The 7th Technological presentation

March, 19th 2010

Sysmex Corporation

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1. Introduction

Hisashi Ietsugu, President and CEO

R&D Investment Policy

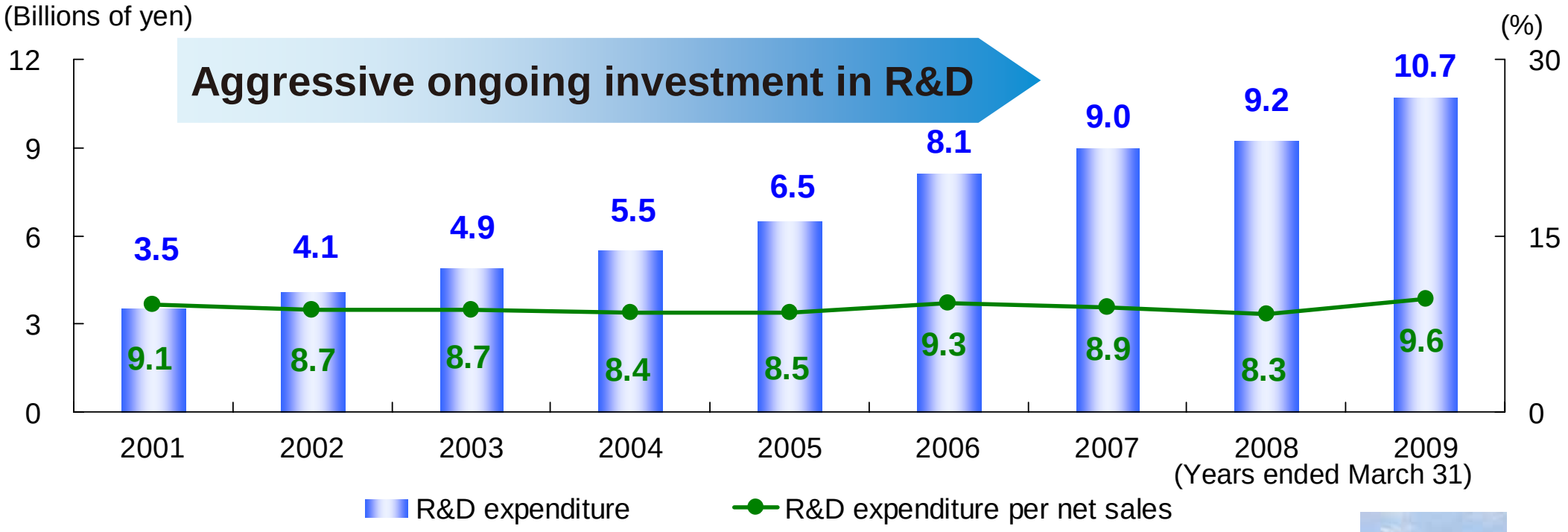
- **More companies boosting healthcare offerings**
  - Companies entering from other fields of business
  - M&A activities accelerating growth

Reinforce R&D, the wellspring of corporate growth

Sysmex's Basic Policy on R&D Investment

As a technology-oriented company,
our R&D investment benchmark is 10% of net sales.

R&D Investment Trends



■ 2002 International Reagents Corporation becomes subsidiary

■ 2004 BMA Laboratory

■ 2008 Technopark

■ 2000 Central Research Laboratories

■ 2006 R&D Center Europe

Expansion of Overseas Development Bases

—Recent Developments—

R&D Center Europe (Germany)

- July 2006 Opening
- October 2009 Lab relocation and expansion

Reasons for Establishment

- Clinical evaluation in hematology and life sciences
- Develop products tailored to European needs

Diagnostic Reagent Development Center in China

- December 2009 Establishment within Sysmex Wuxi Co., Ltd.

Reasons for Establishment

- Development of reagents (mainly immunochemistry)
- Joint research with local university hospitals
- Clinical evaluation

Moving into the 2nd Decade of the Central Research Laboratories

- Reason for establishing Central Research Laboratories (2000)

Contribute to development of preventive and regenerative medicine

- Lymph node metastasis testing technology (expand applicable cancer types)
- Cervical cancer screening technology
- Cancer recurrent prediction technology
- Cancer treatment effectiveness prediction technology
- Minimally invasive glucose monitoring technology
- Clinical condition simulation technology

November 2008

System for rapid detection of breast cancer lymph node metastasis based on OSNA method covered by Japanese health insurance

The gene amplification detector RD-100i

Designated reagent

Technopark (Kobe)

Realizing the “Disease Management” Concept

- **Commercializing high-value-added analysis parameters**
- **Promoting R&D in life sciences (cancer, lifestyle diseases)**

2. Direction & strategy of R&D

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

Vision of R&D activity

Sysmex Way

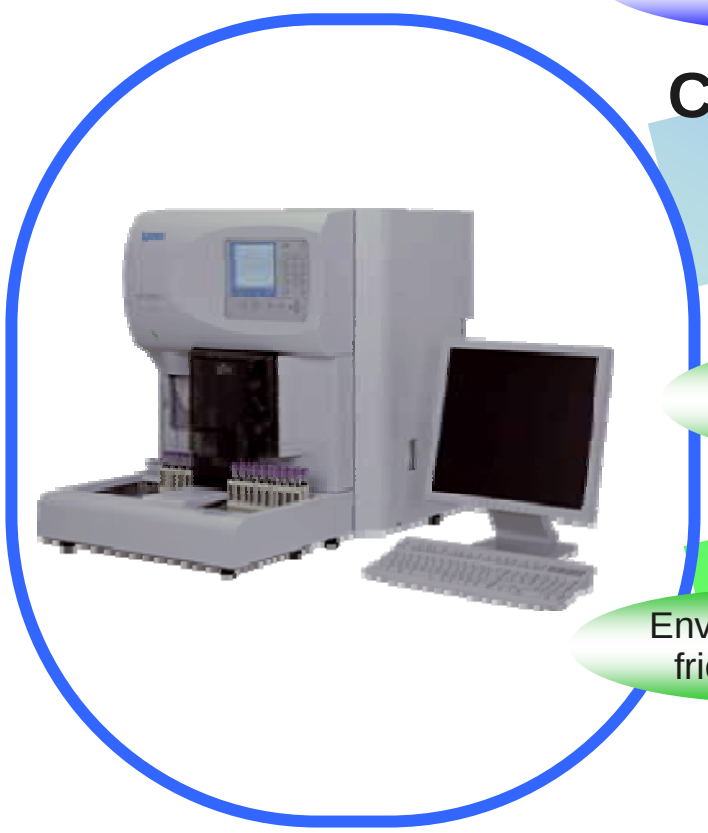
A Unique & Global Healthcare Testing Company

Providing highly valuable diagnostics testing
to optimize and standardize medical care

- Improvement of QOL / extension of healthy life expectancy
- Improvement of Medical economy value

Shaping the advancement of health care

Direction of R&D activity



Early detection

Selection of medical treatment

Clinical value improvement

Efficiency

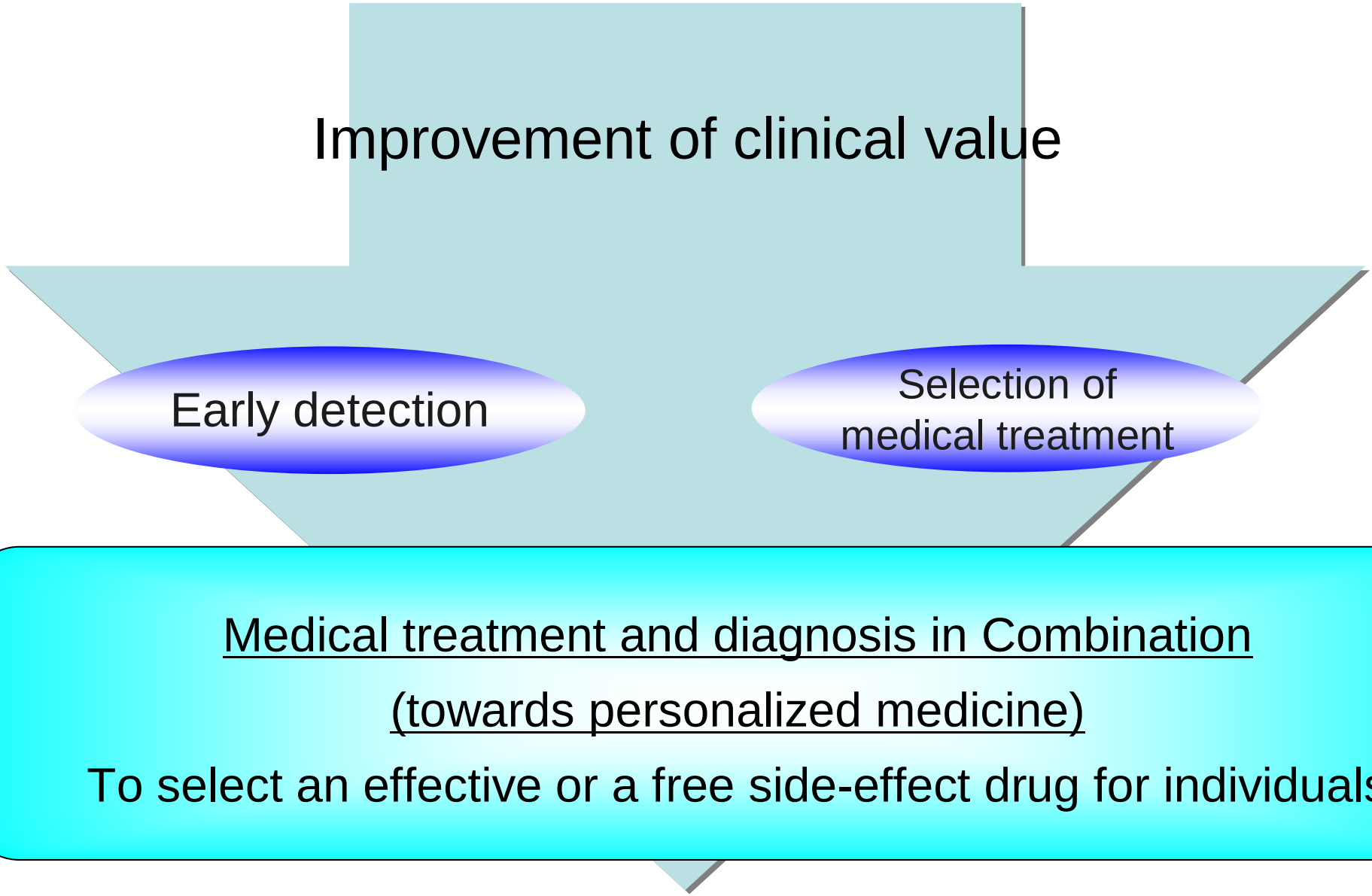
Quality

Usability improvement

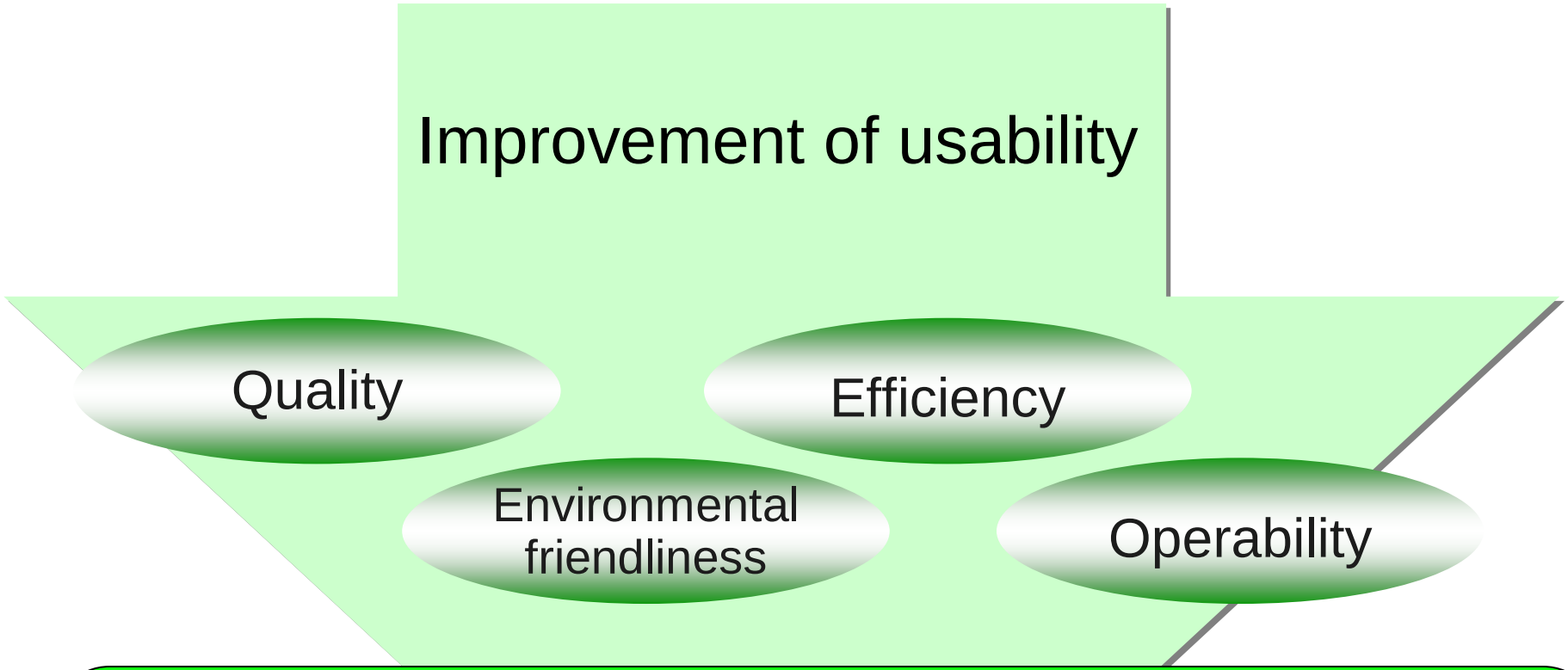
Environmental friendliness

Operability

Outline of technology strategy (1)



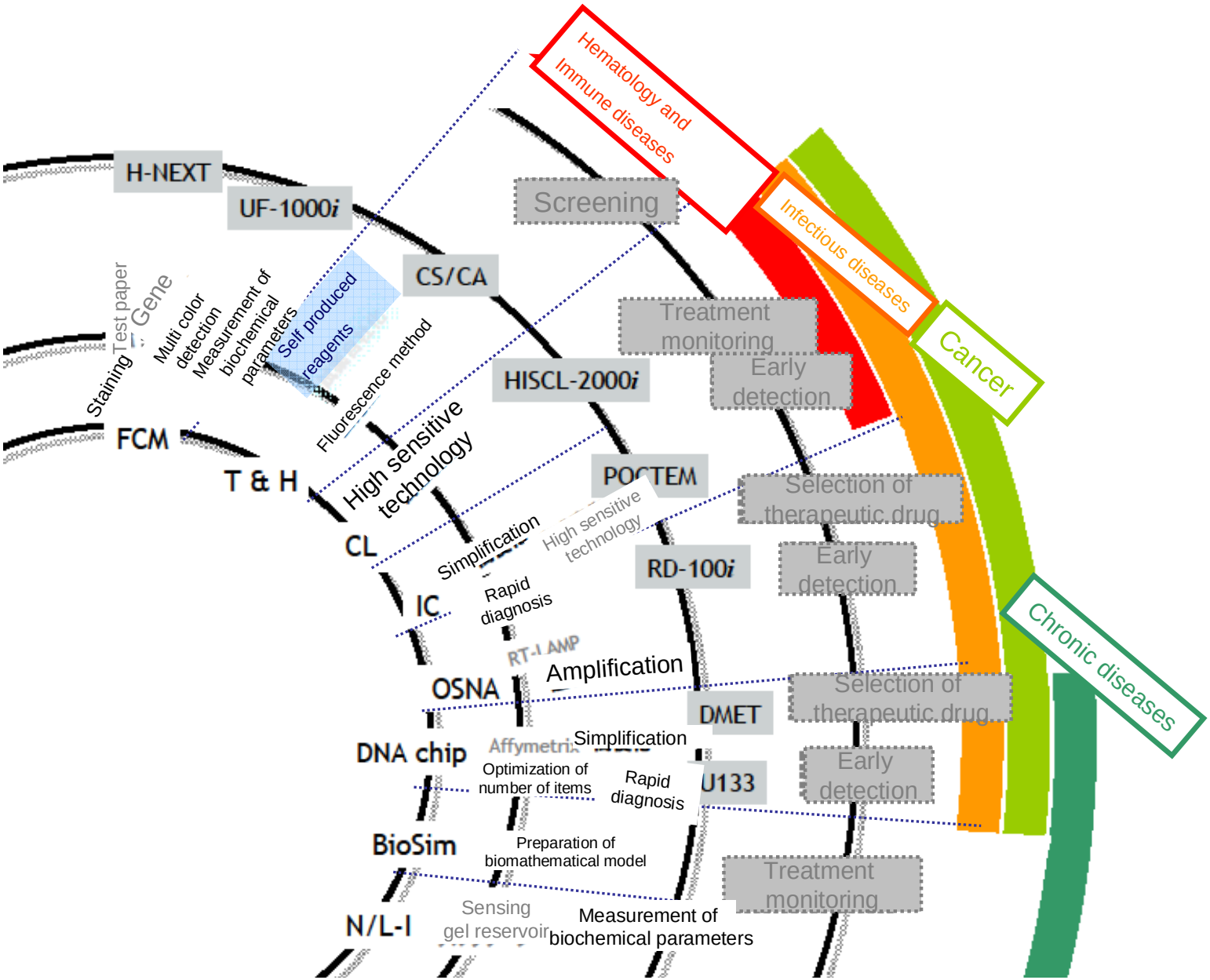
Outline of technology strategy (2)



