



# The 10<sup>th</sup> Technology Presentation

March 15, 2013

Sysmex Corporation

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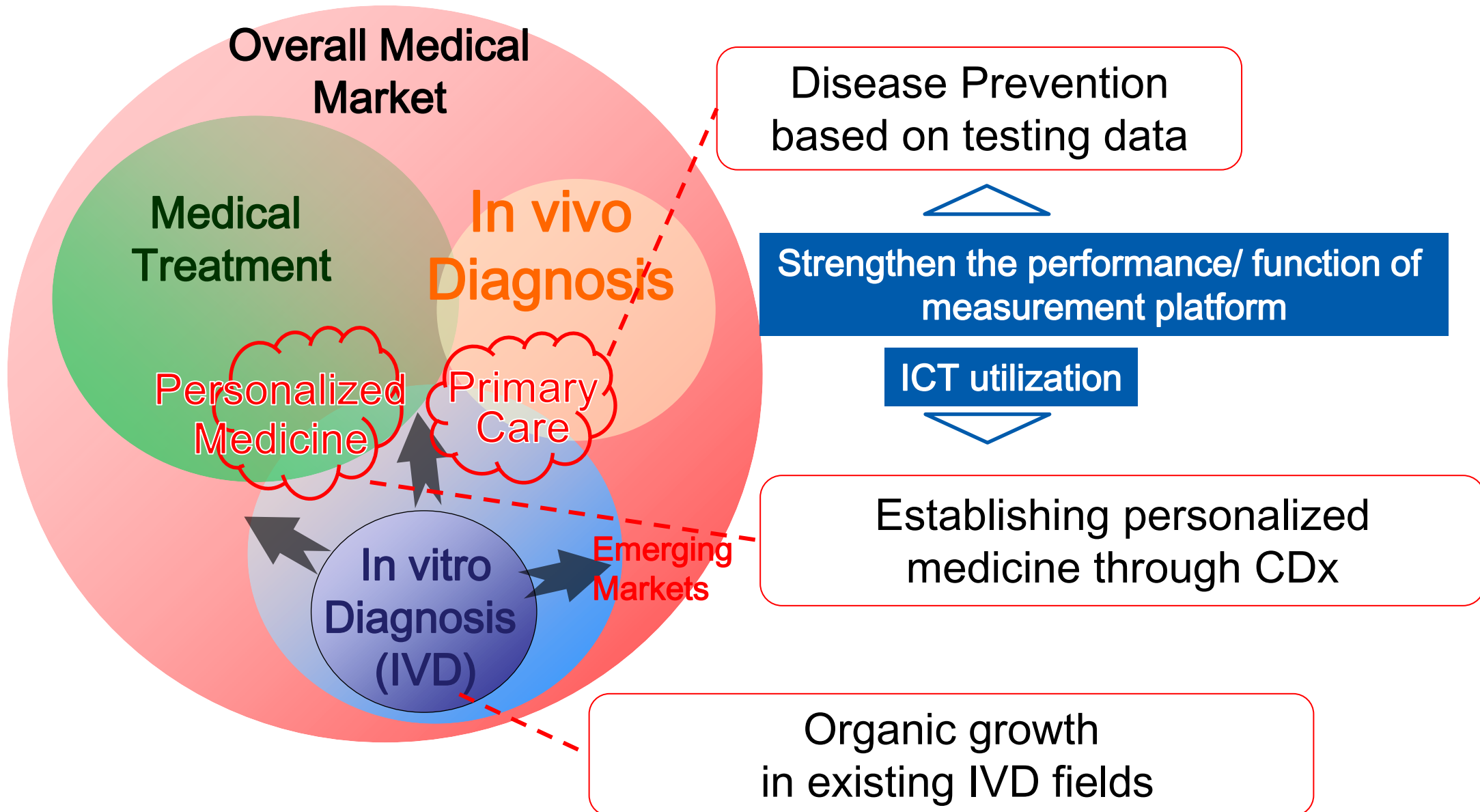
- |   |   |
|---|---|
| 1 . Opening Remarks   | Hisashi Ietsugu, President and CEO  |
| 2 . Strategy for Establishing Personalized Medicine   | Mitsuru Watanabe,<br>Member of Managing Board and Executive Officer,<br>Head of R&D               |
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## 2. Strategy for Establishing Personalized Medicine

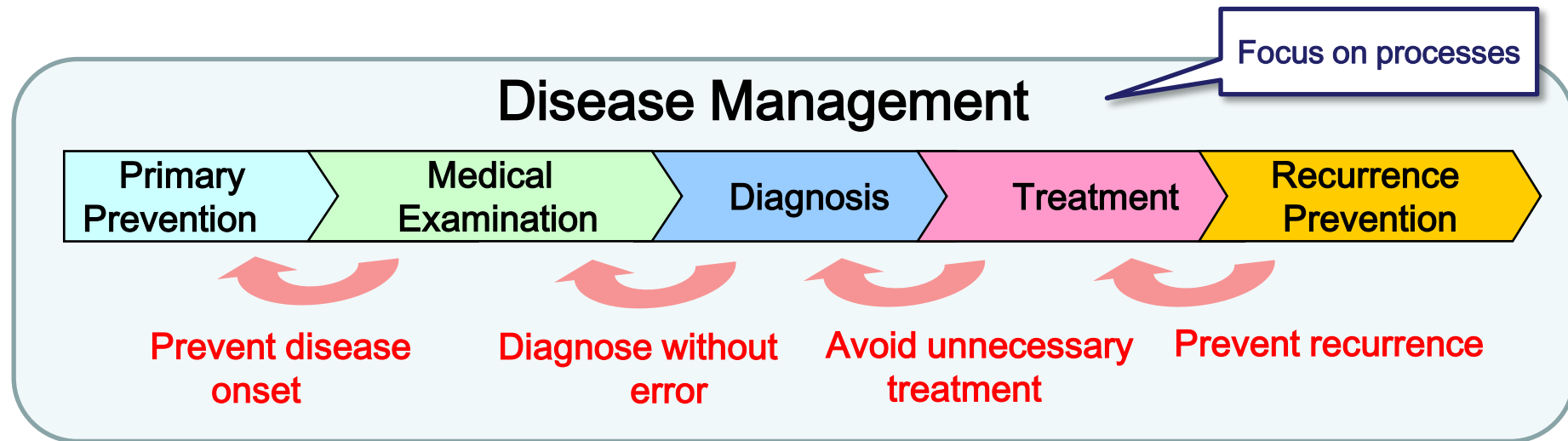
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Mitsuru Watanabe,  
Member of Managing Board and Executive Officer,  
Head of R&D

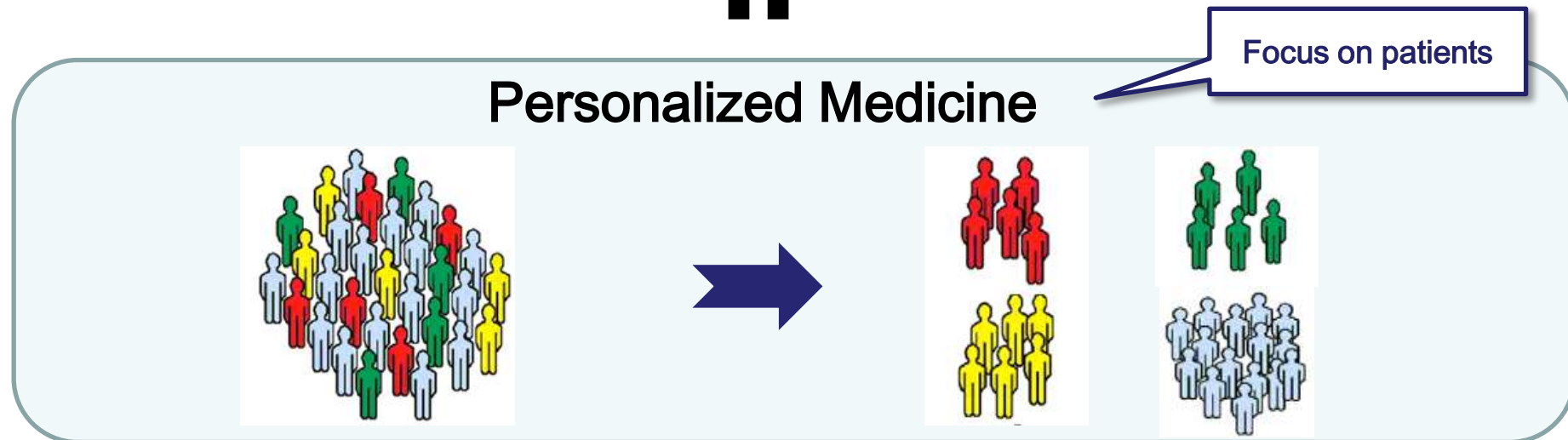
- (1) Outline of Technology Strategy
- (2) Companion Diagnostics
- (3) Founded Course at Kobe University Graduate School  
(Assessment of Clinical Testing)



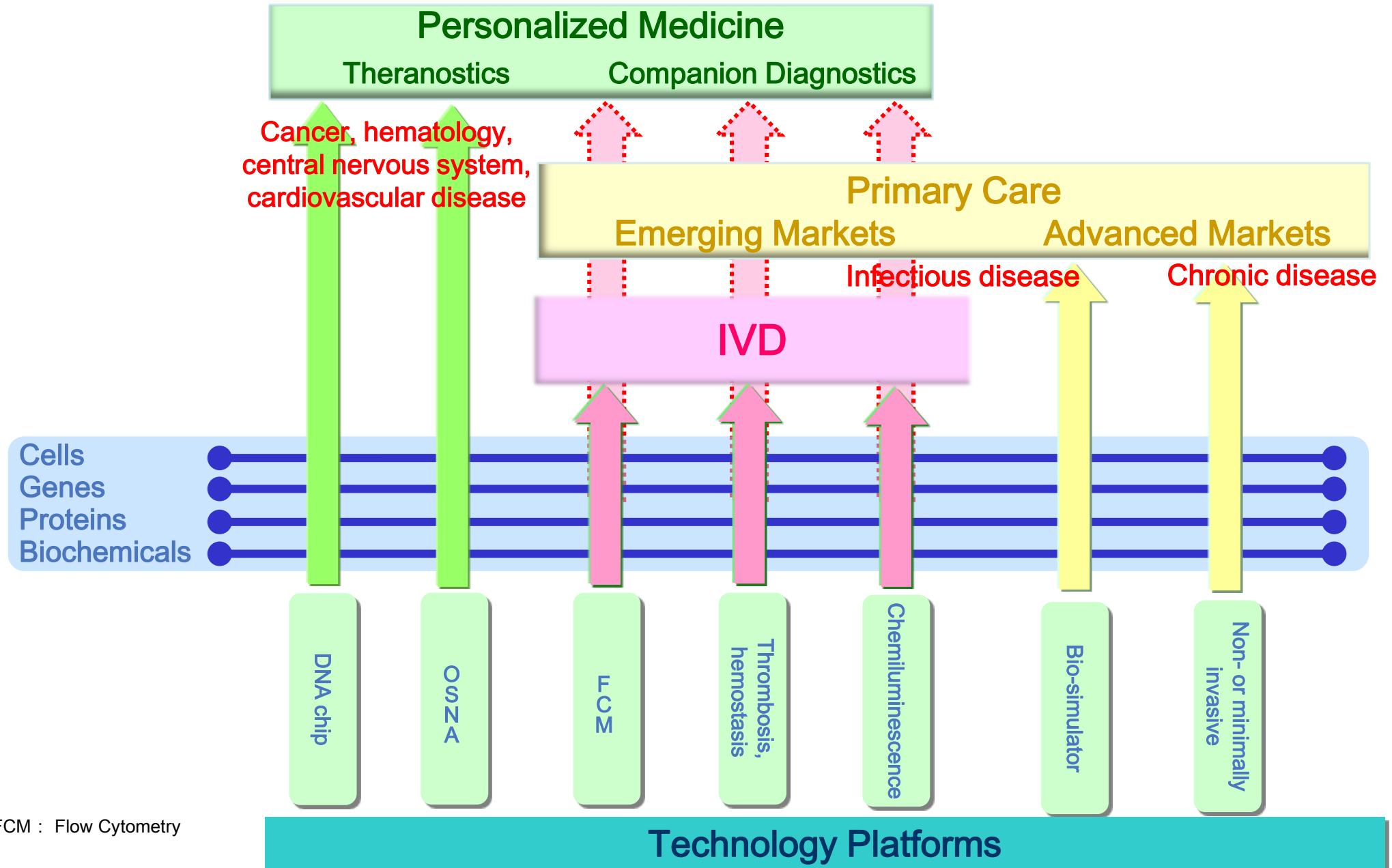
# Disease Management and Personalized Medicine



II

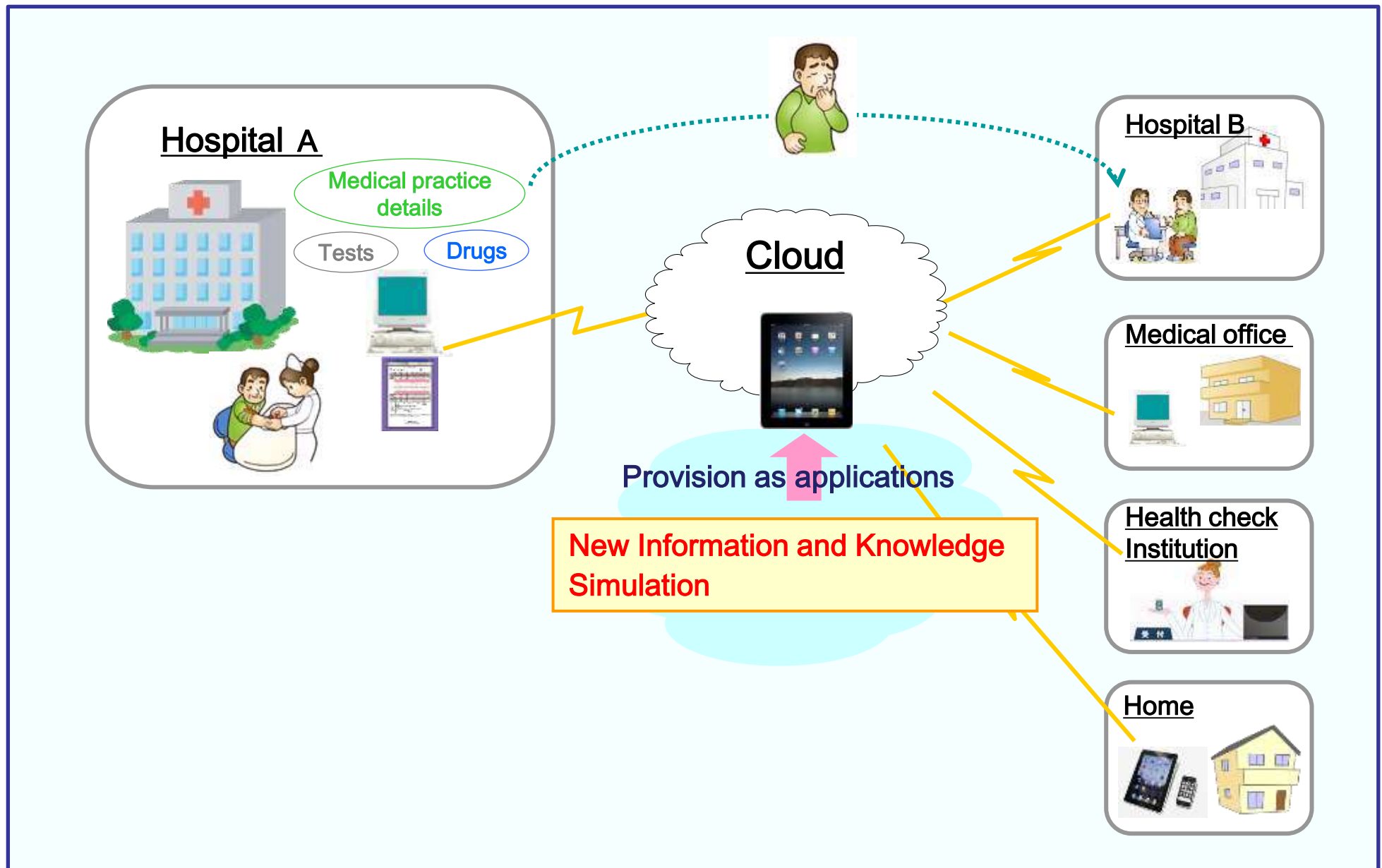


# Strengthening the Technology Platform



FCM : Flow Cytometry

# Primary Care with ICT



## 2. Strategy for Establishing Personalized Medicine

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- (1) Outline of Technology Strategy
- (2) Companion Diagnostics**
- (3) Founded Course at Kobe University Graduate School  
(Assessment of Clinical Testing)

# What is Companion Diagnostics?

## ◇ Companion diagnostics (CDx). . .

Is an effective approach for realizing personalized medicine that involves development of therapeutic and diagnostic reagents in parallel.

