The 9th Technology Presentation

March 16, 2012

Sysmex Corporation

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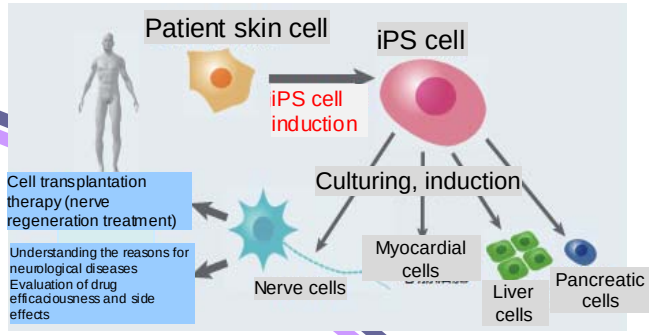
2. (1) Outline of Technology Strategy

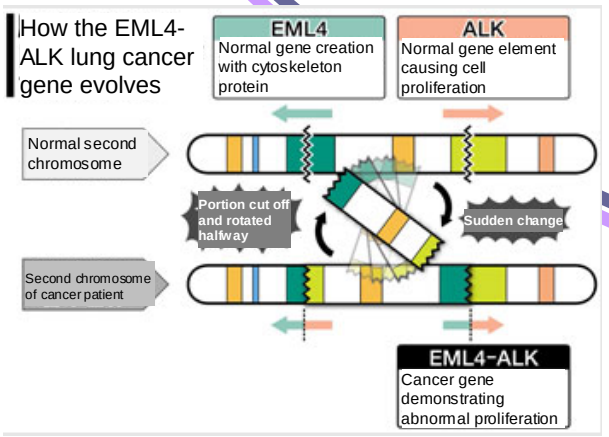
Technologies for Realizing Personalized Medicine/ Changes in the Environment 1)

Drug reaction simulation,
upgrading through structural analysis

"Humanization" of disease model using iPS cells

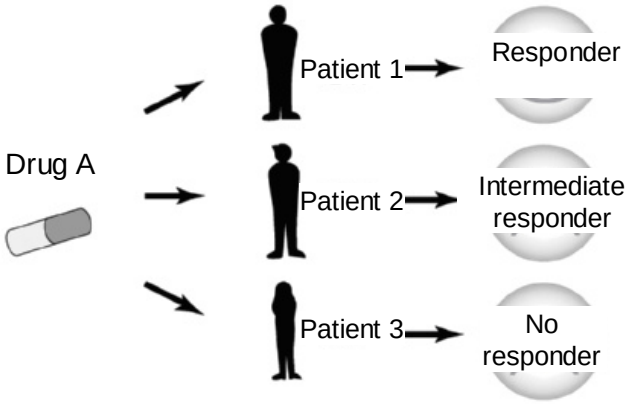


Identification of new treatments and diagnostic targets



Changes in drug manufacturing process

Drug efficacy differs, depending on the patient



Technologies for Realizing Personalized Medicine/ Changes in the Environment 2)

Changes in drug development process:
Opportunities for participation in companion diagnostics

(Major) Diagnostic Agent Manufacturers	(Major) Drug Manufacturers	Target disease (Application)	Technology
Roche	Roche, AstraZeneca, GlaxoSmithKline, MERCK, AMGEN	Cancer (patient selection) Infectious disease (monitoring)	PCR IHC, ISH Microarray
Abbott A Promise for Life	Pfizer, GlaxoSmithKline	Cancer (patient selection)	PCR
BIOMÉRIEUX	IPSEN, GlaxoSmithKline	Cancer (patient selection)	PCR
Dako	Pfizer, AstraZeneca, GlaxoSmithKline, MERCK, NOVARTIS, Genentech A Member of the Roche Group	Cancer (patient selection)	IHC, ISH

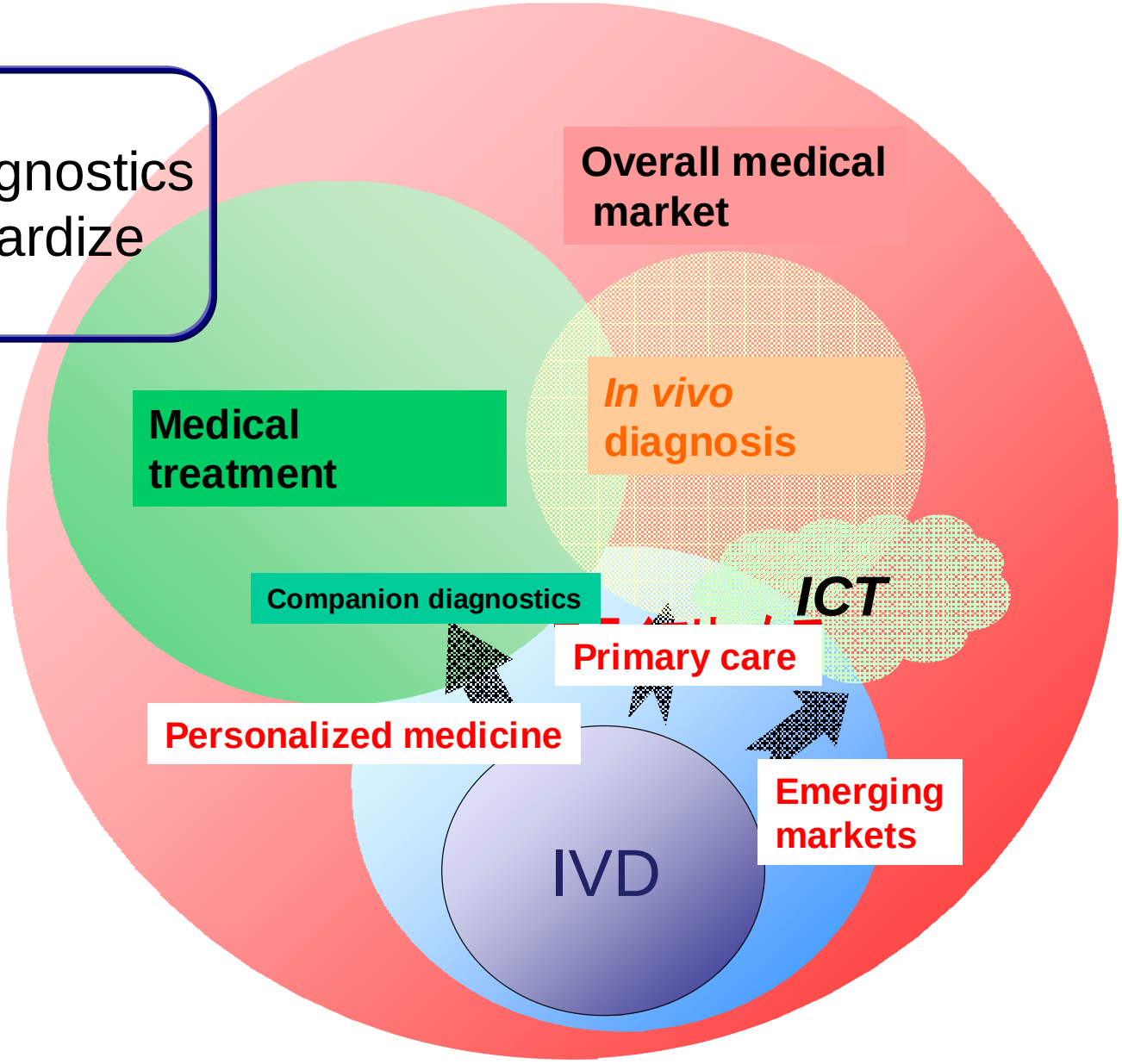
The Japanese pharma industry is moving toward companion diagnostics.

IHC: Immunohistochemistry
ISH: *In situ* hybridization

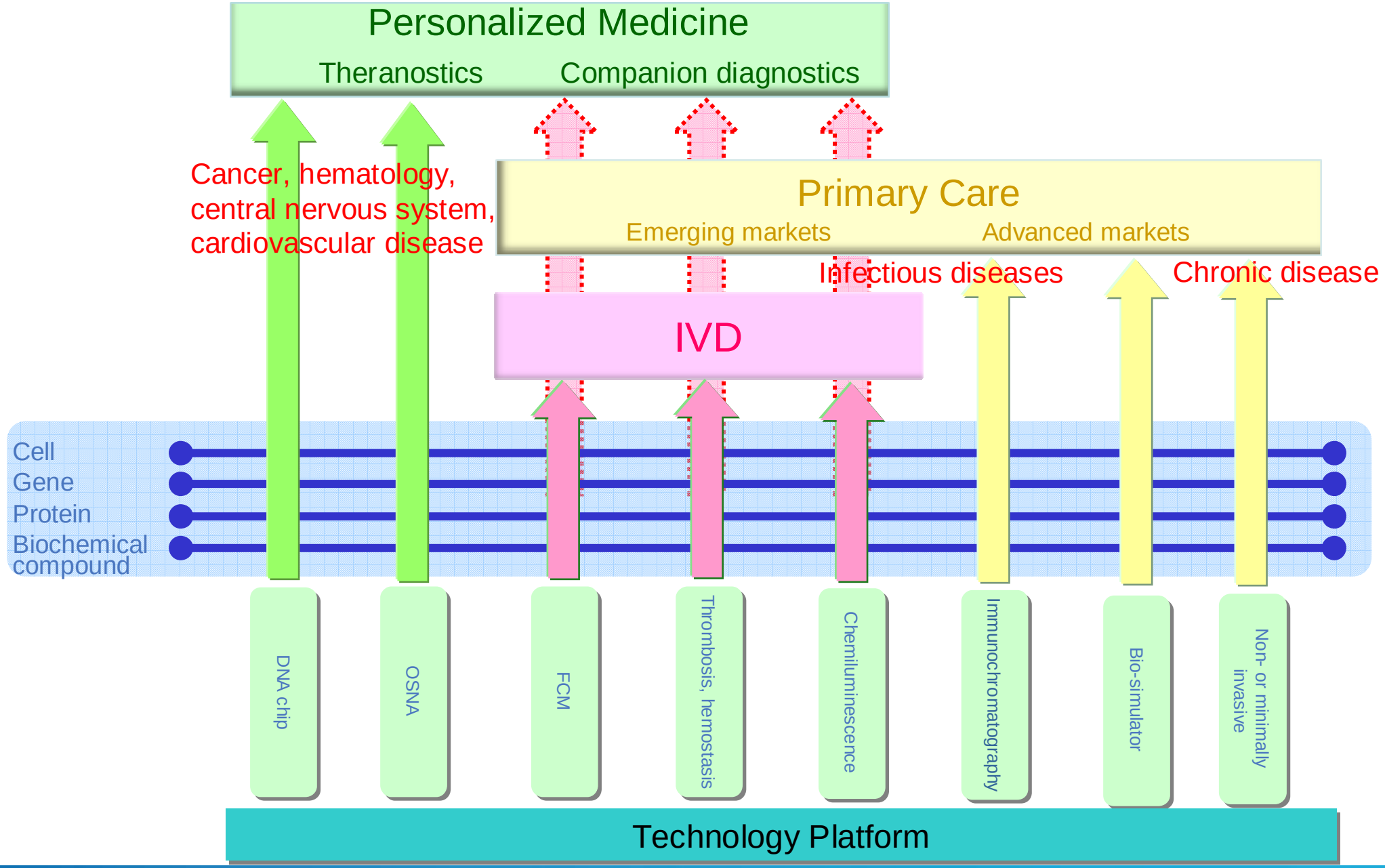
Outline of Technology Strategy

Vision of R&D Activity

Providing highly valuable diagnostics testing to optimize and standardize medical treatment



Creating Diagnostic Value by Strengthening the Technology Platform



Companion Diagnostics

◇ Companion diagnostics (CDx)…

- ✓Is an effective approach for realizing personalized medicine
- ✓Involves development of therapeutic and diagnostic agents in parallel development

Co-Development

Co-Registration

Co-Approval

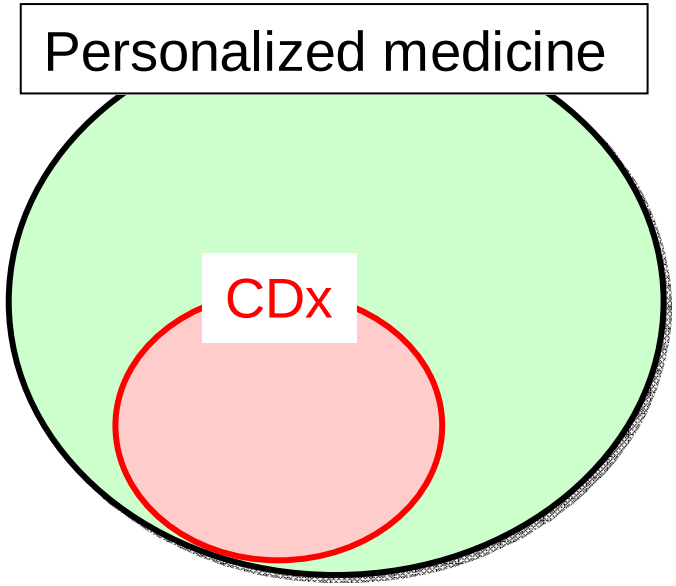
Benefits and drawbacks of CDx

Reduces development risk, shortens development time

V

Realizes patient coverage

Patient benefit:
Early realization of personalized medicine



Strategy for CDx

Main Focuses in Working toward CDx

Biomarker Discovery
- Joint research with outside medical institutes
- Joint business with other companies
- License-in
- Use of established markers

