The 11th Technology Presentation

March 14, 2014

Sysmex Corporation

Table of Contents

1. Opening Remarks — Hisashi Ietsugu, Chairman and CEO

2. Technology Strategy and Enhancement of New Technology Platforms — Kaoru Asano, Senior Executive Officer, Head of R&D

3. Progress on Research and Development Themes

(1) HU Business Unit — Kensaku Aota, Executive Vice President of the UB Product Engineering Div.
- 1) Cervical Cancer Diagnosis Support System
- 2) Minimally Invasive Postprandial Hyperglycemia Monitoring System (Glucose AUC Measurement Technology)

(2) ICH Business Unit — Yoichi Takahama, Executive Vice President of the Immunology & Chemistry Product Engineering Div.
- 1) Hepatic Fibrosis Markers
- 2) Increase in Immunochemistry Testing Parameters

(3) LS Business Unit — Mamoru Kubota, Executive Vice President of the Life Science Product Engineering Div.
- 1) Products Related to the OSNA® Method
- 2) “Genetic Signature” Assay Service Product
- 3) Assay Service Product Using OncoBEAM

1. Opening Remarks

Hisashi Ietsugu, Chairman and CEO

<Today's Themes>

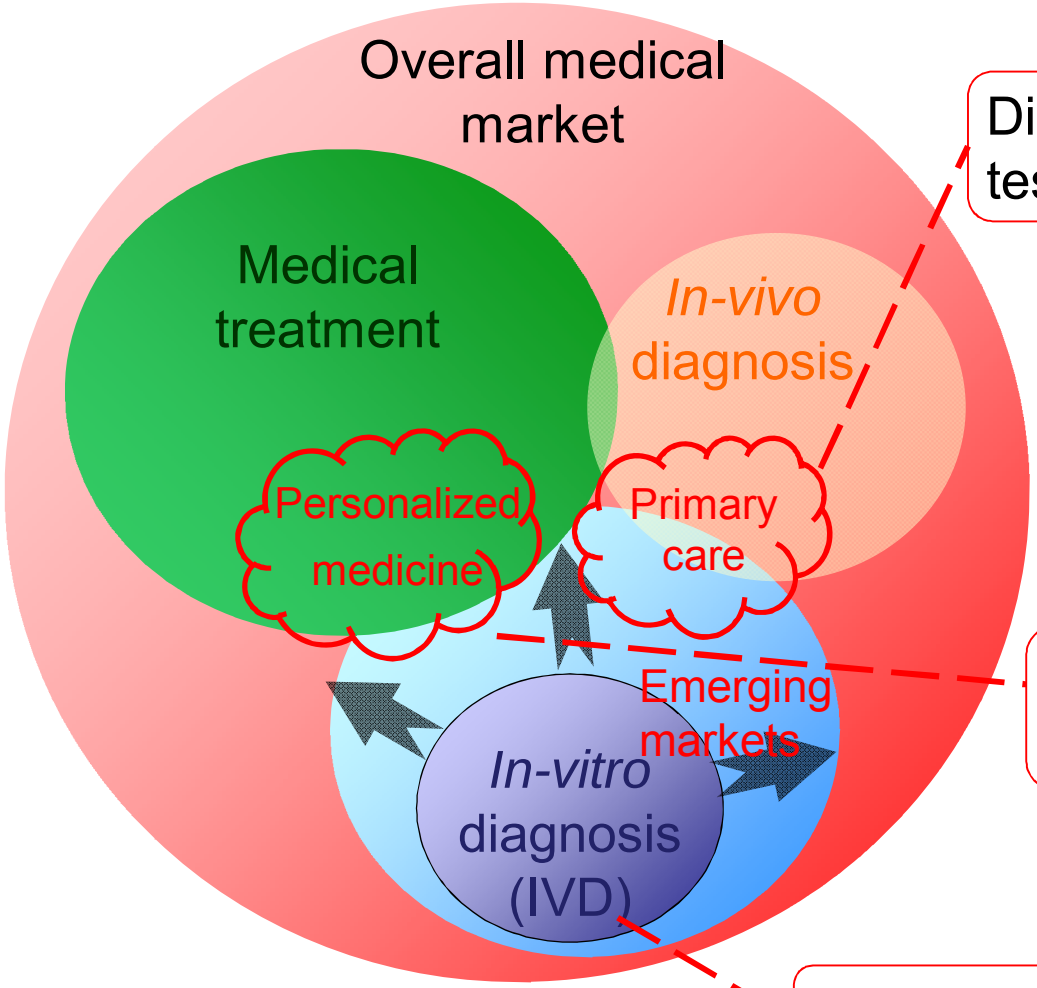
- Enhancing Technology Platforms toward the Realization of Personalized Medicine Based on Sysmex's Technology Strategy
  - Enhancing Technology Platforms
  - Sysmex Inostics and Partec Technologies and Future Developments
  - Acquisition of Biomarkers through Open Innovation
- Progress on Research and Development Themes

2. Technology Strategy and Enhancement of New Technology Platforms

Kaoru Asano, Senior Executive Officer, Head of R&D

(1) Technology Strategy Overview and Enhancement of Technology Platforms
(2) Sysmex Inostics Technologies and Developments
(3) Partec Technologies and Developments
(4) Comprehensive Collaboration with the National Cancer Center Japan and Significance

In-Vitro Diagnostics Markets



Disease prevention based on testing data

Enhance the performance/function of analytical platform

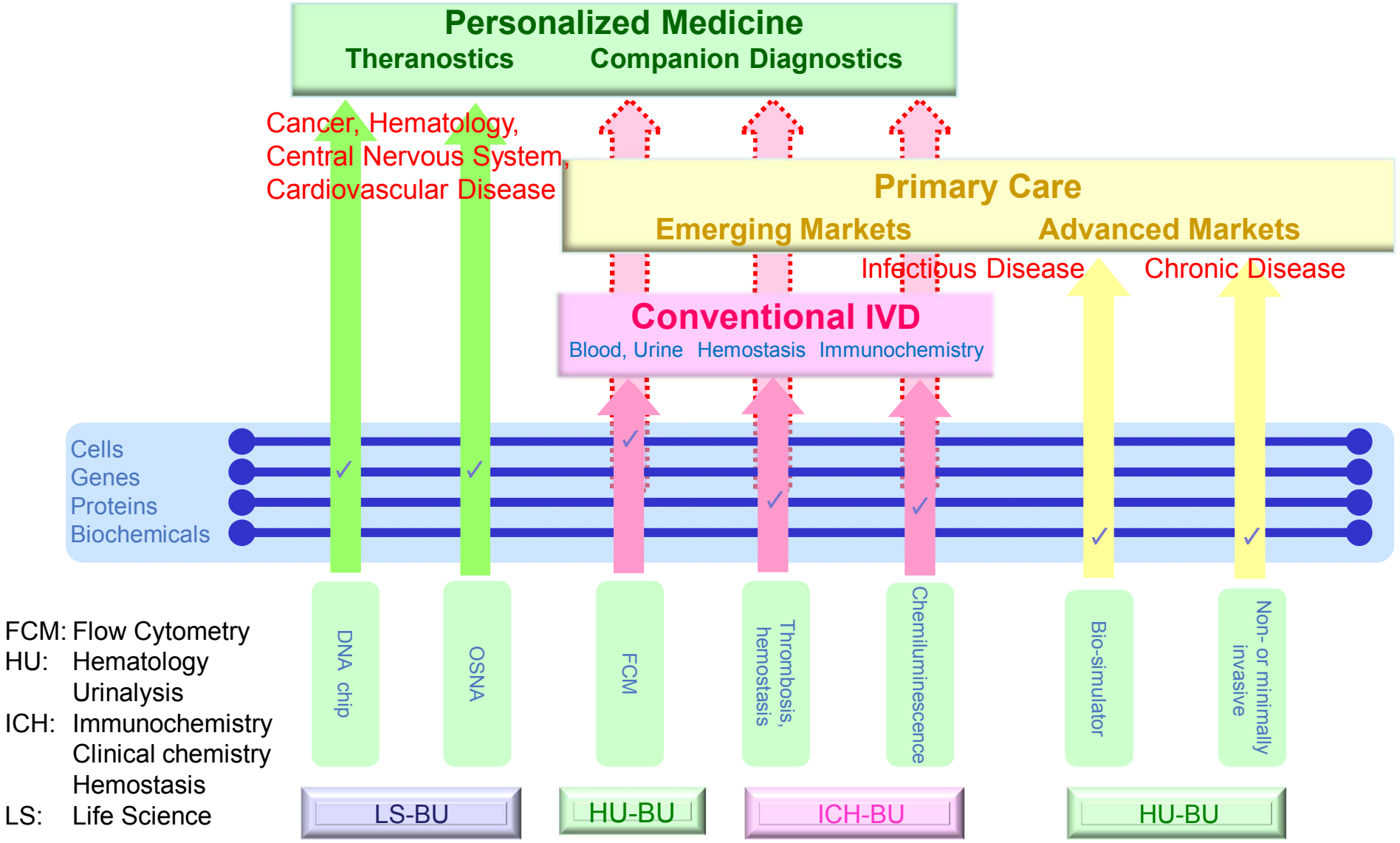
ICT utilization

Establishing personalized medicine through CDx

Organic growth in existing IVD fields

CDx: Companion diagnostics

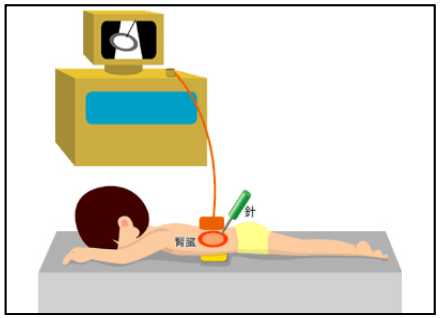
Overview of Technology Platform Enhancement



FCM: Flow Cytometry
HU: Hematology
Urinalysis
ICH: Immunochemistry
Clinical chemistry
Hemostasis
LS: Life Science

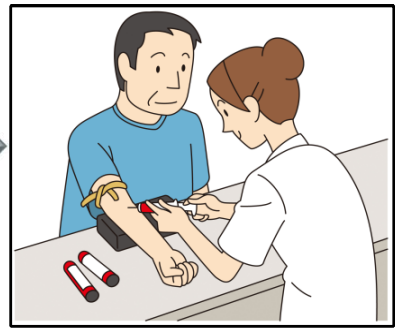
Platform Characteristics Required for Personalized Medicine

Conventionally



From biopsy to liquid biopsy

In Future

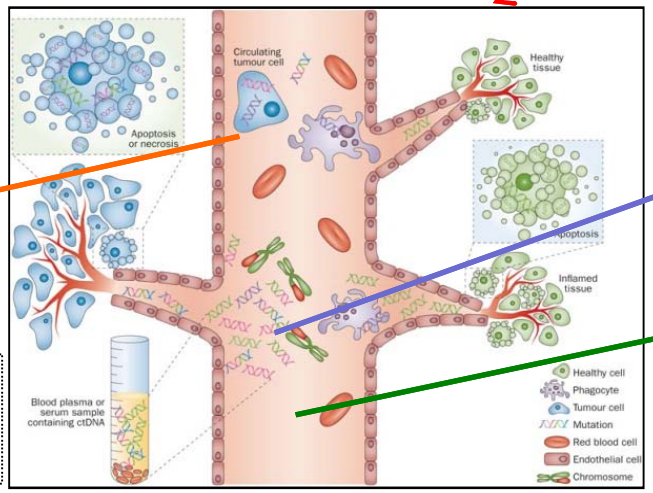


Direct analysis of affected specimen

Analyze disease-derived components that have leaked into the blood (bodily fluid)

Cells

CTC (circulating tumor cells)
CAC (circulating abnormal cells)
Stem cells
Etc.



Genes

CTG (circulating tumor genes)
cfDNA (cell-free genes)
miRNA (micro RNA)
Etc.

Proteins

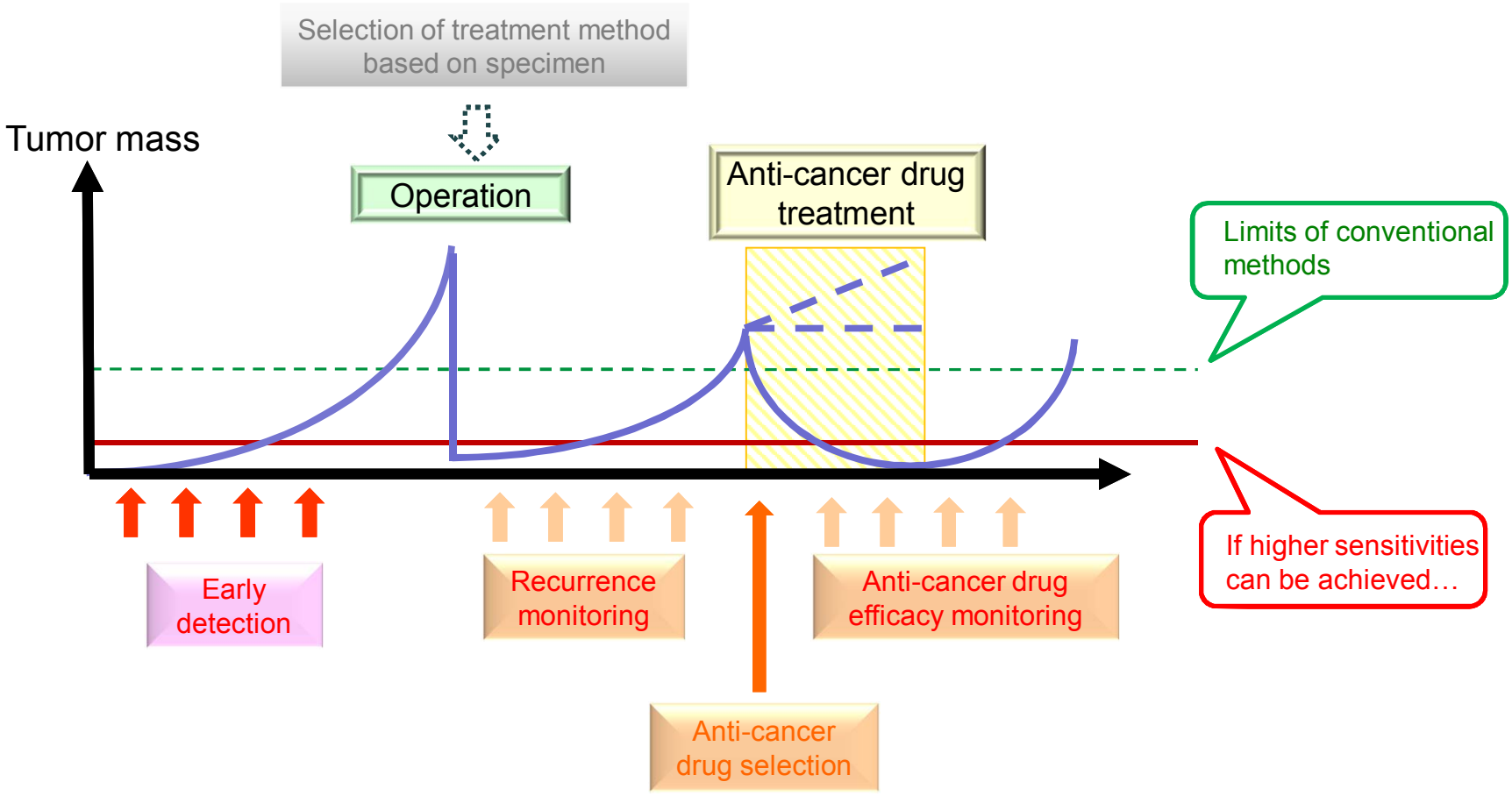
Circulating trace molecules
Peptides
Microparticles
Etc.

Liquid biopsy:
Detection of cancer or other diseases by testing blood or other bodily fluids. This type of testing is less invasive than conventional physical biopsies.

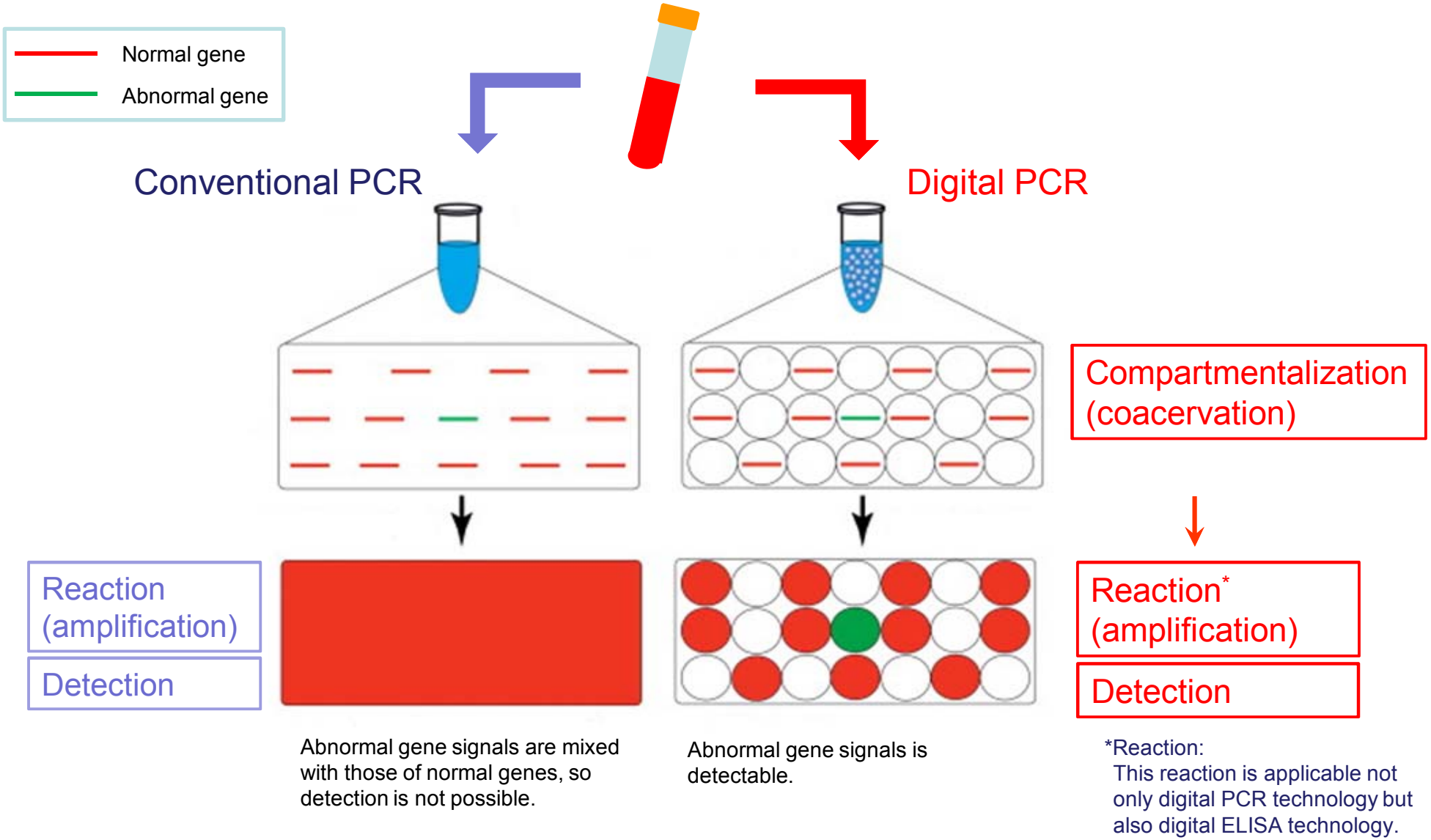
Nature Reviews Clinical Oncology 10, 472-484 (August 2013)

Detection sensitivity will need to be 100 to 1,000 times higher than conventional methods.