Pharmaceutical  
Company



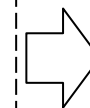
IVD Business  
Company

## Benefits and drawbacks of CDx

Reduced development risk and development time

V

Limited Target patients



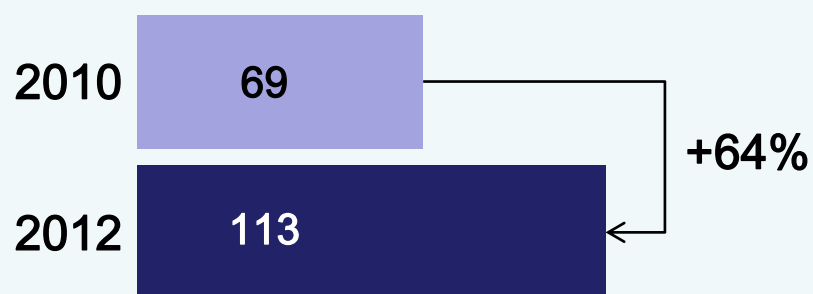
Patient benefit:  
Early realization of  
personalized medicine

# Biomarkers in FDA-Approved Drugs and Companion Diagnostics



(FDA-approved drugs)

- Drugs with description of biomarkers in the package insert  
(Efficacy prediction and patient stratification for conventional drugs)



Examples

Herceptin

Glivec

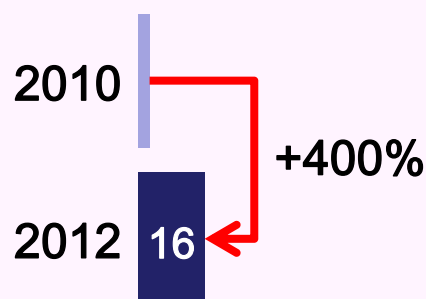
Erbitax

Tarceva

Tegretol

Warfarin

- Diagnostic testing required prior to administration (companion diagnostics )



Xalkori

Zelboraf

Vectibix

Sprycel

Erbitax

Herceptin

Glivec

Ref. Bayer HealthCare; Molecular Med TriCon, Feb. 14<sup>th</sup>, 2013

# Situation in Japan

(As of October 2012)

| Target disease           | Product name (generic name)               | Diagnostic testing to predict efficacy (NHI points)                  |
|--------------------------|---|--|
| Breast cancer            | Herceptin (Trastuzumab)                   | Overexpression/proliferation of HER-2 proteins/genes in cancer cells |
| Stomach cancer           |   |  |
| Lung cancer              | Iressa (Gefitinib)<br>Tarceva (Erlotinib) | Mutation of EGFR genes in cancer cells (2,000 -> 2,100)              |
|                          | Xalkori (Crizotinib)                      | Existence of ALK chimera genes in cancer cells (6,520)               |
| Colon cancer             | Erbitax (Cetuximab)                       | No mutation of KRAS genes in cancer cells (2,000 -> 2,100)           |
|                          | Vectibix (Panitumumab)                    |  |
| Chronic myeloid leukemia | Glivec (Imatinib)<br>Tasigna (Nilotinib)  | Existence of BCR-ABL Chimera genes in cancer cells (1,200/2,000)     |
| Adult t-cell leukemia    | Poteligeo (Mogamulizumab)                 | Existence of CCR4 protein in lymphatic tissue or blood (10,000)      |

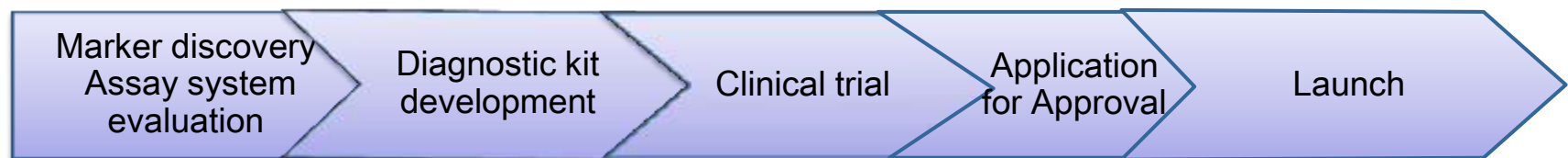
# Companion Diagnostics: Issues

## Drug Development Process



1) Determine the starting point

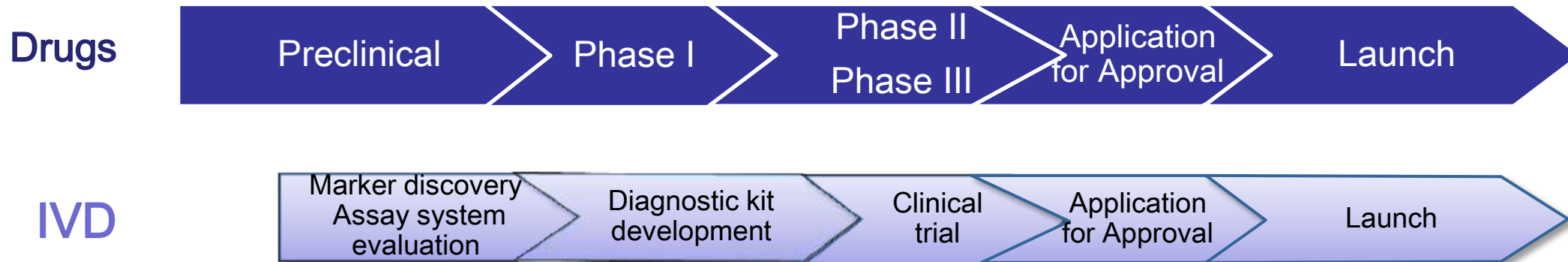
## IVD Development Process



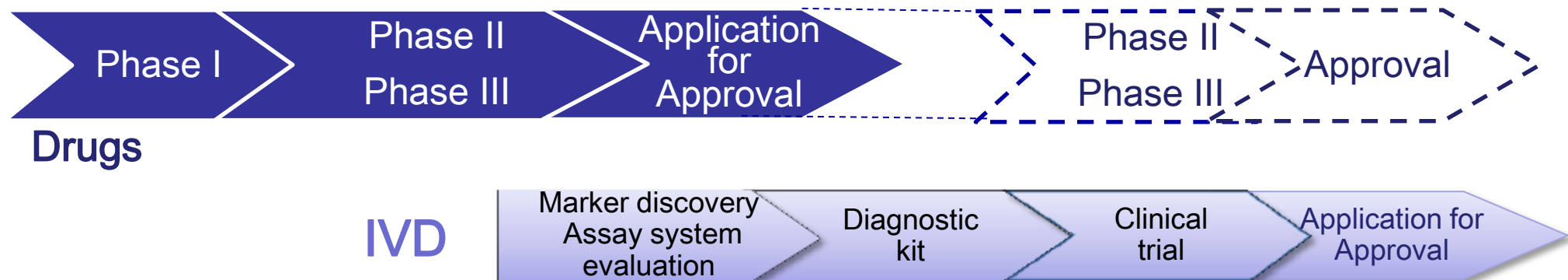
2) Establish seamless process

# Timing of Start

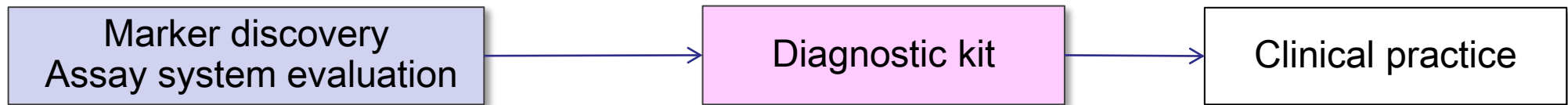
## 1) Early-Stage Collaboration (Investigational New drugs)



## 2) Late-Stage Collaboration (approval/developed drugs)



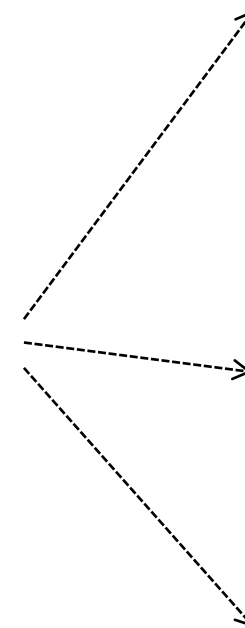
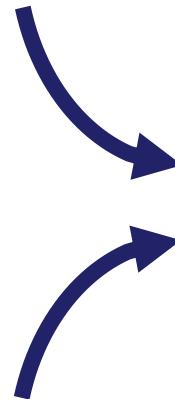
# Sysmex's Approach



## 1) Assay Lab (BMA Lab)



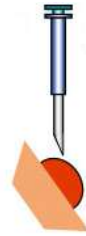
## 2) Use of Bioinformatics



# Technology Platform Necessary to CDx

Current

(Biopsy)



Near Future

(Liquid Biopsy)



|          |           |   |
|----------|-----------|---|
| Genes    | PCR       | (High-Sensitivity) PCR<br>Clinical Sequencer                  |
| Proteins | IHC / ISH | Chemiluminescence<br>(HISCL)<br>Thrombosis/Hemostasis<br>(CS) |
| Cells    | —         | FCM (Cell function analysis)                                  |

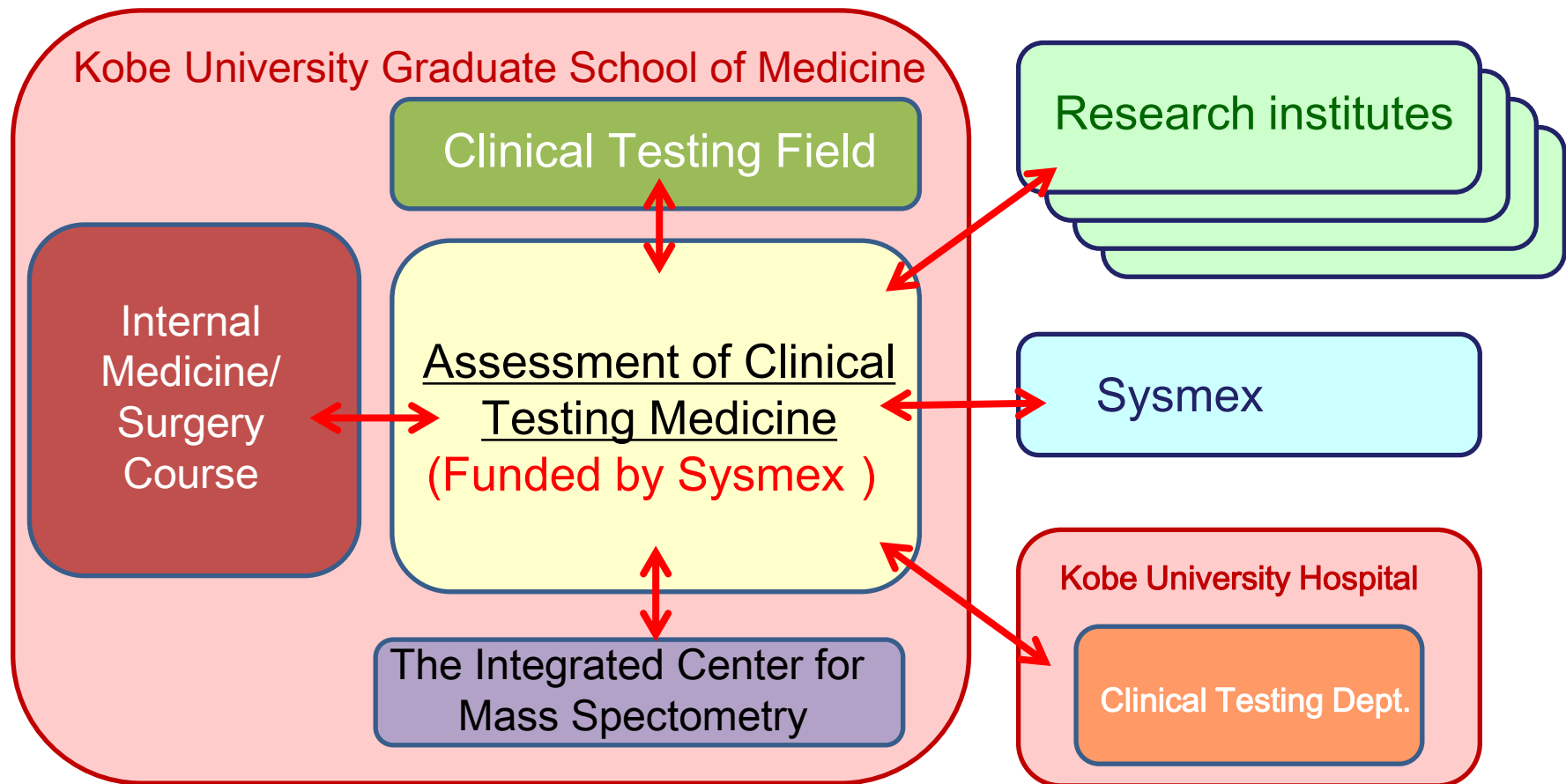
IHC : Immunohistochemistry  
ISH : In Situ Hybridization

## 2. Strategy for Establishing Personalized Medicine

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- (1) Outline of Technology Strategy
- (2) Companion Diagnostics
- (3) Founded Course at Kobe University Graduate School  
(Assessment of Clinical Testing)

# Summary of Founded Course at Kobe University Graduate School



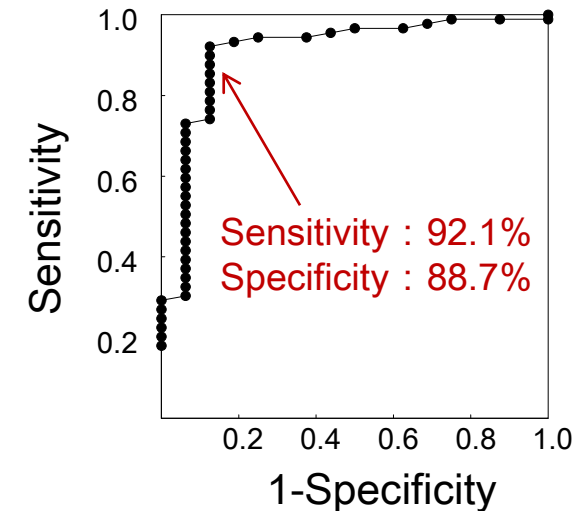
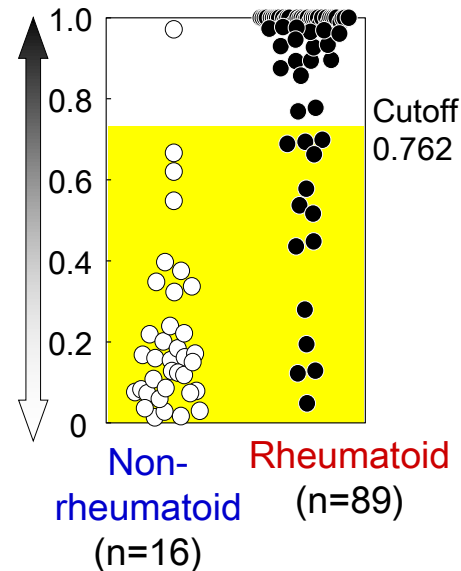
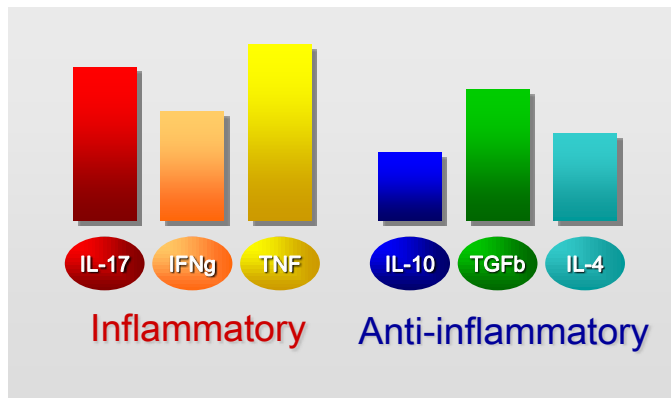
## What is Assessment of Clinical Testing Medicine?

- The gathering of clinical epidemiological evidence concerning basic evaluations and comparisons of clinical test, as well as the utility in diagnosis and disease state monitoring
- The provision to clinical practices of verification of the availability of testing methods as well as efficient use of clinical test based upon that evidence

# Diagnosis for Rheumatoid Arthritis through Serum Cytokine Measurement

Current research:  
Diagnosis for Early-stage rheumatoid arthritis

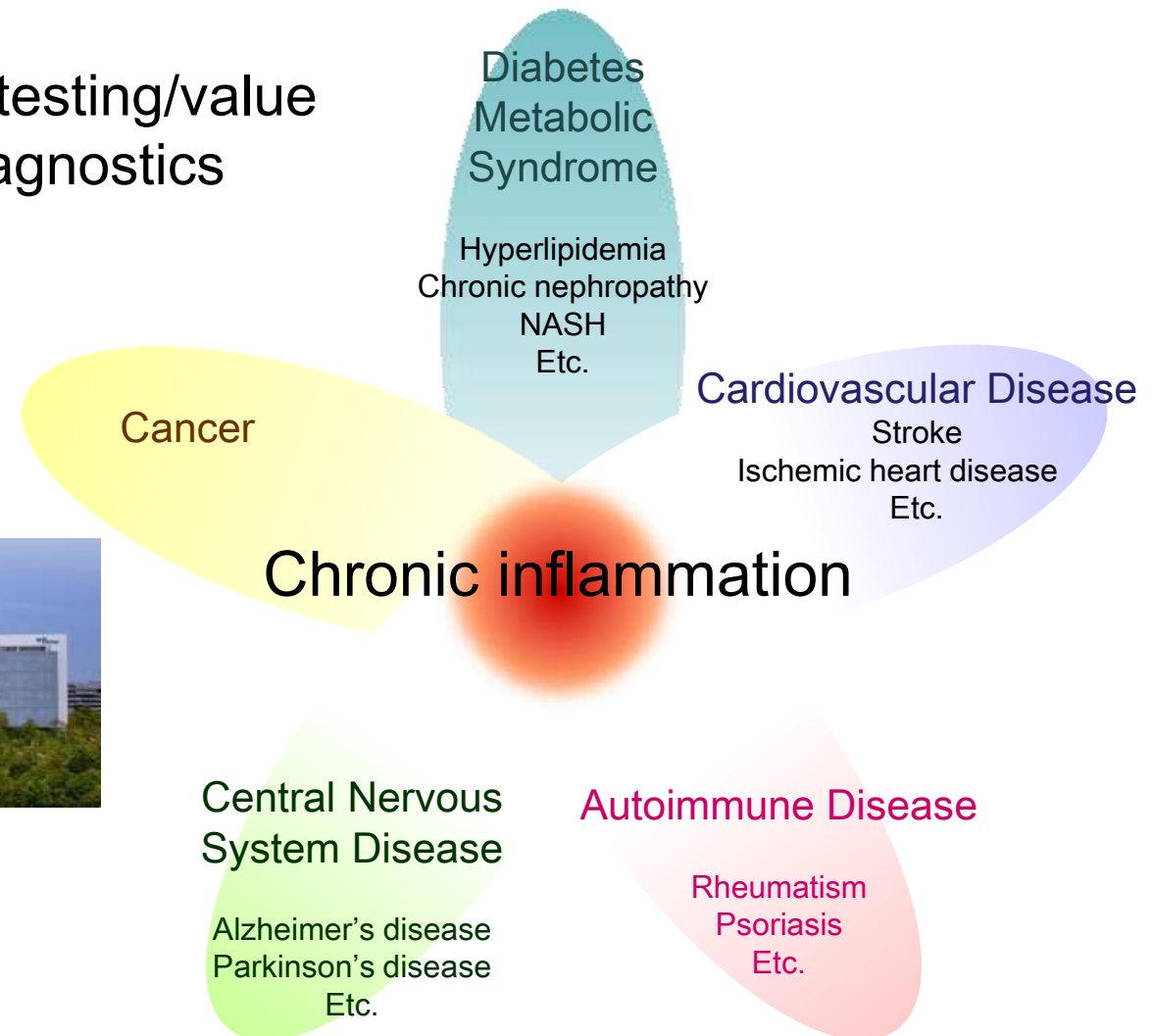
## Multiparameter Cytokine Measurement



Sensitivity : The probability that patients known to have the disease will test positive for it.  
Specificity : The probability that patients known not to have the disease will test negative for it.

