Chugai Digital Strategy Meeting

December 2, 2020

Important Reminders

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the "Company"). These statements reflect the Company's current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company's businesses.

Information regarding pharmaceuticals (including products under development) is included in this presentation, but is not intended as advertising or medical advice.

Agenda

1. CHUGAI DIGITAL VISION 2030

 Satoko Shisai

 Vice President, Head of Digital & IT Supervisory Div.

2. Innovation in the Drug Discovery Process Using AI

 Dr. Hiroyuki Tsunoda

 Head of Discovery Technology Dept., Research Div.

3. Utilization of Real World Data

 Dr. Nobuya Ishii

 Head of Science & Technology Intelligence Dept., Project & Lifecycle Management Unit

4. Digital Marketing Strategy

 Takato Shimauchi

 Head of Customer Solution Dept., Marketing & Sales Div.

CHUGAI DIGITAL VISION 2030

Satoko Shisai

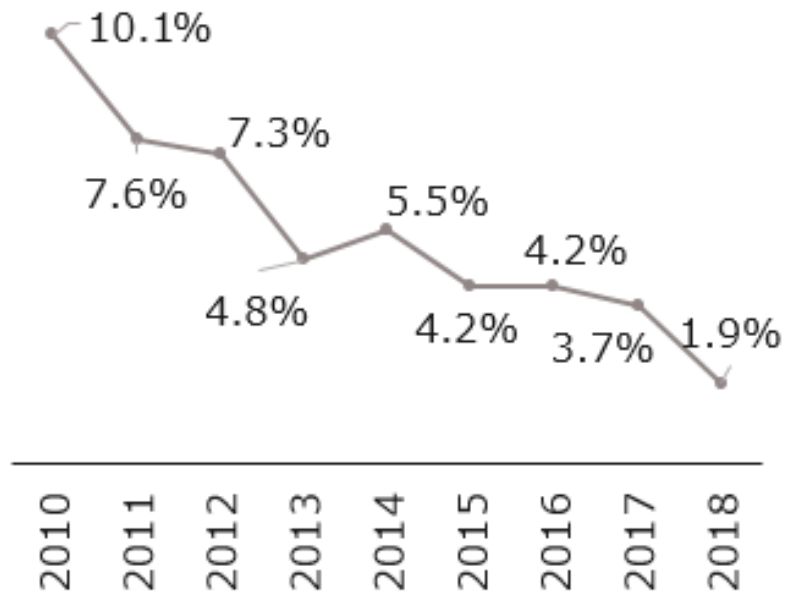Vice President, Head of Digital & IT Supervisory Div.

Agenda

1. **CHUGAI DIGITAL VISION 2030**

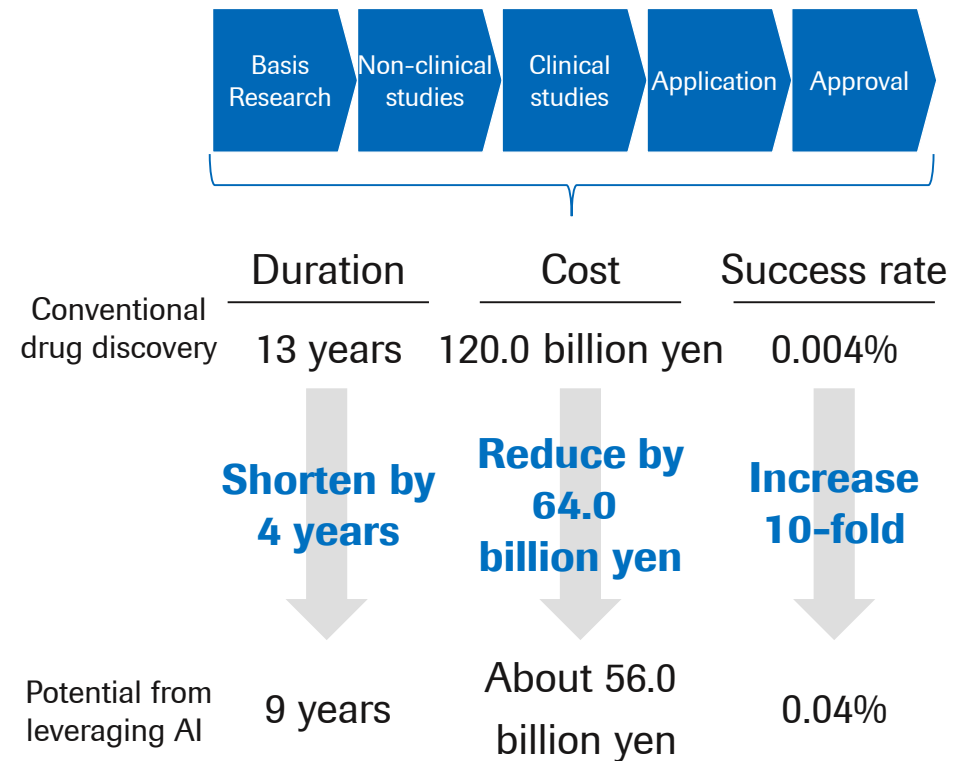2. **Summary of Digital Strategy in Chugai**

Why Does Dx Matter Now?

◆ **Pharmaceutical R&D productivity is declining on yearly basis. Drug discovery increasingly needs to adopt digital technology to tackle what has thought to be impossible**

R&D productivity of mega-pharma (IRR) [1]

Began falling in 2010, recently recording a low of 1.9%

Potential of Leveraging AI in Drug Discovery [2]

	Duration	Cost	Success rate
Conventional drug discovery	13 years	120.0 billion yen	0.004%
	Shorten by 4 years	**Reduce by 64.0 billion yen**	**Increase 10-fold**
Potential from leveraging AI	9 years	About 56.0 billion yen	0.04%

CHUGAI DIGITAL VISION 2030

Transform our business by using digital technologies to make Chugai a top innovator in the provision of society-changing healthcare solutions
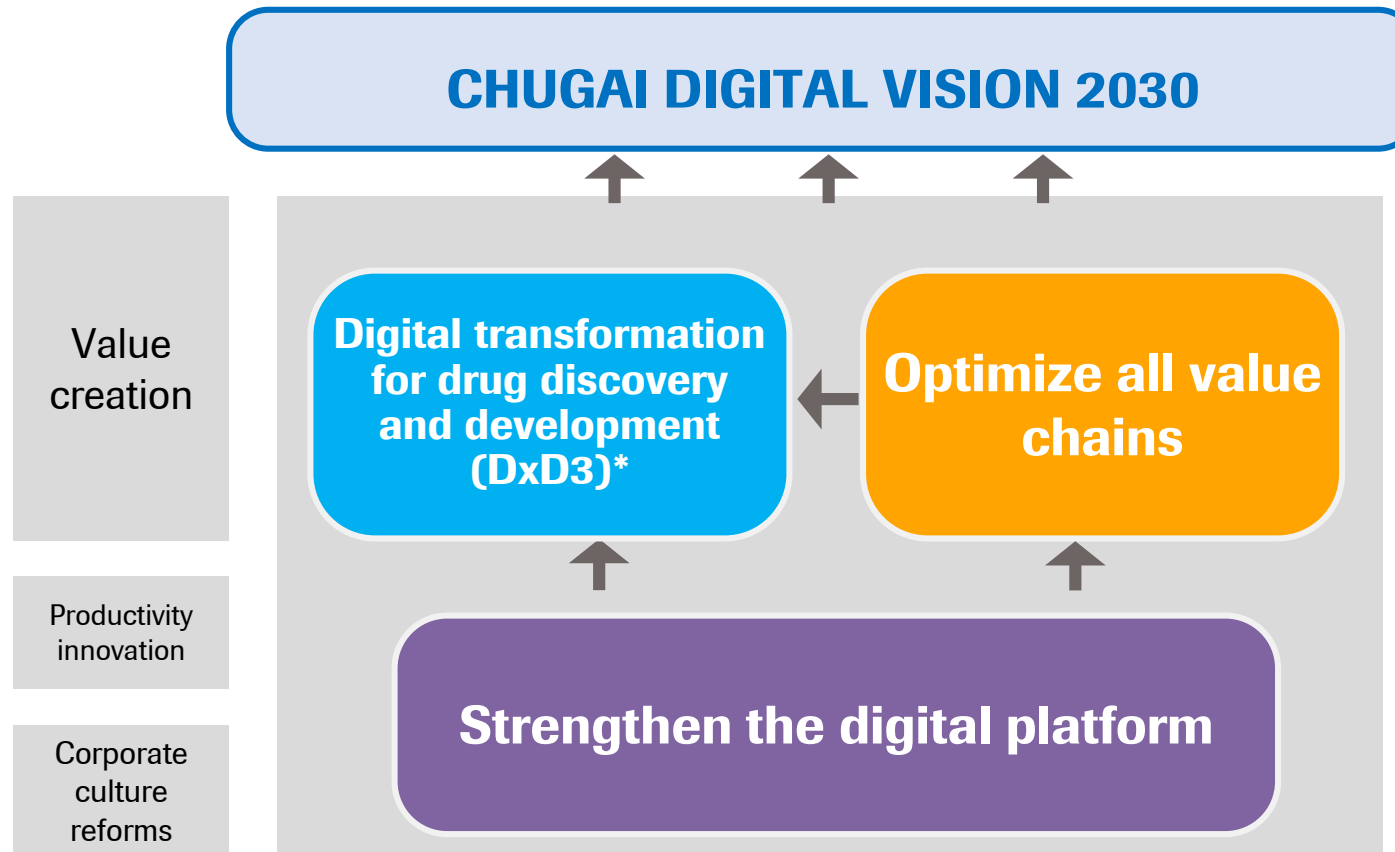
Transform our business

◆ Provide innovative drug products continuously by leveraging digital technologies.

◆ Greatly streamline all value chains.

◆ Create frameworks for providing innovative services.

◆ Change employee awareness and organizational structure and customs at Chugai.
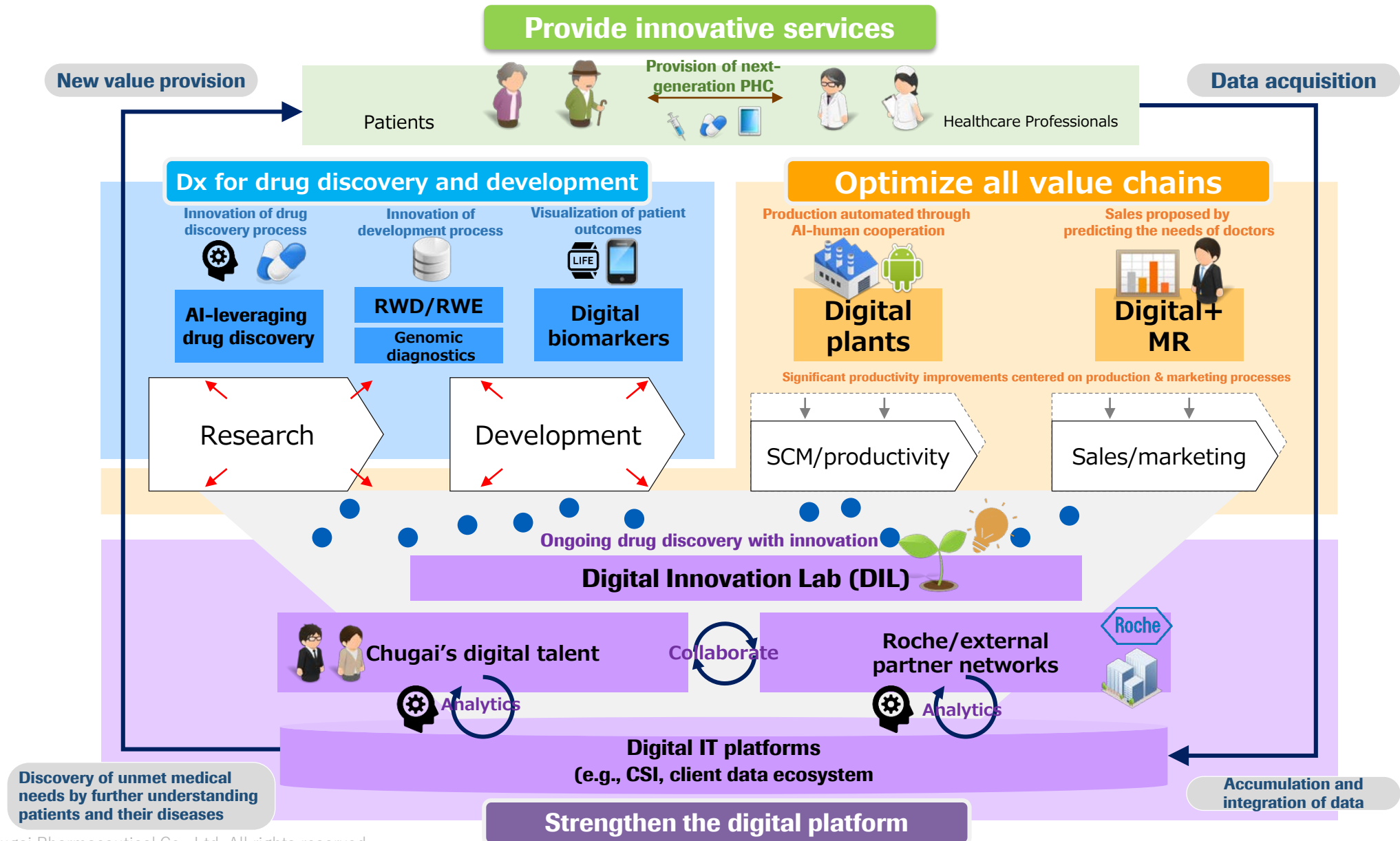
Society-changing healthcare solutions

◆ Provide optimal personalized healthcare suited to individuals.

◆ Produce high QoL throughout life through ultra-early diagnosis, prevention, and treatment.

◆ Bring about social assurance programs sustainable even in shrinking and aging societies.

Three Basic Strategies

◆ **Chugai will strengthen its digital platforms and optimize all value chains to drastically improve productivity and efficiency.**

◆ **Also transform drug discovery by leveraging AI and other cutting edge technologies to create innovative new drugs and provide society-changing healthcare solutions.**

CHUGAI DIGITAL VISION 2030

Value creation

Productivity innovation

Corporate culture reforms

Digital transformation for drug discovery and development (DxD3)*

Optimize all value chains

Strengthen the digital platform

*DxD3: Digital transformation for Drug Discovery and Development

Digital Transformation in Chugai (hypothesis)

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Roadmap of Digital Transformation

CHUGAI DIGITAL VISION 2030 Implementation

Phase 1	Phase 2	Phase 3
Change our people & cultures	Change our business	Change society

Provide innovative services

- ✓ Realize next-generation personalized healthcare

Dx for drug discovery and development (DxD3)

- ✓ Innovations in the drug discovery process and development process (Utilizing AI, RWD and others.)
- ✓ Demonstrate the new value in drugs by visualizing patient outcomes (e.g., digital biomarkers)

Optimize all value chains

- ✓ Significantly increase productivity focused on production & marketing processes

Strengthen the digital platform

- ✓ Establish strategic IT infrastructure and data utilizing strategy
- ✓ Innovate Chugai's corporate culture

2021   2024   2030
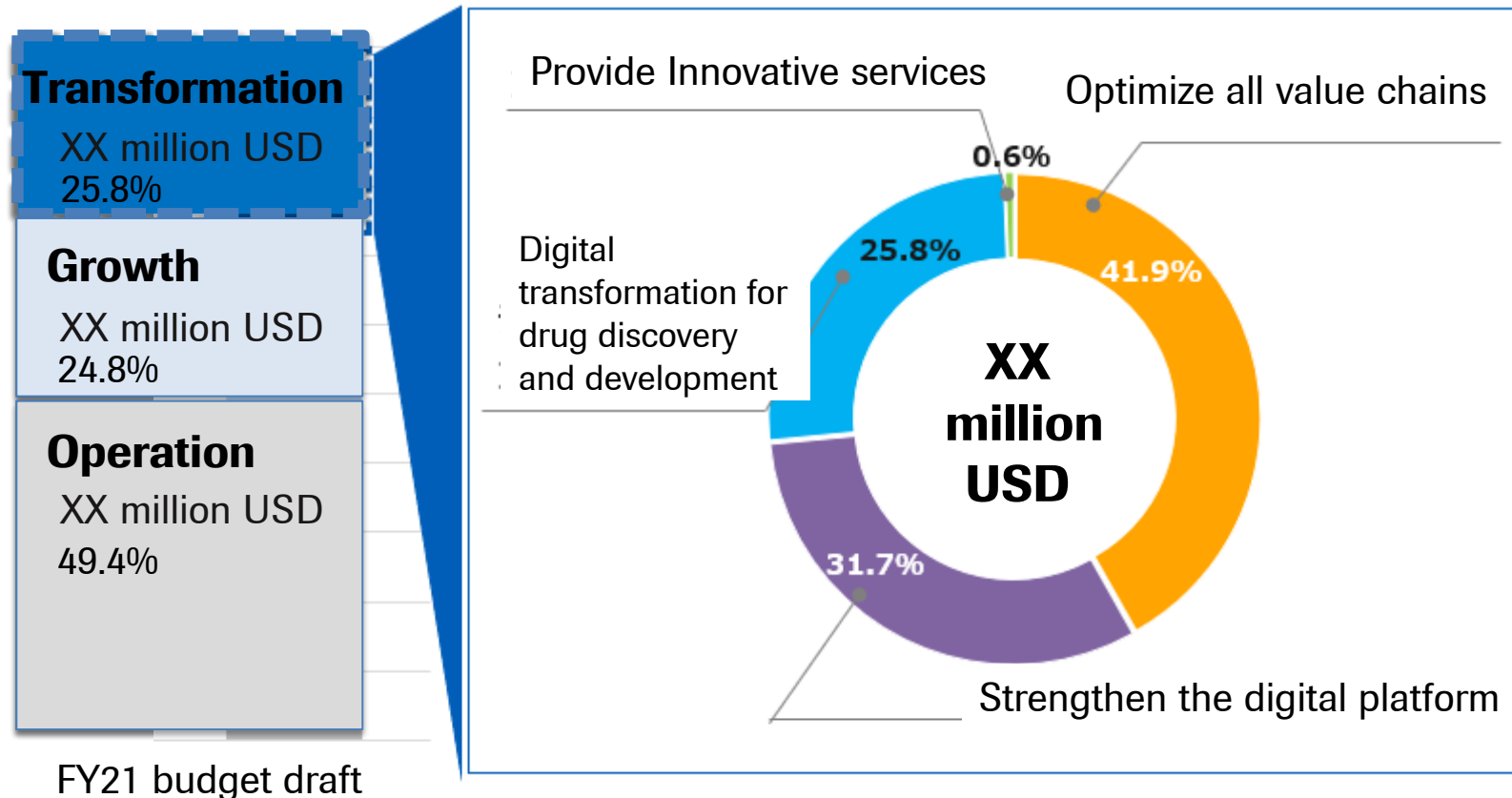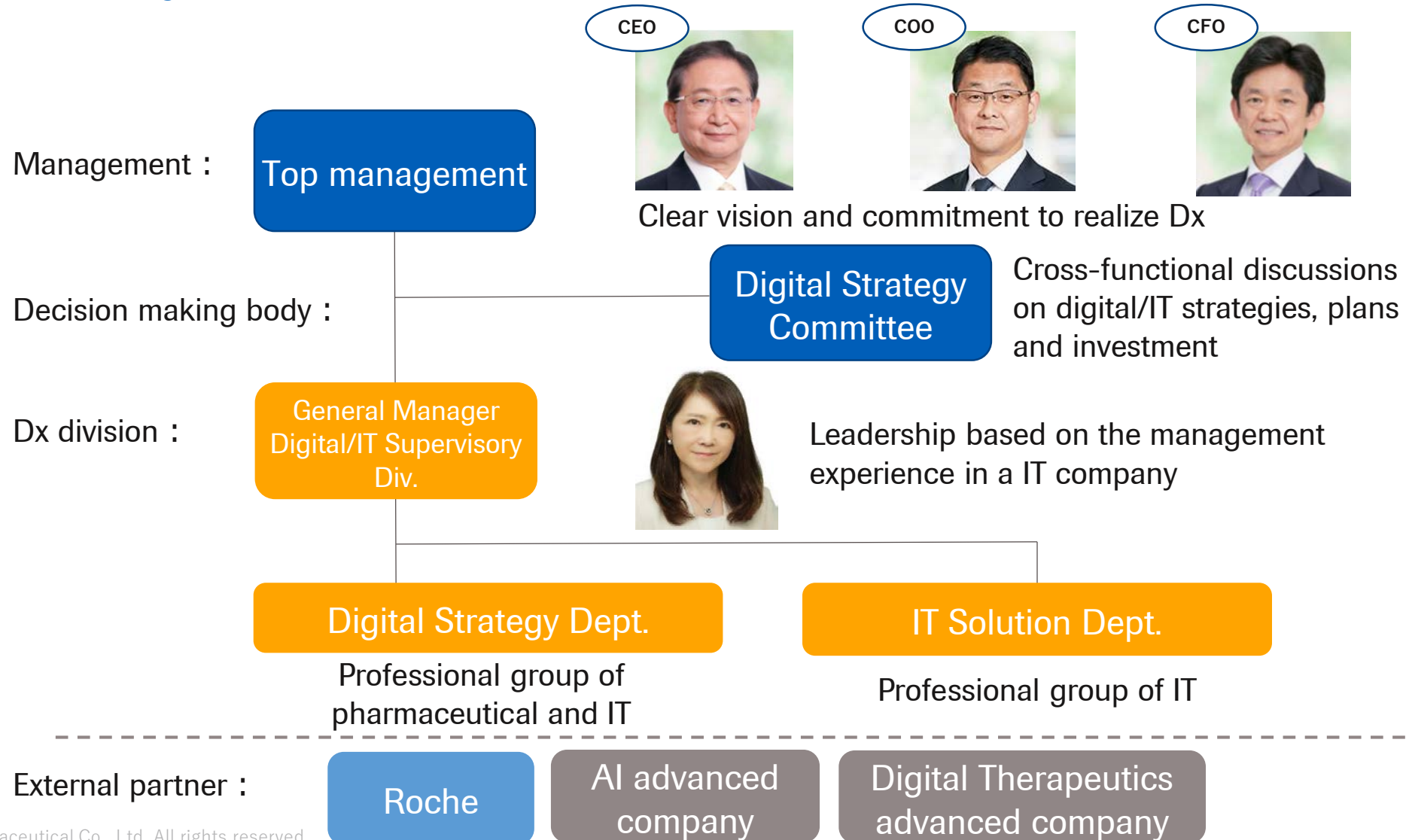
Visualize and Optimize Digital/IT Investment

◆ **Manage company-wide portfolio of digital projects and centralize management of investment in the digital / IT budget**

◆ **Formulate the investment plan by dividing the investment into "Transformation ", "Growth" and "Operation"**

◆ **Secure the annual constant budget as digital PoC cost**

Breakdown of FY21 Digital/IT budget draft [Image]

Transformation
XX million USD
25.8%

Growth
XX million USD
24.8%

Operation
XX million USD
49.4%

FY21 budget draft

Provide Innovative services

Optimize all value chains

Digital transformation for drug discovery and development

0.6%

25.8%

41.9%

XX million USD

31.7%

Strengthen the digital platform

PoC: Proof of Concept

Structure of Digital Strategy Promotion

◆ **The fusion of "top management commitment" and "the power of diverse top talents and top players" is the key to realize Dx**

Management：
Top management

CEO COO CFO

Clear vision and commitment to realize Dx

Decision making body：
Digital Strategy Committee

Cross-functional discussions on digital/IT strategies, plans and investment

Dx division：
General Manager Digital/IT Supervisory Div.