✓Proactively use external R&D resources

Assay Design
- Prototype development
- Evaluation of sensitivity/ specificity for quality-guaranteed samples developed through joint research

✓Apply Sysmex technology (HISCL, FCM) for personalized medicine

✓Introduce PCR technology

Diagnostic Kit Development
- Automation ✓
- Reagent optimization ✓
- Proof of clinical benefits with medium- to large-scale clinical study✓
- Approvals ✓

✓Use Sysmex expertise (Global sales channels)

Strengthening the Technology Platform

Sample Initiative: Measurement of HISCL Hepatic Fibrosis Markers

Sugar Chain

Cell type identification

Protecting protein quality

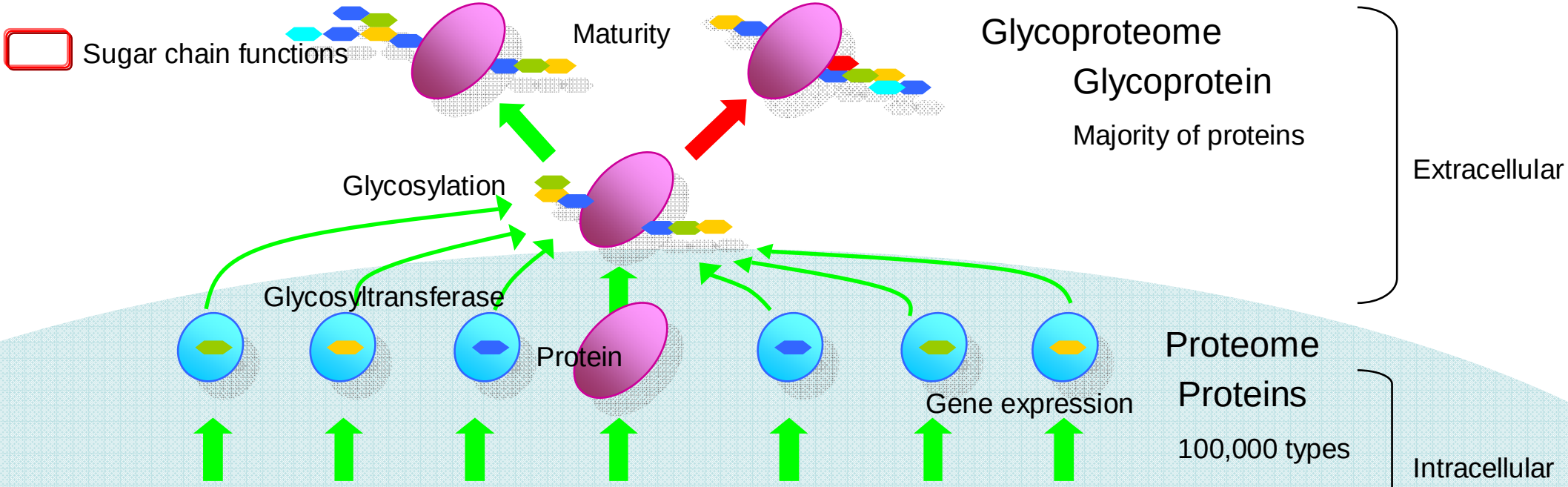
Gateway to infection

Protein quality control

Application in drugs

Transport of drug within body

Sugar chain functions



Glycoproteome

Glycoprotein

Majority of proteins

Extracellular

Proteome

Proteins

100,000 types

Genome

Genes

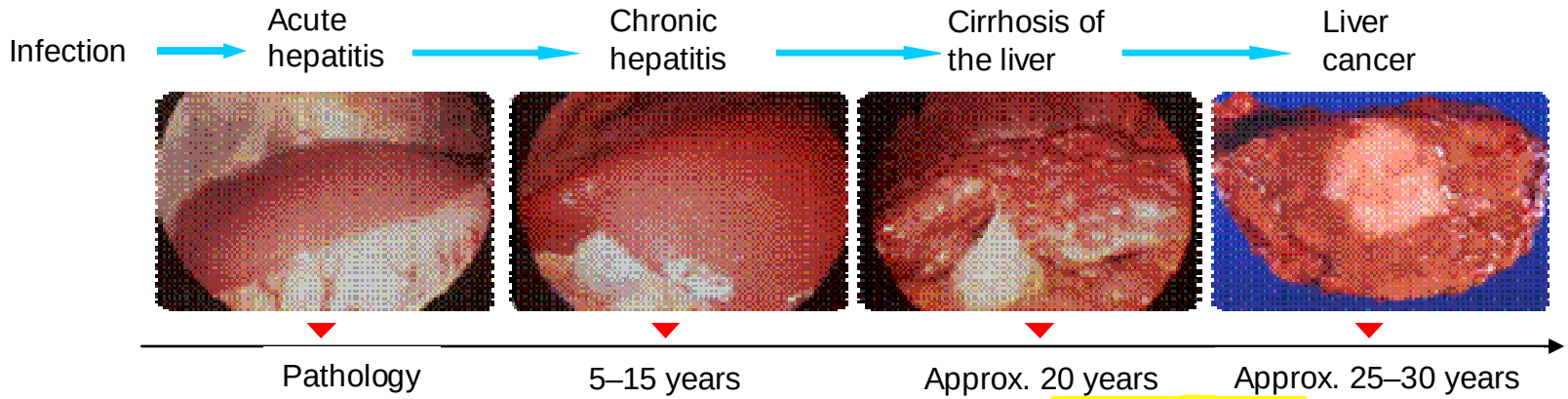
22,000

Intracellular

Nuclear

Various types of stimulation or changes in the environment alter the structure of the sugar chain such that it expresses the “mode of dress” of the protein.

Hepatic Fibrosis and Liver Disease



HCC

Fibrosis progression
+0.10/year

7–8%
per year

Cirrhosis (F4)

3–4%
per year

Severe chronic hepatitis (F3)

1–2%
per year

Moderate chronic hepatitis (F2)

0.5%
per year

Slight chronic hepatitis (F1)

Interferon virus eradication

↓ F1～3

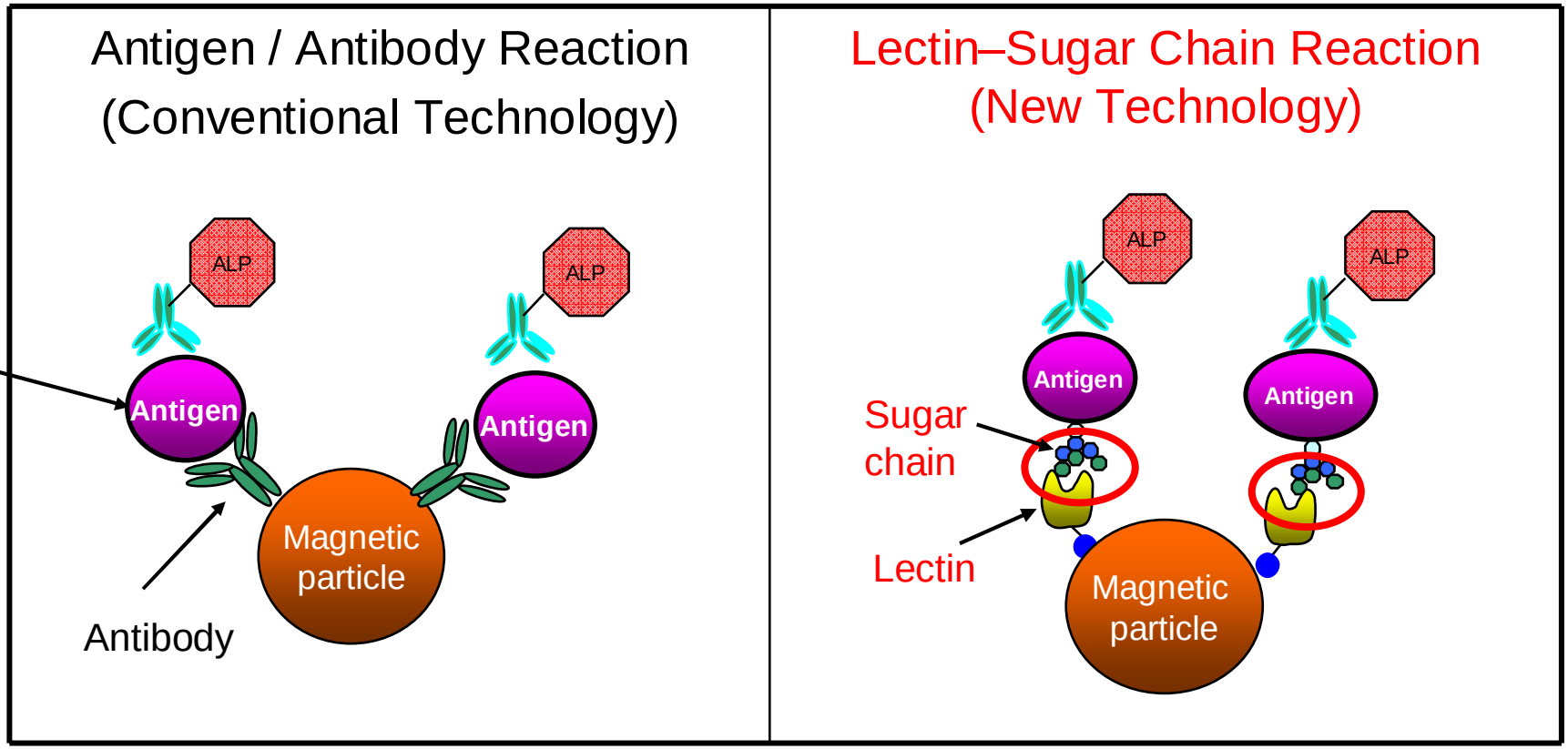
Fibrosis reduction
–0.28/year

Existing method(C.O.I.)

Shiratori Y, *et al*: *Annals Int Med* 32: 517-524, 2000

Lectin–Sugar Chain Reaction and Combination with the HISCL Method

Object of detection: protein (antigen)

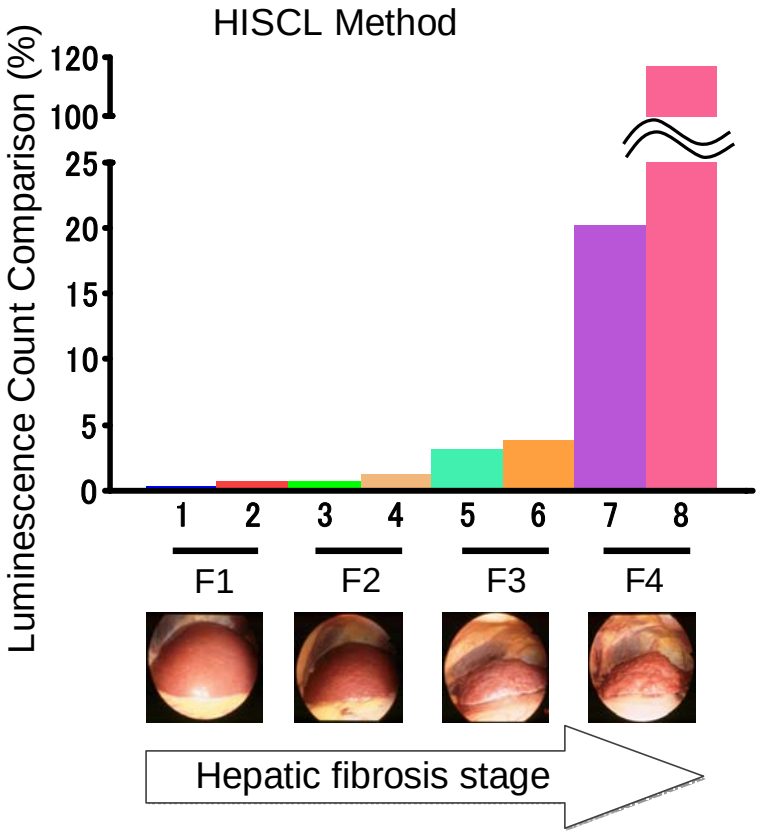


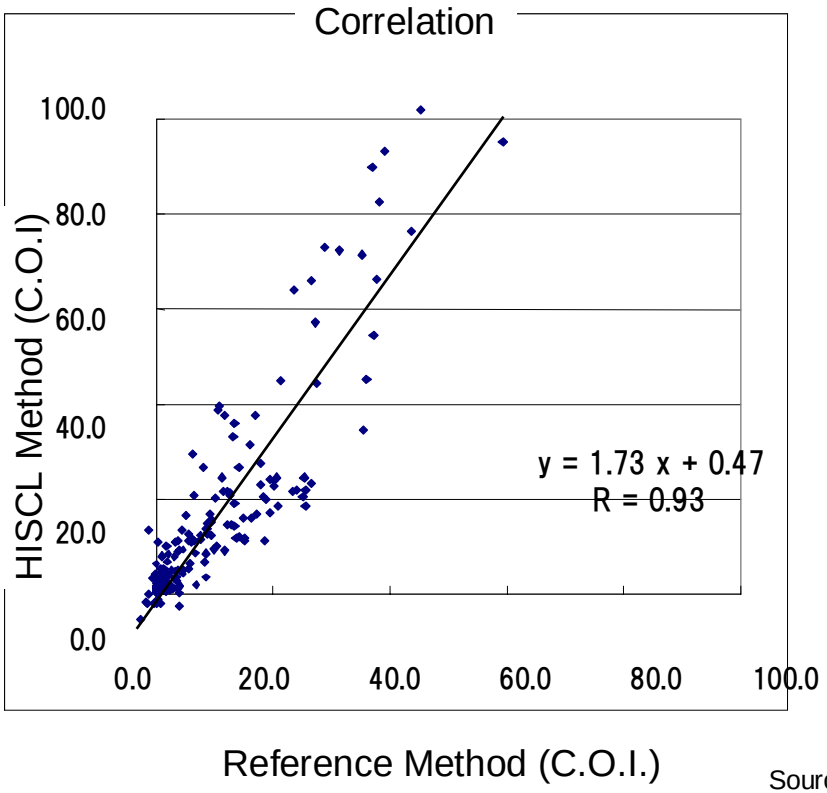
Maintains identification through sugar chain detection, and enables use of the highly sensitive HISCL method a short period of time.

