

H.U. Group Technology Day 2022

December 9, 2022

H.U. Group Holdings, Inc.

(TSE: 4544)

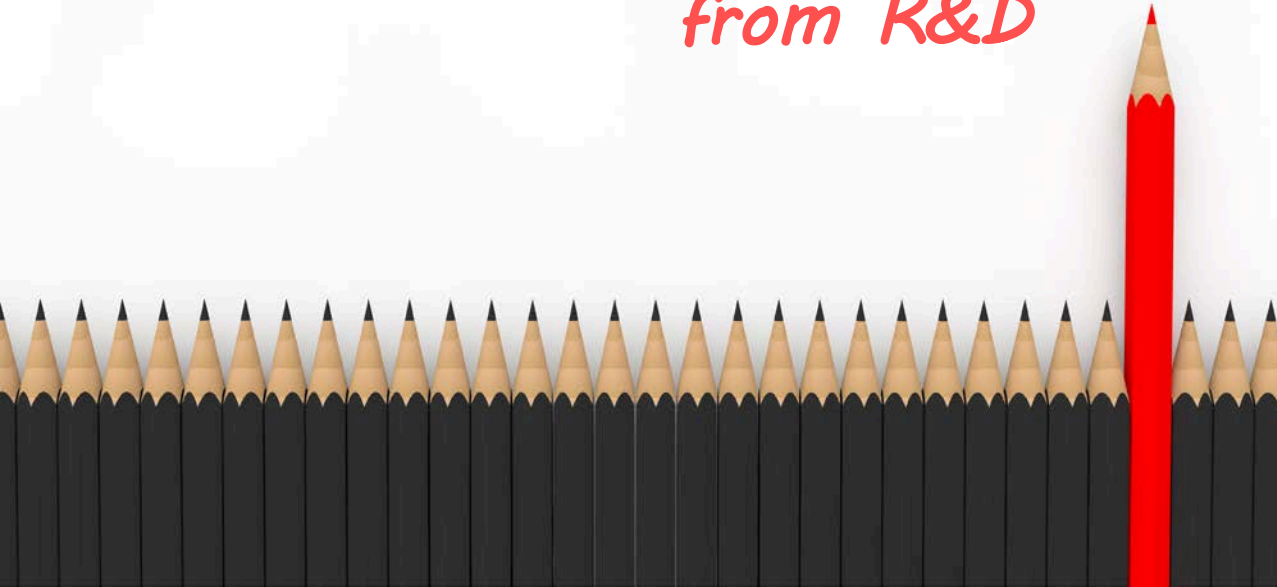
H.U. Group R&D

- 1 Overview
- 2 Pandemic Response
- 3 IVD R&D and Direction
- 4 LTS/Corporate R&D and Direction

【Presenter】

- 1, 2, 4: Kazuya Omi, PhD, Executive Officer (Research & Development), H.U. Group Holdings, Inc.
- 3: Katsumi Aoyagi, PhD, Managing Director, Fujirebio Inc.

*No 1, Only-one
from R&D*



1. Overview

- History of R&D and Value Creation Story

H.U. Group R&D Vision

Mission

Create **new value** in healthcare and thereby contribute to human health and the future of medical care.

Innovate medical care and health care through No. 1, Only-one products and services