Leadership based on the management experience in a IT company

Digital Strategy Dept.

Professional group of pharmaceutical and IT

IT Solution Dept.

Professional group of IT

External partner：
Roche **AI advanced company** **Digital Therapeutics advanced company**

Agenda

1. CHUGAI DIGITAL VISION 2030

2. **Summary of Digital Strategy in Chugai**

Digital Transformation for Drug Discovery and Development　(DxD3)

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Details to follow	**Details to follow**	
AI-leveraging drug discovery	**Utilizing Real World Data/Real World Evidence**	**Digital Biomarkers**

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What are Digital Biomarkers (dBM)?

◆ **Physiological data obtained by digital devices. Expected to be useful for understanding the condition of patients and predicting the onset of diseases through data that could not be obtained before.**

Wearable	Mobile	Others

Physiol Meas . 2020 Jun 19;41(5):054002.

Image copyright: Neuralink

Apple Watch® · Floodlight® by Roche · Neuralink®

Continuous acquisition of biological data (blood pressure, pulse, electrocardiogram, etc.) using skin electrical activity sensors	Patients themselves input their lifestyle, physical condition and symptoms (ePRO: electronic patient-reported outcomes)	Biometric data is measured by the implant, and a smart speaker captures and converts the voice into data.

Specific Initiatives of Chugai

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Endometriosis

Objective and continuous evaluation of endometriosis-related pain with biological data from wearable devices and AI-based platform

- OPINE study: Observational Study (NCT04318275)

- Device: E4®

- Acquired Pain Index (analyzed by AI from dermal electric activity, heart rate, and breath rate) and numerical rating scale (NRS)

- Partnership with Biofourmis

https://www.empatica.com/research/e4/
(Access: 15:05 JST, 14 Sep. 2020)

Hemophilia

Evaluation of the relevance between physical activity and hemorrhagic events reported through ePRO, and biological data from wearable devices
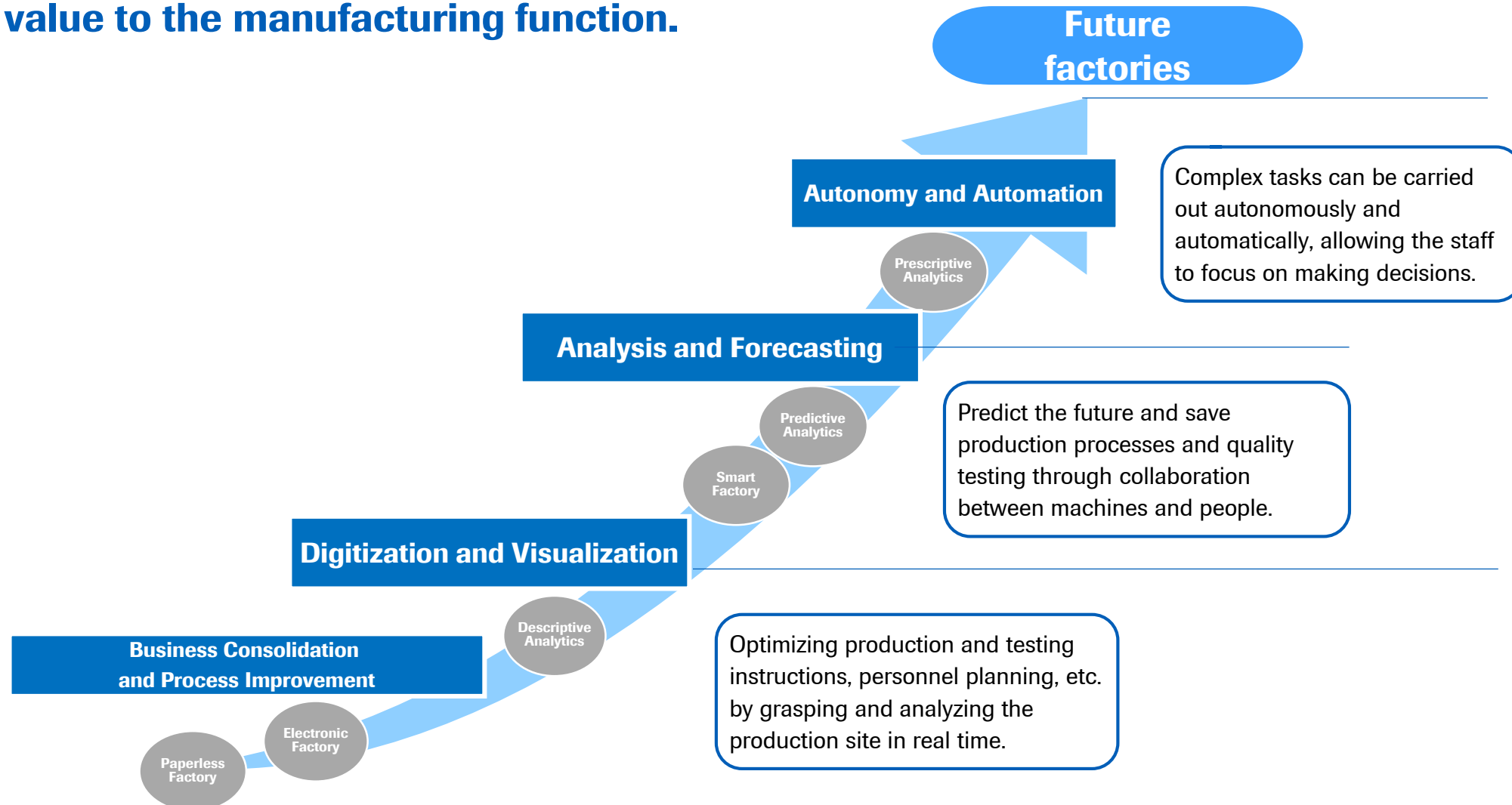
- TSUBASA Study: Observational Study(UMIN000037448)

- Device : Insightwatch (Actigraph)

- ePRO: TSUBASA study app. (Welby)

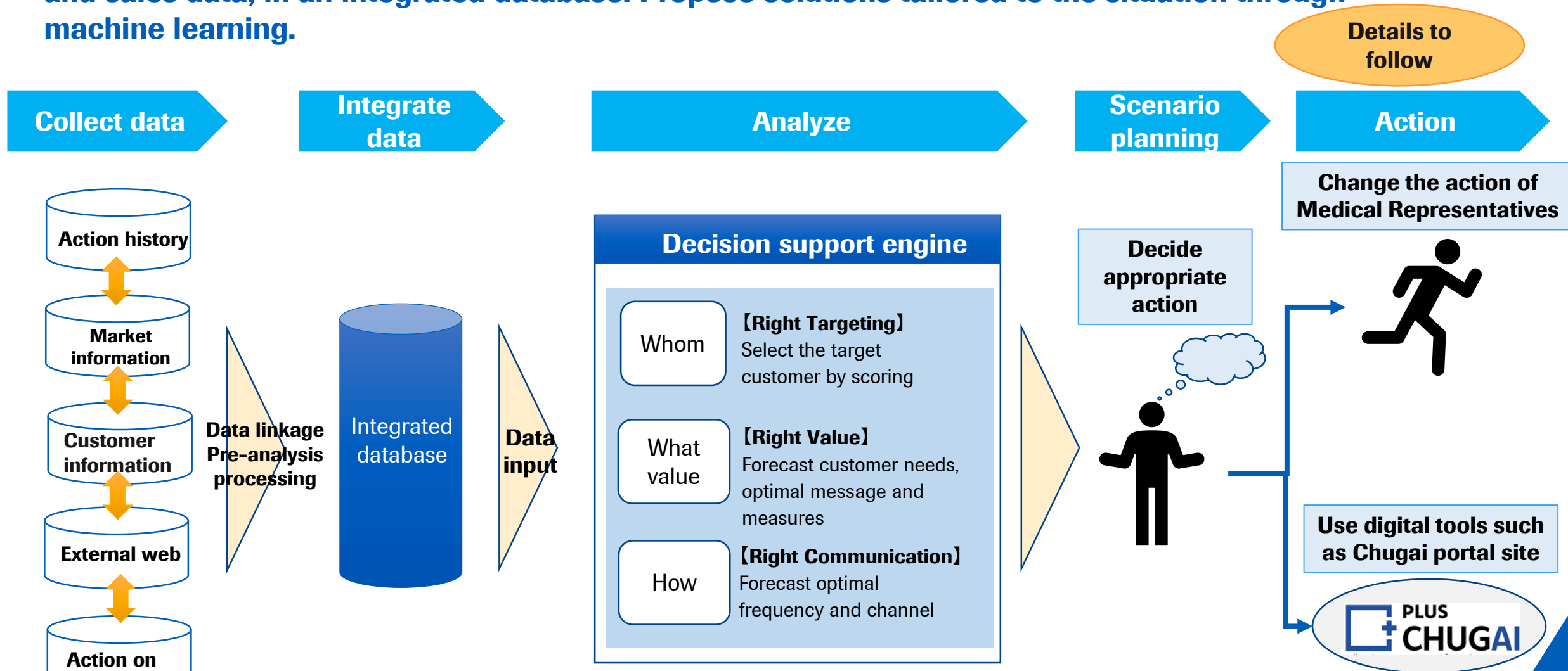ePRO: Electronic Patient Reported Outcomes

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Optimize Value Chains: Initiative to Realize a Future Factory

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◆ **Improve operational efficiency and reliability of the manufacturing function through digital technology, thereby increasing the mobility of human resources and adding value to the manufacturing function.**
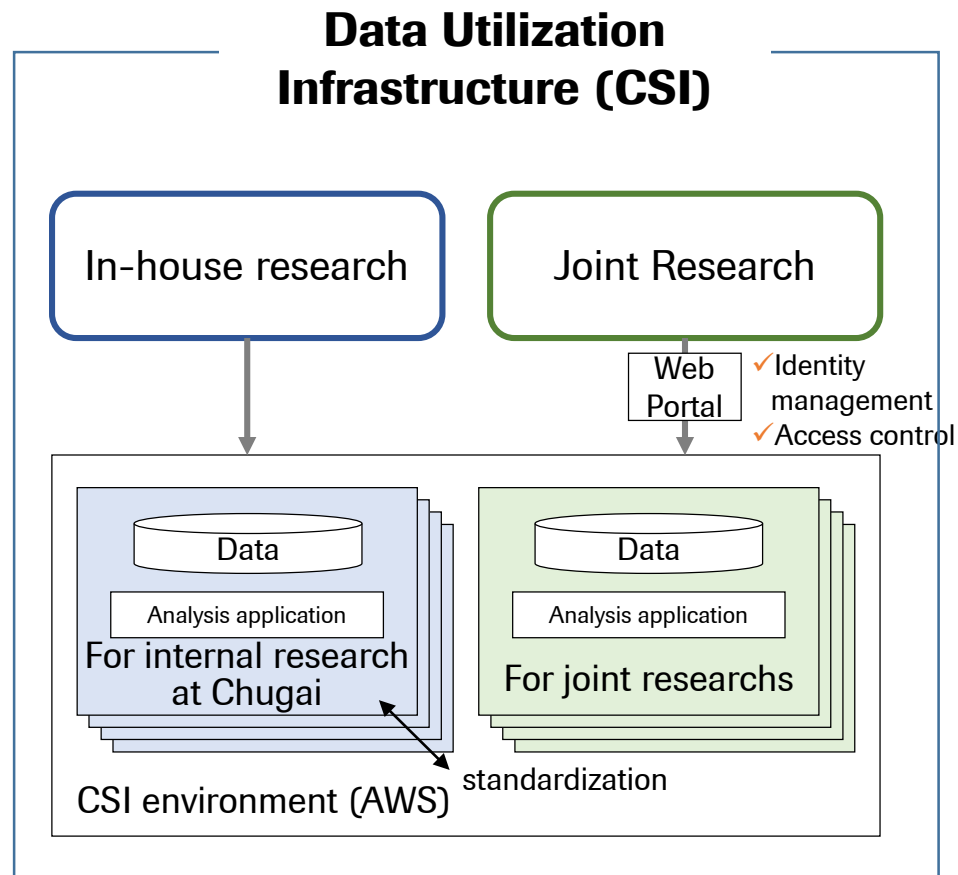
Future factories

Autonomy and Automation

Prescriptive Analytics

Complex tasks can be carried out autonomously and automatically, allowing the staff to focus on making decisions.

Analysis and Forecasting

Predictive Analytics

Smart Factory

Predict the future and save production processes and quality testing through collaboration between machines and people.

Digitization and Visualization

Descriptive Analytics

Business Consolidation and Process Improvement

Electronic Factory

Paperless Factory

Optimizing production and testing instructions, personnel planning, etc. by grasping and analyzing the production site in real time.

Optimize Value Chains: Digital Marketing Initiatives

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◆ **Accumulate a variety of data generated in daily sales activities, such as daily sales reports and sales data, in an integrated database. Propose solutions tailored to the situation through machine learning.**

Details to follow

| Collect data | Integrate data | Analyze | Scenario planning | Action |

Change the action of Medical Representatives

Decide appropriate action

Action history

Market information

Customer information

External web

Action on web page

Data linkage Pre-analysis processing

Integrated database

Data input

Decision support engine

| Whom | 【Right Targeting】 Select the target customer by scoring |

| What value | 【Right Value】 Forecast customer needs, optimal message and measures |

| How | 【Right Communication】 Forecast optimal frequency and channel |

Use digital tools such as Chugai portal site

PLUS CHUGAI

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CSI (Chugai Scientific Infrastructure)

◆ **IT platform for securely using, moving and storing large amounts of data, with the aim of promoting company-wide data utilization.**

Data Utilization Infrastructure (CSI)

In-house research

Joint Research

Web Portal
- ✓ Identity management
- ✓ Access control

Data
Analysis application
For internal research at Chugai

Data
Analysis application
For joint researchs

standardization

CSI environment (AWS)

What CSI Can Realize

- Promoting cross-functional use of internal data
- Providing a research environment that facilitates rapid development of joint research projects with academia and hospitals
- Reduction of environmental construction costs and time by sharing and automating operations
- Secure handling of high-security data, such as genomic data
- Reduction of security risks such as information leakage and external attacks

Acceleration of Digital Transformation (1)

◆ **Connecting digital to employees and outside the company through various measures**

Appointment of digital leaders	Holding Digital Summit	Opening of web page

- ➢ Appointed digital leaders as an interface for the digital aspects of each business unit, aiming to optimize digital throughout the company

- ➢ Held the Digital Summit as a forum for sharing company-wide Dx case studies and creating new initiatives. 300+ employees participated

- ➢ Opened a web page for external audiences. The catchphrase is "Changing the future of healthcare with digital technology"

Acceleration of Digital Transformation (2)

◆ **Connecting digital to employees and outside the company through various measures**

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Communicating role models	Use of note	DigiTube

Digital x Drug discovery
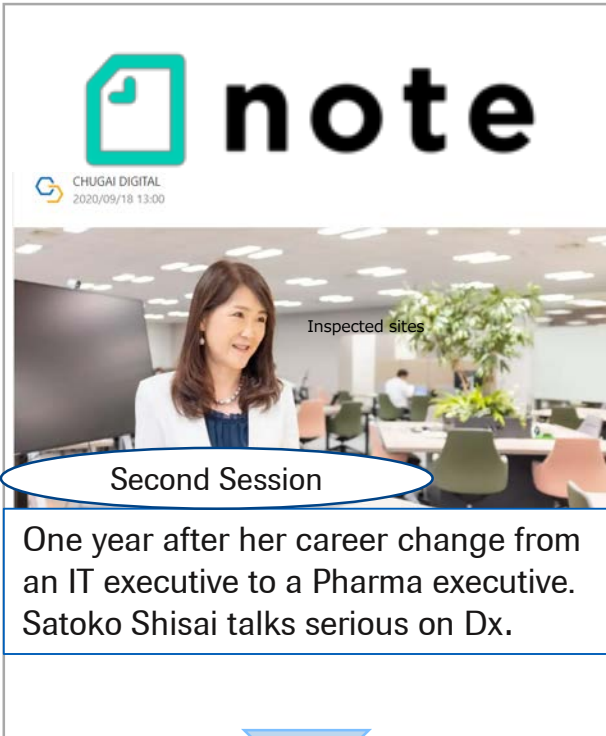
Chugai has formulated a major strategy, CHUGAI DIGITAL VISION 2030, aiming to become a top innovator in providing healthcare solutions that innovate business and change society through digital technology.
Here, three members promoting digitalization at Chugai talk about the excitement and opportunities.

CHUGAI DIGITAL
2020/09/18 13:00

Inspected sites

Second Session

One year after her career change from an IT executive to a Pharma executive. Satoko Shisai talks serious on Dx.

DigiTube - to get digital inspiration and find business partners

Digital corporate briefing, "DigiTube", which is held remotely every other Friday afternoon, is open to everyone

+16

➤ Focusing on the members promoting digitalization within the company, share their activities within and beyond the company

➤ Starting on August 25, 2020
➤ Communicate the voice of employees to raise interest and awareness on CHUGAI DIGITAL
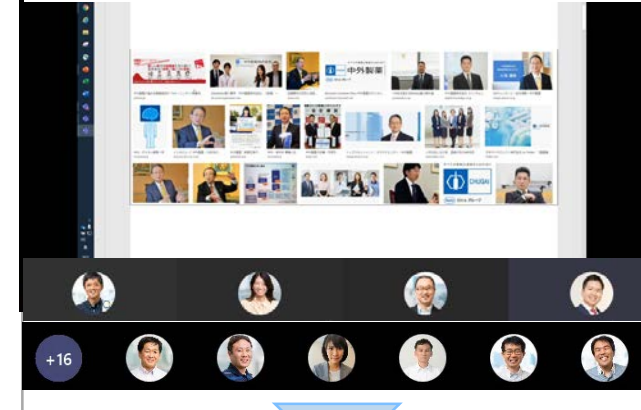
➤ More than 20 digital companies' technical presentations, titled "DigiTube," have been distributed company-wide since March 2020

Strengthen External Collaboration and Actively Disseminate Press Releases

CHUGAI DIGITAL

◆ **Stimulate employees by learning about their activities through external media**

◆ **Disseminate in-house Dx activities to the outside and build win-win relationships with partner companies**

Example of press releases from Chugai

Introduced cloud service by **Amazon Web Service** for data utilizing infrastructure "Chugai Scientific Infrastructure （CSI）"

Aiming to improve the efficiency of the document creation process, such as creating clinical trial-related documents from the clinical trial protocol, we have completed the demonstration of an AI-based clinical trial efficiency solution of **NTT DATA**

Collaboration with Biofourmis

Developing an objective assessment of pain for endometriosis using digital solution of Biofourmis

https://www.empatica.com/research/e4/
(Access: 15:05 JST, 14 Sep. 2020)

Text mining
Collaboration with FRONTEO

Using natural language processing technologies to search information relevant to researchers' hypotheses