ALP: Alkaline phosphatase

Clinical Research Results (Interim Report)

Strong correlation with diagnostic requests, such as measurement of malignant alteration





Source: 2011BioJapan

Future developments:

Seek approval during FY2012, and after approval has been granted, look into simultaneous development of therapeutic and diagnostic agents

Reporting Subjects and Technology Presentation Policies

1. Reporting Subjects

- Technical features of Sysmex technologies and products
- Technical themes on which Sysmex conducts R&D and their clinical benefits
- 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 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

Definition of R&D Stage

Research stage → Practical stage → Launch stage

Start of research or preliminary evaluation

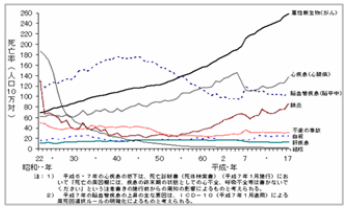
Objective means establishment of measurement principle and verification of clinical value.

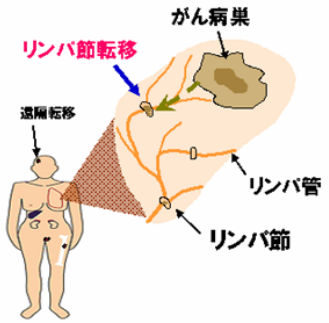
10–50%

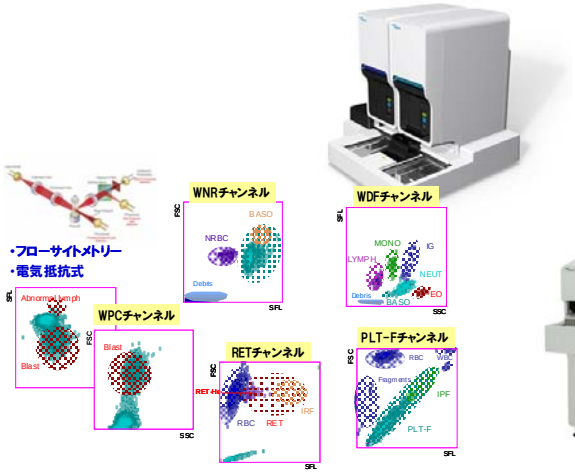
Start of full-scale R&D activity towards commercialization

50–80%

Completion of product commercialization and determination of launch







2. (2) Launch Stage: New Product Technologies

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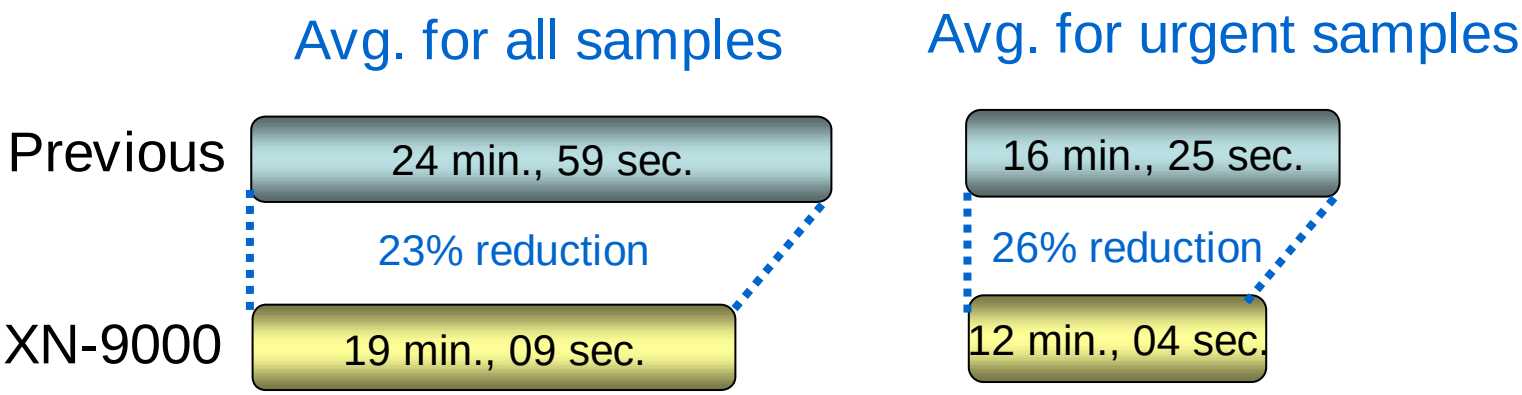
1) XN Series: Proposing Incomparable Laboratory Workflow

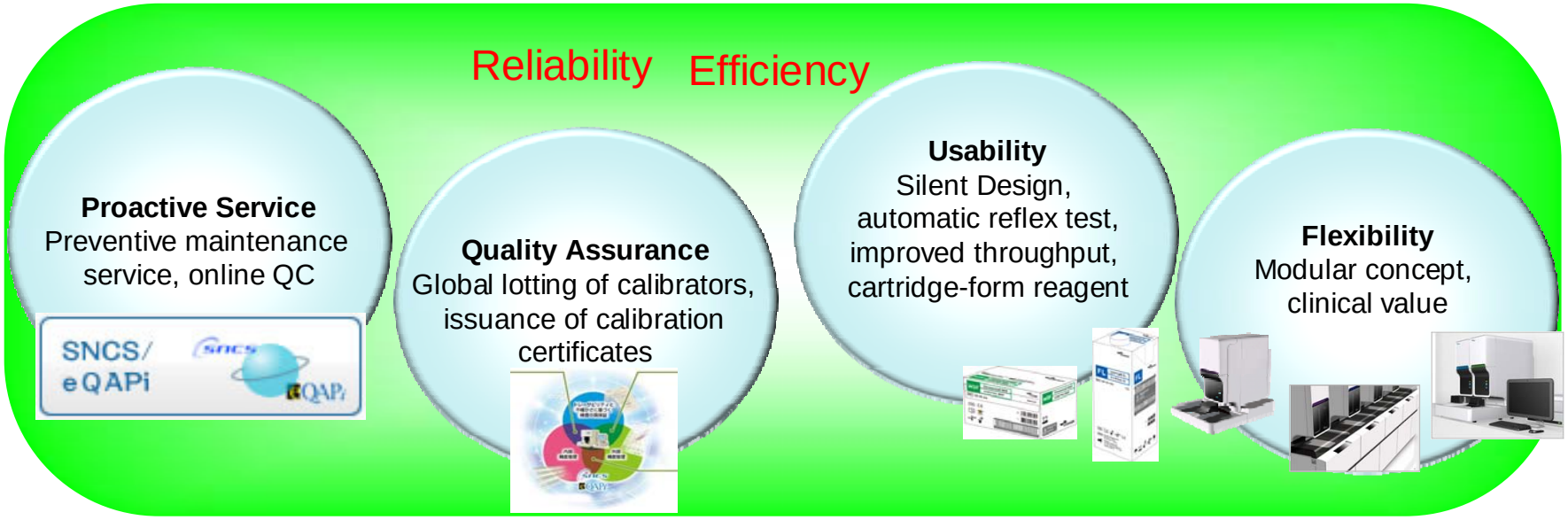
XN Series: Proposing Incomparable Laboratory Workflow

Improving Laboratory Value

Example: Period elapsed until testing results reported

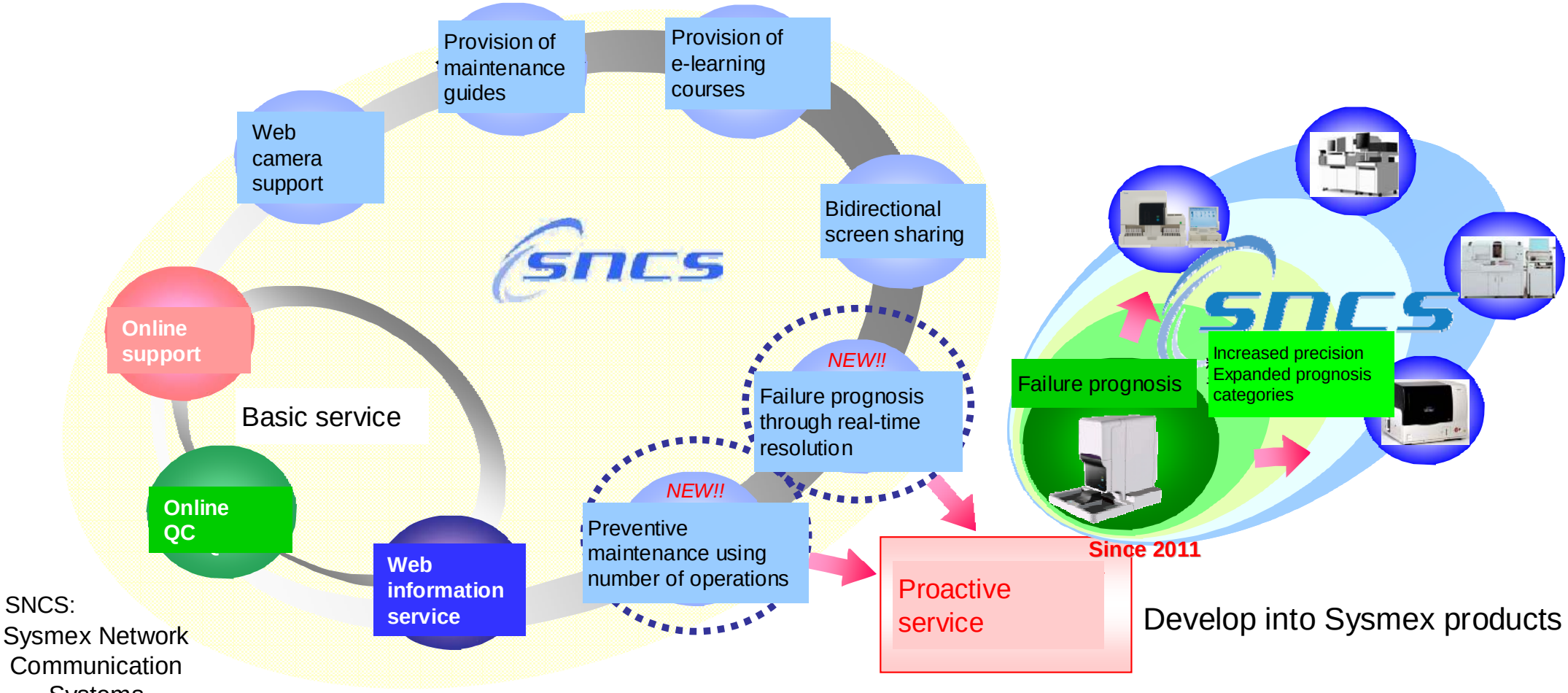


*Previous: Sysmex's former system (University)



XN Series: Proposing Incomparable Laboratory Workflow

Improving operational efficiency and proposing high added value



SNCS:
Sysmex Network Communication Systems

Develop into Sysmex products

2. (2) Launch Stage: New Product Technologies

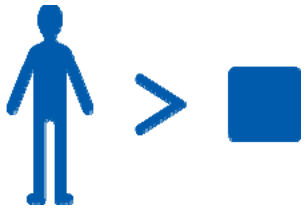
1) Silent Design®

2) Silent Design®

The five elements of Silent Design

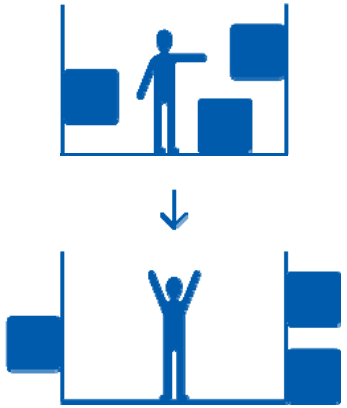
Person

Designed for the people who use it.



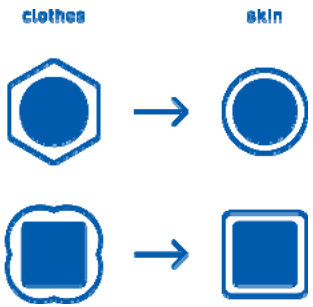
Space

Creates an environment stressing ease of use.



