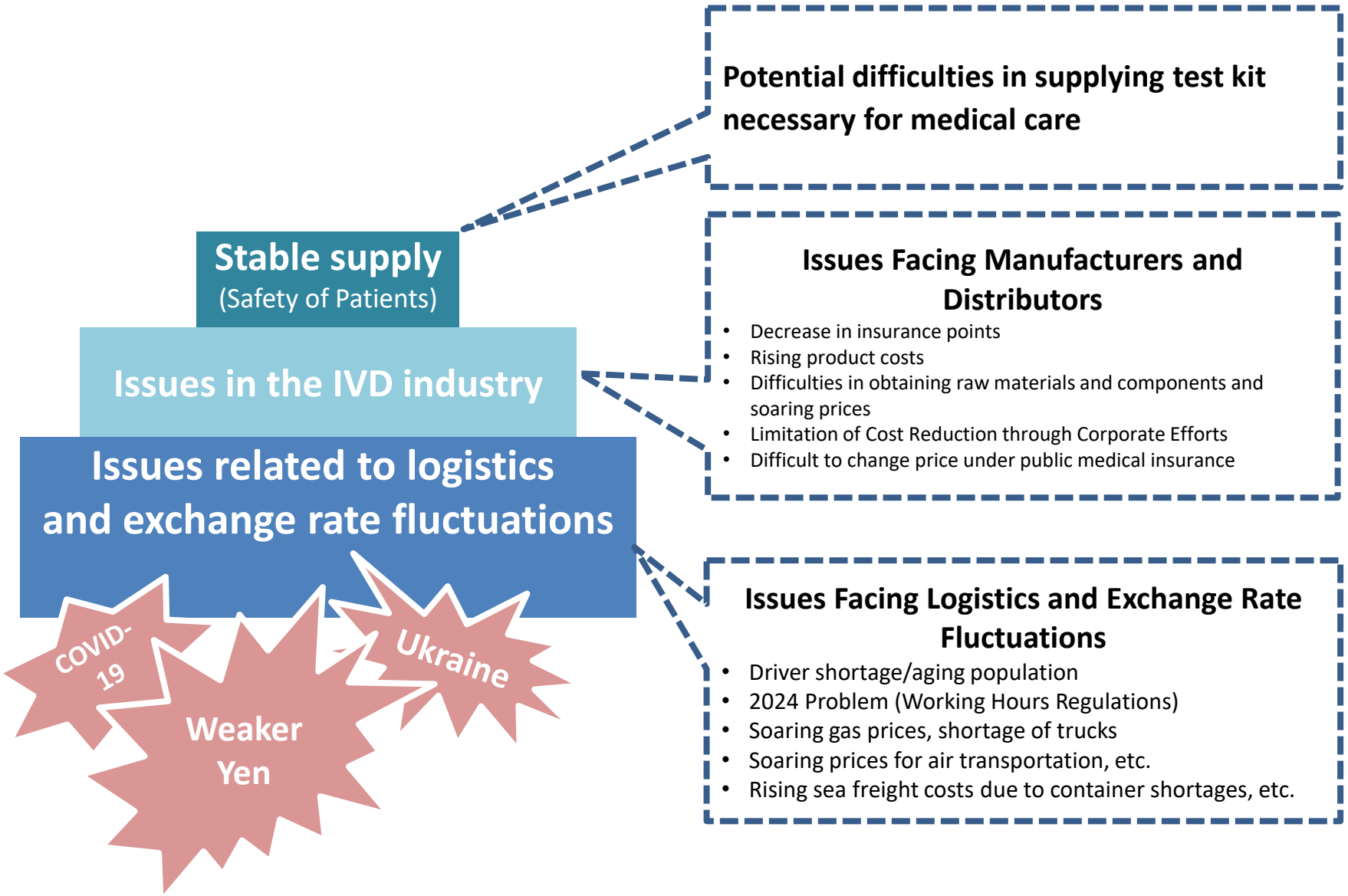
* " Direction of Responses to Prepare for the Next Infectious Disease Crisis Based on Efforts to Date Concerning the Next Coronavirus " (Decision of the Response HQ on June 17, 6, Reiwa 4) P5 From " 3 Strengthening the Examination System " / P6 From " 6 Strengthening the Securing of Medical Supplies " (partially modified)