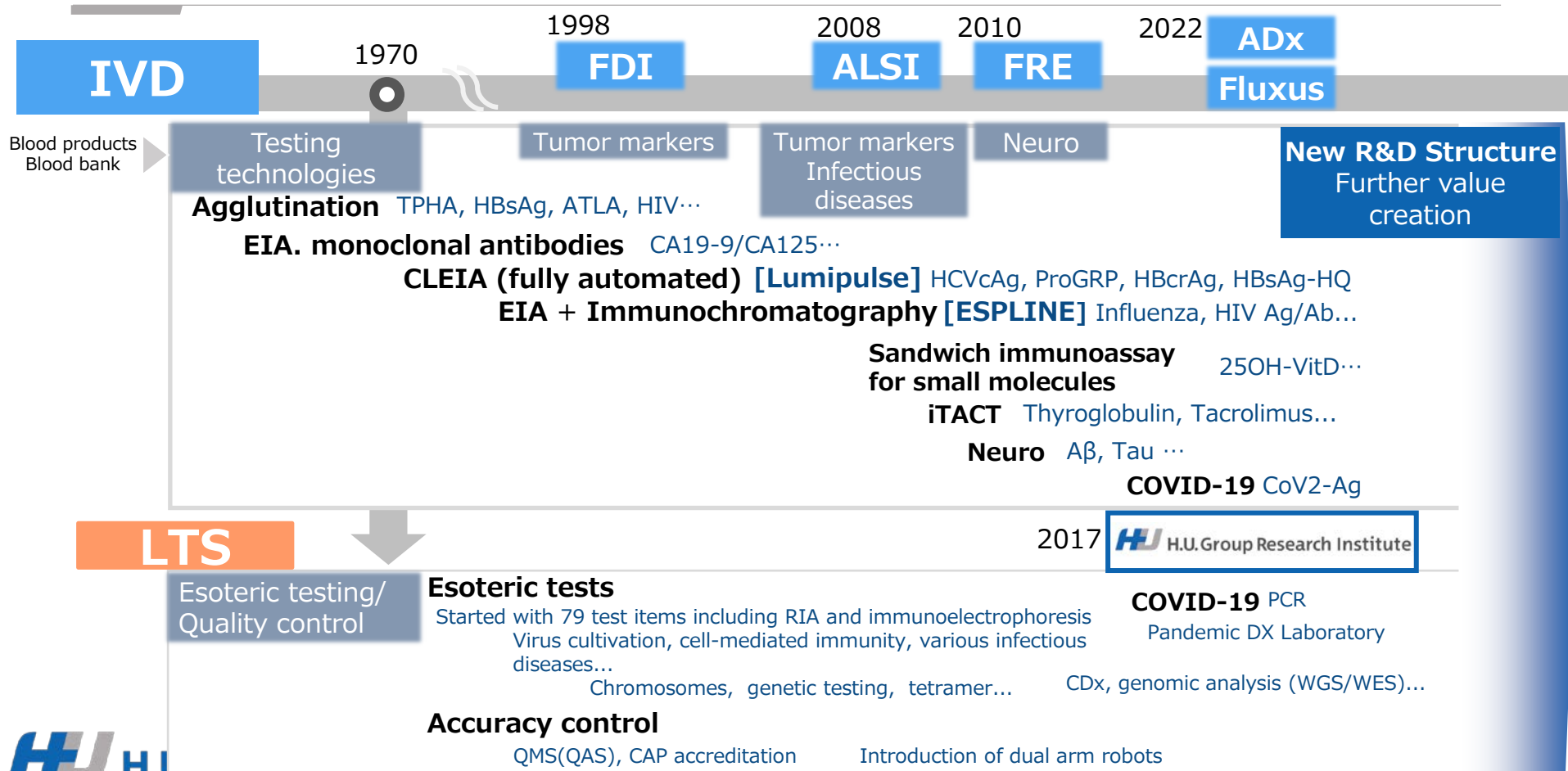
*No 1, Only-one
from R&D*



Best Healthcare
Everywhere



R&D: History of No.1, Only-one

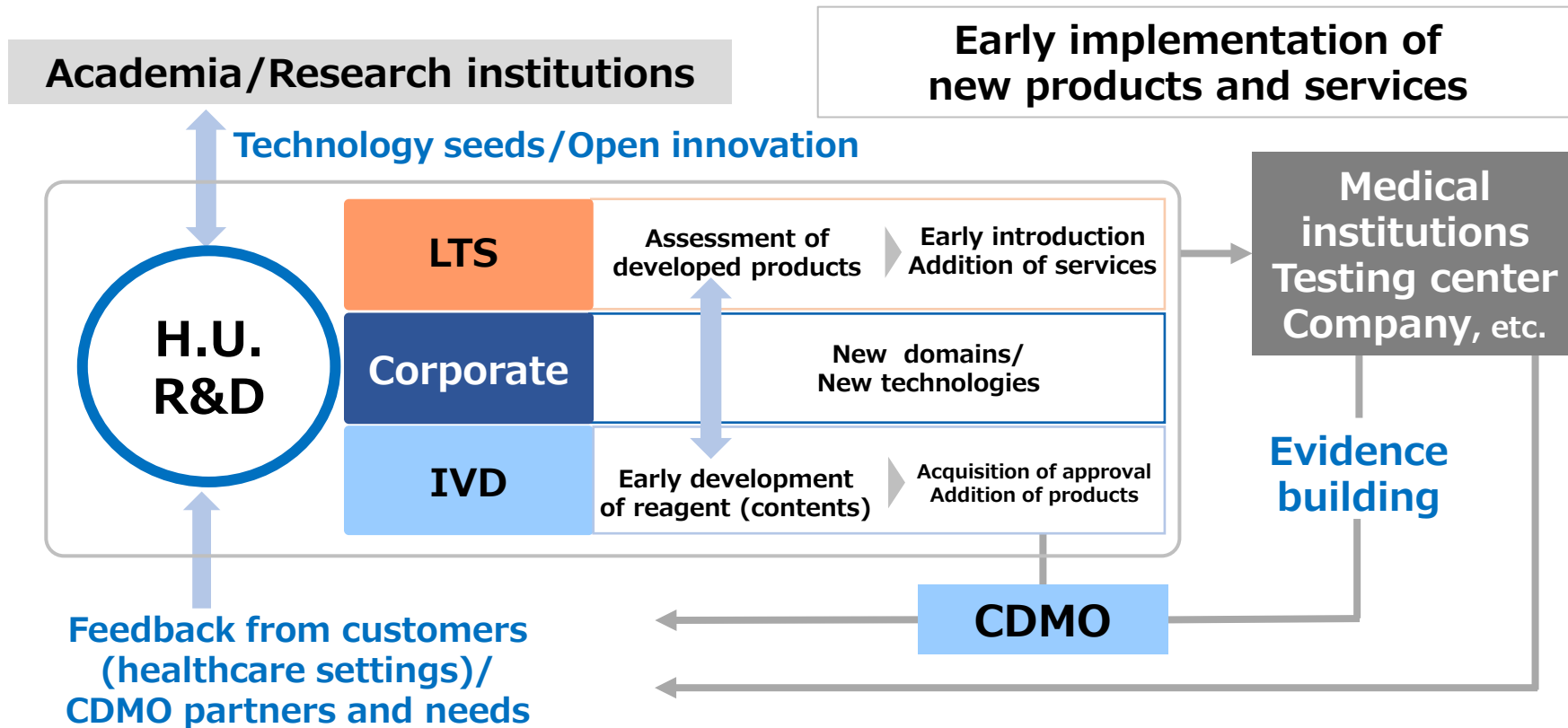


Disparate Activities by Each Company → H.U. R&D Activities



**Achieve early implementation of new technologies,
products and services**

R&D-led Value Creation Story

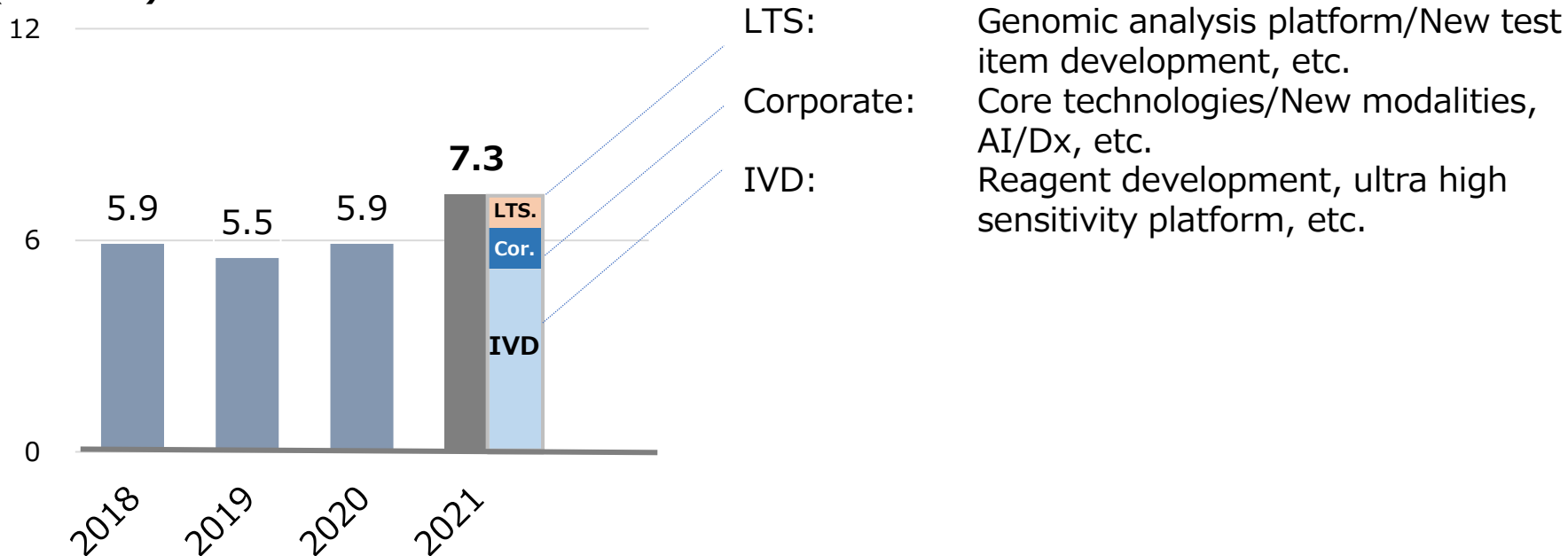


Strengthening of R&D

R&D expenses

FY2021 results: 7,281 million yen

(¥ billion)

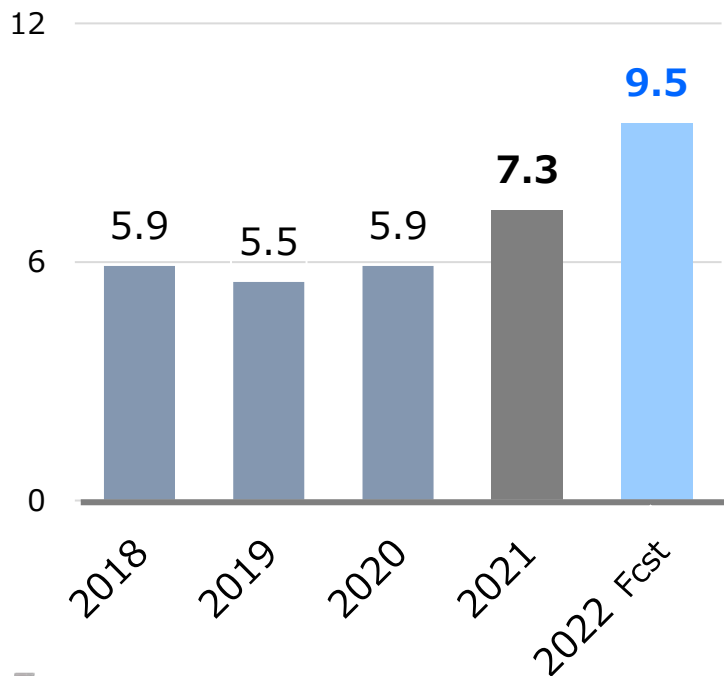


Strengthening of R&D

R&D expenses

FY2021 results: 7,281 million yen

(¥ billion)