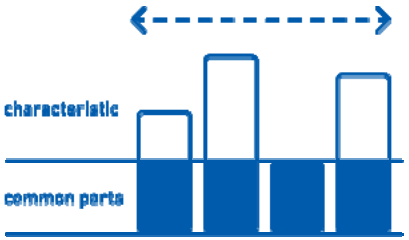
Surface

Considers the skin, rather than the clothing.



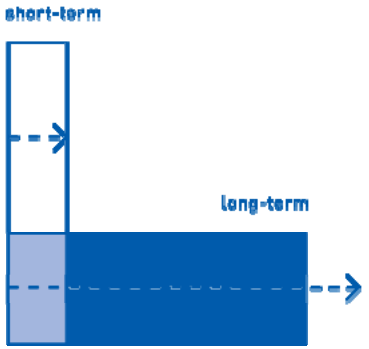
Series

Maintains consistency.



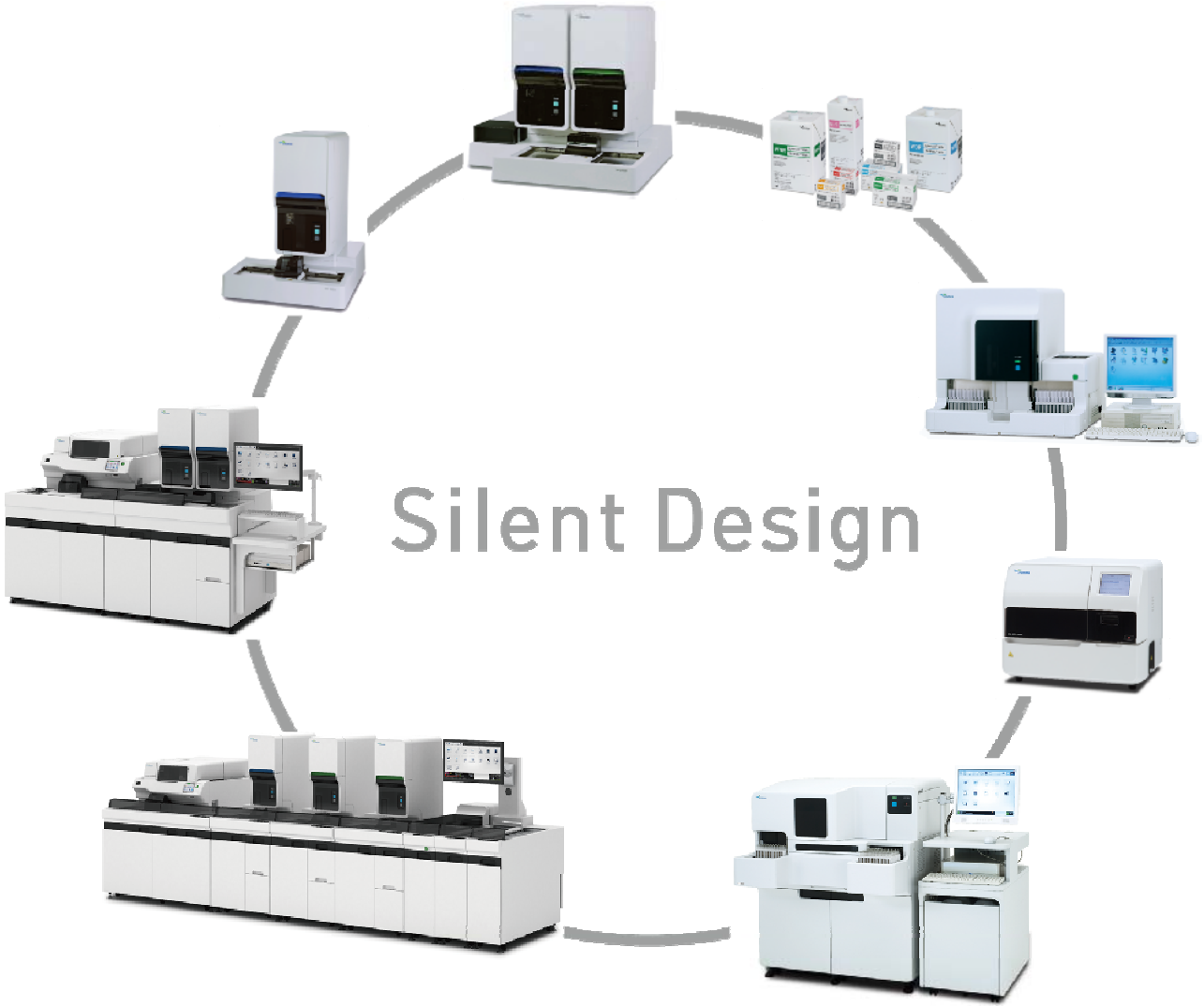
Long life

Offers value that is unaffected by the changing times.



Silent Design® Wins Good Design Gold Award 2011

Developing the concept of product consistency:
“Rather than designing individual pieces of equipment, design the laboratory space”



GOOD DESIGN AWARD 2011
GOLD AWARD

November 2011

2. (2) Launch Stage: New Product Technologies

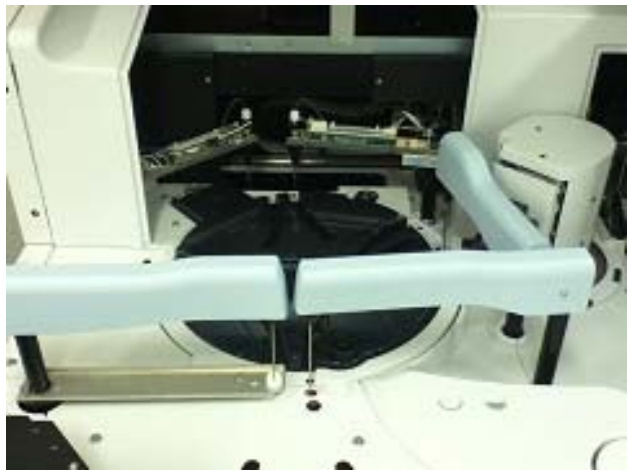
3) CS-5100: Flagship Model in the Hemostasis Field

- High processing capacity
- Connects to transport lines
- Improved sample aspiration mechanism
- Stabilized reagent cooling system

CS-5100: High Processing Capacity

High processing capacity through optimized design for sample processing

Maintains processing capacity* during simultaneous testing of multiple parameters

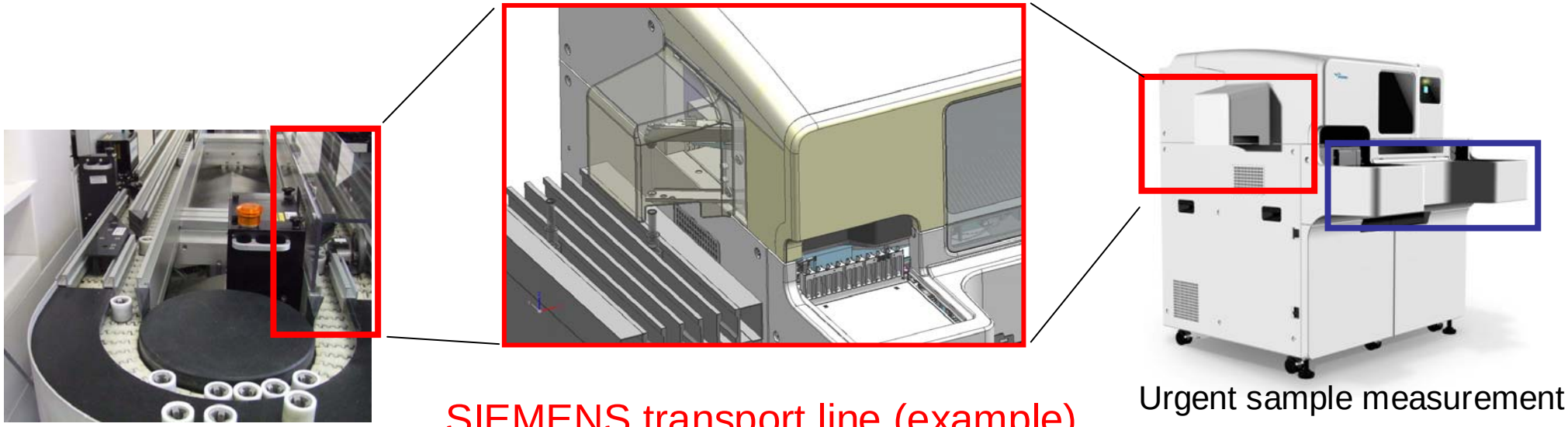


* Compared with previous models, tripled processing capacity (300 tests per hour) for tests that included such parameters as D-Dimer, which had tended to reduce capacity.

- Optimized for high-dimensionality unit placement and software controls
- Realizes compact size and high speed through structural simulation

CS-5100: Connects to Transport Lines

Connects with SIEMENS' and major Japanese manufacturers' sample transport systems



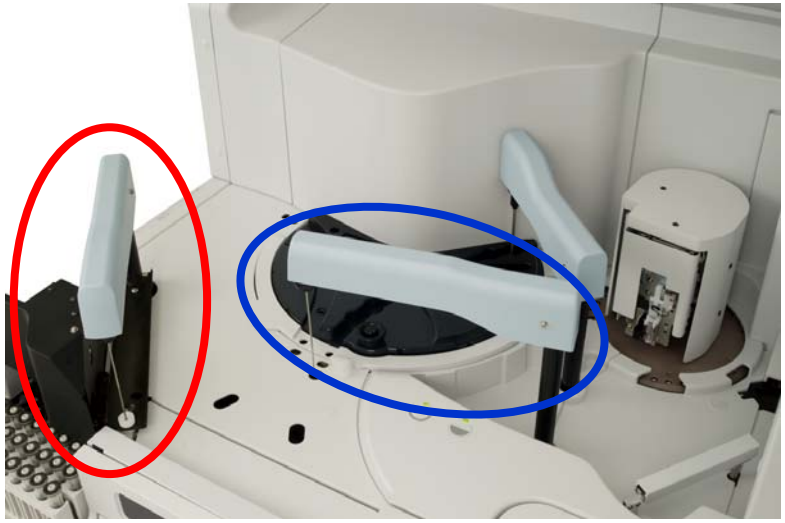
SIEMENS transport line (example)

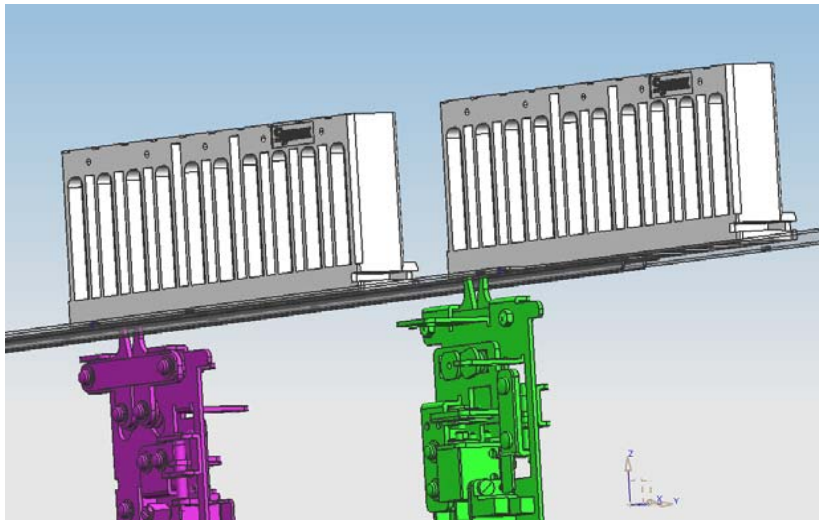
Urgent sample measurement

Provides a workflow that balances high-volume throughput with urgent sample measurement

CS-5100: Improved Sample Aspiration Mechanism

Handles mixed testing of capped blood-collection tubes and small-volume samples





Piercer: Sample aspiration compartment handles biohazard-capped blood-collection tubes

Pipette: Sample aspiration compartment handles small-volume samples

Sampler can sort samples correctly according to test tube type and sample size.