Advanced countries： Providing high-value-added system that improves productivity of clinical test to reach the limit

Rising countries： Providing low cost prevalent instruments

Technology platform



3. Progress of R&D project

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

1) Progress status in launching stage
   (1) Rapid diagnosis of lymph node metastasis technology (OSNA)
   (2) Bird flu diagnosis technology
   (3) Digital blood smear preparation technology
   (4) Reagent preparation technology
2) Progress status in practical stage
   (5) Blood testing technology
   (6) Cervical cancer screening technology
   (7) Postprandial hyperglycemia monitoring technology

Kaoru Asano
Executive Officer, Central Research Laboratories

3) Progress status in research stage
   (8) CTC detection technology
   (9) CNS disease diagnosis technology based on DNA chip

Reporting subjects and policy of technological presentation

1. Reporting subjects

- Technical features of Sysmex technology and product
- Technical themes that Sysmex conducts R&D and their clinical benefits
- Outline of Sysmex Technology Strategy

2. Policy regarding report of technological themes

To explain R&D themes in below 3 steps

＜Research stage＞Start of research and basic consideration

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

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

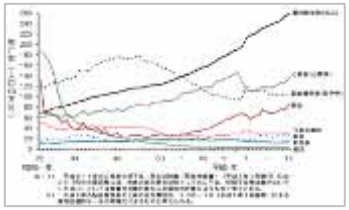
- Technological impact on characteristics of products

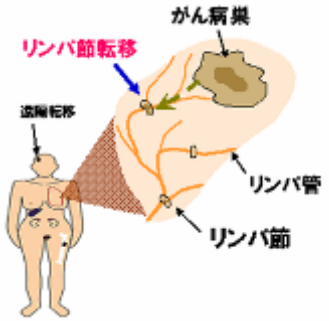
＜Launching stage＞ Accomplishment of development & introduction to market

- Details of technological features and superiority

Definition of R&D stage

Research stage	Practical stage	Launching stage
Start of research or basic consideration Objective means an establishment of measurement principle and a verification of clinical value.	Start of full-scale R&D activity towards commercialization	Completion of product commercialization and determination of launching
10～50%	50～80%	

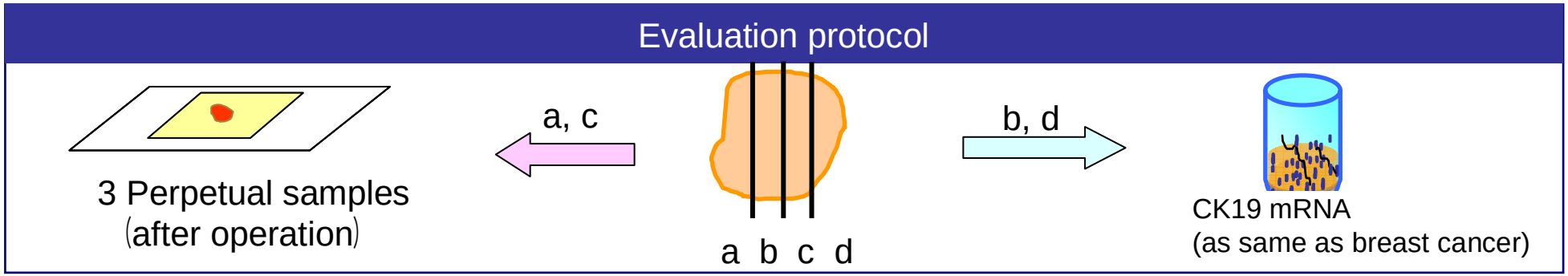




1) Progress status in launching stage

(1) Rapid diagnosis of lymph node metastasis technology (OSNA)

OSNA －Lymph node metastasis of colon cancer－



Clinical research result

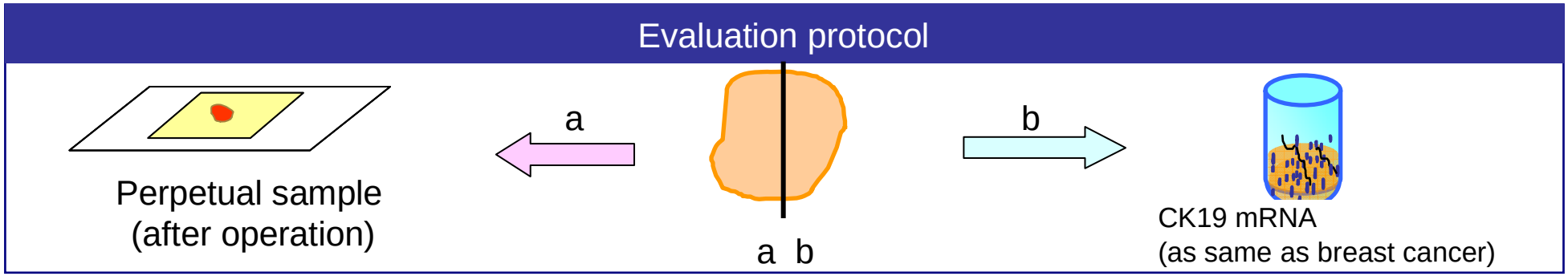
		Pathological test	
		＋	－
OSNA	＋	33	1
	－	2	92

Marker gene： CK19

Concordance rate：97.6%

The 38th Association of Cancer and Lymph node 2006

OSNA – Lymph node metastasis of stomach cancer–



Clinical research result

		Pathological test +	Pathological test –
OSNA	+	40	4
	–	5	113

Marker gene： CK19

Concordance rate：94.4%

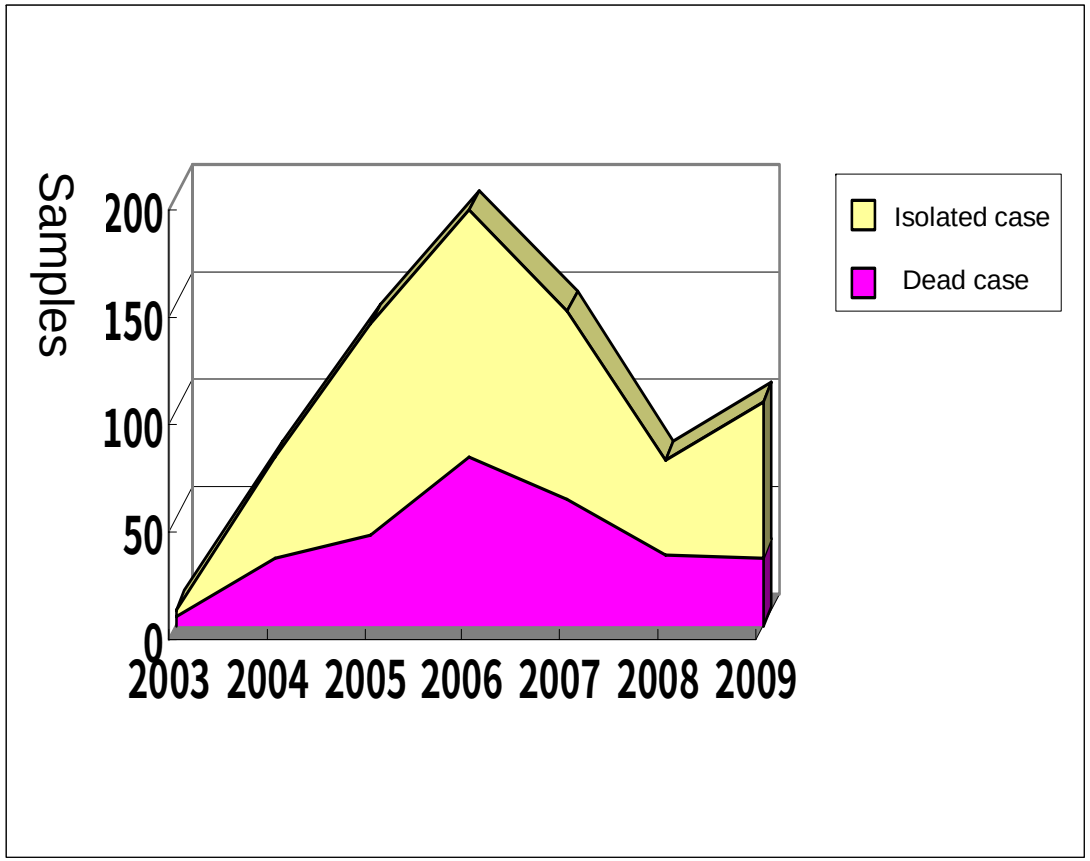
The 62nd Annual Meeting of the Japanese Society of Gastroenterological Surgery(2007)

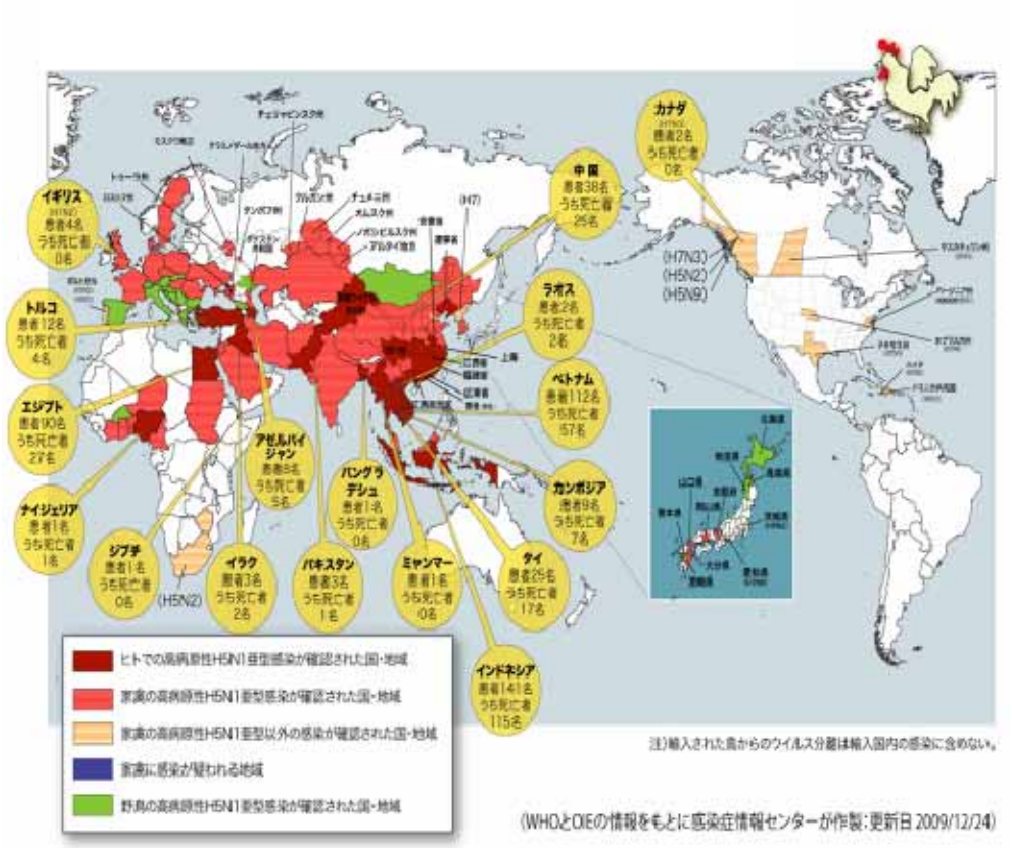
1) Progress status in launching stage

(2) Bird flu Diagnostic technology

Threat of bird (avian) influenza

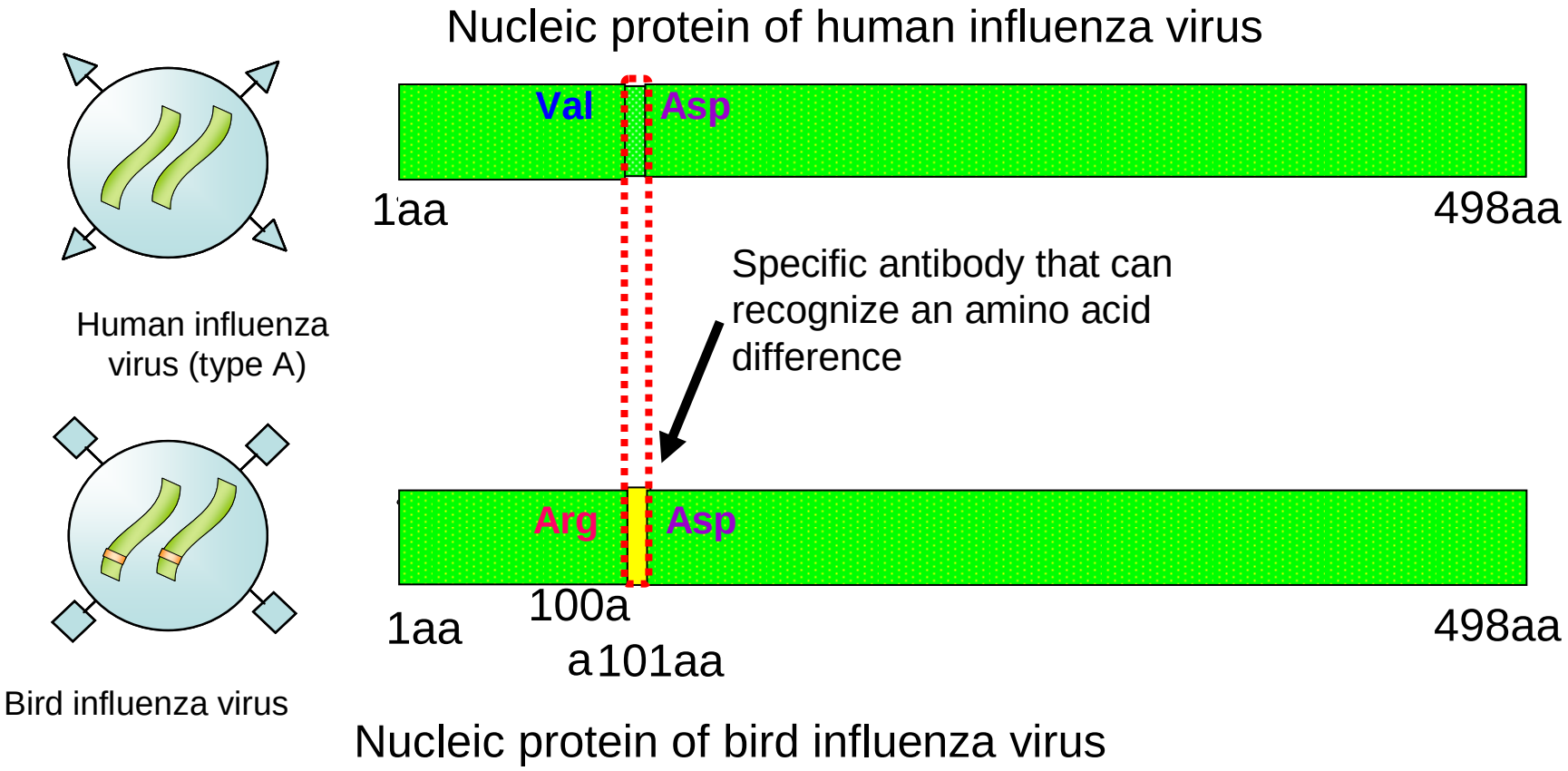
A summary of tracking avian influenza A specimens and viruses shred with WHO from 2003-2009