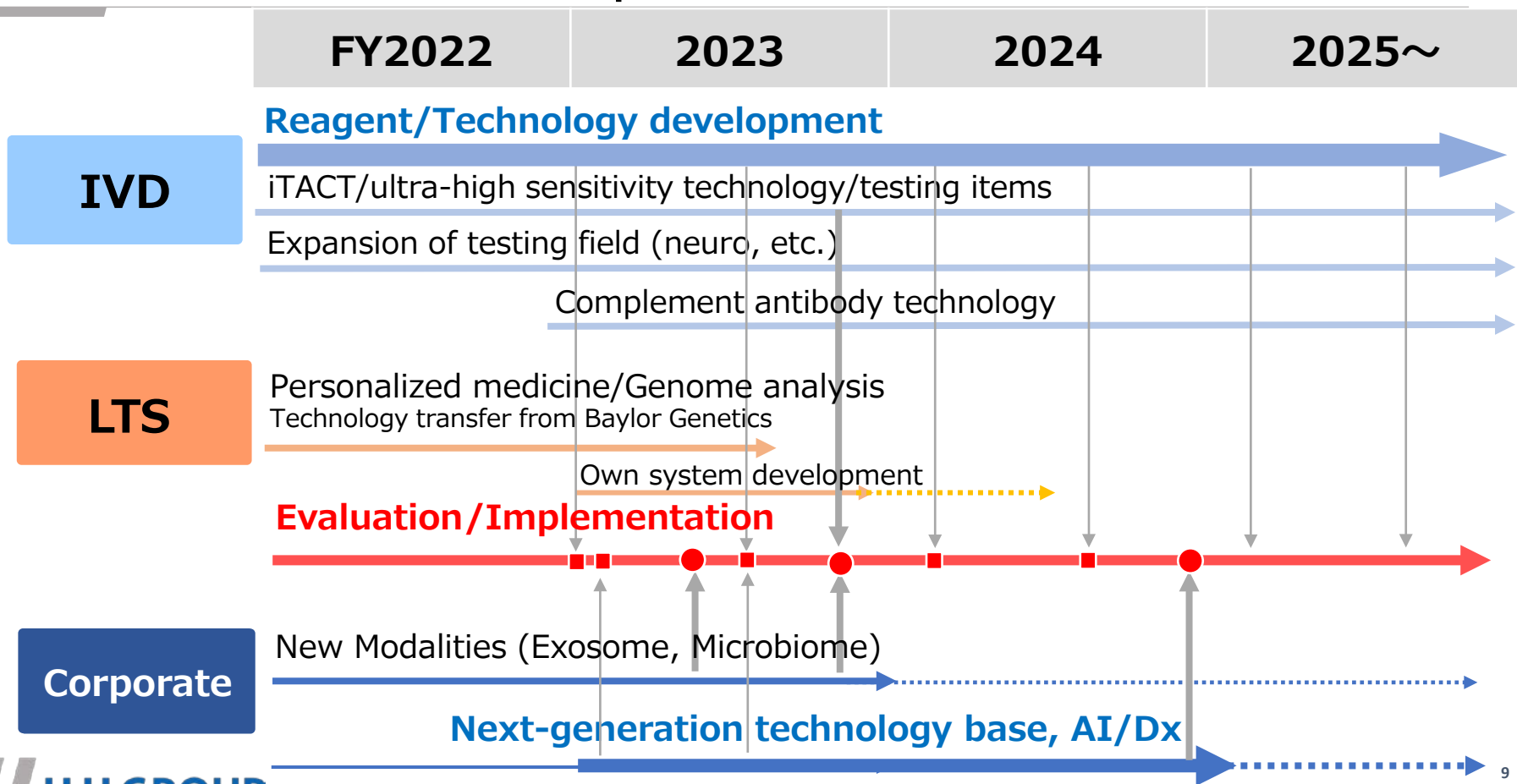


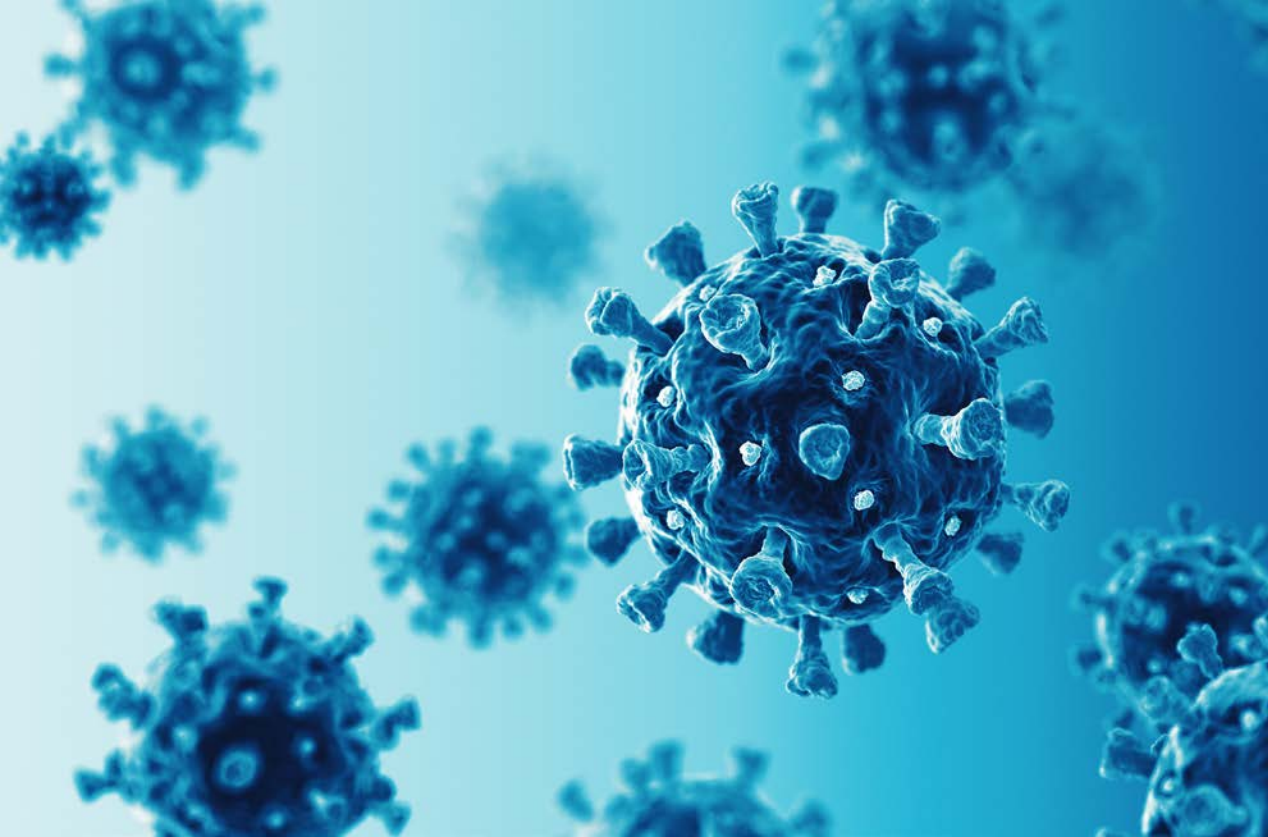
LTS: Genomic analysis platform/New test item development, etc.
Corporate: Core technologies/New modalities, AI/Dx, etc.
IVD: Reagent development, ultra high sensitivity platform, etc.

⇒ **Aim for stable R&D investment at level of 10 billion yen per year during current medium-term plan**

Further development of existing technologies and acquisition of new technologies
Securing of diverse highly skilled talent

Overview of R&D Pipeline





2. Pandemic Response

- R&D-led Japan Firsts/World Firsts

R&D-led Japan Firsts/World Firsts

COVID19 report

December 2019



A certain day in January



Issuance of instructions to develop PCR test/antigen test reagents

R&D-led Japan Firsts/World Firsts

COVID19 report –

December 2019



A certain day in January

Issuance of instructions to develop PCR test/antigen test reagents

February

4

COVID-19 outbreak on Diamond Princess

March

11

WHO's declaration of COVID-19 outbreak as pandemic

April 7

First declaration of state of emergency
(Number of cases in Tokyo: **78**)

May 25

Lifting of state of emergency
(Number of cases in Tokyo: **8**)

R&D-led Japan Firsts/World Firsts

COVID19 report –

December 2019

HU H.U.GROUP

COVID-19 outbreak
on Diamond Princess

WHO's declaration of
COVID-19 outbreak as
pandemic

First declaration of state
of emergency
(Number of cases in Tokyo: 78)

Lifting of state of
emergency
(Number of cases in Tokyo: 8)

February
4

A certain day in January

Issuance of instructions to develop PCR test/antigen test reagents

March
11

February 12

Introduction of PCR testing

Receipt of specimens from people onboard Diamond Princess

First private
company in Japan

April 7

April 27

Application for approval of ESPLINE SARS-CoV-2

May 13

Approval of Espline SARS-CoV-2

Launch of rapid antigen tests

First in
Japan

May 25

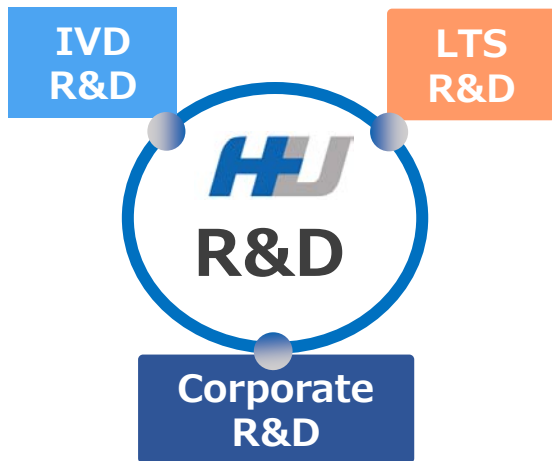
June 19

Approval of Lumipulse SARS-CoV-2

Launch of quantitative antigen tests

World
first

R&D Cooperation and Value Creation



New testing reagents

- **Development of COVID-19-related reagents**
(antibodies, influenza, risk factors for severe disease)

