



# The 14th Technology Presentation

March 10, 2017

Sysmex Corporation

# 1. Opening Presentation

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Hisashi Ietsugu, Chairman and CEO

- (1) R&D History and Structure
- (2) Long-Term Management Targets and Technology Themes

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(1) R&D History and Structure

(2) Long-Term Management Targets and Technology Themes

# Sysmex's R&D and Base Transition

## Kakogawa Factory (From 1973)



Relocation

- Consolidation of sales, development, manufacturing and general affairs divisions

## Kobe Factory (From 1986)

Development wing



Base expansion

- New development base
- Taking on the challenge of becoming the world leader in the hematology field

## Techno Center (From 1991)

Main building



Acquired adjoining site

- A base for the dissemination of technologies and information
- Developing products in multiple fields to become a leading solution provider in the *in vitro* diagnostics field
- Entering the life science field (Central Research Laboratories)

Central Research Laboratories (2000)



Acquired adjoining site

## Technopark (From 2008)

Commemorating 40th anniversary of establishment



- Creation of "knowledge" and its inheritance
- Technologies and the diverse human resources to win out in global competition
- Taking on the challenge of personalized medicine

## Epoch-Making Technologies and Products



The R-1000 automated reticulocyte analyzer, the world's first analyzer to automate reticulocyte measurement



The world's first robotics hematology system



The UF-100 fully automated analyzer of formed elements in urine, the world's first fully automated sediment urinalysis analyzer



The RD-100i gene amplification detector



Environmentally friendly paper packs for reagents



The XN-Series automated multiparameter hematology analyzer, our flagship model



Unique measurement parameters with the HISCL®-Series automated immunoassay system

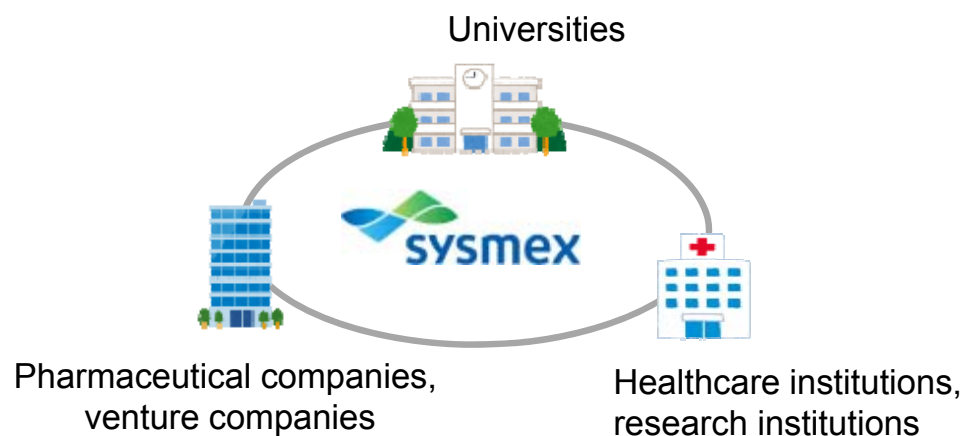
# Creating Value through Open Innovation



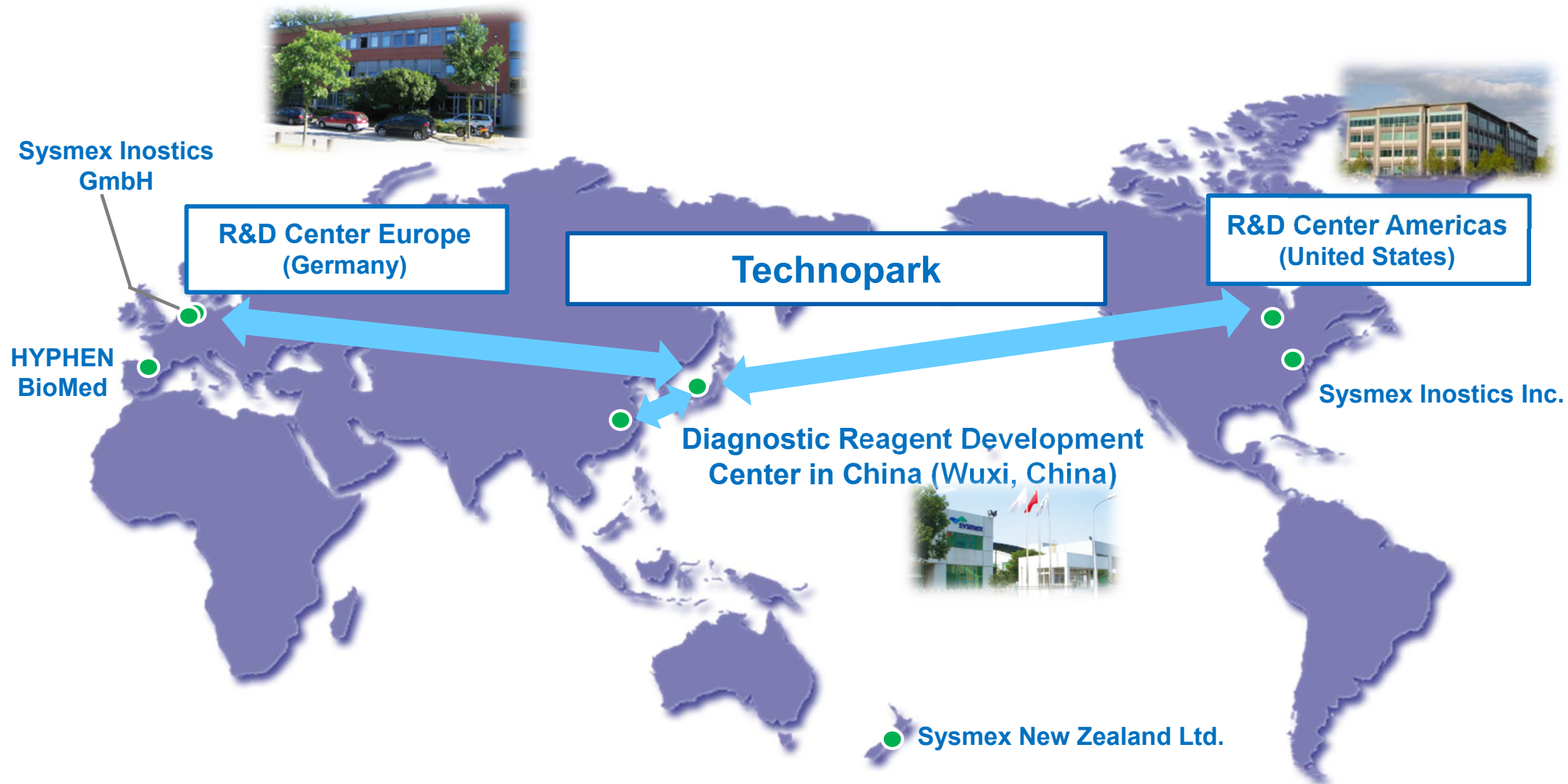
## Establishment of the Sysmex Open Innovation Lab (SOLA) within Technopark

|              |                                                                                                                |
|--------------|----------------------------------------------------------------------------------------------------------------|
| Name:        | Sysmex Open Innovation Lab (SOLA)                                                                              |
| Functions:   | Research and development on new technology platforms and applications aimed at realizing personalized medicine |
| Facilities:  | Lab area, office area, collaboration area, etc.                                                                |
| Floor space: | Approx. 1,950 m <sup>2</sup>                                                                                   |
| Opened:      | October 2015                                                                                                   |

### Proprietary technologies + open innovation

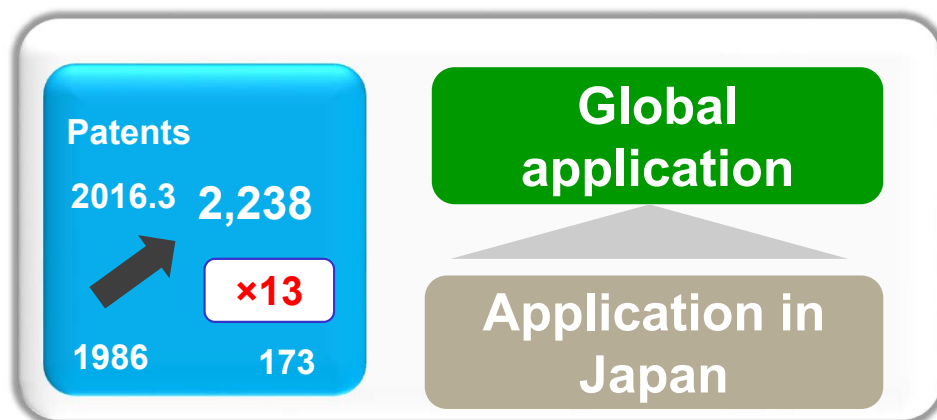
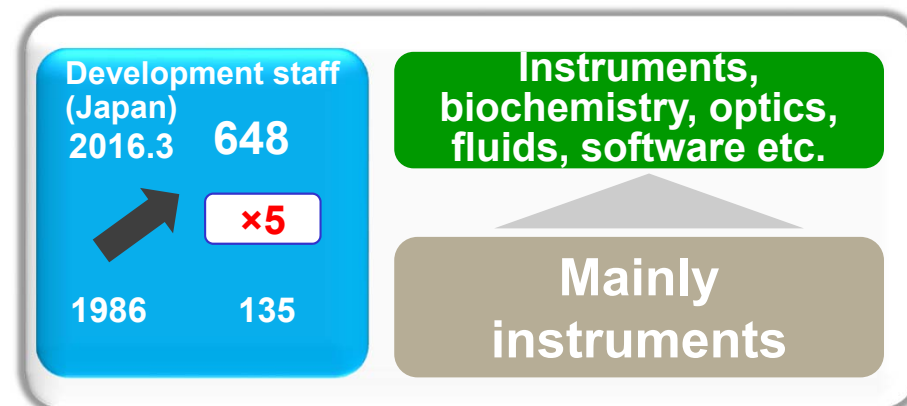
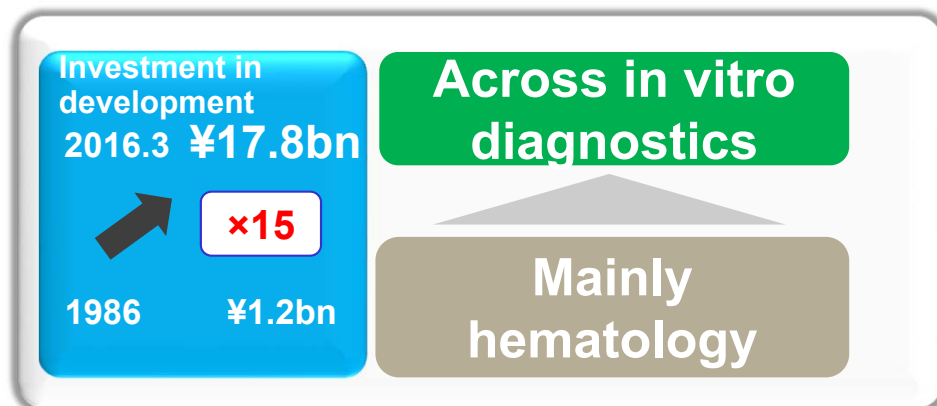