Improved operator workflow, such as in preparation of complicated samples

CS-5100: Stabilized Reagent Cooling Function

Realizes stabilized reagent cooling function through quality engineering

CS-5100

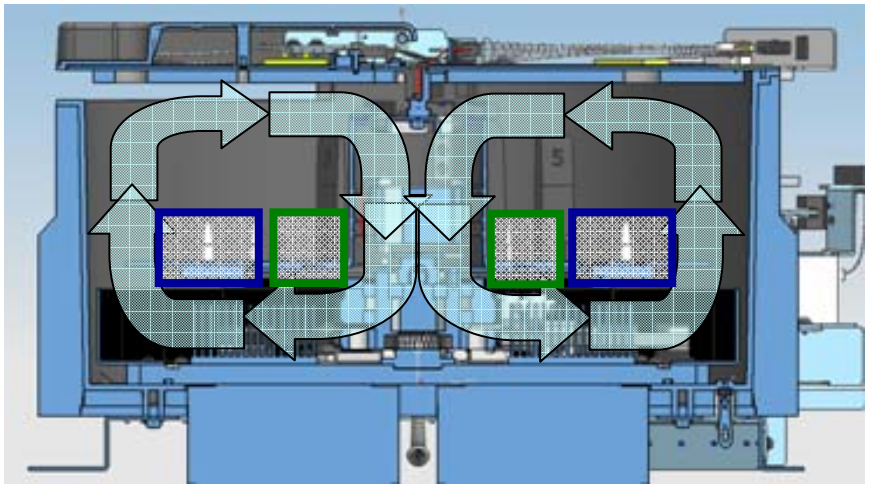


Diagram of interior of reagent cool storage unit (arrows show direction of airflow)

- Reagent stand A
- Reagent stand B

- Reagent cool storage unit construction allows a broad range of changes in device placement and environments
- Effective cooling through coolant and air channel controls (See diagram at left)*

*About twice the stability of previous models, even in severe environments

Provides improved reagent cooling and more accurate testing data

2. (2) Launch Stage: New Product Technologies

4) Lab Assay: C2P

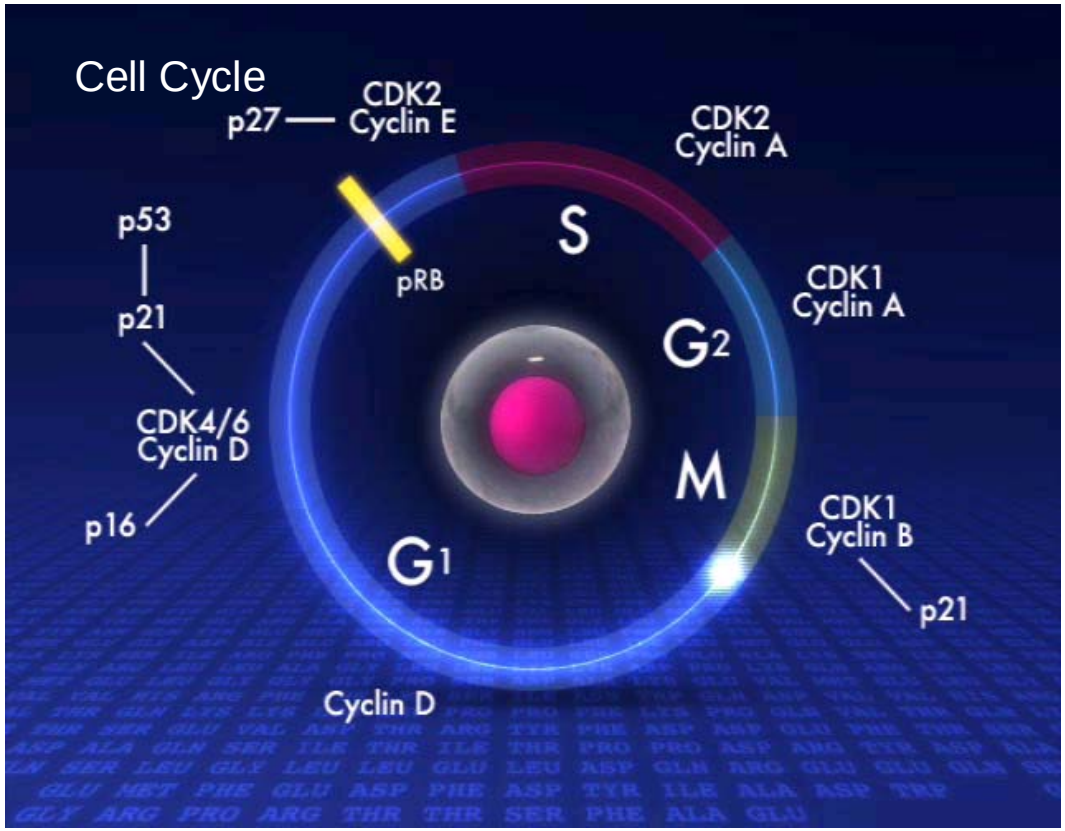
C2P: Cell Cycle Profiling

Lab Assay: C2P

Cell Cycle Profiling (Breast Cancer)

Providing appropriate treatment for each patient

- From surgically dissected tumor tissue, measure the specific activity (activity/expression) of proteins CDK1 and CDK2 related to the cell cycle
- Classify low/medium/high risk of recurrence
- Target patient is lymph note metastasis negative, hormone receptor positive



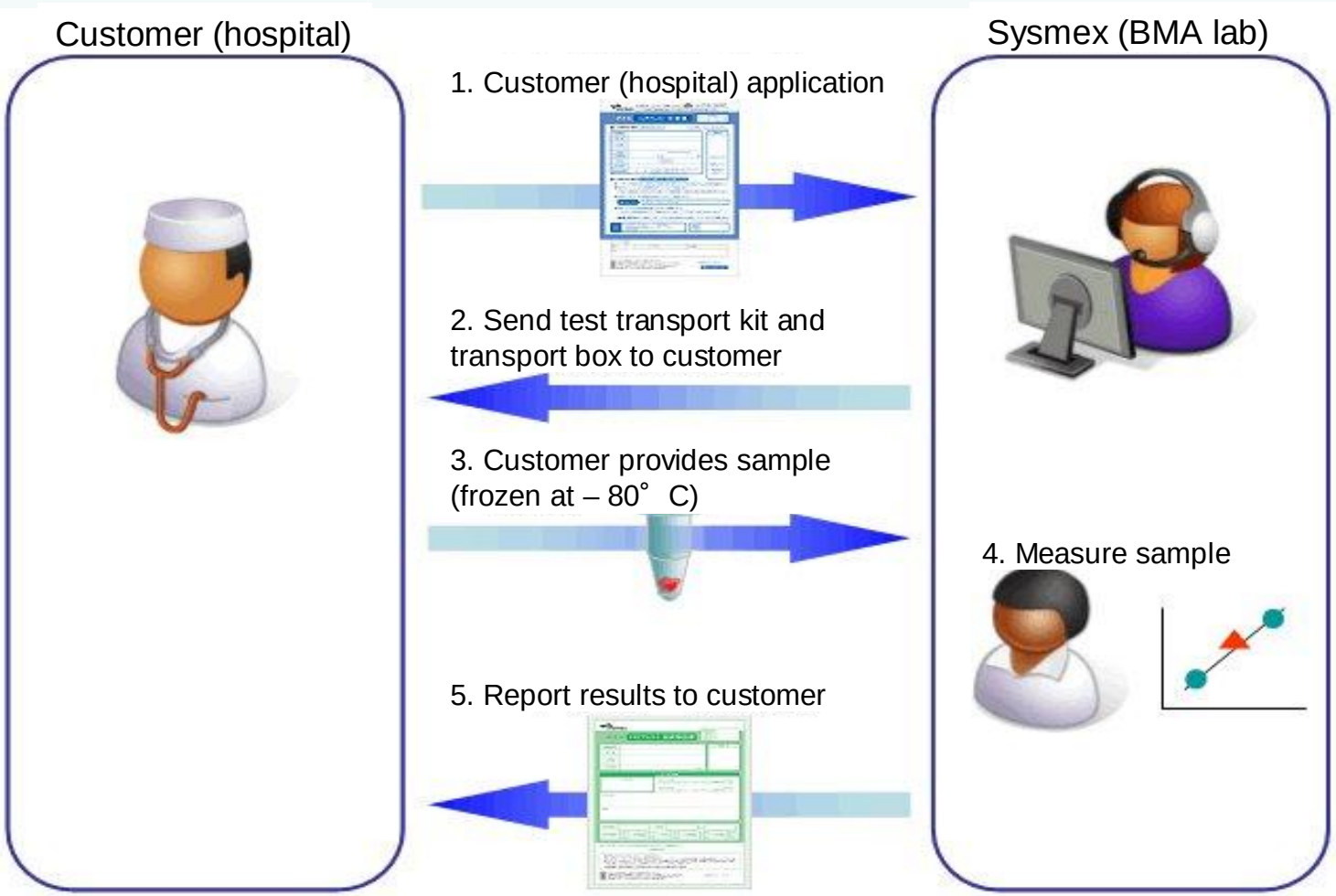
Dynamic state of cell proliferation⇒
CDK2 SA / CDK1 SA

Specific Activity (SA)
= activity / expression

Lab Assay: “C2P Breast”

In January 2012, began a testing service (for research) in Japan involving the risk of recurrence of early-stage breast cancer

Target region: Japan
Cost: ¥200,000/test
Test order flow:



Lab Assay: “C2P Breast”

BMA Lab: Kobe Medical
Industry Development Project

Awareness Activities
Japanese Breast Cancer Society
(Association Booth)

Seeks to make an early contribution to customers and accelerate commercialization

2. (2) Launch Stage: New Product Technologies

4) Progress of OSNA

Progress of OSNA

Expansion of regions where introduced

Breast cancer

- China: Applying
- AP: Preparing for sales
- United States: Reconsidering market launch

Expansion of application

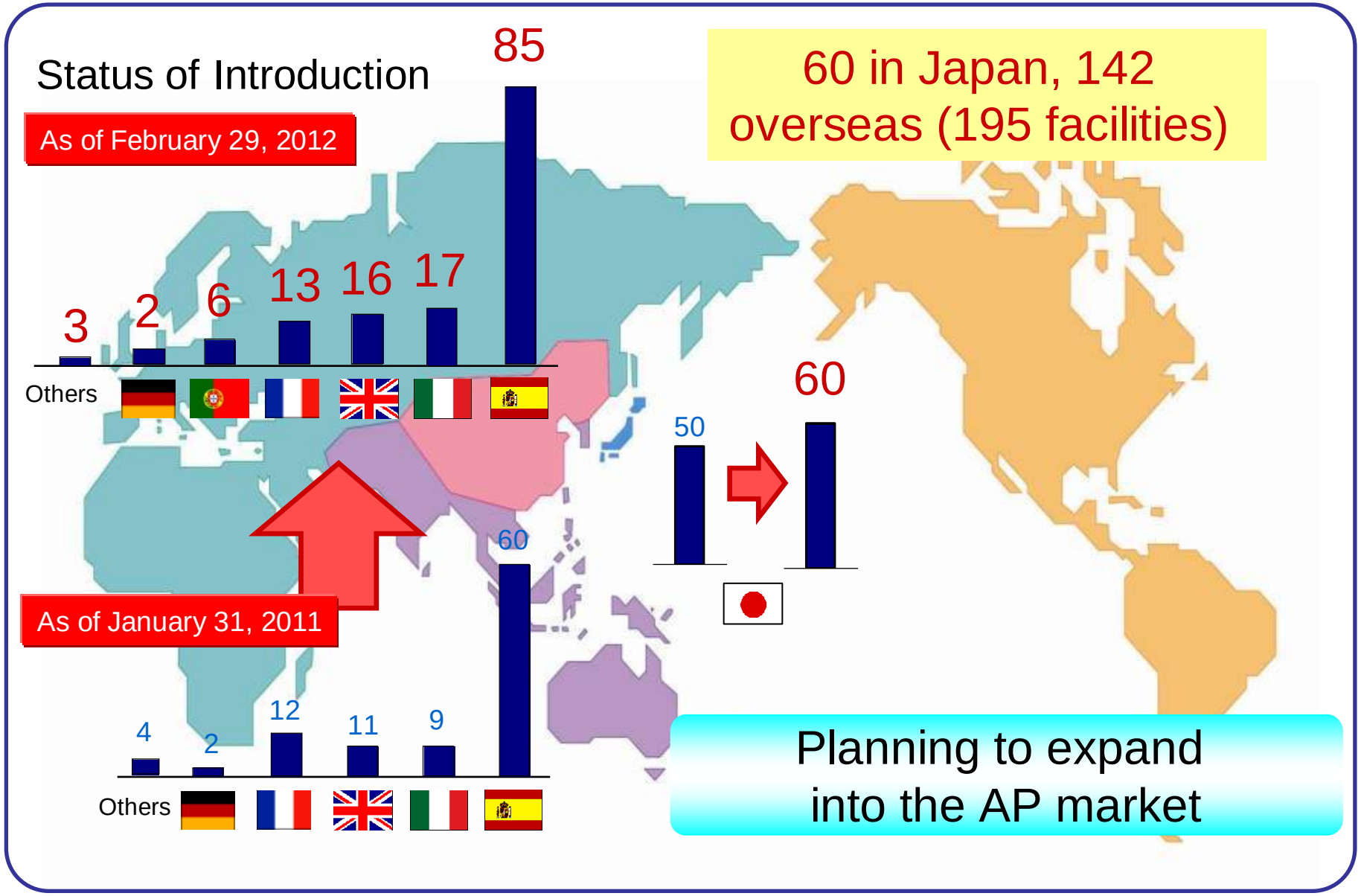
Colon cancer

- Japan: NHI points assigned, considering business prospects, clinical significance and other factors
- Europe: Acquired CE mark, conducting clinical evaluations at multiple centers