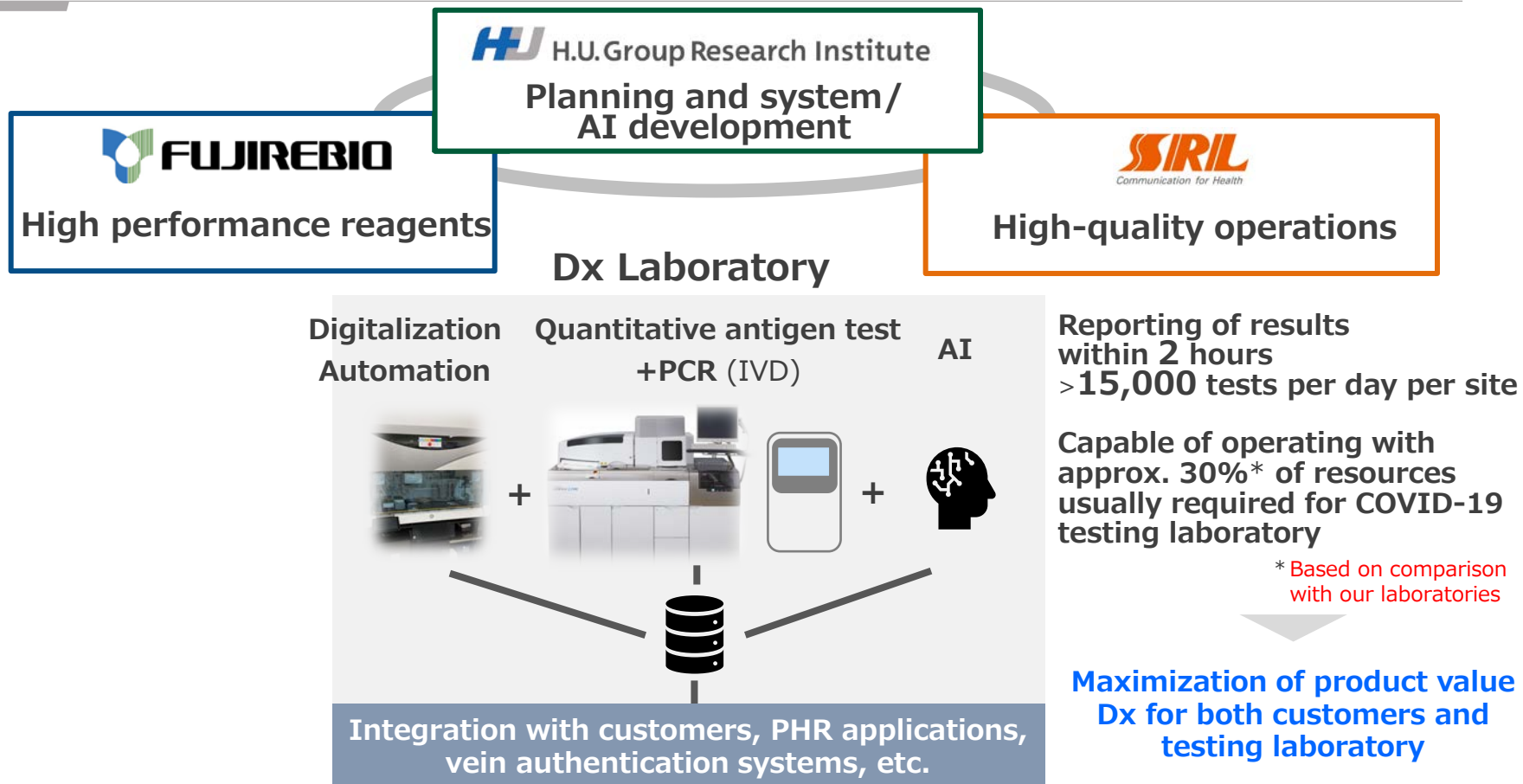
New services and contribution to science

- **Various clinical research services and evidence building**
- **Genomic analysis of variants and viruses**
- **Analysis of viruses in environment**
- **Comparison of test accuracy/Analysis of epidemiological data, etc.**

New testing infrastructure

- **Airport quarantine stations**
- **Large-scale screening**
(events and high-risk gatherings, etc.) → Next page

New Testing Infrastructure: Development and Implementation of Dx Laboratory System in Response to Pandemic



Preparation for Next Pandemic

Novel influenza viruses, unknown viruses, drug resistant bacteria, etc.

Prevalent Eurasian avian-like H1N1 swine influenza virus with 2009 pandemic viral genes facilitating human infection

Honglei Sun^{a,1}, Yihong Xiao^{b,1}, Jiyu Liu^{a,1}, Dayan Wang^{c,d}, Fangtao Li^a, Chenxi Wang^a, Chong Li^a, Junda Zhu^a, Jingwei Song^a, Haoran Sun^a, Zhimin Jiang^a, Litao Liu^a, Xin Zhang^a, Kai Wei^b, Dongjun Hou^a, Juan Pu^a, Yipeng Sun^a, Qi Tong^a, Yuhai Bi^a, Kin-Chow Chang^f, Sidang Liu^b, George F. Gao^{c,d,e,2}, and Jinhua Liu^{a,2}

^aKey Laboratory of Animal Epidemiology and Zoonosis, Ministry of Agriculture, College of Veterinary Medicine, China Agricultural University, 100193 Beijing, China; ^bDepartment of Fundamental Veterinary Medicine, College of Animal Science and Veterinary Medicine, Shandong Agricultural University, 271000 Tai'an, China; ^cChinese National Influenza Center, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, 102206 Beijing, China; ^dWorld Health Organization Collaborating Center for Reference and Research on Influenza, 102206 Beijing, China; ^eKey Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Center for Influenza Research and Early-Warning, Chinese Academy of Sciences, 100101 Beijing, China; and ^fSchool of Veterinary Medicine and Science, University of Nottingham, Loughborough LE12 5RD, United Kingdom

Contributed by George F. Gao, April 28, 2020 (sent for review December 9, 2019; reviewed by Ian H. Brown and Xiu-Feng Henry Wan)

Pigs are considered as important hosts or "mixing vessels" for the generation of pandemic influenza viruses. Systematic surveillance after 2009, the pdm/09 H1N1 virus in humans has spread back into pig herds around the world (12, 13). Subsequently, reassortants

PNAS, 2020 Jul 21; 117(29):17204-17210



H.U. Group Research Institute

Testing technologies (infectious diseases, higher sensitivity)
High-quality, high-capacity processing operations
DX talent