Collaboration with PFN

Concluded a comprehensive partnership agreement to promote multiple projects related to new drug creation using PFN's deep learning technology
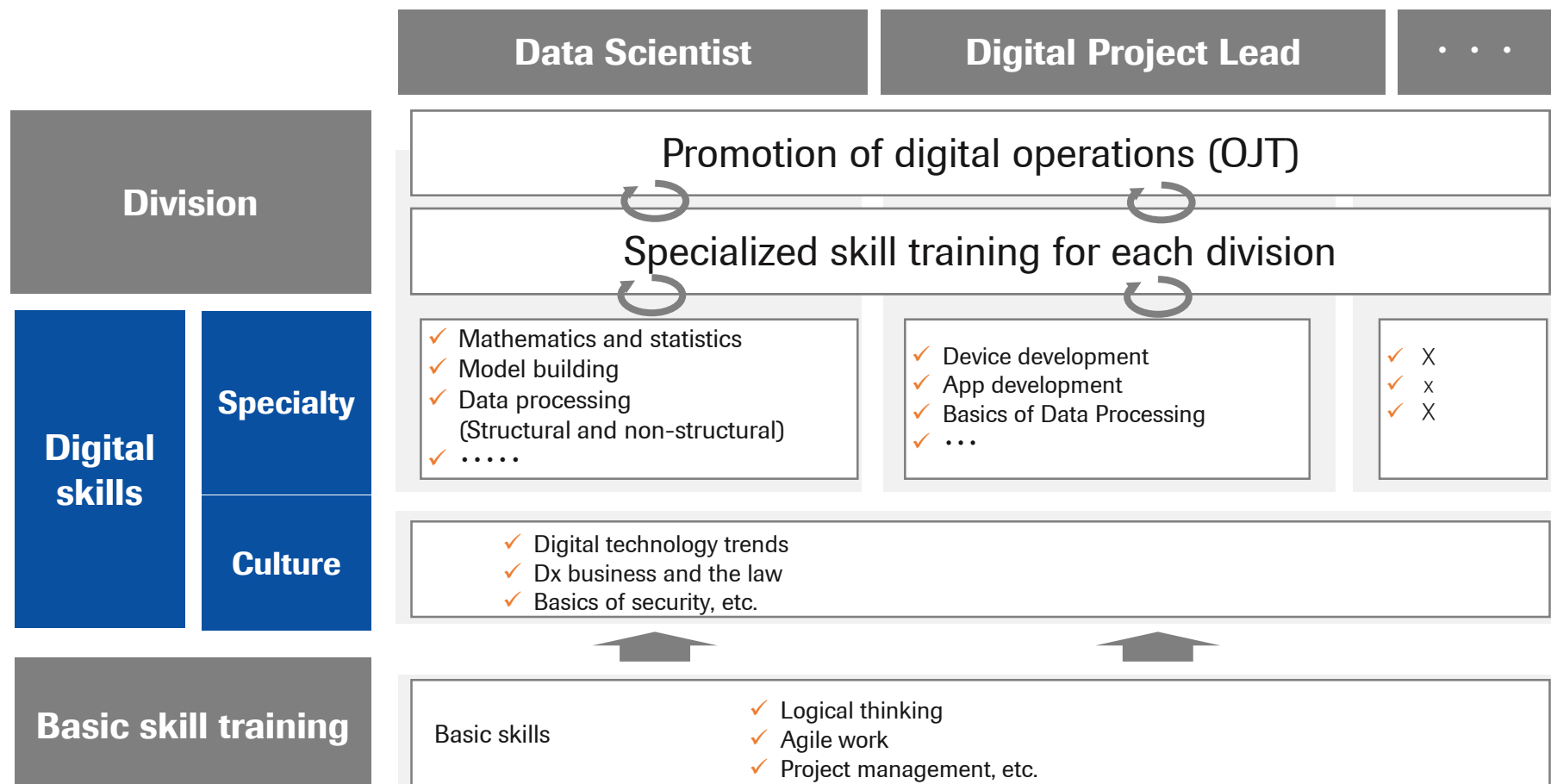
Collaboration with Works Mobile Japan

2,400 Chugai employees including medical representatives started to use **LINE WORKS**, which is a communication app., for interactive communication with medical professionals
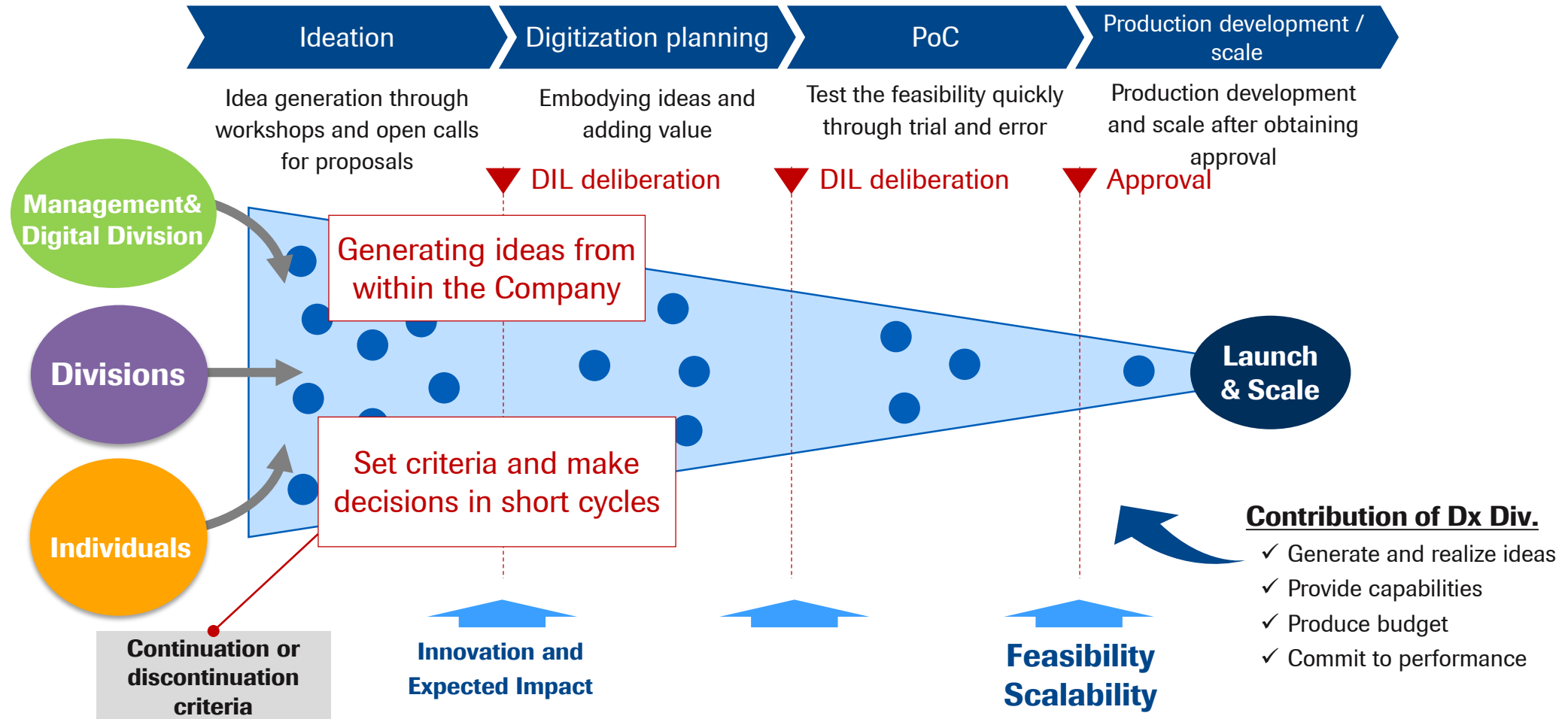
Digital Human Assets Development Initiatives

◆ **Provide structured training programs based on the digital skill level of employees**

CHUGAI
DIGITAL

Overview of initiatives on the development of specific digital human assets

Data Scientist	Digital Project Lead	· · ·

Division

Promotion of digital operations (OJT)

Specialized skill training for each division

Digital skills

Specialty

✓ Mathematics and statistics ✓ Model building ✓ Data processing (Structural and non-structural) ✓ · · · · ·	✓ Device development ✓ App development ✓ Basics of Data Processing ✓ · · ·	✓ X ✓ x ✓ X

Culture

✓ Digital technology trends
✓ Dx business and the law
✓ Basics of security, etc.

Basic skill training

Basic skills
✓ Logical thinking
✓ Agile work
✓ Project management, etc.

Accelerate Transformation with Digital Innovation Lab (DIL)

◆ **Incubate bottom-up ideas to accelerate organizational Dx skills and transform into an agile culture**

Ideation	Digitization planning	PoC	Production development / scale
Idea generation through workshops and open calls for proposals	Embodying ideas and adding value	Test the feasibility quickly through trial and error	Production development and scale after obtaining approval

▼ DIL deliberation   ▼ DIL deliberation   ▼ Approval

Management& Digital Division

Generating ideas from within the Company

Divisions

Set criteria and make decisions in short cycles

Individuals

Launch & Scale

Continuation or discontinuation criteria

Innovation and Expected Impact

Feasibility Scalability

Contribution of Dx Div.
- ✓ Generate and realize ideas
- ✓ Provide capabilities
- ✓ Produce budget
- ✓ Commit to performance

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Maximum Utilization of Roche Resources

◆ **Strategy alignment through regular management meeting**

◆ **Conclude fundamental agreement for interactive use of IT system and resource between Roche and Chugai**

◆ **Develop human resource and create the connection through continuous human resource exchange program**

State of the regular management meeting with IT division of Roche

Frame of fundamental agreement for interactive use of IT

IT FRAME AGREEMENT
FOUNDATION AGREEMENT THAT SETS FORTH LEGAL TERMS, CONDITIONS AND RESPONSIBILITIES OF THE PARTIES TO ENABLE IT SYSTEMS AND SERVICES COLLABORATION

IT SYSTEMS   IT SERVICES

IT SYSTEM USE STATEMENT

– WORK ORDER –

_SCOPE
_SYSTEM INFO
_USER GROUPS
_OPERATIONS MODEL
_COMPENSATION
_LICENSE MANAGEMENT
_CONTENT SHARING
_ACCESS AGREEMENT
_CONFIDENTIALITY

IT SERVICE USE STATEMENT

– WORK ORDER –

_SCOPE
_SERVICE MODEL
_USER GROUPS
_FUNDING TERMS
_VENDOR MANAGEMENT
_ROCHE SME / ISO
_INTELECTUAL PROPERTY

2019.09.16 JITC

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Selected DX Stock 2020

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◆ **Chugai was selected as the only company of DX Stock 2020 in the pharmaceutical industry by the Ministry of Economy, Trade and Industry (METI) and the Tokyo Stock Exchange (TSE)**

◆ **The "CHUGAI DIGITAL VISION 2030" was set forth under the strong commitment of management, and a wide range of initiatives such as drug discovery innovation, culture transformation, and collaboration with external companies was highly recognized.**

DX銘柄2020
Digital Transformation

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Sustainable Growth and Development by Creation of Shared Value

◆ **Accelerate innovation by Dx and develop continuously with society**
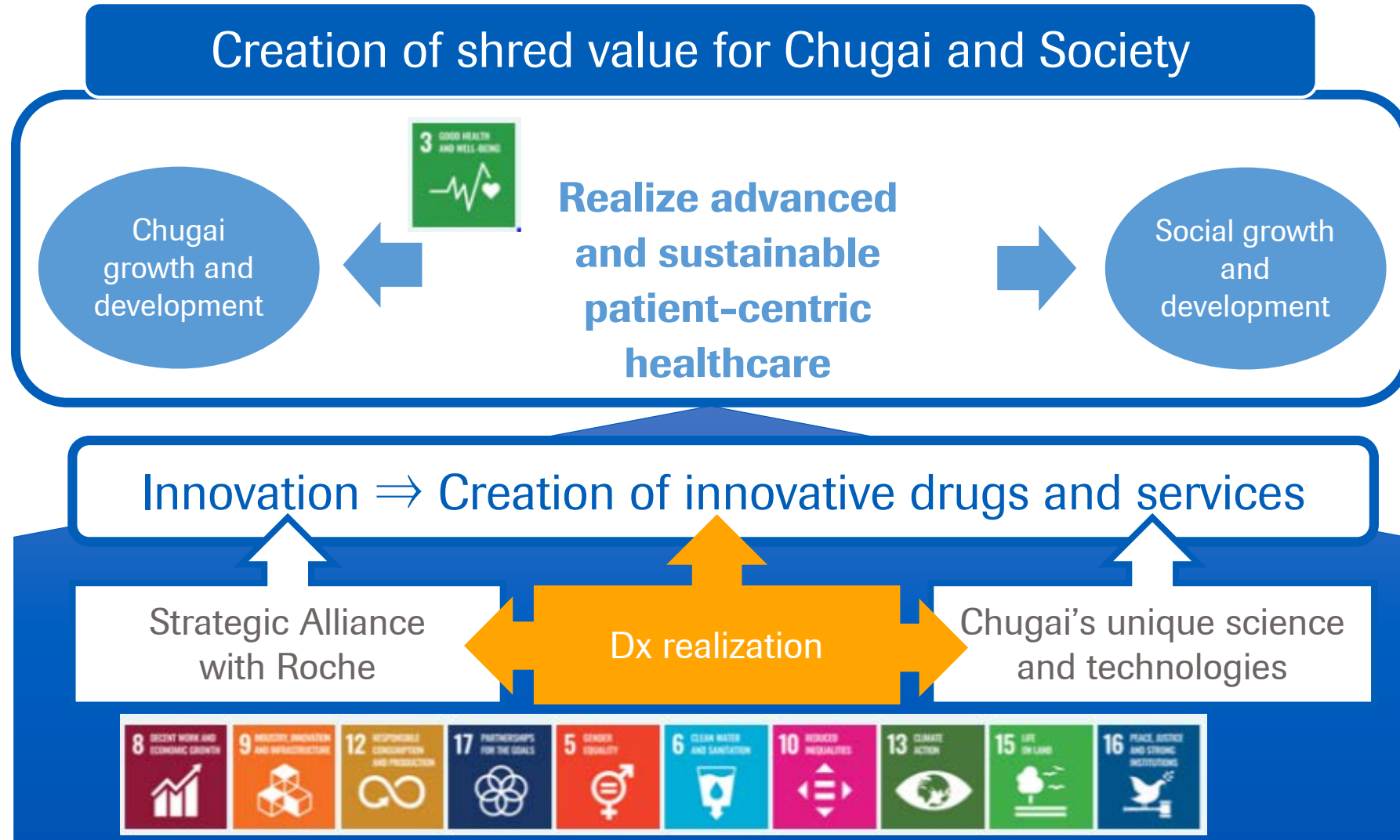
Creation of shred value for Chugai and Society

Chugai growth and development

Realize advanced and sustainable patient-centric healthcare

Social growth and development

Innovation ⇒ Creation of innovative drugs and services

Strategic Alliance with Roche

Dx realization

Chugai's unique science and technologies

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Innovation in the Drug Discovery Process Using AI

Dr. Hiroyuki Tsunoda

Head of Discovery Technology Dept., Research Div.

CHUGAI DIGITAL

DxD3

Digital Transformation for Drug Discovery and Development

AI-powered Drug Discovery	Digital Biomarker initiatives	Utilization of RWD/RWE

Discovery Processes and Platforms of Antibody Therapeutics

Both Chugai's proprietary antibody engineering technologies and the antibody discovery platforms are our major strength

Process flow:

Target validation → Lead antibody Identification (LI) → Lead antibody Optimization (LO) → Clinical candidate Selection (CS) → CMC and IND preparation → IND

- ✓ De-immunization
- ✓ Multidimensional antibody optimization system (COSMO)
- ✓ Rabbit B cell cloning
- ✓ Designed antibody phage library
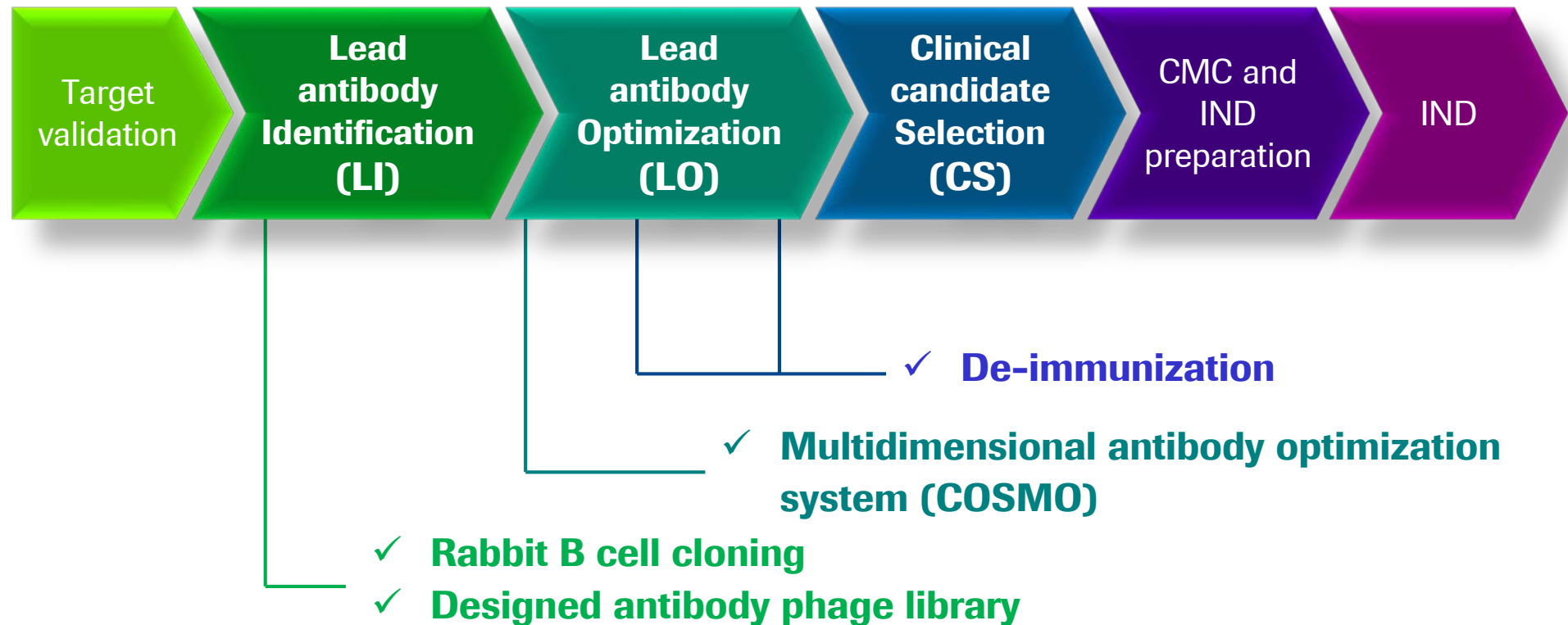
Chugai's four competitive platforms are
at the core of its competitive advantage in antibody drug discovery

MALEXA: <u>Ma</u>chine <u>Le</u>arning <u>x</u> <u>A</u>ntibody

Antibody Drug Discovery Process and Application of MALEXA
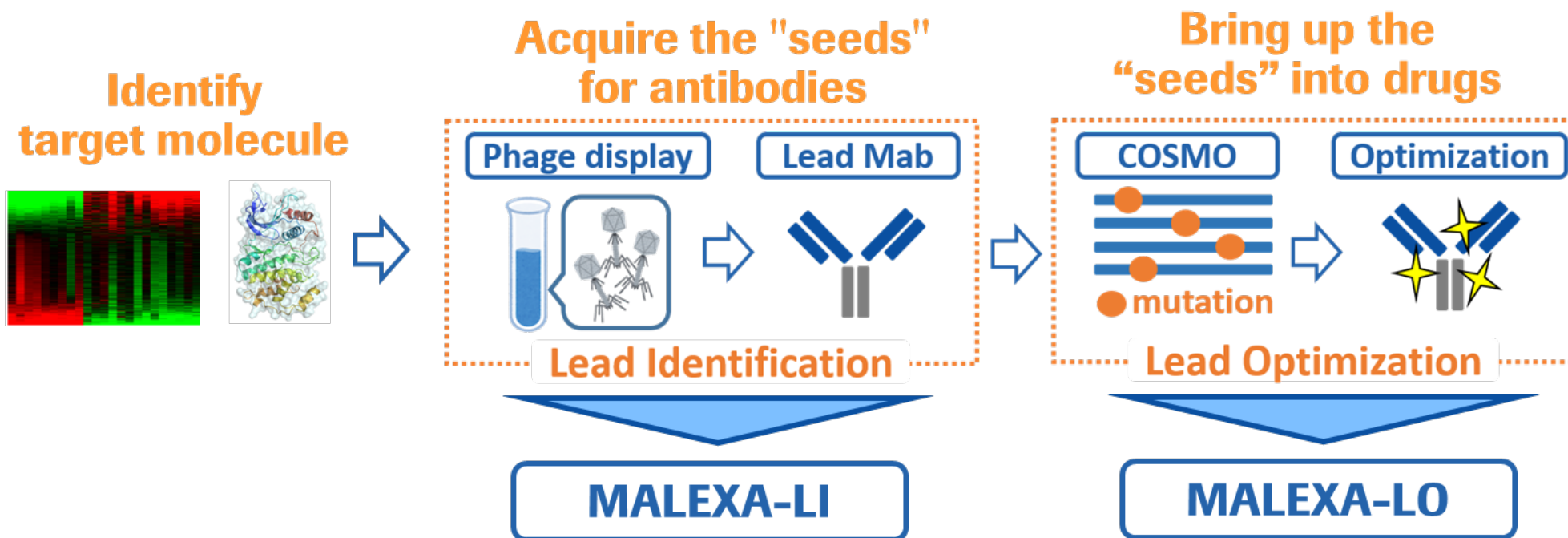
Need to design and develop process-specific machine learning algorithms

Acquiring Lead Antibodies Using MALEXA (MALEXA-LI)

Application to the lead antibody acquisition process

Enrichment of binding molecules from the antibody library
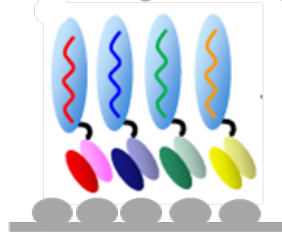
Analysis of enriched antibody molecules using NGS

NGS: next generation sequencing
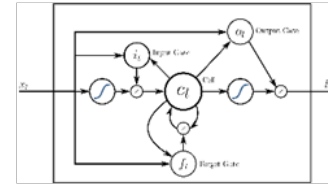
Pattern learning | Generation | Proposal

Machine learning

Antibody Production, Measurement and Evaluation

Successful acquisition of antibodies with strong binding affinity in multiple projects

Comparison of Binding affinity

Binding affinity

Strong

MALEXA | Normal selection

Characterize large amounts of data to find the right sequence for the lead antibody

Multidimensional Antibody Optimization System

COSMO: COmprehensive **S**ubstitution for **M**ultidimensional **O**ptimization

Approximately 1,300 different antibodies (approximately 70 amino acids of antigen binding sites × 19 kinds of amino acid) are prepared per a lead antibody and evaluated multidimensionally

- ✓ **HTP affinity measurement**
  ~2000 Run/Week
- ✓ **Multidimensional evaluation**
  (i.e. stability, solubility, immunogenicity, non-specific binding)
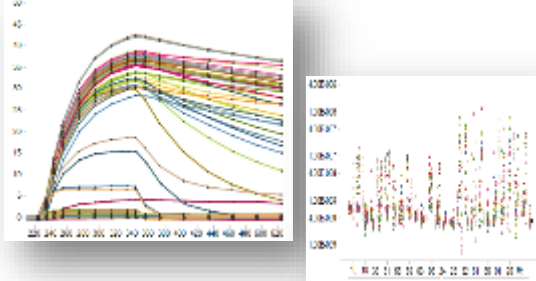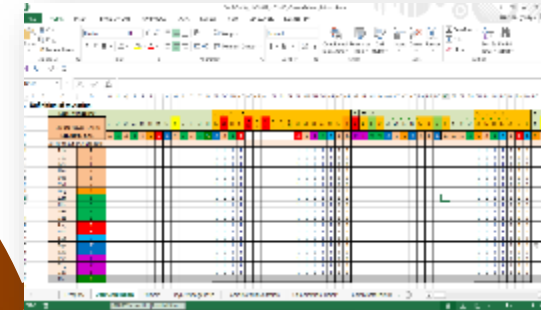
- ✓ **HTP antibody purification**
  ~1500 Abs/Day
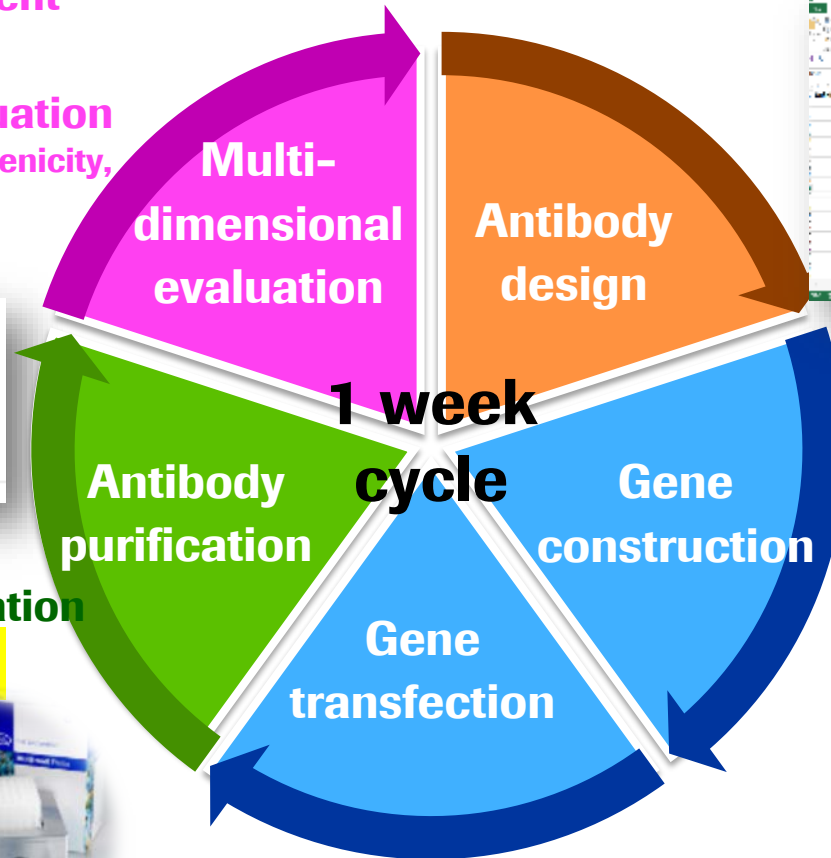
- ✓ **HTP Ab construction and transfection**
  ~3000 Abs/week

1 week cycle

- Multi-dimensional evaluation
- Antibody design
- Gene construction
- Gene transfection
- Antibody purification

Source : Chugai Pharmaceutical Co., Ltd.