Taking Advantage of Easy Sampling and High Sensitivity

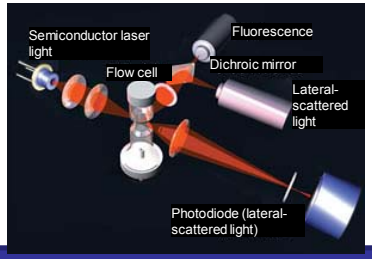


Droplet Digital Technologies



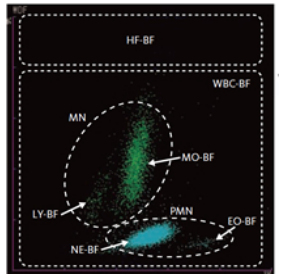
Imaging Flow Cytometry

Flow Cytometry (FCM)



A technology for measuring the characteristics of individual cells in a short period of time from among a large number of cells flowing at high speed

Conventional FCM



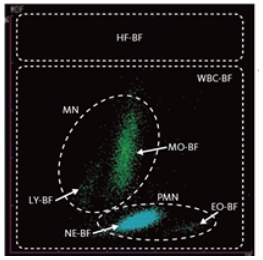
[Good]
- Highly precise quantitative analysis of cells (statistical analysis)

[Poor]
- Difficult to acquire detailed information about cell morphology
- Difficult to acquire localized information on intracellular molecules
- Difficult to detect rare cells

[Circulating abnormal cells]
- Few in number
- Multiple identifying biomarkers
- Acquisition of localized molecular information

Imaging FCM

high sensitive measurements of the shapes and fluorescent images of cells flowing at high speeds



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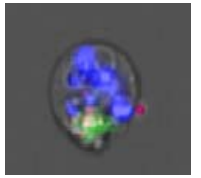
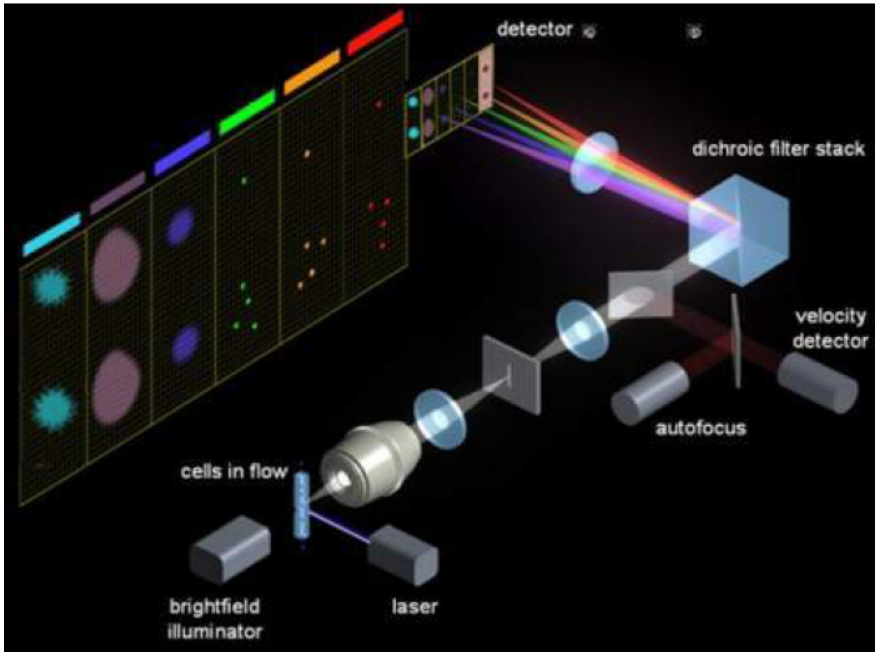


[Advantages]
In addition to conventional FCM information,
- Able to acquire detailed information on cell morphology
- Able to acquire localized information on intracellular molecules
- Can detect rare cells

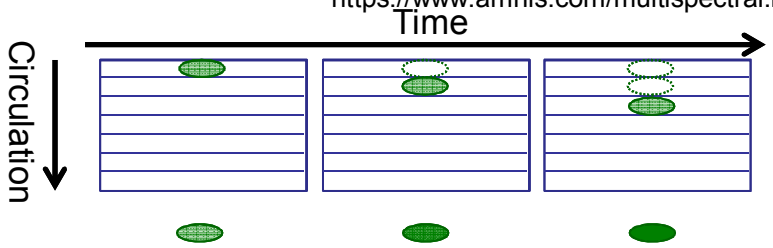
[Issues]
- Processing speed falls
- For research applications; no instruments available for use in clinical settings

Introducing Imaging Flow Cytometry Technologies

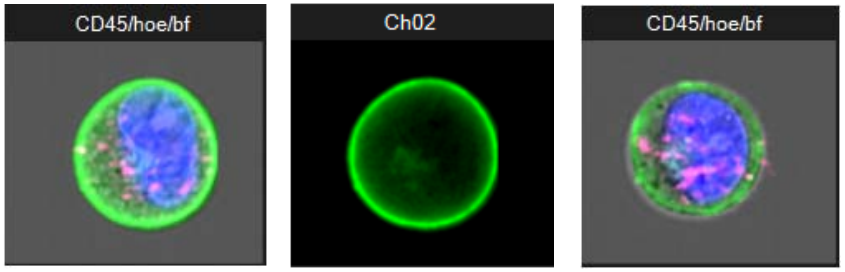
In-licensed from Merck Millipore : Technology for the rapid capture of images of in-flow cell morphology and fluorescent imaging



https://www.amnis.com/multispectral.html



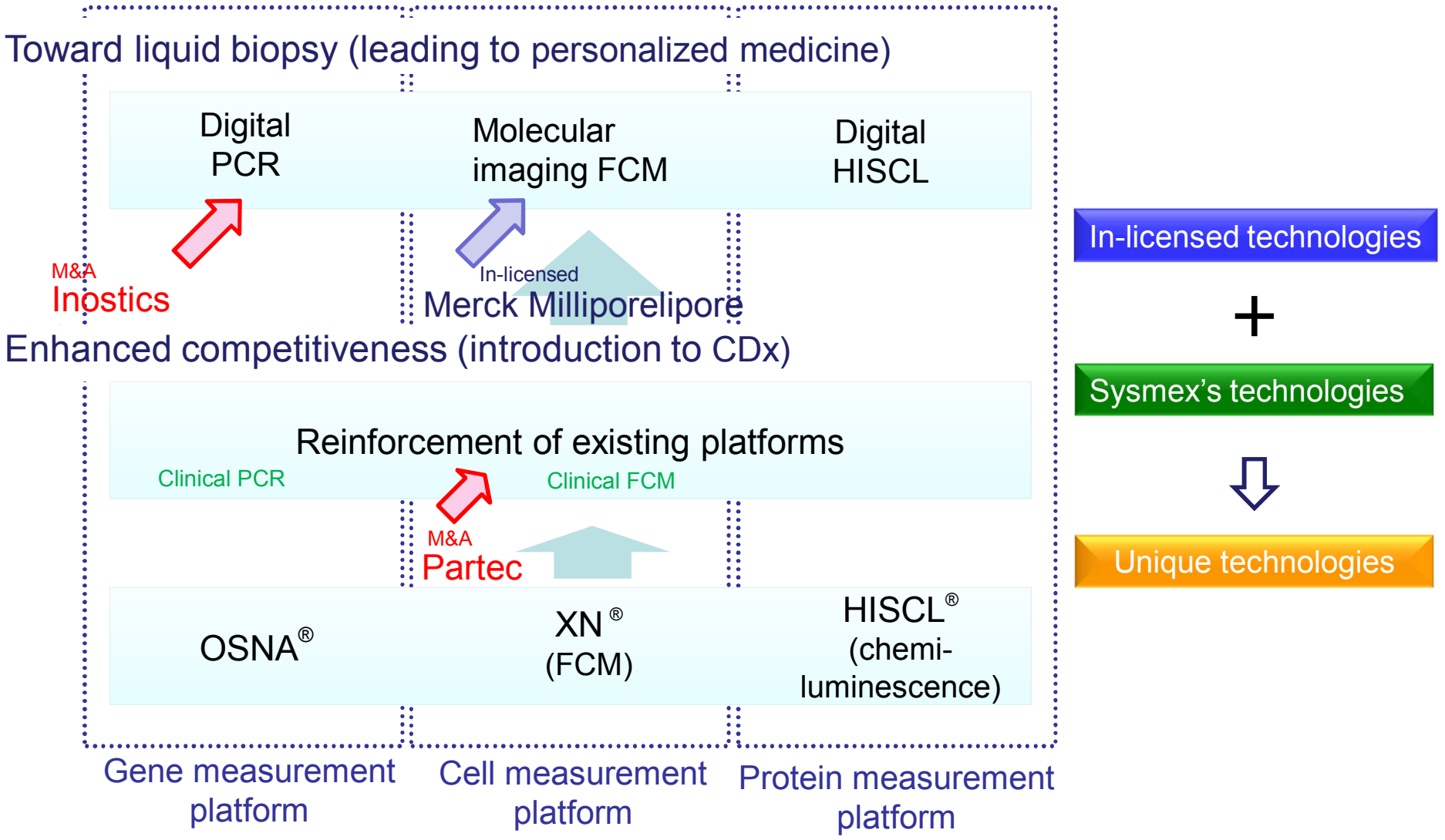
The accumulation of images enables the highly sensitive capturing of cells flowing at high speeds



Fluorescent images of cultured cells

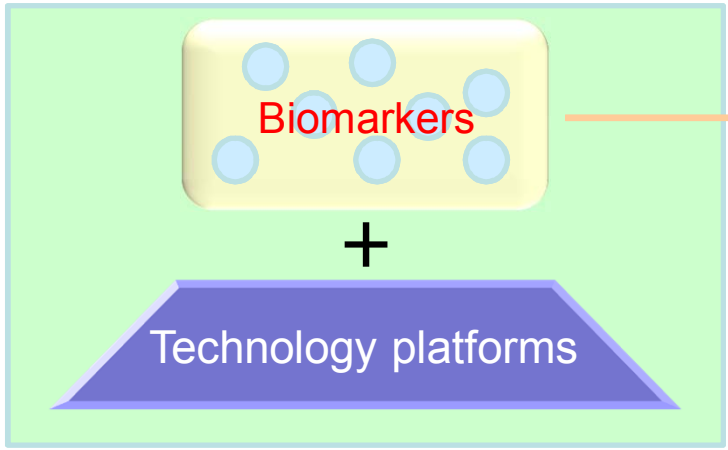
Combining this technology with Sysmex's own technologies will lead to the development of MI (molecular imaging)-FCM, which should enable the highly sensitive measurement in clinical settings of abnormal cells in-flow

Enhancing Platforms for Personalized Medicine



Acquiring Biomarkers through Open Innovation

Clinical Value



Acquiring Biomarkers through Open Innovation

Research Institutions

- National Cancer Center
  → Comprehensive collaboration
- National Institute of Advanced Industrial Science and Technology
  → Glycosylation marker

And others

Joint research with research institutions in Japan and overseas

Universities, Medical Institutions

- Kobe University
  → Endowed course (Evidence-Based Laboratory Medicine Course)
- University of Tokyo, Kyoto University, Osaka University…
- MKCC, JHC…

And others

Joint research with universities and medical institutions in Japan and overseas

sysmex

Pharmaceutical Companies

- Bayer (Sysmex Inostics)
  → Collaborative development agreement

And others

Development of companion diagnostics with pharmaceutical companies

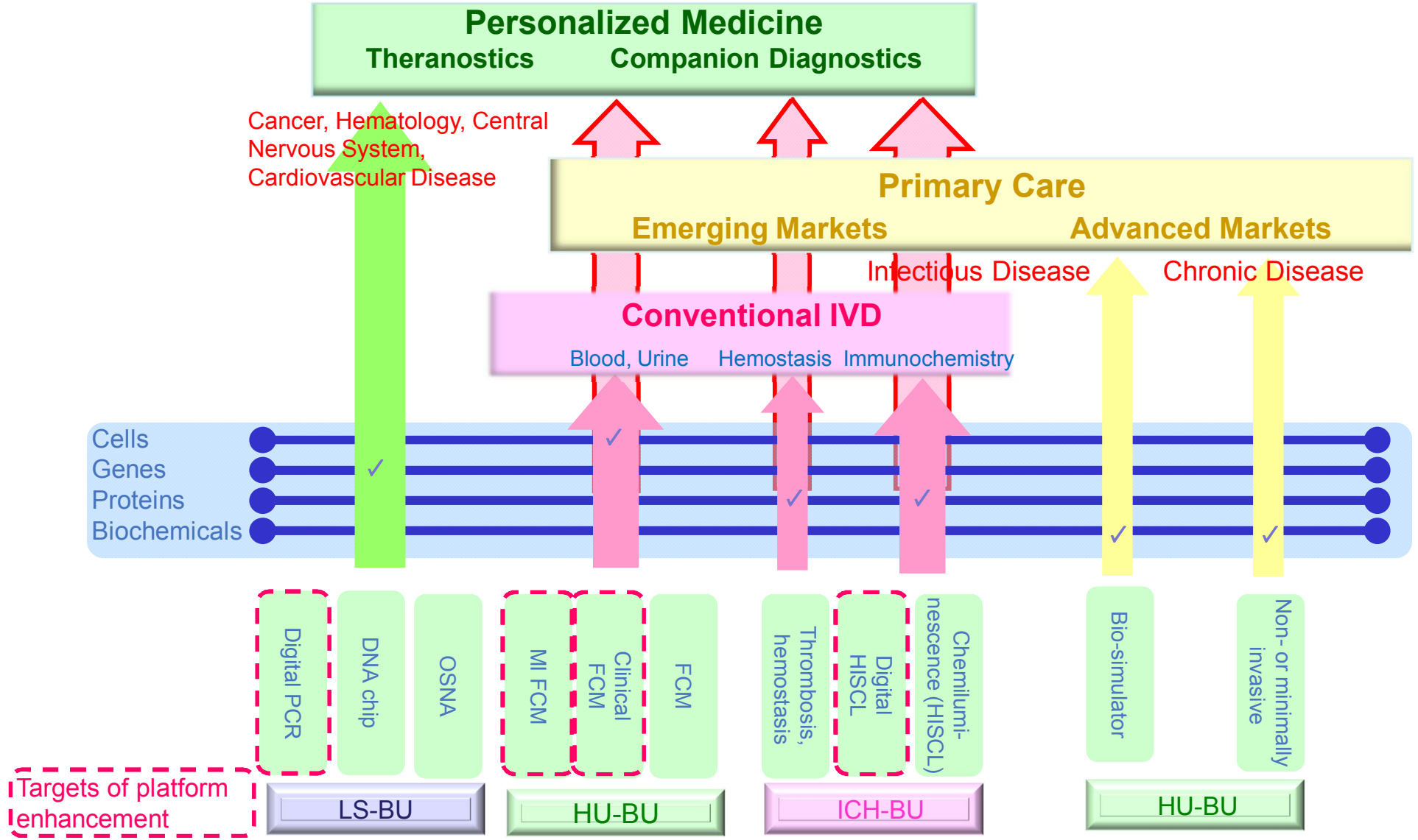
Venture Companies

- Human Metabolome
  → Depression diagnosis

And others

Joint development with venture companies in Japan and overseas

Overview of Technology Platform Enhancement



2. Technology Strategy and Enhancement of New Technology Platforms

(1) Technology Strategy Overview and Enhancement of Technology Platforms
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(3) Partec Technologies and Developments
(4) Comprehensive Collaboration with the National Cancer Center Japan and Significance

Sysmex Inostics Technologies

BEAMing Technology

One method of digital PCR

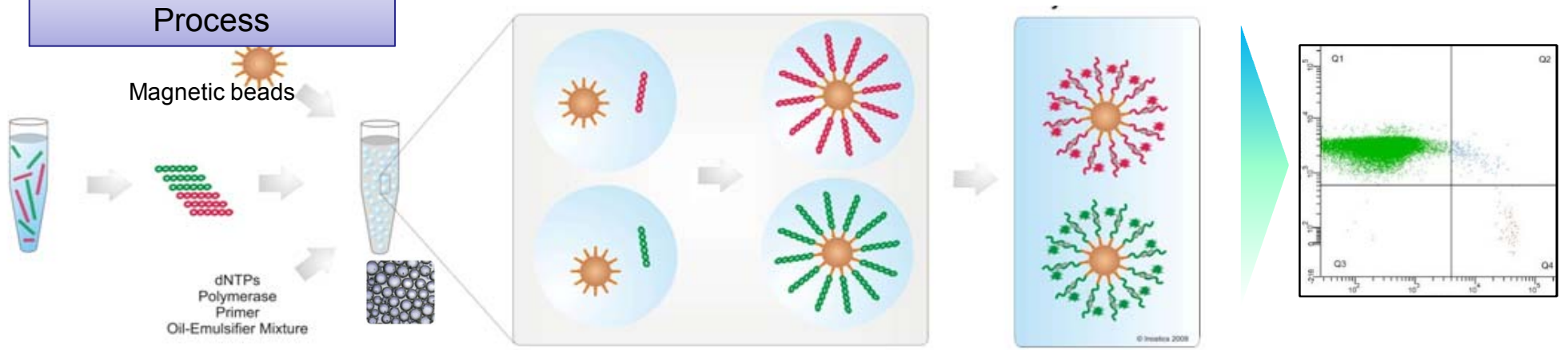
[Advantages]

High sensitivity, relatively easy conversion to multi-parameter, abundant clinical data

[Issues]

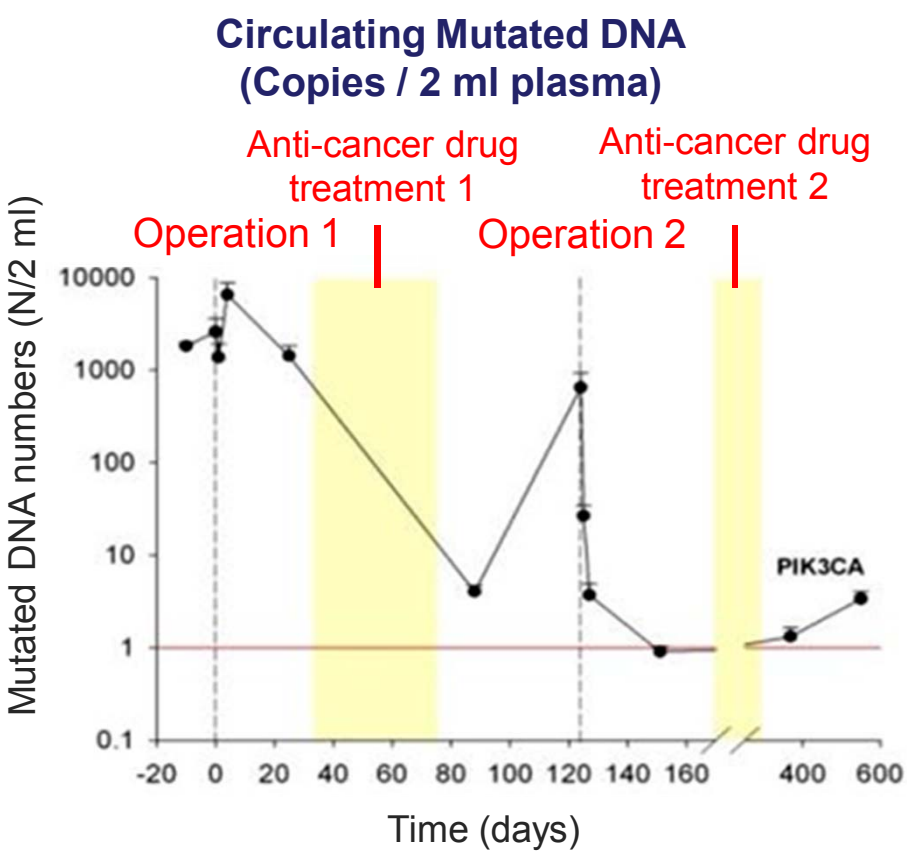
Processes are complex

BEAMing Technology Process



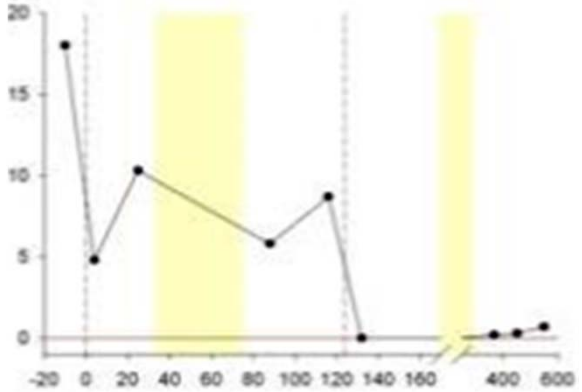
Pre amplification | Coacervation | On-beads PCR | Labeling | Droplet dissolution | FCM detection