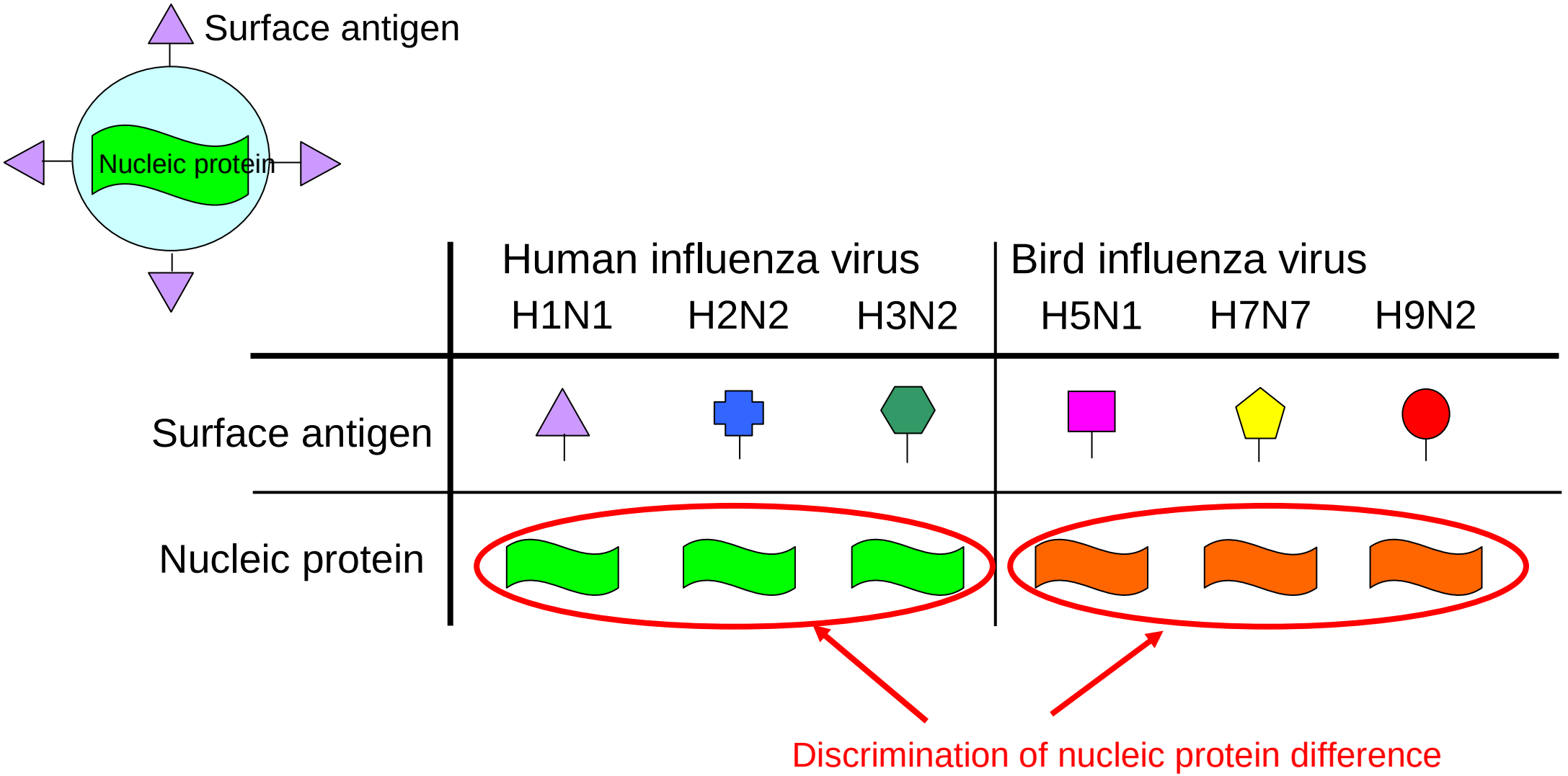
Infection risk still remains due to circulation of bird influenza virus

Key technology of detection for corresponding with bird influenza



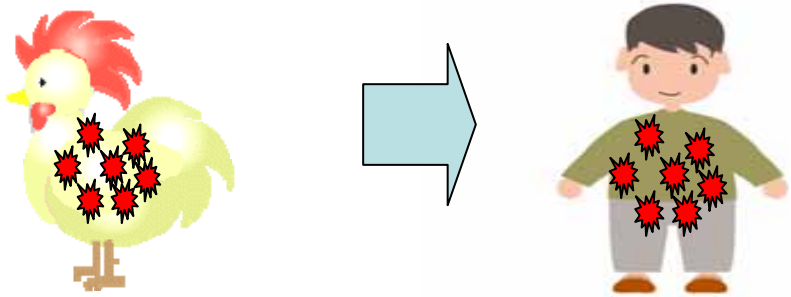
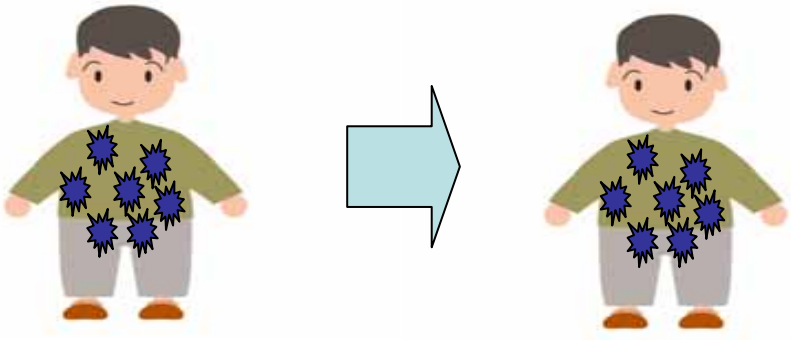
Successful development of a specific antibody that recognizes an amino acid difference in between human and bird influenza virus

Advantages of nucleic protein detection



Covering all bird influenza viruses except H5N1 by targeting nuclear protein

Features of bird influenza corresponding kit

	Bird influenza corresponding kit	Human influenza rapid diagnosis kit
Bird influenza virus 	Detection	Detection
Human influenza virus 	— Not detected	Detection

Specific detection of bird influenza and elimination of seasonal influenza/swine influenza

1)Progress status in launching stage

(3) Digital blood smear preparation technology

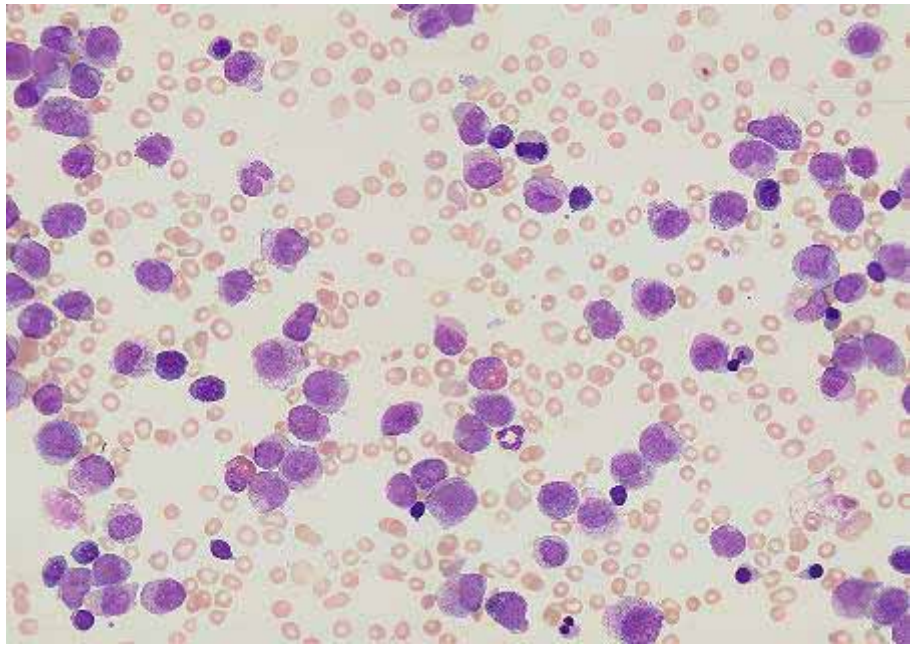
Medical needs in blood smear preparation

Utilizing part time doctor or external body is the only way to perform bone marrow diagnostic examination at the institutions having no permanent hematologist who is in shortage.

Realization of telediagnosis by digitized microscope image of blood smear

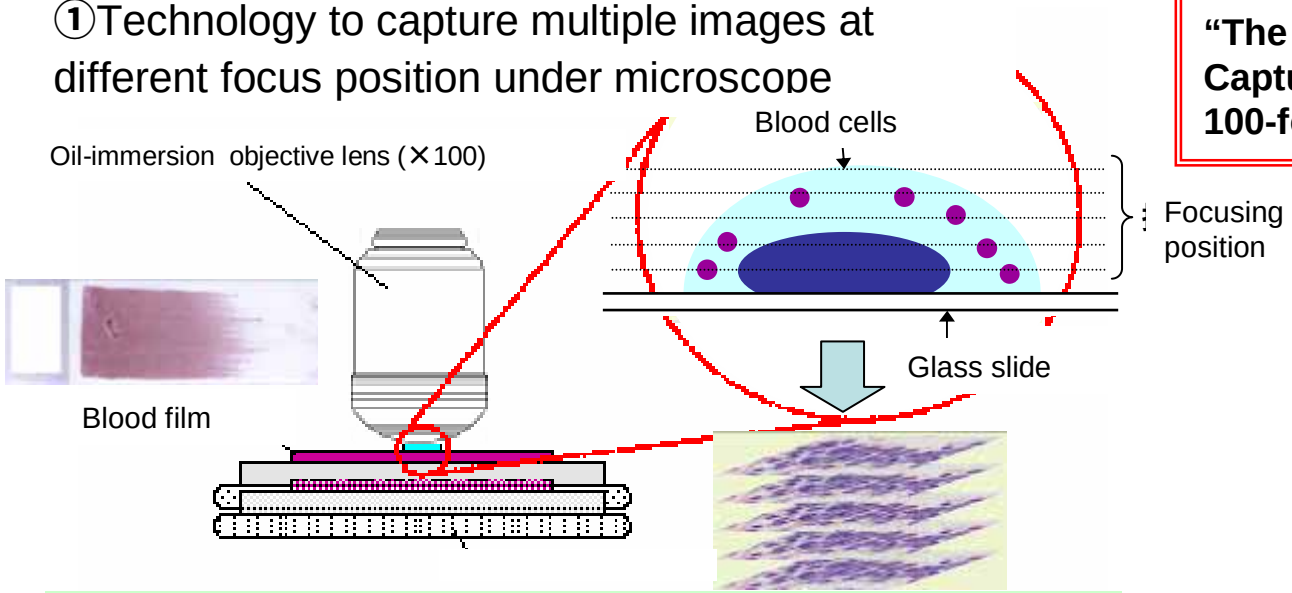
Blood film

Digital blood smear

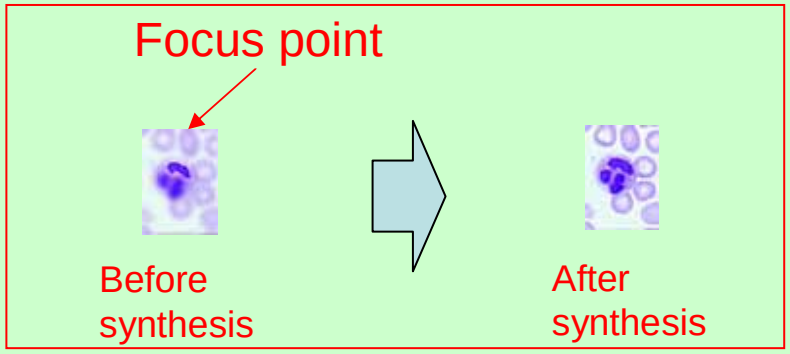


Digital blood smear preparation technology

①Technology to capture multiple images at different focus position under microscope

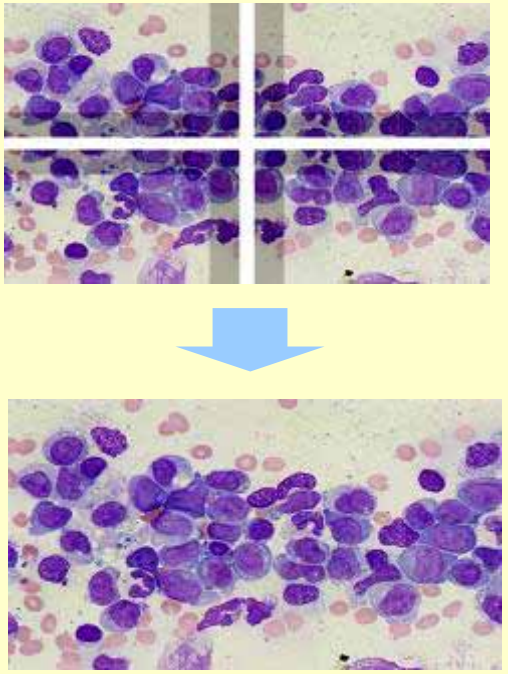


②Synthesis technology of images captured at different focus position



"The first achievement in the world"
Capture and synthesis of blood smear images with 100-fold oil-immersion objective lens.

③ Image tiling technology to synthesize images captured at neighboring area into one image



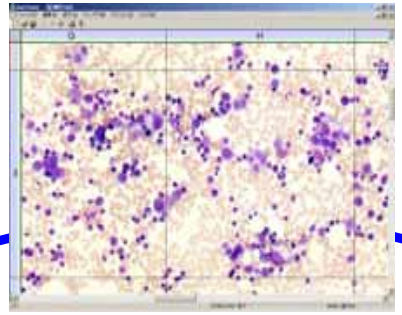
Target segment of digital blood smear

Clinical case study

Morphology standardization

Informed concent

Training



Survey

u-Japan framework

Contribution to realize digitization of medical information and advancement and integration of medical information system

e-Japan strategy II

Improvement of operational efficiency at medical institutions and medical service

Local supporting hospital

Core local hospital

[Hematologist]

Satellite lab.

Medical area having no permanent hematologist

Efficient operation of medical resource

Physicians' office

Physicians' office

Physicians' office

Physicians' office

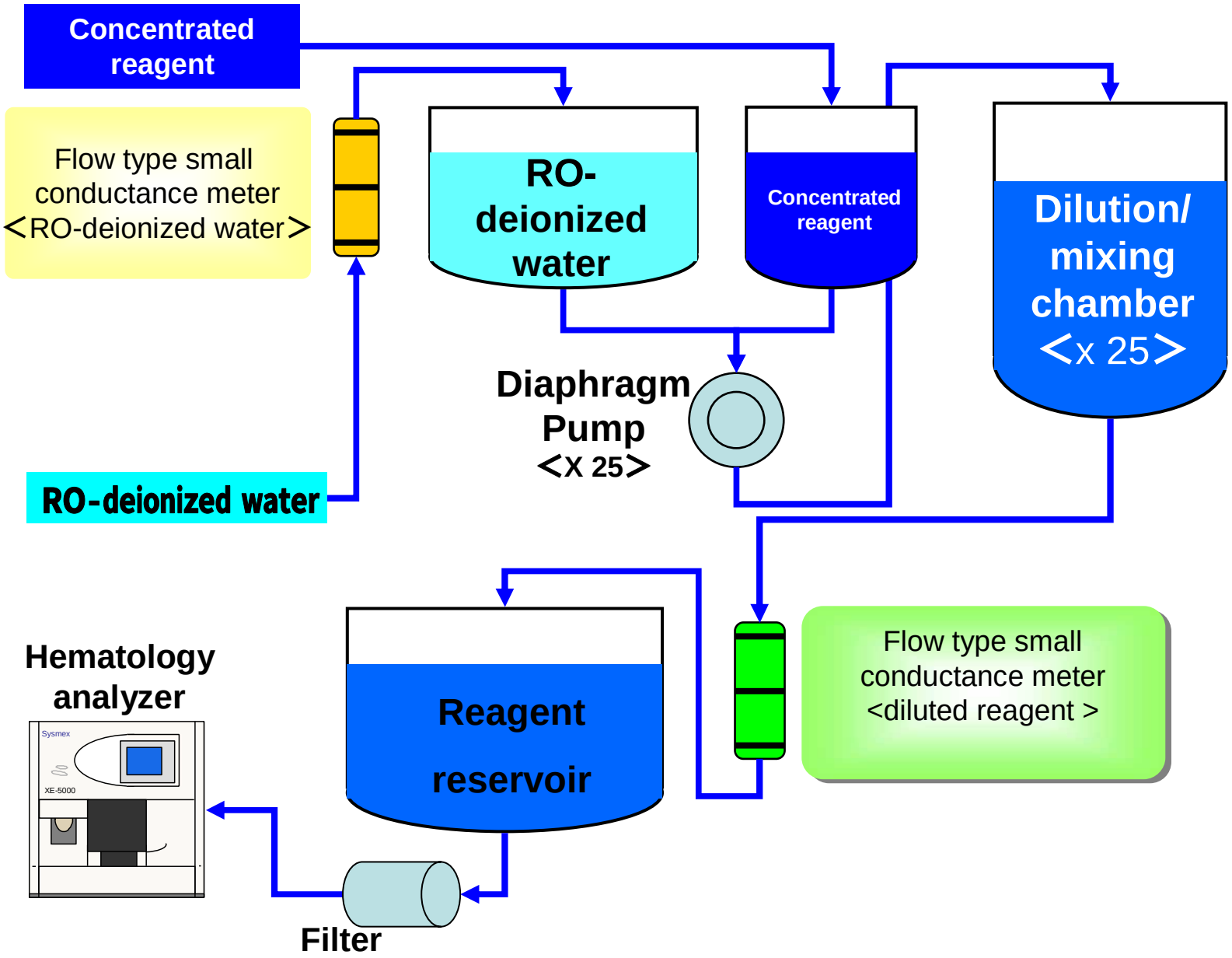
Overseas Inst.