# Summary

- Focusing **chronic inflammation**, which is caused by a number of diseases, including lifestyle diseases
- Providing of importance of new testing/value
- Establishing evidence-based diagnostics



NASH : Non-Alcoholic Steatohepatitis

### 3. Progress on Development Themes

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Kaoru Asano,  
Executive Officer,  
Executive Vice President of the R&D Strategic Planning Div.

(1) New Product Launch (New Products)

(2) Progress Status of Development Theme at Practical Stage

# New Models for Immunological Test (Fully Automated Immunoassay Analyzer HISCL<sup>®</sup>-5000)



New model focusing on midrange and high-end models, which advance functionality and speed.



HISCL<sup>®</sup>-5000

## Rapid measurement

- Reaction to all parameters in 17 minutes
- Simultaneous measurement of 24 parameters (max)

## Highly sensitive measurement

- Uses CDP-Star<sup>®</sup> to achieve a highly sensitive measuring system

## Minimized samples

- Sample amount used for all parameters: 10-30μL

## High usability

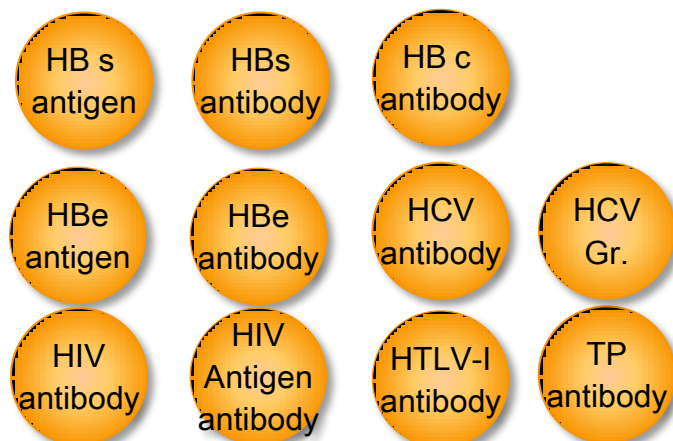
- Continuous measurement
- Flexible connectivity to transport systems
- Reagent controllability through RF-ID

Continuous measurement: Measurement is conducted continuously, without interruptions to reagent supply

# HISCL<sup>®</sup> Reagents



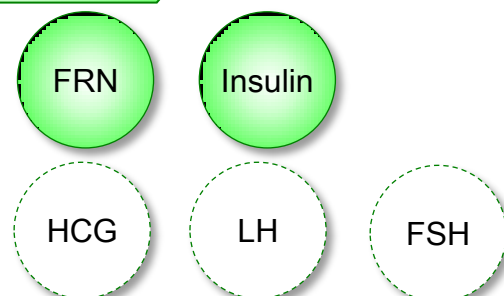
## Infectious disease



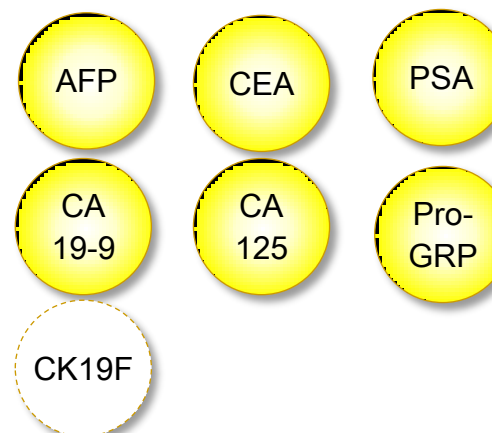
## Thyroid disease



## Other

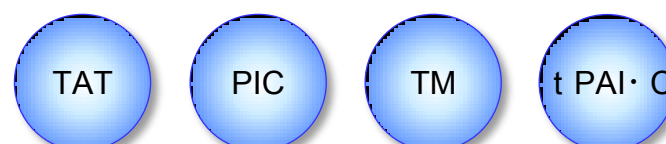


## Tumor markers



Under Development

## Coagulation molecular markers



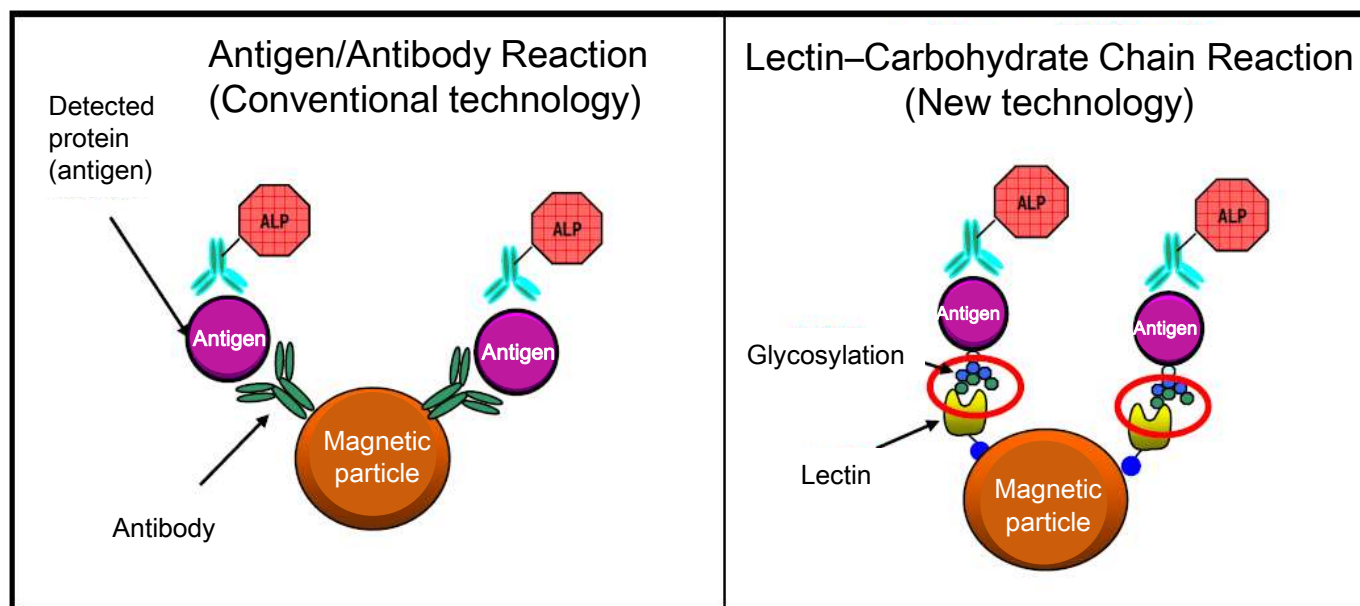
## Cardiovascular disease



## Hepatitis



# Liver Fibrosis Markers



SUBJECT AREAS:  
GLYCOBIOLOGY  
BIOCHEMICAL ASSAYS  
ASSAY SYSTEMS  
EUSA

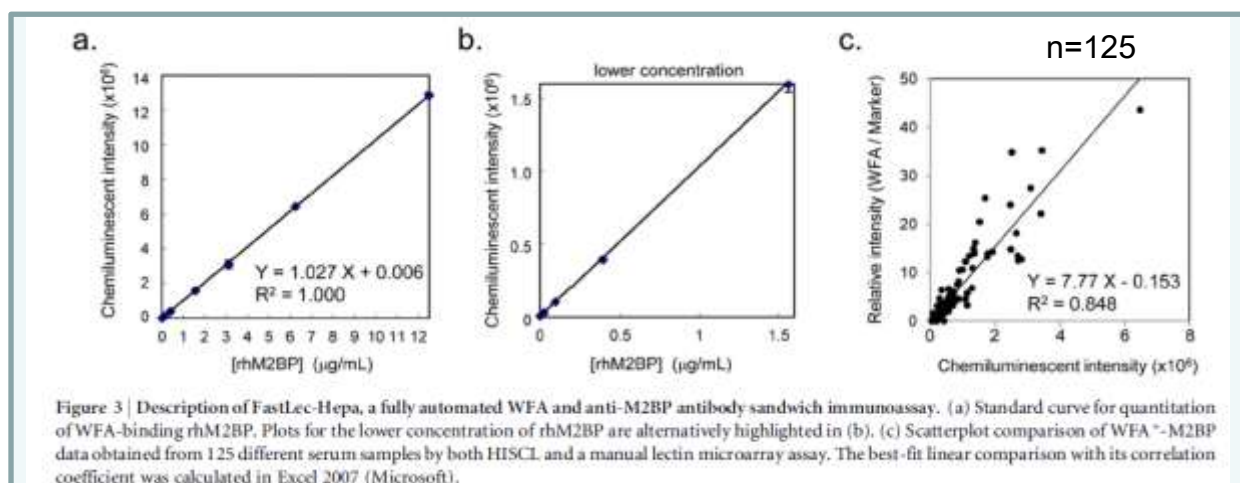
A serum “sweet-doughnut” protein facilitates fibrosis evaluation and therapy assessment in patients with viral hepatitis

Atsushi Kuno<sup>1\*</sup>, Yuzuru Ikehara<sup>1\*</sup>, Yasuhito Tanaka<sup>2</sup>, Kiyooki Ito<sup>3</sup>, Atsushi Matsuda<sup>1</sup>, Satoru Sekiya<sup>1</sup>, Shuhei Hige<sup>4</sup>, Michiie Sakamoto<sup>5</sup>, Masayoshi Kage<sup>6</sup>, Masashi Mizokami<sup>3</sup> & Hisashi Narimatsu<sup>1</sup>

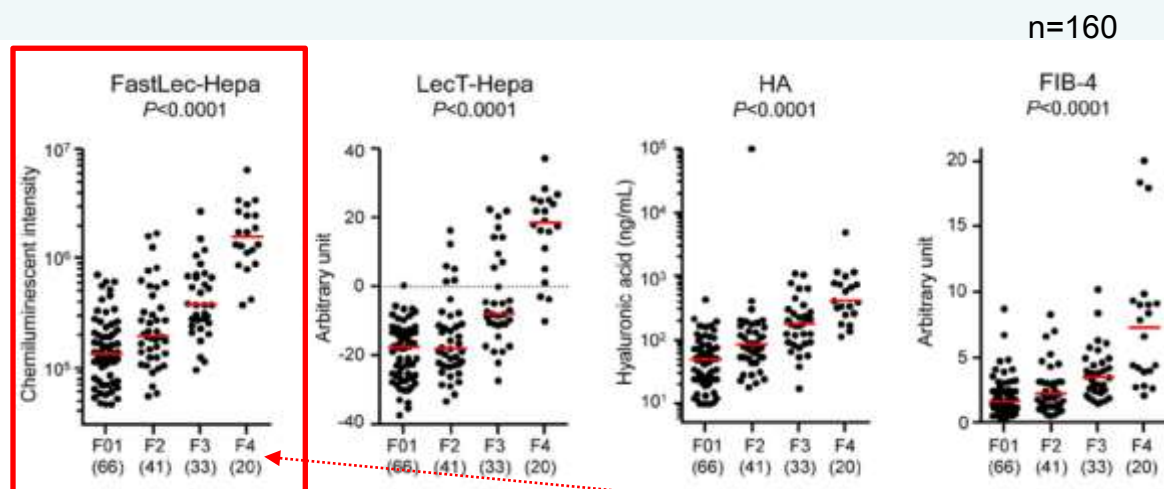
ALP: Alkaline Phosphatase

Nature *Scientific Reports* 3 : 1065 doi: 10.1038/srep01065 (2013)

# Clinical Research Outcomes Using HISCL<sup>®</sup>



## Analytical Performance



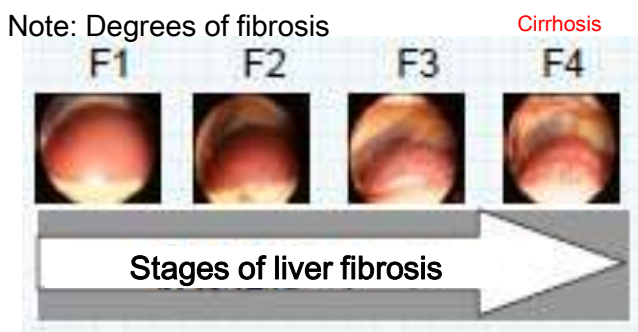
## Clinical Performance

Taken from Nature JAPAN WEB Comment

Although liver fibrosis reflects disease severity in chronic hepatitis patients, there has been no simple and accurate system to evaluate the therapeutic effect based on fibrosis. We developed a glycan-based immunoassay, FastLec-Hepa, to fill this unmet need. FastLec-Hepa automatically detects unique **fibrosis-related glyco-alteration in serum hyperglycosylated Mac-2 binding protein within 20 min**. The serum FastLec-Hepa counts increased with advancing fibrosis and illustrated significant differences in medians between all fibrosis stages. **FastLec-Hepa is sufficiently sensitive and quantitative to evaluate the effects of PEG-interferon- $\alpha$ /ribavirin therapy in a short post-therapeutic interval.**

<http://www.natureasia.com/ja-jp/srep/abstracts/42129>

Note: Degrees of fibrosis



Nature *Scientific Reports* 3 : 1065 doi: 10.1038/srep01065 (2013)

# Compact Models for Hematology (XP Series)



XP-300

Featuring high reliability established in the skills of the previous model, these hematology analyzers accommodate expanding demand in emerging markets.

- Touch panel for better operability
- Increased specimen memory
- Space-saving
- Compatible with in-hospital networks and SNCS®
- Silent design



Menu screen



Quality control chart screen

SNCS : Sysmex Network Communication Systems

# Expanding Application of OSNA<sup>®</sup> to Stomach Cancer



RD-100i gene amplification detector



LYNOAMP<sup>®</sup> BC  
(Same reagent for breast and colon cancer)

Clinical trial results for stomach cancer

| N=394 lymph nodes        |          | 2mm space histopathological examination |          |
|--------------------------|----------|---|----------|
|                          |          | Positive                                | Negative |
| OSNA <sup>®</sup> method | Positive | 45                                      | 14       |
|                          | Negative | 9                                       | 326      |

Sensitivity: 0.833  
Specificity: 0.959  
Concordance rate: 0.942

Approved by the Ministry of  
Health, Labor and Welfare as of July 12, 2012

### 3. Progress on Development Themes

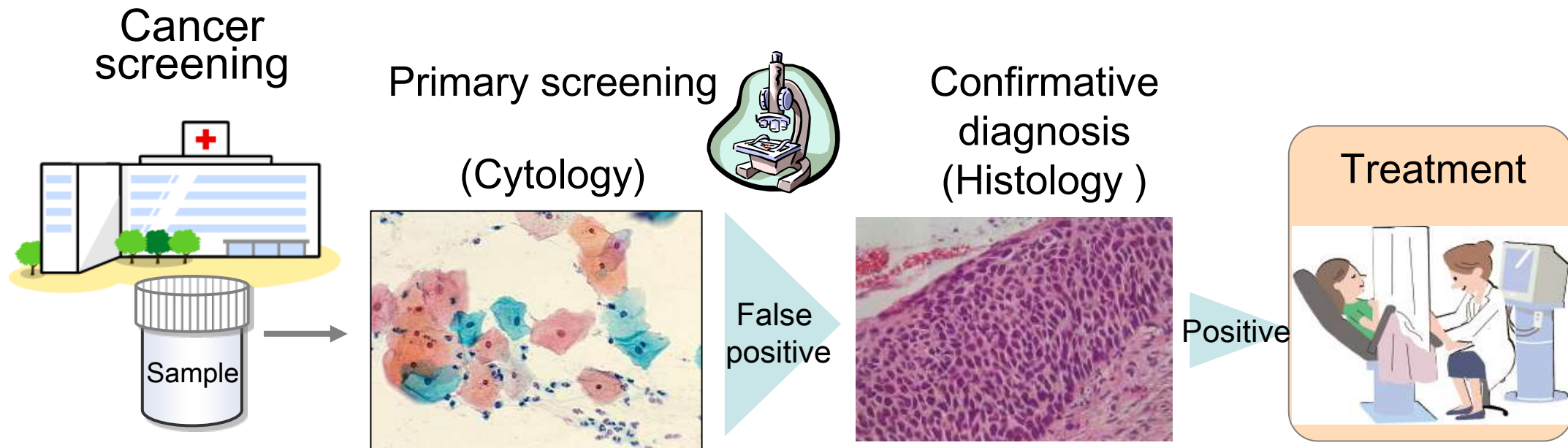
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(1) New Product Launch (New Products)