# Accelerating R&D Globalization



# Strengthening R&D Capabilities

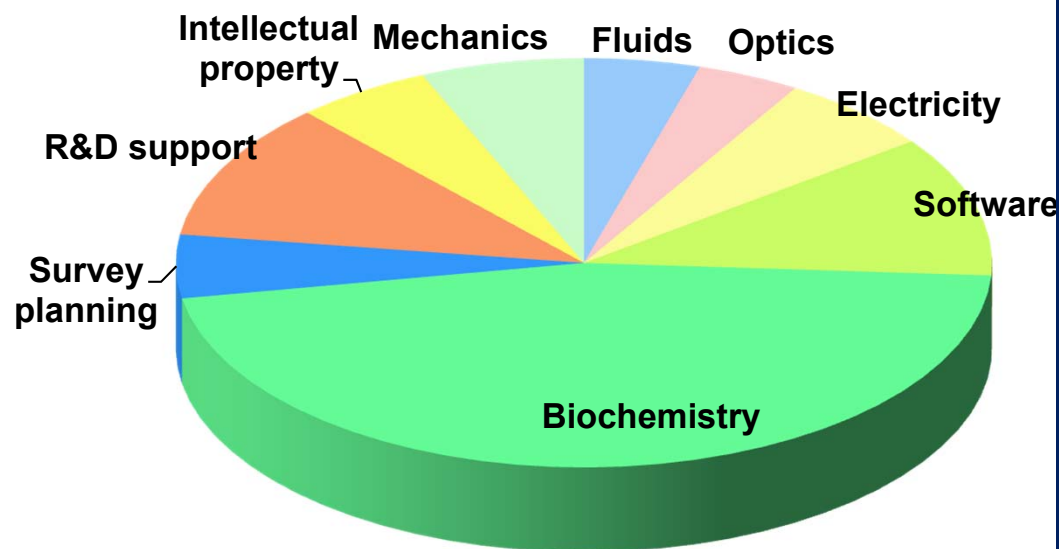
## Our R&D Capabilities by the Numbers (Japanese Standard)



# Diverse Human Resource Generating New Value



## Human Resources with Diverse Specialties

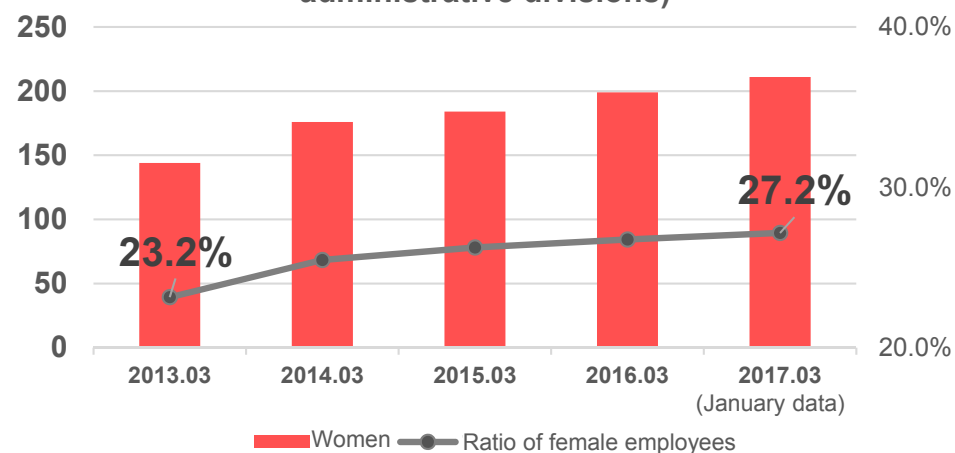


R&D personnel at Technopark: Approx. 650\*

\*Including contract and part-time employees  
(excludes temporary employees)

## Promoting Women's Career Activities

Ratio of Female Employees at Technopark  
(Includes R&D, business planning and administrative divisions)



Sysmex Kids Park, an in-house daycare center



“Eruboshi” mark, certifying Sysmex as an excellent company based on the Act on Promotion of Women's Participation and Advancement in the Workplace (Top-level certification received September 2016)

# 1. Opening Presentation

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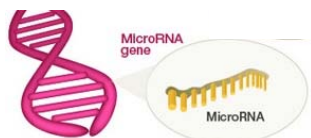
Hisashi Ietsugu, Chairman and CEO

- (1) R&D History and Structure
- (2) Long-Term Management Targets and Technology Themes

# Changes in the External Environment

## Technological Innovation

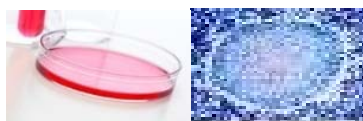
### miRNA



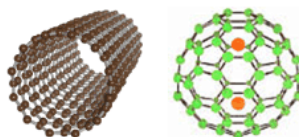
### Next-generation sequencers



### Regenerative medicine



### Nano materials



### Big data analysis



### AI



### Robotics



### Wearable devices



## Market Environment

### Advanced countries

Advances in personalized medicine and advanced medical care

Curbing medical expenses

Falling childbirths, graying populations

### Emerging markets

Increasing lifestyle diseases

Growing populations

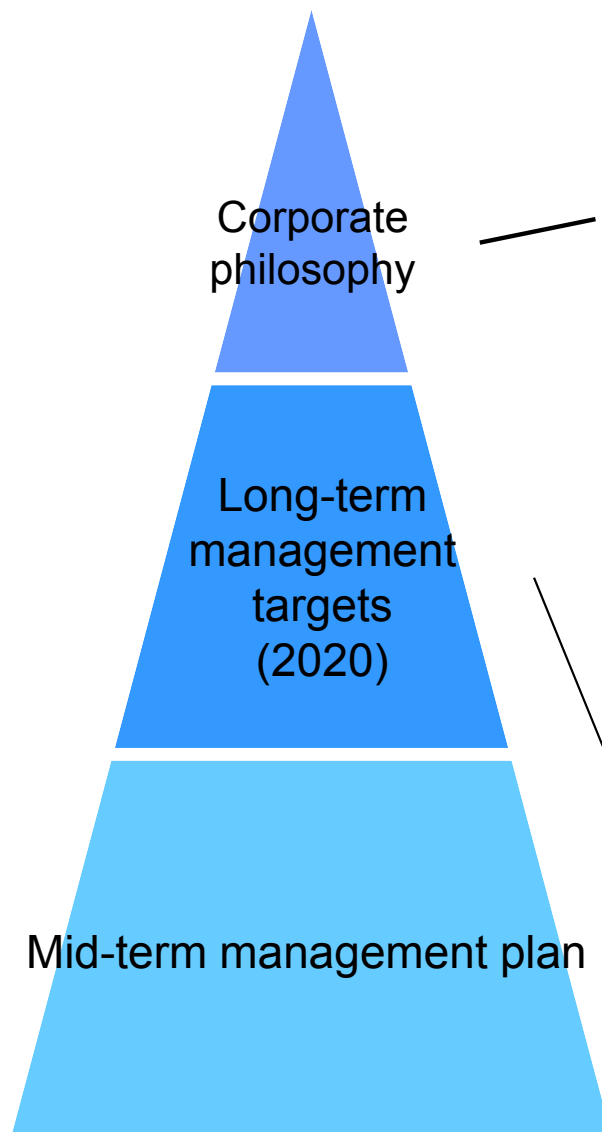
Development of healthcare infrastructure

Measures in response to infectious diseases

Greater access to healthcare

### Developing countries

# Corporate Philosophy, Long-Term Management Vision



**Sysmex Way**

## Mission

Shaping the advancement of healthcare.

## Value

We continue to create unique and innovative values, while building trust and confidence.

## Mind

With passion and flexibility, we demonstrate our individual competence and unsurpassed teamwork.

## ■ Long-term management target: vision

A Unique & Global Healthcare Testing Company

# Long-Term Management Targets (2020): Positioning



Undisputed global leader in hematology, hemostasis and urinalysis (including alliances)

A leading company in the Asian *in vitro* diagnostic (IVD) market

A unique and competitive player in the immunology field

A leading global player making a contribution to personalized medicine

An attractive company providing value and confidence

One Sysmex carrying out high-speed management

# Long-Term Management Targets and Technology Themes



Undisputed global leader in hematology, hemostasis and urinalysis (including alliances)

A unique and competitive player in the immunology field

A leading global payer making a contribution to personalized medicine

Life science

FCM

Research and industry

Immunochemistry

Hematology

Urinalysis

Hemostasis

## 14th Technology Presentation Themes

### Automation of BEAMing technology

- OncoBEAM3.0

### Increasingly precise gene analysis

- Plasma Safe SeqS (PSS)
- Clinical PCR

### Analysis of circulating cells using MI-FCM

- Automation of FISH testing (leukemia)
- CTC detection technology (detection of circulating tumor cells)

### Super-resolution molecular imaging technology

- Super-resolution microscopes

### Realization of Alzheimer's testing

- Ultrahigh-sensitivity HISCL (quantitative analysis of proteins)

### Expanded HISCL measurement parameters

- Cancer immunotherapy: PD-L1 measurement
- Cardiovascular disease risk diagnosis system: HDL function evaluation

### Compact immunoassay

### Modular concept for urinalysis testing

- UC-3500 (urine chemistry analyzer)
- UF-5000 (analyzer of formed elements in urine)
- UD-10 (imaging unit for formed elements in urine)

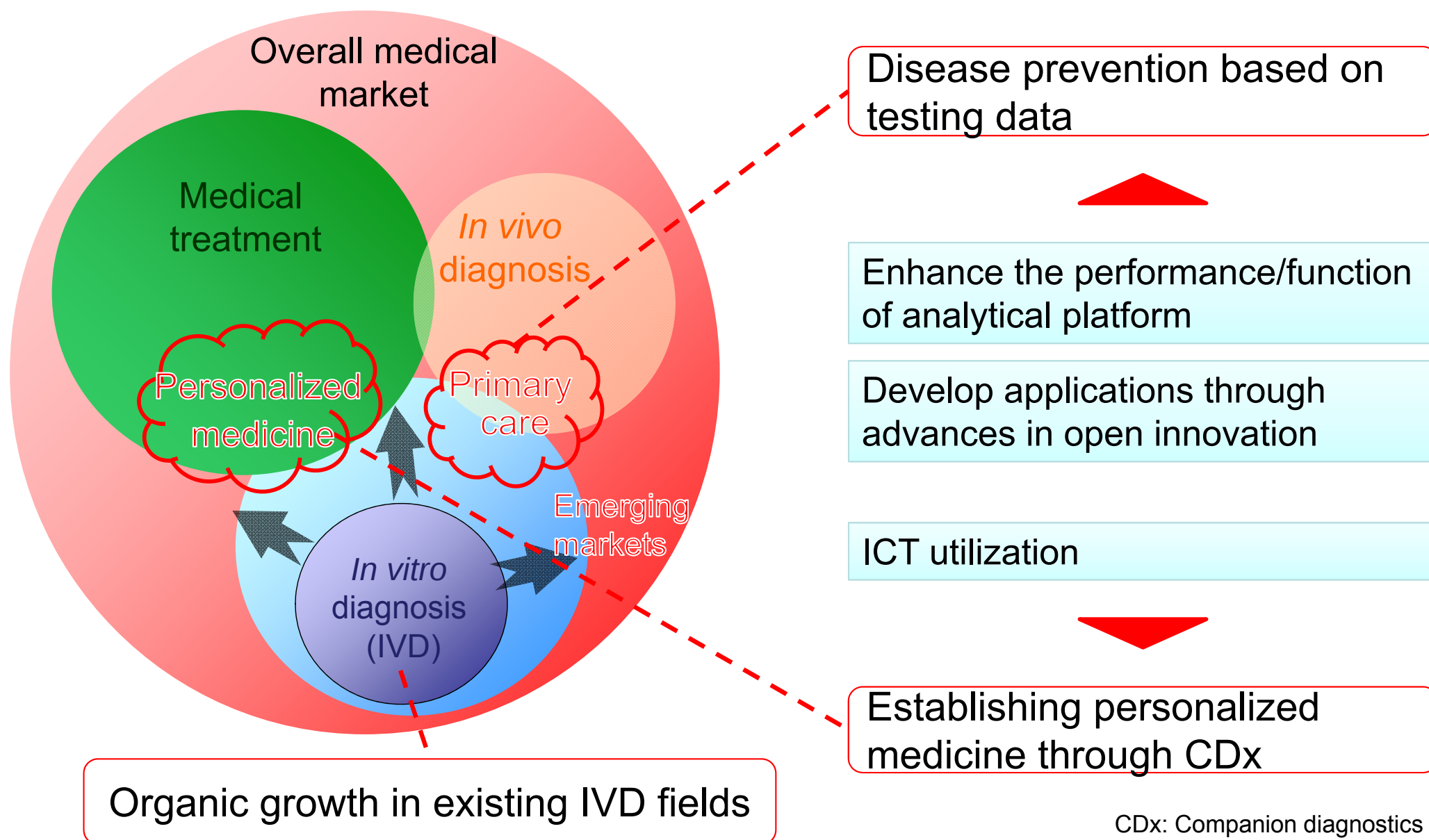
## 2. Technology Strategy Overview and Topics