Clinical Progress of Colonic Cancer Patients

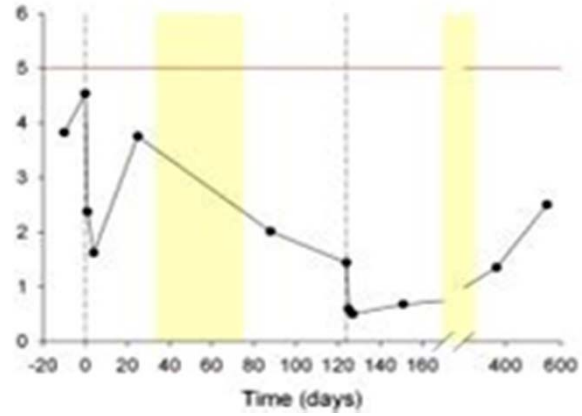


CEA: Carcinoembryonic antigen, a serum tumor marker in of the stomach, colon, pancreas and liver cancer

Tumor Mass (cm)



CEA (ng/ml)

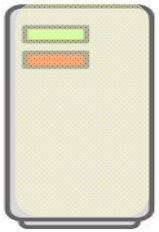


Diehl *et al.* Nature Medicine 2008

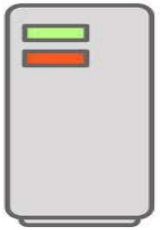
Future Development of BEAMing Technology

From Lab Assay to Automated System

Coacervation

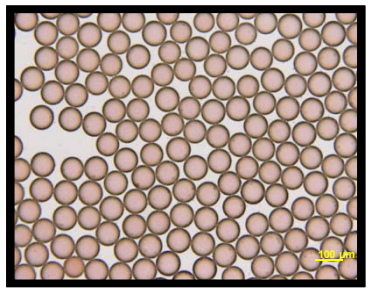


Reaction

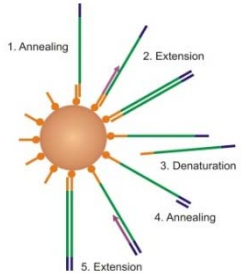


Detection

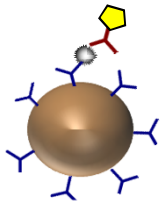
Detection of Partec FCM



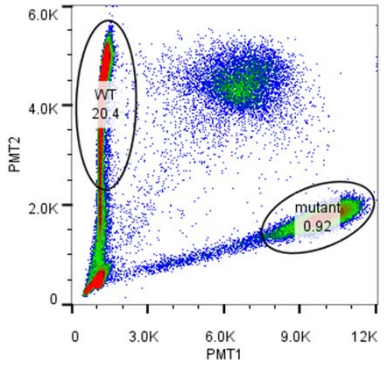
Uniform coacervation



On-beads PCR



Antigen, antibody reactions



Multiparameter analysis

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Partec Technologies

Basic research field

Clinical research field

Clinical testing field

CyFlow Space

CyFlow Cube8

For research

CyFlow® miniPOC

For HIV monitoring in emerging markets and developing countries

General applicability, flexibility

FCM

Simplicity, efficiency

Elemental technologies

Optical design technologies

PARTEC

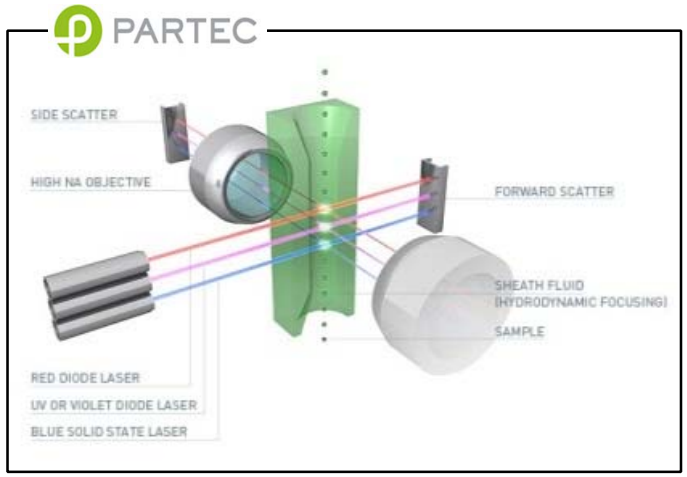
sysmex

Pretreatment technologies

Data Analysis technologies

Future Developments

Combine Partec and Sysmex technologies to develop
unique clinical FCM



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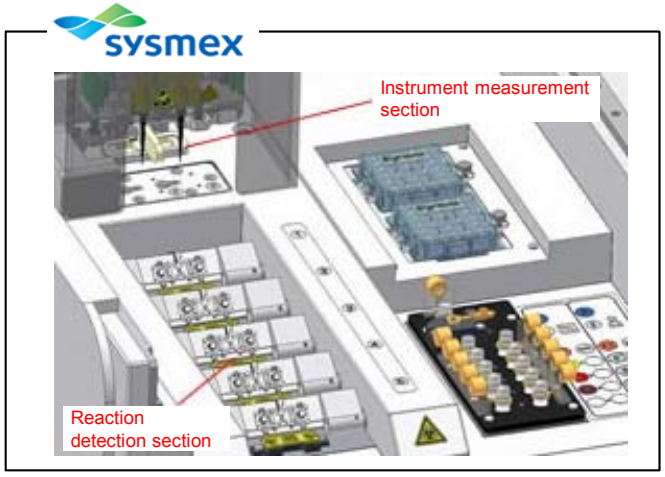

Clinical FCM

- Approximately how many hematopoietic stem cells?
- Any functional abnormality in lymphocytes?
- Disease condition analysis for leukemia and lymphoma

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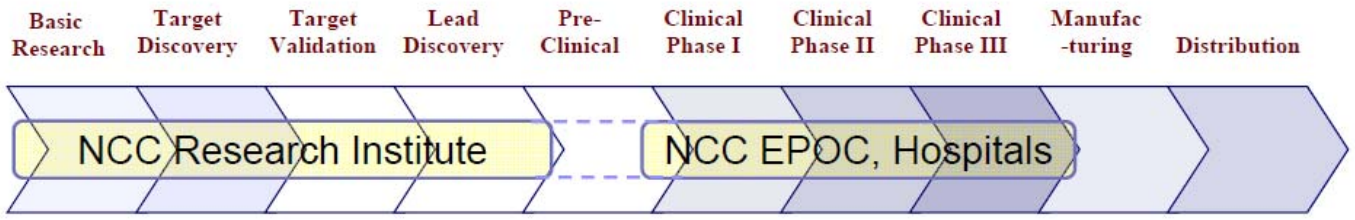
Status of Industry–Academia Collaboration with the National Cancer Center Japan

Promotion of Drug Discovery Research through Industry–Academia Collaboration

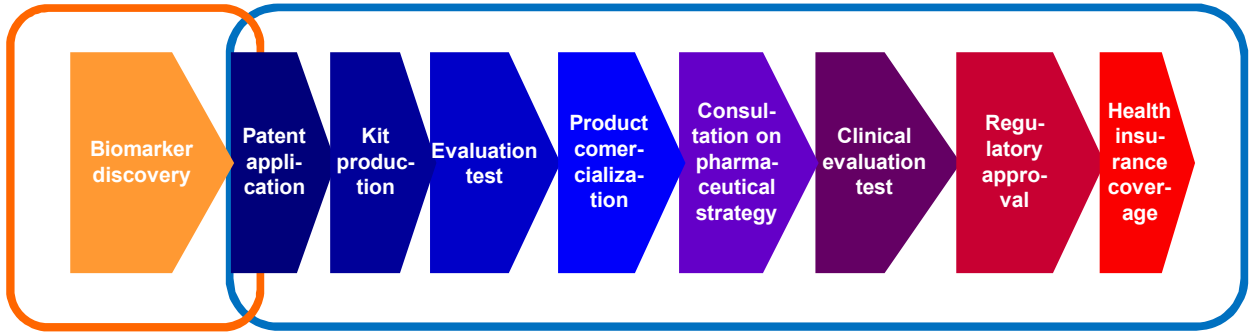


Daiichi Sankyo	Drugs for treating lung cancer, leukemia, etc.
Venture company	Kinase inhibitors
Astra Zeneca, Merck Serono, etc.,	
Shimadzu	Analysis using mass spectrometry method
Sysmex	Development of biomarkers, reagents
AIST	Drug discovery molecule profiling
RIKEN	Ovarian cancer, leukemia (program for drug discovery and medical technology platforms)
Drug Discovery Support Strategy Office, National Institute of Biomedical Innovation	Drug discovery support network

http://www.ncc.go.jp/jp/information/press/pdf/20131028/shiryo2-1.pdf

Comprehensive Collaboration Agreement with the National Cancer Center Japan

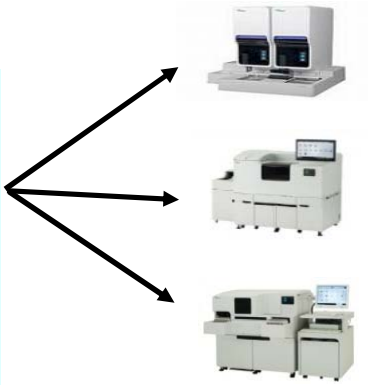
New biomarkers discovered at the National Cancer Center Japan will be developed into new *in-vitro* diagnostic reagents for delivery to patients.



National Cancer Center Japan

Sysmex

Development of *in-vitro* diagnostic reagents (reagent kits)

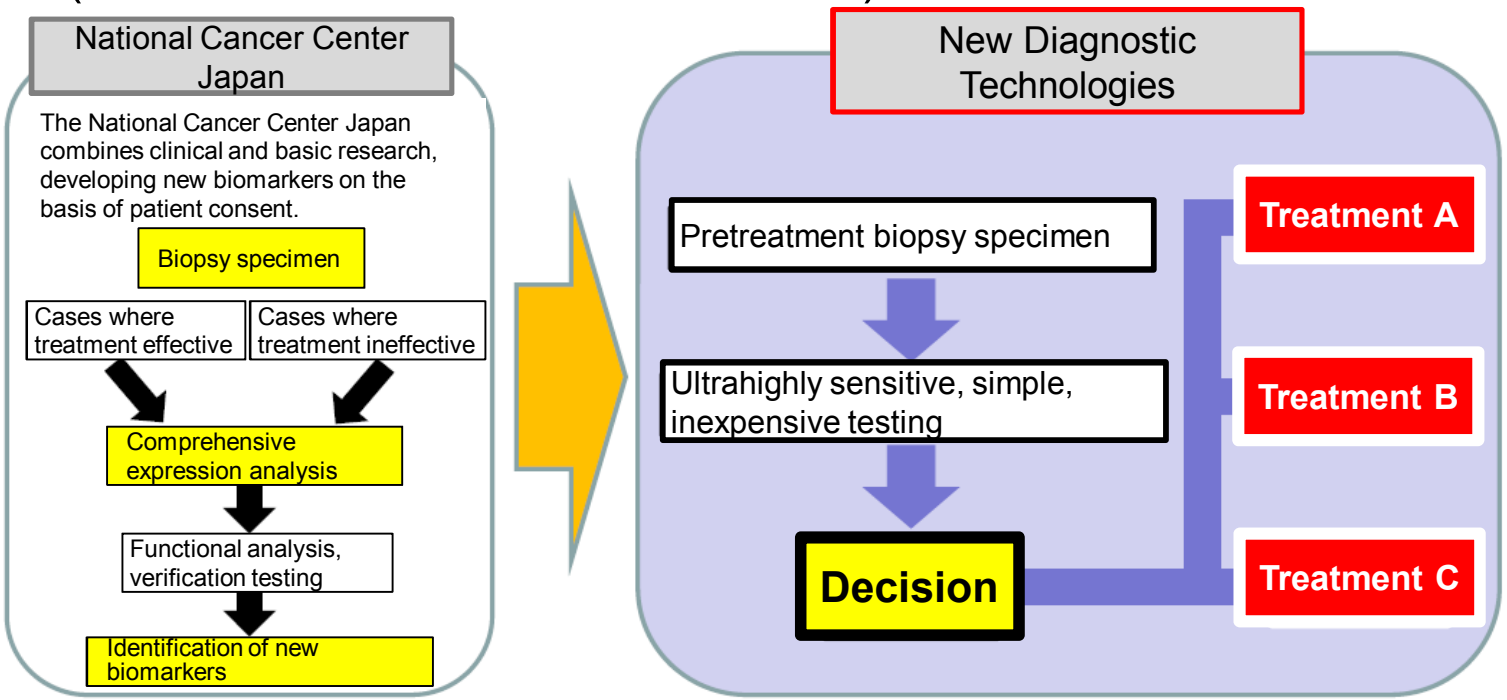


Sysmex platforms

Hold regular conferences to determine themes for practical application

First Joint Research Projects

New Methods for Bone Cancer Diagnosis (Decisions on Treatment Methods)



Bone cancer is a malignant type of cancer that is frequent among children. Undergoing chemotherapy prior to surgery (preoperative chemotherapy) enables the disease to be cured in many instances. Predicting the effectiveness of chemotherapy prior to treatment allows treatment methods to be selected more precisely. Our new diagnostic technologies should contribute to personalized medicine for bone cancer.

http://www.ncc.go.jp/jp/information/press/pdf/20131028/shiryo2-2.pdf

Summary of Progress on Ongoing R&D Themes

Theme	Items Planned at the 10th Technology Presentation (March 15, 2013)	Progress in Fiscal 2013	Items Planned in and after Fiscal 2014
Cervical cancer screening	Japan Conduct clinical trials for IVD application	Completed clinical evaluation	In fiscal 2014, commence sales as medical device (general FCM) and promote awareness activities
	Overseas Evaluate clinical utility	Conducting clinical evaluation in China	In China, begin preparing for pharmaceutical application and health insurance coverage application
Glucose AUC (Minimally invasive interstitial fluid extraction technology)	Japan Conduct clinical trials (2Q–4Q of fiscal 2013)	Conducting clinical trials (expected to conclude in 1Q of fiscal 2014)	Apply for approval of application
Diabetes bio-simulation (Disease state simulation technology)	Japan Aim for application as diabetes diagnosis support system	Began consulting with the regulatory authorities on application under the Pharmaceutical Affairs Act revisions in November 2013	Conduct clinical trials
Development of raw materials for diagnostic reagents using silkworms	Increase expression efficiency and productive efficiency of glycosylation modification protein	Neared human glycoproteins for approximately 50% of glycosylation	Apply to reagent

3. Progress on Research and Development Themes

(1) HU Business Unit

Kensaku Aota,
Executive Vice President of the UB Product Engineering Div.

1) System to Support Cervical Cancer Diagnosis
2) Minimally Invasive Postprandial Hyperglycemia Monitoring System
(Glucose AUC Measurement Technology)

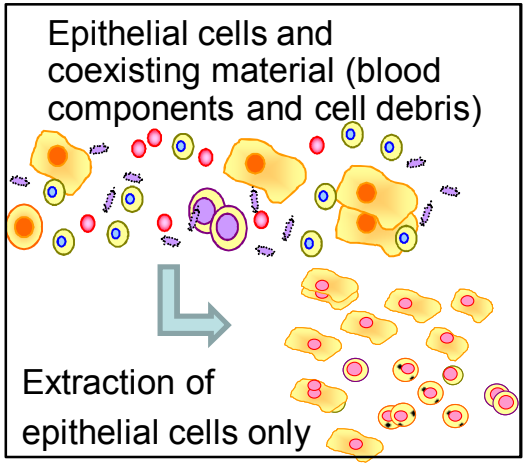
1) System to Support Cervical Cancer Diagnosis

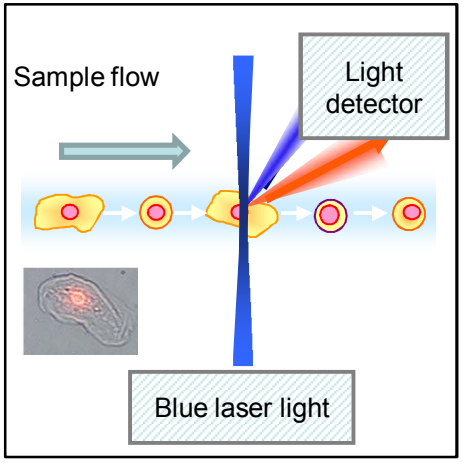
System to Support Cervical Cancer Diagnosis

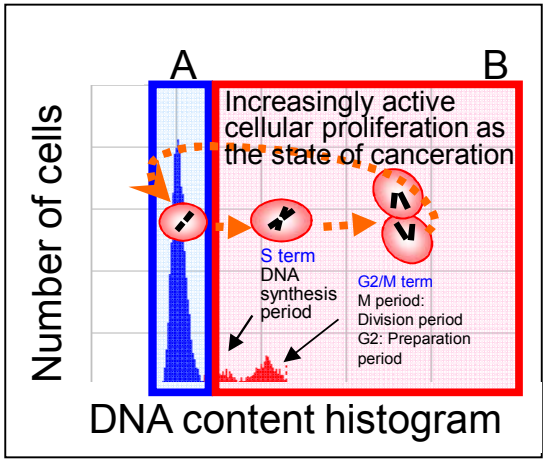
Epithelial cells only are extracted from cells harvested from the cervix. They are then DNA stained and irradiated with laser light. The DNA content in each of the cells is then measured and analyzed using cell proliferation activity (original index). Sysmex has developed this technology, which allows the cancer progression (disease state) to be determined.