(2) Progress Status of Development Theme at Practical Stage

# 1) Cervical Cancer Screening

# Cervical Cancer Screening: Diagnostic Flow

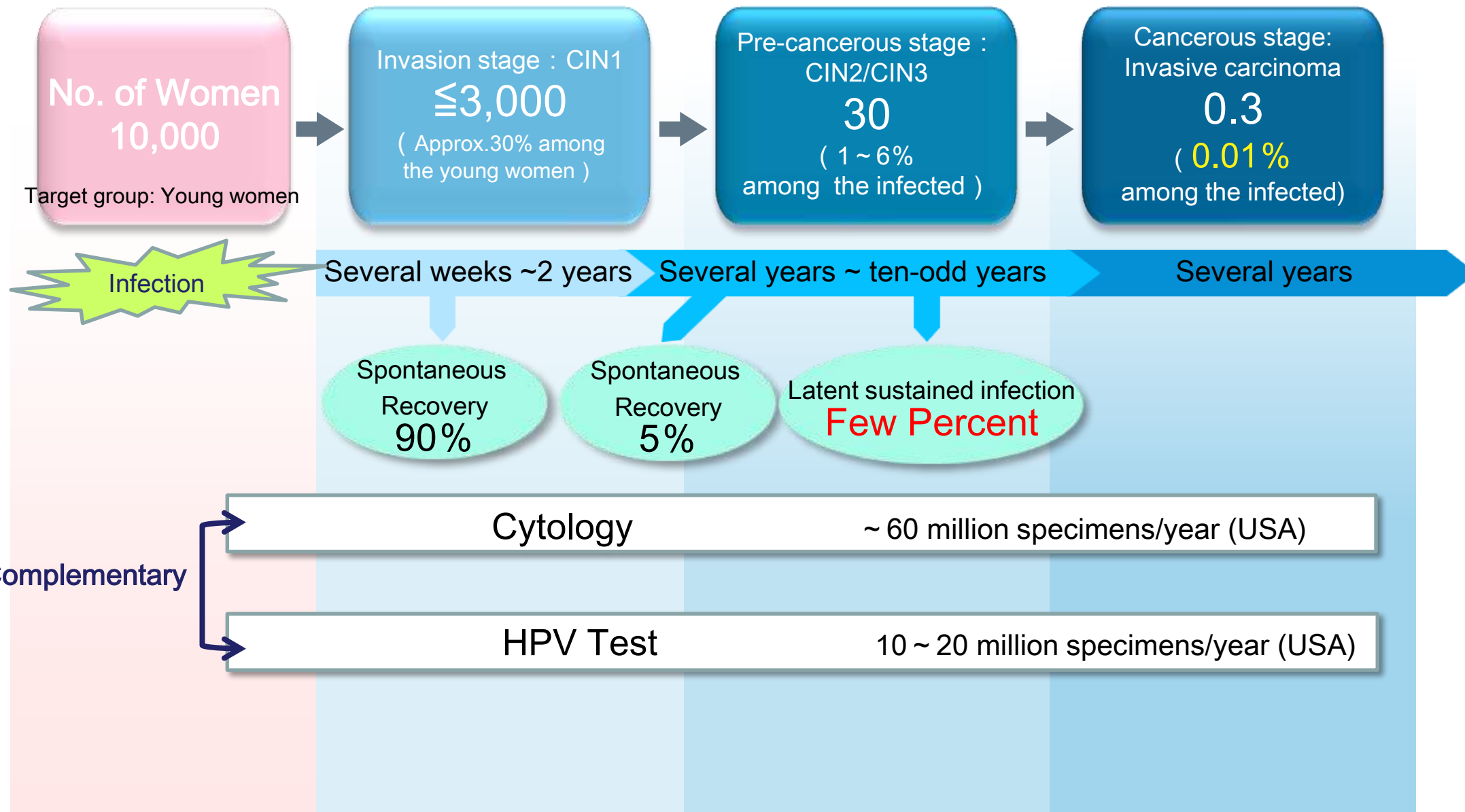


## Cytological Issues

- Low sensitivity (44%~78%)
- Screening results can vary according to the cytologist.
- Shortage of cytologists (especially in emerging markets)

**Strong need for automation**

# Relationships between HPV Infection and Cervical Cancer



CIN: cervical intraepithelial neoplasia

# Cervical Cancer Screening System



## Newly-Developed Technologies



1) Pretreatment technology for LBC specimens  
Technology for dissociating cells while maintaining their morphology

2) DNA staining and FCM technology  
Technology for measuring cell diameter, nuclear diameter, and nuclear DNA content

3) Analyzing technology  
Technology for detecting abnormal cells based on original parameters

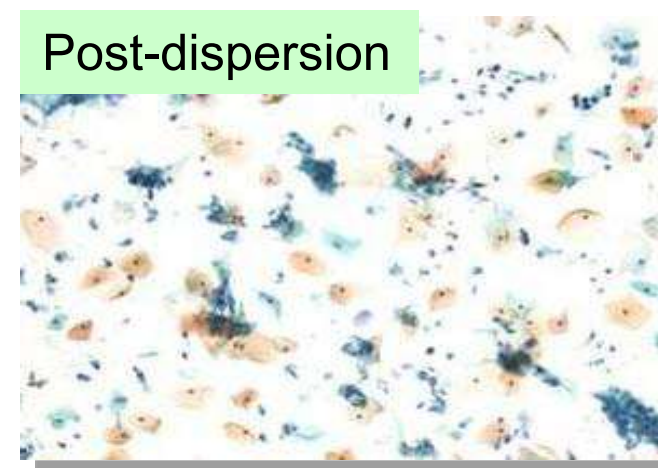
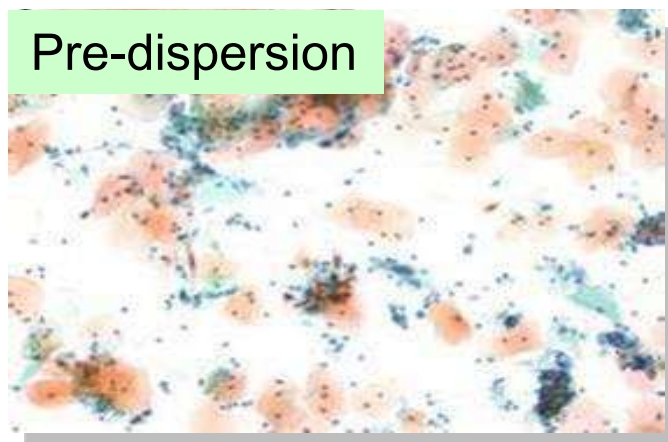
Development for these technologies

LBC: liquid-based cytology

# 1) Pretreatment Technology for LBC specimens

## ● Cell dispersion (mucolytic agent, mechanical stirring, etc.)

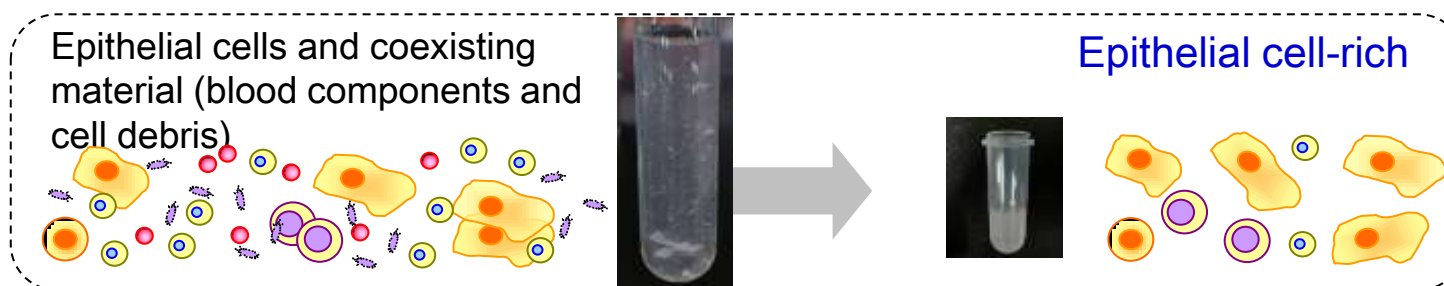
Dissociating cell clusters while maintaining cell morphology



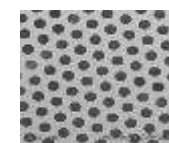
## ● Concentration of cell density (Using a metal micropore filter)

Concentration of epithelial cell density (approximately 10X)

Reduce the amount of coexisting material, such as blood components and cell debris.



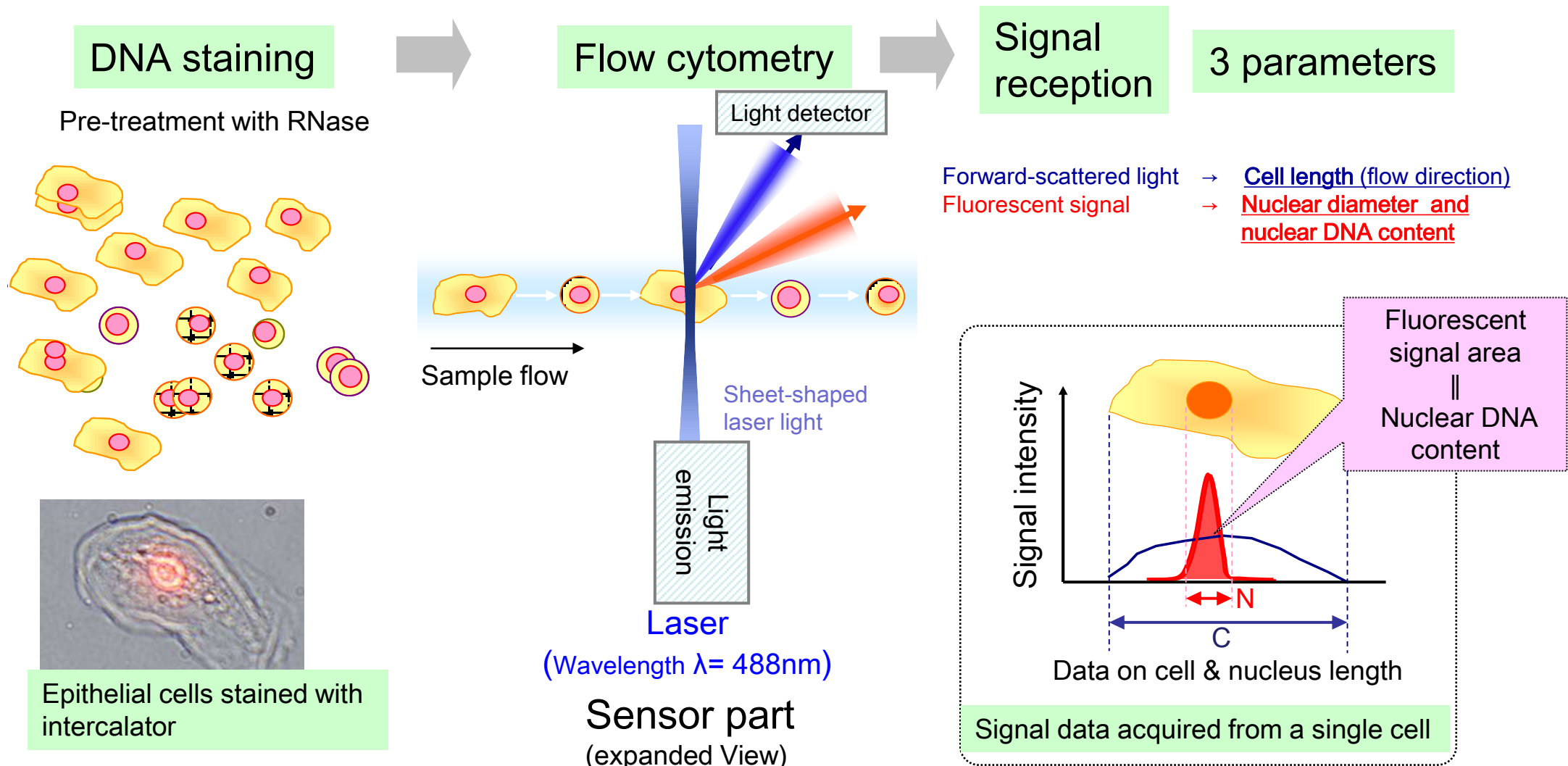
Metal filter surface  
(enlarged image)



Epithelial cell-rich: Sample with concentrated epithelial cells

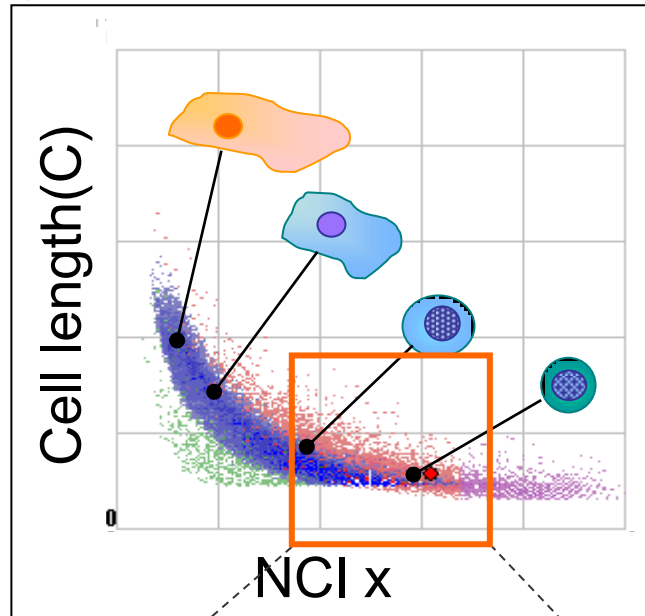
## 2) DNA Staining and FCM Technology

Those cells are exposed to a narrow, long laser beam to measure the nuclear DNA content, cell diameter, and nuclear diameter of individual cells. All of the data acquired is then processed, and the characteristics of sample are analyzed by statistical methods.



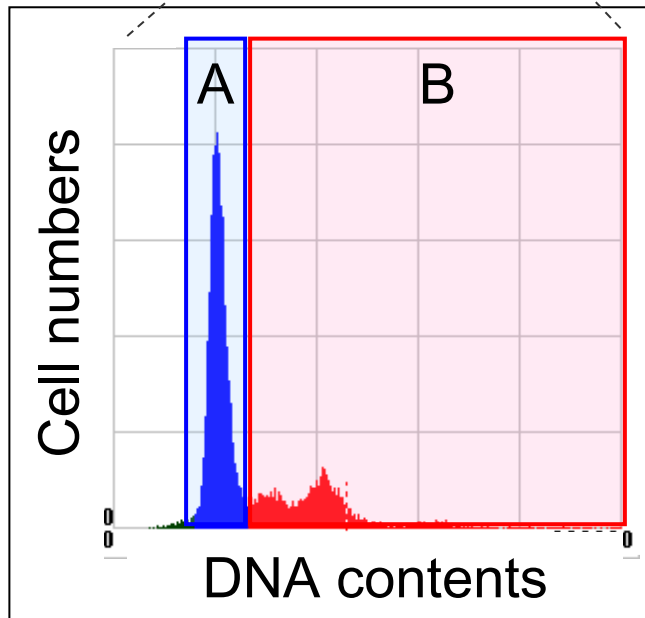
# 3) Analyzing Technology

## (Signal Waveform Processing and Judgment Algorithms)



### 1. Analysis of cell morphology

$$NCI_x = \frac{\text{Nuclear diameter (N)}}{\text{Cell length (C)}}$$



### 2. Analysis of DNA content

$$CPI_x = \frac{\text{Cell numbers in Region B}}{\text{Cell numbers in Region A}}$$

[CPIx: Cell Proliferation Index]

# Evaluation of This System

High sensitivity and specificity in detection of moderate or higher-level pathological changes

| Accuracy    |        | n         | 95% confidence interval |
|-------------|--------|-----------|-------------------------|
| Sensitivity | 100.0% | 15 / 15   | 79.6 – 100.0            |
| Specificity | 85.1%  | 841 / 988 | 82.8 – 87.2             |

|             |          | Existing testing |          | Total |
|-------------|----------|------------------|----------|-------|
|             |          | Positive         | Negative |       |
| This system | Positive | 15               | 147      | 162   |
|             | Negative | 0                | 841      | 841   |
| Total       |          | 15               | 988      | 1003  |

Positive : CIN2 or above  
Negative : CIN1 or below  
(including normal)