Stomach cancer

- Japan: Applying to have NHI points assigned

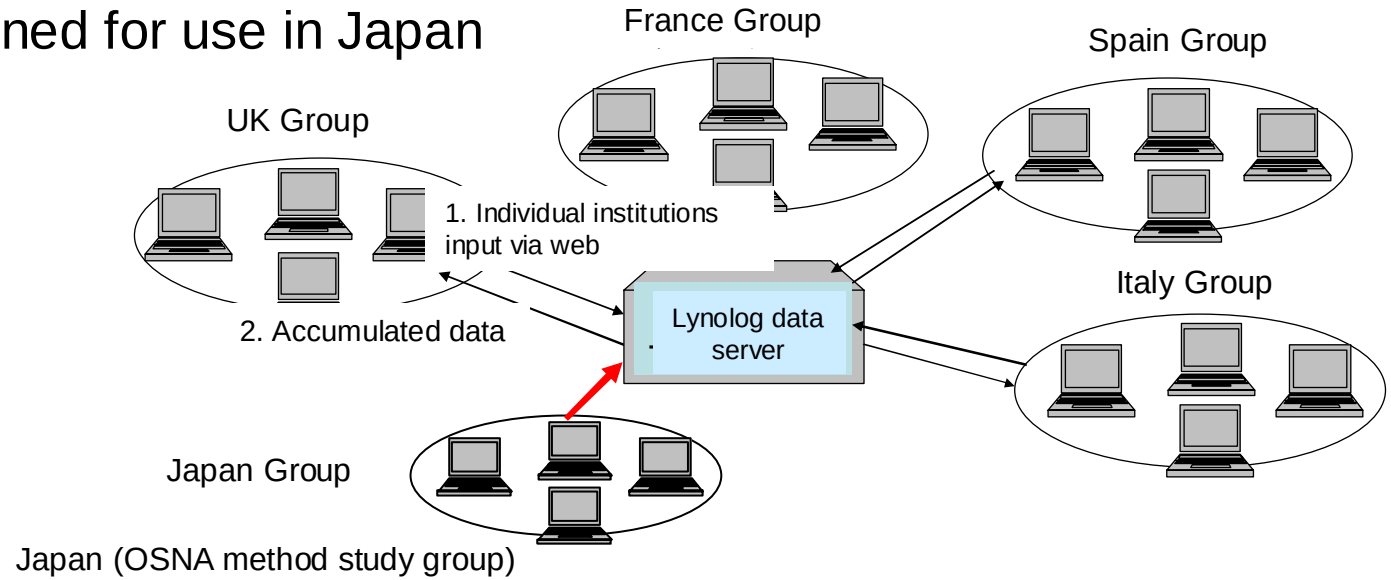
Progress of OSNA: Status of Introduction for Breast Cancer



Initiatives to Encourage OSNA Prevalence (Centered on Europe)

- Amass data using the OSNA web database (Lynolog)

Amass clinical information using examples of OSNA introduction on common database
Each country group amasses data, structures evidence and consolidates data across countries
Note: Planned for use in Japan



Future developments:
Increase clinical value of OSNA method, accelerate awareness activities to expand market

2. (3) Practical Stage: Status of Progress on Development Themes

2. (3) Practical Stage: Status of Progress on Development Themes

1) Cervical Cancer Screening

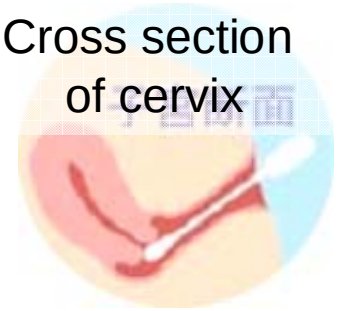
Cervical Cancer Screening: New Diagnostic Flow

Proposed new diagnostic flow

Definitive test (tissue diagnosis)

False positive

Cross section of cervix



Sample

(Primary test) FCM

Positive

(Secondary test) cytodiagnosis

Clinical value: Improved overall accuracy

Economic value: Labor savings, increased efficiency, allows acceptance of higher percentage of tests

Negative

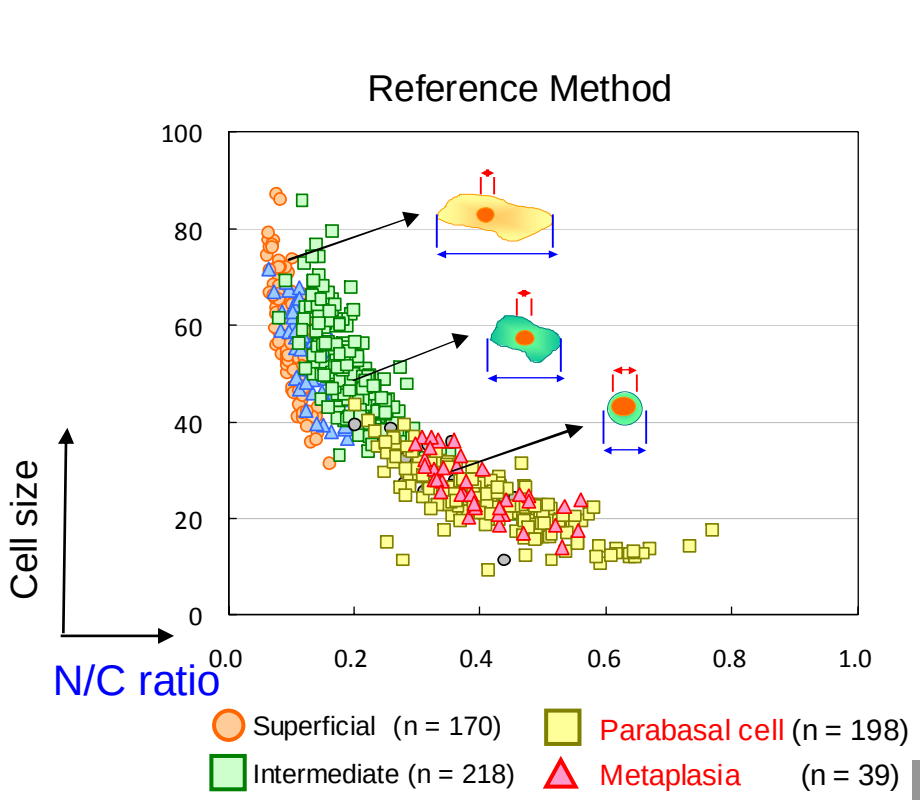
Negative

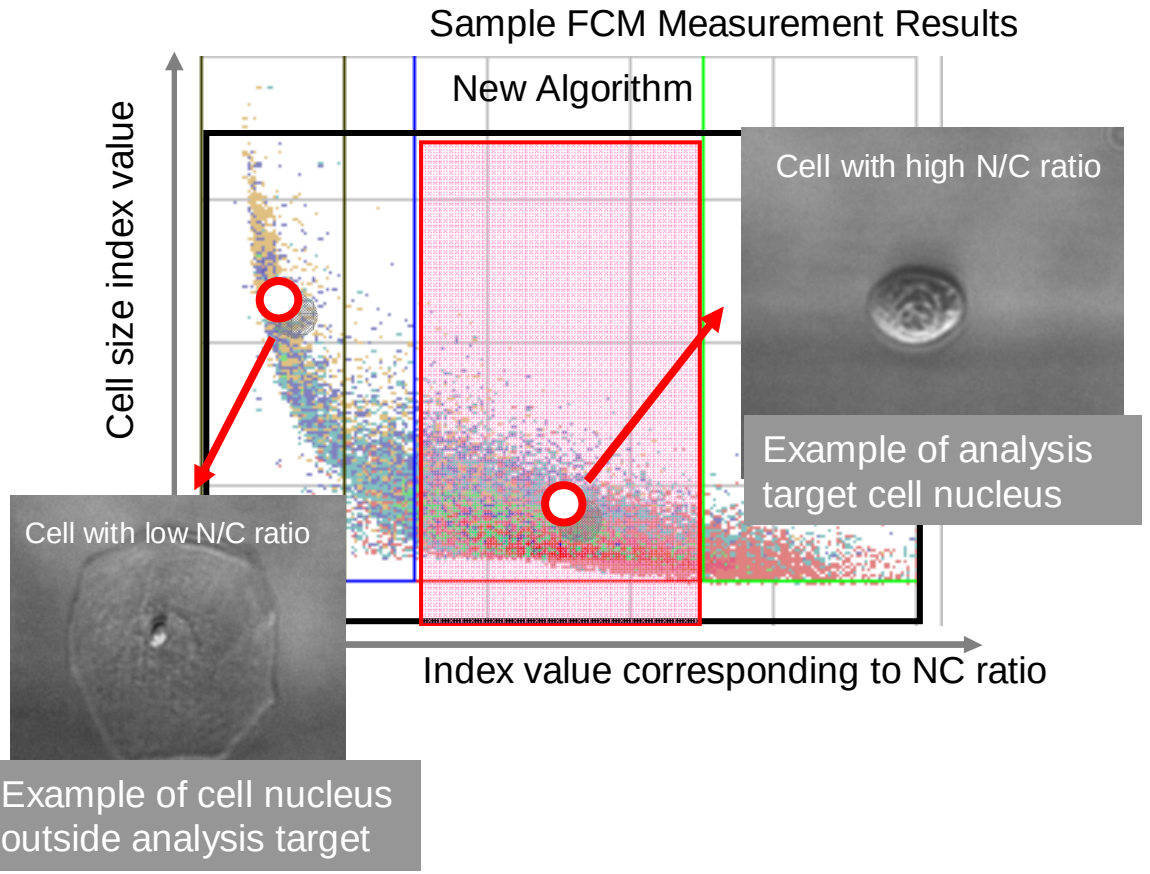
Sort out

Next regular examination

Cervical Cancer Screening: Improvement with New Algorithm for Classification by Target Character

- Extract resolution target cell nuclei using index of cell and nuclei sizes (N/C ratio)
- Analyze ploidy and proliferation using quantitative analysis of DNA





Cervical Cancer Screening: Confirmation of Clinical Performance

Target performance

For a practical system, sensitivity of 90%, specificity of 80%, and a sort-out rate of ≧ 70 %

(Note: The cutoff is tissue diagnosis CIN2+ or higher)

Based on internal evaluations, nearly on target

⇒ External market evaluation of clinical value is underway

	Sensitivity	Specificity
N=633	100% (21/21)	87% (529/612)

Future developments:
In fiscal 2012, verify clinical value in Japan, Europe and China (the United States is under consideration), and in fiscal 2013, launch into the market a system for research use

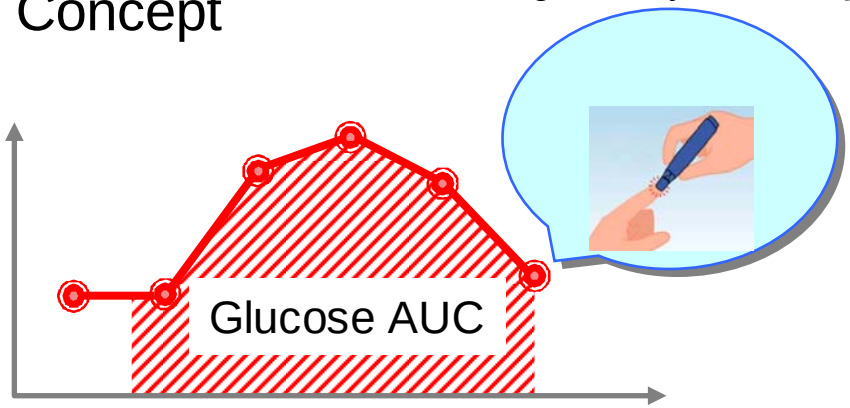
2. (3) Practical Stage: Status of Progress on Development Themes

2) Glucose AUC (Minimally Invasive Body Fluid Extraction Technology

Glucose AUC (Minimally Invasive Body Fluid Extraction Technology): Proposal of New Diabetes Screening

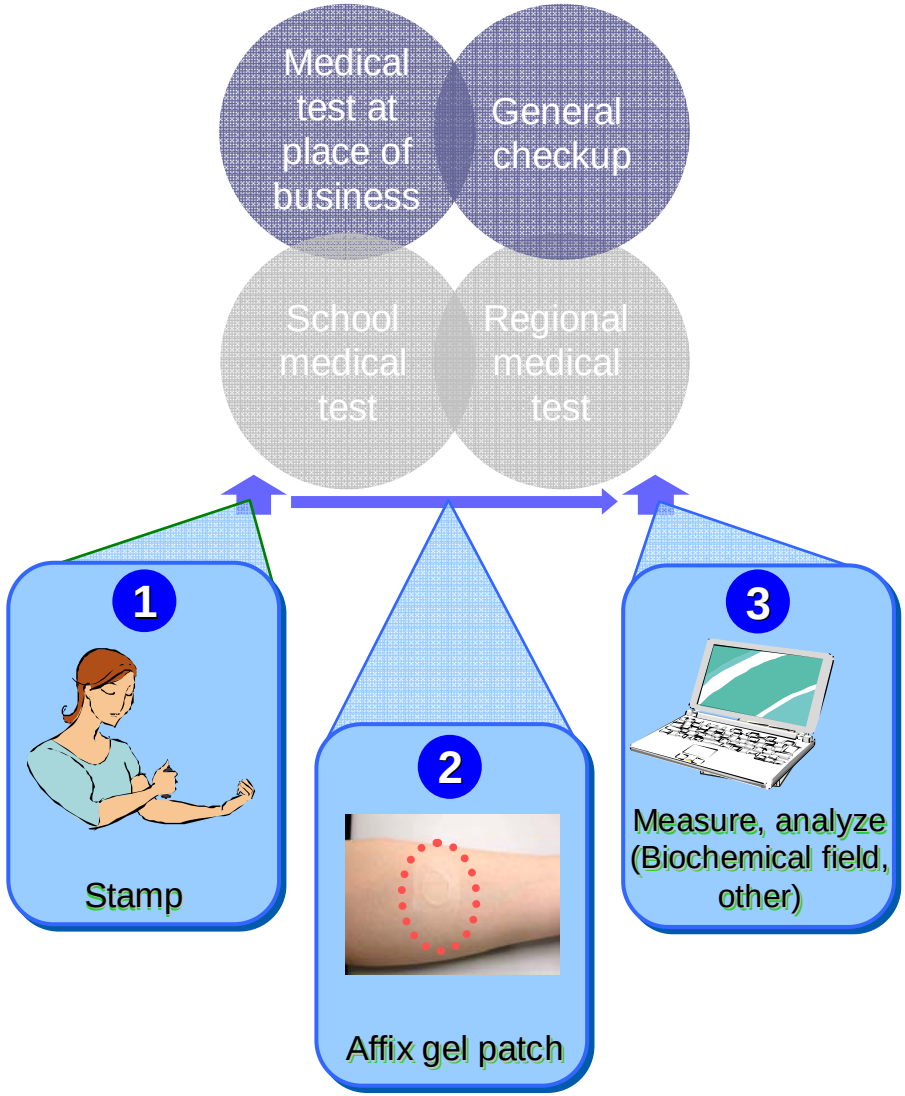
Concept

Taking blood samples to measure post-prandial hyperglycemia significantly reduces QOL