Specimen collection, pretreatment → DNA staining, flow cytometry → Data analysis

Final prototype





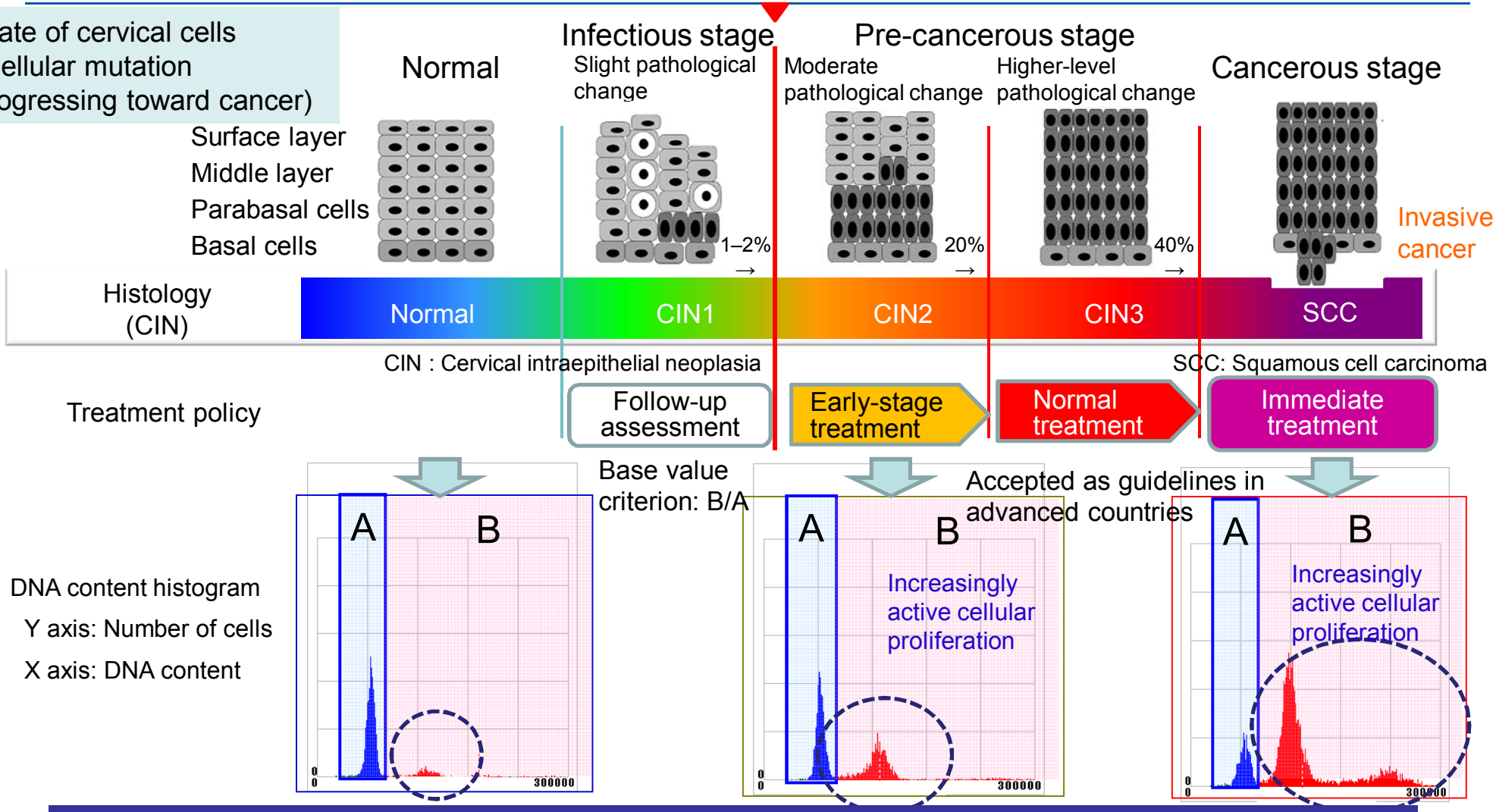


Cell proliferation activity : Increasingly active cellular proliferation as the state of canceration

Measurement time: Approx. 30 min.
Processing capacity: 20 tests/hour

Supports rapid screening for cervical cancer at a cost comparable to cytology

Verification of Principle



Cell proliferation activity changes as cancer advances, allowing disease states of CIN2 or higher to be detected with a high degree of accuracy

Results of Clinical Evaluation in Japan

Clinical evaluations at four facilities (including three hospitals specializing in cancer treatment)

- Require treatment (CIN2/CIN3/cancer): 192 cases
- Negative or require follow-up assessment (NILM*/CIN1): 2,302 cases

		Pathology (Pathological diagnosis/cytology)		
		Require treatment	Negative or Require follow-up assessment	Total
This system, FCM method	Positive determination	182	696	878
	Negative determination	10	1,606	1,616
	Total	192	2,302	2,494

Detection sensitivity for CIN2 or higher (moderate/higher-level pathological change, cancer) = **95% (182/ 192)**
Specificity = **70% (1,606/2,302)**
Negative predictive value = **99.4% (1,606/1,616)**

*NILM: Negative for intraepithelial lesion or malignancy

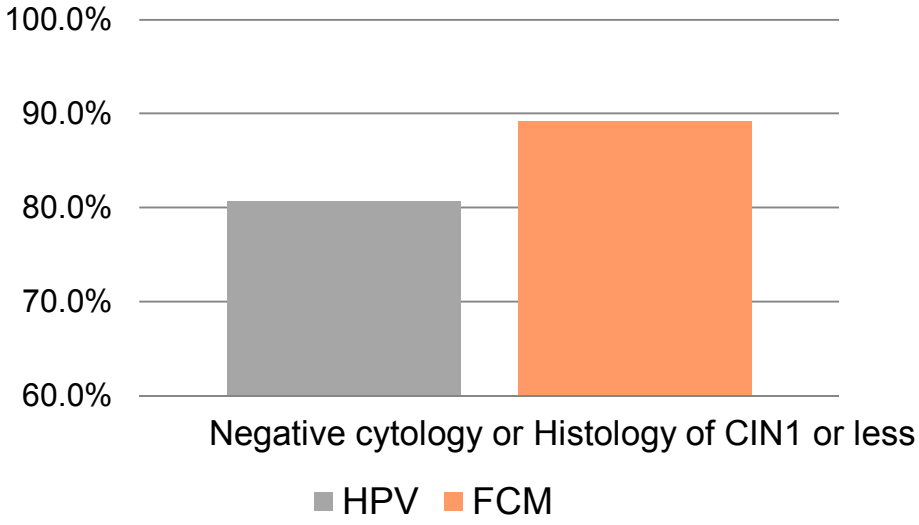
- Highly sensitive screening of cases where commencement of treatment at level CIN2 or above is desirable
- Cases not requiring immediate treatment can be precluded with a high degree of accuracy

Interim Results of Clinical Evaluation Overseas

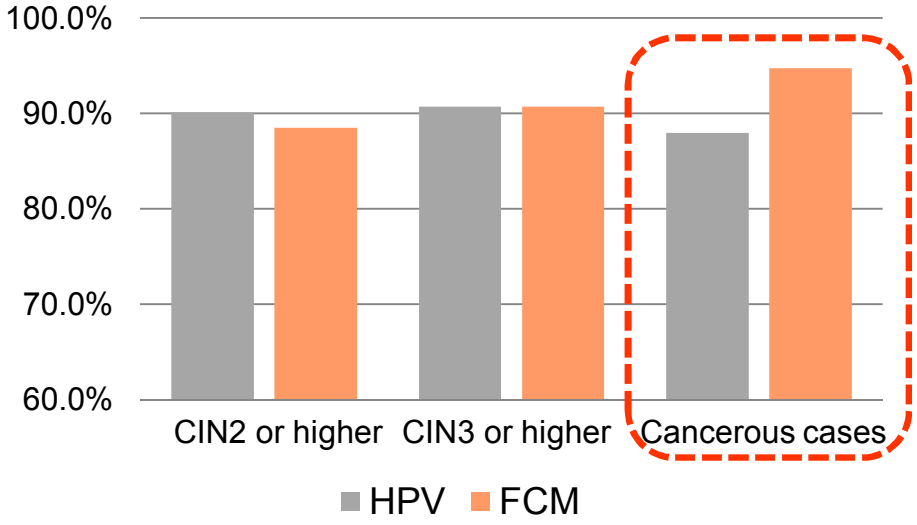
One facility (hospital specializing in cancer treatment)　Results compared with HPV testing (gene testing)

- Require treatment (CIN2/CIN3/cancer*): 182 cases
- Negative or require follow-up assessment (NILM/CIN1): 93 cases

Specificity comparison of cases that are negative or require follow-up assessment



Sensitivity comparison of cases that require treatment



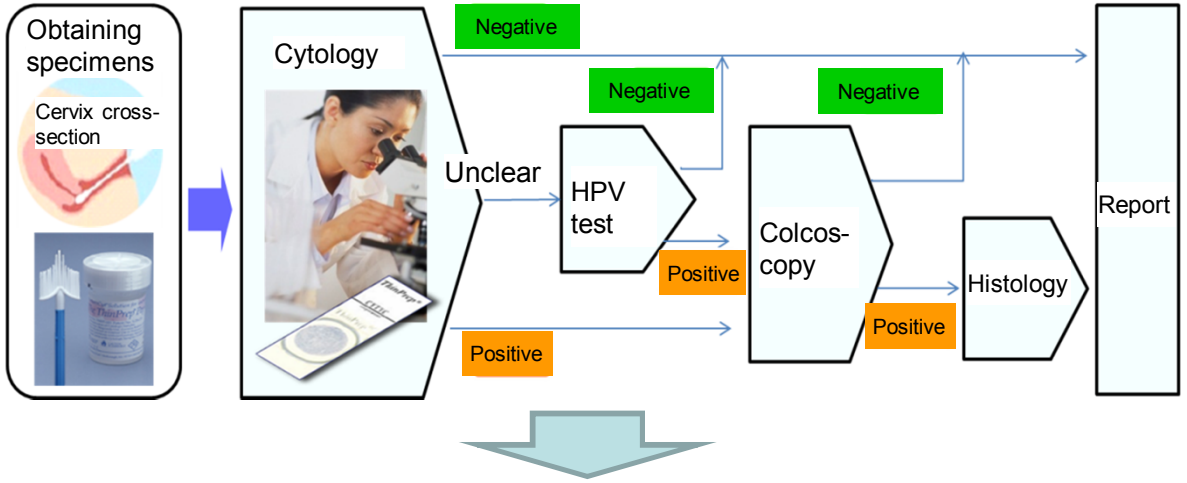
* Of 133 cases of cancer, 115 cases of squamous cell cancer, 18 cases of adenocarcinoma

Cancer detection sensitivity: FCM > HPV

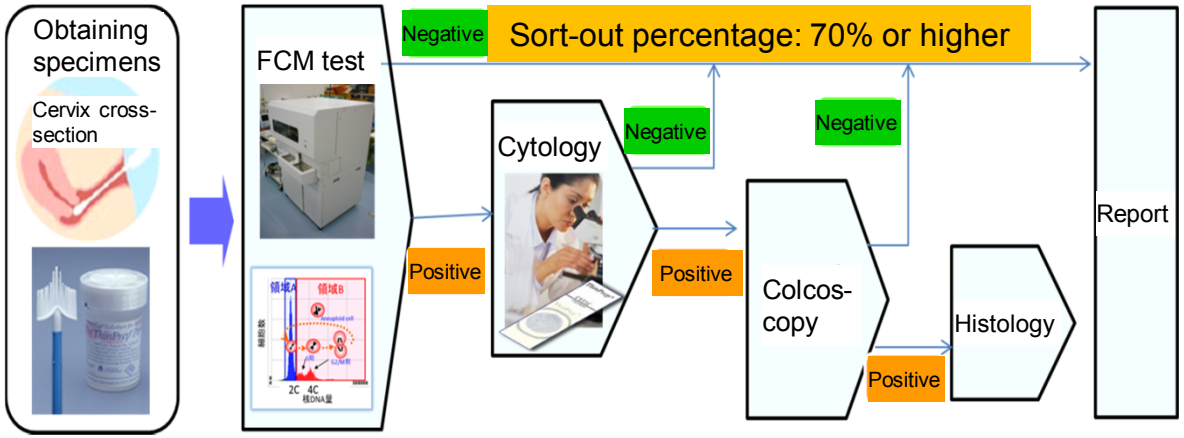
During HPV screening, the virus is drawn into the cell nucleus. If cancerous, the amount of virus is reduced, so detection sensitivity possibly falls. This leads to instances in which cases requiring immediate treatment are overlooked. This system, however, uses cell proliferation activity for measurement, allowing cancer to be detected to a high degree of sensitivity.

Proposing a New Test Flow

Current test flow

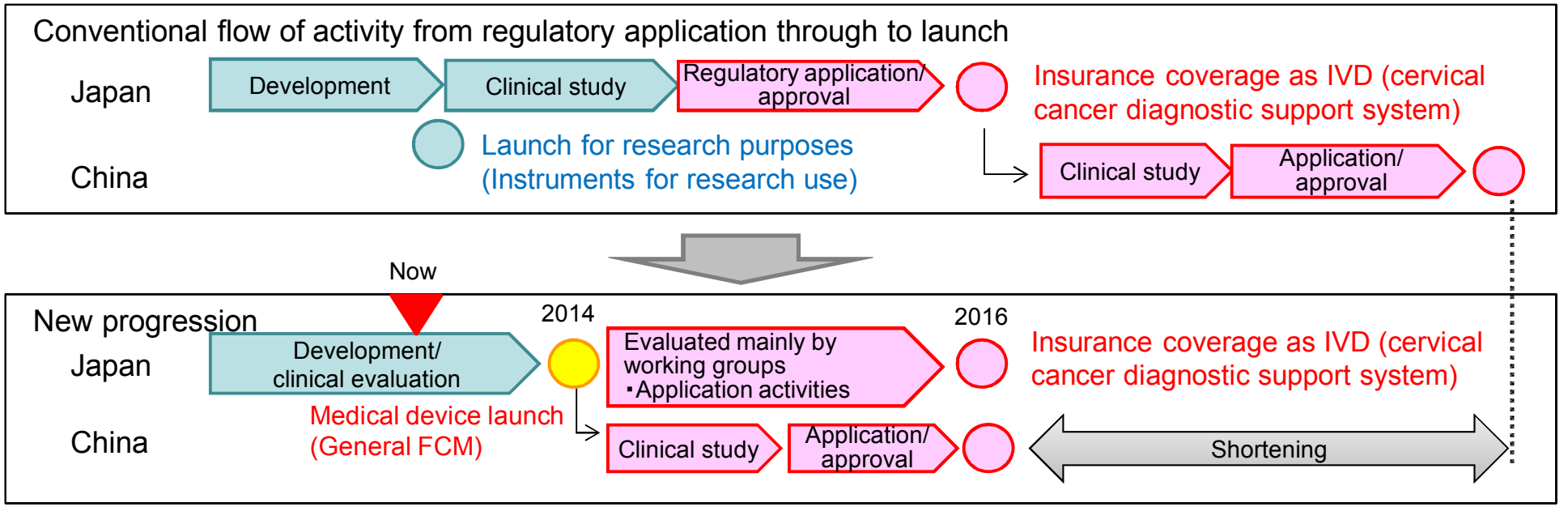


Sysmex's newly proposed test flow



Enhances testing efficiency and standardization, reduces burden on cytologists and contributes to cost reductions

Current Progress and Future Expectations



Releases as a medical device in fiscal 2014

[Japan]

In addition to organizing working groups and evaluating clinical utility, evaluating economic performance and evaluation on an operational front, as well as conducting market introduction and popularization activities. At the point where valid evaluation data is accumulated, aiming to apply for and receive insurance coverage.

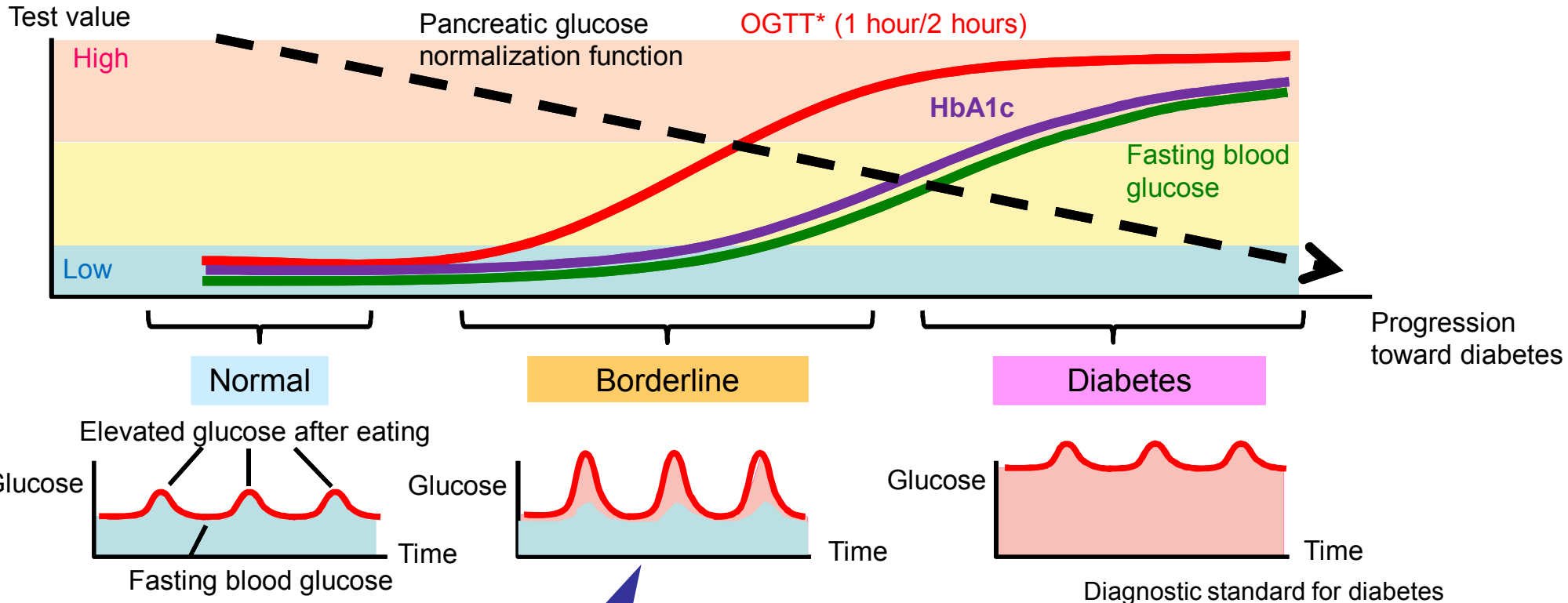
[Overseas]

First, have begun preparing for Chinese regulatory approval and applying for insurance coverage, and working toward an early-stage market introduction. In advanced countries, aiming to promote early recognition by making an appeal on superior factors such as non-inferiority certification in comparison with HPV tests, as well as economic performance and other factors.

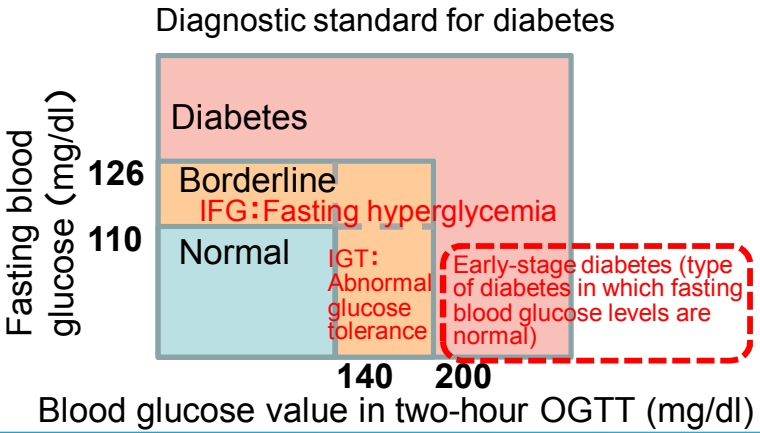
2) Minimally Invasive Postprandial Hyperglycemia Monitoring System (Glucose AUC Measurement Technology)

AUC: Area Under the blood Concentration time curve

Diabetes Progression and Testing Methods



- HbA1c reacts to fasting blood glucose and average blood glucose levels for one to two months previously, making it difficult to detect in moderate diabetes (impaired glucose tolerance), where glucose levels are elevated only after eating, and in early-stage diabetes
- OGTT is an effective method for the early detection of diabetes



*OGTT: Oral glucose tolerance test

Current Issues in Diabetes Screening

Current flow of testing

Screening
(Medical checkup/
general health screening)

- Fasting blood glucose level
- HbA1c

→ Test needed

Confirmed diagnosis
(Health clinic, etc.)