## Future Plans

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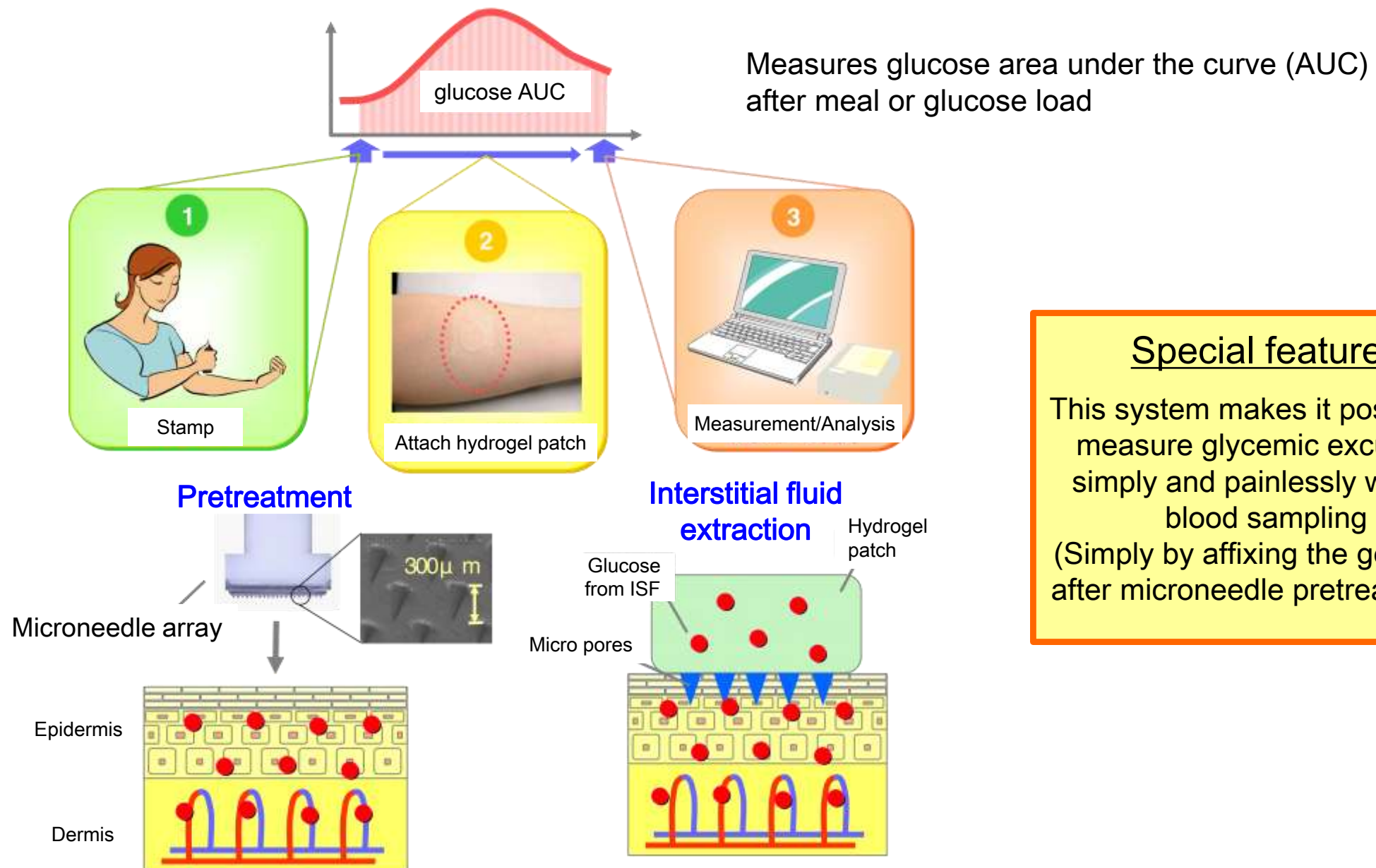
- Japan
  1. Organization for working groups
  2. Implementation of clinical evaluation
  3. Pharmaceutical application
- Outside Japan
  - Implementation of clinical evaluation in fiscal 2013  
(under preparation)

## 2) Glucose AUC

(Minimally Invasive Interstitial Fluid Extraction Technology)

AUC : Area Under the blood Concentration time curve

# Glucose Monitoring System without blood sampling



## Special features

This system makes it possible to measure glycemic excursion simply and painlessly without blood sampling  
(Simply by affixing the gel patch after microneedle pretreatment.)

# Evaluation of Clinical Utility

## 1. Screening for early stage diabetes

Can it easily find early stage diabetes (impaired glucose tolerance) during health checkups?

## 2. Determining the efficacy of diabetes treatments

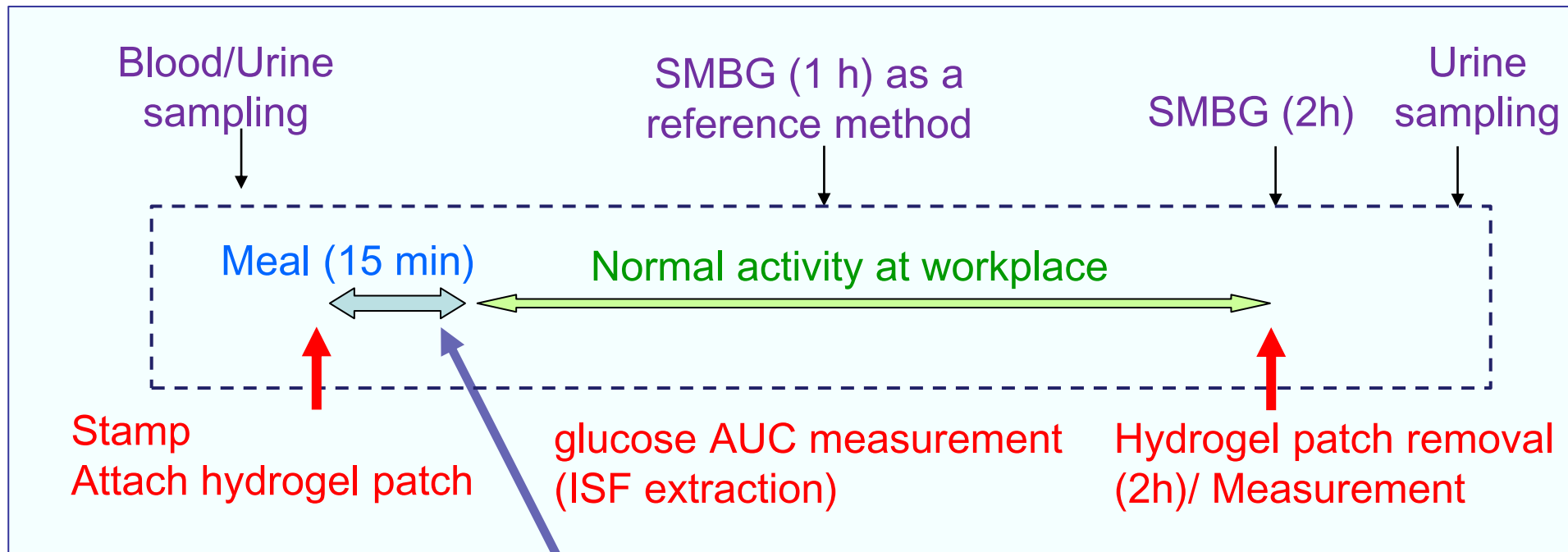
Can the efficacy of diabetes treatments be monitored?

## 3. Application to the individualized dietary therapy

Can it be used to determine the optimal diets for individuals?

# 1) Screening for Early Stage Diabetes

## Evaluation Protocol in routine health checkups

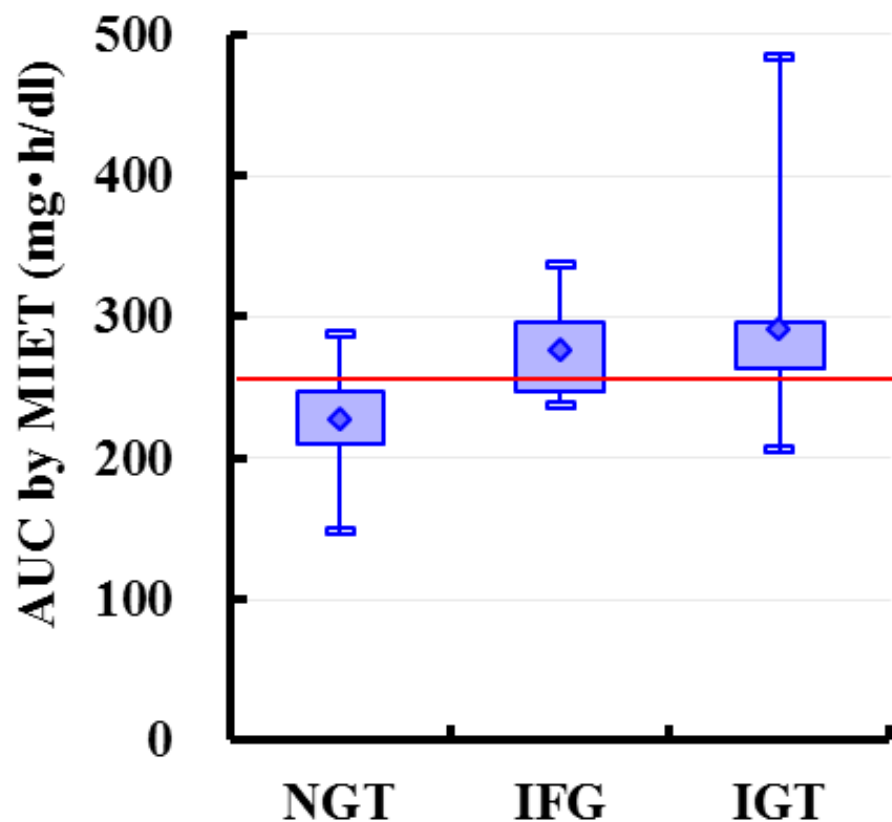


(57g carbohydrate, developed by Japan Diabetes Society test meal working group)

SMBG : Self-Monitoring of Blood Glucose

# Screening Performance Using Glucose AUC

Glucose AUC

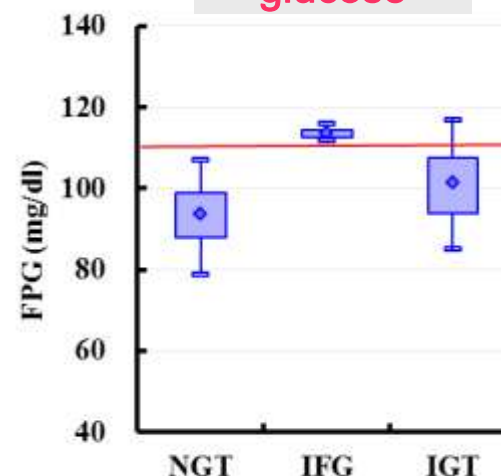


Normal

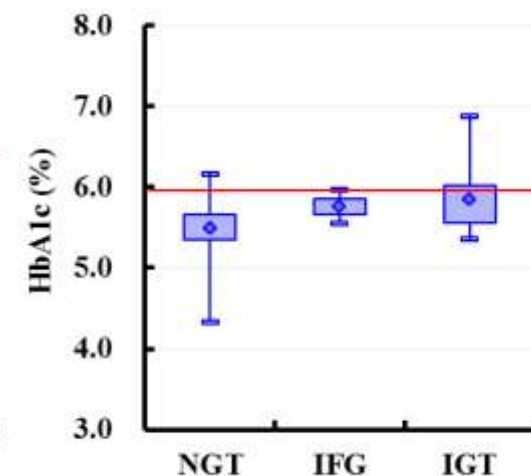
Borderline diabetes  
(early stage diabetes)

NGT : Normal Glucose Tolerance  
IFG : Impaired Fasting Glycaemia  
IGT : Impaired Glucose Tolerance

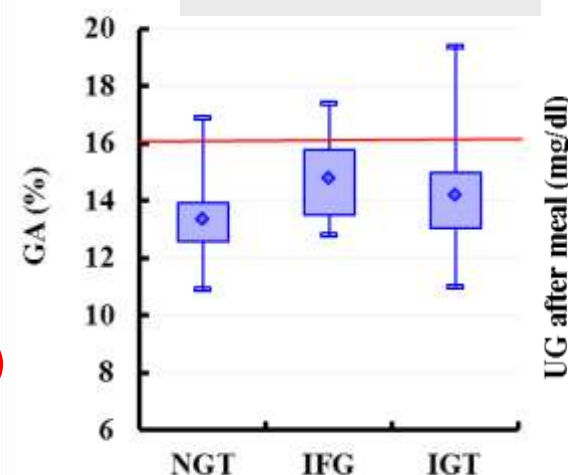
Fasting glucose



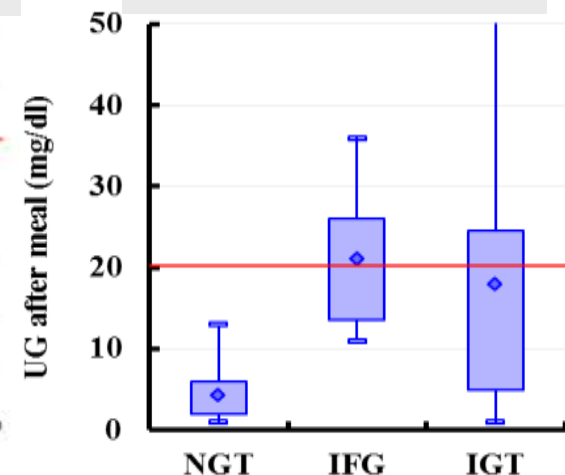
HbA1c



Glycoalbumin



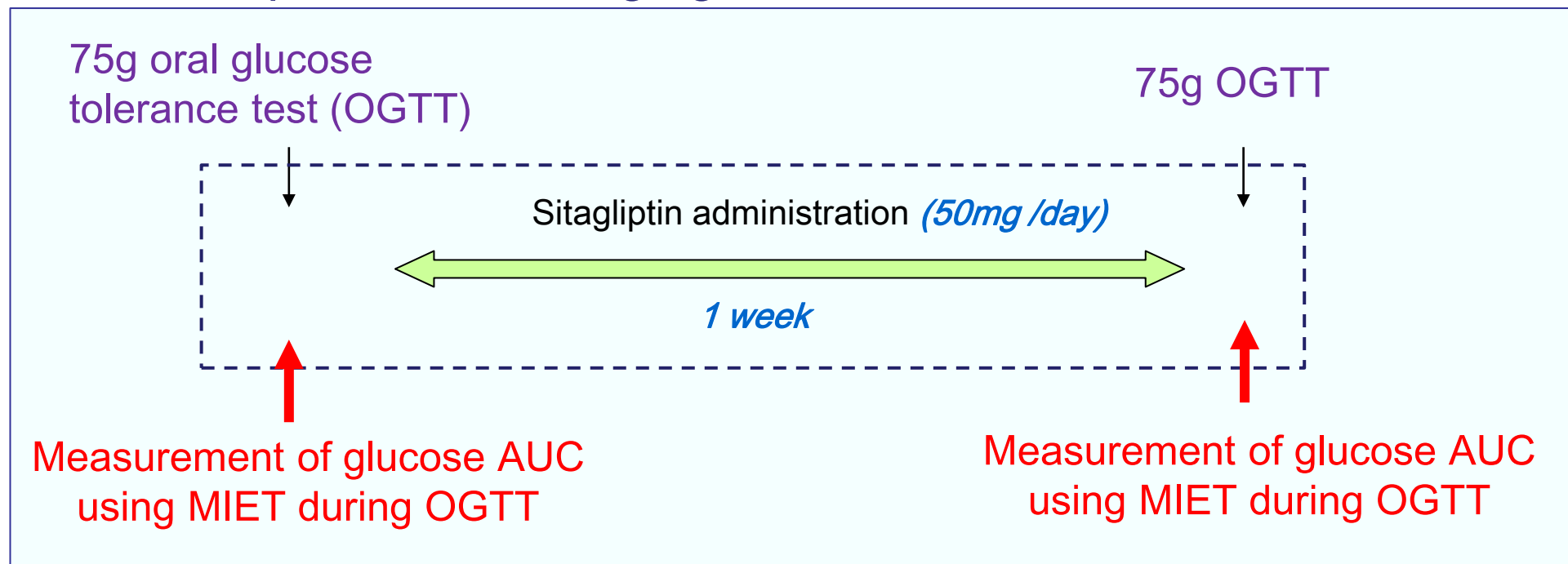
Urinary glucose



## 2) Determining the Efficacy of Diabetes Treatments

Subjects: 8 Type-2 diabetes patients being administered an antidiabetic drug (Sitagliptin)

Evaluation protocol envisaging clinical use



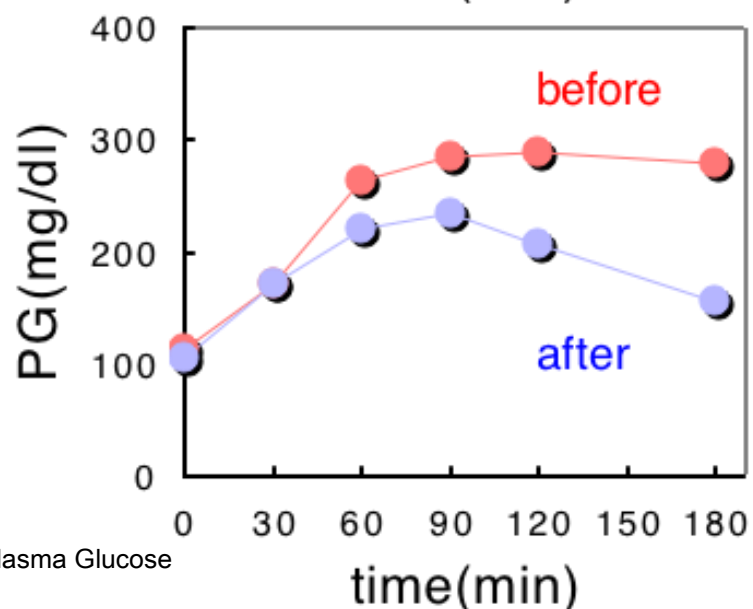
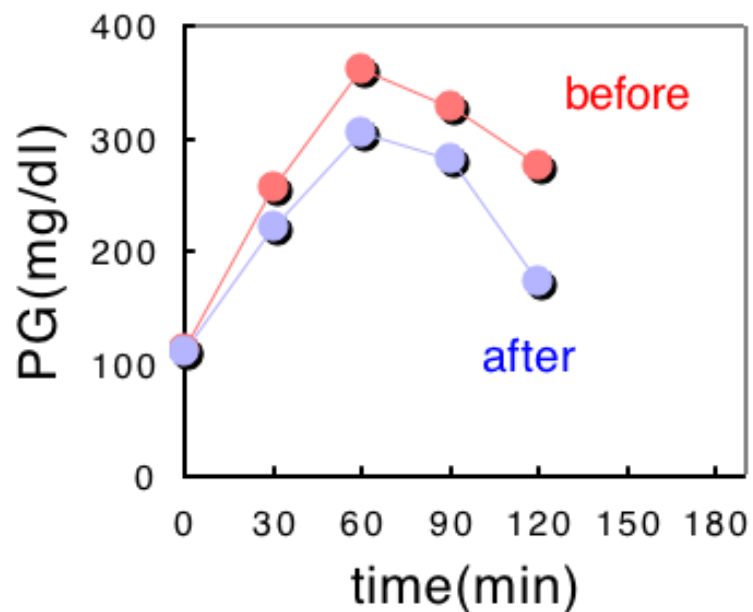
Sitagliptin: DPP-4 inhibitor

Controls blood glucose level by inhibiting the enzyme DDP-4, which degrades the gastrointestinal hormone incretin that is secreted after glucose intake.