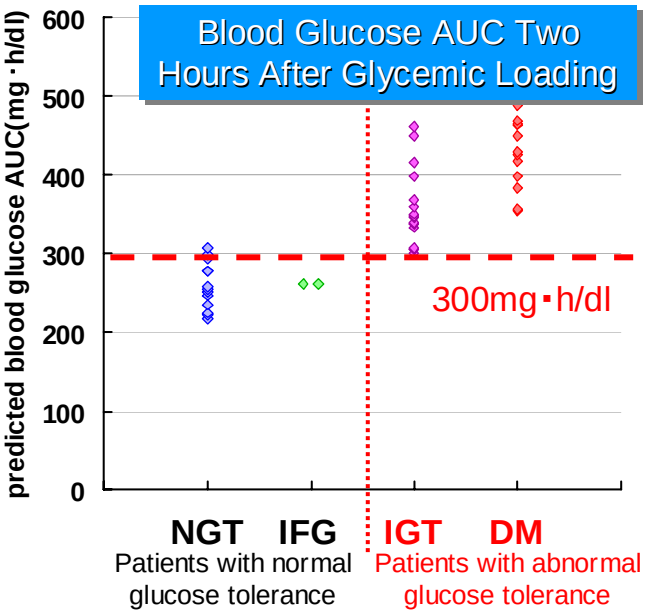
A method is needed for measuring post-prandial hyperglycemia that is simple and inconspicuous

Note: Post-prandial hyperglycemia:
A risk factor for large vessel disease (cerebral apoplexy, myocardial infarction)



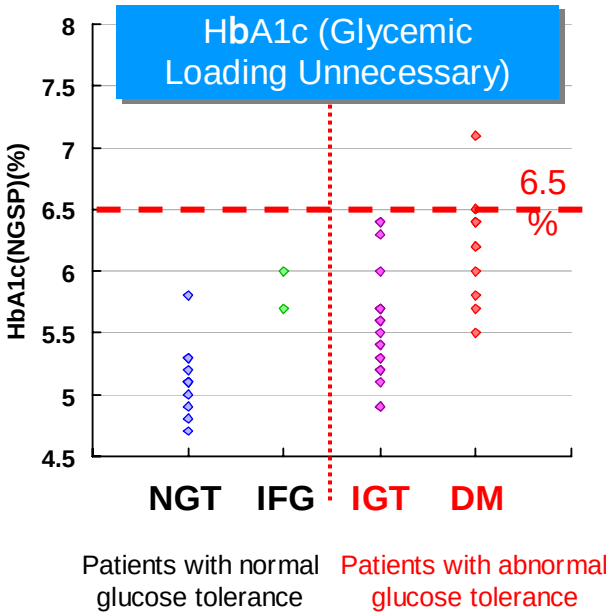
Glucose AUC (Minimally Invasive Body Fluid Extraction Technology): Verification Results through Clinical Research

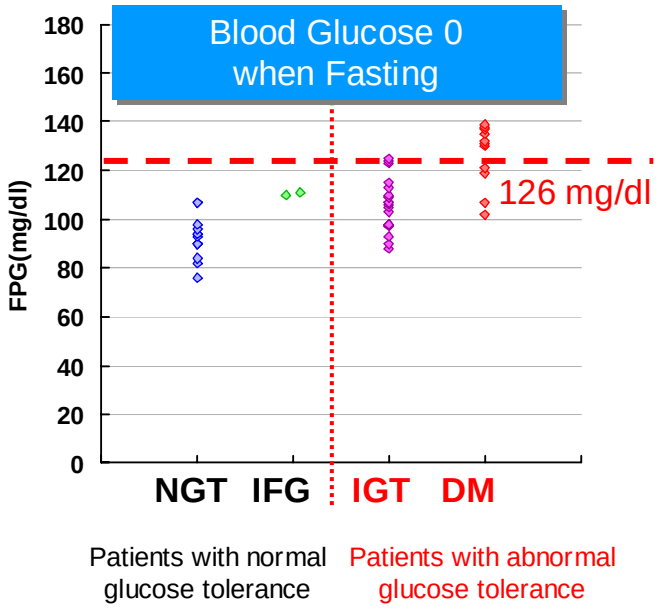
Diabetes Screening



Measured by administering OGTTs to 50 outpatients undergoing diabetes tests

Comparison with Conventional Screening Indicators





Note: Published in article in *Diabetes Technology and Therapeutics*, June 2012

Continue efforts at academic conferences to heighten recognition of AUC as novel diagnostic parameter for early-stage diabetes

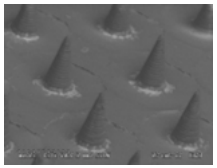
OGTT: Oral glucose tolerance test

Glucose AUC (Minimally Invasive Body Fluid Extraction Technology): Structural Unit

Body Fluid Sampling Kit

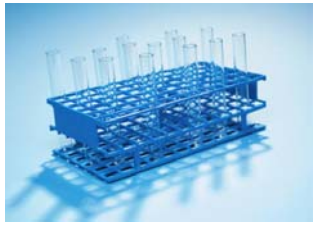
Paracentesis tool

Gel patch



Micro needle array

Assay Kit



Tubes for collecting tissue fluid within gel

High-sensitive reagent for glucose measurement

Future developments:

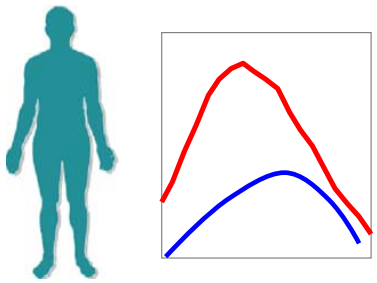
With the aim of receiving approval within one year, establish study group, while at the same time conducting body fluid sampling and developing assay kits

2. (3) Practical Stage: Status of Progress on Development Themes

3) Diabetes Bio-Simulation

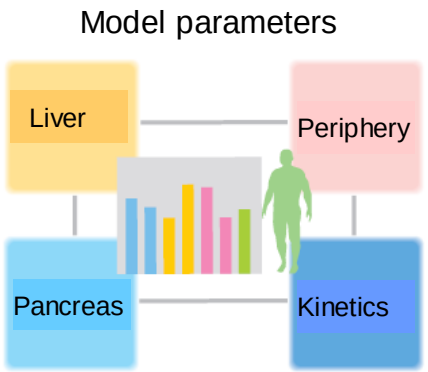
Diabetes Bio-Simulation

Input



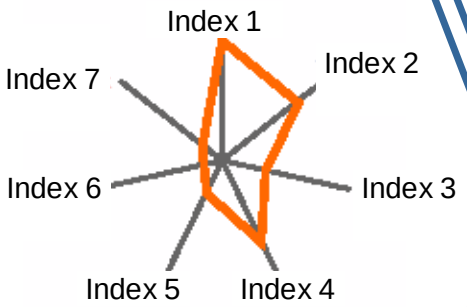
Input of test values for diabetes patients

Analysis



Analysis of clinical conditions from the viewpoint of insulin secretion and action

Output



Output of disease profiles as analysis results

Treatment

Support information for personalized therapeutic strategies

Quantification of individual's disease state by simulation of pancreas function, insulin function and sugar metabolism

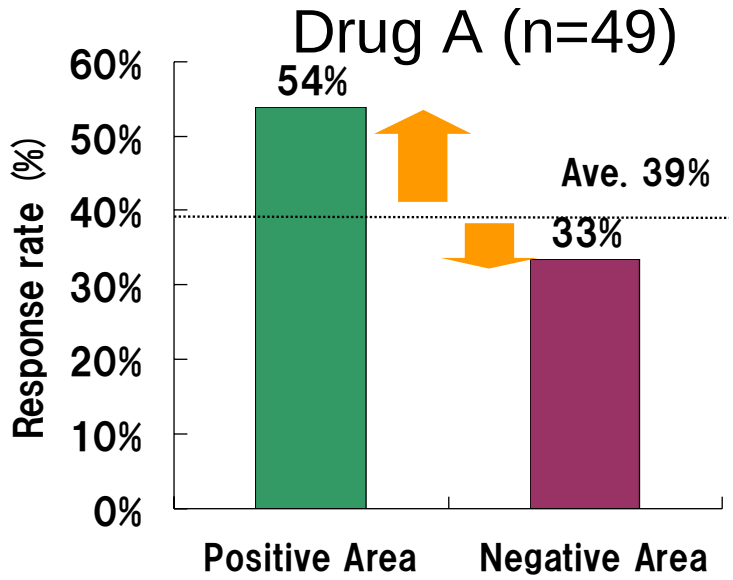
Diabetes Simulation: Clinical Research Result Showing Predicted Response to Oral Preparation

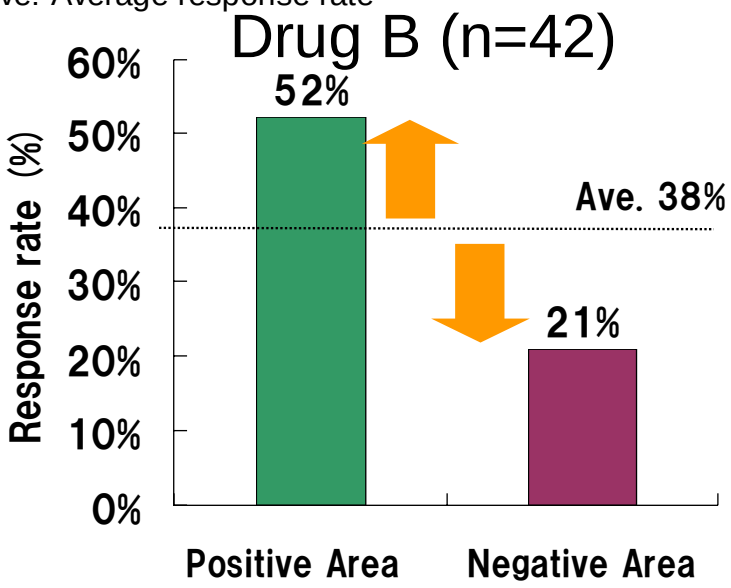
Shanghai Jiao Tong University School of Medicine Renji Hospital

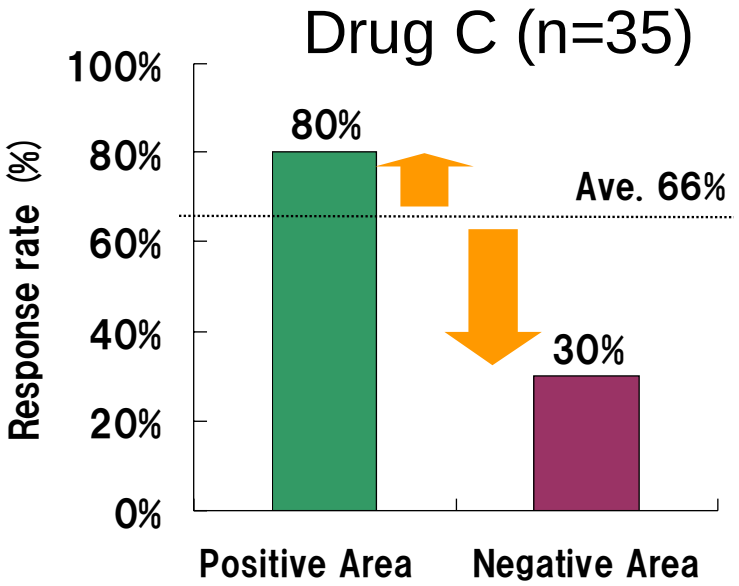
Response prediction based on the disease status inferred from OGTT data at the start of treatment

10% or more reduction in HbA1c after six months of treatment with oral preparation = response

Ave: Average response rate







(IDF @ Dubai, 2011/12, Seike et al)

Status of Clinical Research at Multiple Centers

- Objective　Using the diabetes simulator, confirm predictive capabilities of response to oral preparation at multiple institutions
- Target cases　200

- Participating institutions
  Total of five institutions, including level 3 hospitals, centered on Shanghai Jiao Tong University