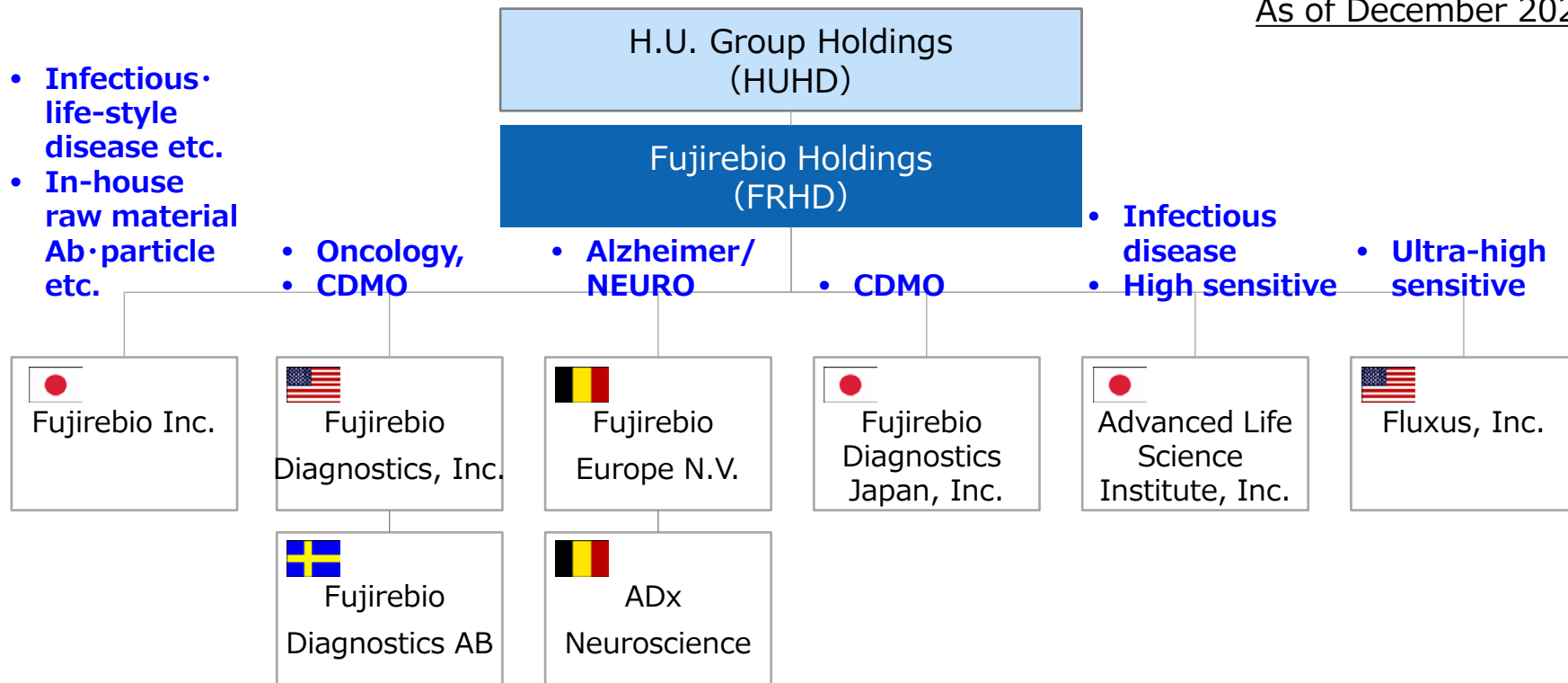




3. IVD Technological Development and Direction

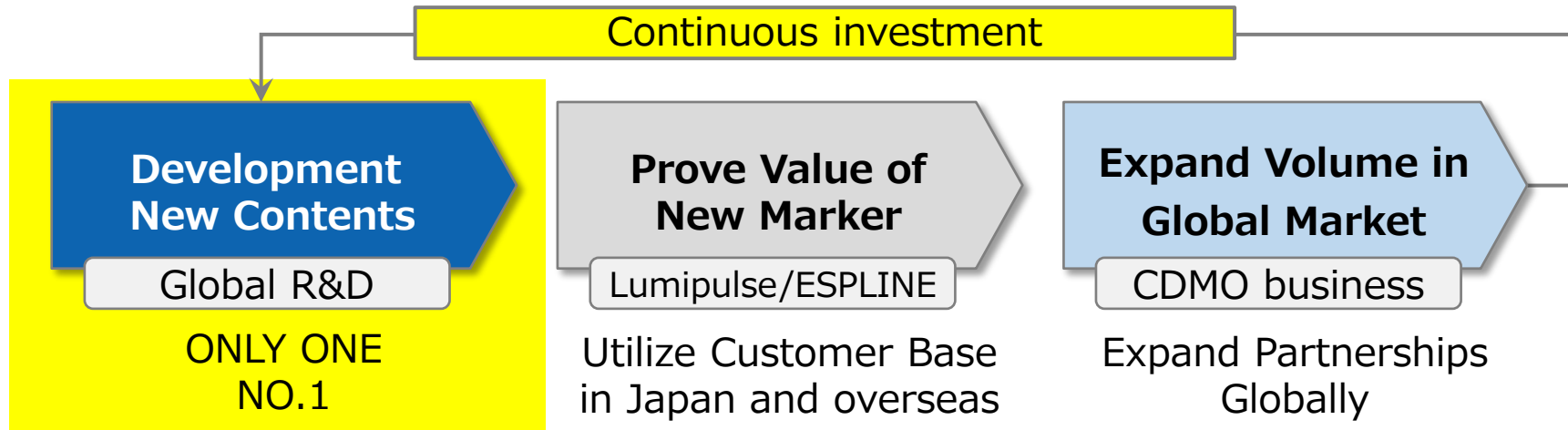
Global Organization

As of December 2022



Expanding R&D structure globally as a pioneer in the development of immunoassay technology/system development in each clinical domain

R&D at New Global Strategy



Basic Policy :

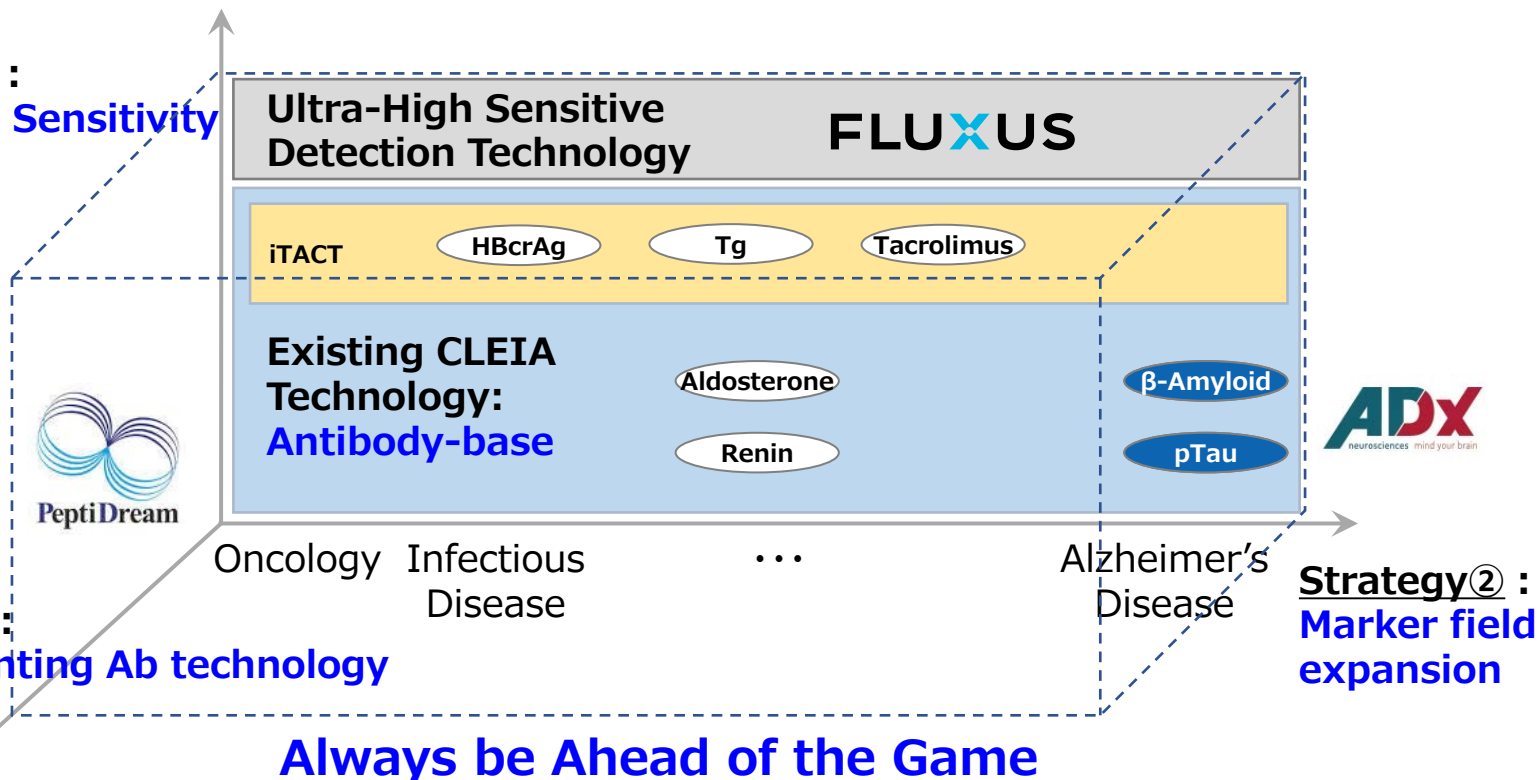
**"Contribute to more accurate testing,
wider clinical applicability, and correct clinical diagnosis"**

- Accurately measure & detect analytes presented in specimens
- Pursue novel clinical usefulness of each marker/test

R&D Technology / Business Strategy

Strategy① :

Increasing Sensitivity



All output can be supplied to our global partners through CDMO model

Achievement and Progress

Strategy ① Increasing Sensitivity

- **Developed “iTACT”, effective pre-treatment for high sensitive test**
 - Patent: HBcrAg (Hepatitis B), Tg (Thyroid Cancer)
- **Acquired Fluxus Technology**
 - Accelerate new platform development by Ultra-high sensitive technology

Strategy ② Marker Field Expansion

- **Applied Sandwich method to markers of lifestyle-related diseases**
 - Patent: Aldosterone, Renin(Hypertension), 25-OH Vitamin-D(Osteoporosis)
- **Acquired ADx raw material and know-how**
 - Accelerate Neuro/Alzheimer markers through

Strategy ③ Complement Anti-body Technology

- **Technology License Agreement with PeptiDream**
 - Complement Ab-based reagents development with peptide
 - Practical application to new biomarkers, more stable production and supply chain