OGTT: Oral Glucose Tolerance Test

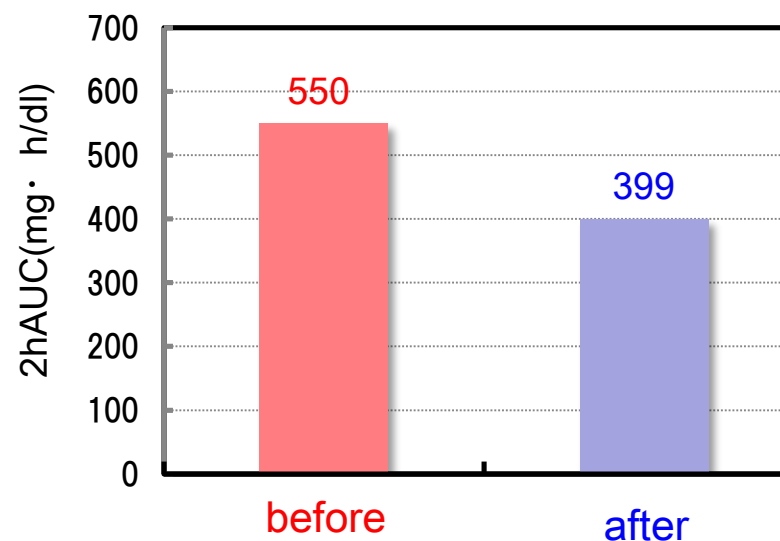
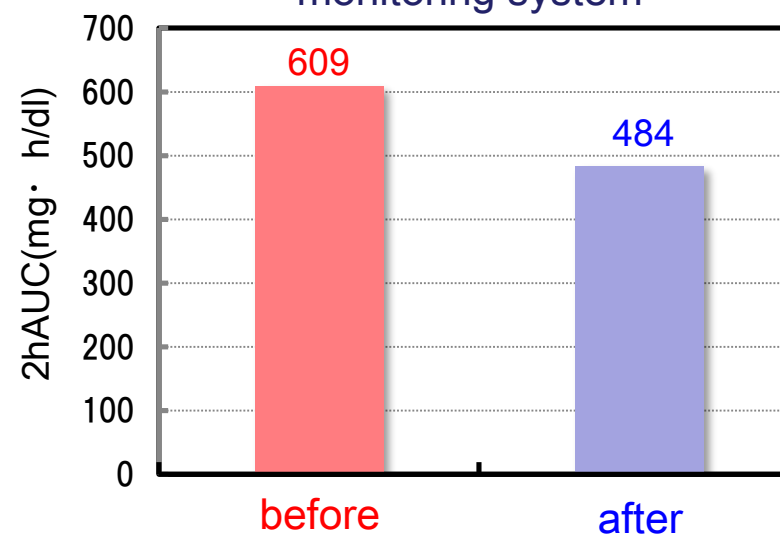
# Drug Efficacy Monitoring

OGTT results

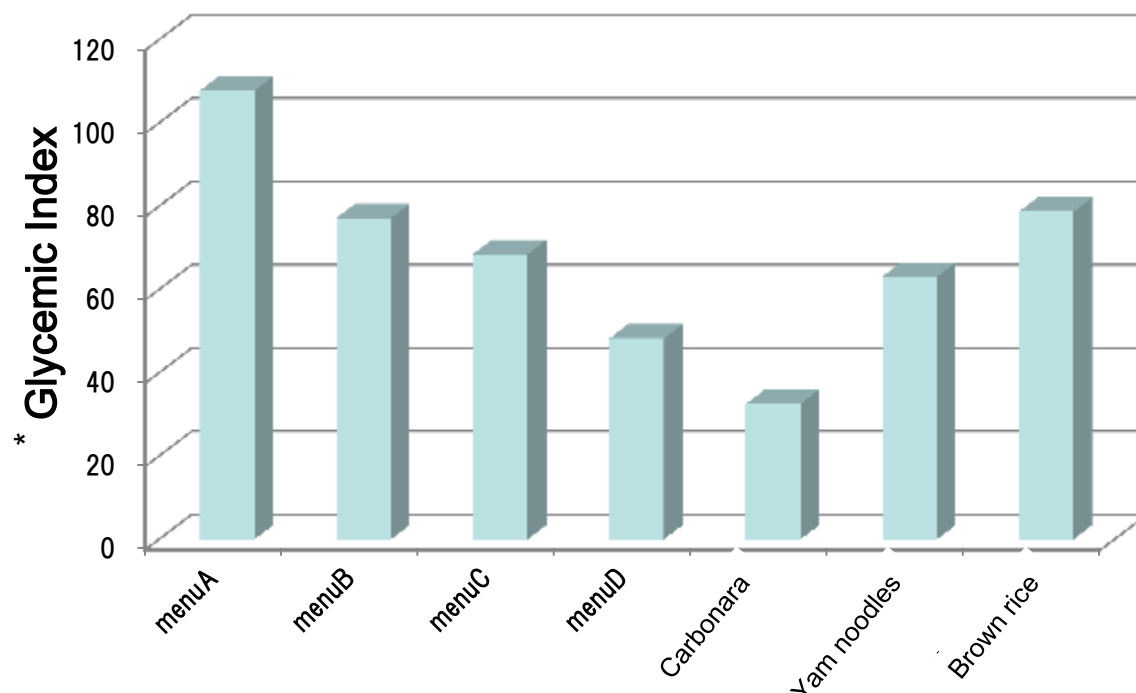


PG : Plasma Glucose

Results of glucose AUC monitoring system



# Individualized Dietary Therapy



\*Increment Level of glucose AUC by a diet, which is normalized by the level after white rice (carbohydrate 50g) intake

Glucose AUC monitoring system will be useful for individualized dietary therapy, which enables to understand the relationship between food and glycemic excursion after intake of the food easily.

## Menu A

Rice, Japanese greens in sesame sauce, vinegared cucumbers; 1 dish

## Menu B

Rice, Japanese greens in sesame sauce, vinegared cucumbers; 2 dishes

## Menu C

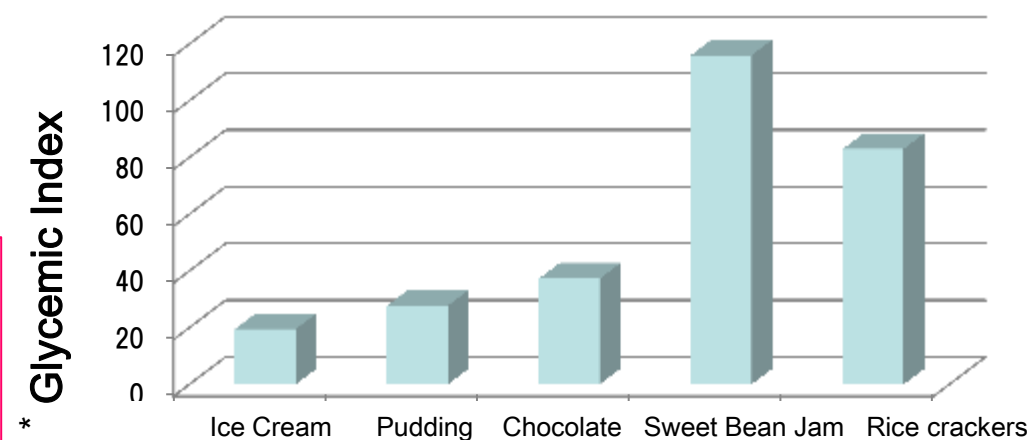
Rice, Japanese greens in sesame sauce, vinegared cucumbers; 1 dish

Tuna sashimi (lean tuna)

## Menu D

Rice, Japanese greens in sesame sauce, vinegared cucumbers; 2 dishes

Tuna sashimi (fatty tuna)



## Future Plans

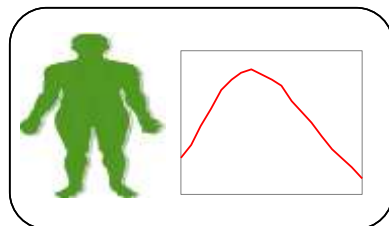
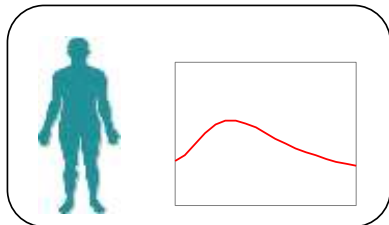
### Planned clinical study and approval application

|                        |   |
|------------------------|---|
| Clinical study details | The screening performance for impaired glucose tolerance using the minimally invasive glucose AUC monitoring system is verified as not inferior to either the combined fasting blood glucose/HbA1c screening or the 2-hour glucose level during OGTT. |
| No. of target cases    | Approximately 180   |
| Facilities             | Five facilities participating in the AUC Study Group  |
| Period                 | 2Q-4Q fiscal 2013   |

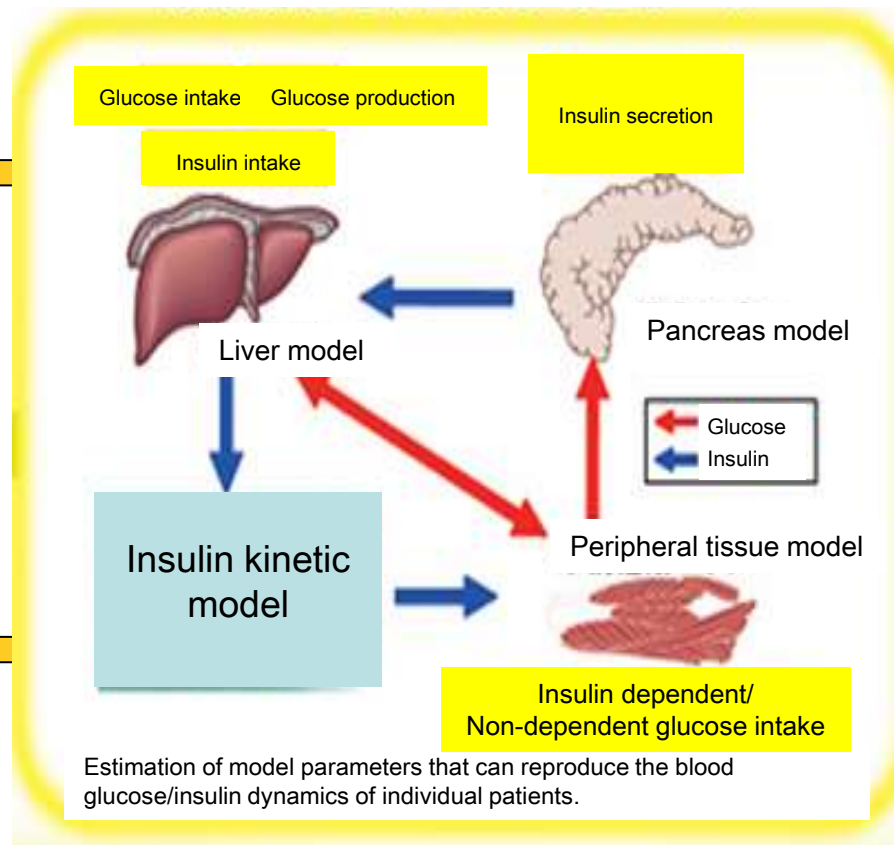
### 3) Diabetes Simulation (Disease State Simulation Technology)

# Diabetes Simulation

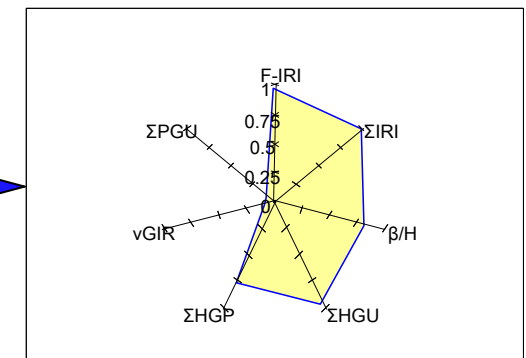
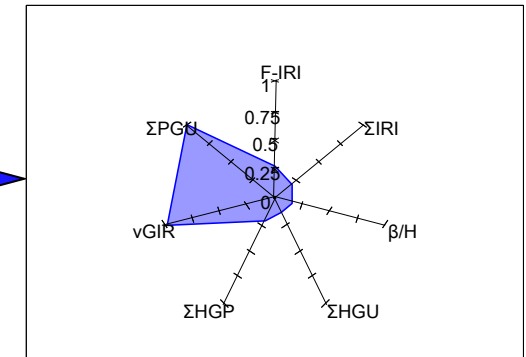
## Clinical test data



## Diabetes Simulator based on mathematical models

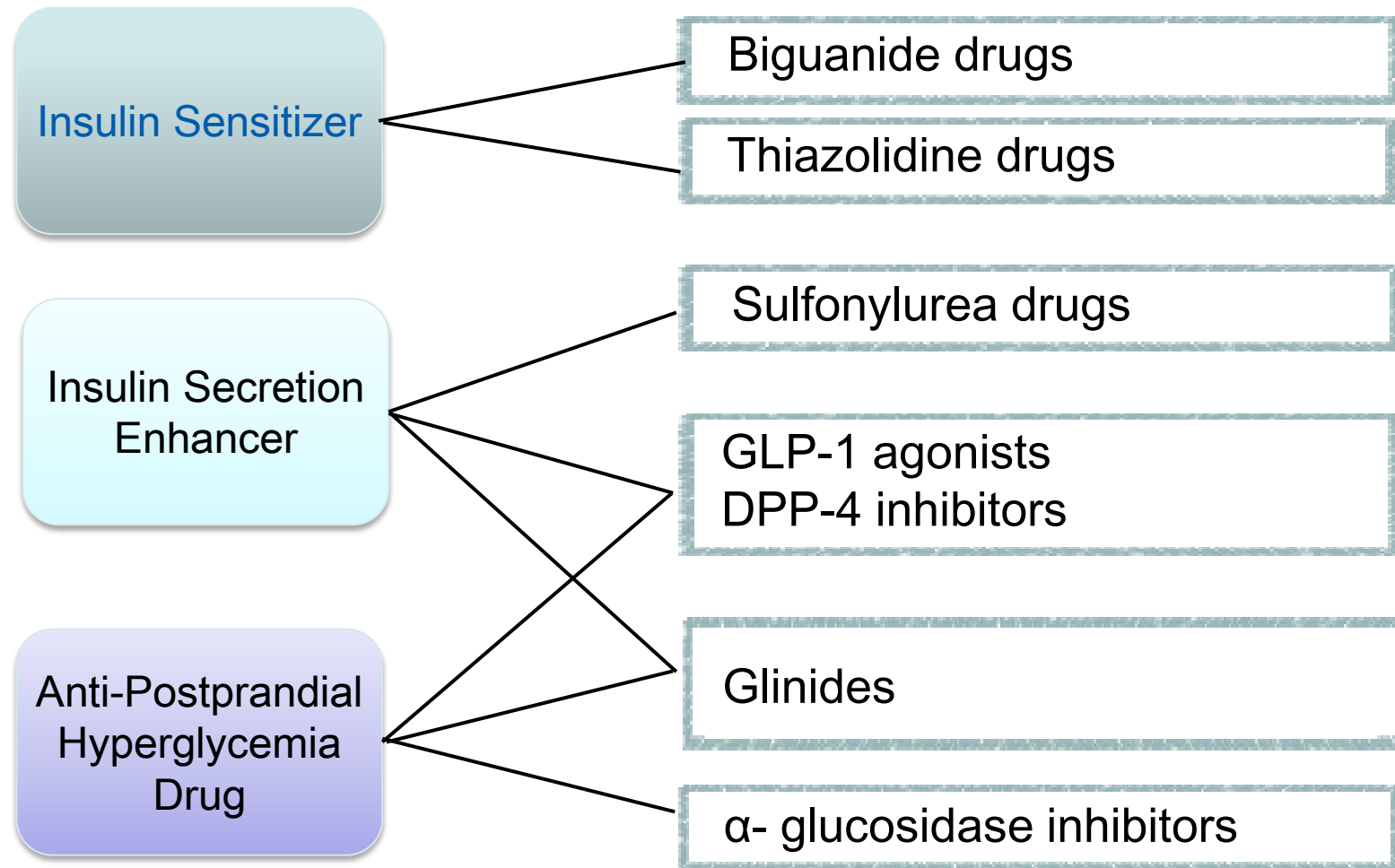


## Quantified Disease States “Disease State Profile”



Quantification of disease states by simulation

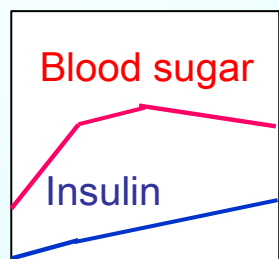
# Anti-diabetic Drugs



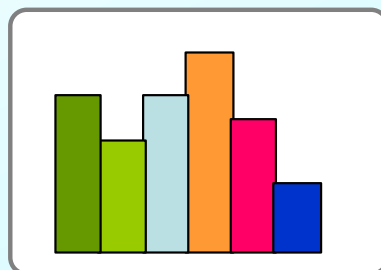
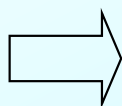
Drug selection is based on doctors' knowledge and experience