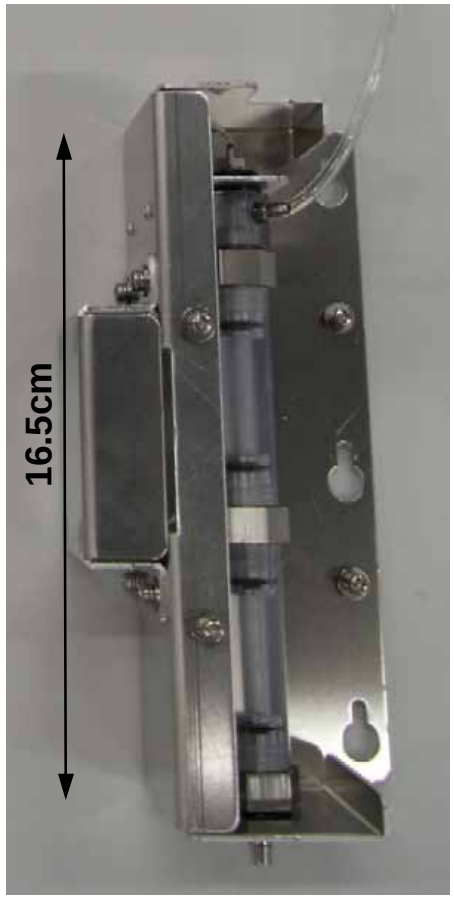
International contribution to medical care

1)Progress status in launching stage

(4) Reagents preparation technology

Reagents preparation technology
(dilution unit and accurate conductance meter)





Flow type small conductance meter <RO-deionized water>

Reagent preparation unit：RU -10

- Size : 30(W) x 30(D) x 57(H) cm, Weight : 24 kg
- Footprint : 20L reagent pack size (Space-saving)

Application system employing reagent preparation technology

RO-deionized water

Preparation device RU-10

Concentrated dilution buffer 10L

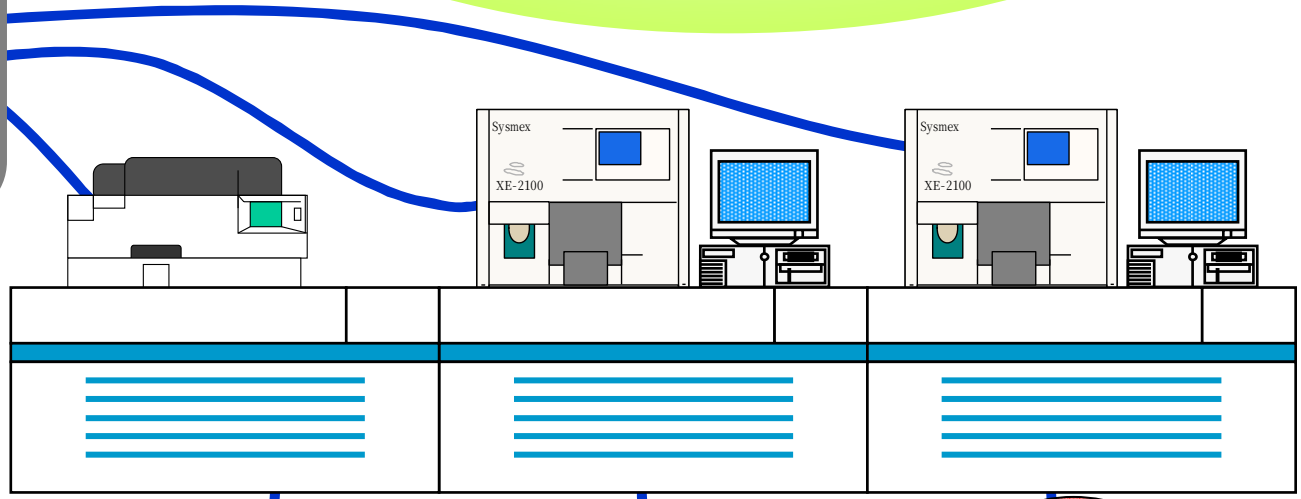
20 box/month

20L

1 box/month

10Lconcentrated dilution buffer

10L



20L

20L

20L

- low-frequency event of reagent exchange
- Reduction of trash/CO_2
- Easy-to-use by small package

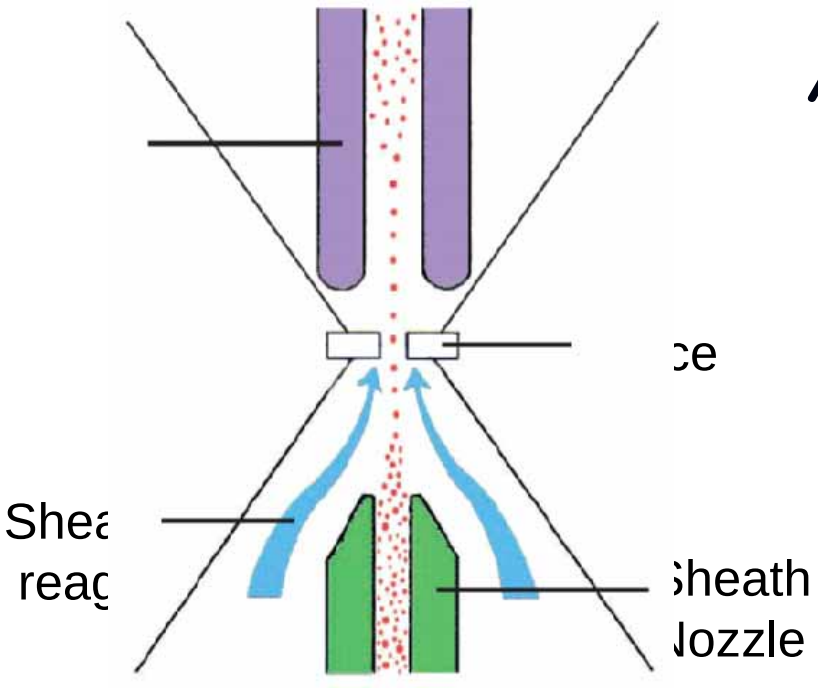
2) Practical stage

(5) Blood testing technology

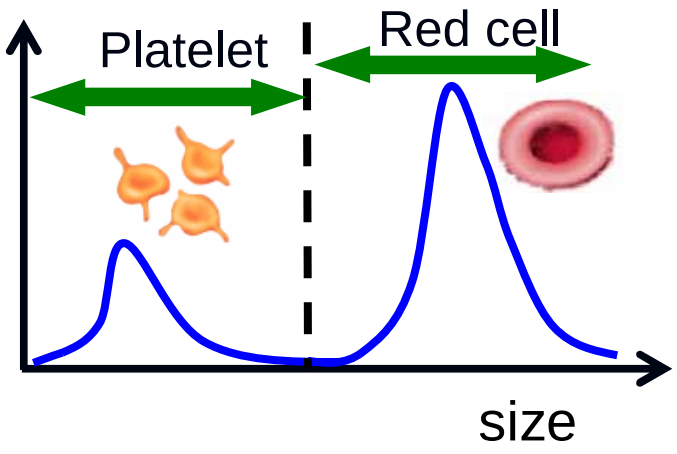
- Accurate detection technology of low platelet counting
- Efficacy management technology for wide-range Lab test settings

Conventional technology for platelet counting

Aperture impedance method with hydrodynamic focusing



<Normal>



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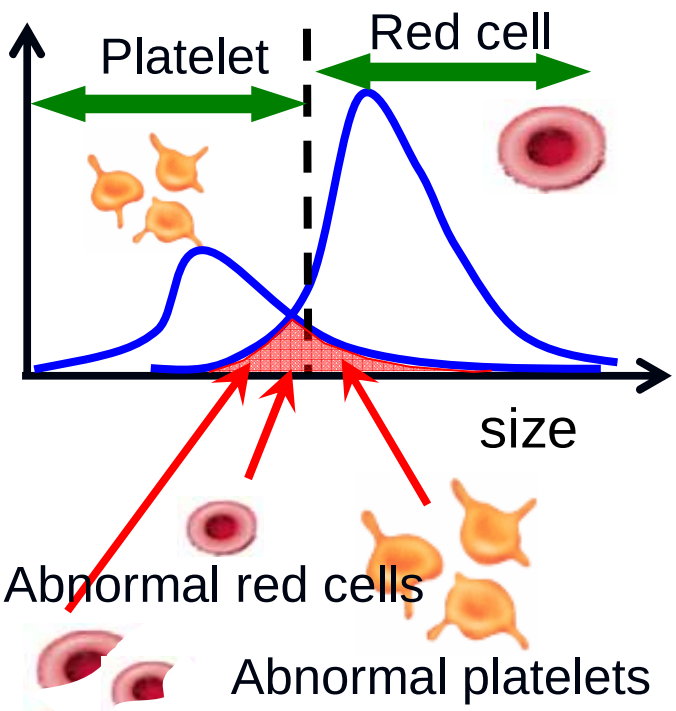
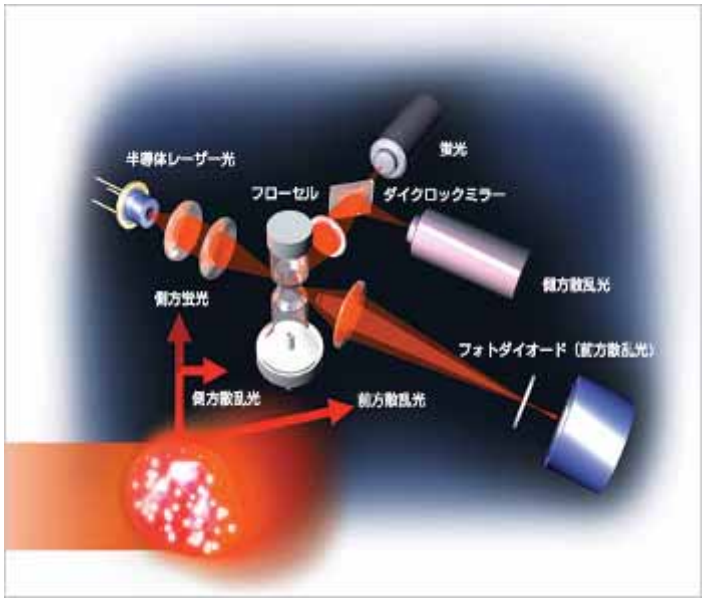


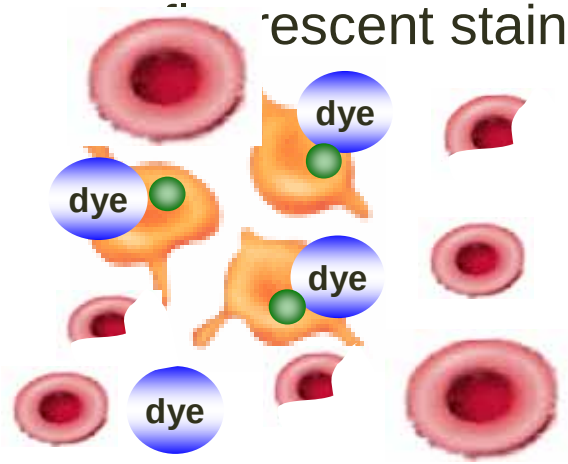
Difficult to count platelet accurately for patient who has a particular disease

New platelet counting technology

Flowcytometry

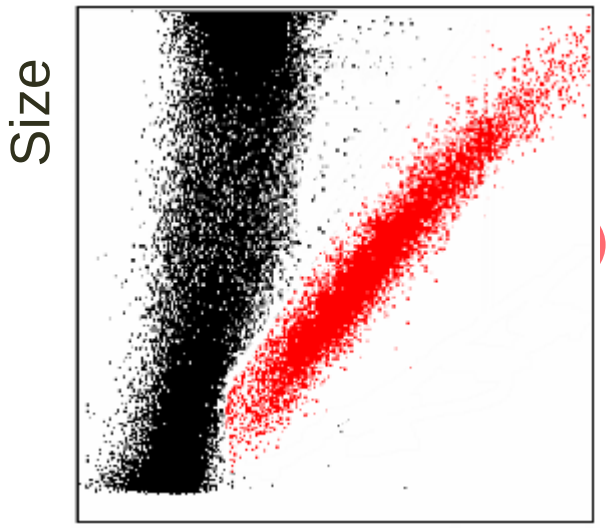


Platelet specific fluorescent staining



Realization of staining specificity that is equivalent to MAb

Result



Enhanced accuracy in abnormal cell detection

Successful development of accurate platelet counting technology by using specific fluorescent staining on Flowcytometry

Clinical value of low platelet counting

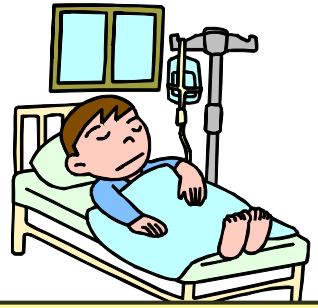
Diagnosis

Test

Necessity of Platelet transfusion and determination of dosage

Platelet≦20,000/μL

Platelet＞20,000/μL



Transfusion

No-Transfusion

Reducing blood transfusion risk
Side effects, Infection, Medical cost

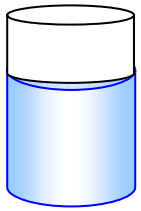
Optimization of platelet transfusion
Contribution to QOL (side effect, prevention of infection)
Contribution to improvement of medical economy

2) Practical stage

(6) Cervical cancer screening technology

Cervical cancer screening system

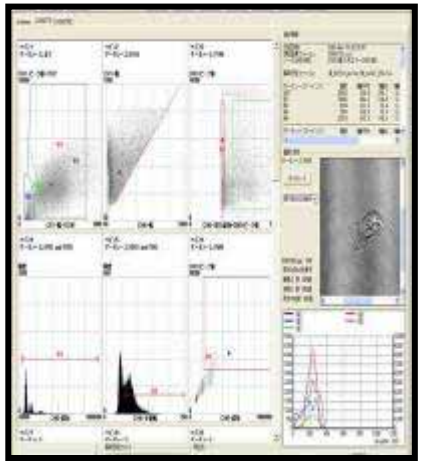
Preservative solution



Pretreatment device

Measurement device (FCM)