- Fasting blood glucose level
- HbA1c
- OGTT

→ Positive

Diabetes diagnosis, commencement of treatment

OGTT desirable: Fasting blood glucose level = 100–109 mg/dl or HbA1c (JDS) = 5.2–5.5%

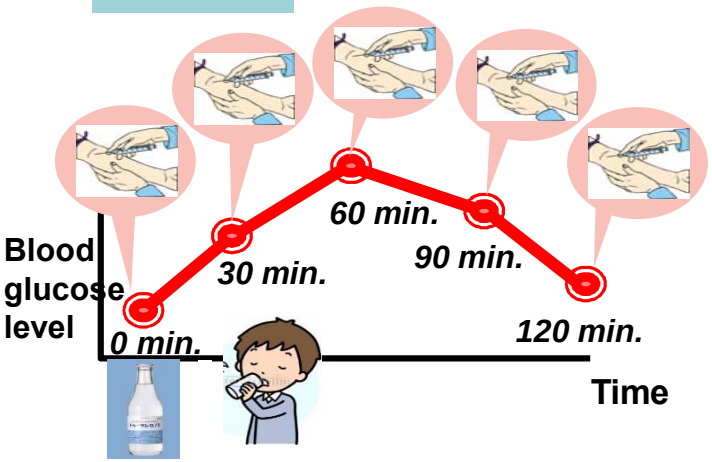
OGTT strongly recommended: Fasting blood glucose level = 110–125 mg/dl or HbA1c (JDS) = 5.6–6.0%

Issue (1)
At the locations where medical checkups and general health screenings take place, confirmed diagnoses of moderate diabetes are overlooked
⇒During medical checkups, tests with high detection capabilities are needed

Issue (2)
Because OGTT requires a number of samples and is complicated in other ways, it places a high burden on patients and has a low rate of execution (of around 16%)
⇒Simple test needed that can replace OGTT

Minimally Invasive Postprandial Hyperglycemia Monitoring System without Blood Sampling

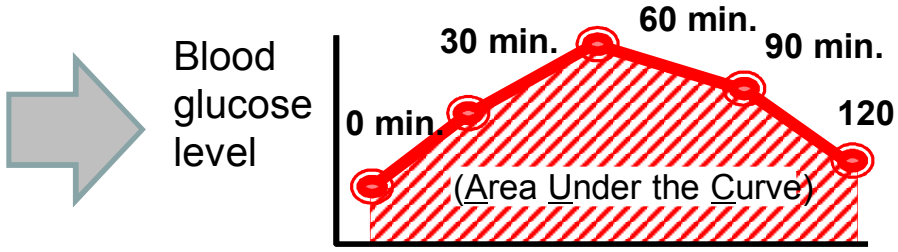
OGTT



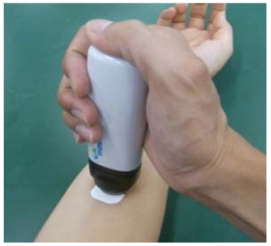
OGTT: 75g oral glucose tolerance test (test to monitor the ability to metabolize glucose after a fixed amount of sugar uptake)

Glucose AUC

After two hours, AUC values are calculated to determine glucose tolerance, expressing the amount of glucose elevation. This method aims to be as good or better than OGTT at detecting diabetes.



Pretreatment

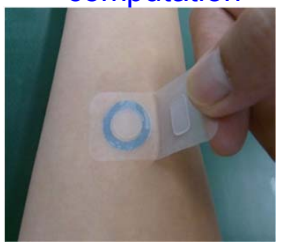


Microthin needle array used to form path through layers

Interstitial fluid extraction

Patch attached to collect tissue fluid

AUC value computation



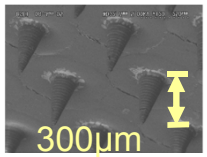
Removed two hours later, AUC value computed using collected tissue fluid

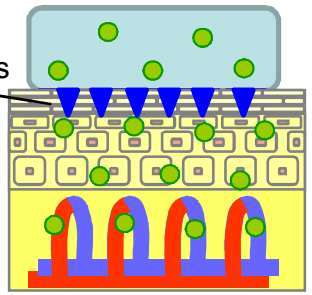
Minimally invasive for subjects

- No blood sampling, no pain
- Just wear patch during measurement

Simple and convenient for healthcare professionals

- No techniques such as sampling needed
- Handling required only twice: before and after start

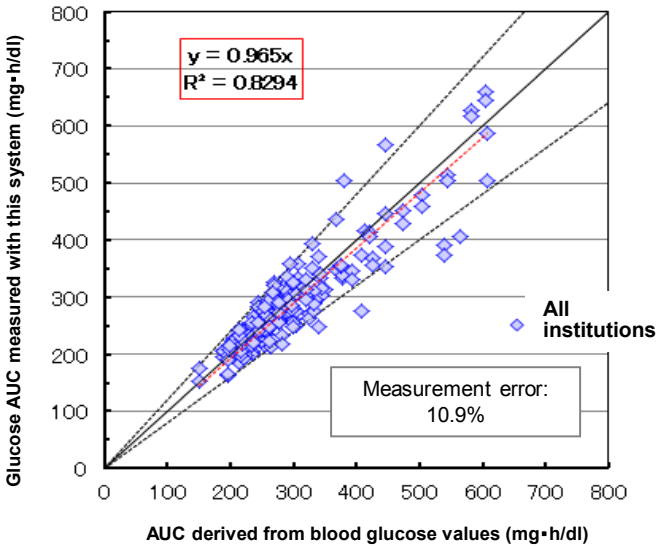




Measuring instrument

Clinical Evaluation Results (Verification of Principle)

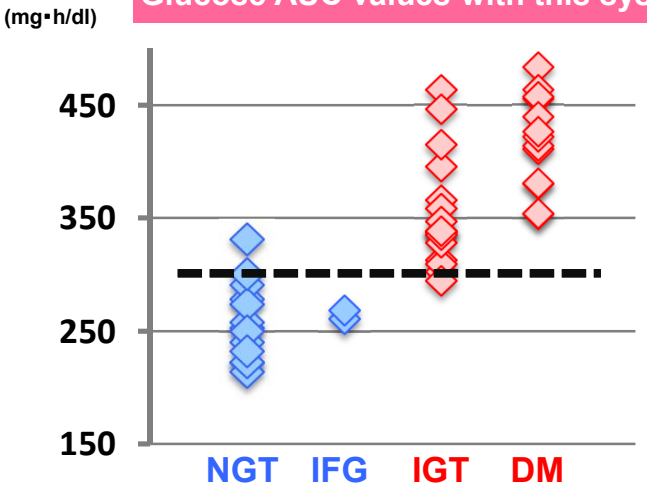
Correlation between glucose AUC from blood sampling and from using this system



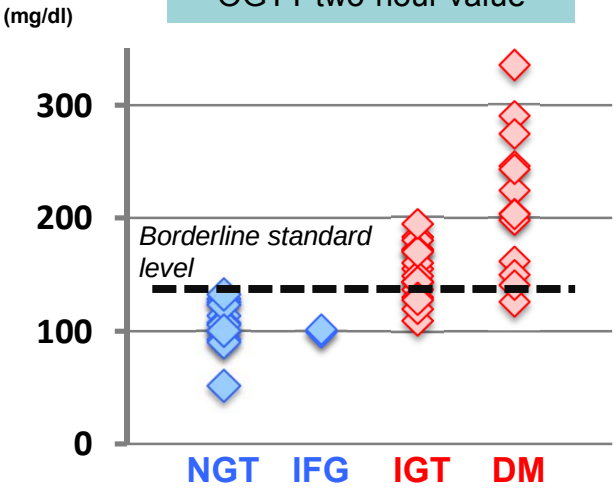
NGT: Normal
IFG: Fasting hyperglycemia
IGT: Abnormal Glucose Tolerance
DM: Diabetes

Postprandial Hyperglycemia
- Normal
- Abnormal

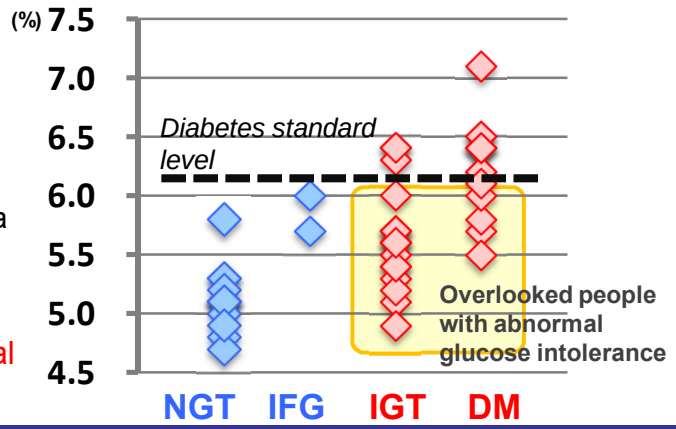
Glucose AUC values with this system



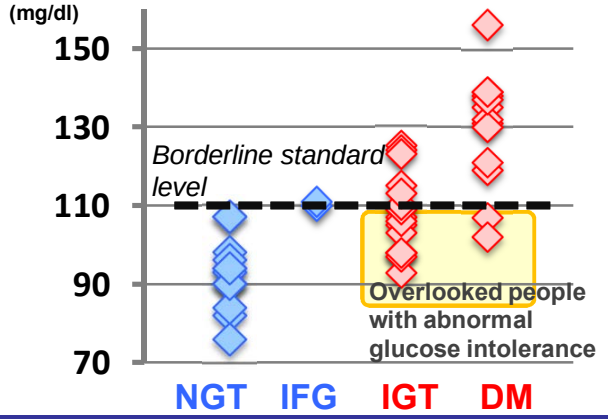
OGTT two-hour value



HbA1c level (JDS)

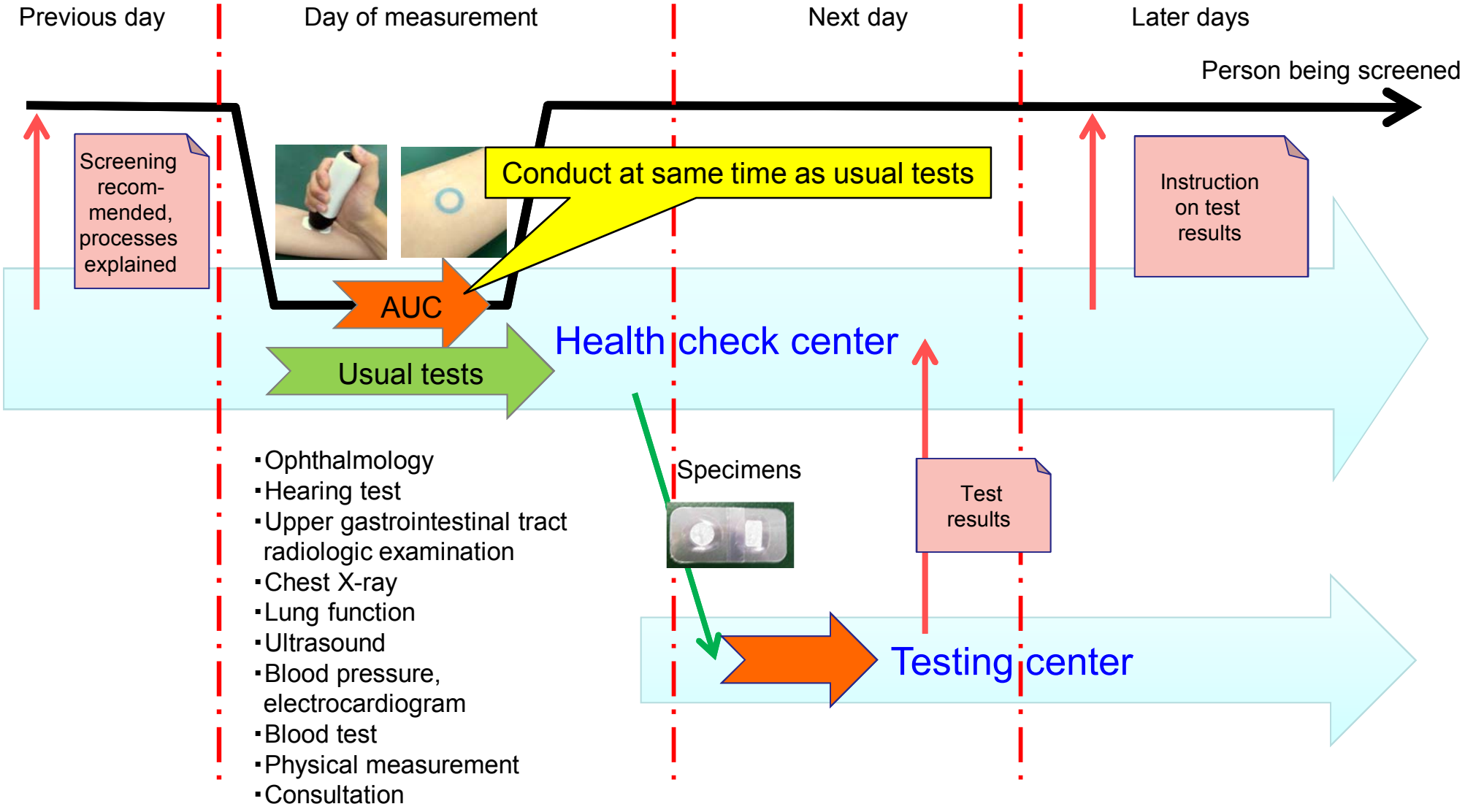


Fasting blood glucose level

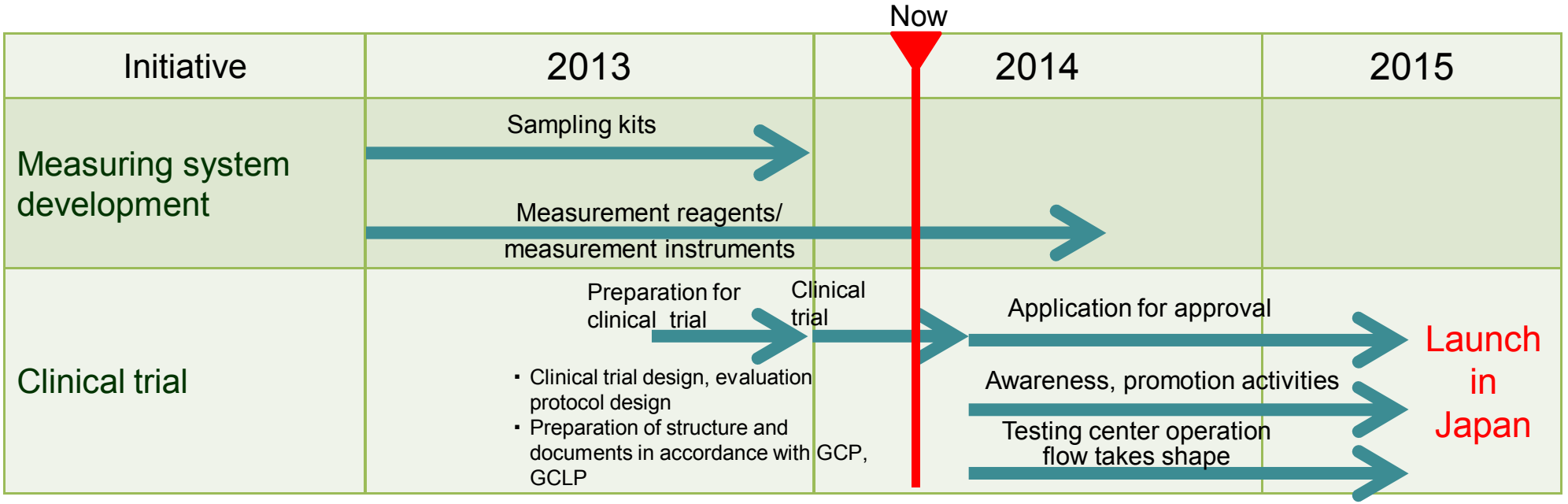


Ability to detect impaired glucose tolerance: Glucose AUC values with this system > OGTT two-hour values, fasting blood glucose levels, HbA1c

Proposed New Testing Flow



Current Progress and Future Expectations



GCP: Good Clinical Practice (Ministerial order related to standards on clinical trials for drugs)
GCLP: Good Clinical Laboratory Practice

Content of clinical trial

This system (glucose AUC) is verified to be no less effective than current testing methods in its performance on screening for impaired glucose tolerance	
Number of target cases	Approximately 200, including healthy people and people with impaired glucose intolerance
Facilities employing	Three facilities, including those participating in AUC working groups
Period	January–April 2014

3. Progress on Research and Development Themes

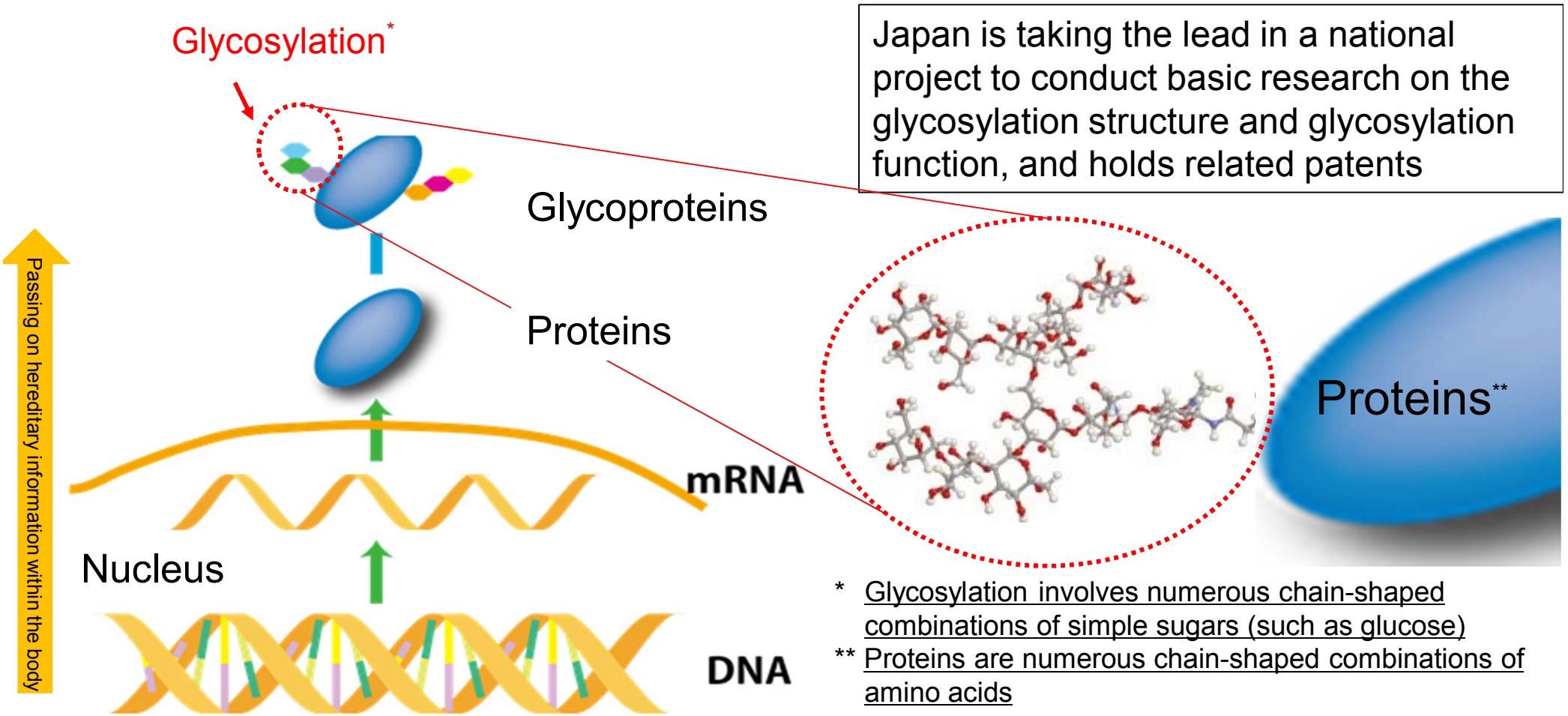
(2) ICH Business Unit

Yoichi Takahama,
Executive Vice President of the
Immunology & Chemistry Product Engineering Div.