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Kaoru Asano, Member of the Managing Board and  
Senior Executive Officer, Managing Director, Head of R&D

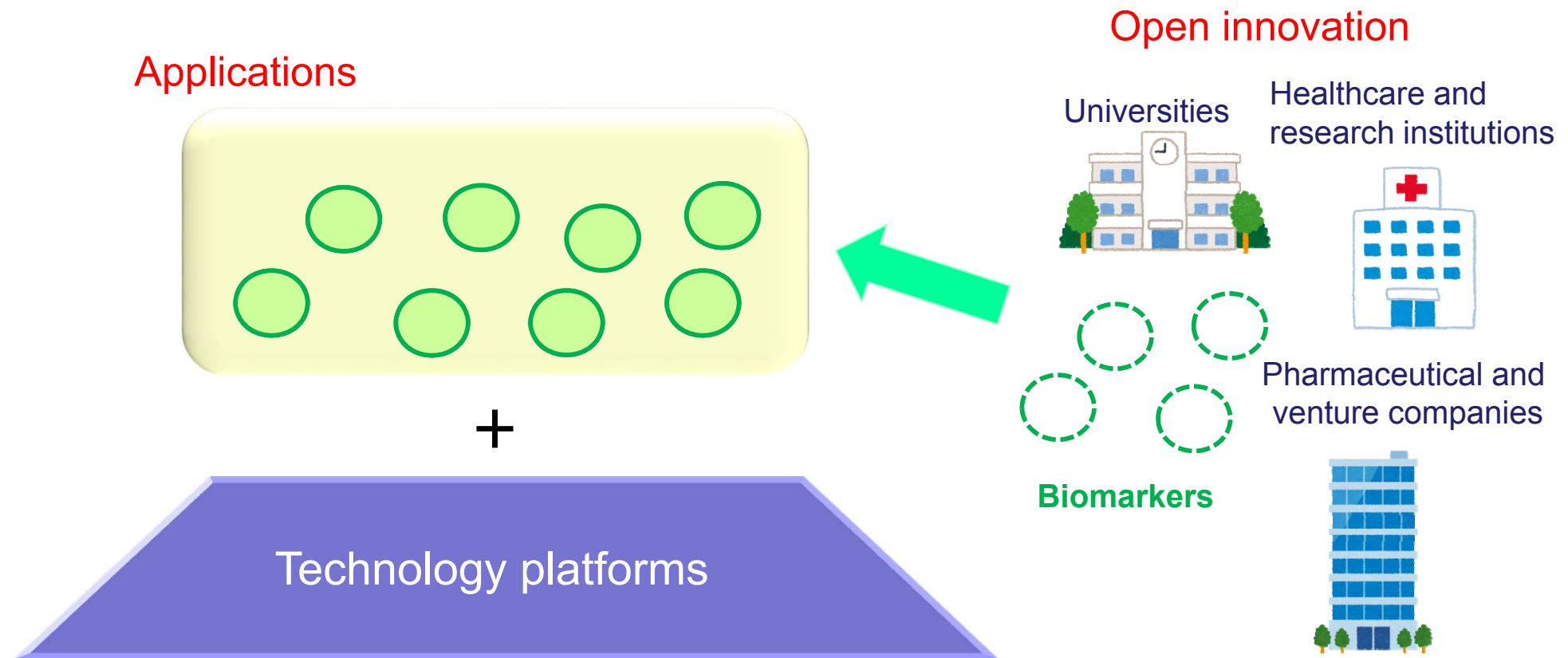
- (1) Technology strategy overview and summary of progress
- (2) Topics
  - ① Attempt toward genomic medicine
  - ② Circulating tumor cells (CTC) detection system

# Technology Strategy Overview

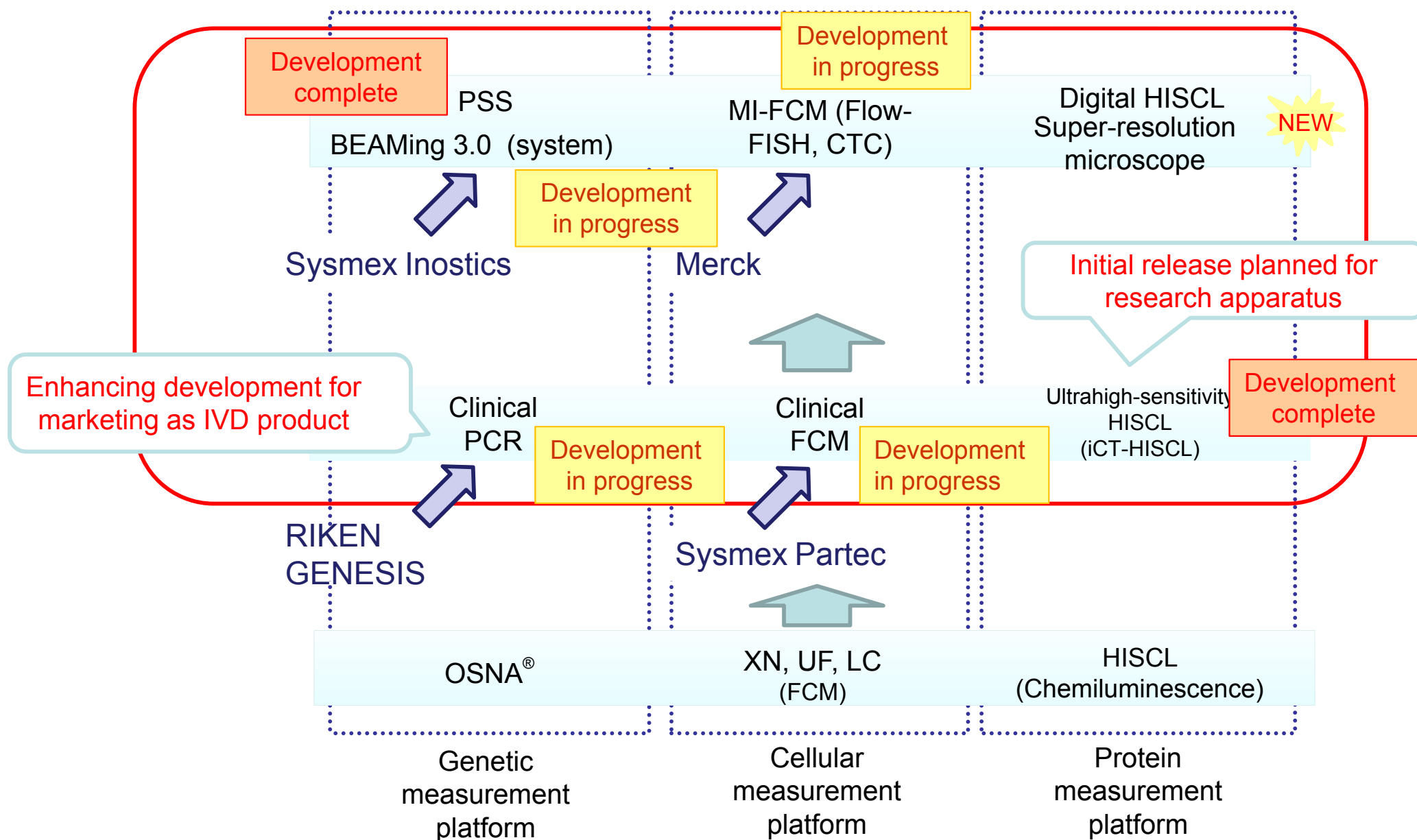


# Development of Applications through promoting Open Innovation

Promote open innovation and develop applications with high clinical value

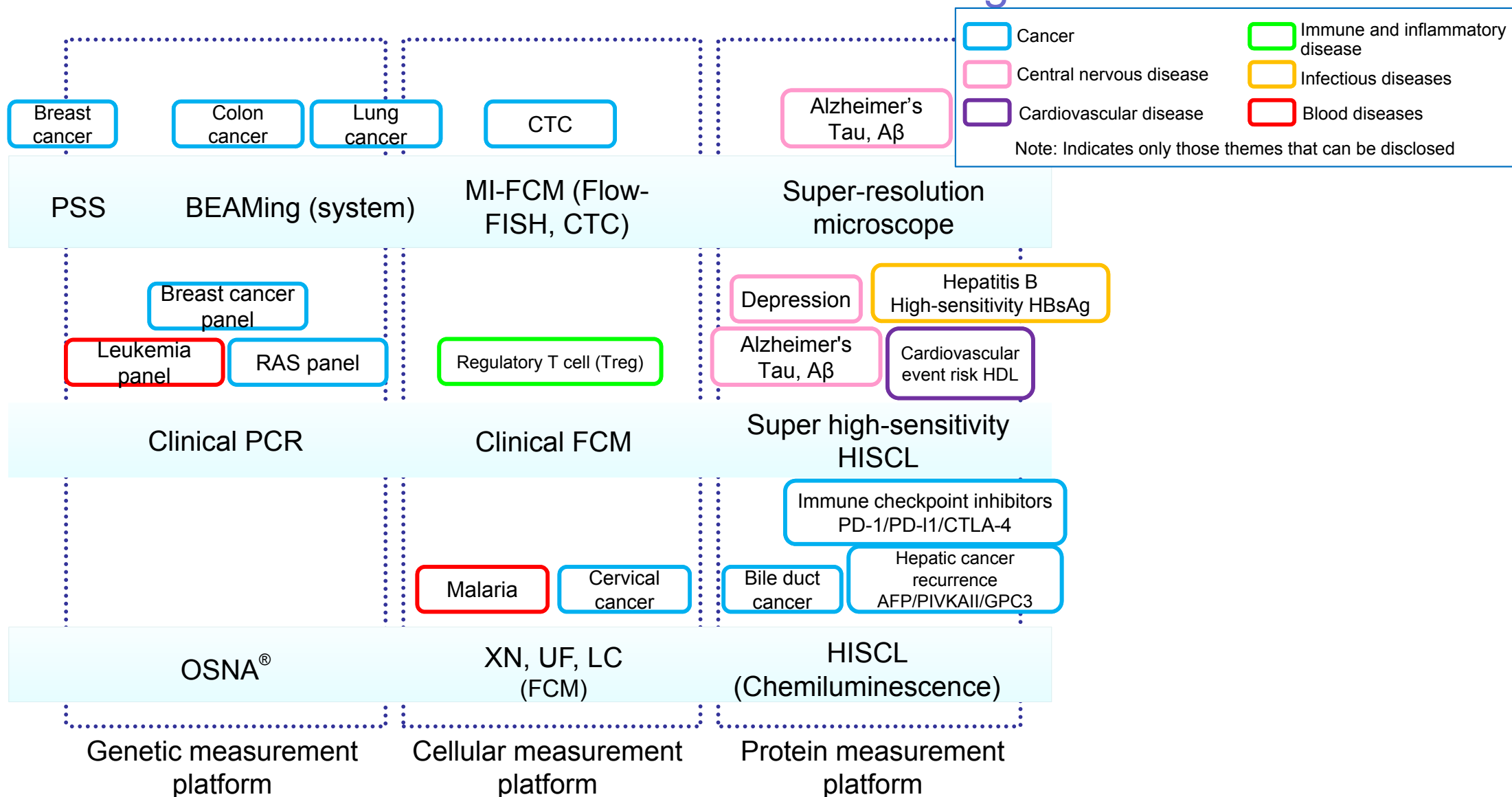


# Technology Platform Enhancement



# Application Portfolio

Promote R&D in the aim of creating new value



## 2. Technology Strategy Overview and Topics

---

Kaoru Asano, Member of the Managing Board and  
Senior Executive Officer, Managing Director, Head of R&D