Proposal

- When considering the establishment of a system, we are in charge of the development and supply of test reagents and the diagnostics industry would like to participate in the discussion at an early stage.
  - It is expected that more companies' contribution and the response will be speeded up by unifying the contact points for administrative and industry sides and developing a system to transmit and collect necessary information in a timely and efficient manner.
  - Providing opportunities for the development of systems on the part of the diagnostics industry at an early stage will enable a more prompt and flexible response.
- As a risk management measures implementation of " maintenance of measuring instruments, etc. " and " recruitment and training of clinical laboratory specialists and clinical laboratory technicians " in medical institutions in peacetime (including maintenance of equipment and human resources that have been improved recently) is recommended.

C) Measures for Stable Supply in the times of Price Increases

Recent environmental changes such as rapid exchange rate fluctuations



C) Measures for Stable Supply in the times of Price Increases

Recent environmental changes such as rapid exchange rate fluctuations

Background

- Increased costs for imported goods and raw materials procurement due to the sharp depreciation of the yen
- Even for member companies of the Japan Association of Clinical Laboratories, the impact of fluctuations in foreign exchange rates and consumer prices will increase costs by about 10-30%.
- Under public medical insurance with reimbursement prices, it is difficult to pass on these cost increases to medical institutions by raising selling prices.

Recent changes in the environment

- Effects of COVID-19
- High commodity prices due to disruption of distribution networks
  (Cost increases of 2-4 times for airfreight and 2-5 times for sea freight)

Request for Immediate Measures

- Development of an environment that facilitates the use of Temporary Subsidies for Reginal Development by medical institutions
- This is within the framework of public medical insurance, but we would like to pass on increased costs to sales prices.

** Reference materials

A) Evaluation of innovation for clinical laboratory testing

Innovativeness : " Cancer gene panel examination " using next-generation sequencer

Advanced technology (next-generation sequence technology) is introduced into clinical examinations, and items that have been examined individually can be examined collectively.

- Contribution to early decision on treatment plan
- Contributing to the reduction of the burden on both patients and medical personnel

Individual examination

- EGFR genetic testing () qPCR method
- ALK fusion gene test () IHC method
- ROS1 Fusion gene test RT-PCR method
- BRAF genetic testing () NGS method
- RET fusion gene test () NGS method

Batch examination

- EGFR gene mutation test
- ALK fusion gene test
- ROS1 fusion gene assay
- BRAF genetic testing
- RET fusion gene test

Next-generation sequencer

✓ Repetition of individual checks
⇒ It is necessary to take a long time to decision on treatment plan
✓ Larger sample volume is needed because each gene mutation is tested individually
⇒ Re-biopsy due to specimen shortage

✓ Shortening of the waiting period until the test result is obtained by the batch examination
⇒ **It is possible to decide on an early treatment policy and start treatment**

✓ Multiple items can be tested with a smaller sample volume
⇒ **Reduce the burden on patients and medical personnel involved in re-biopsy due to specimen shortage**

Improvement : Cases in which there was a change in medical care due to improvement in test performance - High-sensitivity troponin test -

" Changes in the guidelines for troponin testing "

2007 : United States and Europe (ESC/ACCF/AHA/WHF) Task force : The diagnostic criteria for MI (myocardial infarction) were completely revised and " Universal Definition of MI " was issued.

- The biomarker with specificity for myocardium is troponin, and the recommended diagnostic criterion is less than 10% CV below 99% tile of a healthy person.

2013 : Guidelines for the management of ST-segment elevation acute myocardial infarction

- Cardiac troponin is highly myocardial specific and is not elevated in healthy individuals.
- With the conventional troponin test, it was not possible to make a judgment until 6 hours or more had passed, but the high-sensitivity cardiac troponin measurement system has high measurement accuracy and has been shown to be useful for diagnosis in the hyperacute phase (within 2 hours after onset).