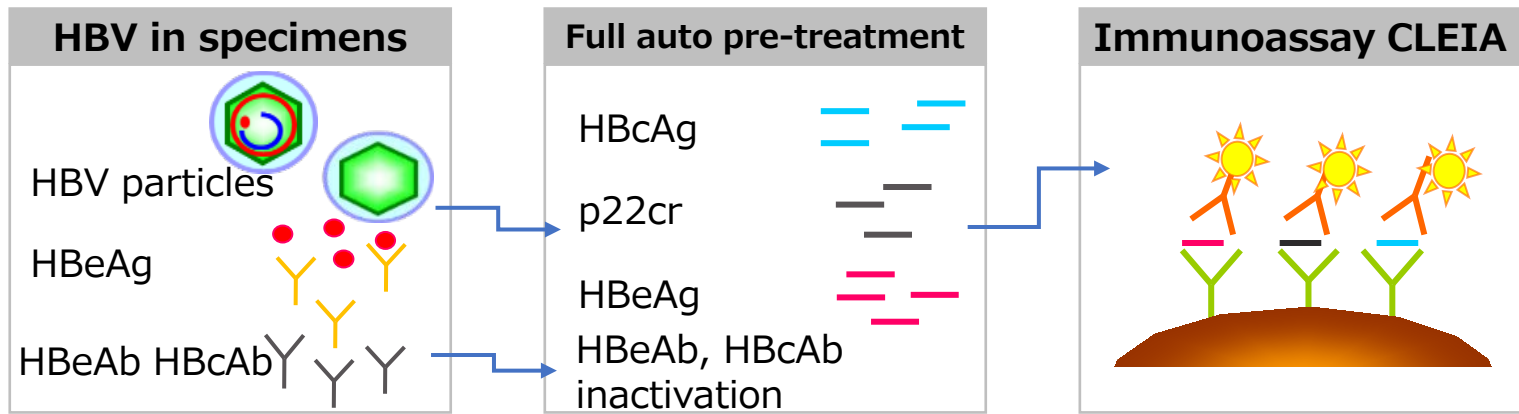
Strategy①: iTACT¹ HBcrAg (Hepatitis B)

Issue

Pitfall : Inhibitors of immune response in specimens

- Host-derived antibodies against infectious disease antigens
- Autoantibodies and binding proteins against endocrine & tumor markers

iTACT Solution



Fully automated process from sample preparation to immunoassay,
achieving 8-10 times higher sensitivity

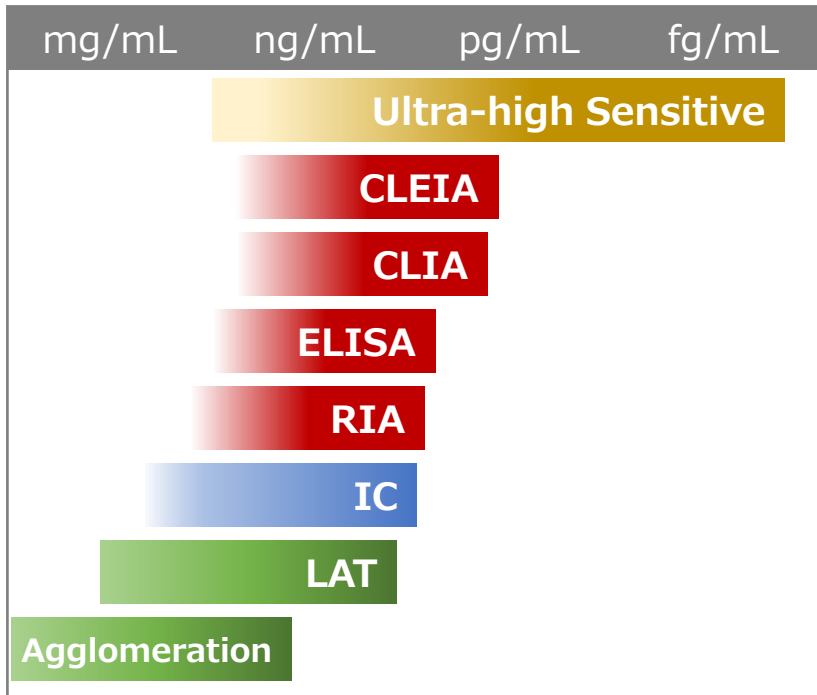
**Expected application: fully automated routine in-hospital testing,
treatment/reactivation monitoring, etc.**

Strategy①: Ultra-high Sensitive Detection

Strategic Point

- Platform development by Fluxus technology
 - Single molecule detection method
 - Launch RUO by FY23
- Marker development with clinical significance
 - Alzheimer's disease, Cancer, Infectious diseases, etc.
- Enhance platform strategy
 - Combine to existing CL method
- Expand CDMO strategy
 - Supply partners globally

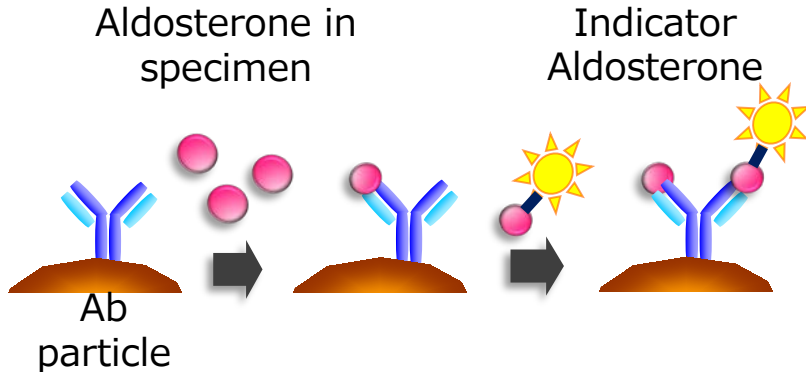
Expected Benefit



Strategy②: Aldosterone (Hypertension)

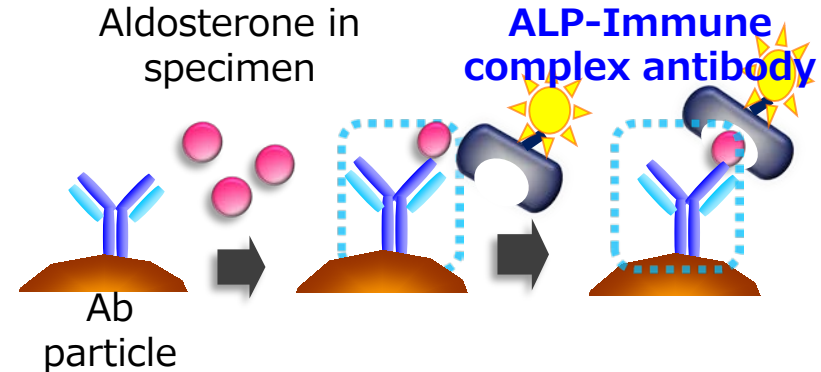
One-Ab competitive method

- Low sensitivity: low reproducibility in low value range
- Limited cross-reactivity/specificity



Two-Ab sandwich method

- Ab development against immune complexes
- Non-competitive Ab development with solid phase Ab within small molecules
 - High reproducibility in low value range
 - Low cross-reactivity/high specificity



**Accurate diagnosis and treatment decisions
by providing highly sensitive, highly specific, and highly accurate tests**

Strategy② Expand line-up for Alzheimer

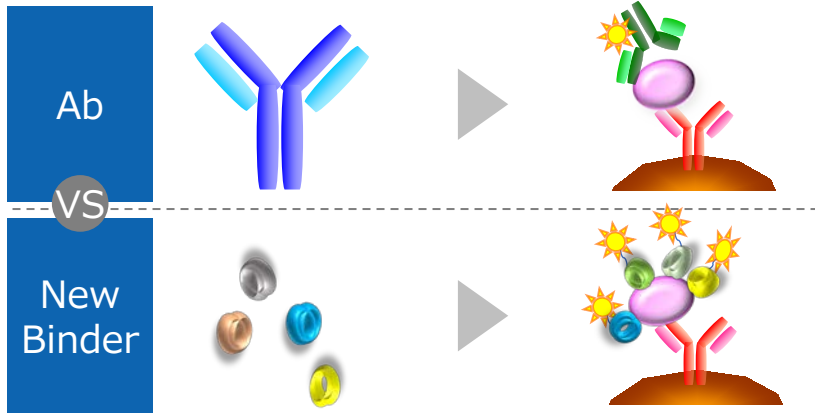
	CSF Markers	Plasma Markers	
IVD	<ul style="list-style-type: none">• β-Amyloid 1-42• β-Amyloid 1-40• pTau181• Total Tau	<p>※ Based on our strategic story, will proceed global application after acquiring data</p>	
RUO	<ul style="list-style-type: none">• Neurofilament Light (NfL) <div>Black : Launched Blue : Under development</div>	<ul style="list-style-type: none">• β-Amyloid 1-42• β-Amyloid 1-40• pTau181• pTau 217• pTau 231	<ul style="list-style-type: none">• GFAP• BDNF• ApoE4• ApoE• Neurofilament Light (NfL)

Strategy③: Complement Ab Technology

Strategic Point

- New clinical diagnostics reagents by PeptiDream technology PDPS¹
 - Low molecular weight cyclic peptide binders with high specificity for detection
- Practical application for novel biomarkers
- Prove value on each platform
- Add line-up of CDMO business

Expected Benefit



- Binding to recognition sites which are difficult to obtain antibodies
- Improved performance of various immunoassay methods
- Developed in a very short time
- Reduction of raw material costs, reduction of lot-to-lot differences, etc.