Analysis unit



Liquid cytology sample

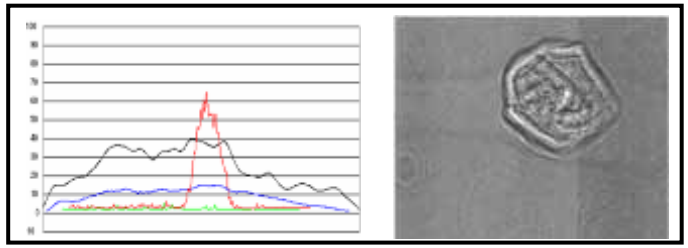
Cell dispersion

Epithelial cell collecting

DNA staining

FCM

Analysis/Result



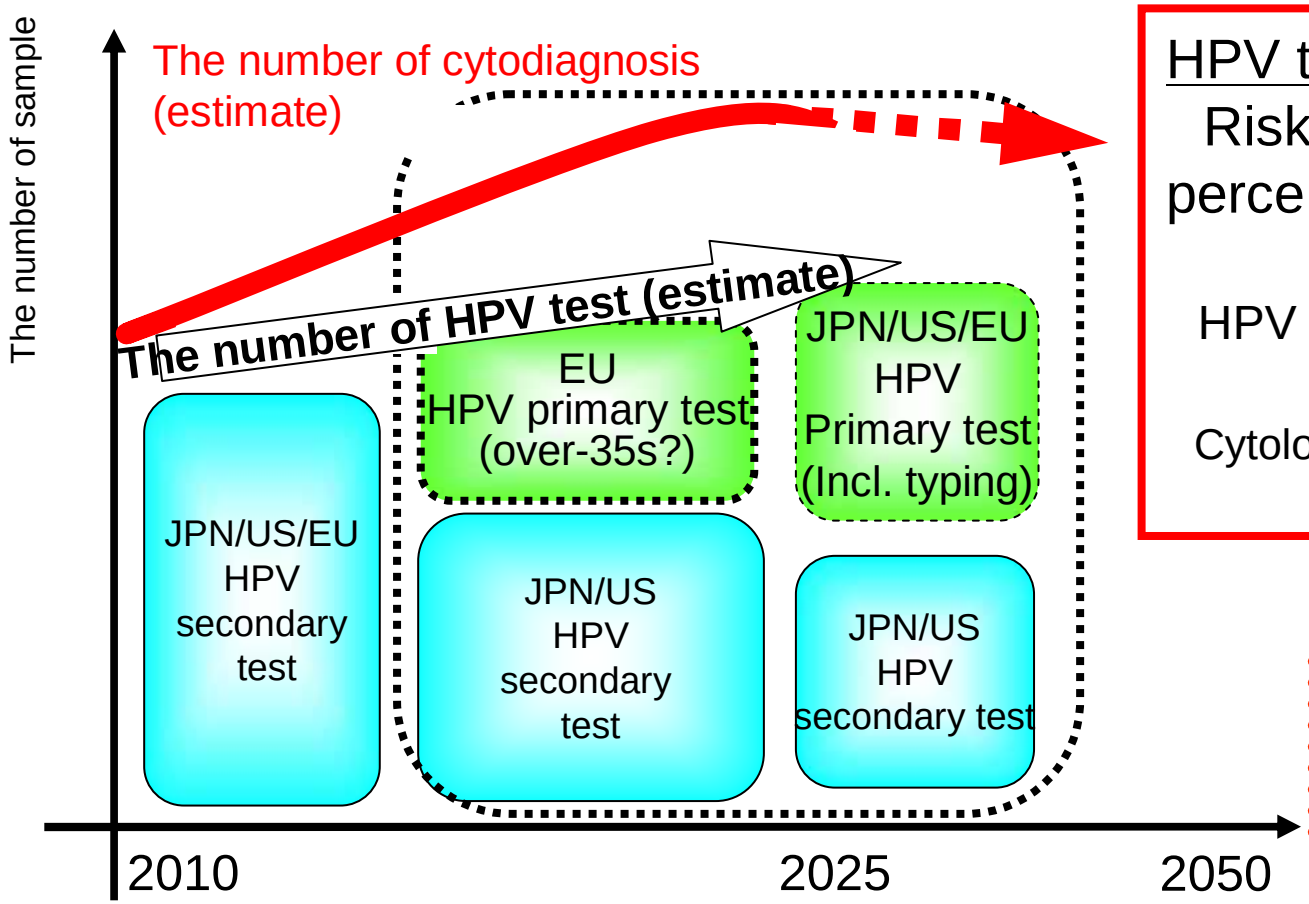
- ✓ **Under development of fully-automated high-speed system**
- ✓ **Under consideration of stability improvement with sample preservative solution**

Future of HPV test (estimate)

✓**Cytology screening would increase by introducing automation technology in not only advanced countries but also rising countries.**

✓**HPV test would gradually increase, especially in advanced country.**

✓**The number of cytology screening will be influenced by introducing preventive vaccine after 2020.**



HPV test

Risk of cancer is a small percentage of infected patient.

HPV test : Risk test

Cytology screening : Test for presence of "cancer"

Complementary test

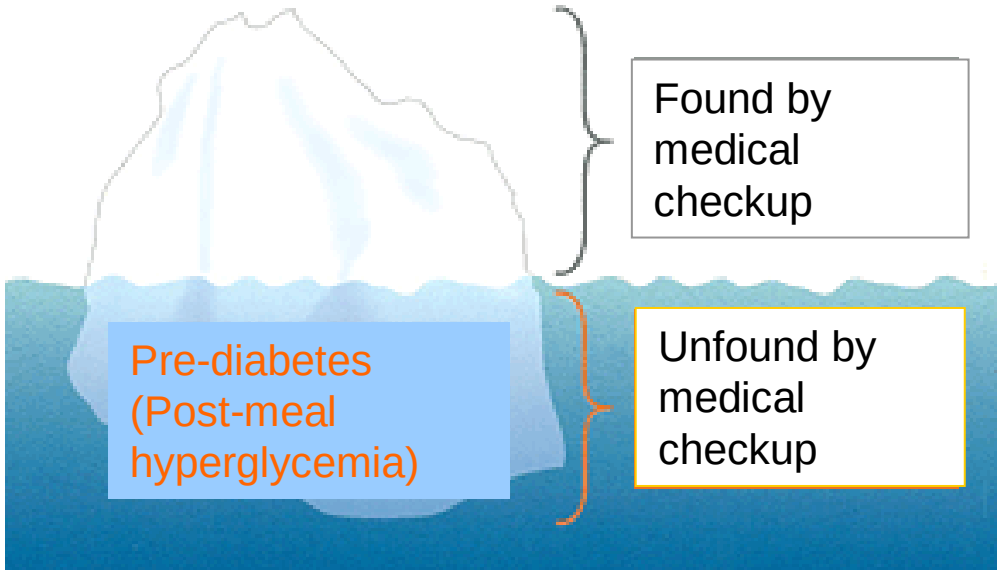
Under discussion to cover HPV testing

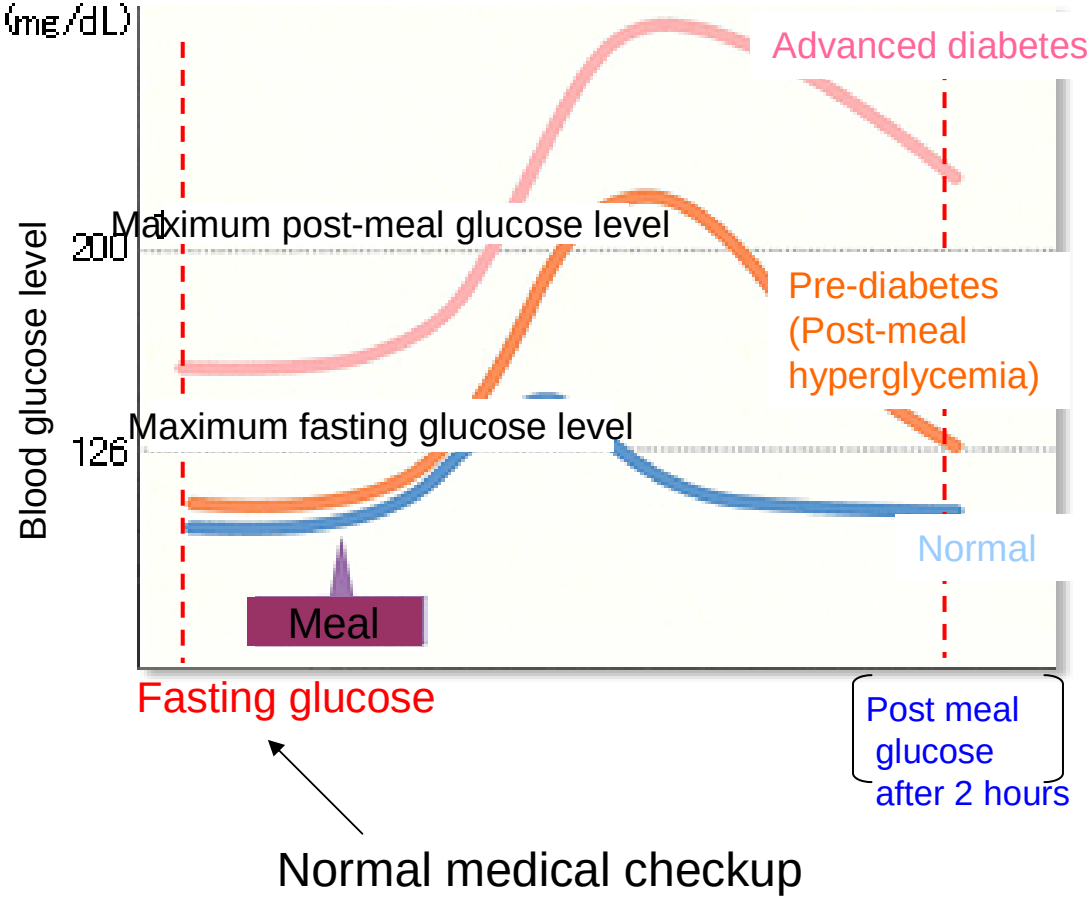
Estimate of cytodiagnosis for cervical cancer and HPV test in advanced country

2) Practical stage

(7) Postprandial hyperglycemia monitoring technology

What is post-meal hyperglycemia?



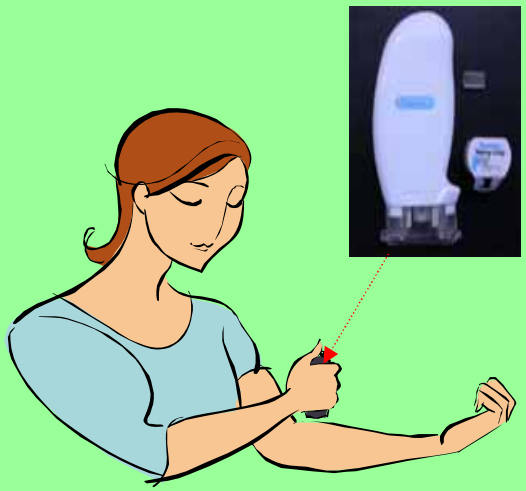


Post-meal hyperglycemia : risk factor of large vessel disease (cerebral accident, myocardial infarction)

Development of device which is able to simply and exactly monitor post-meal hyperglycemia

Body fluid extraction technology

Pore making



Painless!

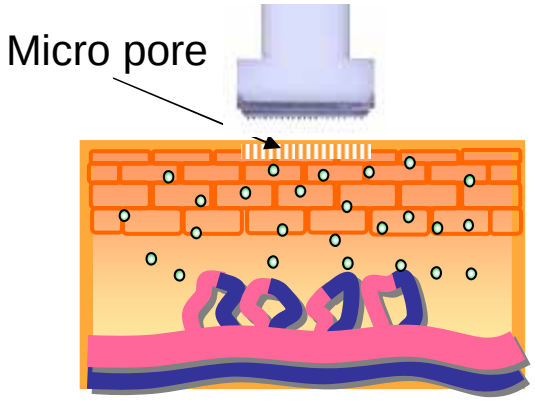
Body fluid extraction

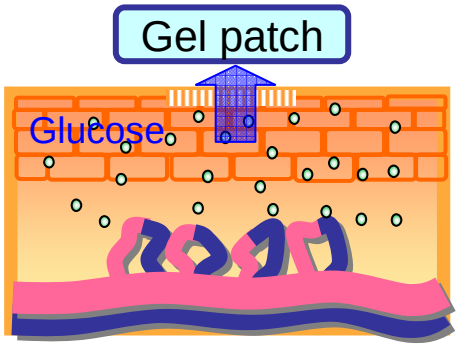
Stick gel patch
(for 2hours)

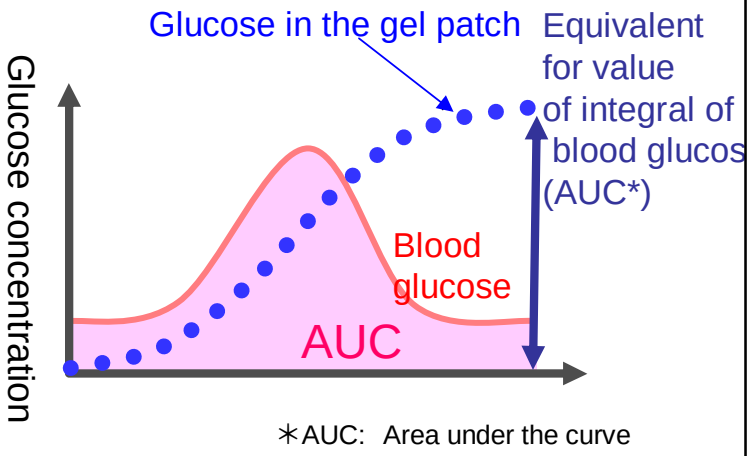
Nonrestrain!

Glucose measurement

Measurement of glucose in the gel patch





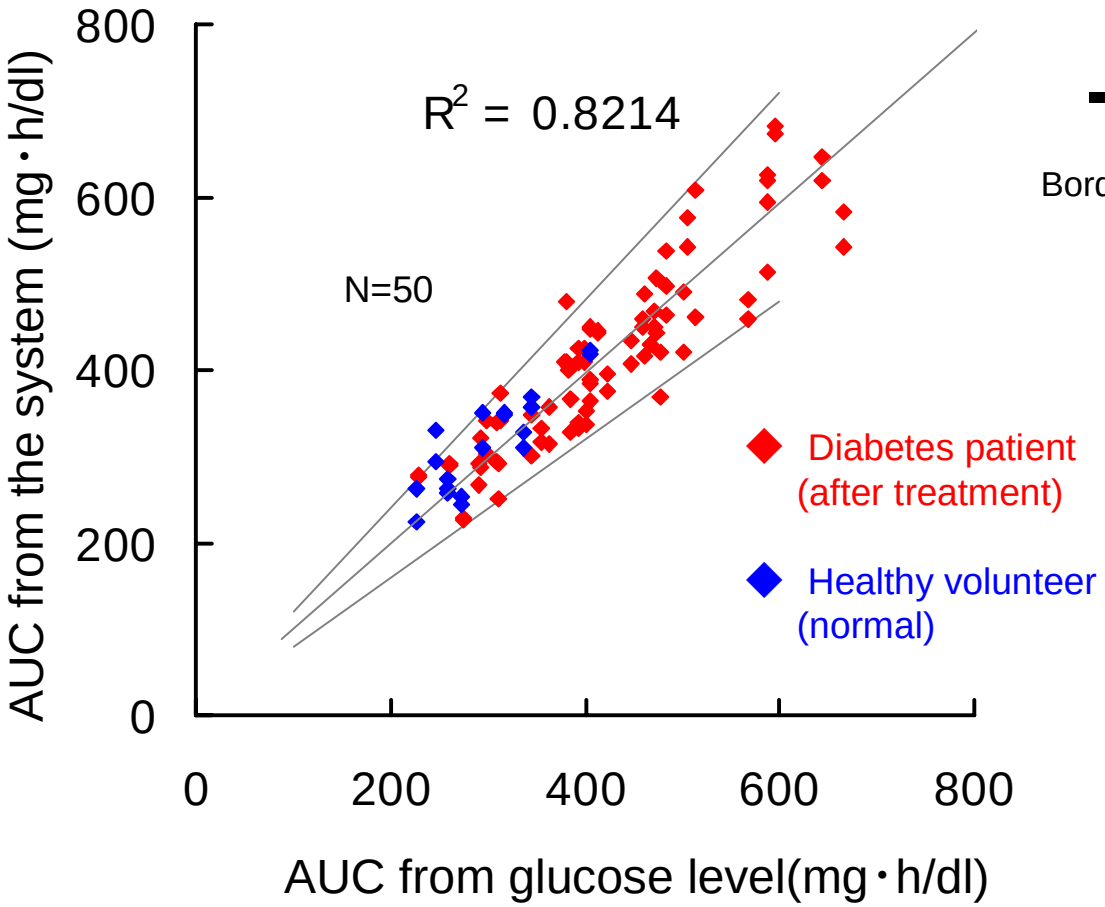


∗AUC: Area under the curve

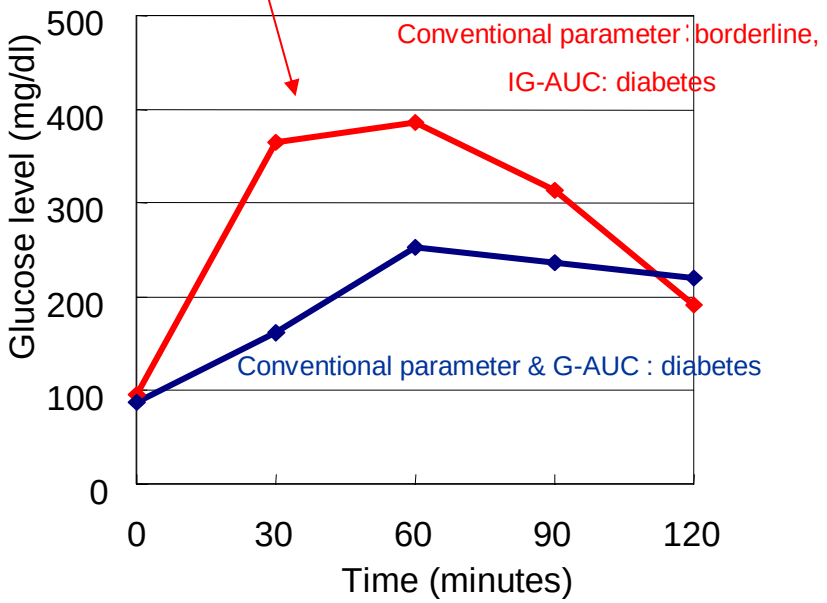
Promoting commercial realization

Clinical evaluation result

＜Screening of pre-diabetes status＞



IG-AUC / Glucose	Diabetes (>320mg/dl・h)	Borderline	Normal (<275 mg/dl・h)
Diabetes	31	1	0
Borderline diabetes	7	2	1
Normal	0	3	5