2018 : Acute coronary syndrome guidelines

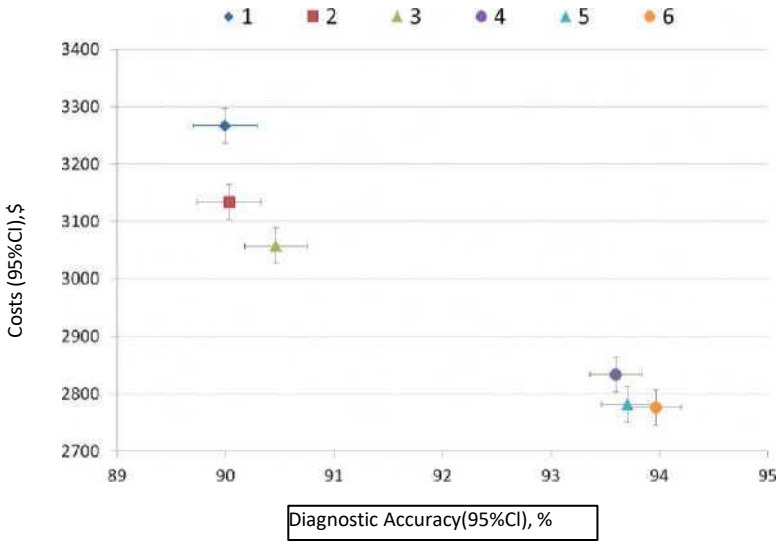
- High-sensitivity cardiac troponin measurement systems have been shown to be more accurate than conventional troponin systems and it is also useful for diagnosing the hyperacute phase within 2 hours after onset.
- Higher values at admission are associated with higher mortality risk.

High sensitivity enables early diagnosis
Diagnosis become possible within 2 hours from 6 hours

Improvement of diagnosis accuracy and improvement of patient outcomes by early diagnosis

Reflected in Guidelines

Improvement : Cases in which there was a change in medical care due to improvement in test performance - High-sensitivity troponin test -



Method:

In patients with suspected ACS (acute coronary syndrome), we compared the diagnostic method by the following troponin tests 1, 2, 3,

1. Conventional test : 6 hours after visit,
2. High-sensitivity troponin test : 2hours after visit +LoD and
3. ADP (accelerated diagnostic protocol = early diagnostic protocol)

Results :

High-sensitivity troponin and ADP compared with conventional troponin testing (#1). When ADP was introduced (#5), the diagnostic accuracy improved from 90% to 94%, and medical costs decreased by about $500.

Moreover, an early diagnostic protocol for high-sensitivity troponin LOD and 2 hours after visit was associated with a 7.5% reduction in short term hospital admission **and a 25% reduction in cardiac ward admissions.**

Juilicher P, et al. BMJ 2017;7:e013653.

Marketable (rare) : RAS Gene mutation (plasma)

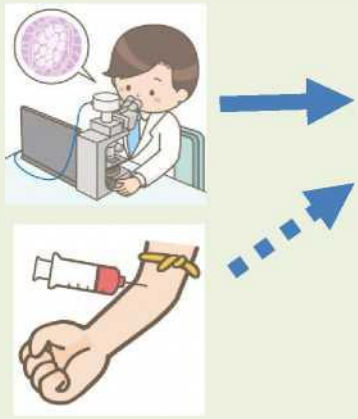
" Outline of the examination "

Anti EGFR antibody reagents are used 1st line in patients with advanced / recurrent colorectal cancer, but it is recommended to test for RAS mutation before making a decision on administration because RAS there is no therapeutic effect if there is a mutation.

Example : Efficacy of cetuximab (RAS wild-type unresectable advanced or recurrent colorectal cancer that is not candidates for curative resection)

" Clinical usefulness evaluated at the time of application for insurance coverage "

It is a highly sensitive plasma RAS gene mutation test combining digital PCR and flow cytometry for patients for whom obtaining a tissue specimen is difficult or who are at high risk of complications due to re-biopsy, it is possible to make a decision to administer a therapeutic drug quickly and with low invasion.



In the conventional development of molecular-targeted drugs, patients are selected based on the results of tissue examination

Therefore, even though technical improvements have led to the development of blood-based tests handling for insurance is " when the examination using tissue is difficult " and evaluation is limited (Although the manufacturer can show the analytical equivalence of tissue and blood, long-term prognostic outcomes of interventions are difficult to explan)

Physicians are aware of the advantages of rapid and minimally invasive procedures and have begun to accumulate positive evidence regarding treatment options based on blood tests.

National Cancer Center (ncc. go. jp) : Proving Validity of Genome Analysis by Liquid Biopsy