1) Liver Fibrosis Marker
   - About Glycosylation Marker
   - Progression to Liver Cell Carcinoma and Understandings from Liver Fibrosis Marker
   - Future Developments

2) Progress on and Expectations for Increase in Immunochemistry Testing Parameters
   - HISCL TARC Reagent
   - HISCL Instrument Superiority

About Glycosylation



Japan is taking the lead in a national project to conduct basic research on the glycosylation structure and glycosylation function, and holds related patents

* Glycosylation involves numerous chain-shaped combinations of simple sugars (such as glucose)

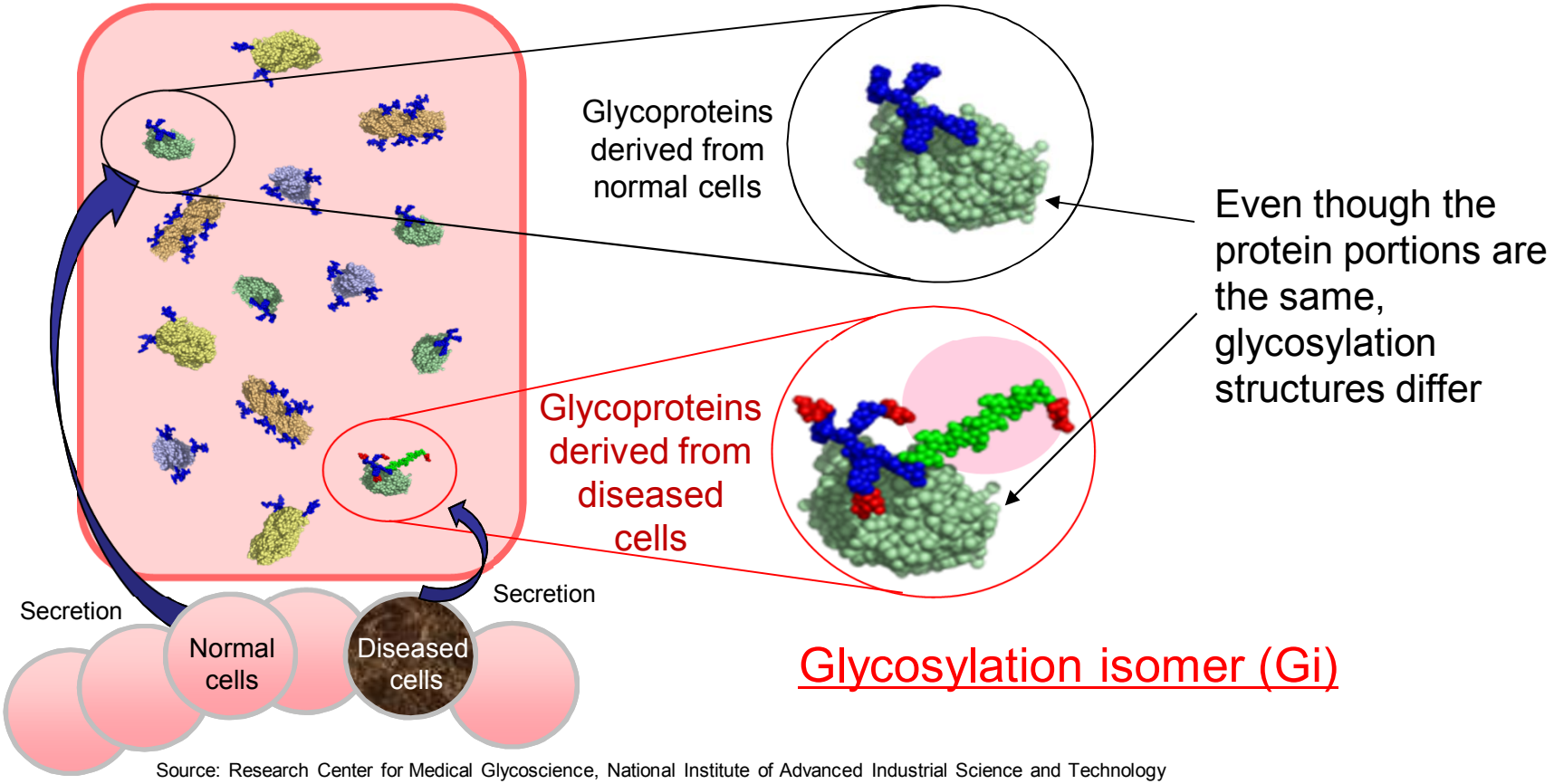
** Proteins are numerous chain-shaped combinations of amino acids

Source: Research Center for Medical Glycoscience, National Institute of Advanced Industrial Science and Technology

Glycosylation contains important information about the body, leading to expectations for its application in clinical testing

The Concept of Glycosylation Markers

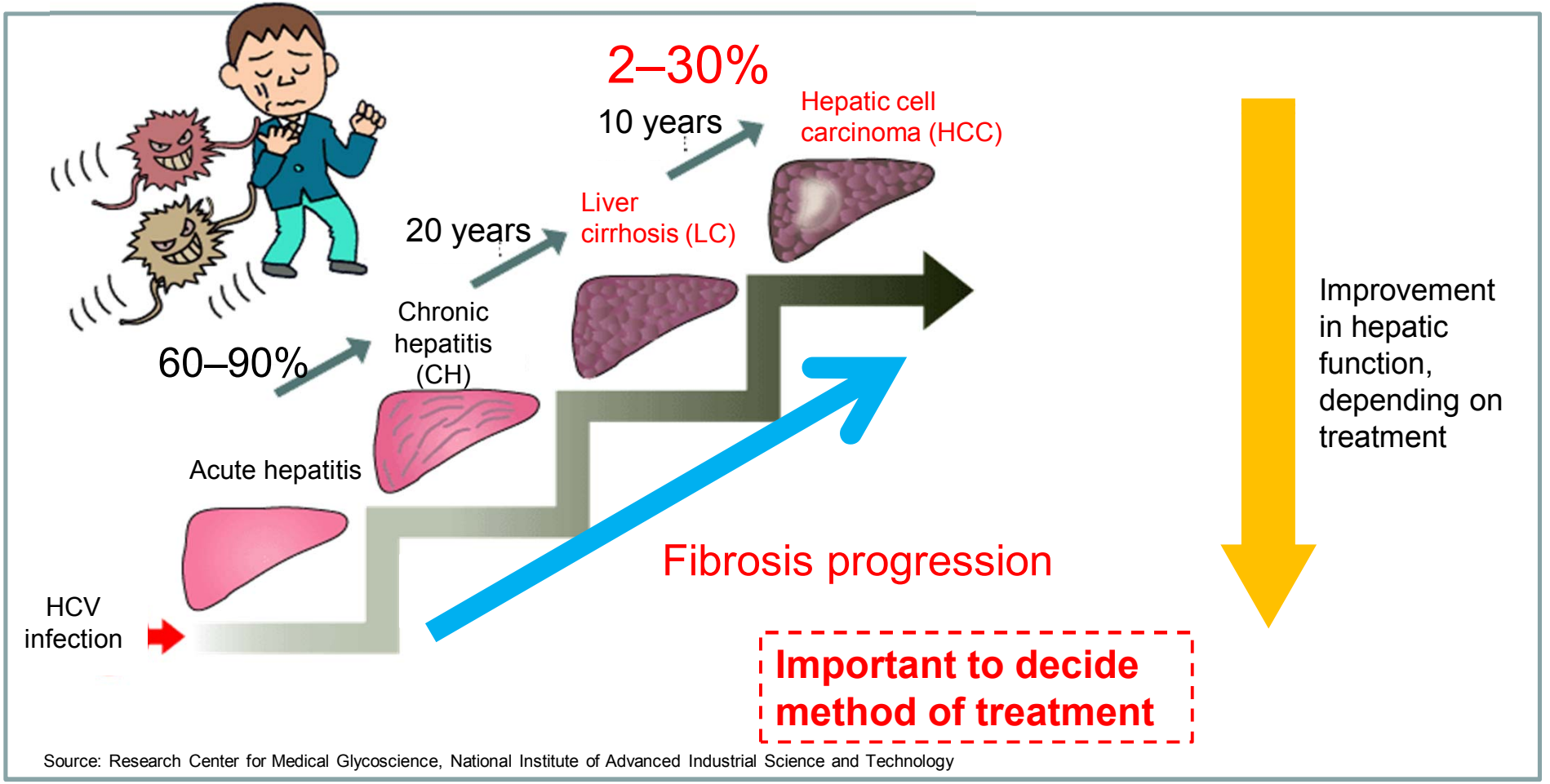
Proteins present in body fluid (blood)



Source: Research Center for Medical Glycoscience, National Institute of Advanced Industrial Science and Technology

Disease state mutations cause changes in the structures of the glycosylation on the proteins. By detecting those structural changes, through the blood it has become possible to differentiate between diseases that in the past were indistinguishable.

Liver Fibrosis Progression and Carcinoma Following HCV Infection

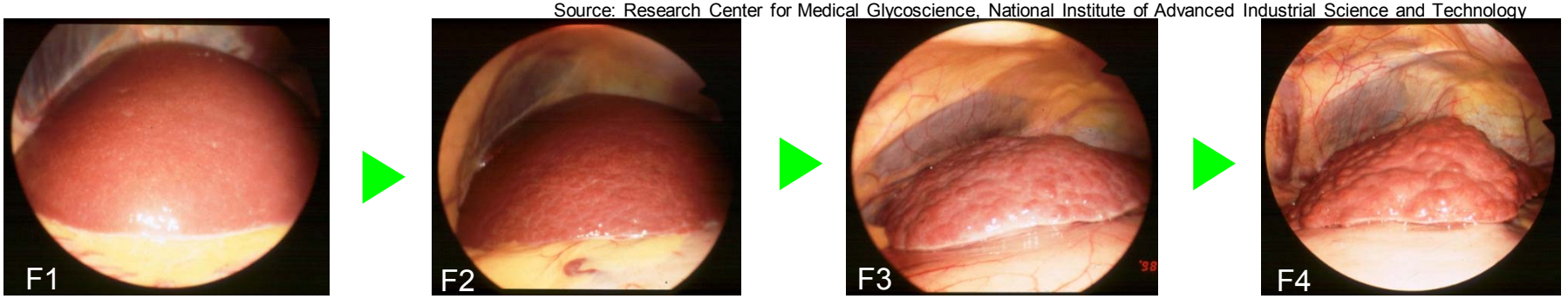


Source: Research Center for Medical Glycoscience, National Institute of Advanced Industrial Science and Technology

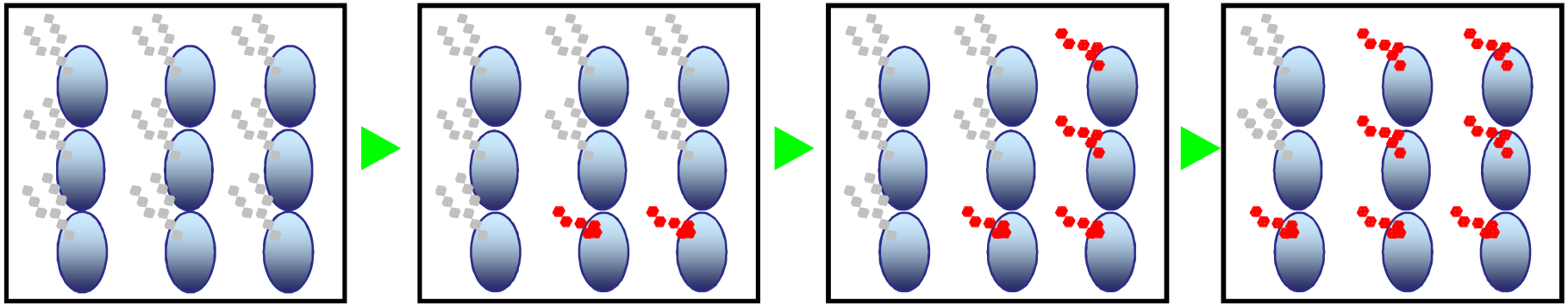
Currently, the progression of Liver fibrosis is diagnosed primarily through biopsies and image scanning, but the use of a simple serum is desirable (from the Hepatitis Seven-Year Plan)

Using a Glycosylation Marker as a Liver Fibrosis Marker (HISCL® M2BPGi)

Source: Research Center for Medical Glycoscience, National Institute of Advanced Industrial Science and Technology



Progression of Liver fibrosis



Quantitative protein changes

(quantitative changes)

- Hyaluronic acid
- Collagen
- PIIIP

Changes in the glycosylation structure

Measurement of qualitative changes (glycosylation isomer)

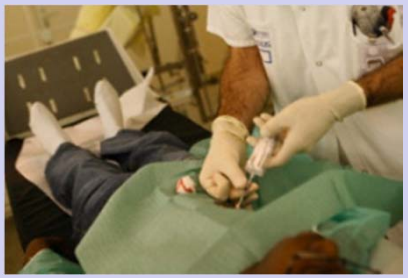
Liver fibrosis progression can be measured simply by means of a blood test (liquid biopsy)

Clinical Utility of the HISCL M2BPGi Reagent

M2BPGi reagent

- Non-invasive (blood)
- Fully automated measurement (17 minutes)
- High repeatability
- Numeric (objective)
- Low-cost

Liver biopsy
(Gold standard)



Source: medical-checkup.info website

Invasive ✕

Use non-invasive testing to determine fibrosis stage ○

Performance issues ✕

Existing tests

- Elastography imaging test
- FIB-4 Index
- Hyaluronic acid
- PIIIP
- Collagen

Frequent testing problematic ✕

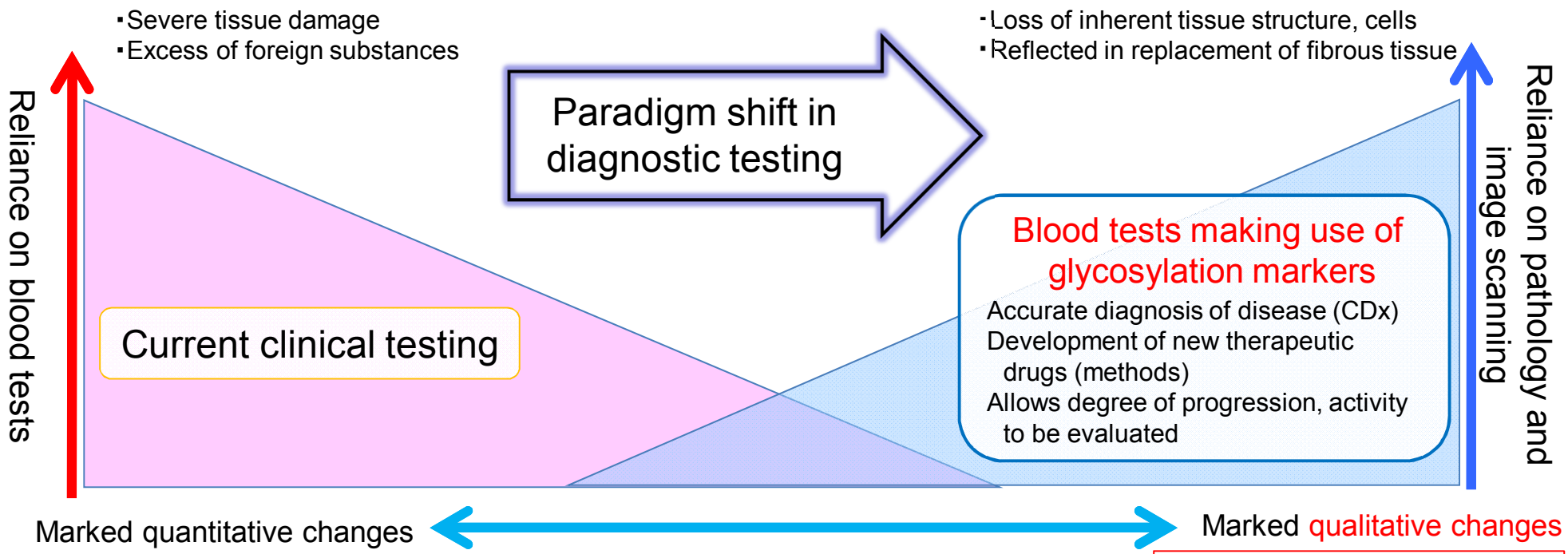
Monitoring of therapeutic gains ○

Liver cell carcinoma risk diagnosis ○

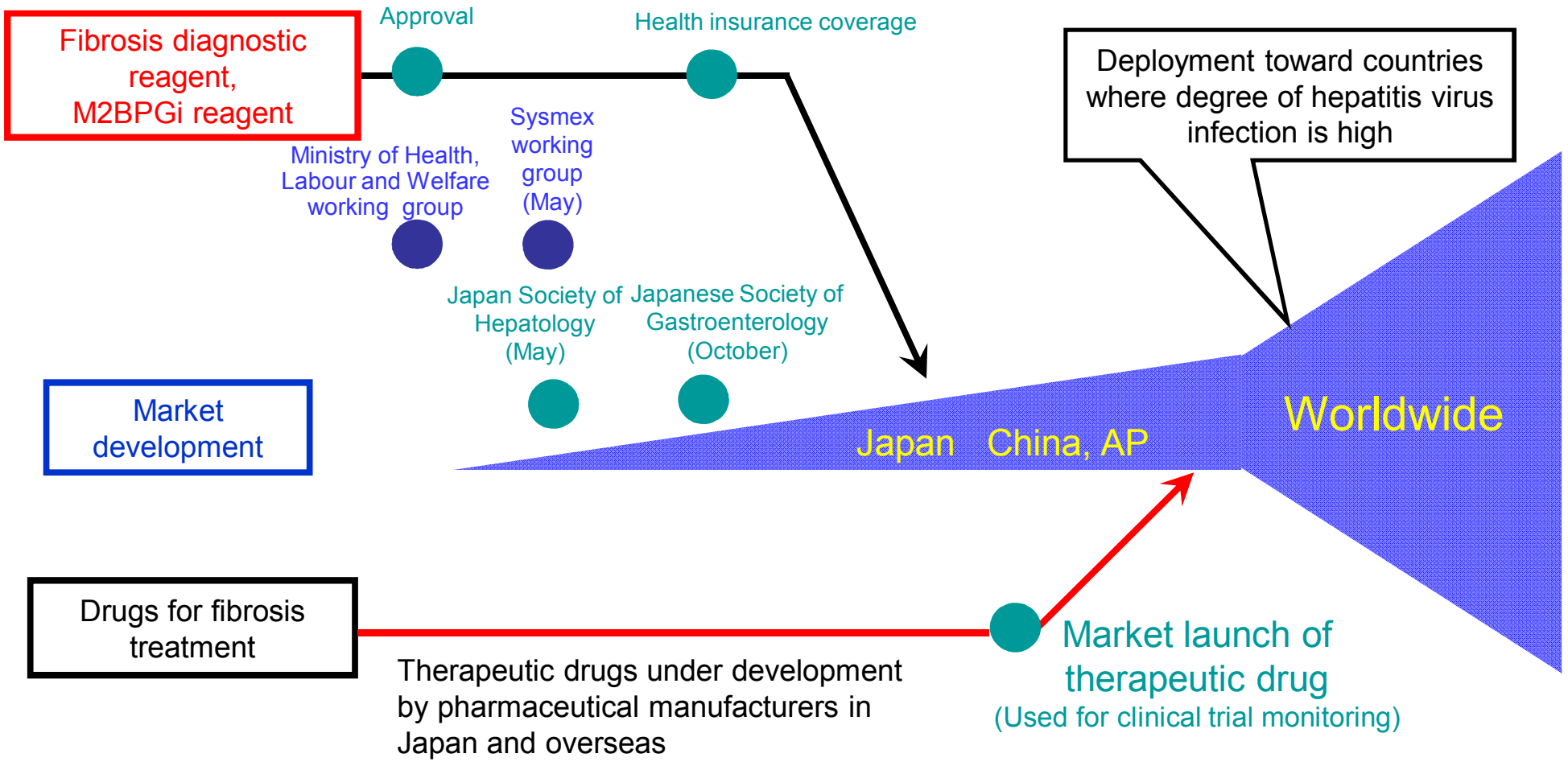
Relies on tumor markers ✕

Reducing the number of liver biopsies leads to increases in patient QOL. Also, early detection of liver cell carcinoma helps to hold down medical costs and increases the rate of survival.