Summary

By **3 strategies**, IVD R&D aims to develop **ONLY ONE/NO.1** products which other companies do not have and supply globally through the CDMO business

- **Strategy ① Increasing sensitivity :**
 - 1. Apply iTACT to products, 2. Go to market with Fluxus technology
- **Strategy ② Marker field expansion :**
 - 1. Apply small molecule sandwich method to products,
2. Marker development by raw material and know-how of ADx
- **Strategy ③ Complementing Ab technology**
 - 1. Develop products with PeptiDream technology

Fast “go-to-market” with high clinical significance by **Global R&D Team**



4. LTS/Corporate R&D and Direction

- Increasingly Sophisticated Medical Care and Healthcare

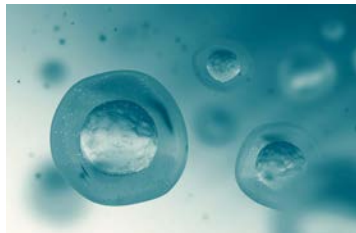
Impact of COVID-19 Pandemic

Increasingly sophisticated medical care and related technologies

Personalized medicine
Genome medicine



Cell therapy and regenerative medicine
New modalities



Nature of medical care and healthcare

Digital and healthcare



Preventive medicine



The technologies that will be required in the future in the healthcare field will be essentially the same (As we expected)

Some are being introduced today

LTS/Corporate:
Main R&D
Fields

Increasingly sophisticated medical care
Digital and healthcare
Preventive medicine

Genome/Omics analysis new modalities
Next-generation laboratories, medical data, AI
POCT analysis technologies/Collaboration with different industries

Increasingly Sophisticated Medical Care: Current Clinical Laboratory Testing



**Positive
or
Negative**



Receipt of antibodies

- Issuance of ID

Pre-processing

- Centrifugation and pipetting

Measurement

- Loading into measuring machine and measurement

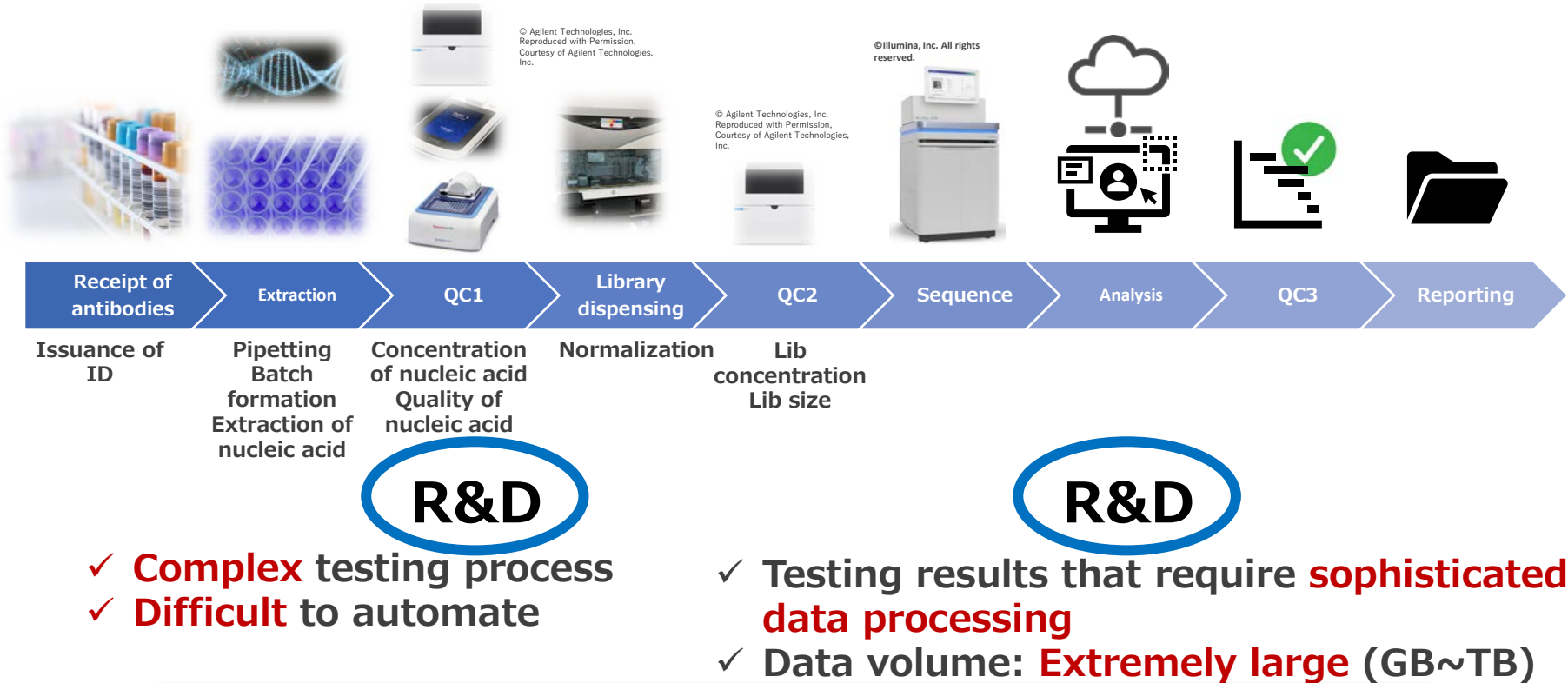
Reporting

- Creation of report based on results produced by measuring machine

- ✓ Simple testing process
- ✓ Easy to automate

- ✓ Simple measurement results
- ✓ Data volume: Small (KB~MB)

Increasingly Sophisticated Medical Care: Age of Personalized Medicine



Importance of R&D is dramatically increasing

Increasingly Sophisticated Medical Care: Genome/Omics Analysis



H.U.Group Research Institute

Development of R&D-led large-scale genomic analysis structure

- ✓ Informatics
- ✓ Robotics
- ✓ Data science

Formation of teams of engineers
and researchers for new fields

Implementation of large-scale Whole
Genome Sequencing (WGS) under
clinical laboratory testing level QMS*

* QMS: Quality Management System

Based on Reference Material 10 of 6th Meeting of Expert Committee on
Promotion of Whole Genome Analysis held on November 18, 2021
<https://www.mhlw.go.jp/content/10901000/000855706.pdf>

(List only in Japanese)

領域	AMED 公募研究開発課題	研究代表者・分担研究者	所属	解析企業
1-7	患者還元	上野貴之 部長	がん研究会 有明病院	株式会社 Cancer Precision Medicine
1-7	患者還元	浦上研一 副所長・部長	県立静岡がんセンター	エスアールエル・静岡がんセンター共同検査機構株式会社
1-7	患者還元	山本昇 副院長・科長	国立がん研究センター	タカラバイオ株式会社
1-7	患者還元	山本昇 副院長・科長	国立がん研究センター	株式会社エスアールエル
1-8	消化器がん	柴田龍弘 教授	東京大学/国立がん研究センター	株式会社エスアールエル
	分担：消化器がん	谷内田真一 教授	大阪大学	株式会社エスアールエル
	分担：消化器がん	渡邊雅之 先生	がん研究会 有明病院	株式会社 Cancer Precision Medicine
	分担：消化器がん	石川俊平 教授	東京大学	株式会社iLAC
	分担：消化器がん	三森功士 先生	九州大学	Genomedia 株式会社
1-9	血液がん	南谷泰仁 特定准教授	京都大学	株式会社エスアールエル
	血液がん	南谷泰仁 特定准教授	京都大学	タカラバイオ株式会社
1-10	小児がん	加藤元博 教授	東京大学	株式会社エスアールエル
		"	"	タカラバイオ株式会社
		"	"	株式会社 理研ジェネシス
1-11	希少がん	松田浩一 教授	東京大学	タカラバイオ株式会社
	分担：希少がん	鈴木啓道 分野長	国立がん研究センター	株式会社エスアールエル
	分担：希少がん	谷内田真一 教授	大阪大学	株式会社エスアールエル
	分担：希少がん	小笠原辰樹 先生	京都大学	タカラバイオ株式会社
1-12	婦人科がん	森城一 先生	がん研究会 有明病院	株式会社 Cancer Precision Medicine
1-13	呼吸器がん	河野隆志 分野長	国立がん研究センター	タカラバイオ株式会社
			がん研究会 有明病院	株式会社 Cancer Precision Medicine
		藤井陽一 先生	京都大学	タカラバイオ株式会社

Companies highlighted in yellow are H.U. Group companies

Increasingly Sophistical Medical Care: Genome/Omics Analysis



AkirunoCube T-cube

Pathology

- Preparation of slides by embedding, sectioning and staining tissue samples
- Digital pathology



Nucleic acid extraction/Genes

- Extraction of nucleic acid from embedded tissue and personalized genetic testing
- Quality evaluation
- Extraction methods to meet various needs



NGS/Genome

- WGS/WES
- RNA-Seq
- etc.