- (1) Technology strategy overview and summary of progress
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  - ① Attempt toward genomic medicine
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# Topic ① Attempt toward genomic medicine

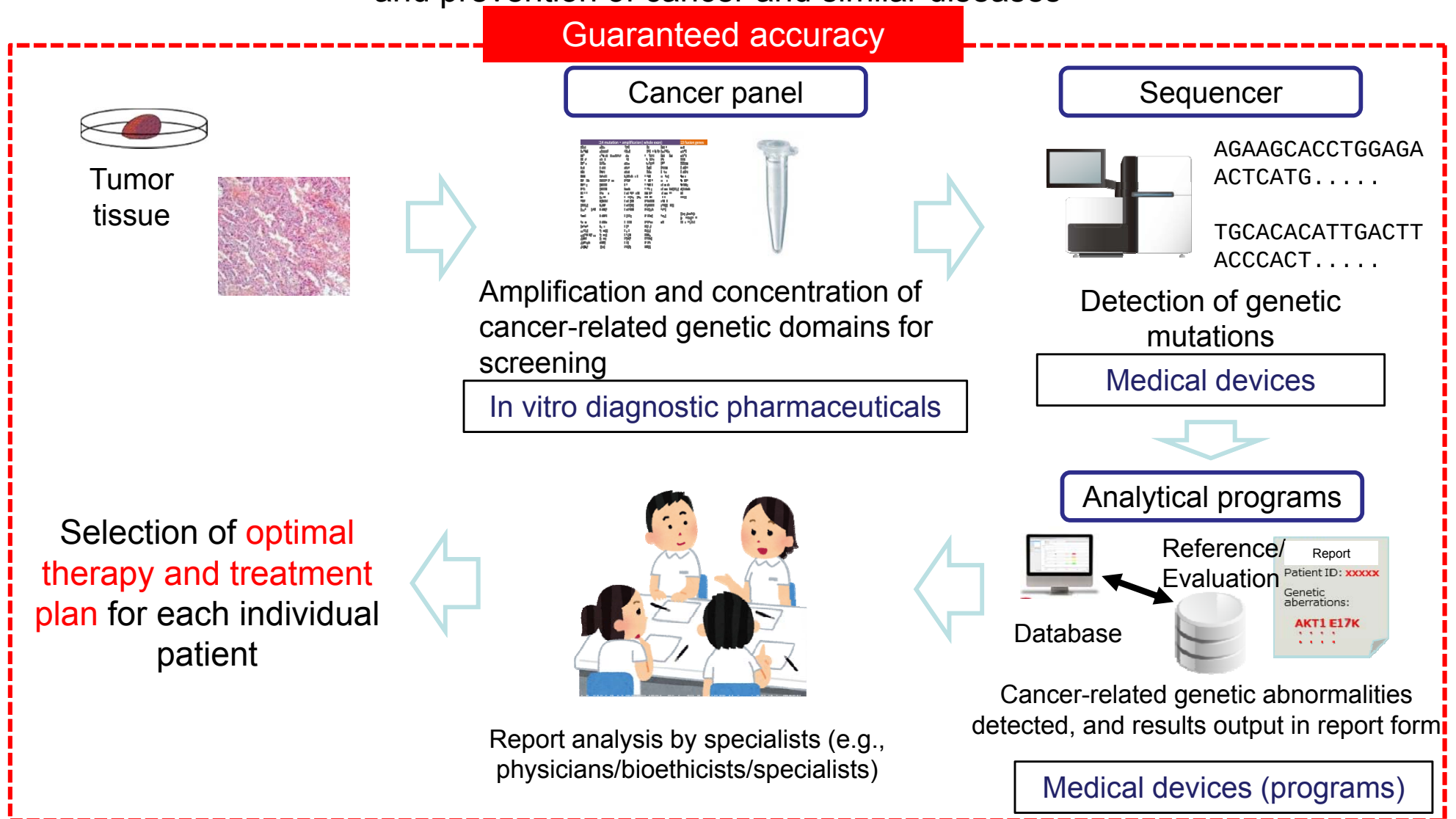


- June 2014      Sysmex and Toppan Printing to Collaborate in the Genetic Analysis Testing Industry  
-- Equity participation in RIKEN GENESIS --
  
- November 2015      Sysmex Opens Lab within the National Cancer Center to Promote the Development of New Cancer Diagnosis Methods  
-- start of clinical research at the lab that will aim to incorporate comprehensive gene analysis information into routine treatment --
  
- June 2016      Sysmex Acquires Additional Shares in RIKEN GENESIS and Converts Company to a Subsidiary  
-- Reinforcing Our Structure Toward the Practical Realization of Genomic Medicine --
  
- February 2017      Sysmex Enters into Research Collaboration Agreement in Relation to Cancer and Rare Diseases with the University of Tokyo  
-- Aiming for the Clinical Application of Genomic Medicine --Cancer-Related Gene Panel Testing System Designated Under the Ministry of Health, Labour and Welfare's Sakigake Designation System

# Topic ① Attempt toward genomic medicine

-- Promotion of clinical sequencing --

Clinical sequencing = Comprehensive analysis of disease-related genes for diagnosis, treatment, and prevention of cancer and similar diseases

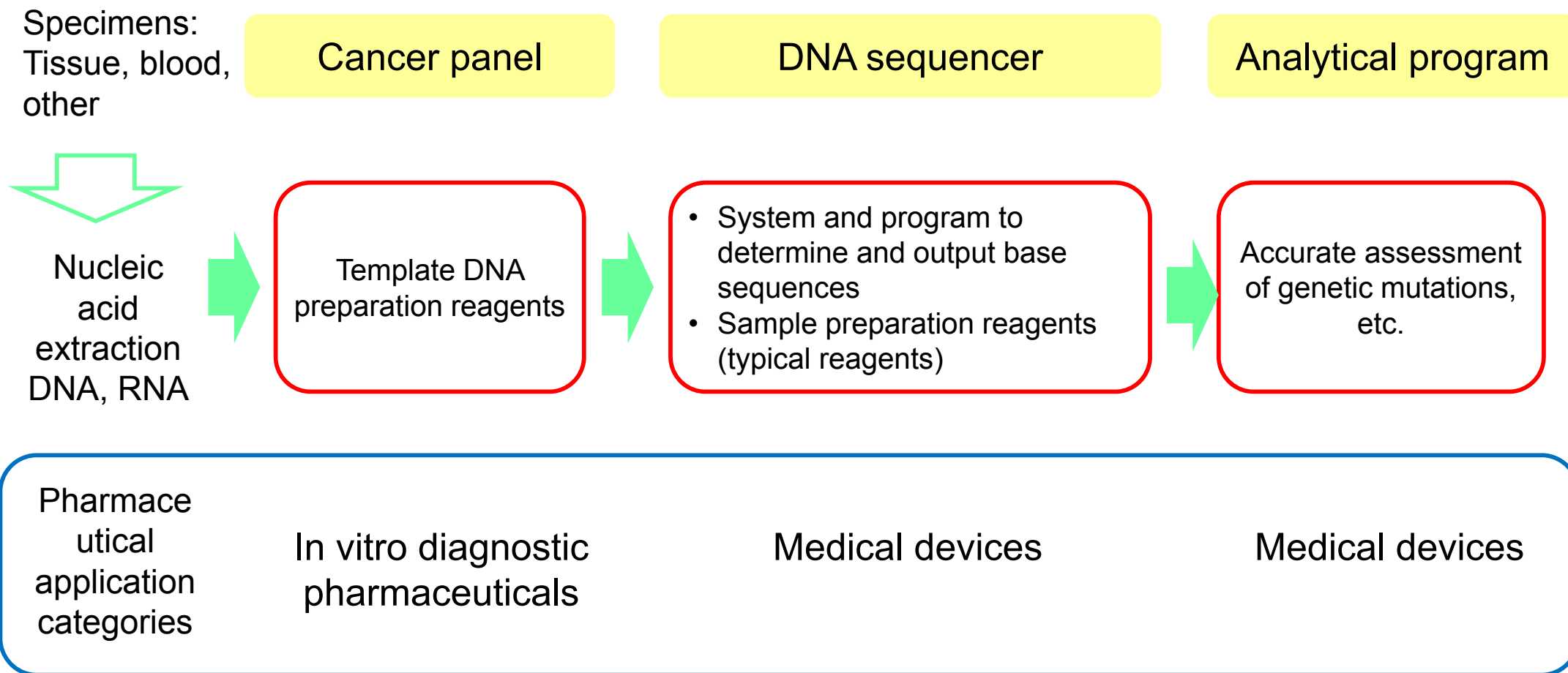


# Topic ① Attempt toward genomic medicine

-- Develop cancer panel for IVD (in vitro diagnostic pharmaceuticals) adaptation --



Approval of DNA sequencers and analytical programs as medical devices also require for IVD adaptation of cancer panels