Development of Tests Making Use of Glycosylation Markers



Future Developments for the HISCL M2BPGi Reagent

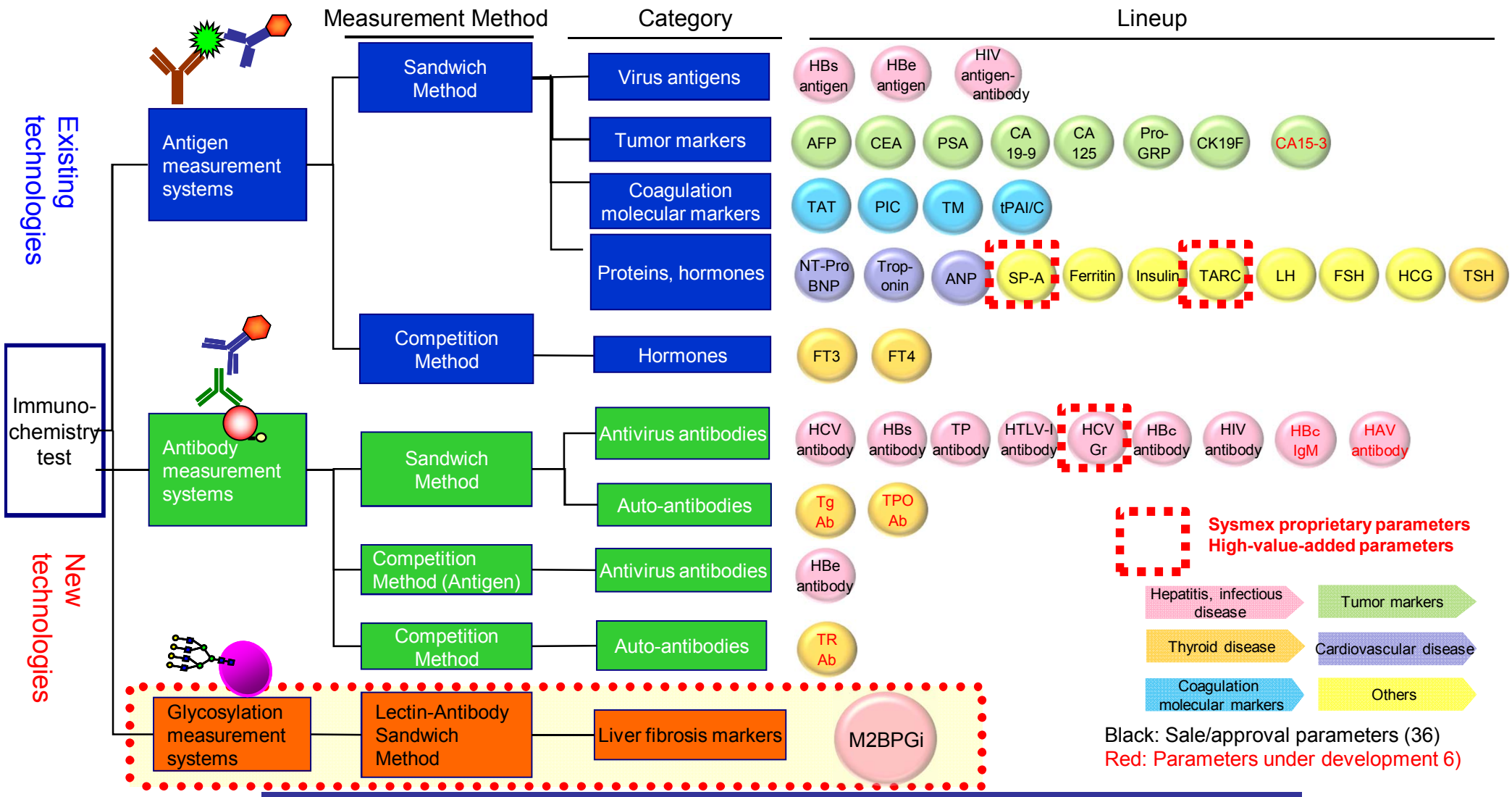


While working to develop a market in Japan, work toward global deployment and the entrenchment of CDx testing

2) Increase in Immunochemistry Testing Parameters

- HISCL TARC Reagent
- HISCL Instrument Superiority

Status of HISCL Reagent Development
(Approval and Sale for 36 Parameters)

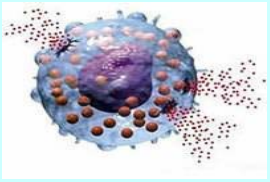


All test parameters can be measured in 17 minutes

HISCL TARC Measurement Reagent
(Product Developed in Cooperation with Shionogi)

Stimuli
- Allergies
- (Living) environment
- Lifestyle habits
- Stress…

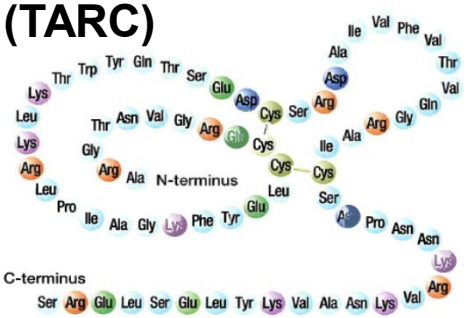
TARC production



Lymphocyte activation

Symptomatic worsening of atopic dermatitis

Thymus and Activation -Regulated Chemokine (TARC)



Note: Reprinted from an overview of product information (Alaport TARC) by Shinogi

MW: 8083 (71aa)
2008 points: 200
Note: In-flow human TARC insurance quantity measurement (auxiliary evaluation of degree of atopic dermatitis)
2009 Listed in the atopic dermatitis examination guidelines

TARC is an objective marker for evaluating the disease state of atopic dermatitis and supports treatment based on the degree of severity

■Alaport TARC: Microplate EIA Method

Blood sampling → Three hours → Measurement of light absorption

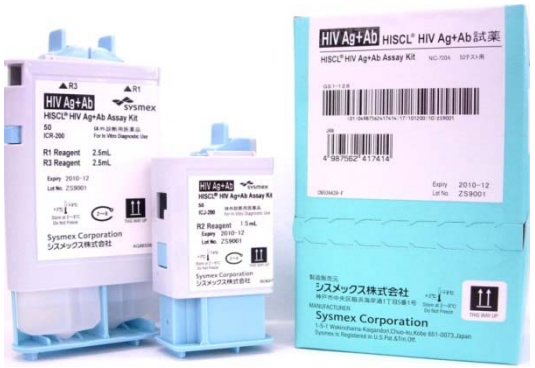
■HISCL TARC: Fully automated measurement

Blood sampling → 17 minutes → Chemiluminescence measurement

Shortening (measurement in 17 minutes) testing time enables pre-examination testing

Directions for HISCL Reagent Development

Higher diagnostic value



Early detection

Clinical value

Selection of treatment method

Lineup of basic parameters

- Hepatitis, infectious disease
- Tumor marker
- Thyroid hormone

Establishment of disease panels

(Hepatic disease, lung disease, DIC, thyroid disease)

Sysmex proprietary parameters

- HCV-Gr: Decide on IFN treatment method after determining serotype (Type 1, Type 2)
- SP-A: Distinguish between interstitial pneumonia and alveolar pneumonia

Unique parameters to increase clinical value

High-value-added parameters

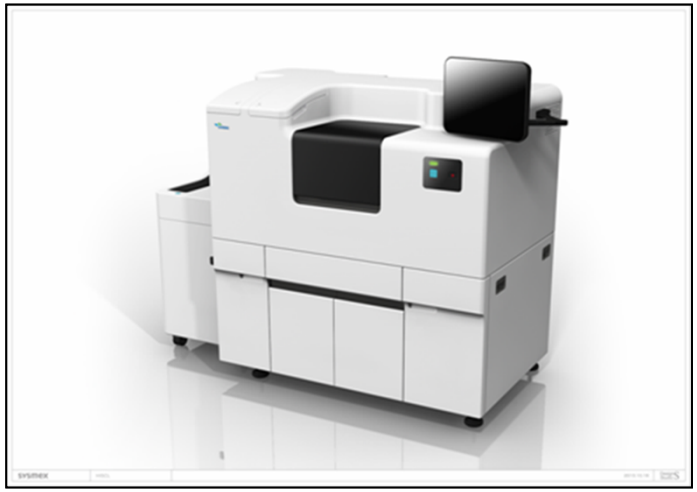
- M2BPGi: Diagnose stage of liver fibrosis
- TARC: Diagnose severity level of atopic dermatitis

Collaborative Japan-wide research structure involving companies, government agencies and universities

IFN: Interferon, DIC: Disseminated intravascular coagulation

HISCL Instrument Superiority

Manufacturer	Sysmex	Company A	Company B	Company C
Principle	Chemiluminescent enzyme immunization method			Bioluminescent enzyme immunization method
Measurement time	17 min.	29 min.	20 min.	46 min.
Processing capacity (tests/h)	200	200	240	120
Simultaneous measurement parameters (reagent setting positions)	Up to 24	Up to 25	Up to 24	Single-parameter analysis (six sets)



Simultaneous measurement of multiple samples allows the maximum speed of 17 minutes to be achieved, and testing precedence can be set in cases of urgent testing

3. Progress on Research and Development Themes

(3) LS Business Unit

Mamoru Kubota,
Executive Vice President of the
Life Science Product Engineering Div.

1) Products Related to the OSNA® Method
2) “Genetic Signature” Assay Service Product
3) Assay Service Product Using OncoBEAM

1) Products Related to the OSNA® Method

OSNA®: One-Step Nucleic Acid Amplification

(Registered trademark of the lymph node metastasis gene testing technology developed by Sysmex)

OSNA Method Contributing to the Standardization of Sentinel Lymph Node Biopsy for Breast Cancer

- Japanese Breast Cancer Society's breast cancer diagnosis guidelines (published in June 2013)

  Recommendation grade of "A" in the (2) Epidemiology/Diagnostic Edition

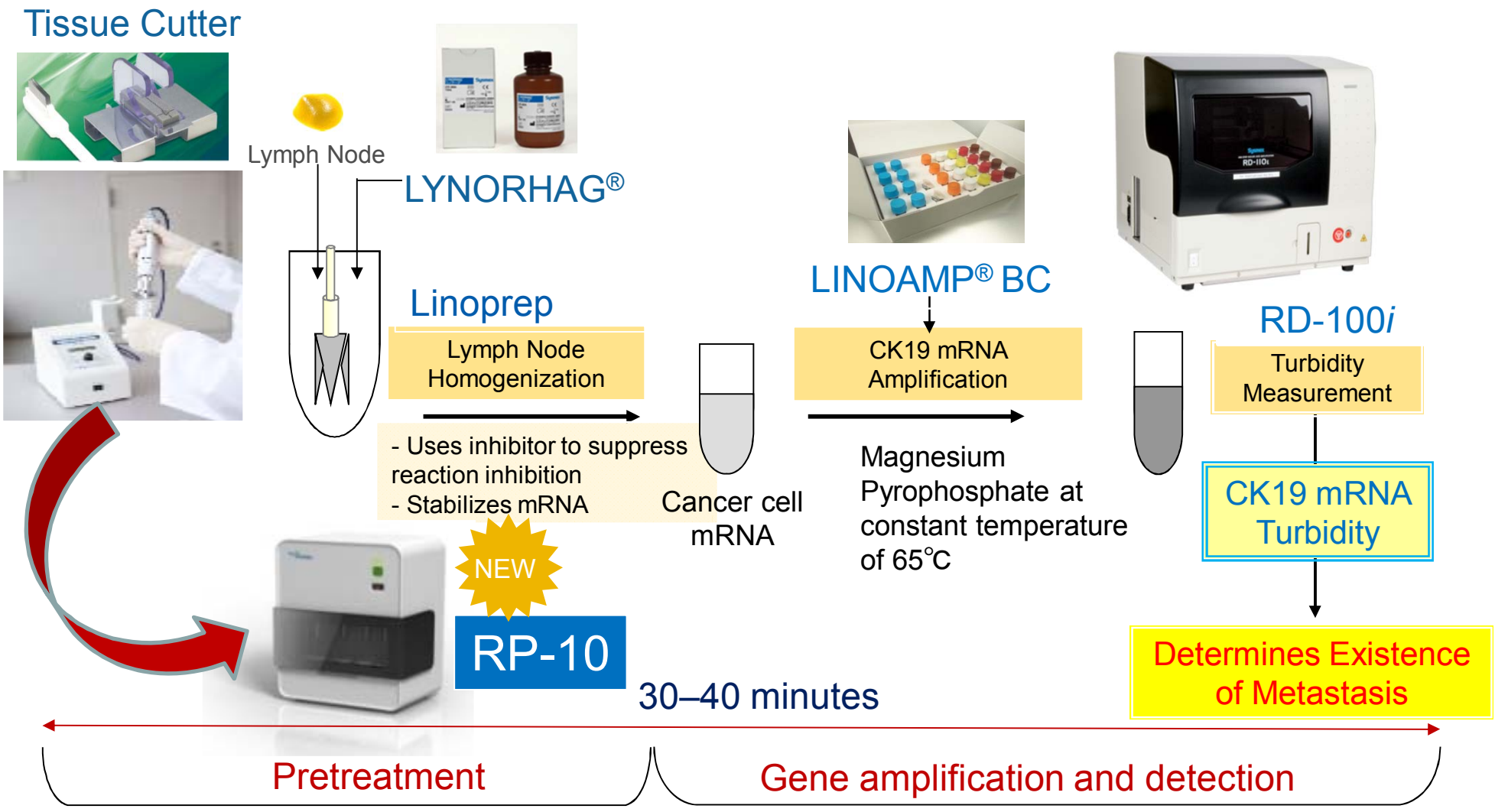
  - Pathological examination (HE staining) recommended for sentinel lymph nodes
  - Among molecular biological methods, the OSNA method is recommended as an alternative to typical pathological examination
    - ✓ Few false negatives, high specificity
    - ✓ Setting cutoff values facilitates determination of macro versus micro metastasis
    - ✓ Simple and requires little time, so helps reduce burden on pathologists and laboratory operators
    - ✓ Globally recognized clinical utility

- UK NICE Diagnostics Guidance 8 (published in August 2013)
  - For patients with early-stage invasive breast cancer, recommends using the OSNA method for measurement of the whole lymph node as a method for intra-operative analysis for sentinel lymph node metastasis

HE staining: Hematoxylin-Eosin staining, the most fundamental, important and general staining method

NICE: National Institute for Health and Clinical Excellence, a nationally run UK organization for evaluating medical technologies

OSNA-Method Assay Flow and Commercialization of the RP-10 as an Instrument to Automate Pretreatment

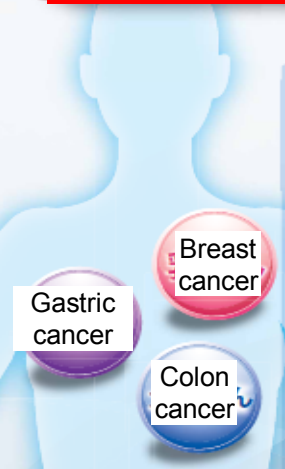


CK19: Cytokeratin 19, a tumor marker for epithelial cells

Clinical Applications, Insurance Coverage and Scientific Articles Related to the OSNA Method

Insurance Coverage of Testing for Lymph Node Metastasis of Colon Cancer and Gastric Cancer

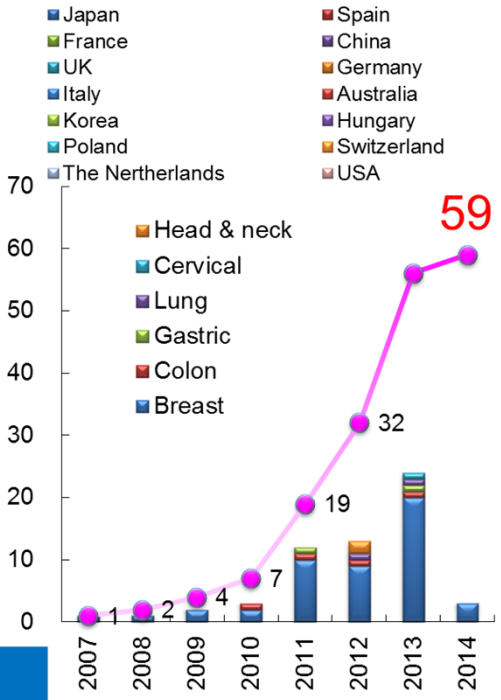
As of October 1, 2013



Parameter measured	Measurement method	Principal measurement objective	Points
Cytokeratin 19 (KRT19) mRNA detection	OSNA (One-Step Nucleic Acid Amplification) method	Detection of CK19 mRNA in lymph nodes in regions of excised breast cancer, colon cancer and gastric cancer (assist diagnosis on lymph node metastasis of breast cancer, colon cancer and gastric cancer)	2400

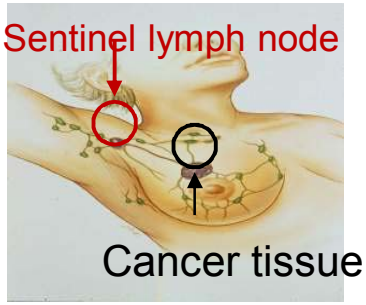
(Notes)
With regard to cytokeratin 19 (KRT19) mRNA detection, for patients with breast, colon and gastric cancer for which lymph node metastasis is unclear as a result of visual diagnosis or preoperative scanning, in the event the OSNA (One-Step Nucleic Acid Amplification) method is used for measurement in detecting cytokeratin 19 (KRT19) mRNA in regional lymph nodes of excised breast, colon or gastric cancer tissue to aid in determining the presence of lymph node metastasis or selecting the type of operation and other treatment methods, calculation limited to once per course.