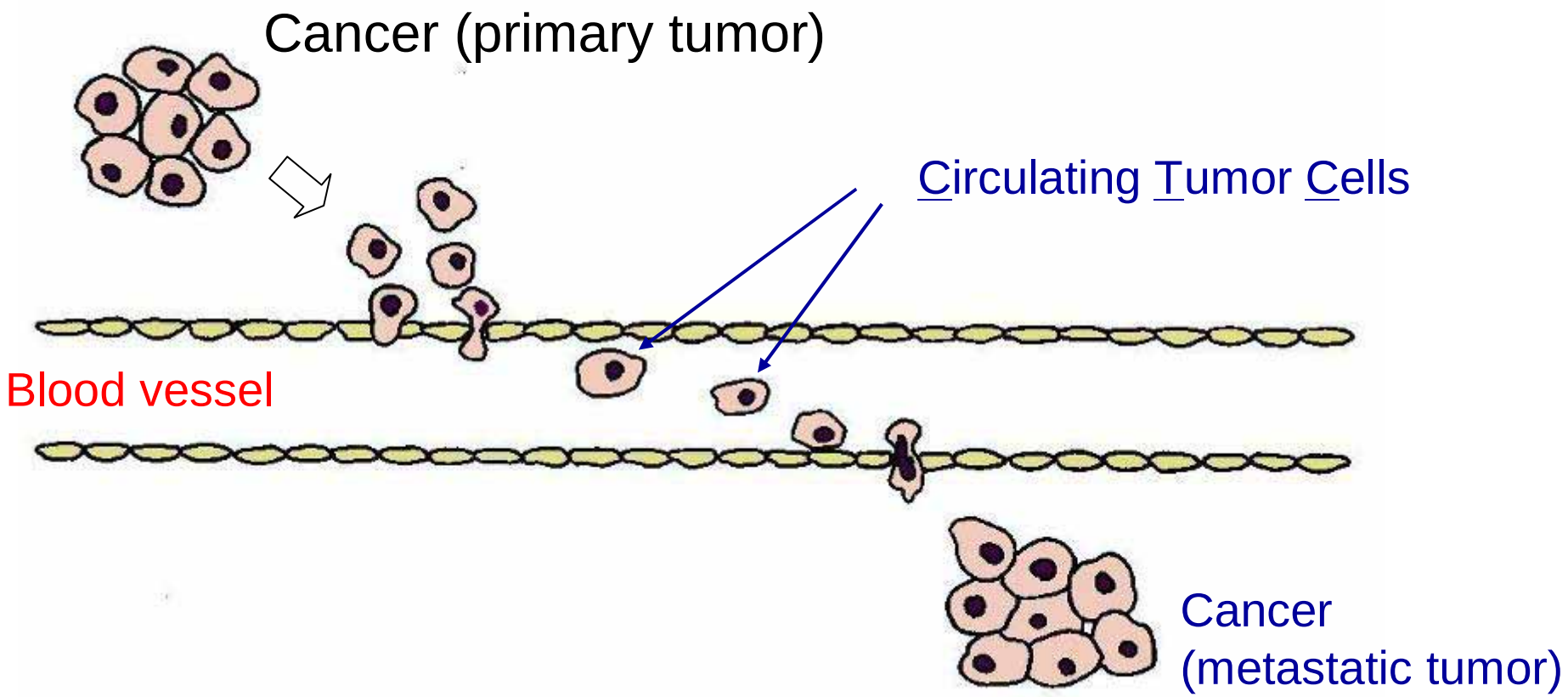


The Japan Diabetes Society(2009)

3)Research stage

(8) CTC (Circulating Tumor Cell) detection technology

What is CTC?

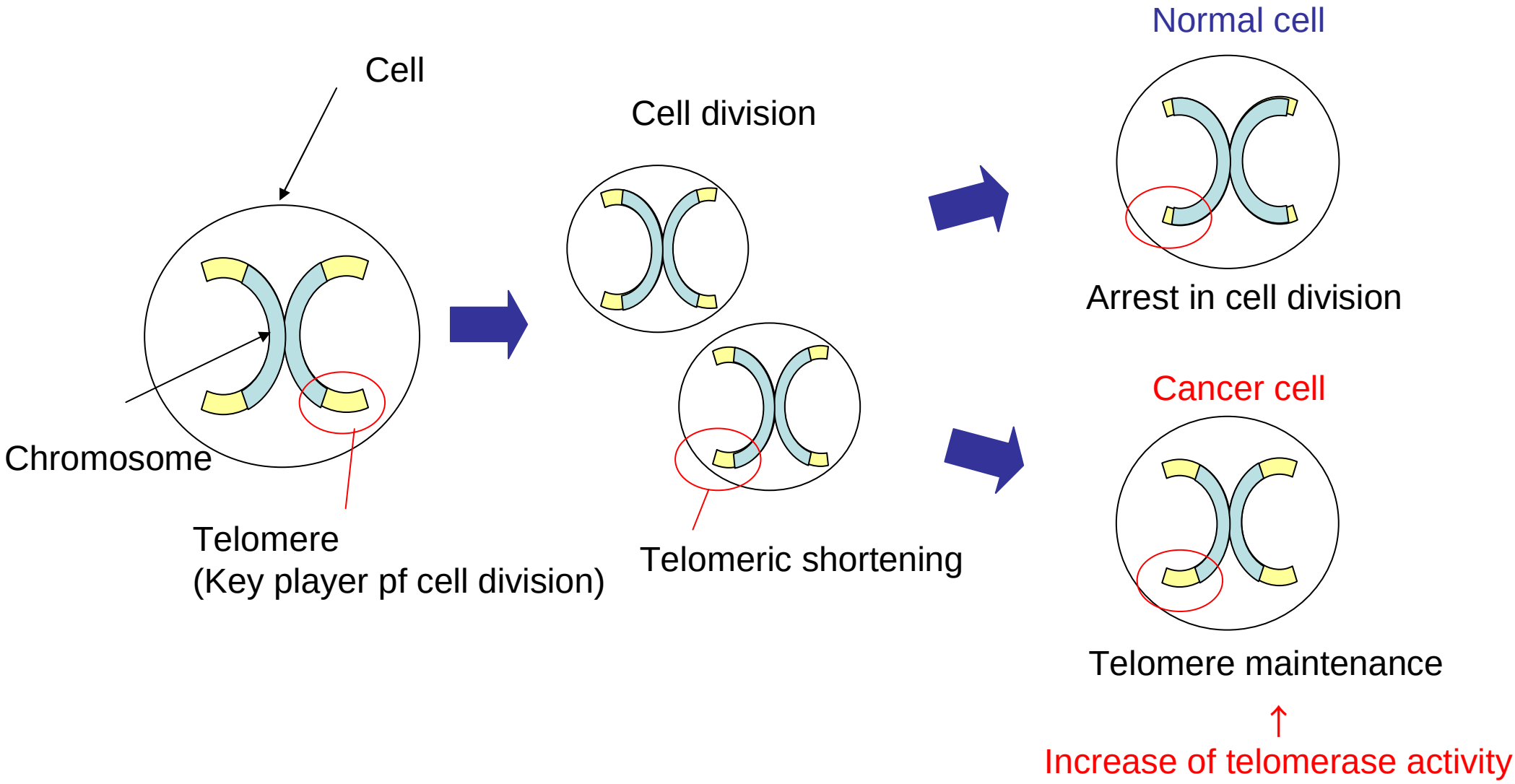


Cancer cells from a few to hundreds of thousands in 10ml blood

(40 - 50 billion RBC and 30 - 90 million WBC in 10ml blood)

Requirement of ultra-high sensitive measurement

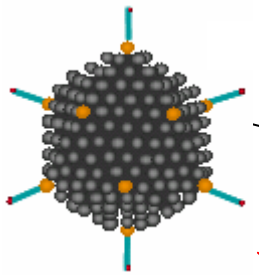
Diagnostics by using virus (1)



Telomerase activity is observed in almost cancer.

Diagnostics by using virus (2)

Virus



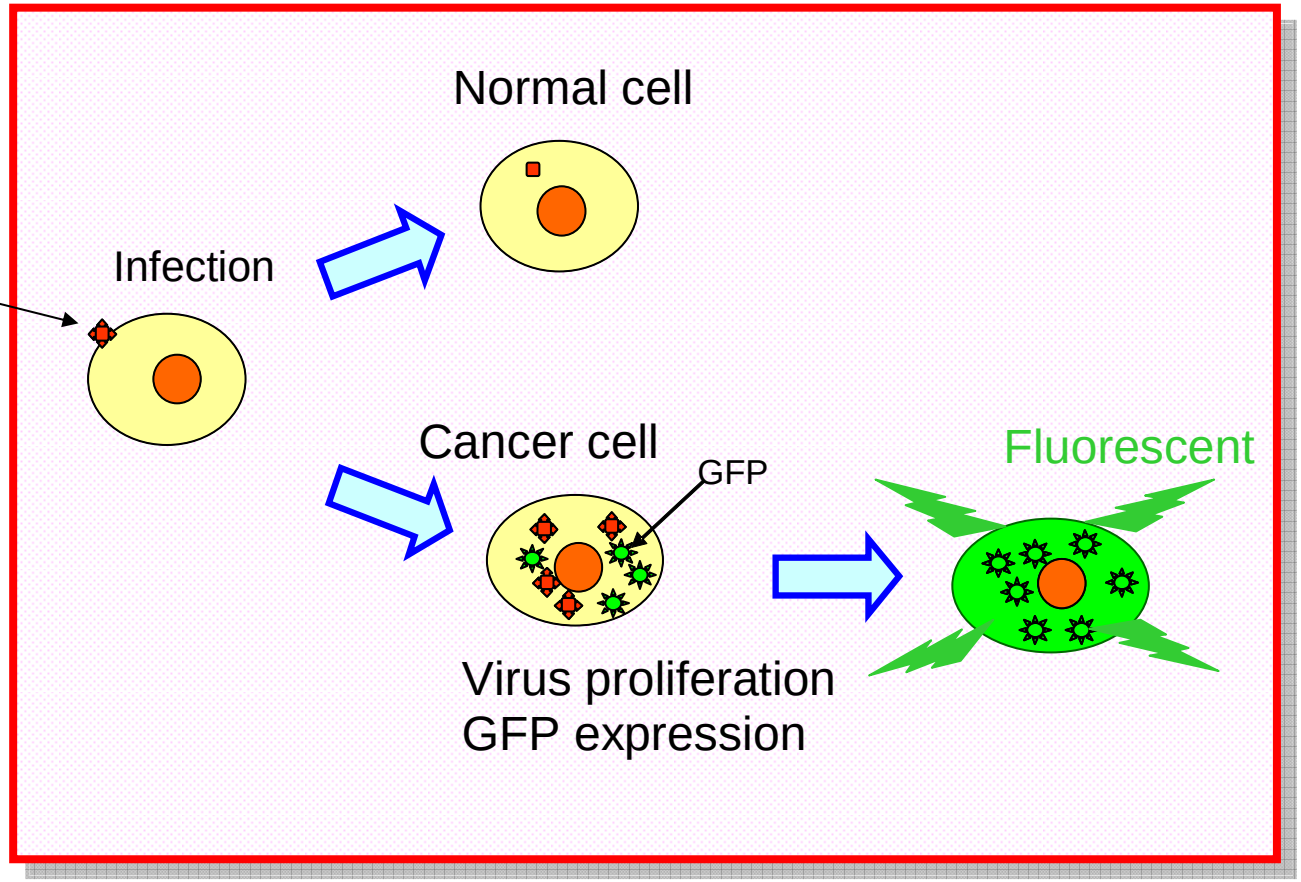
OBP-401-(TelomeScan®
Oncolys BioPhama Inc.)

Genetic modification

hTERT promoter **GFP**

Adenovirus genome

Replication
In activated telomerase cell

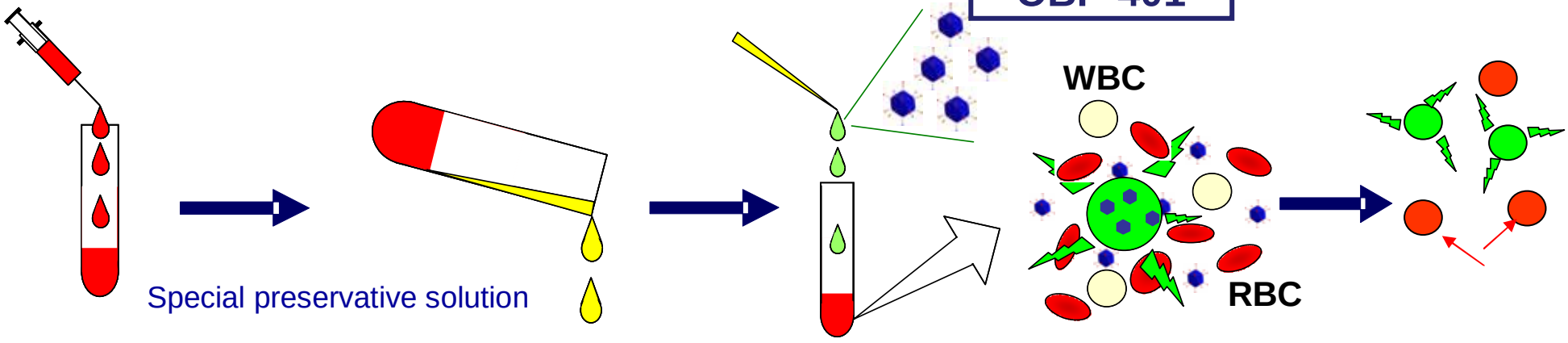


Detection of proliferative and live cancer cell

*GFP：green fluorescent protein from Aequorea victoria

Diagnostics by using virus (3): Establisment measurement system

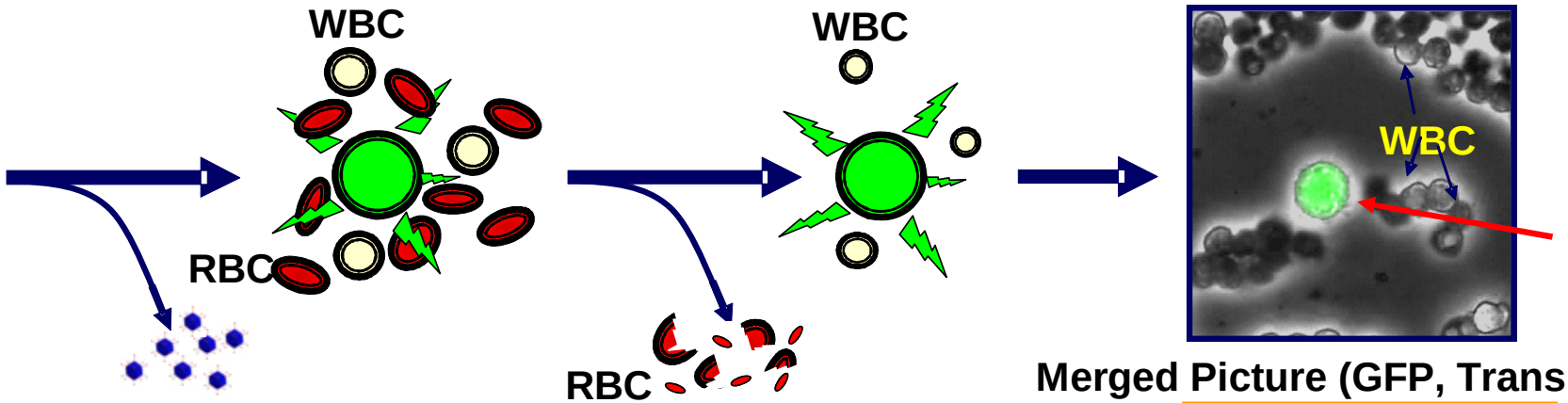
OBP-401



(1) Blood drawing

(2) Serum removal

(3) Virus infection



(5) Incubation (24h)