Integration of technology platforms required for personalized medicine of the future within the same laboratory/area



R&D

LTS

Corporate

IVD

Early implementation of new technologies and platforms both inside and outside the company

Become an essential presence for increasingly sophisticated medical care

Increasingly Sophisticated Medical Care: Strengthening of Human Resource Development and Technology Platforms

Securing computer science researchers and engineers

Reference: Genomics England Job Offer Website
Website for recruitment

Current status
in Japan

Absolutely
insufficient

IT companies
→ No knowledge of clinical
practice/medical care

Genomic England, a national project in the UK, is promoting recruitment activities focusing on IT-related human resources

Acquisition and enhancement of technology platforms

- Technology transfer/Licensing agreement with Baylor Genetics (equity-method affiliates in the US)
- Acquisition and implementation of new technologies through open innovation

Nurturing "next-generation testing talents" to realize implementation of genomic medicine

Develop own internal training and development structure

Programming in general

Lectures

- Programming basics, data science basics
- Development of analysis environment using Python/R
- Software development process, machine learning

Practice

- Program development practice using Progate
- Data analysis practice using Python/R
- Development of AWS cloud environment

Bioinformatics

Lectures

- History of NGS, basic NGS data analysis content
- Developing analysis environment, ensuring reproducibility in data analysis
- Program version management and sharing, use of public data

Practice

- Data analysis practice using SARS-CoV-2 genomic data

AI

Lectures/Practical training

- Overview of image analysis AI
- Image analysis AI annotation experience
- Development of AI to support improvement of operational efficiency

Increasingly Sophisticated Medical Care: New Modalities

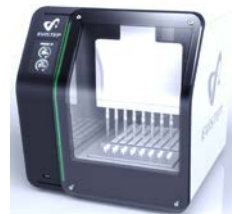
The sophistication of medical care opens up possibilities for the practical application of diverse new technologies (modalities) in the future

Examples of H.U. R&D Initiatives

Extracellular Vesicles(EVs) Exosomes

EVs Research Platform EViSTEP®
Fully automated EV extraction technology
AutoEViS®

→ Utilizing research and building evidence with
pharmaceutical companies and academia



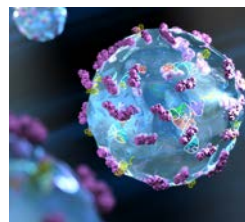
Microbiome/Bacterial flora

JIFE Japan Institute of Foods Ecology

SIRIL
Communication for Health

Expertise in the analysis of diverse antibodies
Utilization of proprietary technologies at every
stage, from extraction to analysis

→ Many contracted analysis projects and collaborative
research projects are in progress and being
implemented by other companies

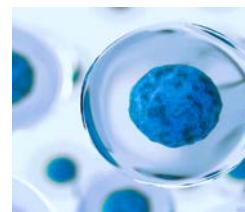


Cell therapy and regenerative medicine

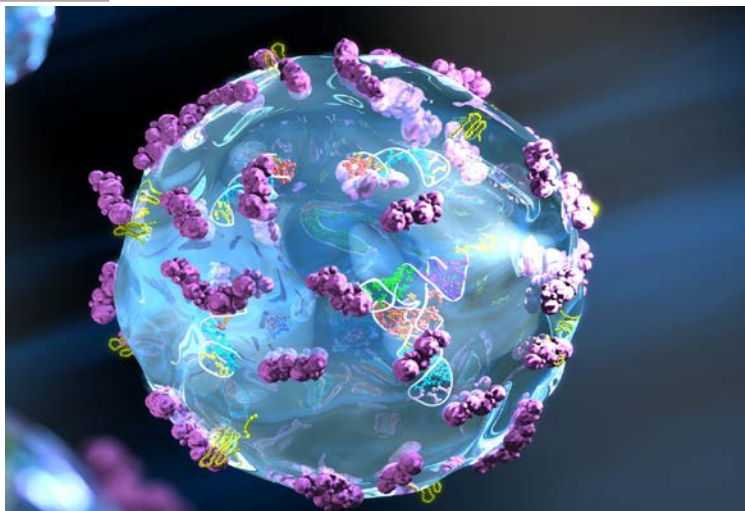
Development of quality testing and research
testing

Development/Cell Processing Center (CPC*)

→ Utilizing H.U.'s technology platforms to become a
partner for the realization of regenerative medicine



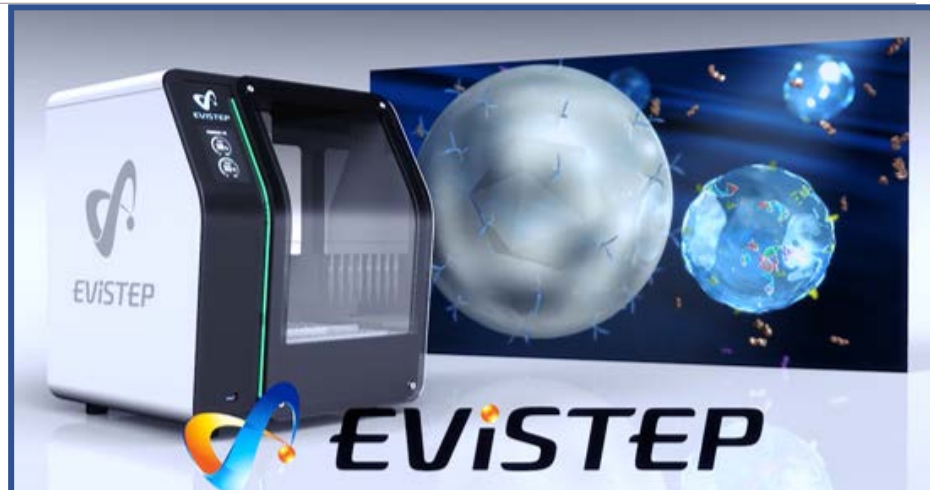
Example of Research Field: Extracellular Vesicles (EVs)/Exosome



Extracellular Vesicles

- Vesicles secreted from parental cells
- Containing proteins, mRNA, miRNA, etc.
- Promising as biomarkers and therapeutic modalities

In the absence of testing level extraction/analysis techniques, data reproducibility is an issue



H.U.'s EVs extraction and analysis platform

- Extraction of high purity EVs using in-house developed materials
- Improvement of reproducibility and throughput through automation

⇒ **Many contracted research projects and collaborative research projects related to EVs including biomarker exploration are in progress**

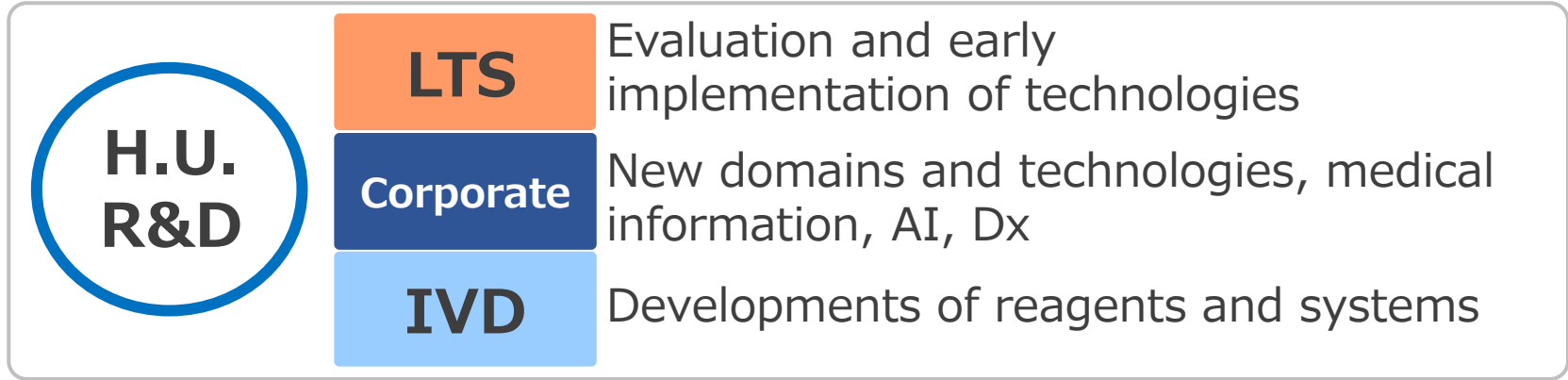
Publications

Ikeda C. et al., *Sci Rep.* 11, 1195, (2021)

Nagao K. et al., *J Biochem.* 171(5):543-554. (2022) , etc.

Summary: R&D of H.U. Group

Acceleration of value creation through new R&D structure



- Lead the healthcare in the rapidly changing medical environment
- Early implementation of new technologies and platforms

Increasingly sophisticated medical care
Digital and healthcare
Preventative medicine

Human capital, IP, technology base
→ Essential presence for future medical care/healthcare