HTP: high throughput

Challenges in Lead Optimization

Antibody lead optimization: Modifying amino acids in antibody binding region to develop optimal antibodies

Challenges

Researchers repeatedly produce and evaluate antibodies with different amino acid replacements. However, **the combinations of replacements are limited within the scope of the acquired data**

Lead Mab → COSMO → Combination → Best seq.

● mutation

Multidimensional profile data of antibody

KD   Koff   expression
polymerization   stability

Researcher
Antibody
mutation

Image
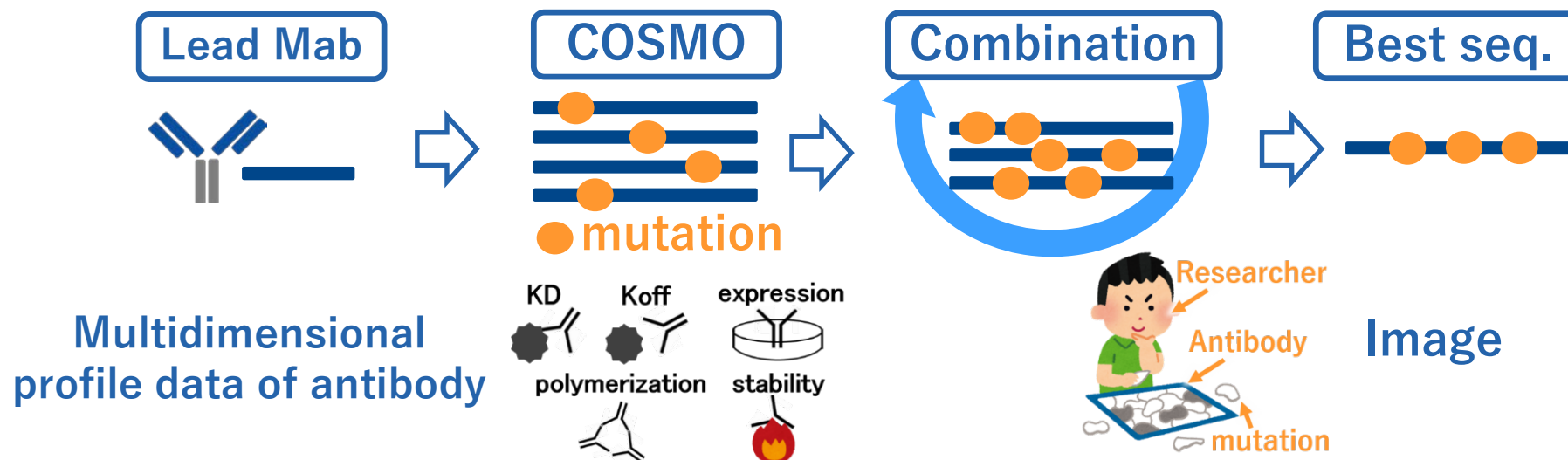
Antibodies with suitable properties and activation should be acquired from a large amount of data

Development of Machine Learning Workflow and Performance of MALEXA-LO

Data from COSMO

Predictive modeling

Sequence Generation

Proposal

Assessment

Experiment

Computer

Experiment
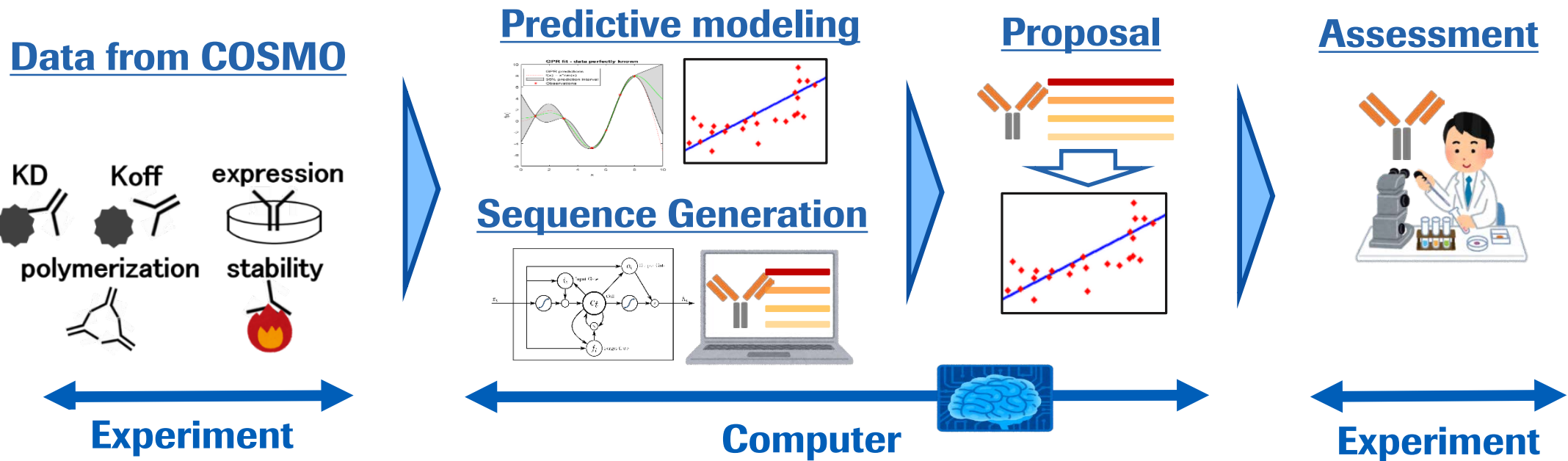
By applying MALEXA-LO, the optimal antibody sequence group can be proposed based on various elements such as binding affinity, pH dependency, physical properties, etc.

Strong binding

Dissociation at low PH

Binding affinity

Before application

After application of MALEXA
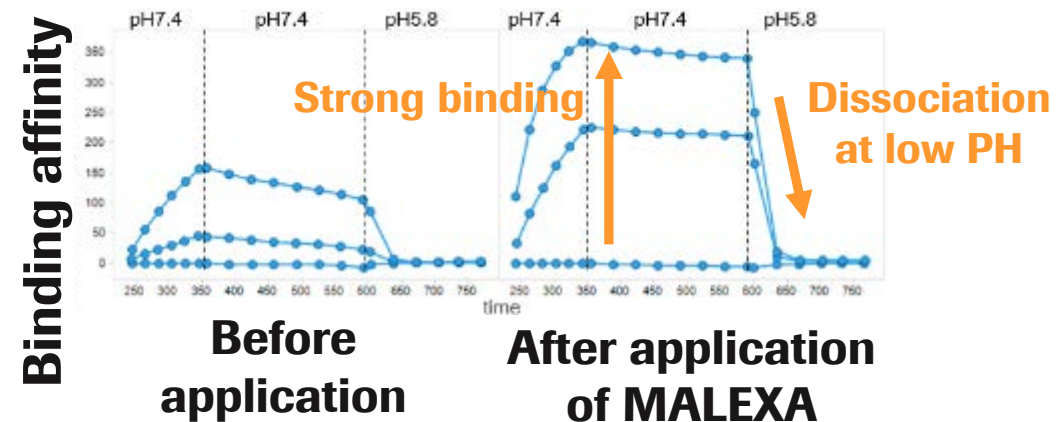
Machine Learning Workflow: Sequence Generation

The variation of amino acid sequences of an antibody is enormous

Generate computer-analyzed sequences using a generative model

Analyzed data — 1300 sequences

All combinations — Over 10^{22} (10^{89} seqs.)

Computational limits — 10^{10}

Generative model — 10^8
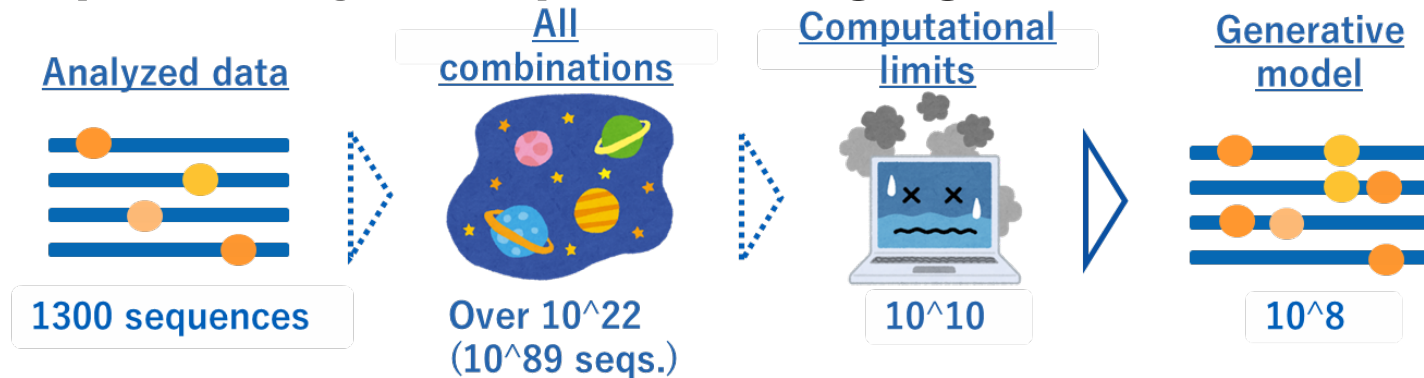
LSTM (Long Short Term Memory) : Learning the dependency of words in a statement

Training sequence
I eat curry
I play the piano.
I ride a car.
I ride a bicycle.

Learning model
I — eat / play / ride — curry / the piano / a car / a bicycle
Random
LSTM
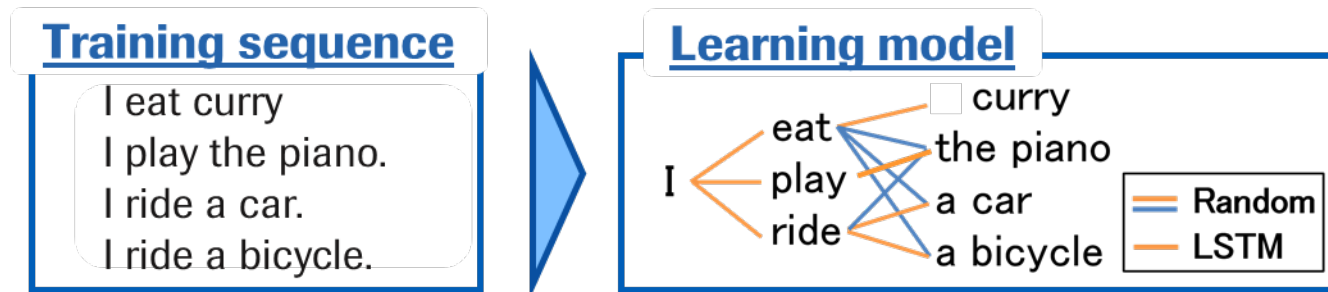
"Word and Sentence" applied to "Amino acid and Antibody sequences"

With LSTM, sequences similar to the data can be sampled

Accelerate Antibody Discovery Processes through the Application of MALEXA

Target validation	Lead antibody Identification (LI)	Lead antibody Optimization (LO)	Clinical candidate Selection (CS)	CMC and IND preparation	IND

MALEXA under consideration ⇒ **De-immunization**

MALEXA-LO – ✓ **Multidimensional antibody optimization system (COSMO)**

MALEXA-LI

✓ **Rabbit B cell cloning**
✓ **Designed antibody phage library**
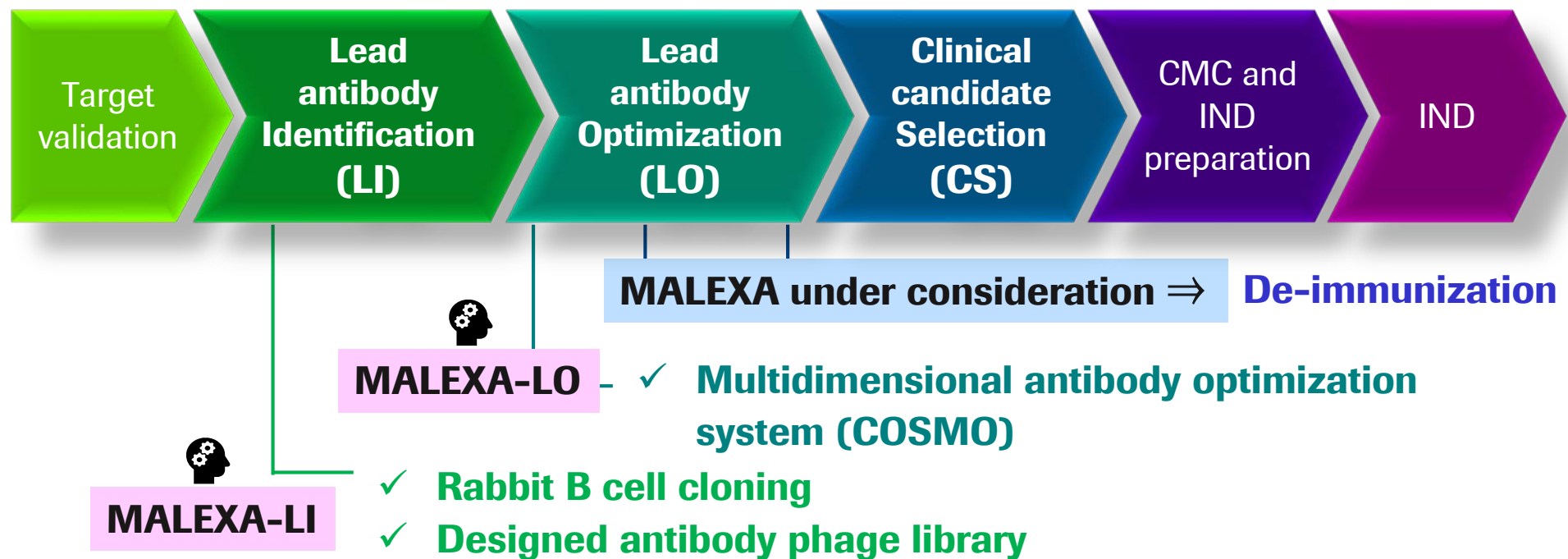
✓ **Application of MALEXA for immunogenicity reduction is under consideration to further streamline the entire process**

✓ **Initiatives have begun to apply machine learning technology to the mid-sized molecule drug discovery platform**

AI Utilization for Image Analysis in Drug Discovery Research
- Innovation in Drug Discovery Processes through Digital Pathology -

in research productivitySubstantial improvement
AI technology applied: 1 day/500 slides
Human: 7000 days/500 slides

Ensure quantitation
Deepening understanding of pathological conditions through integrated analysis with other data (such as genetic development)

Laboratory researcher

Data scientist

**Extraction of characteristics of various forms
(size, shape, color, position, etc.)**

Approx. 1000 slides
(1 project)

Training

Integrated analysis with other data

Individual algorithms
(deep learning) are
applied in the analysis
of each project
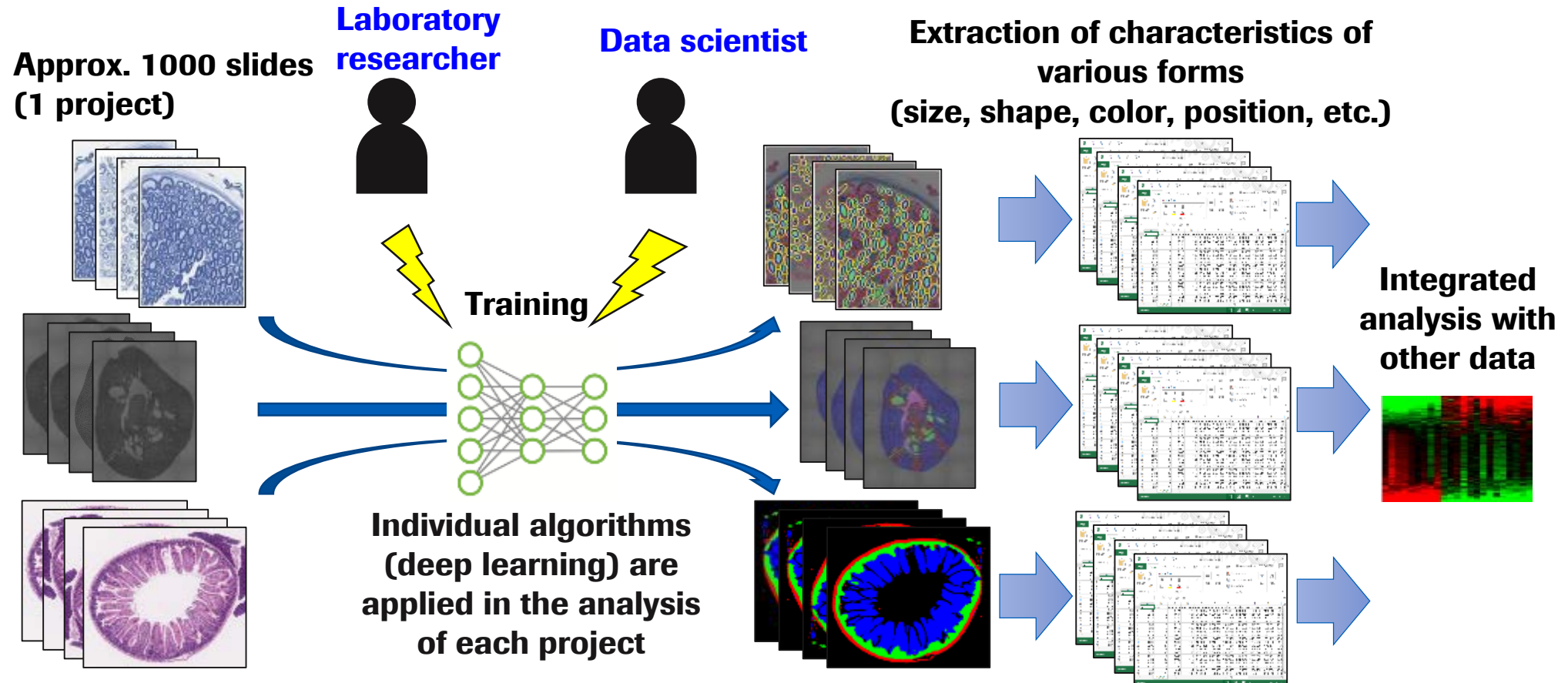
Shape Recognition through Deep Learning

Using deep learning, we can now accurately and automatically outline and identify the shape of an object

CNN model
(Convolutional Neural Network)

① Pre-processing

③ Speculation

④ Restructuring

Converted to AI-easy-to-learn data

② Learning

Reconstruct the identification results so that they are visually easy for human to interpret