# Prediction of Drug Responders Using Diabetes Simulators

## Quantification of disease states



Test data



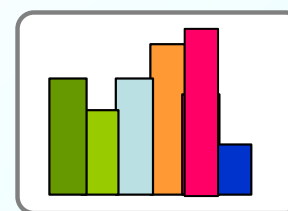
Parameters

Therapy in silico

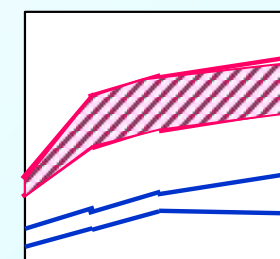
## Prediction of drug effectiveness

Insulin sensitizer

Simulation of glucose change



Resistivity parameters

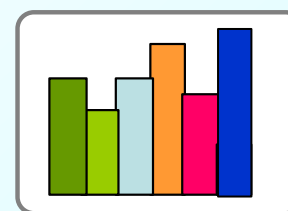


$\Delta G_{EST\_IS}$

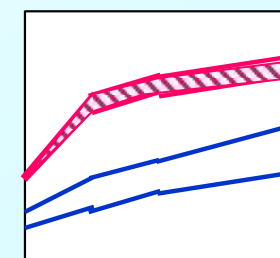
$\Delta G_{EST\_IR}$

Insulin secretion enhancer

Simulation of glucose change



Secretion parameters



$\Delta G_{EST\_IS}$

$\Delta G_{EST\_IR}$

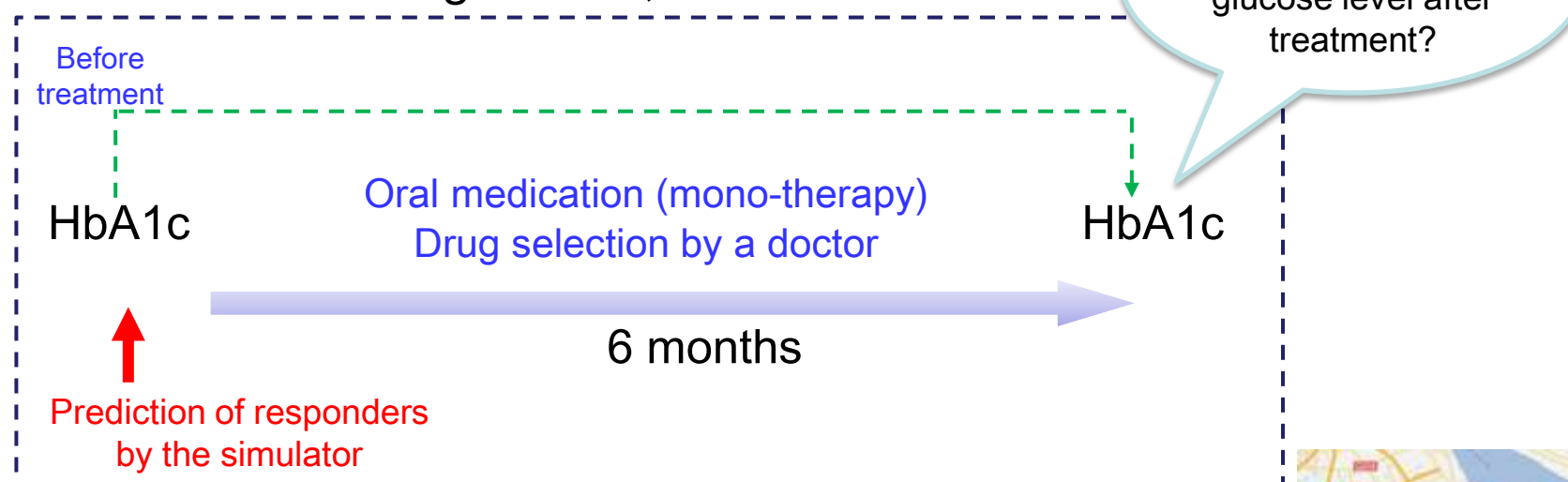
$\Delta G_{EST\_IS}$ : Simulated glucose change when insulin secretion is normalized.

$\Delta G_{EST\_IR}$ : Simulated glucose change when insulin resistance is normalized.

# Verification of Clinical Utility

## Prediction of Drug Responders Using Diabetes Simulators

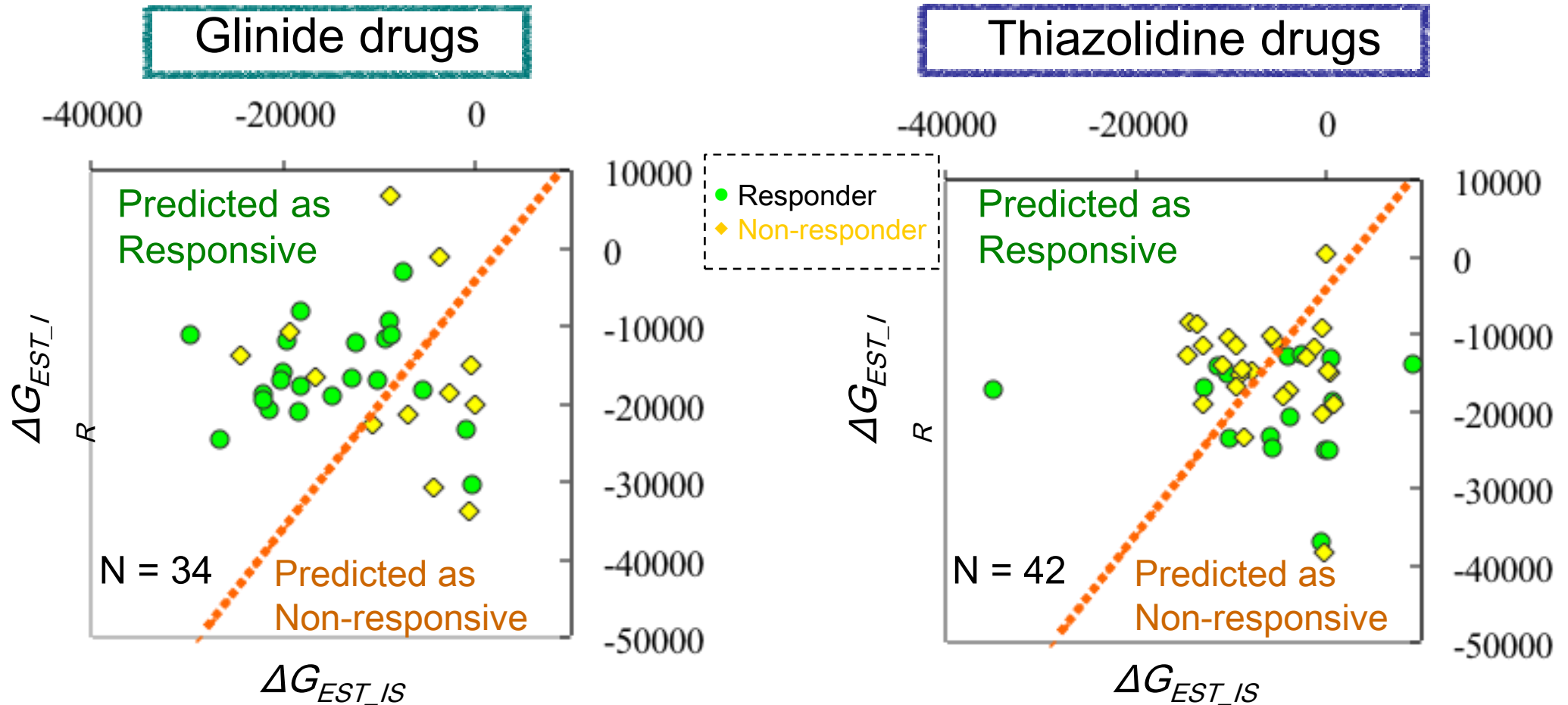
- Planned number of cases 200
- Drugs Metformin, Glinides, Pioglitazone, DPP-4 inhibitors



- Participating facilities Total of five facilities: Shanghai Jiao Tong University School of Medicine, other level 3 hospitals, etc.



# Performance in Drug Responder Prediction (1)



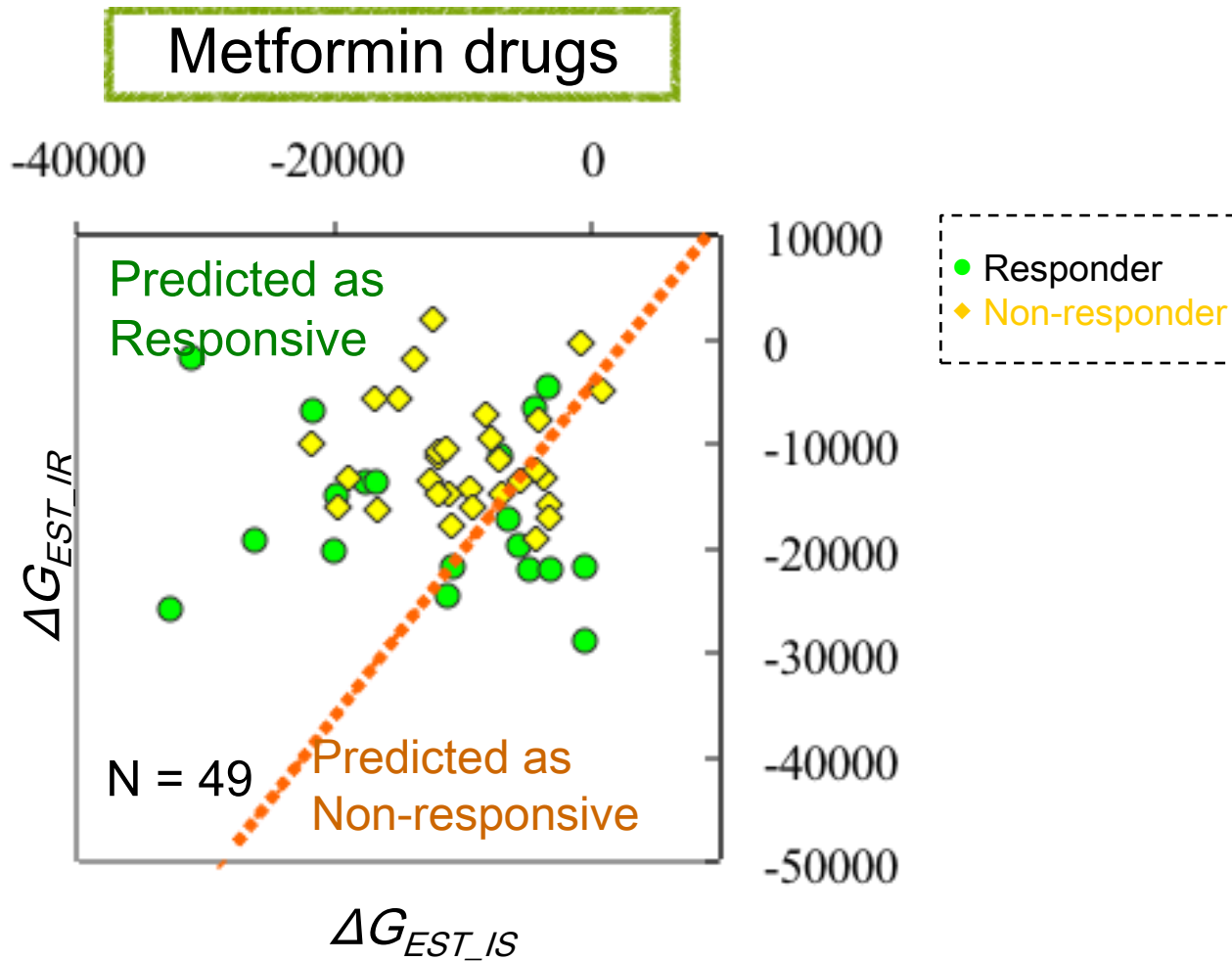
Response rate 66%  $\Rightarrow$  79%

Medical Specialists Simulator

Response rate 38%  $\Rightarrow$  52%

Medical Specialists Simulator

# Performance in Drug Responder Prediction (2)



Response rate 39% ⇒ 53%

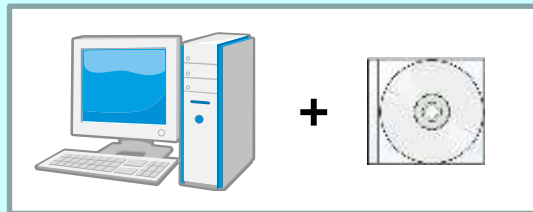
Medical Specialists

Simulator

# Future Plans

## Medical Software

Current

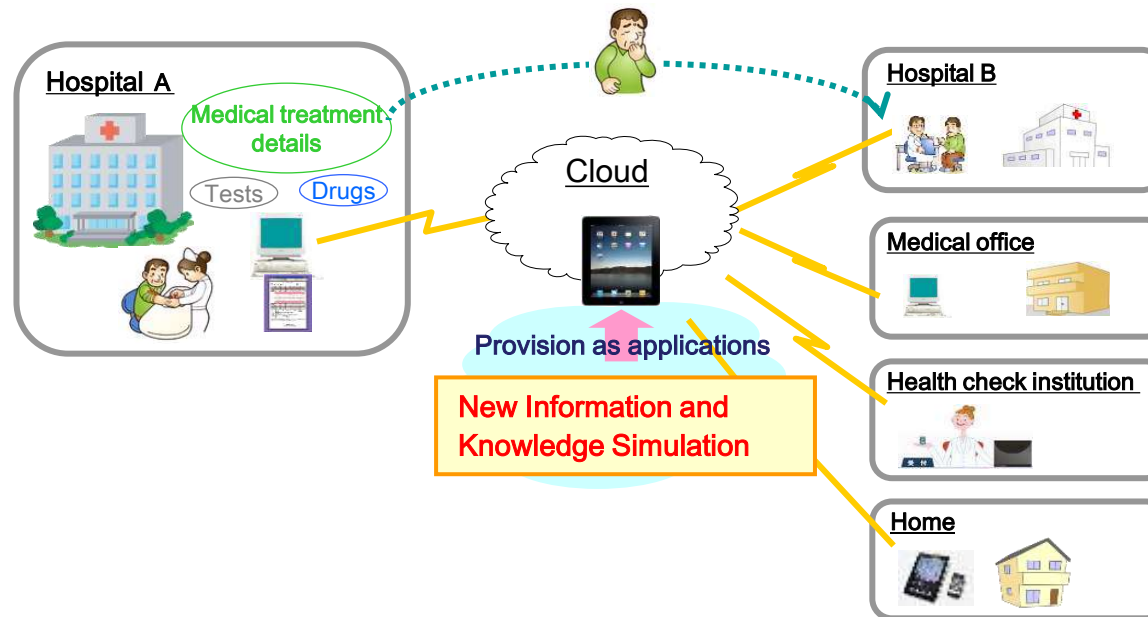


Medical devices used together

Future



Medical devices using software independently

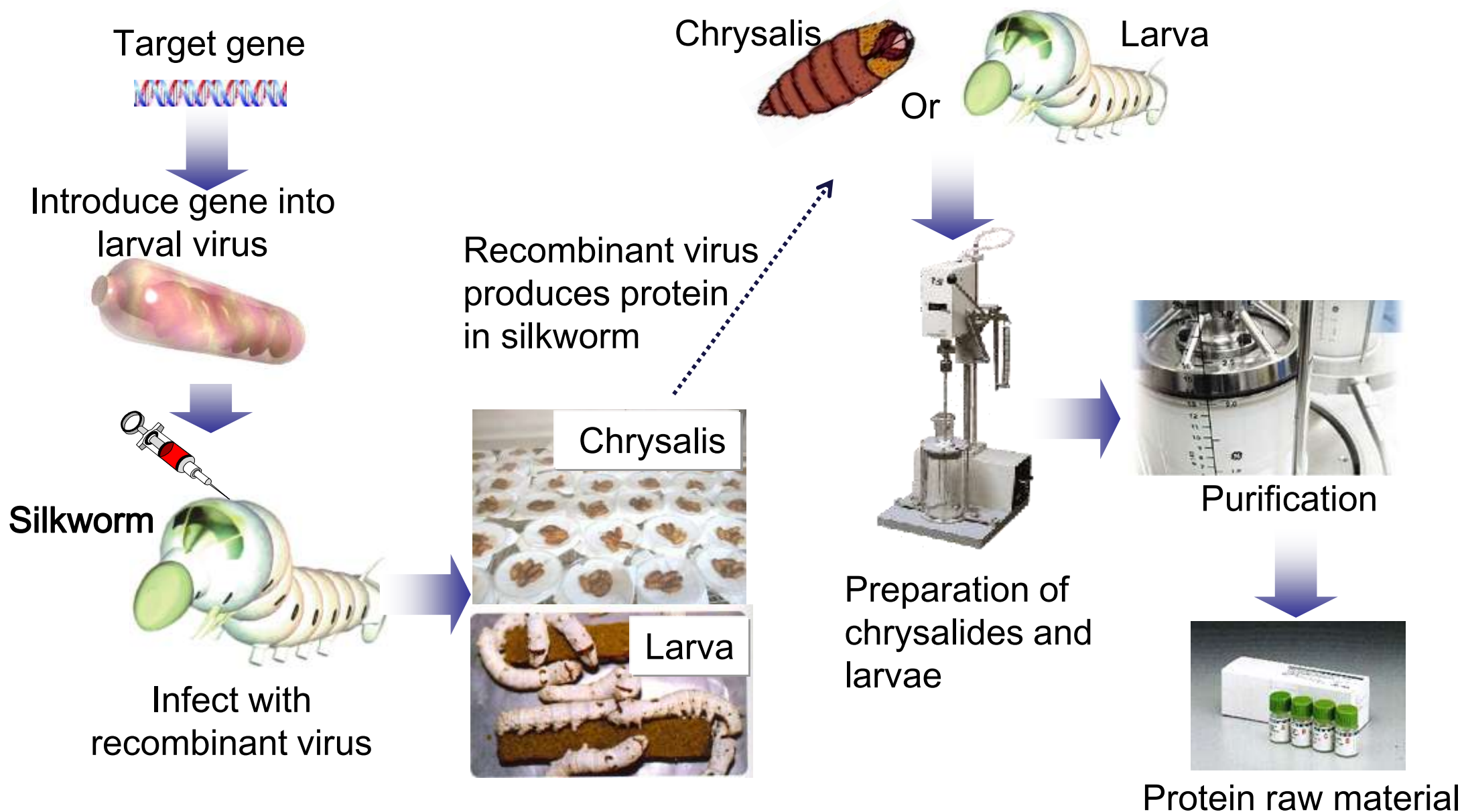


## Diabetes Simulation

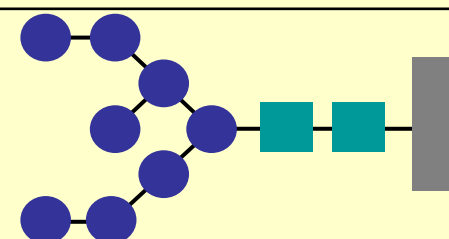
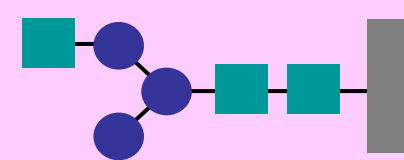
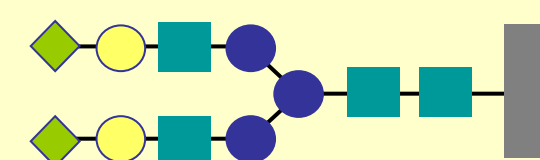
Plans to form study groups, implement clinical performance studies, apply for approvals