(6) RBC removal

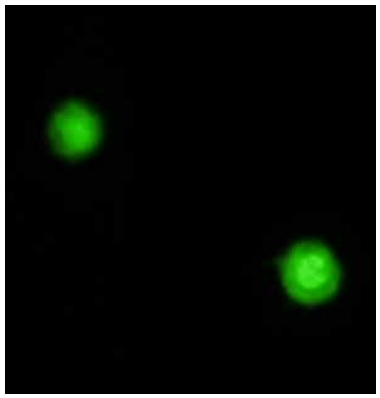
Merged Picture (GFP, Transmission)

(7) CTC detection (microscope)

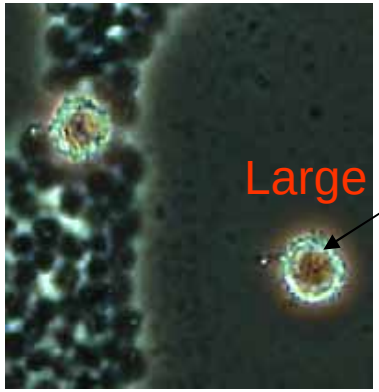
Combination of venture's and Sysmex technology

Evaluation study using clinical sample

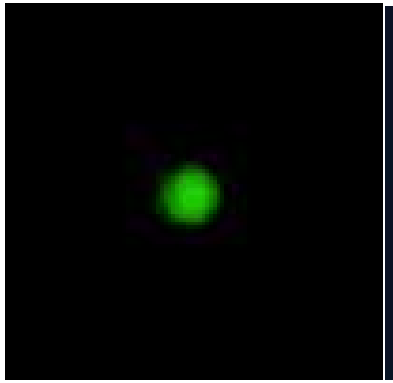
Breast cancer recurrent patient　GFP positive cell



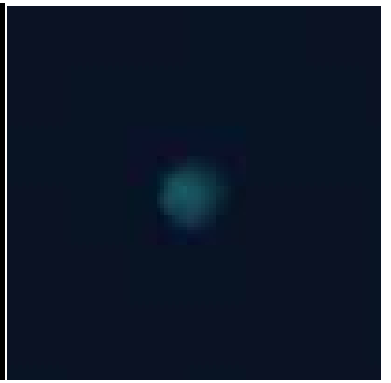
Fluorescent image



Phase contrast image



Fluorescent image



Immunostaining image
(CA 15-3)

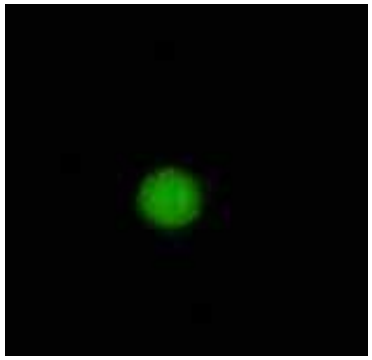
CA15-3：breast cancer marker

Capturing cancer cell

Lung cancer patient　GFP positive cell

Fluorescent image

Stomach cancer patient　GFP positive cell

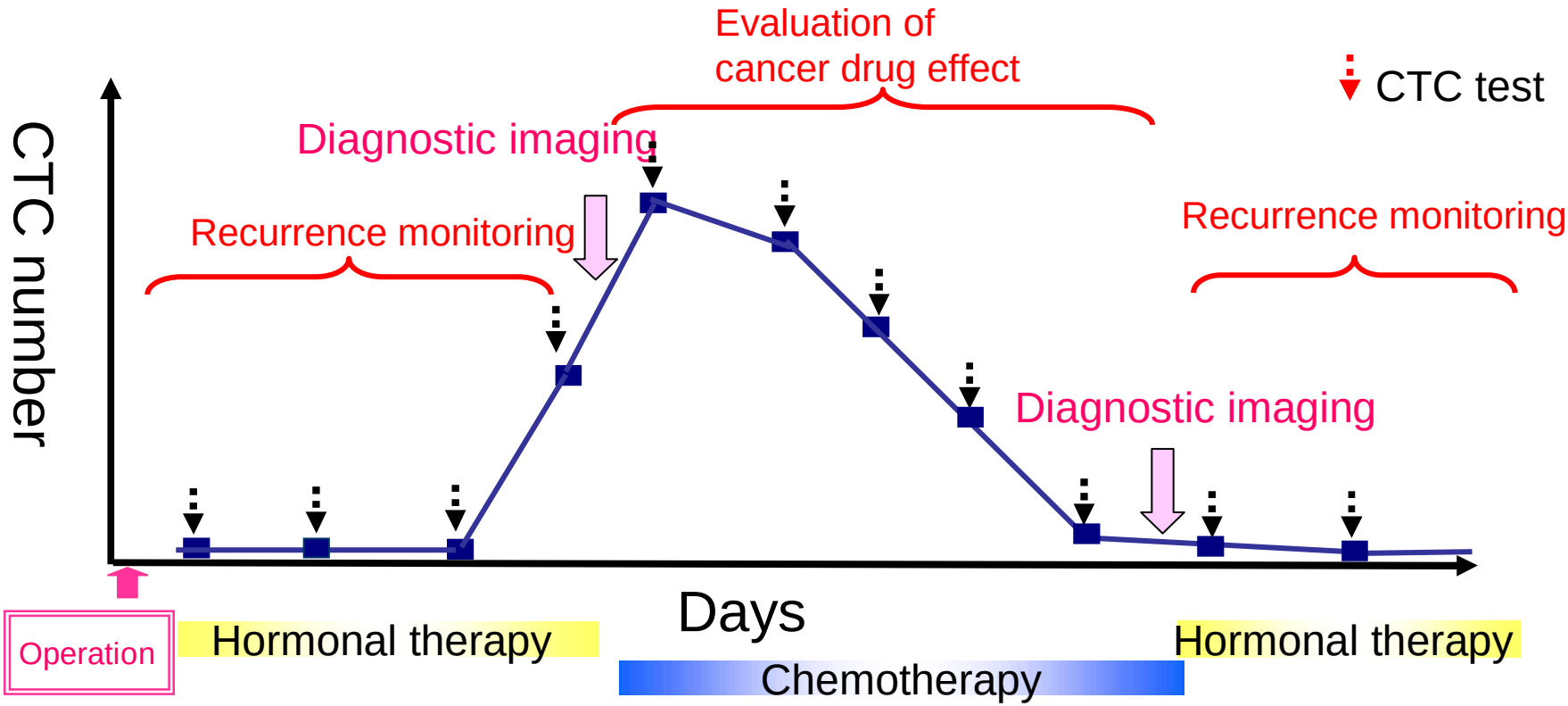


Fluorescent image

Clinical value

- Risk prediction
- Early detection
- Prognosis (recurrence prognosis)
- Evaluation of cancer drug effect
- Monitoring

Possibility of various application



Promotion of clinical research

All cancer other than lung & breast cancer

National cancer center hospital

Lung cancer

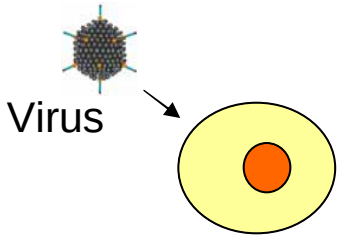
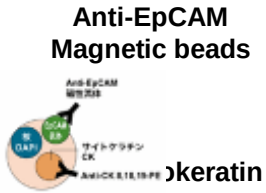
Kitazato university

Breast cancer

Osaka university

Other research institution

Comparison with competitor's technology

	Sysmex	Veridex(J&J) CellSeach®
Principle	 Telomerase activity	 Antibody stain
Characteristics	●Detection and count of live cell that is key factor of metastasis.	●Detection* and count of cancer cell from image of nuclear stain and immunostaining * Subjective judgment
Notes	●Suitable for several type of cancer	●FDA approval (metastatic breast cancer, colon cancer, prostate cancer)

3) Research stage

(9) Technology of CNS disease diagnosis based on DNA chip

What is DNA chip?

Affymetrix GeneChip®

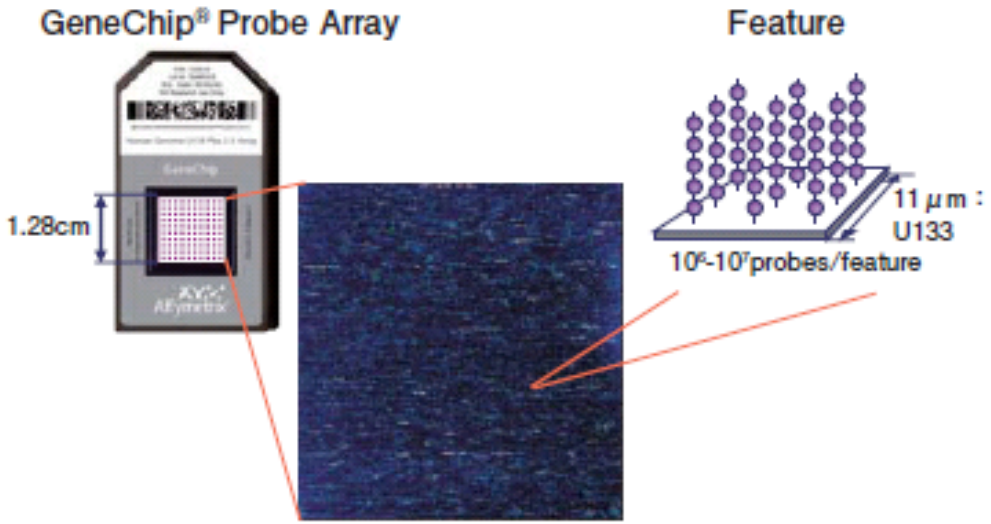
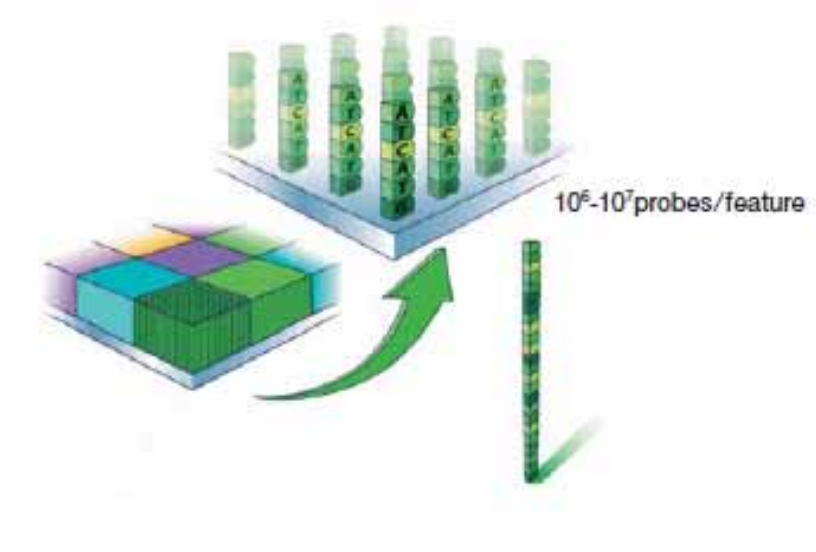


Image of fluorescence signal



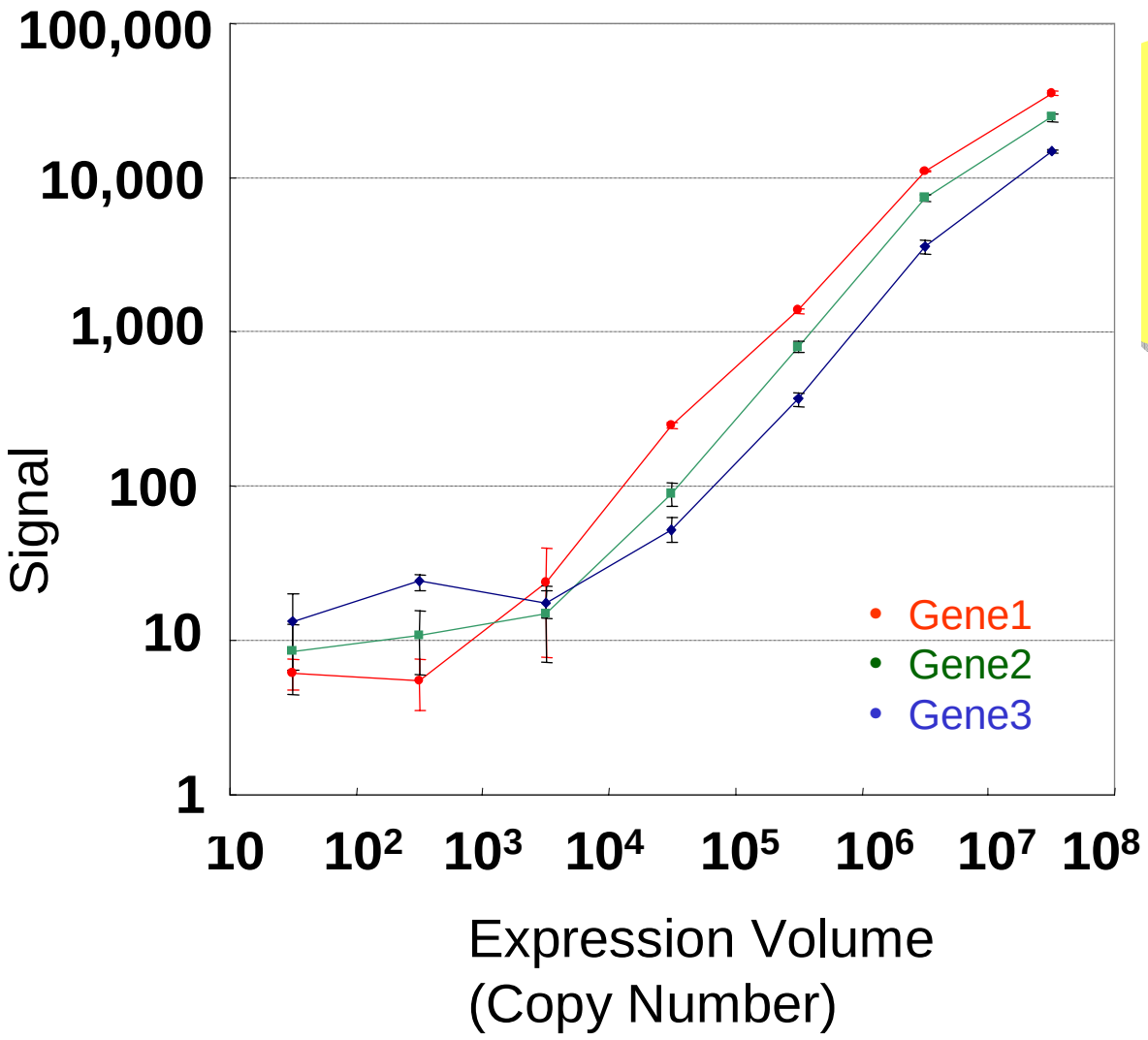
Constitution of 1.3 million features ＊

Different probes in each compartment

Possible to a comprehensive analysis of gene

＊：in case of U133 plus2.0

Performance of DNA chip (expression analysis)



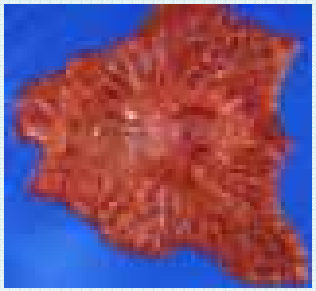
Dynamic range : 6.0×10^3 ～ 1.2×10^6 copy/μL
Sensitivity : 600 copy/ μL
Reproducibility : CV < 15%

Performance of QRT-PCR

Adequate performance for multi-parameter measurement PF

Issue of DNA chip for diagnosis

Conventional analysis method

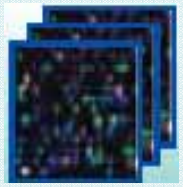


Cancer tissue

Disease state 1

Example：recurrence

Disease state 2



Example： non recurrence

Signature

Gene set (different expression level)

$(g_1、\ g_2 \cdot \cdot \cdot \cdot \cdot g_n)$

Algorithm

$= a_1 \cdot g_1 + a_2 \cdot g_2 + \cdots\cdots\cdots\cdots + a_n \cdot g_n$

Issue

Easily obtainable desired out come with several terms of thousands of parameters (Over-training)

↓

Different results in each test

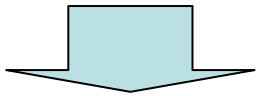
Condition of clinical DNA chip as diagnostic tool

- **Essential** requirements

  To obtain stable clinical result by any laboratories

- Sufficient requirements

  To obtain adequate and clinical performance



- ✓ Sample preparation method
- ✓ Quality assurance method
- ✓ Analysis method

Development of original DNA chip technology

Technology acquisition strategy of clinical DNA chip

Diagnosis by DNA chip

Cancer

Primary tumor

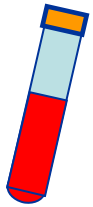
Disease analysis (directly)

Approaches
by companies or
research institutes

Technology introduction+

Sysmex technology

Chronic disease



Blood

Disease analysis (indirectly)

Few approach
in the world

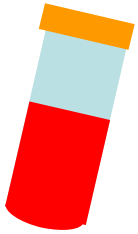
Development of DNA chip

in Sysmex

Development of clinical DNA chip for chronic diseases

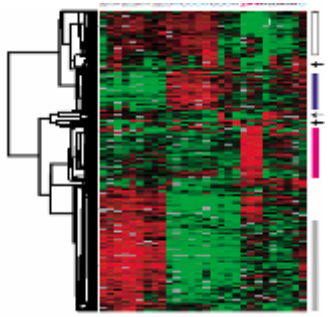
Chronic disease：

How to elucidate disease condition from blood?