Have AI learn our image data

epoch=1

Identify the object in the image using the training model

Deep learning model
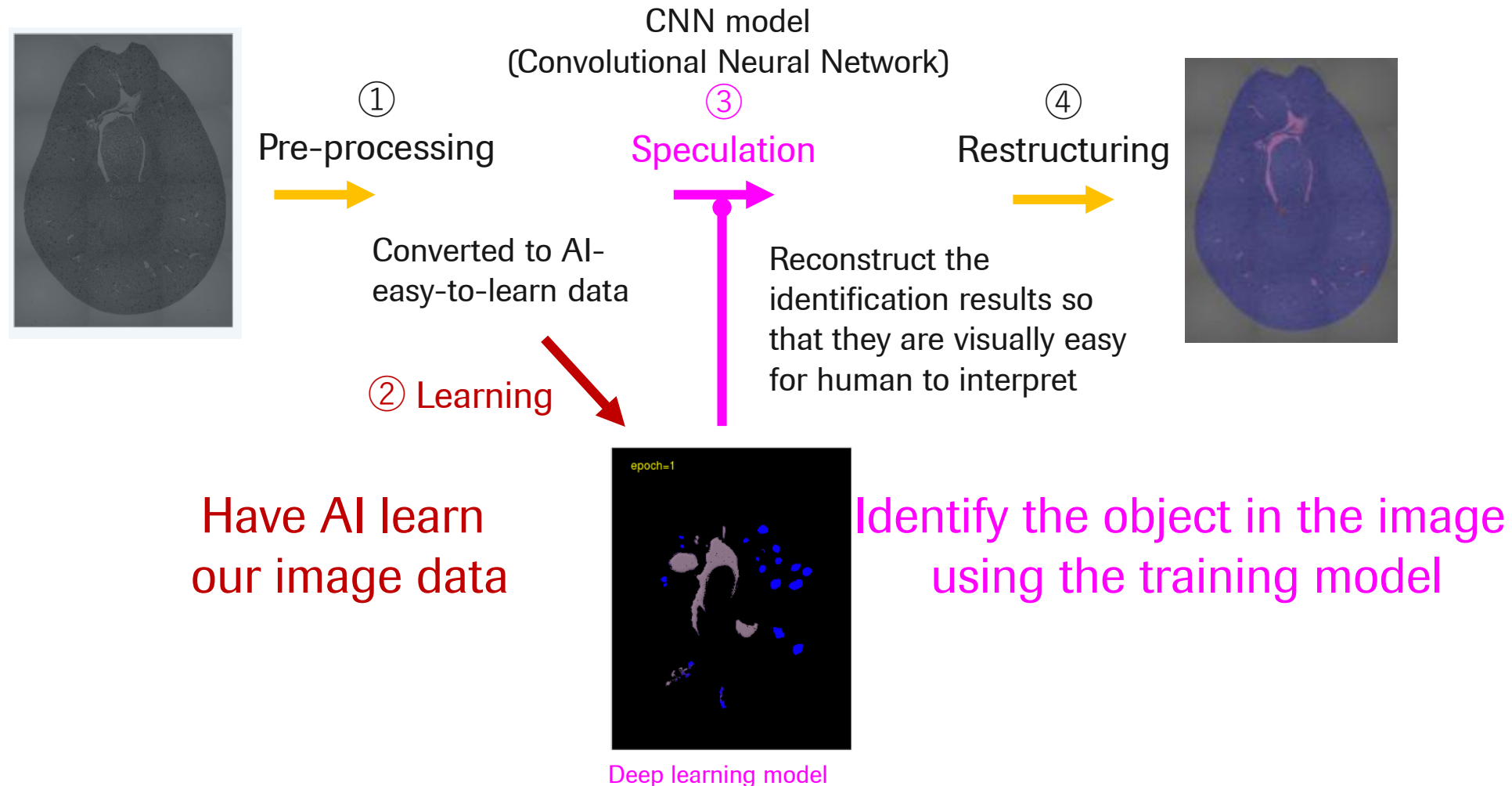
TACTICS: System for Creating Drug Discovery Ideas Across the Research Function

TACTICS **T**eams **A**ctively **C**hanneling **T**actical **I**ngenuity for **C**urative **S**olutions

Activities organized across the research division to create drug discovery ideas

✓ Promotion of unique biological discoveries

✓ Sublimation to "invention" that leads to highly effective products
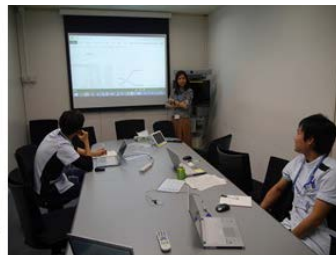
Idea
Hypothesis
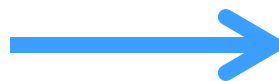
Experiment
Discovery
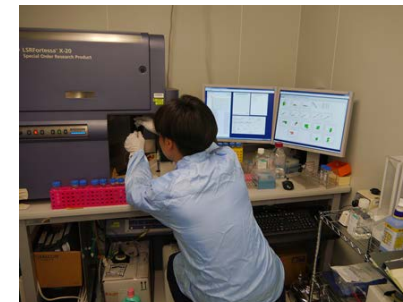
Examples of Text Mining AI Technology in Drug Discovery Research in Collaboration with FRONTEO

Issues in the Early Stages of Target Discovery and Drug Discovery Research

- Researchers have a limited amount of time for close reading of a huge number of published papers.

- It is difficult to obtain information from surrounding areas and different fields.

Features of FRONTEO Concept Encoder and Amanogawa

- Concept Encoder vectorizes words and sentences in 300–1000 dimensions.

- Amanogawa searches 16 million vectorized articles by using words and natural sentences as queries.

- Vector operations enable concept extraction, analogy search, clustering of papers, and etc.

Amanogawa
Cluster of search papers plotted
on the vector space

Source (Accessed November 20, 2020):
https://lifescience.fronteo.com/aidiscovery/amanogawa/

Construction of Idea Database and Utilization of AI technologies in TACTICS activities

- **Construct proprietary database with structured information on the cause of diseases and related molecules**

- **Relates ideas as a set of elements and define as a function on the DB**
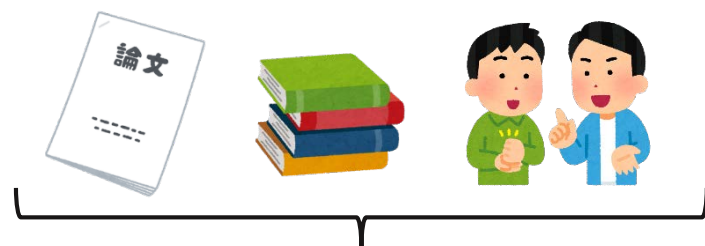
DB including literatures and proprietary ideas

AI
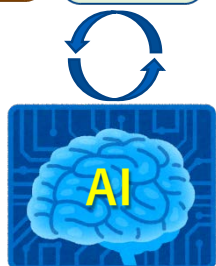
The relationship between the molecules directly mentioned

F.VIII → Binding → F.X ·····&····· F.IX
Proximity Effects
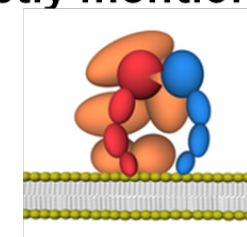
Search for identical relationships and apply the rules

BiAb → Binding → Mol.A ·····&····· Mol.B
Proximity Effects

Generate ideas efficiently from proprietary information（DB）

BiAb → Binding → F.X ·····&····· F.IX
Proximity Effects
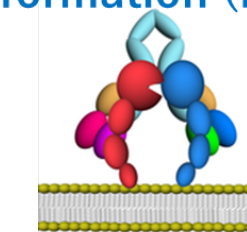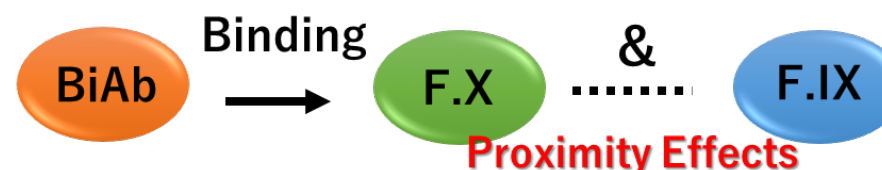
Summary: Innovation in the Drug Discovery Process Using AI

We are transforming the entire drug discovery process using AI technology, mainly machine learning, and applying it to drug discovery projects.

- **Molecular design of small molecules, mid-size molecules and antibodies using AI technology**
- **Improvement of productivity in pathology using image analysis technology and integrated analysis through quantitative evaluation**
- **Cell identification using image analysis technology and organ selection, measurement and determination after pharmacological testing**
- **Use of AI technology in multi-omics analysis of gene expression, etc.**
- **Clustering of papers and network analysis using text mining AI technology**
- **Building an idea database and use of AI technology**
- **Development of robots to support experimental work…and more**

The new laboratory, which is currently under construction, will be equipped with an IT infrastructure that actively utilizes AI and various digital technologies to create a next-generation laboratory with high productivity.

Chugai Life Science Park Yokohama (scheduled to be completed in 2022)

Utilization of Real World Data

Dr. Nobuya Ishii

Head of Science & Technology Intelligence Dept., Project & Lifecycle Management Unit
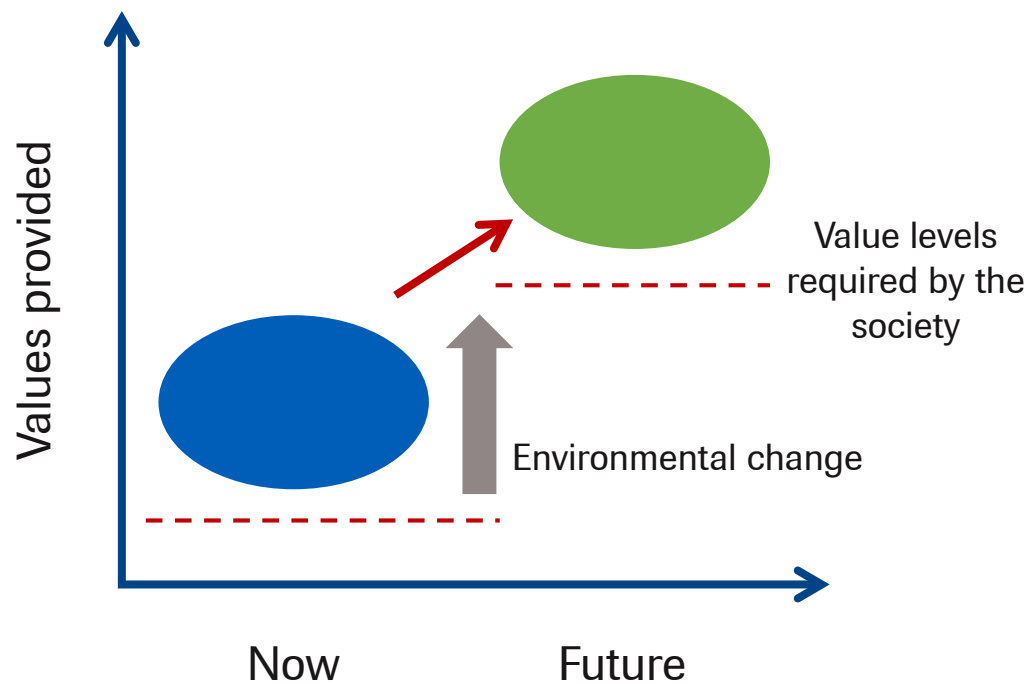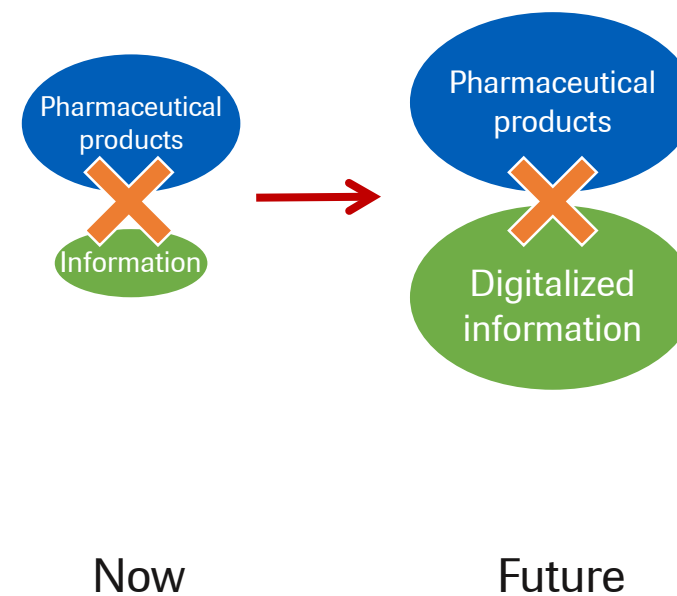
CHUGAI DIGITAL

Agenda

1. **Goals for Utilization of Medical Data Including Real World Data**

2. **Current Status and Issues for Utilization of Medical Data**

3. **Initiatives Led by Chugai**

Future Ideal Pharmaceutical Products

Increase in expected values

Values provided

Value levels required by the society

Environmental change

Now   Future

Value improvement by offering pharmaceutical products + α

Pharmaceutical products

Information

Pharmaceutical products

Digitalized information

Now   Future

What is Real World Data?

Real World Data (RWD)

- Medical data collected in daily clinical setting

- Information on patients/medical practice collected from sources other than clinical studies, including medical payment invoice data, DPC* data, electronic medical record data, medical checkup data, patient registry data, and data from wearable devices

Real World Evidence (RWE)

- Evidence obtained from analyses of RWD

Data source → Data processing → Data validation → RWD → Analytical Methods → RWE → Application
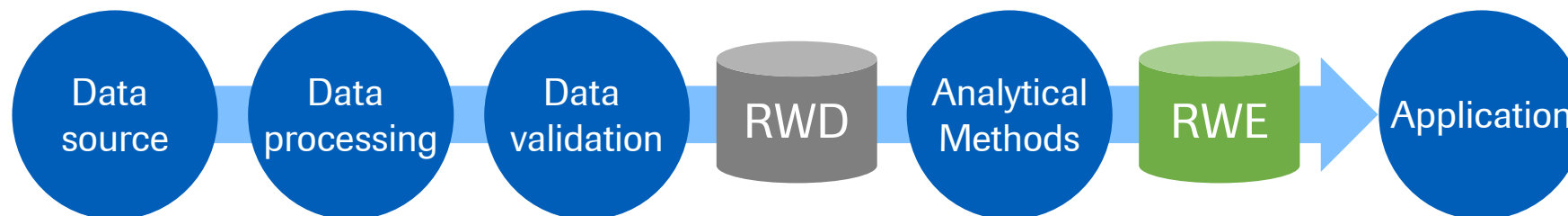
*DPC: Diagnosis Procedure Combination

Examples of Utilization of Medical Data including RWD

Medical data

Data from clinical studies

RWD

Genome data

Extension of healthy life expectancy	• Healthcare / improvement of lifestyle / prevention
Scientific nursing care practice	• Quality and efficacy improvement of nursing care service, based on science
Partnership with community healthcare	• Continued access to healthcare
Support for clinical decision-making	• Proper diagnosis and treatment
Provision of optimal treatment	• Provision of information on proper use • Provision of safety information
Marketing authorization application	• Early access by patients • Reimbursement based on values
Drug discovery and basic research	• Breakthrough treatment / diagnosis / prevention

Extension of healthy life expectancy

Provision of adequate healthcare

Development / provision of new healthcare services

Promptly and continuously give back benefits to the public and patients (including restoration of the soundness of healthcare finance)

New Aspects of RWD: Can Respond in Real Time

Evidence of the effect of expanding U.S. public insurance coverage (Obama care) to eliminate racial disparities in access to timely cancer treatment.

- Validation of effects of the Affordable Care Act (ACA)

- Racial comparison of percentage of patients who have received treatment within 30 days after the diagnosis

Changes in healthcare environment under COVID-19 pandemic can be detected in a real-time manner

- Changes such as decreases in enrollment in clinical studies and hospital visits by patients

Accrual to NCTN trials by week

NCTN: NCI's National Clinical Trials Network

Access: 20 June, 2020.11:32 JST
https://www.urotoday.com/conference-highlights/asco-2020/asco-2020-prostate-cancer/121905-asco-2020-ensuring-cancer-research-progress-during-a-global-pandemic.html
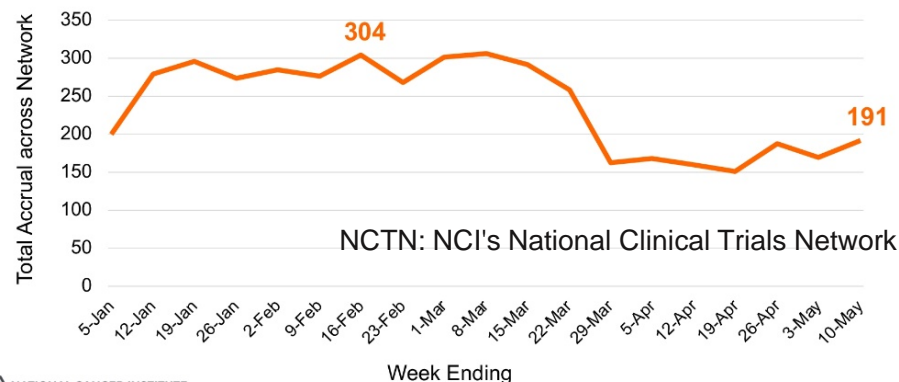
COVID-19 AND U.S. COMMUNITY ONCOLOGY
Trends in patient visit type
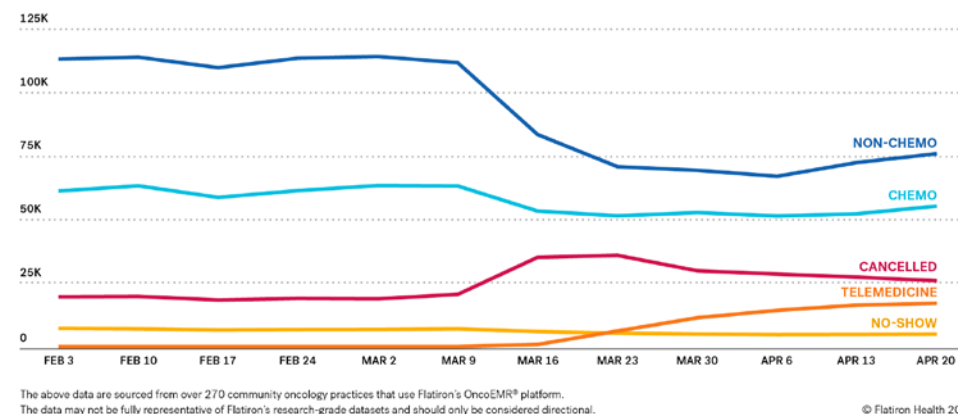
Access: 20 June, 2020.11:40 JST
https://cancerletter.com/articles/20200501_1/

[Conceptual image]

Expected Effects by Utilization of RWD

Patients

- ✓ Prompt access to optimal treatment
- ✓ Achievement of high outcomes

Government

- ✓ Understanding the reality of healthcare in a real-time manner
- ✓ Verification of the effects of healthcare policies in a real-time manner
- ✓ Assessment of the efficacy and safety of real-world treatment

Healthcare-related companies

- ✓ Creation of new service opportunities based on scientific evidence

Healthcare professionals

- ✓ Understanding of the reality of the treatment at each clinical site
- ✓ Comparison of the reality of the treatment between their clinical sites and other clinical sites
- ✓ Support to make a treatment strategy decision based on RWD/RWE

Academia

- ✓ Studies with the use of real-time medical data

Pharmaceutical companies

- ✓ Marketing authorization applications
- ✓ Post marketing surveillance
- ✓ Research and development efficiency
- ✓ Assessment of cost-effectiveness to secure reimbursement and negotiate drug price
- ✓ Marketability survey

Importance of Regulatory-Grade RWD

Potential for rapid patient access to effective therapies by enabling marketing authorization applications for approval based on RWE
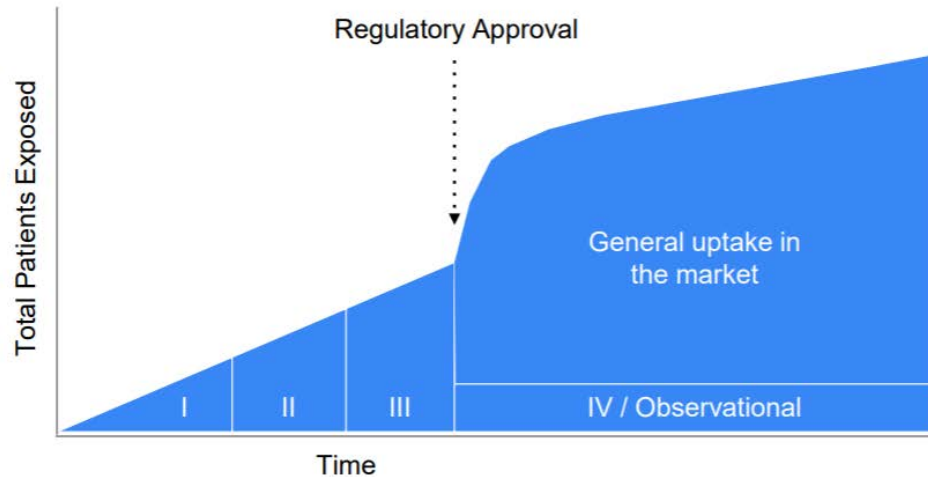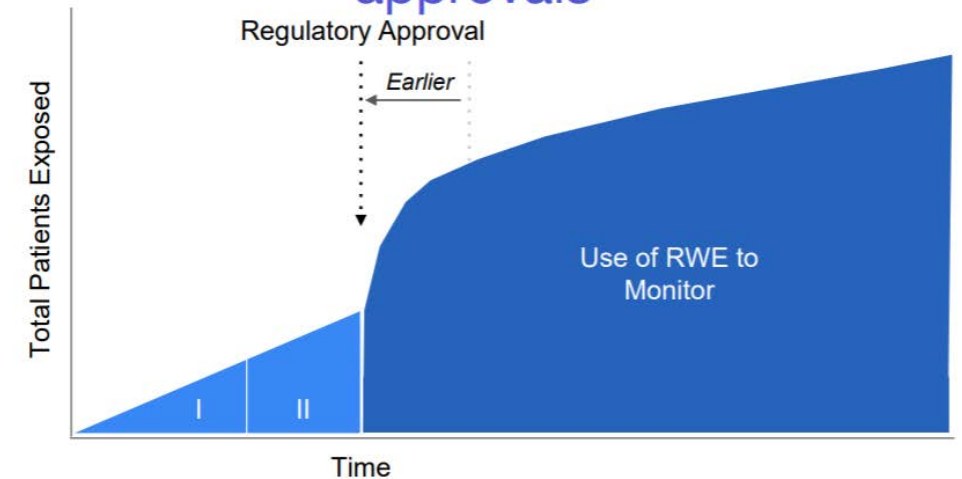
Issues to Utilize Medical Data

Ensure access to RWD that can be used for marketing authorization applications

✓ Quality of data
Two articles on studies with RWD, associated with the risk of drug administration to patients with COVID-19, were withdrawn due to data reliability issues.