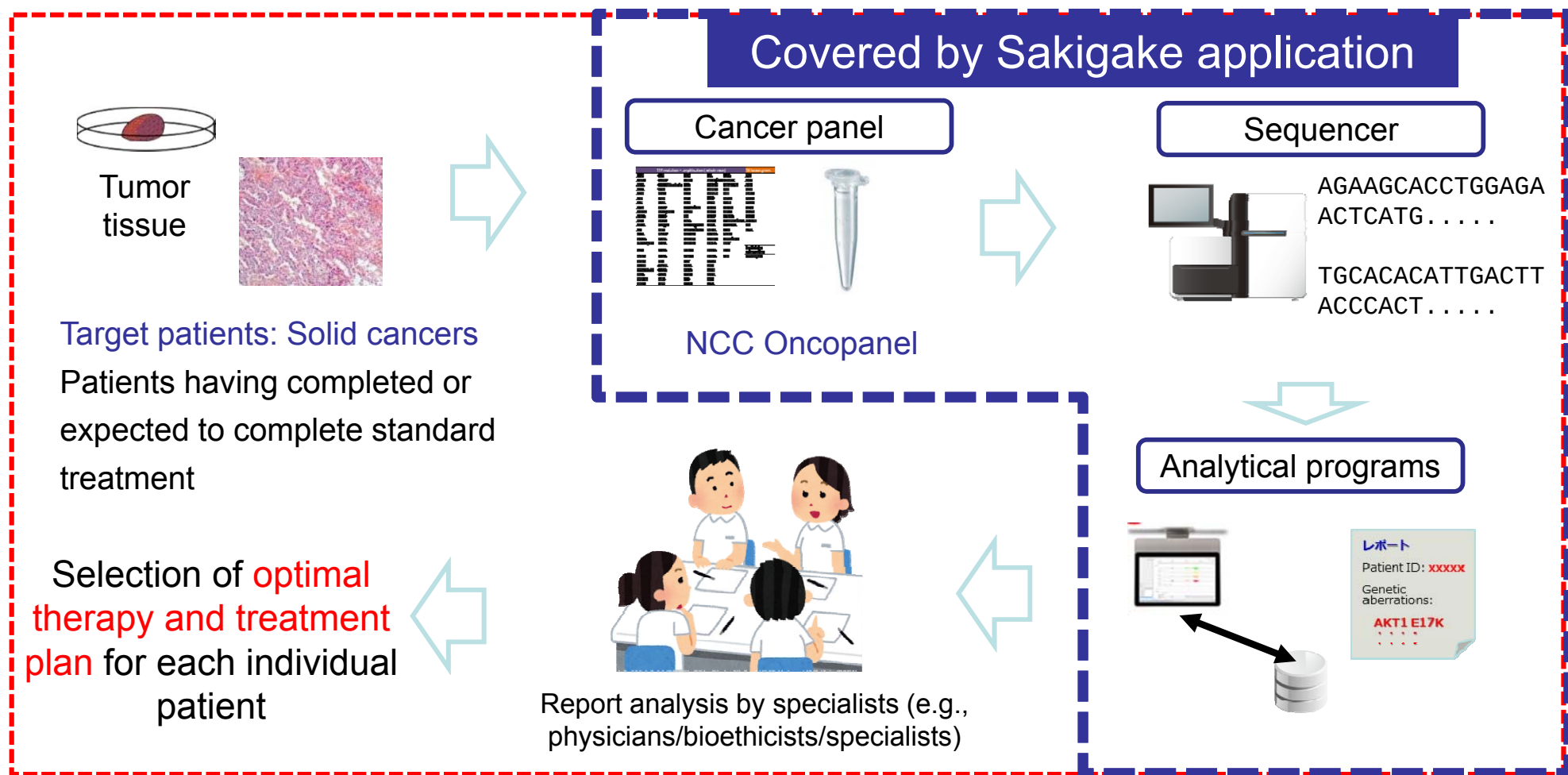


# Topic ① Attempt toward genomic medicine

-- Sakigake Designation System: Cancer-related gene panel --

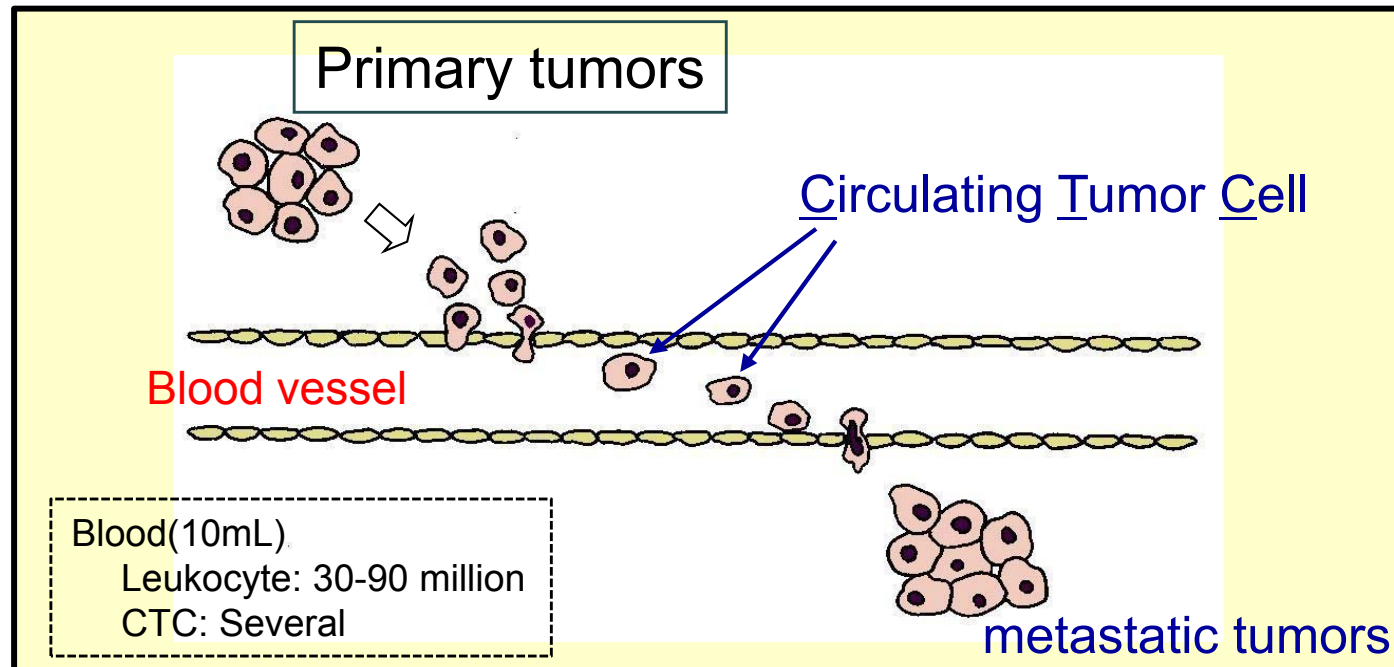
## Sakigake Designation System,

which is a scheme including Rapid Authorization, to lead the world, and to promote R&D in Japan aiming at early practical application for innovative pharmaceutical products, medical devices, and regenerative medicines



Joint development with business partners

## Topic ② Circulating tumor cells (CTC) detection system



Evaluate  
characterization  
of individual CTC  
at a cellular level

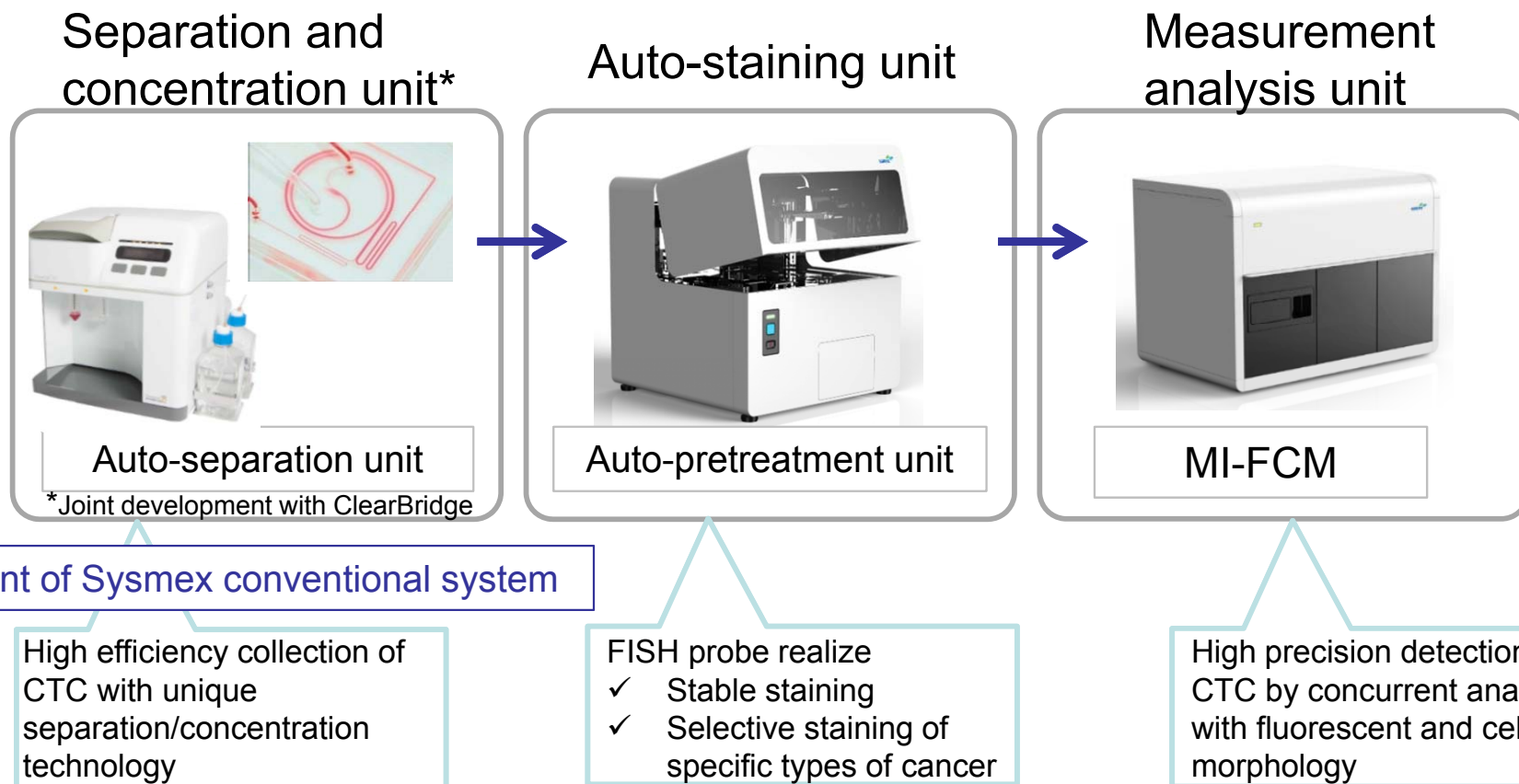
CTC is an important target for Liquid Biopsy, together with ctDNA.

- ✓ The level of ctDNA does not reflect the progress of cancer patients in all cases
- ✓ CTC provide complementary information of ctDNA.

ctDNA: Circulating Tumor DNA

## Topic ② Circulating tumor cells (CTC) detection system

Combination of cell separation/concentration technology and MI-FCM improve measuring capability for CTCs substantially



Joint research began with Astellas Pharma and Daiichi Sankyo

## 3. Progress Report on Technology Development

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Fumio Kubota, Executive Vice President,  
R&D Strategic Planning Division

### (1) Technology platform

- ① Development of automation for BEAMing technology
- ② Development of Plasma-Safe-SeqS technology
- ③ Development of Compact Immunoassay System
- ④ Development of super resolution microscopy technology

### (2) Application

- ① Attempt toward immunotherapy by liquid biopsy
- ② Development of diagnostic techniques for heart disease risk