Scientific articles on the OSNA method: 59 articles in 14 countries (February 28, 2014)

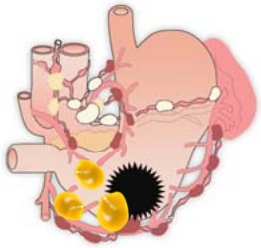


Intra-operative determination of lymph node dissection region

Breast cancer



Gastric cancer



More accurate staging judgment

Colon cancer

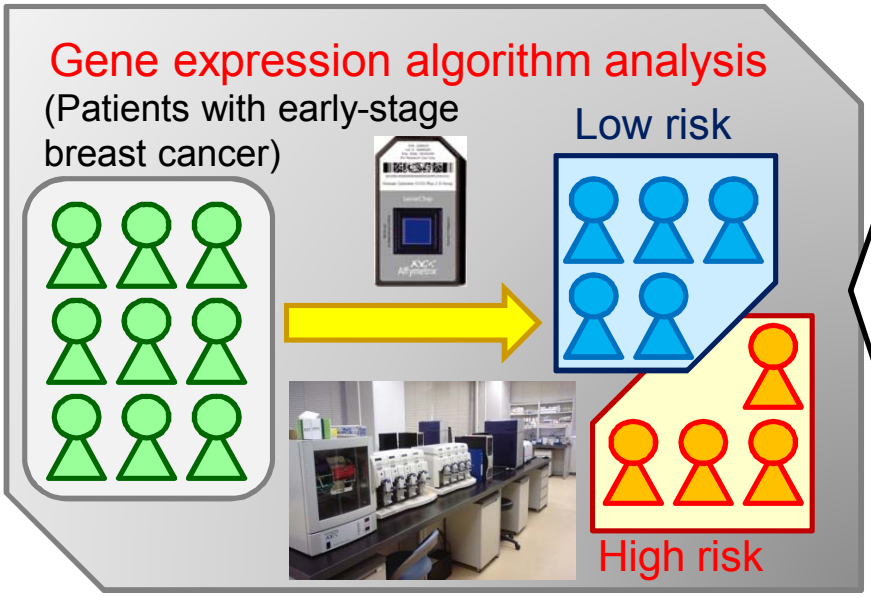
Cases of pathological non-metastasis	Lymph node metastasis negative	Lymph node metastasis positive
Pathology	131	0
Pathology + OSNA	116 (89%)	15 (11%)

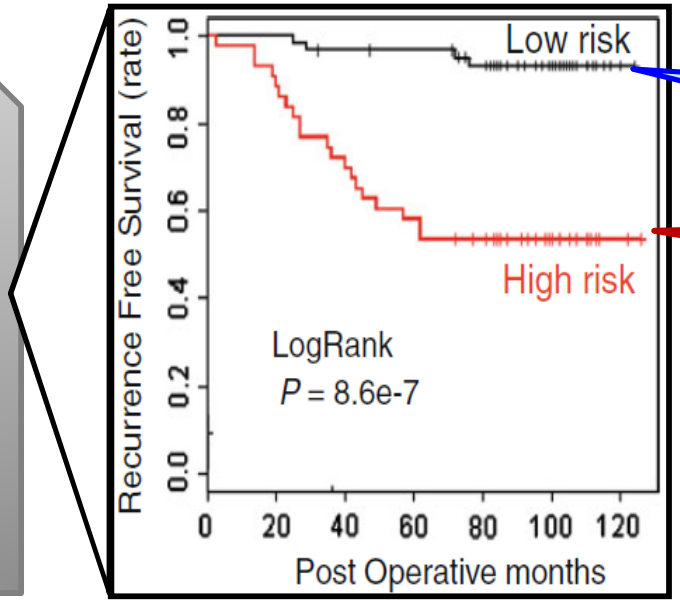
Planning to expand scope of application to lung cancer

2) “Genetic Signature” Assay Service Product

“Genetic Signature” Assay Service Product

Use of Affymetrix gene microarray to determine recurrence risk in patients with early-stage breast cancer





Retrospective study results

Nonrecurrence rate of approximately 90%

Recurrence rate of approximately 50%

Consider chemotherapy and other aggressive treatments

Winner of the Research Encouragement Prize (2011) by the Japanese Breast Cancer Society

Development of 95-gene classifier as a powerful predictor of recurrences in node-negative and ER-positive breast cancer patients

Breast Cancer Res Treat. 128(3):633-41, 2011.

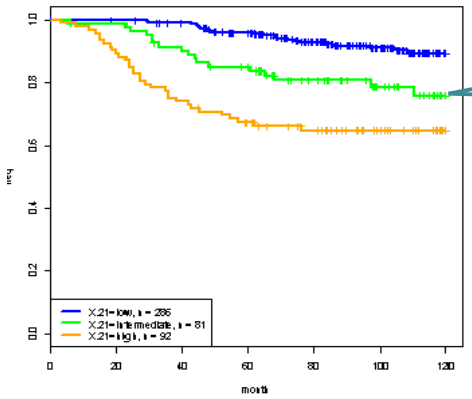
Yasuto Naoi · Kazuki Kishi · Tomonori Tanei · Ryo Tsunashima · Naoomi Tominaga · Yosuke Baba · Seung Jin Kim · Tetsuya Taguchi · Yasuhiro Tamaki · Shinzaburo Noguchi

Superior Characteristics of the "Curebest 95GC Breast"

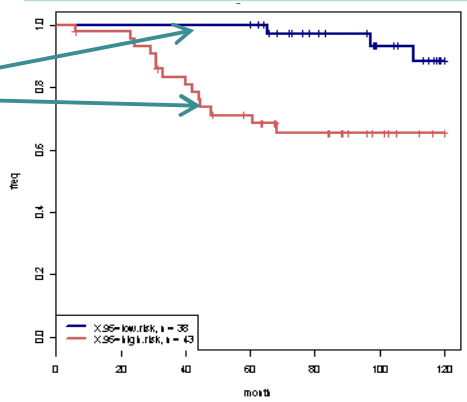
Product name (common name)	PAM50	Oncotype Dx	MammaPrint	Curebest 95GC Breast*
Developer (analysis)	NanoString Technologies (United States)	Genomic Health (United States)	Agendia (Netherlands)	**Sysmex (Japan)**
IVD approval guidelines	FDA 510K	Not approved NCCN-recommended	FDA 510K	**Not approved**
Biomarkers	50 types of mRNA	21 types of mRNA	70 types of mRNA	**95 types of mRNA**
Categories	Three: L/M/H	Three: L/I/H	Two: L/H	**Two: L/H**
Service price	Not available in Japan	¥450,000	¥380,000	**¥350,000 (Recommended)**

Note: Service (for research) involving analysis of genetic expression in breast cancer tissue

Oncotype Dx



Curebest 95GC Breast



Mircroarray analysis of 459 cases of patients with early-stage breast cancer

- Classification capabilities essentially equal to the Oncotype DX
- Can be classified among risk categories with the Oncotype DX (50:50)

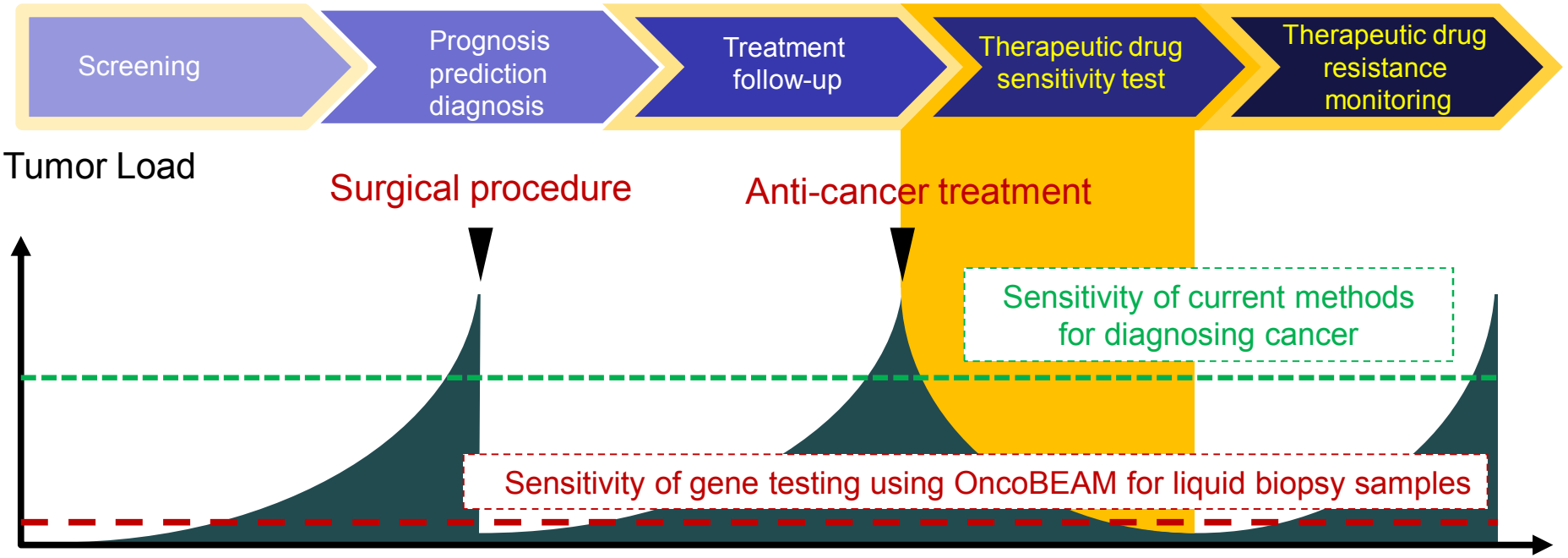
Naoi et al. *Breast Cancer Res Treat* 2013

3) Assay Service Product Using OncoBEAM

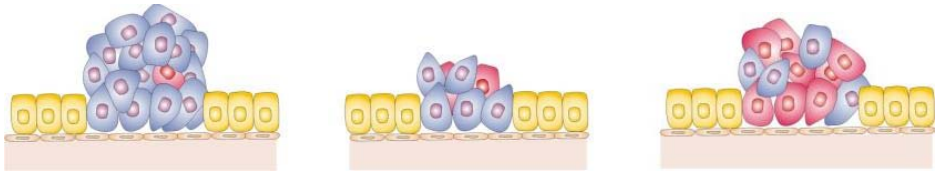
OncoBEAM: Brand Name of the assay service using the digital PCR (highly sensitive PCR) technology developed by Sysmex Inostics

Expected Clinical Significance of OncoBEAM

Steps in cancer treatment



- Sharp increase in diagnostic detection sensitivity
- Allows quantification of circulating tumor load



Normal cell Tumor cell Genetically mutated treatment-resistant tumor cell

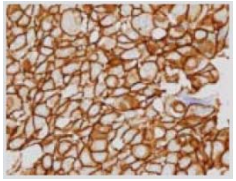
Concordance Rate of Genetic Mutation in Cancer Cells and Blood Samples

Sample ID	*PIK3CA* Tumor Tissue	*PIK3CA* Plasma
1	WT	WT
2	WT	WT
3	WT	WT
4	WT	WT
5	WT	WT
6	WT	WT
7	WT	WT
8	E545K (13%)	E545K (7%)
9	WT	WT
10	H1047R (19%)	H1047R (0.7%)
11	WT	WT
12	WT	WT
13	WT	WT
14	WT	WT
15	WT	WT
16	WT	WT
17	H1047R (6%)	H1047R (0.7%)
18	WT	WT
19	WT	WT
20	WT	WT
21	WT	WT
22	WT	WT
23	WT	WT
24	H1047R (10%)	H1047R (6%)
25	WT	WT
26	WT	WT
27	WT	WT

Sample ID	*PIK3CA* Tumor Tissue	*PIK3CA* Plasma
28	WT	WT
29	WT	WT
30	WT	WT
31	E542K (4%)	E542K (4%)
32	WT	WT
33	H1047R (39%)	H1047R (3%)
34	E545K (13%)	E545K (0.05%)
35	WT	WT
36	H1047R (16%)	H1047R (0.5%)
37	WT	WT
38	WT	WT
39	WT	WT
40	WT	WT
41	WT	WT
42	WT	WT
43	H1047L (31%)	H1047L (7%)
44	H1047R (44%)	H1047R (0.2%)
45	WT	WT
46	H1047R (35%)	H1047R (3%)
47	WT	WT
48	E545K (11%)	E545K (5%)
49	H1047R (20%)	H1047R (2%)
50	WT	WT
N=50	13/50	13/50

- 100% detection sensitivity for diseases involving genetic mutation
- 100% concordance rate with tissue (Sanger method) on genetic mutation

Liquid biopsy testing using OncoBEAM indicates high concordance rate with genetic testing of tissue



OncoBEAM may be an alternative to existing CDx

Bayer Health Care presentation , AACR 2013, Higgins MJ et al. *Clin Cancer Res* 2012; 183462-3469

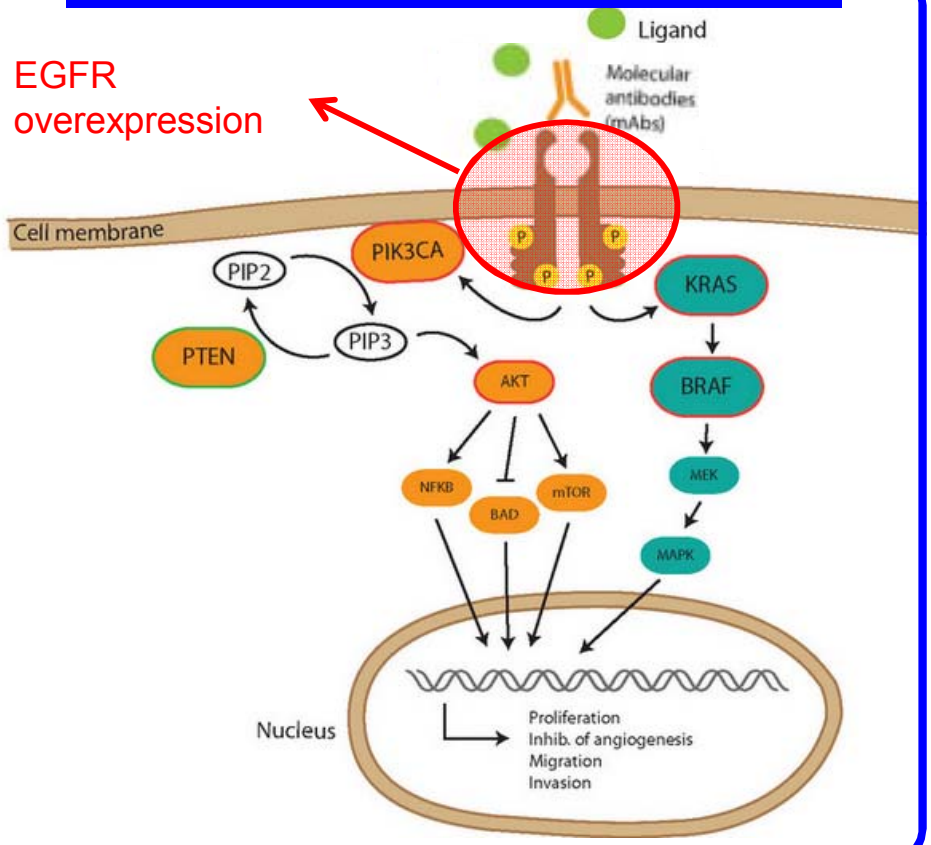
Selection of Colon Cancer Patients for Application of Anti-EGFR Antibody Drugs

- NCCN guidelines recommend that the presence of KRAS and NRAS genetic mutations be confirmed before using anti-EGFR antibody drugs for colon cancer treatment[1]
- If treatment with anti-EGFR antibody drugs has become ineffective, the presence of BRAF genetic mutation may be considered[1]

Tumor marker gene	Mutation rate (%)
KRAS	40
PIK3CA	15
BRAF	5
NRAS	3

Creation of a ligand biopsy testing system for colon cancer patients using OncoBEAM (CLIA-certified lab in Baltimore, United States)

Mechanism for the abnormal proliferation of colon cancer tumor cells



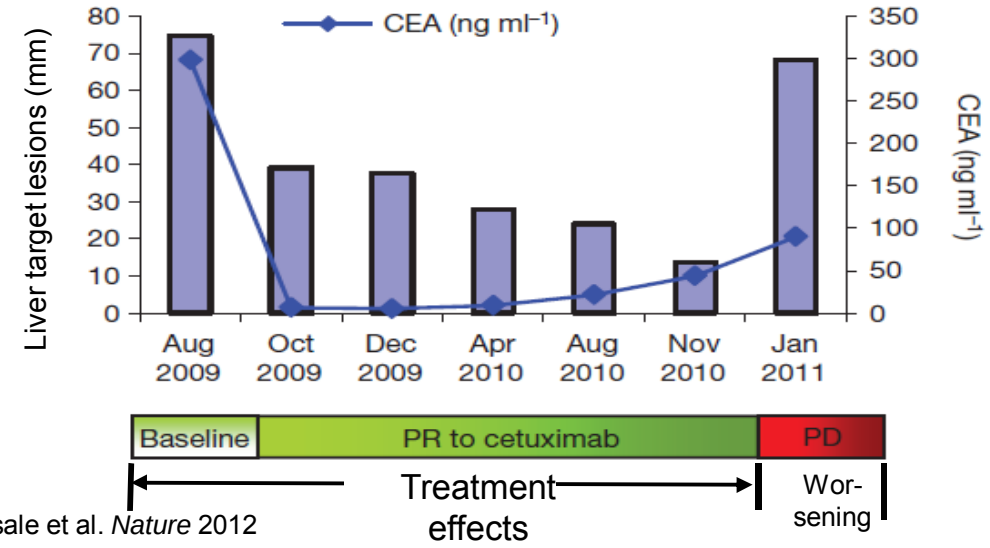
Berg M et. al. *Discov Med.* 2012, 14(76):207-14, revised

[1] NCCN Clinical Practice Guidelines in Oncology™: colon cancer. Version 3. 2014

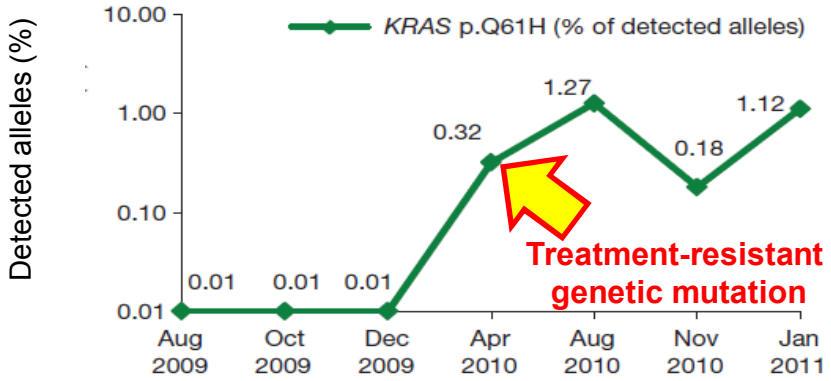
NCCN: U.S. National Comprehensive Cancer Network
EGFR: Epidermal growth factor receptor
CLIA: Clinical l Laboratory Improvement Amendments

Clinical Utility of Monitoring for Treatment-Resistant Genetic Mutation

Acquired resistance to cancer treatment
Molecular targeting therapies on the EGFR signal transduction pathway (hepatic cell carcinoma)



Misale et al. *Nature* 2012



Diaz et al. *Nature* 2012

Current issues

[Method]

- CT
- Cancer tumor markers

[Issues]

Delays in discovering acquired resistance to cancer treatment

Proposed solution

[Method]

Use OncoBEAM for detecting treatment-resistant genetic mutation

By monitoring for genetic mutations in liquid biopsy samples, resistance to treatment can be determined at an early stage

CEA: Carcinoembryonic antigen, a circulating tumor marker in patients with stomach, colonic, pancreatic, liver, gastrointestinal system and other cancers

Business Model and Full-Fledged Entry into Companion Diagnostics

Development of therapeutic drugs

Pharmaceutical companies

Drug discovery → Preclinical studies → Clinical trials → Regulatory approval → Market launch → Standard-ization

Molecular targeting therapeutic drugs

Companion Diagnostics

Research support (CRO business*)
Search for molecular markers, validation

Increased efficacy and safety of clinically investigational drugs (CDx business)
Selection and monitoring of applicable diseases

Patient treatment method selection (patient testing business)
Insurance coverage, listing of examination guidelines

Sysmex Inostics lab in Hamburg, Germany

Sysmex Inostics CLIA Lab in Baltimore, United States

Large commercial labs

Hospital laboratories

CRO business: Business handled by clinical research organizations

CLIA: Clinical l Laboratory Improvement Amendments

We Believe the Possibilities.

Sysmex Corporation

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