✓ Data scale (number of data)
Data are generated at individual institutions and also at the individual level, with a lot of fragmented data, which is mainly utilized by single or few institutions.

Establishment of RWD analysis platform

✓ Establishment of analysis methods / platform with high transparency with the use of RWD

Readiness of the environment to utilize RWD, including marketing authorization applications

✓ Development of guidelines for the use of RWD for marketing authorization applications

Initiatives for Application of RWD in the U.S.

In February 2009, the American Recovery and Reinvestment Act (ARRA) was enacted.

- Post-financial crisis economic-stimulus act

- The Health Information Technology for Economic and Clinical Health Act (HITECH Act) was enacted to promote the use of electronic health records.

In December 2016, the 21st Century Cures Act was enacted.

- The goal of the act is to clarify the scope of FDA regulations and approval process and to implement strategic budget investment projects, to further accelerate discovery, development, and introduction of new therapies available in the 21st century. For example, regenerative medicine and digital health, into clinical setting.

- Section 3022. Real world evidence

  Programs to evaluate the availability of RWE that supports the approval process for additional indications and post-marketing safety assessment shall be started.
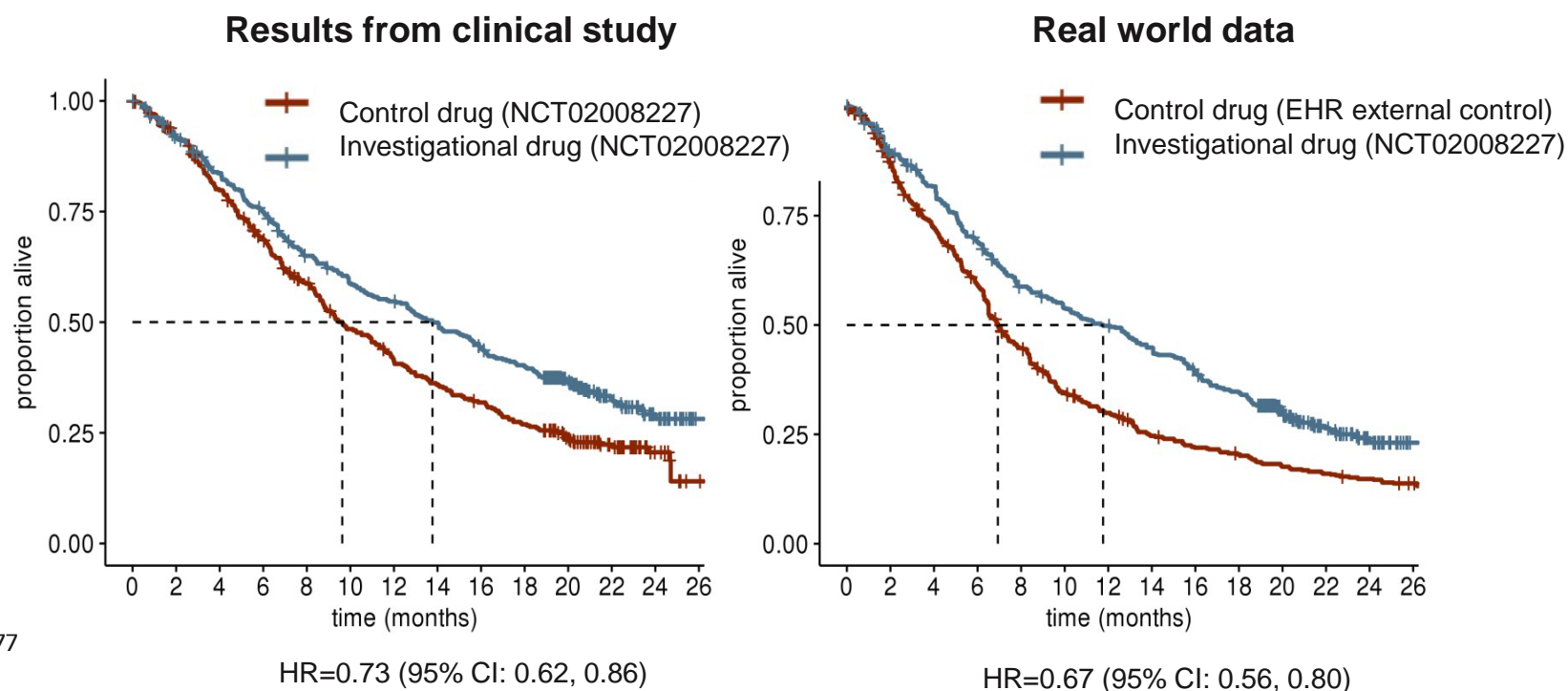
Collected and regularly updated electronic medical record data of 2.2 million patients with cancer.

Collaborated with over 280 cancer clinics, 7 academic cancer centers, and top 15 companies in oncology area and conducted a joint research with FDA.

Comparison of results from clinical study and those from real world data

Results from clinical study

Control drug (NCT02008227)
Investigational drug (NCT02008227)

HR=0.73 (95% CI: 0.62, 0.86)

Real world data

Control drug (EHR external control)
Investigational drug (NCT02008227)

HR=0.67 (95% CI: 0.56, 0.80)

Collected and regularly updated electronic medical record data of 2.2 million patients with cancer.

Collaborated with over 280 cancer clinics, 7 academic cancer centers, and top 15 companies in oncology area and conducted a joint research with FDA.

Comparison of hazard ratios calculated in clinical studies
and those calculated from real world data

Summary Results

weighted correlation coefficient = 0.86 (95% CI: 0.54, 0.96)
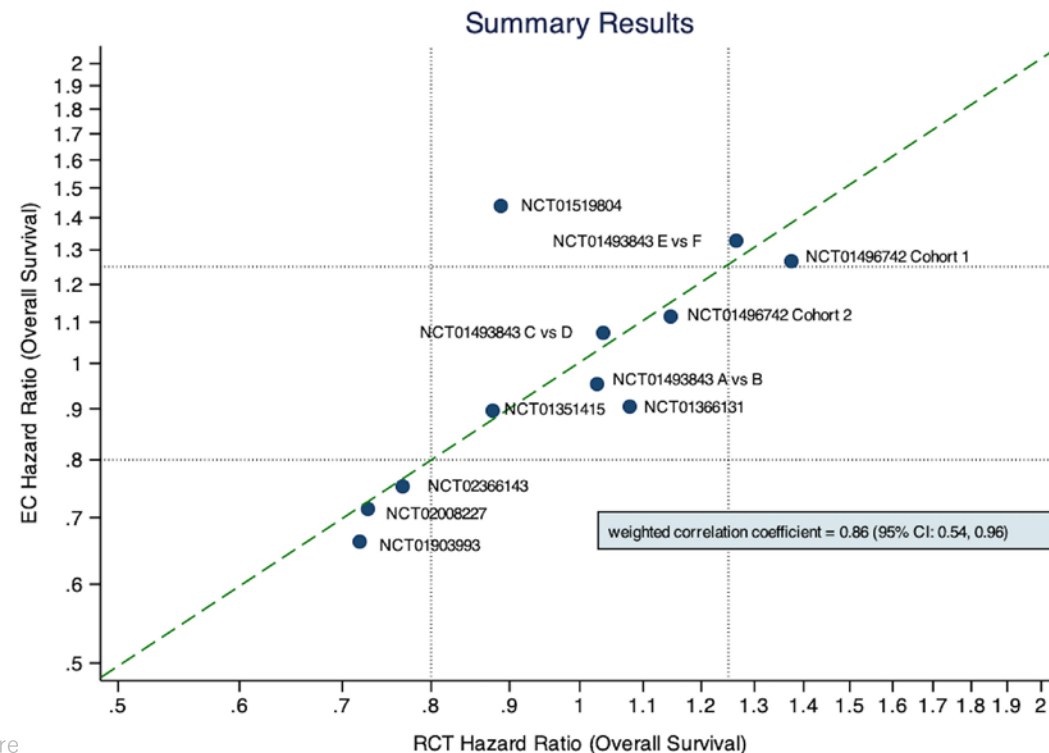
Case Examples of Applications of RWD by Flatiron Health

RWD were used to support regulatory applications for drugs to treat rare types of cancer.

Pharmaceutical Product	Regulatory Authority	MOA	Target Disease	Number of Patients	Purpose of Application
Drug A （Pfizer）	FDA	CDK4/6inhibitor	hormone receptor +/HER2- male breast cancer patients	2,670/year （US）	Efficacy and safety information from RWD of off-label use
Drug B （Janssen）	FDA	FGFR inhibitor	FGFR2 or FGFR3 mutation + advanced or metastatic urothelial cancer patients	3,000/year （US）	As a virtual control arm for the single arm study

RWD were used in cost-effectiveness assessment to negotiate drug-pricing and reimbursement.

Pharmaceutical Product	Regulatory Authority	MOA	Target Disease	Purpose of Application
Drug C （Roche）	EMA	ALK inhibitor	2L ALK+ NSCLC patients	As a virtual control arm for the single arm study against ceritinib
Drug D （Roche）	NICE	Anti-PD-L1 antibody	Previously treated locally advanced / metastatic non-small cell lung cancer	Responded to the request from the regulatory authority demanding submission of the five-year survival rate data by creating a predictive model. The validity of the predictive model was verified using RWD.

FDA: US Food and Drug Administration, EMA: European Medicines Agency, NICE: National Institute for Health and Care Excellence (UK)
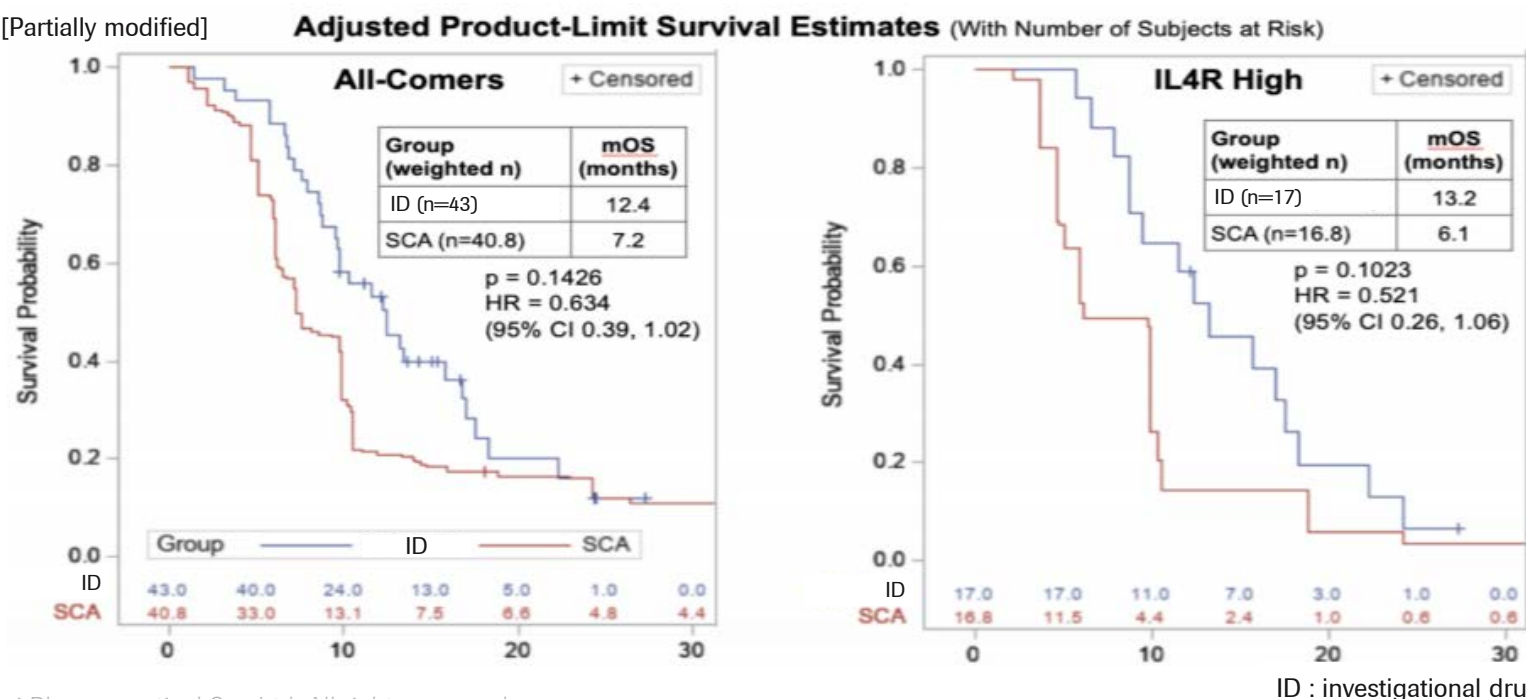
FDA Supported Expanded Use of RWD

FDA accepted the use of RWD in a phase 3 trial including a hybrid external control (combining synthetic control arm patients with randomized control arm patients).

- A phase 3 registrational trial in recurrent glioblastoma (rGBM)

- The hybrid external control arm reduced the number of patients enrolled to the control therapy in the randomized trial.

- A comparison was made with the synthetic control arm using the results of phase 2 trial.

[Partially modified]

Adjusted Product-Limit Survival Estimates (With Number of Subjects at Risk)

All-Comers + Censored

Group (weighted n)	mOS (months)
ID (n=43)	12.4
SCA (n=40.8)	7.2

p = 0.1426
HR = 0.634
(95% CI 0.39, 1.02)

Group	ID	SCA
ID	43.0 40.0 24.0 13.0 5.0 1.0 0.0	
SCA	40.8 33.0 13.1 7.5 6.6 4.8 4.4	

IL4R High + Censored

Group (weighted n)	mOS (months)
ID (n=17)	13.2
SCA (n=16.8)	6.1

p = 0.1023
HR = 0.521
(95% CI 0.26, 1.06)

ID	17.0 17.0 11.0 7.0 3.0 1.0 0.0	
SCA	16.8 11.5 4.4 2.4 1.0 0.6 0.6	

ID : investigational drug

Access: 13:29 JST, 16 Nov., 2020.
https://www.oaoa.com/news/business/medidata-synthetic-control-arm-supported-by-the-us-food-and-drug-administration-fda-for-use/article_0b3af804-560e-51d4-8f63-e27361da014d.html

Access: 15:29 JST, 16 Nov., 2020
https://s1.q4cdn.com/460208960/files/News/2020/Zacks_SCR_Research_06032020_T.MDN_Bautz.pdf

RWD Introduction Status in Japan

Creation of registry data

- Clinical Innovation Network (CIN) which promotes the use of patient registries in Japan and supports information collection for cohort studies and other similar activities

Discussions are ongoing to develop guidelines (GL) for the application of registry data.

- The discussions are focusing on; 1) how we can utilize RWD for marketing authorization applications and 2) how we can ensure reliability of registry data.

- Pharmaceutical Evaluation Division, Ministry of Health, Labour and Welfare

Next Generation Medical Infrastructure Law (effective as of May 2018)

- In addition to opt-in, by following opt-out process that meets certain requirements, it is now possible for ; 1) medical institutions to provide medical information that is personal information requiring special consideration to authorized providers, and 2) authorized providers to provide anonymized processed medical information to users.

- Certification as a certified business operator that can create anonymized medical information

Documents for application of real world data in pharmaceutical development (prepared by Japan Pharmaceuticals Manufacturers Association)

- 1) The First Step toward the Marketing Authorization Application Using External Control Data, 2) Application of Real World Data for Marketing Authorization Applications, 3) Promotion of Application of RWD among Pharmaceutical Companies.

Ideal Image of Application of RWD at Chugai

An environment that enables the timely and appropriate use of medical data, including RWD, has enabled rapid patient access through approval applications, along with decision-making and collaboration activities to achieve patient-centric healthcare.
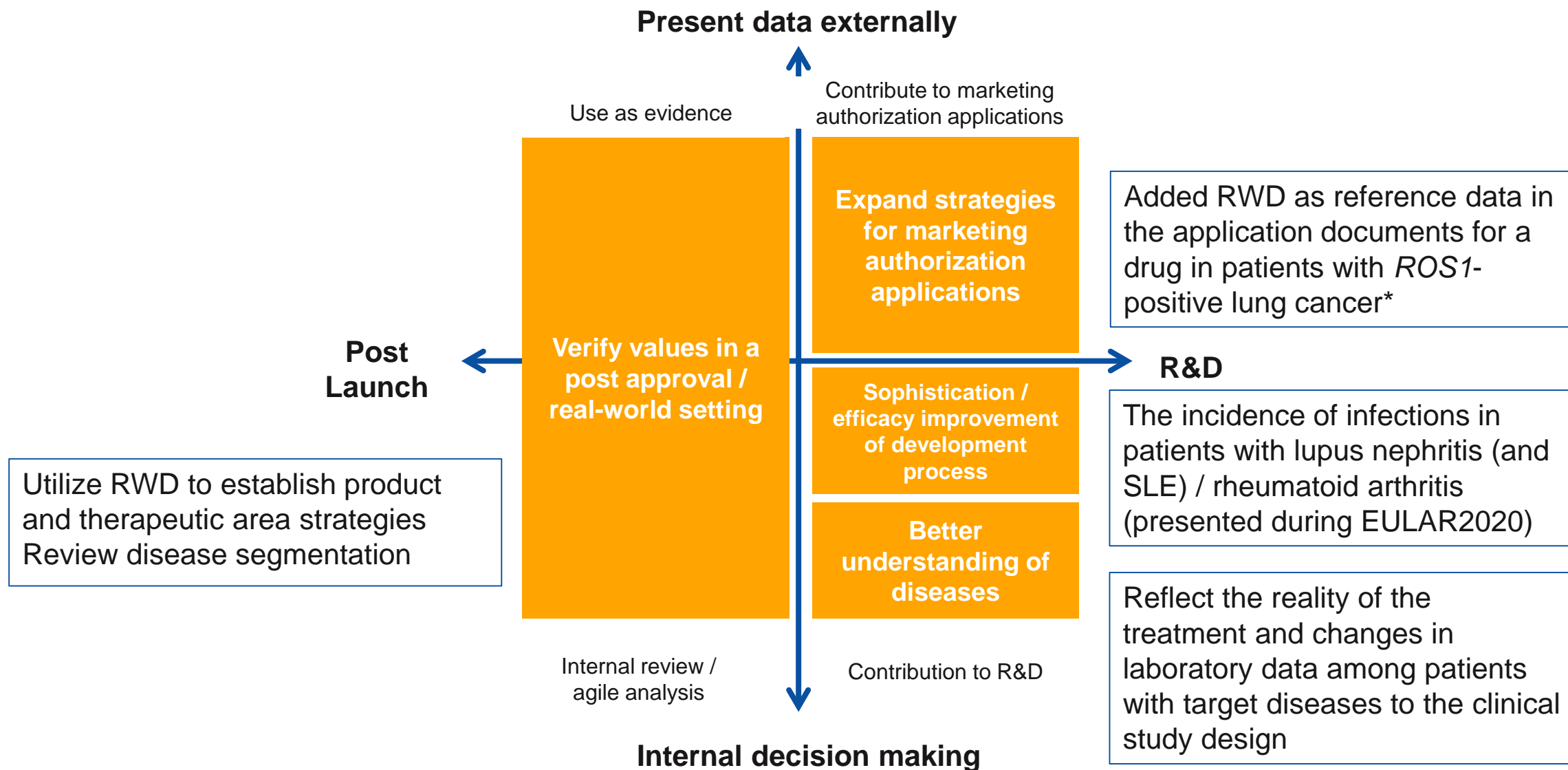

RCT

A validated tool to prove causality

+

RWD

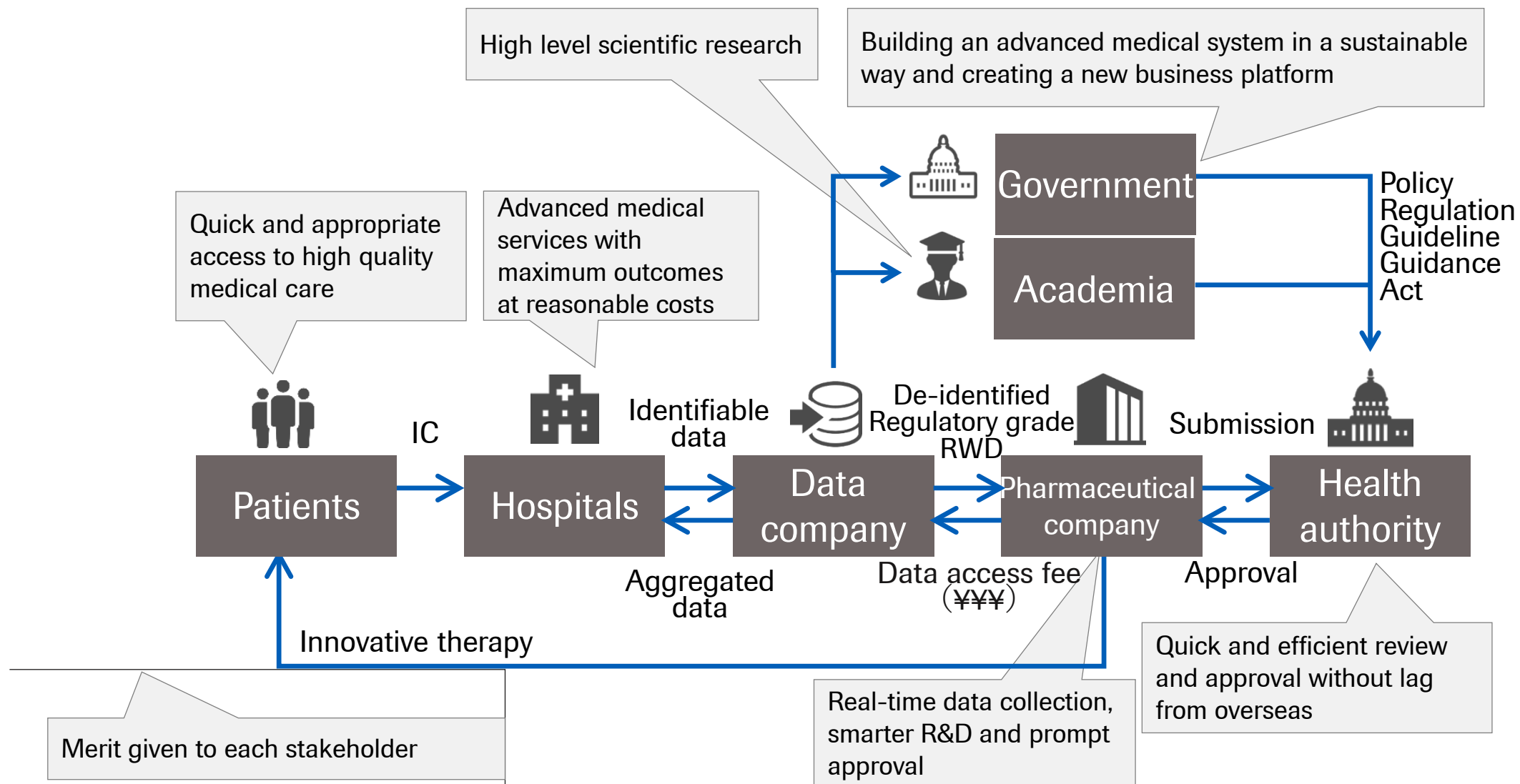Information source that brings us new approach

RCT: Randomized Clinical Trial

Promote Various Activities within Chugai in Four Quadrants

Present data externally

Use as evidence

Contribute to marketing authorization applications

Expand strategies for marketing authorization applications

Added RWD as reference data in the application documents for a drug in patients with *ROS1-positive lung cancer**

Post Launch

Verify values in a post approval / real-world setting

R&D

Sophistication / efficacy improvement of development process

The incidence of infections in patients with lupus nephritis (and SLE) / rheumatoid arthritis (presented during EULAR2020)

Utilize RWD to establish product and therapeutic area strategies
Review disease segmentation

Better understanding of diseases

Reflect the reality of the treatment and changes in laboratory data among patients with target diseases to the clinical study design

Internal review / agile analysis

Contribution to R&D

Internal decision making

*According to the view of regulatory authorities, there were limitations in explaining the clinical position of RWD

Establishment of Sustainable RWD Eco-System toward Promoting Utilization

High level scientific research

Building an advanced medical system in a sustainable way and creating a new business platform

Quick and appropriate access to high quality medical care

Advanced medical services with maximum outcomes at reasonable costs

Government

Academia

Policy
Regulation
Guideline
Guidance
Act

De-identified
Regulatory grade
RWD

IC

Identifiable data

Submission

| Patients | Hospitals | Data company | Pharmaceutical company | Health authority |

Aggregated data

Data access fee
(¥¥¥)

Approval

Innovative therapy

Quick and efficient review and approval without lag from overseas

Merit given to each stakeholder

Real-time data collection, smarter R&D and prompt approval

Summary

The use of medical data, including RWD, is expected to increase the efficiency and sophistication of medical care and provide rapid and sustainable value to the public and patients.