# Sysmex Genetic Platform for High Sensitivity



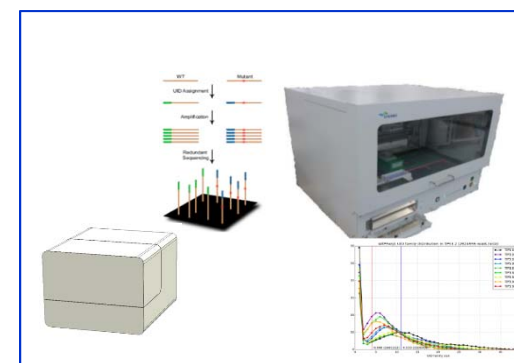
## Clinical PCR



## BEAMing



## Plasma-Safe-SeqS



Nucleic acid  
extraction

Nucleic acid  
amplification

Detection/  
Analysis

DNA/RNA purification

BNA Clamp PCR

Emulsion PCR

UID Tag PCR

Real-time PCR

FCM

Sequencing

**Easy, rapid, high-  
sensitivity (0.1%)**

Original tissue screening

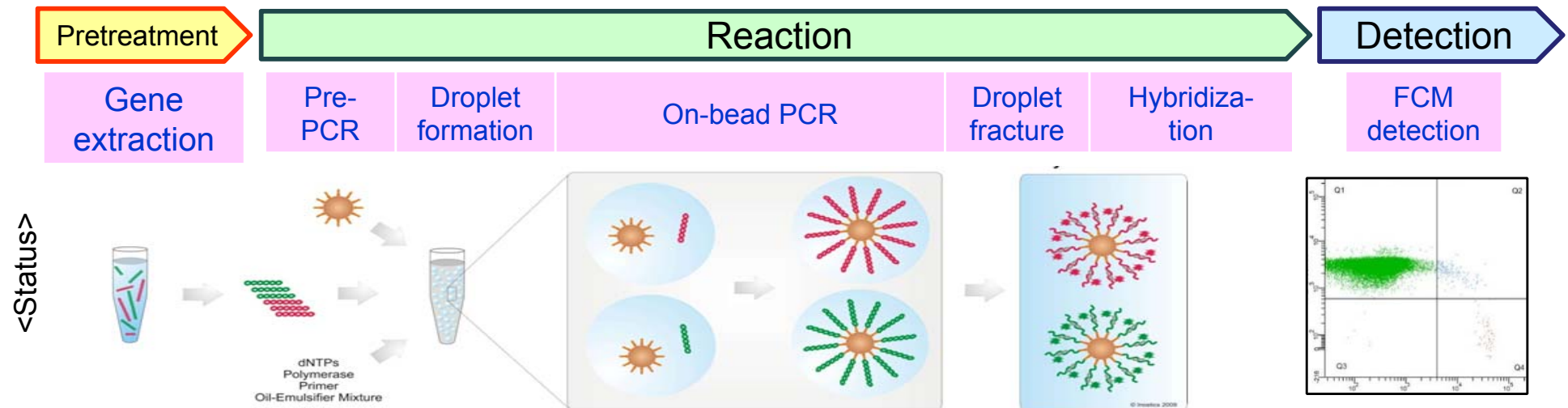
**High sensitivity (0.02%)**

Screening for free DNA  
mutation in plasma

**High sensitivity (0.06%)**

Screening required for  
sequence analysis in free  
DNA in plasma

# ① Issues of BEAMing



- ✓ Complex operation
- ✓ 2 - 3 days needed to complete measurement

Development of fully automated system for short-term measurement (6 hours) and quantification

Clinical evaluation for practical use and development of diagnostic reagent

# ① Creation of Automated System for BEAMing Technology

Pretreatment

Reaction

Detection

Gene  
extraction

Pre-  
PCR

Droplet  
formation

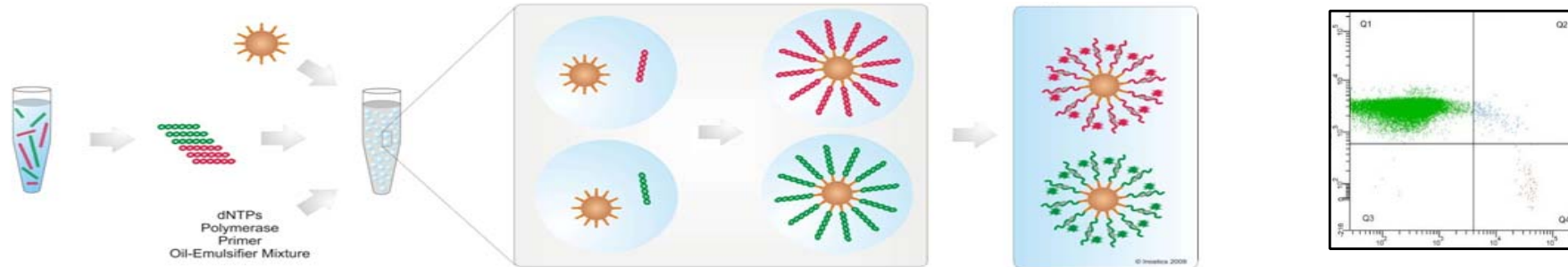
On-bead PCR

Droplet  
fracture

Hybridiza-  
tion

FCM  
detection

<Status>

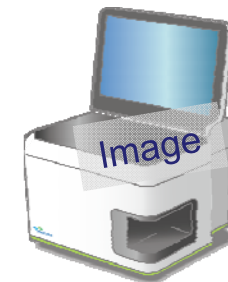
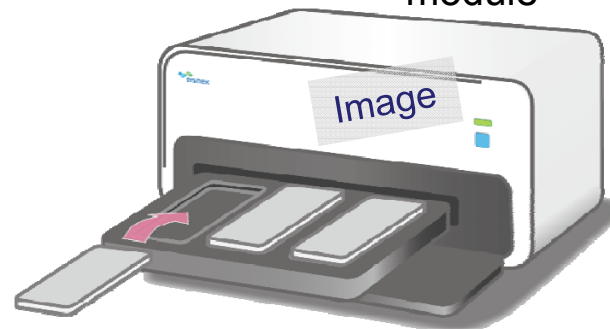


Nucleic acid  
extraction module

Reaction  
module

Detection  
module

<Concept  
images>



# ① Creation of Automated System for BEAMing Technology

Pretreatment

Reaction

Detection

Gene  
extraction

Pre-  
PCR

Droplet  
formation

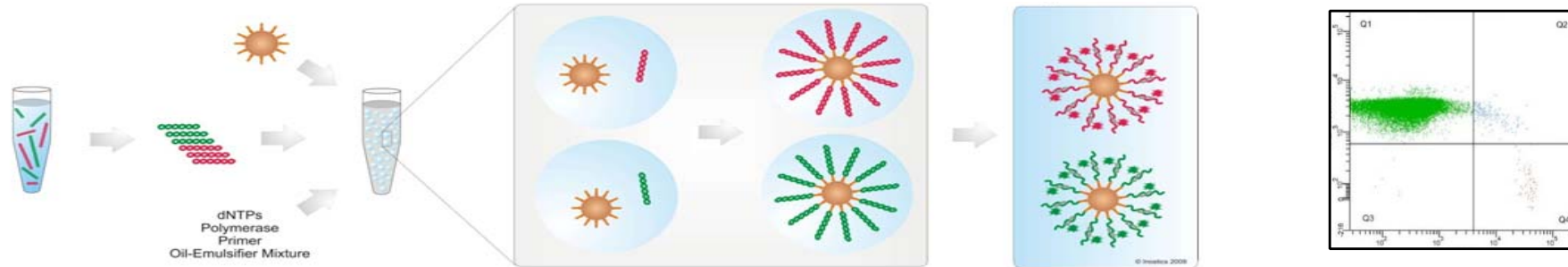
On-bead PCR

Droplet  
fracture

Hybridiza-  
tion

FCM  
detection

<Status>



Nucleic acid  
extraction module

PrePCR  
module

EmPCR  
module

Breaking/Hybridization  
module

Detection  
module

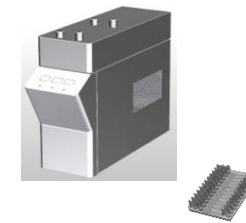
<Concept  
images>



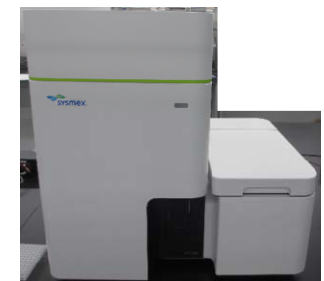
Development  
complete



Prototype Developed



Development  
complete



Development  
complete

In FY 2017, setup in Sysmex labs and sequential start of operation (start from Clinical Research Organization business)

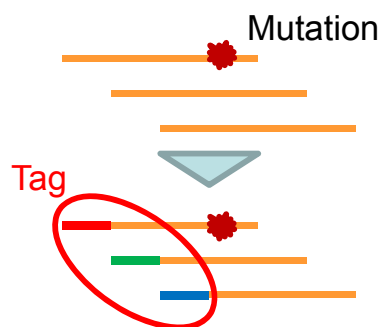
\*CRO : Clinical Research Organization

## ②Development of Plasma-Safe-SeqS Technology

### Plasma-Safe-SeqS Technology for detection of rare genes in blood

#### Pretreatment

##### Gene tagging



Gene tagging  
for grouping

#### Measurement

##### Next-generation sequencer (NGS)



Togo picture gallery by DBCLS is Licensed  
under Creative Commons Expression 2.1  
Japan (c)

Allows distinction of reading  
errors from mutant genes

#### Analysis

##### Genetic analysis technologies



And also allows higher  
precision detection and  
analysis

## ②Development of Plasma-Safe-SeqS Technology

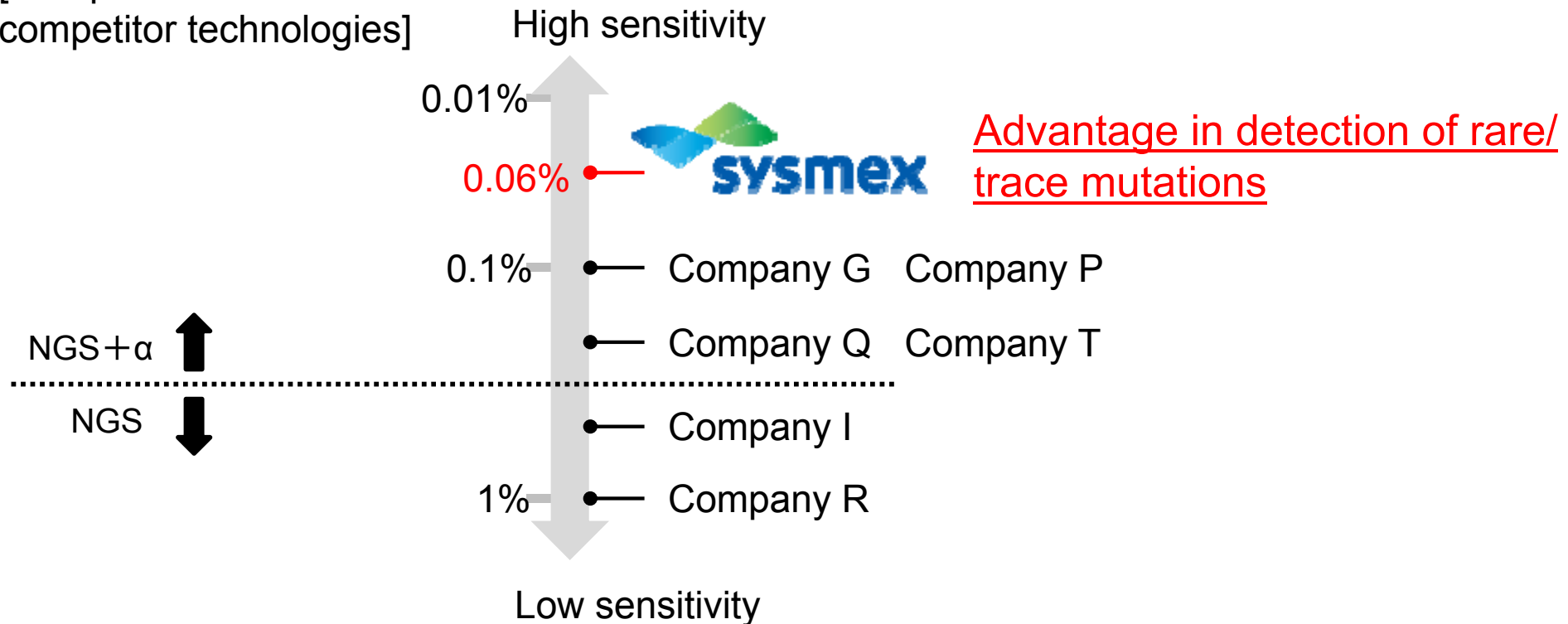
[Plasma-Safe-SeqS Technology Principle]



## ②Development of Plasma-Safe-SeqS Technology



[Comparison with competitor technologies]