Blood

U133 human genome expression



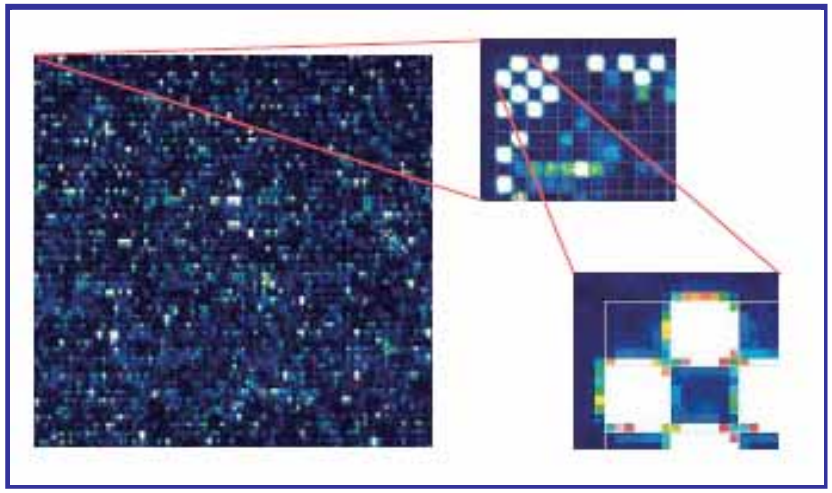
Establishment
of diagnostic method

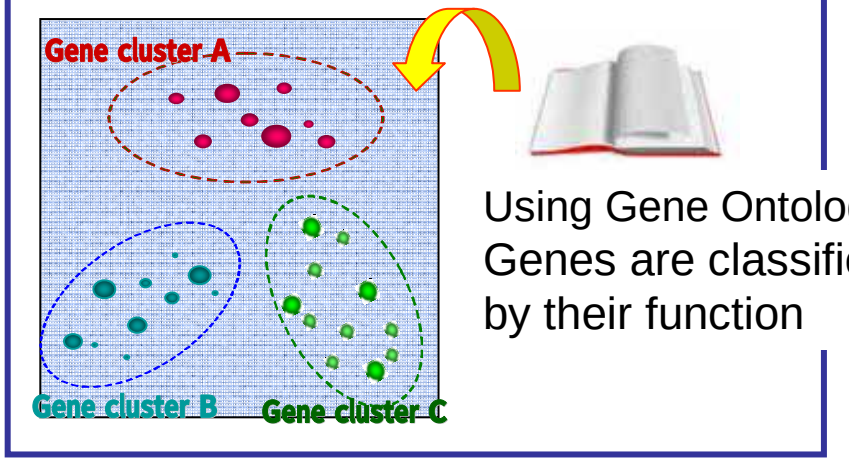
Target：

- ✓ Systemic diseases
- ✓ No effective biochemical marker available

} Central nervous system

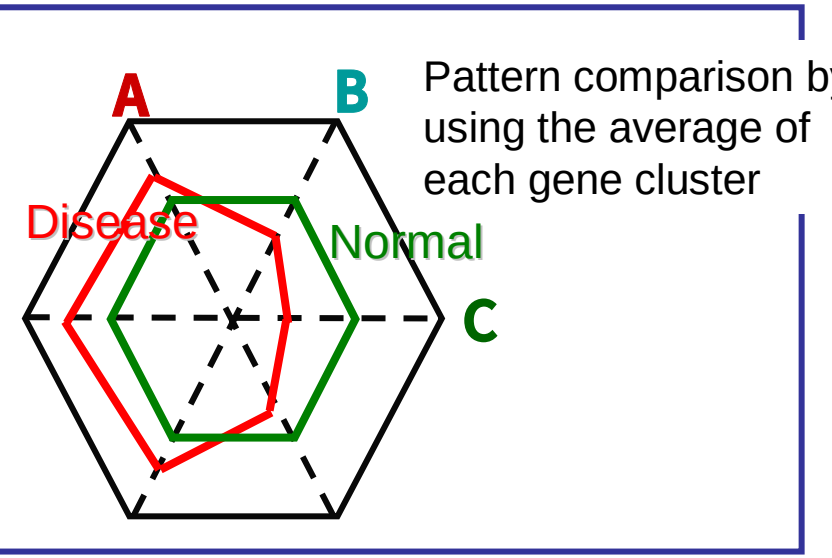
Original analysis technology





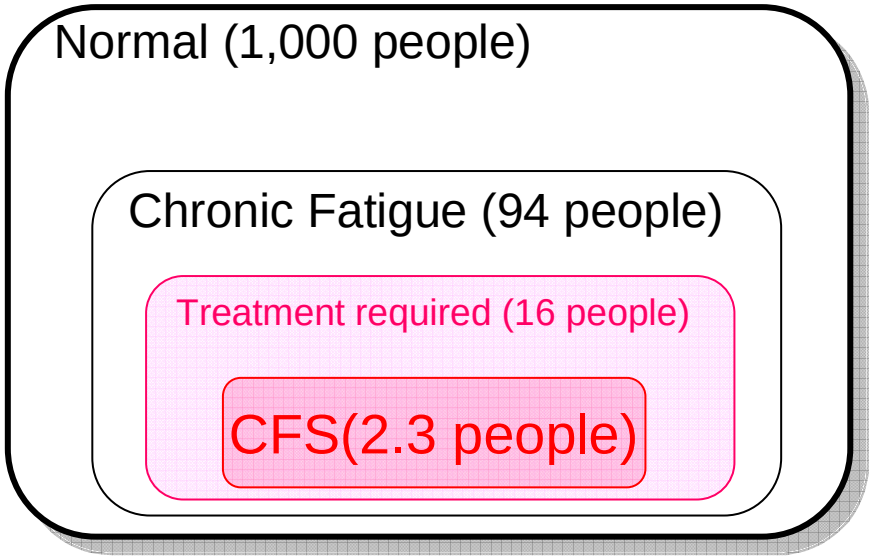
Expected merit

- Stable analysis result (robust)
- Easy interpretation of relation between clinical findings and disease condition



Chronic Fatigue Syndrome

For a long time..



CFS is

✓a complicated disorder caused by infection and/or stress (chemical, biological, psycho-social situation).

✓Central nerve system dysfunction that is triggered by abnormal immune system (TGF-β and IF etc.).

Current issue

1. There is no objective diagnostic method.
2. Difficult to diagnose by non-specialist.

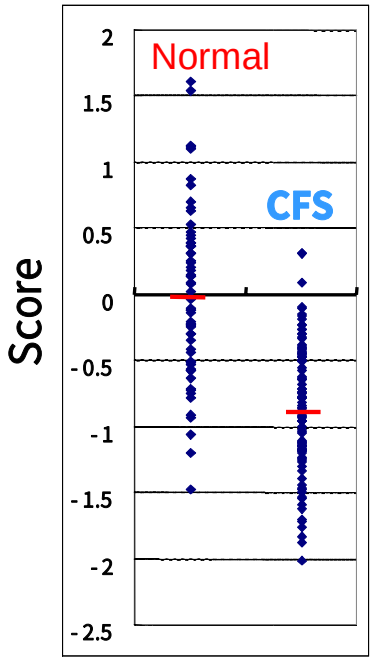
* Difficulty in early detection leads to severe condition

* Repeating doctor shopping

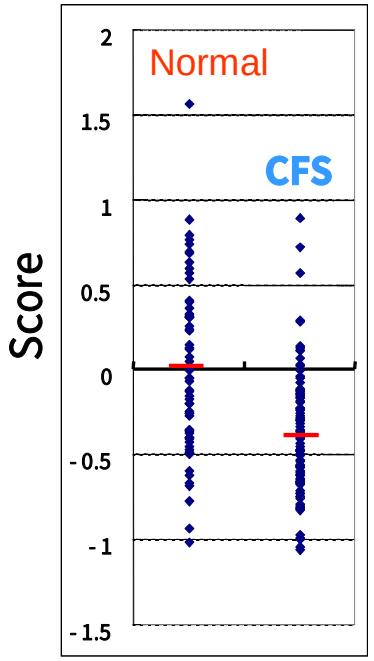
CFS analysis by DNA chip (1)

Extraction of 9 gene clusters (function) for disease condition analysis

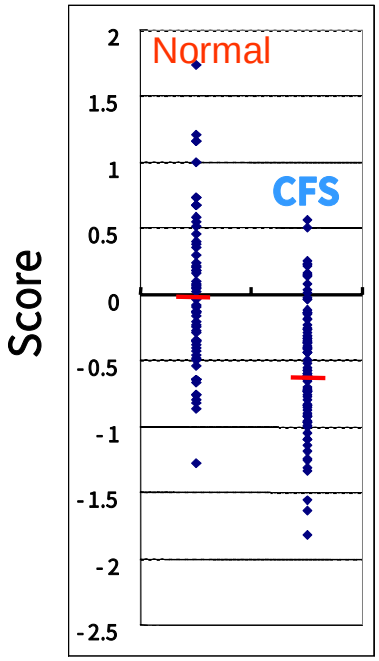
Energy production



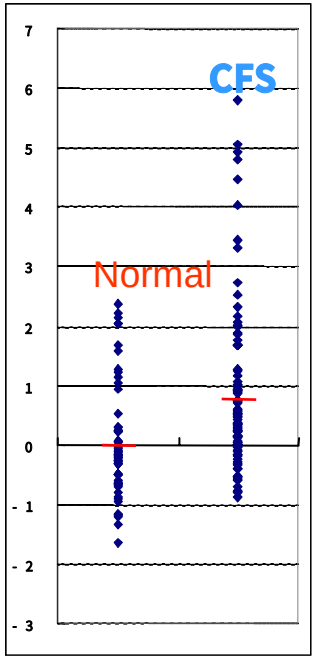
Anti-oxidation



T-cell function



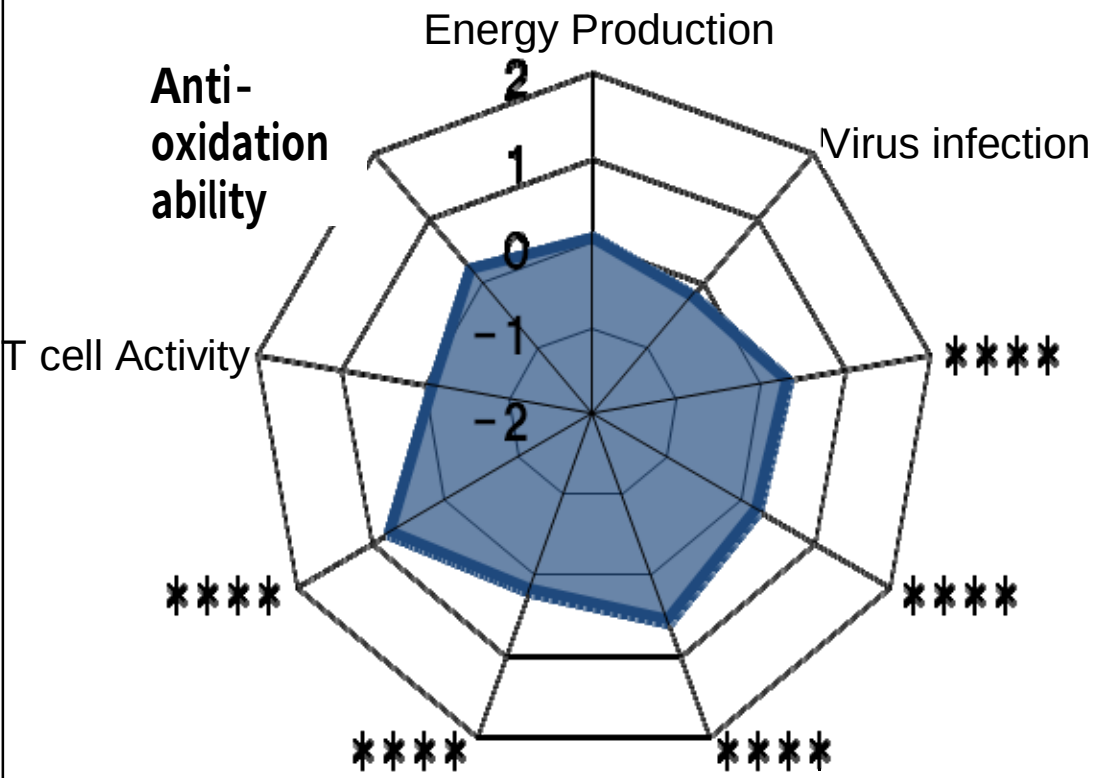
Virus infection



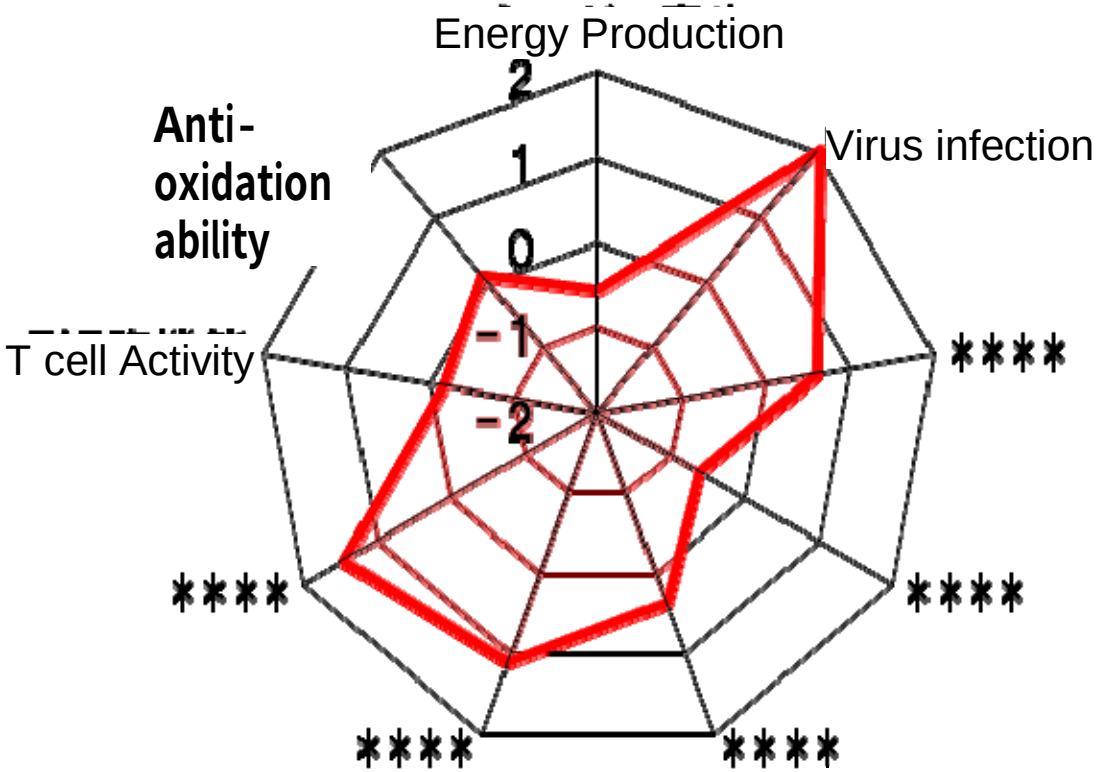
Score = The average of [(Signal-the average of healthy individual) / SD of healthy individual]

CFS analysis by DNA chip (2)

Normal



CFS



CFS analysis by DNA chip (3)

～ Comparison between normal and CFS by matching ages ～

	DNA chip	
	+	-
CFS	94	6
Normal	5	58

Sensitivity 94.0%
Specificity 92.0%
Concordance 93.3%

～ Comparison between young normal and CFS ～

	DNA chip	
	+	-
CFS	94	6
Normal	13	187

Sensitivity 94.0%
Specificity 93.5%
Concordance 93.7%

The 16th Japan Mibyou System Association (2009)

We Believe the Possibilities.

Sysmex Corporation

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