In Western countries, RWD are gradually used for marketing authorization applications and assessment of cost-effectiveness to secure reimbursement and negotiate drug price.

In Japan, we also must establish a sustainable ecosystem that allows us to collect high-quality RWD available for marketing authorization applications.

Chugai aims to achieve goals such as patient-centric health care based on decision-making and collaborative through improving the environment to use medical data, including RWD in a timely and appropriate manner; and timely patient access to therapies through regulatory filing.

Digital Marketing Strategy

Takato Shimauchi

Head of Customer Solutions Dept.,
Marketing & Sales Div.

CHUGAI DIGITAL

Agenda

1. **"PLUS CHUGAI," A New Customer Touchpoint**

2. **Creation of System Environment for Digital Marketing**

3. **Online Workshops for Team Medical Approach**

Agenda

1. **"PLUS CHUGAI," A New Customer Touchpoint**

2. **Creation of System Environment for Digital Marketing**

3. **Online Workshops for Team Medical Approach**

Website for Healthcare Professionals

Launched on Tuesday, April 23, 2019

**0.14 million
unique users**
per month on average from
January to October 2020

Three-Layer Structure of "PLUS CHUGAI"

Three-layer structure

Values provided to customers

3F

**Partnership
=
Encourage customers to sign in**

Enhance communication between customers and Chugai

Realization of digital marketing

Provide exclusive services for members

2F

Extension
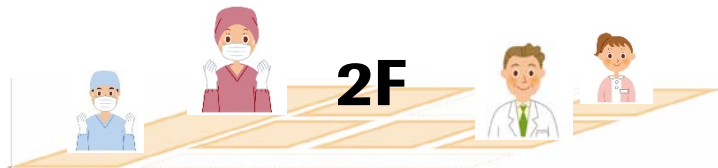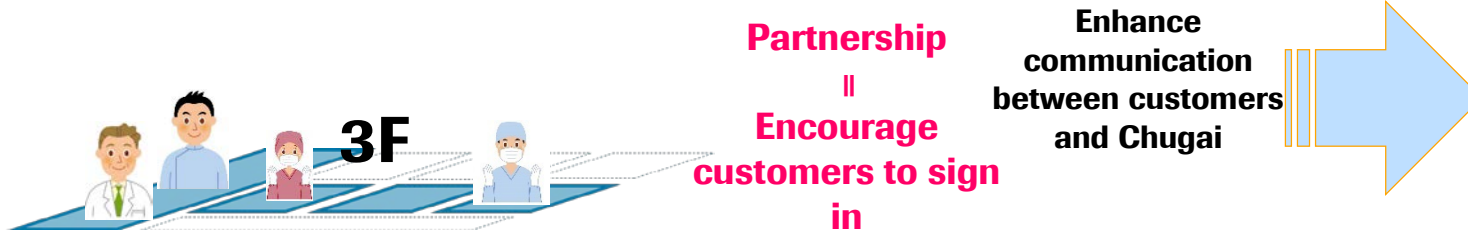
Provide new information/values

Information Provision Other Than Drug Information
- ・Information on diseases and therapies (introduction of medical institutions, guidelines, and techniques, etc.)
- ・Useful information (communications and illustrations, etc.)
- ・Ordering of materials
- ・Utilization of Chatbot AI in FAQ

1F

Infrastructure
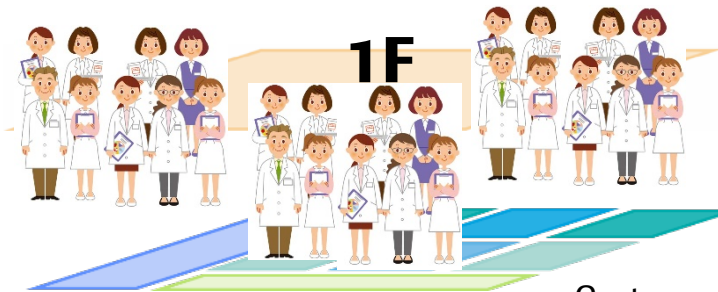
Promptly settle questions/ problems

Provision of Drug Information / Safety Information
- ・Product information
- ・Drug Information(FAQ・RMP)...

Customer segment

Attractive Contents with Rich Quality and Quantity

A wide variety of contents responded to a wide range of customer needs

High-quality contents meeting high needs from specialists

Online literature search

Database tool on adverse reactions

Online lecture meetings
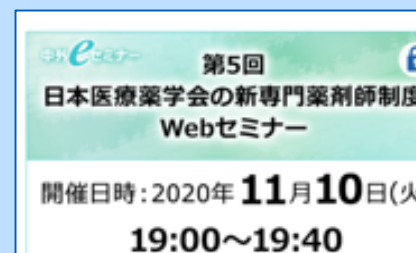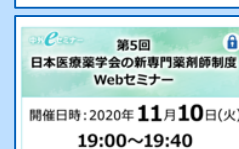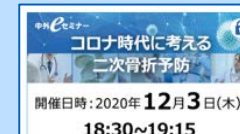
Online Lecture Meetings Exclusive for Members (Area Version)

✓ Carefully respond to regional needs of customers

✓ Members can register and watch regional lecture meetings regardless of their location

Members Can Directly Contact MR through "PLUS CHUGAI"

Interactive communication, rather than one-sided communication, is possible.

To: Doctors as members of "PLUS CHUGAI"

To: Contact MR
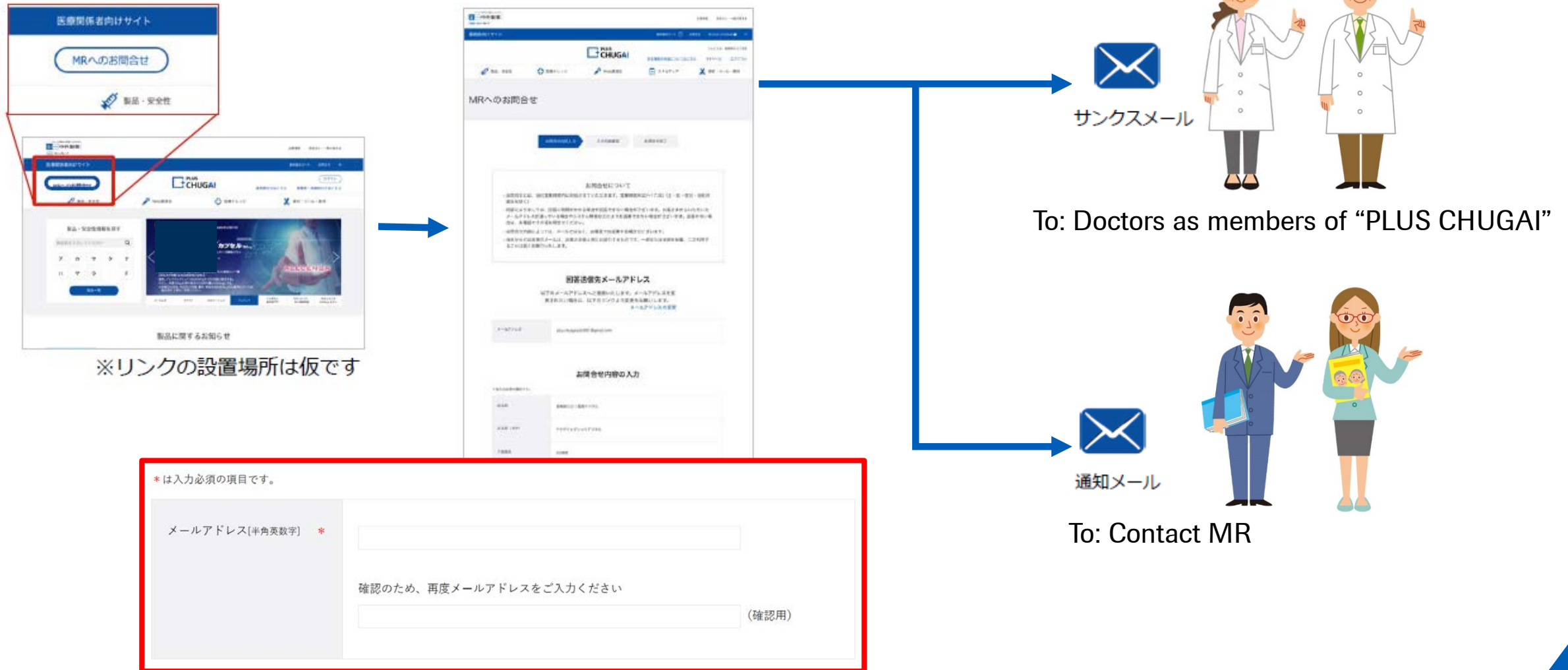
Active Use of External Media to Deliver Information

More than 400 postings
are planned next year.

Agenda

1. "PLUS CHUGAI," A New Customer Touchpoint

2. **Creation of System Environment for Digital Marketing**

3. Online Workshops for Team Medical Approach

Establishment of Digital Platform for New Marketing Processes

Customer interface based on Chugai's customer communication way
In-house developed system infrastructure to ensure a flexible response to customer needs

1. **Highly specialized product portfolio focused on oncology and specialty areas**
   Shift from the conventional mass information provision to Chugai's proprietary MR-digital fusion model

2. **Shift from the waterfall model to agile model**
   Developed a system that can respond flexibly to environmental changes from the users' perspective to address customer needs

3. **Data analysis with Chugai's unique approach**
   Give feedback to MR taking advantage of data utilization and analysis with Chugai's unique approach

4. **Cross-organizational marketing focused on customers**
   Developed by a cross-functional team including Marketing & Sales / Medical Affairs / Drug Safety / Clinical Development / Foundation Medicine Unit.

CHUGAI DIGITAL

OCC
Organic Communication

0C (Zero C, Organic Communication)
A cross-functional task to achieve organic communication

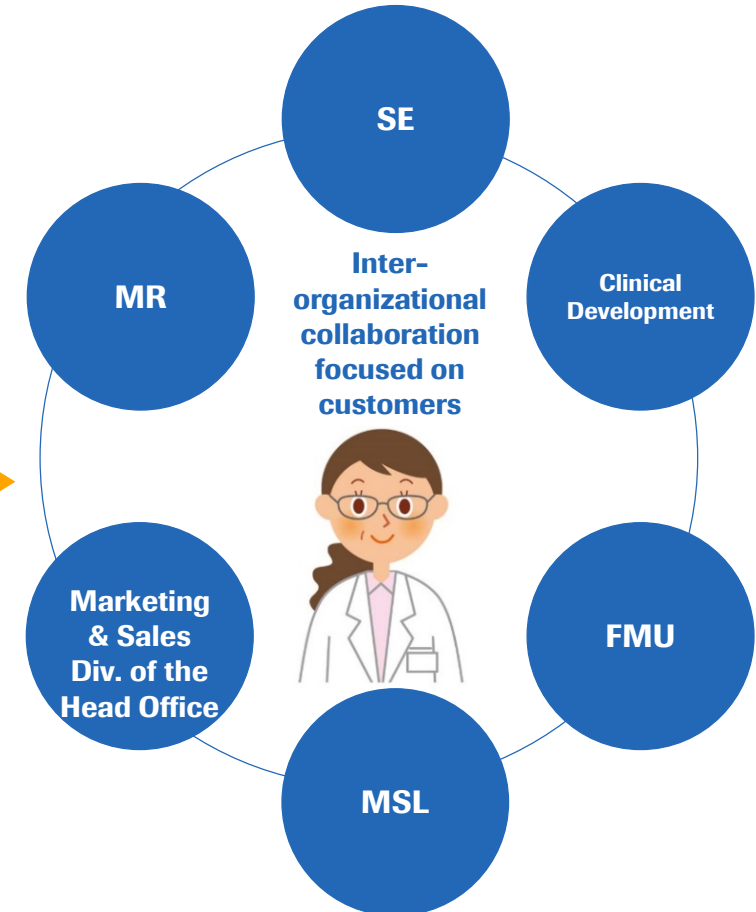| 0C1 Data visualization | 0C2 Quality improvement of marketing data | 0C3 Approach to new customers |

Digital Strategy
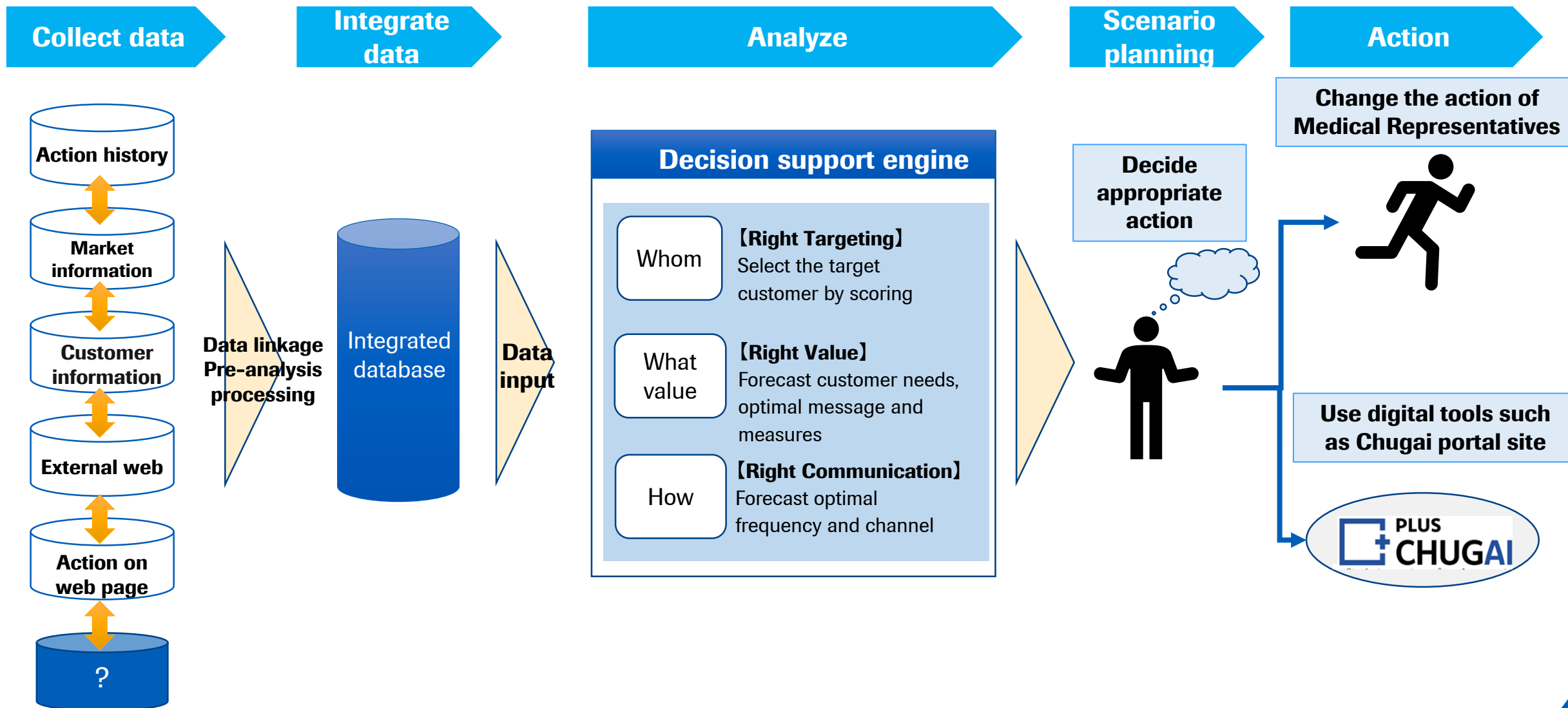
Drug Safety

MA

Marketing & Sales

Clinical Development

Foundation Medicine Unit

SE

Clinical Development

MR

Inter-organizational collaboration focused on customers

FMU

Marketing & Sales Div. of the Head Office

MSL

MSL: Medical Science Liaison
MA: Medical Affairs
SE: Safety Expert
FMU: Foundation Medicine Unit

Integrated Database Collects Extensive Data from Daily Sales Activities Propose Solutions Tailored to the Situation through Machine Learning

Collect data → **Integrate data** → **Analyze** → **Scenario planning** → **Action**

Collect data
- Action history
- Market information
- Customer information
- External web
- Action on web page
- ?