## 4) Development of Raw Materials for Diagnostic Reagents Using Silkworms

# Protein Expression Using Recombinant Silkworms



# Production Characteristics of Various Recombinant Proteins

|          | Productivity | Cost | Production Period | Similarity to Human Type | Sugar Chain Structure (N Type)  |
|----------|--------------|------|-------------------|--------------------------|---|
| E. Coli  | ○            | ⊙    | ○                 | ×                        | (None)  |
| Yeast    | ○            | ○    | ○                 | △                        |    |
| Silkworm | ○            | ○    | ○                 | ○                        |   |
| Animal   | ×            | ×    | ×                 | ⊙                        |  |

 Acetylgucosamine

 Mannose

 Galactose

 Sialic acid

# Reagent Development Using Silkworms

Silkworm gene engineering



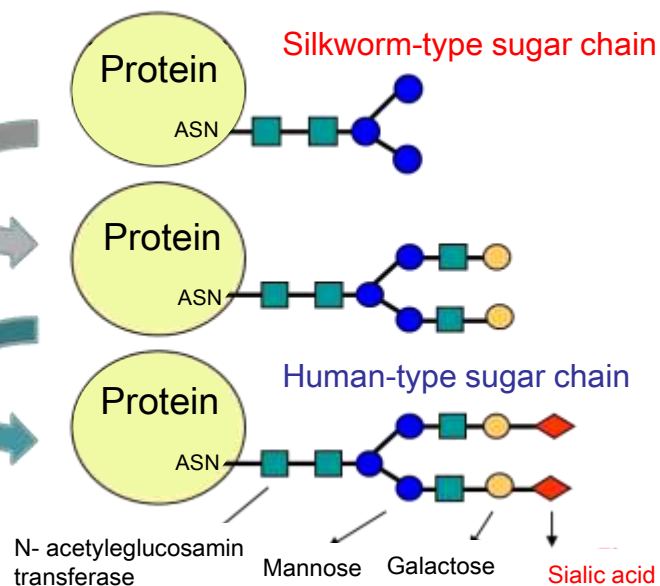
◆ Improve accuracy and stability ◆ Improve product reliability

◆ Acquire sugar-chain marker antibodies ◆ Provide standards

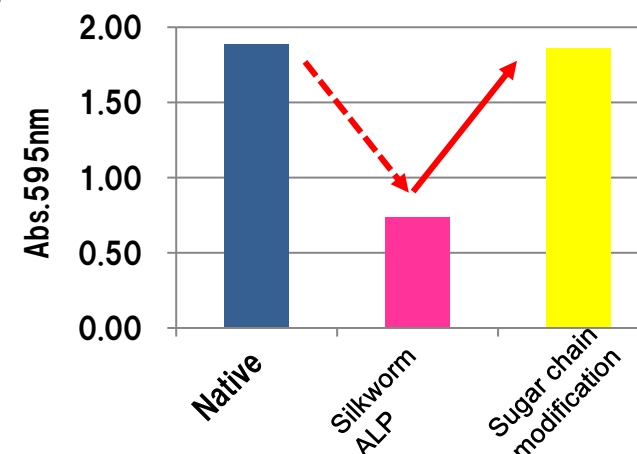
Progress in change to human-type sugar chain

Technology acquired  
fiscal year ended  
March 31, 2012

Technology acquired  
fiscal year ended  
March 31, 2013



Comparison of activity with human-type enzymes



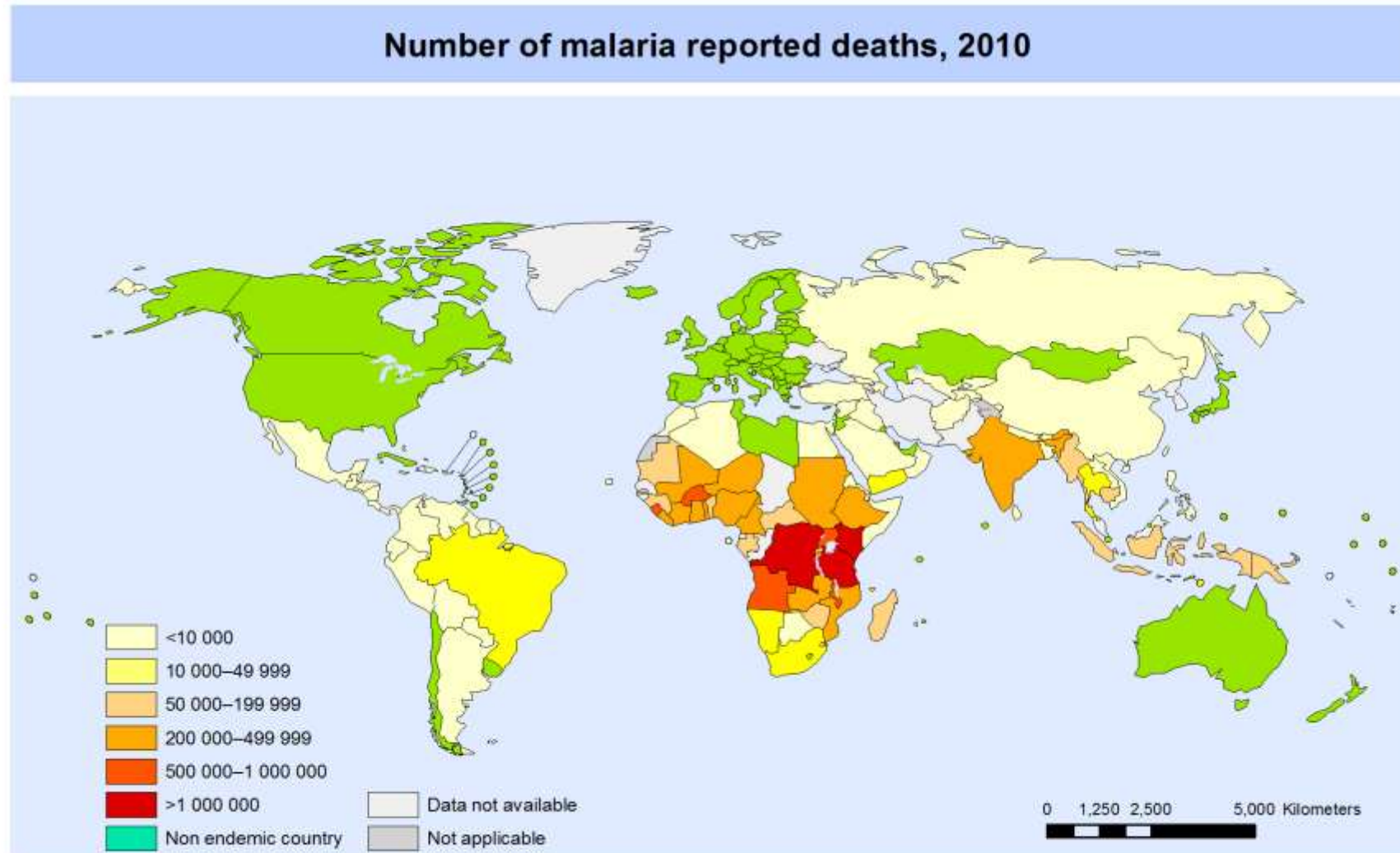
Activity acceleration through modification of human-type sugar chain

Aiming for improved expression efficiency and productivity

ASN : Asparagine

## 5) Malaria Detection Technology

# Number of Malaria Deaths



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization  
Map Production: Public Health Information and Geographic Information Systems (GIS)  
World Health Organization



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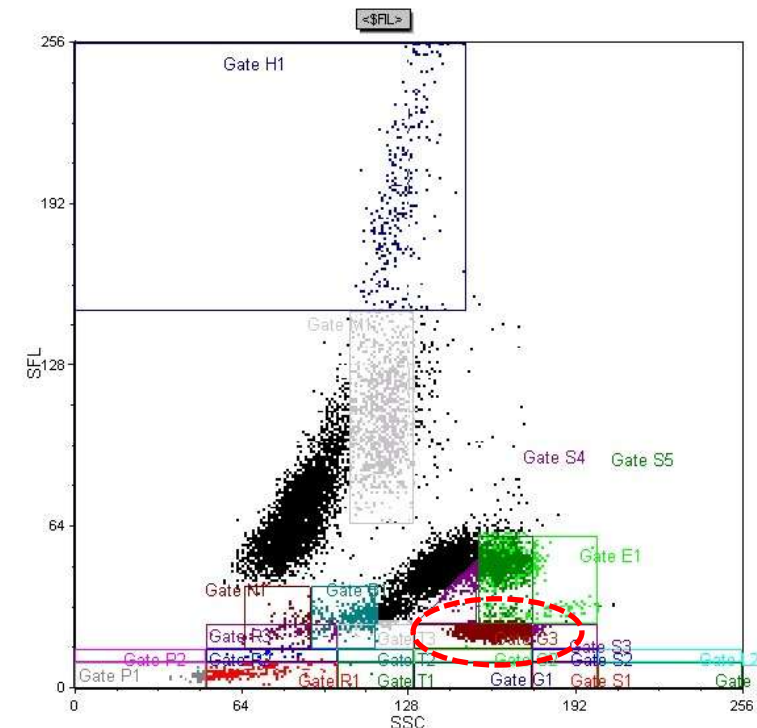
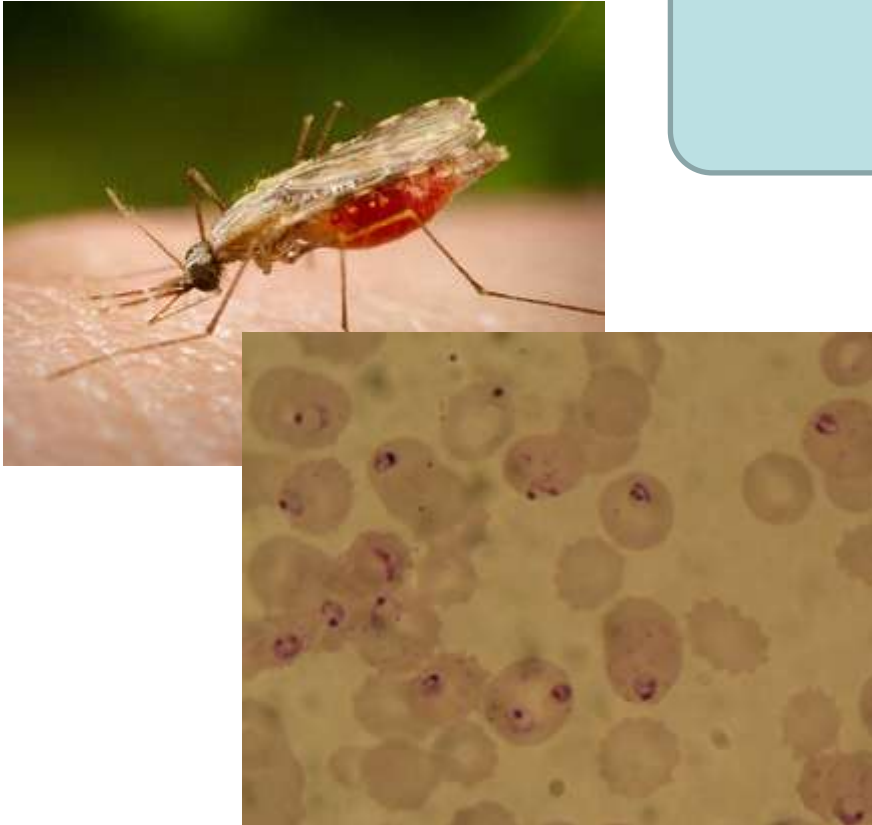
[http://gamapserver.who.int/mapLibrary/Files/Maps/Global\\_Malaria\\_ReportedDeaths\\_2010.png](http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Malaria_ReportedDeaths_2010.png)

# Malaria Detection Technology

## Technology Characteristics

### Hematology Analyzer

Flagging infected cells with malaria  
Hypothetical data about malaria sample



Mainly tropical African malaria = ring-form

Vivax malaria, mainly in Asia = gametocyte, schizont

# (Reference) Reporting Subjects and Policies for Technology Presentation

---



## 1. Reporting Subjects

- Technical features of Sysmex technologies and products
- Technical themes on which Sysmex conducts R&D and their clinical utilities
- Outline of Sysmex technology strategy

## 2. Policy Regarding Reporting of Technological Themes

Explain R&D themes at the three stages below:

<Research stage> Start of research and preliminary evaluation

- Magnitude of clinical value in practical use
- Explanation of future R&D plans

<Practical stage> Elemental research, practical and product commercialization stage

- Technological impact on characteristics of products

<Launch stage> Accomplishment of development and introduction to market

- Details of technological features and superiority

# (Reference) Definition of R&D Stage

## Research stage

Start of research or preliminary evaluation

Objective means of establishment of measurement principles and verification of clinical value

10 ~ 50%

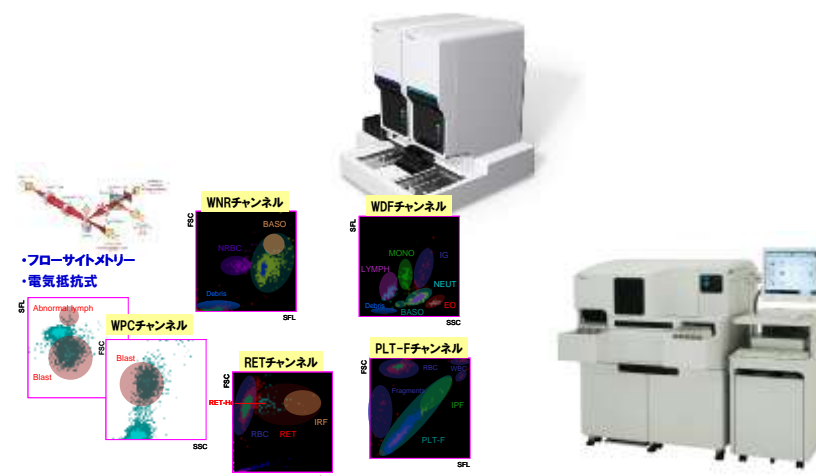
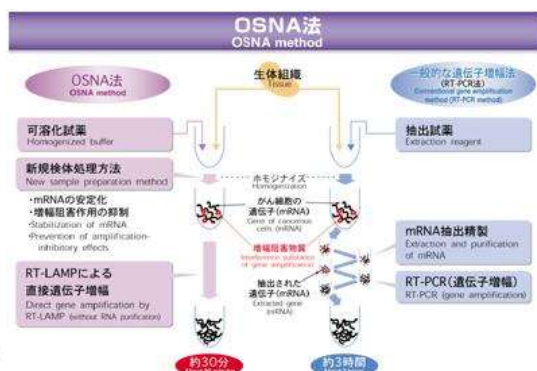
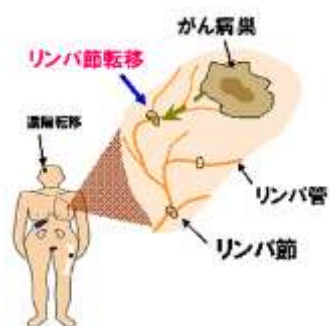
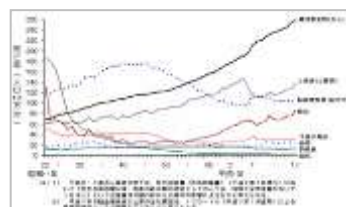
## Practical stage

Start of full-scale R&D activity towards commercialization

50 ~ 80%

## Launch stage

Completion of product commercialization and determination of launch



# We Believe the Possibilities.

## Sysmex Corporation

Contact:

IR & Corporate Communication Dept.

Phone: +81-78-265-0500

Email: [info@sysmex.co.jp](mailto:info@sysmex.co.jp)

URL: [www.sysmex.co.jp/en/](http://www.sysmex.co.jp/en/)