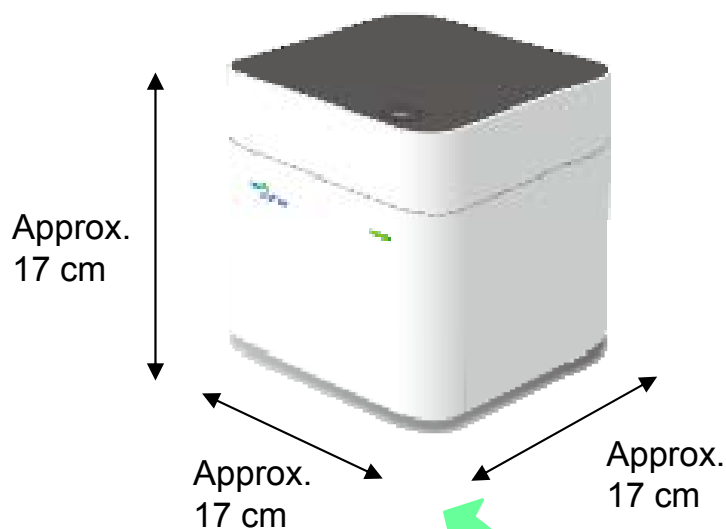
Starting assay service based on screening for TP53 gene observed in many types of cancer and prioritizing development of small-scale panels including target genes with clear indication for therapeutic drugs

Beginning laboratory assay service with RIKEN GENESIS/Sysmex Inostics in Q1, FY2017

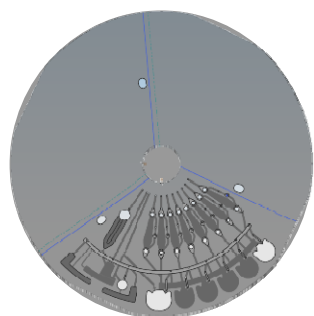
### ③ Compact Immunoassay System



A compact Immunoassay platform designed for primary care

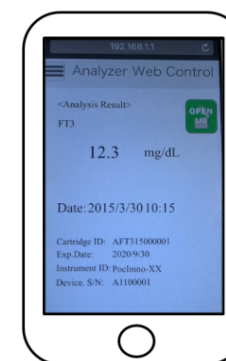


- High-sensitivity and rapid measurement (within 20 min.) provided by use of HISCL reagents
- Compact unit allowing clinical installation
- IoT function
- Simple to operate with smart phones or other IT devices



Cartridge reagents  
φ120 mm t1.2 mm

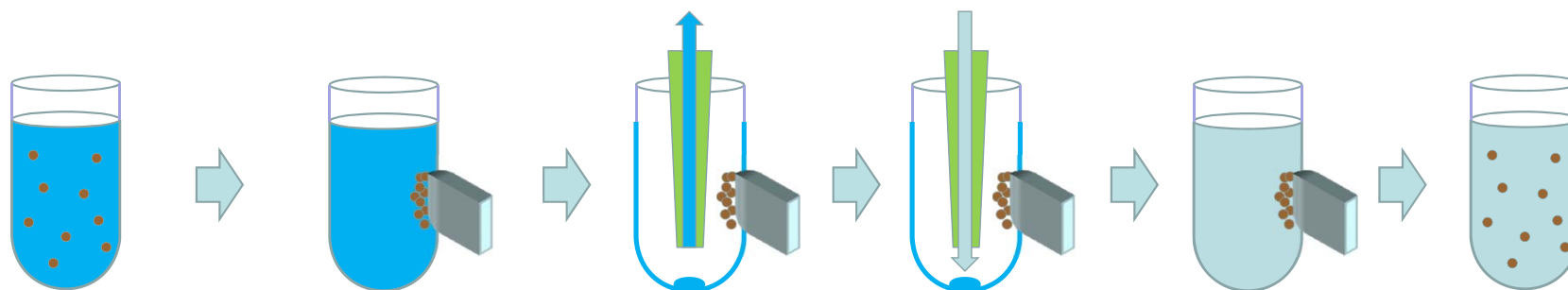
- All reagents pre-sealed
- No effluent



### ③ Compact Immunoassay System

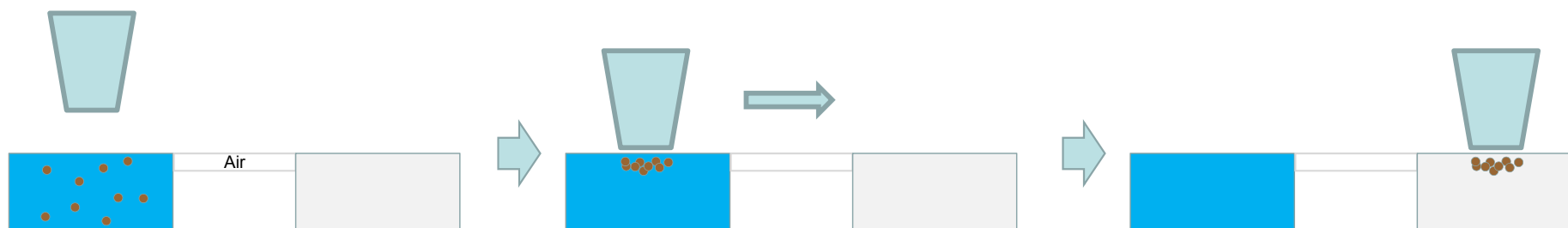
-- MINT Technology for Compact Size --

B/F separation provided by ordinary magnetic particles



Large quantity of wash solution not suitable for compact unit

B/F separation provided by **MINT technology (Magnetic-particle INDuced Transportation)**

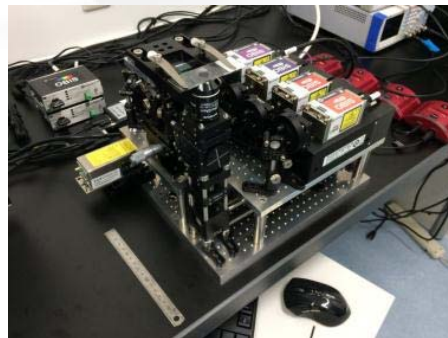


Direct movement of particles by magnet reduces wash solution volume to roughly 1/30 or lower versus HISCL, allowing compact size

## ④ Super-Resolution Microscope NEW



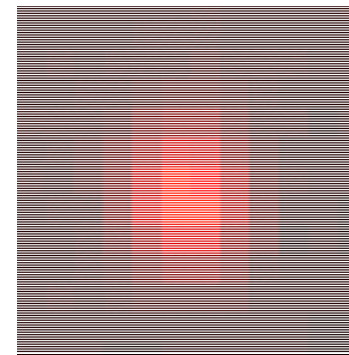
Understanding of protein structural abnormalities  
for development of revolutionary diagnostic techniques



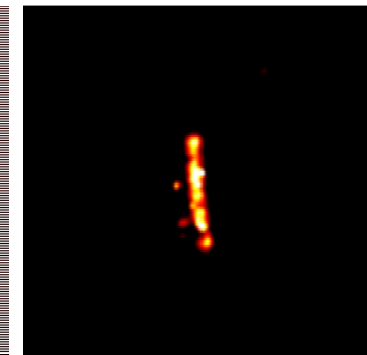
Practical implementation of Nobel  
prize in chemistry technologies

### Amyloid- $\beta$ measurement images

Fluorescent  
microscopy



Super-resolution  
microscopy

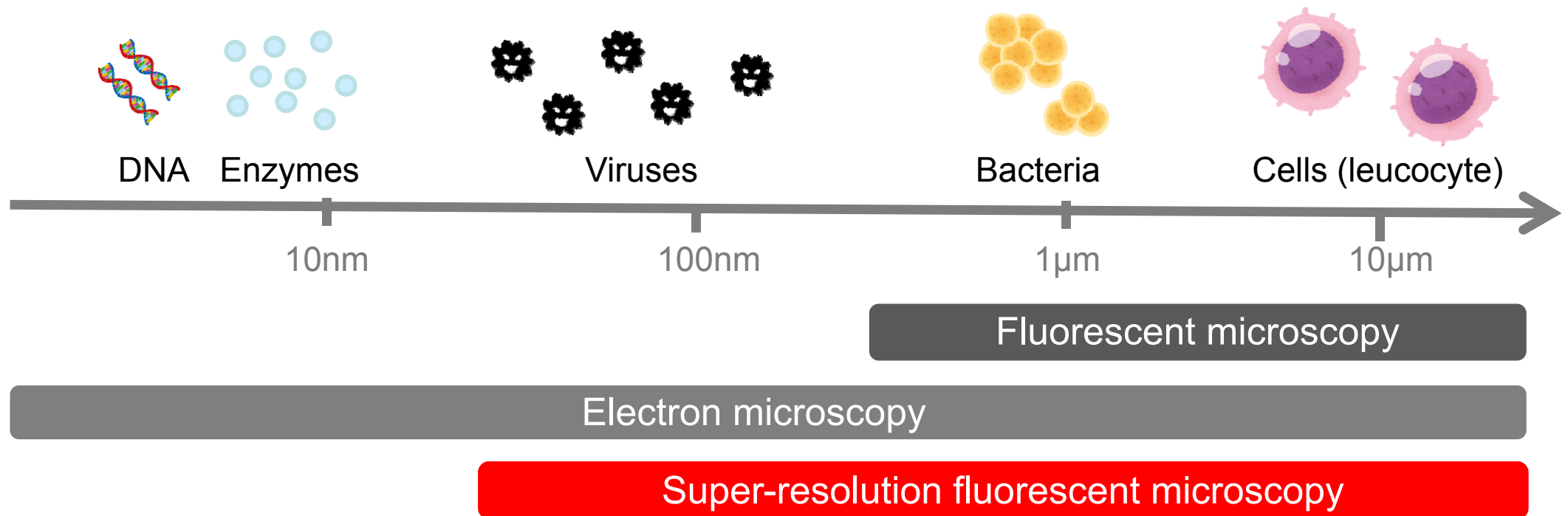


Useful in diseases caused by protein  
degeneration

Huntington's disease, Alzheimer's disease,  
Parkinson's disease, prions, ALS (amyotrophic  
lateral sclerosis), other

## ④ Super-Resolution Microscope

-- Comparison with Other Microscope --



Using fluorescent microscope limits observable substances. Operation of electron microscopes is complex and large unit size also limits locations for use

## ④ Super-Resolution Microscope

### -- Practical Application Examples --

## Alzheimer's screening by liquid biopsy

Principal pathologies of Alzheimer's disease (AD)

- Senile plaques due to accumulation of  $A\beta$  (Amyloid- $\beta$ )
- Neurofibrillary tangle due to tau protein

<Image-based screening>



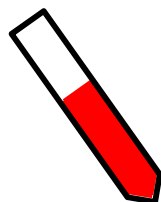
- ✓ High cost
- ✓ Limited facilities

<Spinal fluid test>



- ✓ Highly invasive

<Blood test>



$A\beta$  quantity in blood:  $A\beta$  quantity in spinal fluid = **1 : 50**

(National Center for Geriatrics and Gerontology; Proc. Jpn. Acad., Ser. B, 2014)

[Issues]

- Detection of minute protein amounts
- Identification of brain-specific target proteins

Quantitative analysis



iCT-HISCL



Structural analysis

Super-resolution microscope



Used in joint development with Eisai Co.