Integrate data
Data linkage Pre-analysis processing → Integrated database → **Data input**

Analyze

Decision support engine

Whom	【Right Targeting】 Select the target customer by scoring
What value	【Right Value】 Forecast customer needs, optimal message and measures
How	【Right Communication】 Forecast optimal frequency and channel

Scenario planning
Decide appropriate action

Action
- Change the action of Medical Representatives
- Use digital tools such as Chugai portal site
- PLUS CHUGAI

Explore New Ways to Provide and Obtain Information with Digital Tools

For analysis	For action
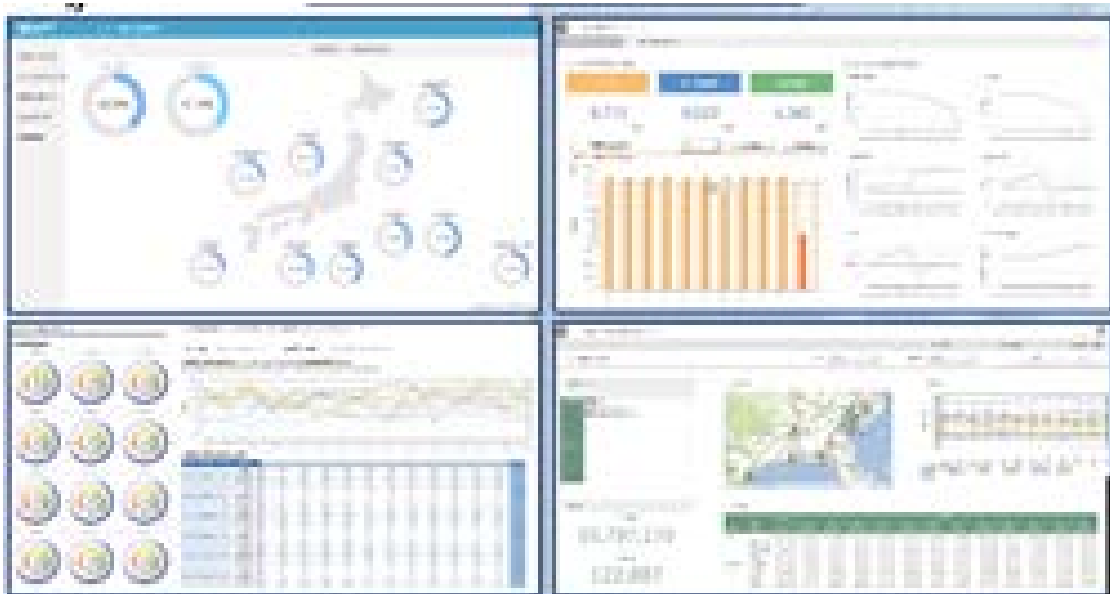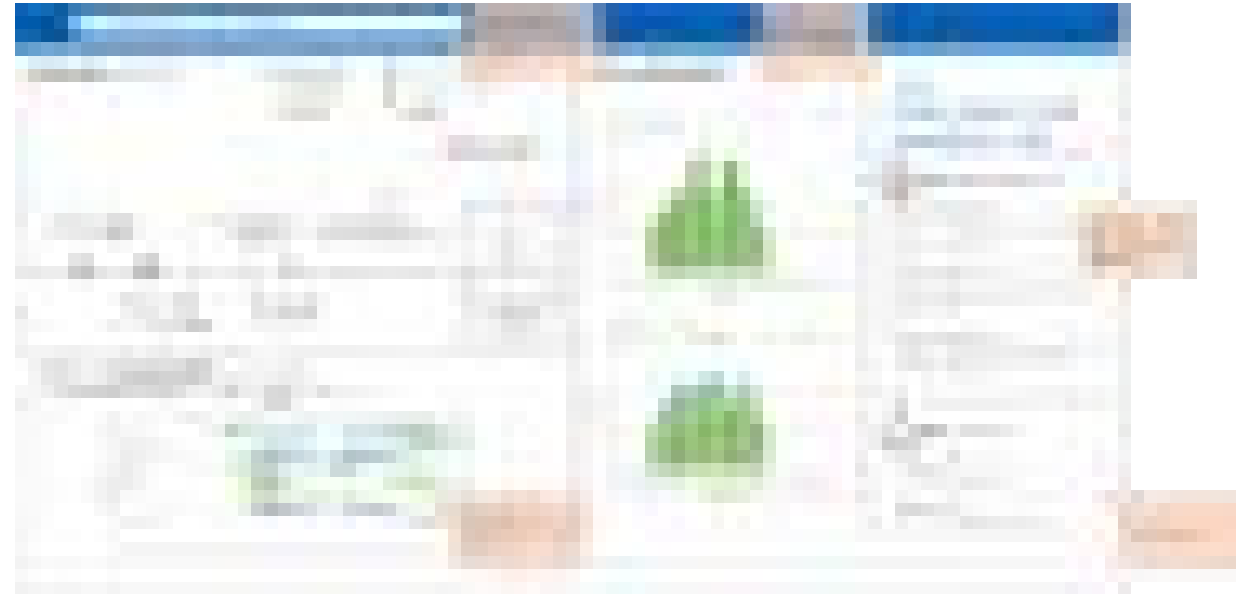
Select Proper Channels Depending on Each Customer's Needs
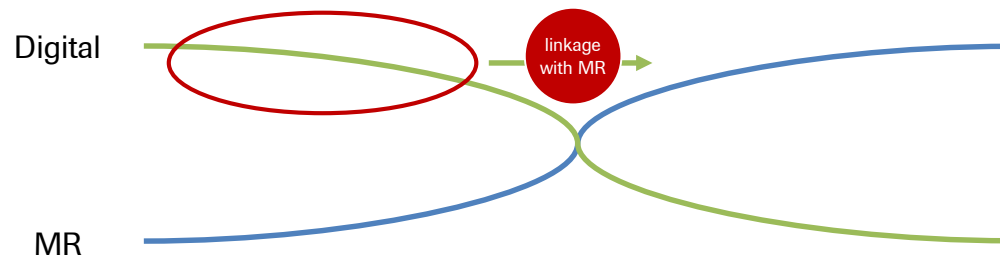
■ **MR** + **Digital**
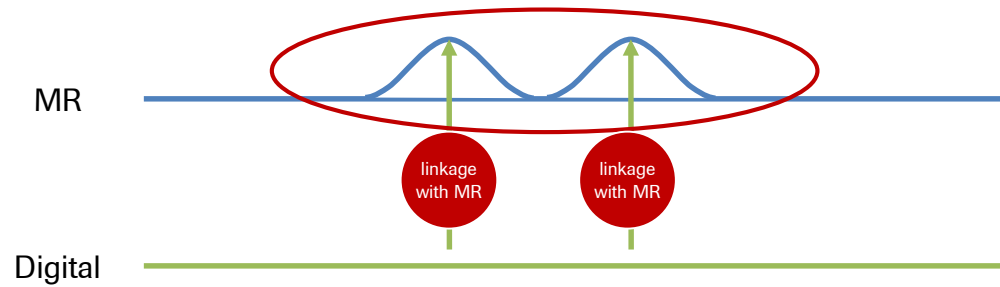
Offer topics / see from a fresh dimension / opportunities to provide product information
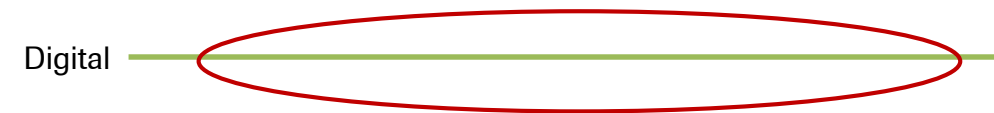
■ **MR** → **Digital** → **MR**
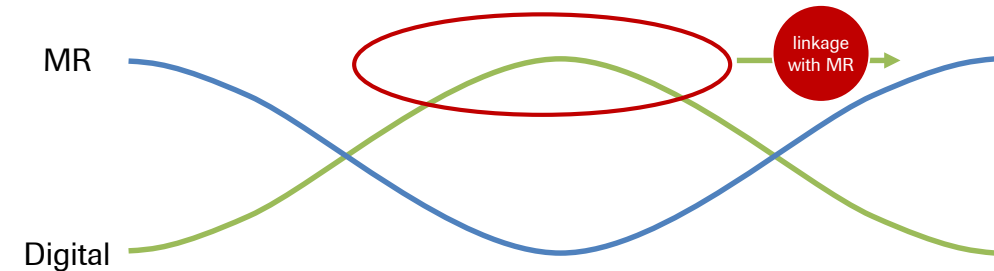
Efficiency improvement in MR activities

■ **Digital→MR**

Increase interest with the use of digital tools → Passed on to MR

■ **Digital Only**

Completed with digital communication only

Agenda

Section 1: Overall Objectives

"Let people in the country including patients with cancer understand and overcome the disease."

1) improve cancer prevention and screening based on scientific evidence, 2) achieve patient-centered cancer care, 3) build a society where people can live with dignity and peace.

Section 2: Measures to be Taken in Each Area

1. Cancer Prevention

1) Primary prevention of cancer
2) Early detection of cancer and cancer screening (secondary prevention)

2. Improvement of Cancer Care

1) Genomic medicine in treating cancer
2) Surgical therapies, radiotherapies, pharmacotherapies, and immunotherapies for cancer
3) **Team medical approach**
4) Rehabilitation for patients with cancer
5) Supportive therapies
6) Rare cancer and refractory cancer (Measures should be taken depending on cancer characteristics)
7) Pediatric cancer in patients in AYA generation*, cancer in the elderly
   * Adolescent and Young Adult
8) Pathological diagnosis
9) Cancer registration
10) Initiatives for early development of / approval for pharmaceutical products / medical devices

3. Cohabitation with Cancer

1) Palliative care from the time of diagnosis of cancer
2) **Support for consultation and information provision**
3) Cancer control / support for patients with cancer in cooperation with society
4) Social issues including employment of patients with cancer
5) Cancer control according to life stages

**4. Development of the Supporting Infrastructure**

1) Cancer Research 2) Human Resources Development 3) Education and Awareness Building on Cancer

Section 3: Requirements for Comprehensive and Systematic Promotion of Cancer Control

1. Further strengthened cooperation among relevant parties
2. Development of plans by prefectural governments
3. Efforts by people in the country including patients with cancer
4. Cooperation with patient groups

5. Implementation of required financial measures and efficient use / prioritization of the budget
6. Follow-up of the achievement status of the goals
7. Review of the basic plan

Source: Basic Plan to Promote Cancer Control Programs, MHLW (March 9, 2018)

Benefits of Multidisciplinary Team Care Workshops

The goal is to help various medical professionals involved in patient care exercise each specialist knowledge to increase satisfaction of the patients.
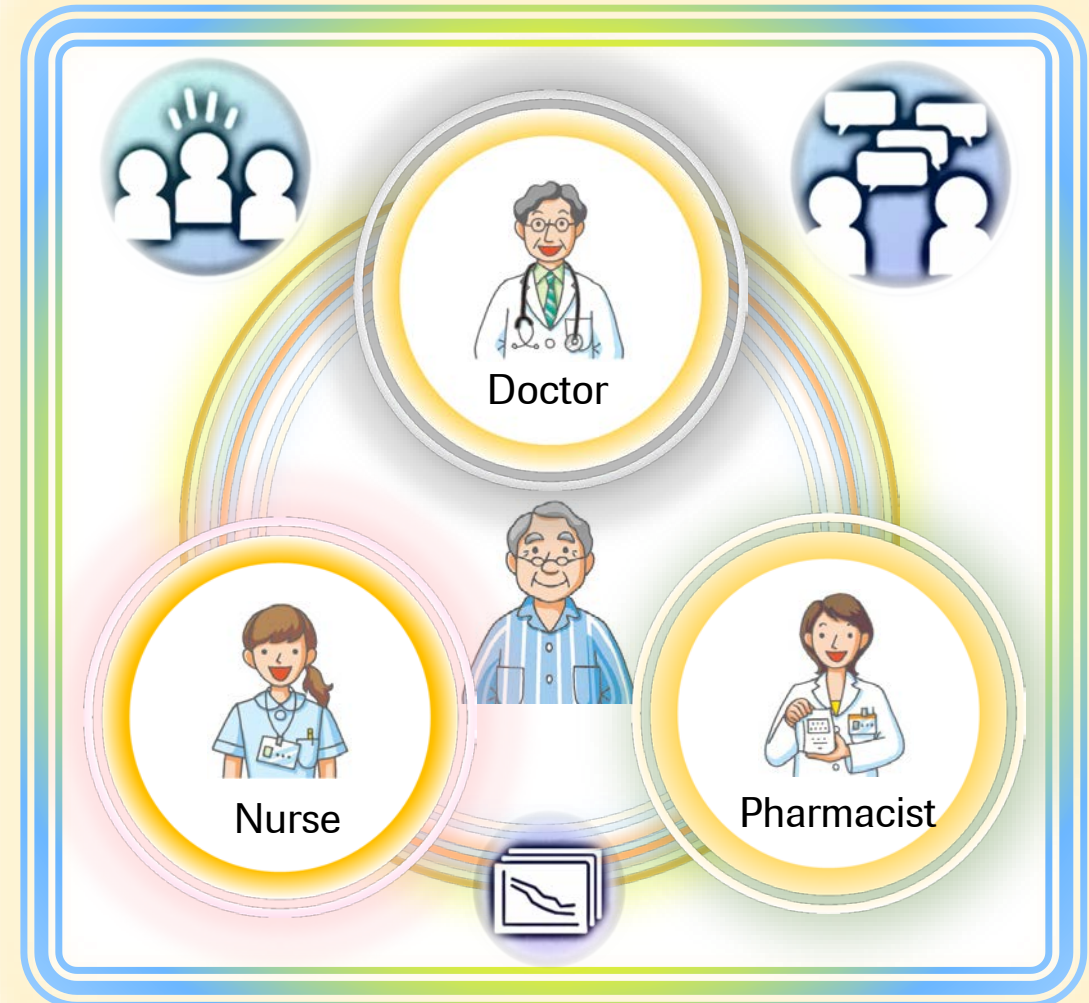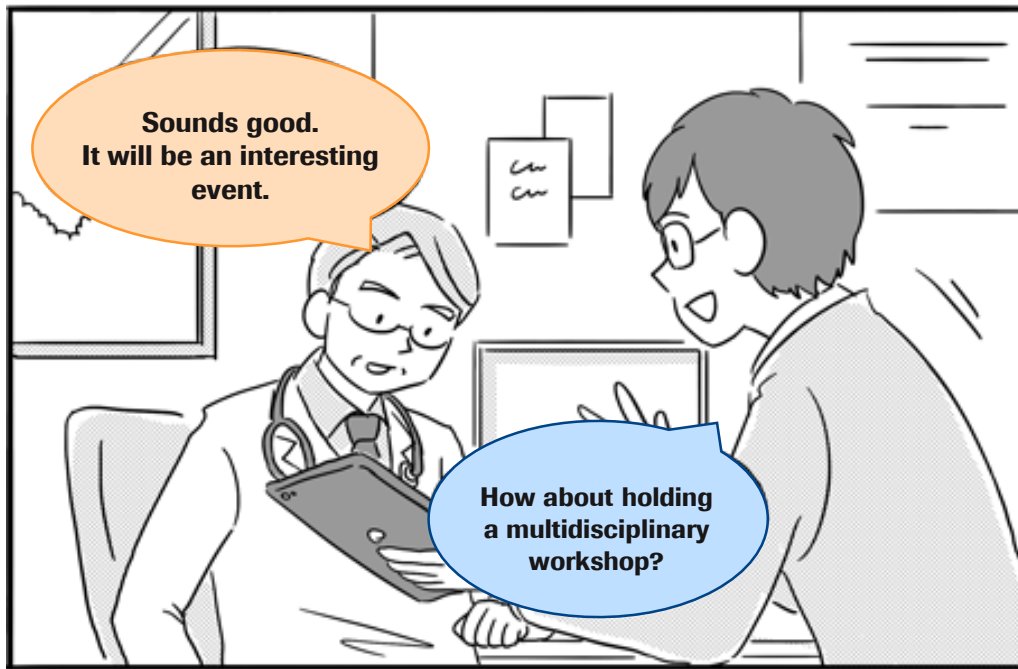
A Scene from the Workshop

A program including discussion, role-playing and other exercises can help participants learn knowledge and skills that conventional classroom training cannot offer.
Chugai MRs participate in the workshop with healthcare professionals as a member of the medical team.

Zoom de Workshop

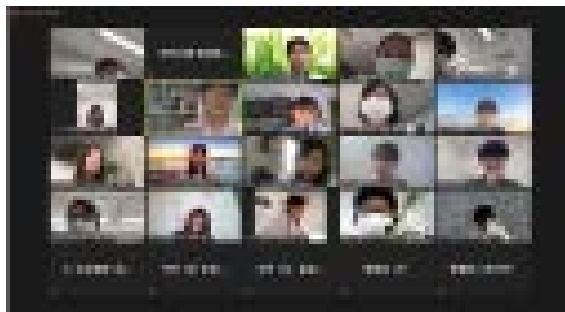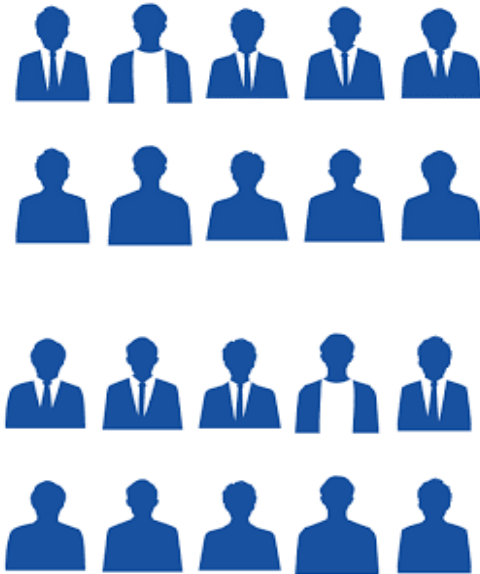# Effective Utilization of the Online System
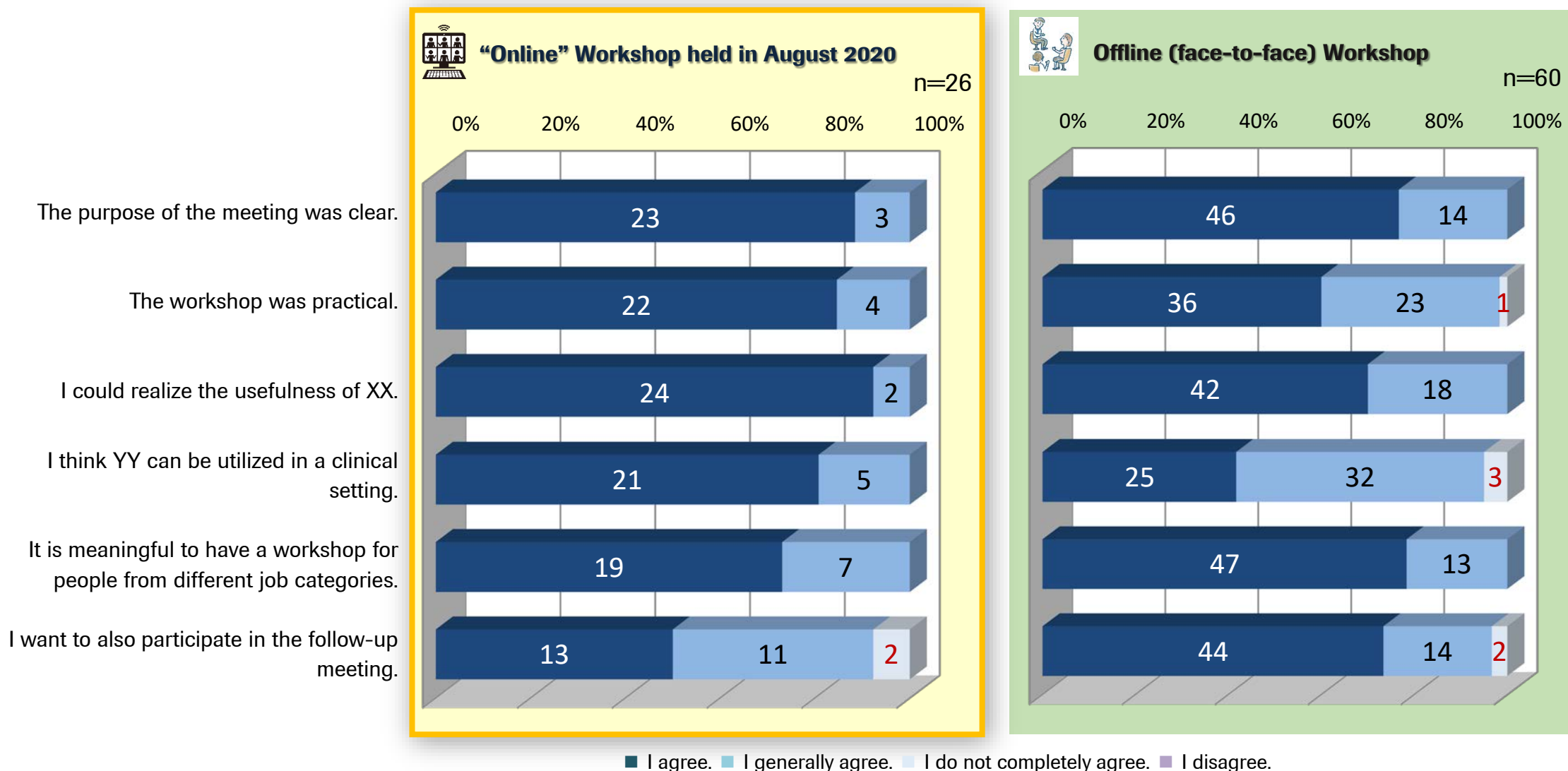
■ **Plenary meeting**

■ **Group discussion**

Separate participants into small groups. They can deepen awareness and learning with discussion.

In some programs, a 360 degree camera will be used to bring the realism of the workshop into each participant's location.

Comparison of Results from the Questionnaire Survey for Participants

"Online" Workshop held in August 2020

n=26

| | 0% | 20% | 40% | 60% | 80% | 100% |

Question	I agree	I do not completely agree	I disagree
The purpose of the meeting was clear.	23	3	
The workshop was practical.	22	4	
I could realize the usefulness of XX.	24	2	
I think YY can be utilized in a clinical setting.	21	5	
It is meaningful to have a workshop for people from different job categories.	19	7	
I want to also participate in the follow-up meeting.	13	11	2

Offline (face-to-face) Workshop

n=60

| | 0% | 20% | 40% | 60% | 80% | 100% |

I agree	I do not completely agree	I disagree
46	14	
36	23	1
42	18	
25	32	3
47	13	
44	14	2

■ I agree. ■ I generally agree. ■ I do not completely agree. ■ I disagree.

We Received Positive Feedback from Participants

Compared to the face-to-face role-playing exercise, I could concentrate more and enjoy the exercise as though it were a game, because I did not mind what others may think during the exercise through a screen.

It is great that we can exchange opinions with doctors in different areas whom we usually cannot talk with, because there is no limitation in access to online workshops.
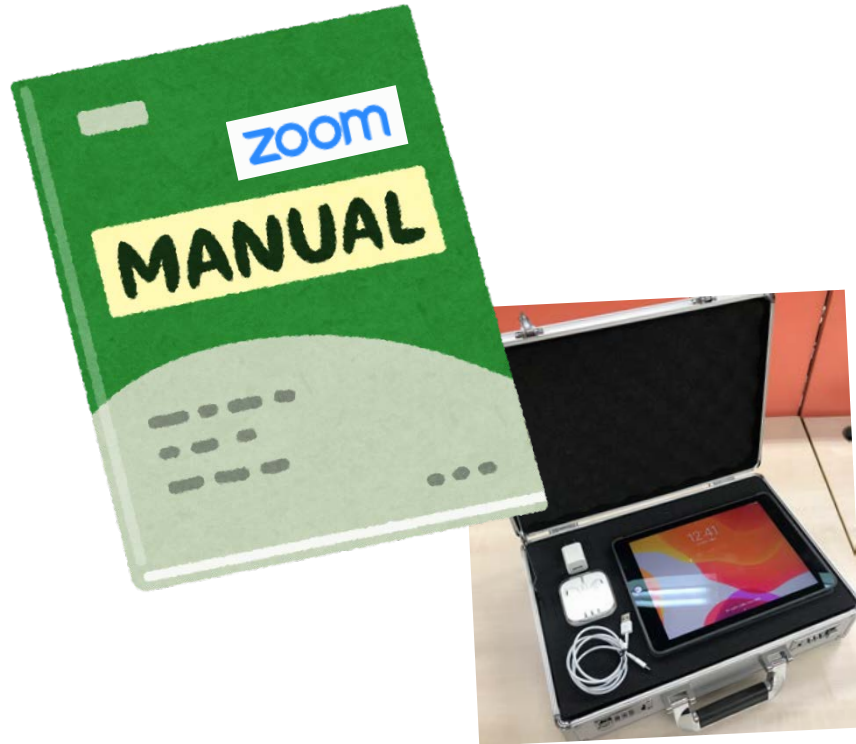
Participants

I am grateful for Chugai's efforts to implement this project proactively taking advantage of online service, despite the recent chaotic situation.

Successful results of the online project as a new initiative gave me confidence.

MR

I could win over customers who do not usually participate in workshops.

The quality has been increasing each time.

We Can Enhance Communication with Customers Taking Advantage of Online Workshops

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