## 3. Progress Report on Technology Development

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Fumio Kubota, Executive Vice President,  
R&D Strategic Planning Division

### (1) Technology platform

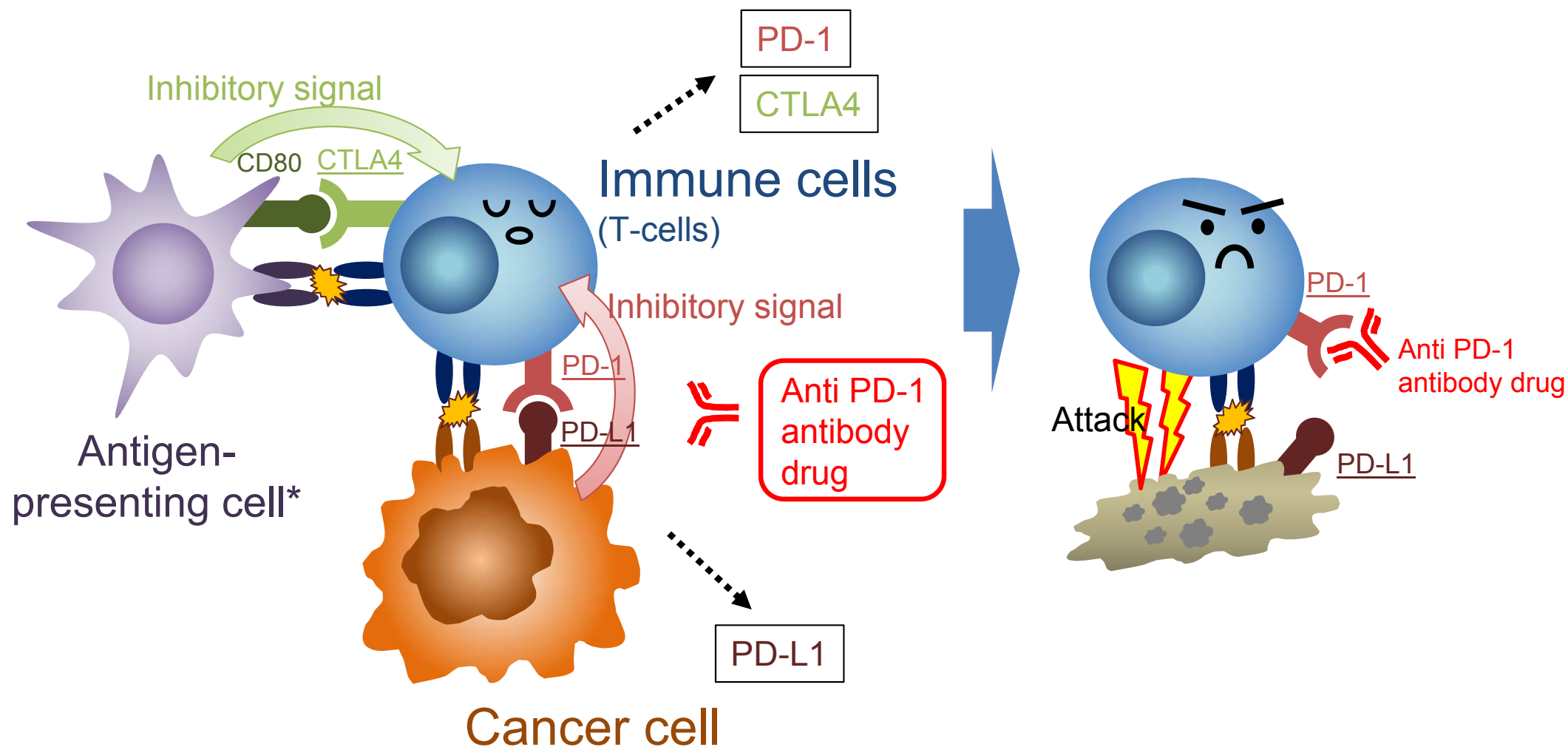
- ① Development of automation for BEAMing technology
- ② Development of Plasma-Safe-SeqS technology
- ③ Development of Compact Immunoassay System
- ④ Development of super resolution microscopy technology

### (2) Application

- ① Attempt toward immunotherapy by liquid biopsy
- ② Development of diagnostic techniques for heart disease risk

# ① Attempt toward Immunotherapy by Liquid Biopsy

What are immune checkpoint inhibitors?



\*Antigen-presenting cells activate T-cells by presenting antigens on their own cell surface, for example, fragments of bacteria invading the body or virus-infected cells

# ① Attempt toward Immunotherapy by Liquid Biopsy

## -- Establishing Prediction Method for Efficacy --



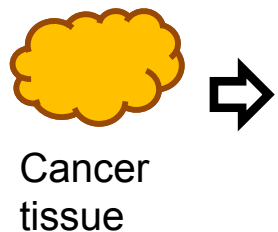
Expectations for immune checkpoint inhibitors

- Full-scale development by pharmaceutical firms
- Increased CDx demand

Issues for immune checkpoint inhibitors

- High drug costs
- Insufficient accuracy in prediction of effect

[Conventional] Pathology screening: Time-consuming, individual differences depending on pathologist



Immunostaining  
PD-L1 -positive  
determination

[New] Blood test: Rapid, simple, and objective



Cancer patient  
peripheral blood



HISCL (Actual model)

HISCL measuring system built for 3 markers in blood  
Start of joint research with Kyoto University  
using clinical specimens

## ②Development of Diagnostic Techniques for Heart Disease Risk Development of Functional Evaluation Techniques for HDL



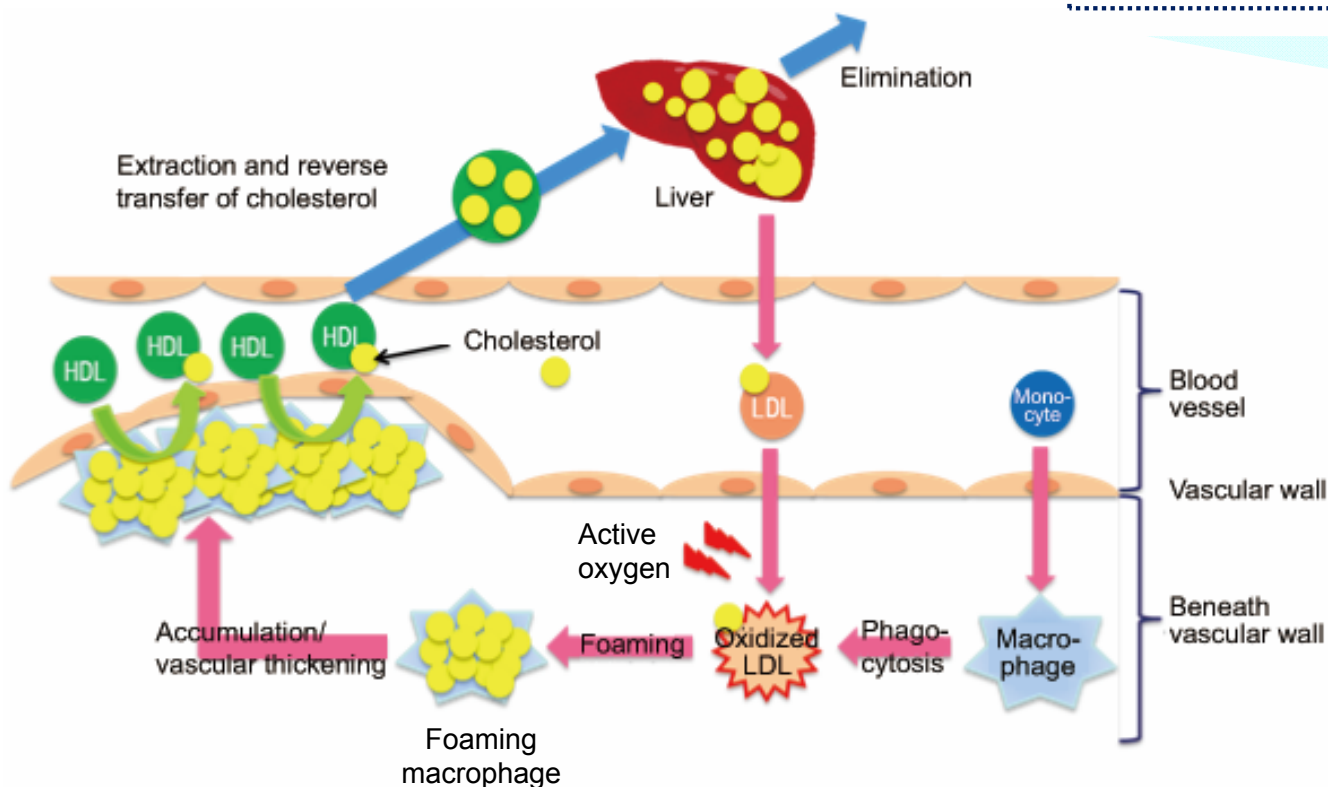
### Development of diagnostic techniques for cardiovascular risk through HDL functional evaluation techniques

“How functional is HDL?” is an increasing focus  
for prediction of atherosclerotic disease risk

(Khera et al. Jan 13, 2011, New England Journal of Medicine)

#### [Issues]

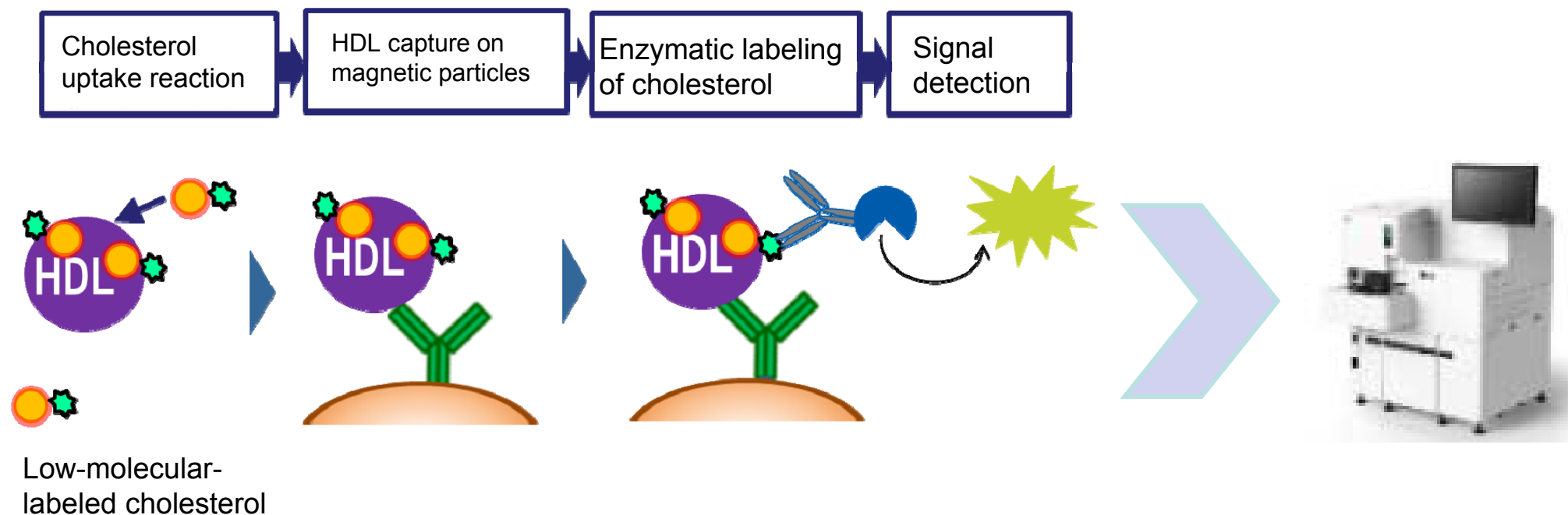
Complexity of conventional techniques and difficulty of  
clinical application and standardization due to need for  
specialized facility environment



Measurement by iCT-HISCL

## ②Development of Functional Evaluation Techniques for HDL -- Measurement by iCT-HISCL --

[Measuring techniques with HISCL]



Start of large-scale clinical research (approx. 3,000 cases) with  
Kyushu University (Hisayama Study)

# We Believe the Possibilities.

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