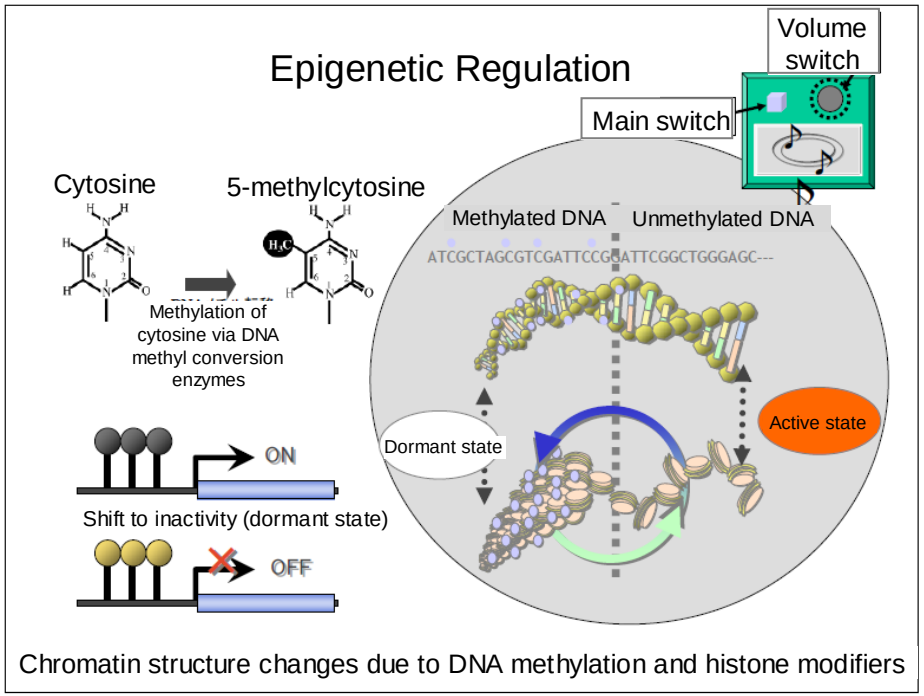
Future developments:

During fiscal 2012, conduct clinical evaluations in target markets in China and other emerging markets. Aim to move to practical stage from fiscal 2013, and consider expanding business into ICT-based personalized medicine and the drug development process

2. (3) Practical Stage: Status of Progress on Development Themes

4) Methylated DNA

Methylated DNA



Contributes to onset of cancer

Initiatives

- Establishment of methylation measurement system
  - Develop OS-MSP method
  - Construct automated pre-treatment system
- Collaborative research with Epigenomics
  - Colon cancer marker (SEPT9)
- Epigenomics submits PMA application in December 2011

Methylated DNA: Evaluation of the Clinical Value of Colon Cancer Diagnostics

Target

Nearly the same function as Epigenomics' results for a large-scale clinical study of Europeans and Americans (sensitivity of 67%, specificity of 88%)

Patients with colon cancer	Positives / Total	Sensitivity (%)	Specificity (%)
	24 / 37	65	-
Healthy patients	Negatives / Total	Sensitivity (%)	Specificity (%)
	6 / 42	-	86

Future developments:

From fiscal 2012, verify clinical value, such as early detection of colon cancer. Based on these results, conduct clinical research (expected to take 3–7 years) in advance of application/approval.

3. Status of Progress at the Research Stage

Kaoru Asano,
Executive Officer, Executive Vice President

3. Status of Progress at the Research Stage

(1) New Activity: Metabolome Analysis Technology

1) Early Detection of Diabetic Nephropathy

(2) High-Performance Protein Recombination Technology

1) Sugar Chain Modification Technology

(3) Approach toward e-Health

1) Genetic Diagnosis Support System Using Secret Sharing Scheme

3. Status of Progress at the Research Stage

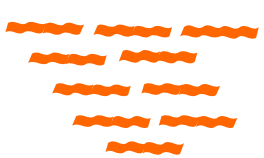
(1) New Activity: Metabolome Analysis Technology

1) Early Detection of Diabetic Nephropathy

About Metabolome

Gene

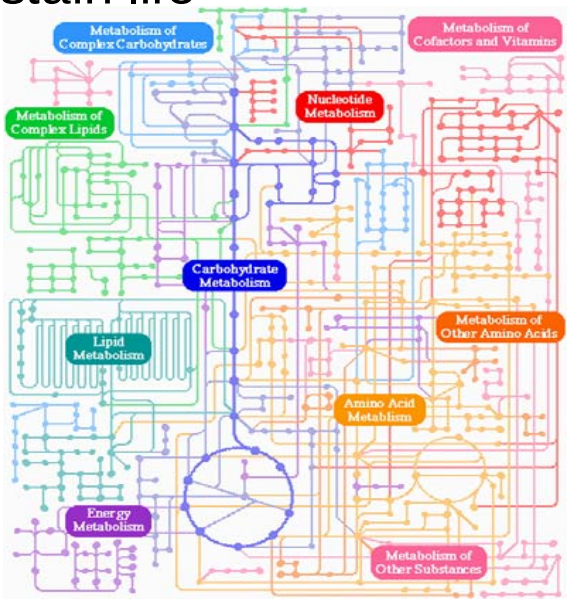
mRNA



Protein

Cell

- Metabolism:
  Homeostatic regulation of biochemical reactions that sustain life

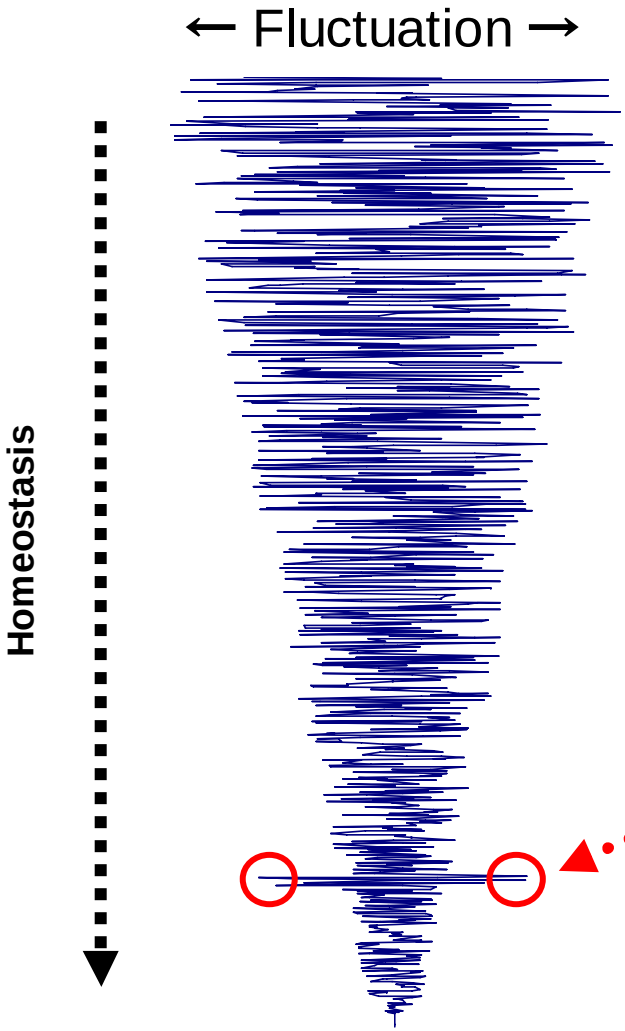


Metabolic map
= Route map of chemical reactions

- Metabolites:
  The intermediates and products of metabolism

- Metabolome:
  Randomized approach of metabolism

Metabolic Disorders a Source of Homeostatic Breakdown



transcriptome
(100,000)
Very complex

proteome
(20,000)
Very complex

metabolome
(3,000)
Relatively simple

Homeostasis is:
The behavior of a system that tends to maintain a stable, constant condition of properties

II

For example, maintaining a balance between blood's many components

Homeostatic breakdown results in diseases, such as diabetes, hyperlipidemia and gout

These diseases can be distinguished by changes in the level of metabolites in the blood

Transcriptome: Comprehensive analysis and research procedure involving the total set of transcripts, including mRNA, of an organism

Proteome: Comprehensive analysis and research procedure involving the proteins expressed by an organism

Metabolome: Comprehensive analysis and research procedure involving the metabolic products (low-molecular compounds) present in an organism

Metabolomics is an effective means of pursing changes in condition owing to lifestyle diseases, aging and other acquired factors

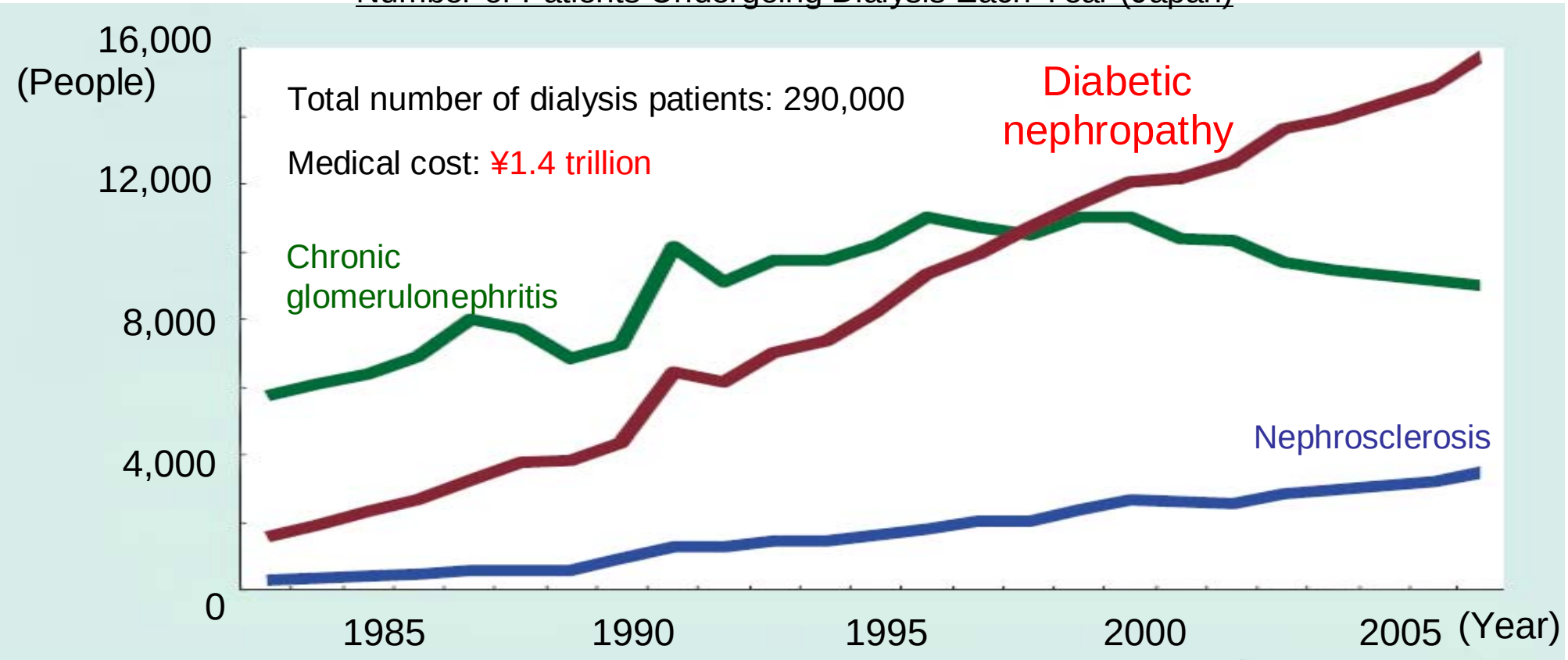
1) Early Detection of Diabetic Nephropathy: The Background of Diabetic Nephropathy

Number of patients: Worldwide, 28 million (3 million in Japan), occurring in approximately 30% of diabetes patients

Of patients with chronic kidney disease, there is a marked increase in the percentage of people undergoing dialysis

→ Management of diabetic nephropathy enables the control of patients on dialysis

Number of Patients Undergoing Dialysis Each Year (Japan)



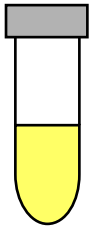
From the CKD Medical Care Guide

1) Early Detection of Diabetic Nephropathy: Marker Discovery Concept

Ongoing hyperglycemia → Early stage of kidney pathology: Kidney tissue disease resulting from metabolic disorders in kidney cells → Manifestation stage of kidney pathology: Breakdown of the filtration function = albumin leakage

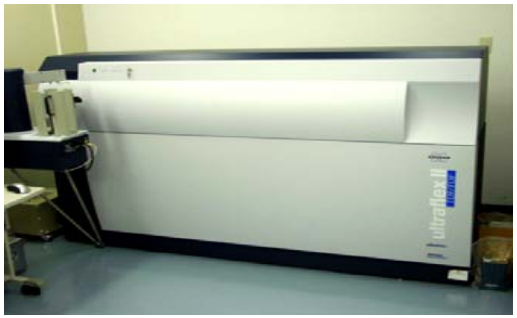
Metabolites in the urine detected during the early stage of kidney disease ⇒ Metabolome marker

Perform marker discovery using metabolome analysis



Early-stage urine

Metabolite extraction →



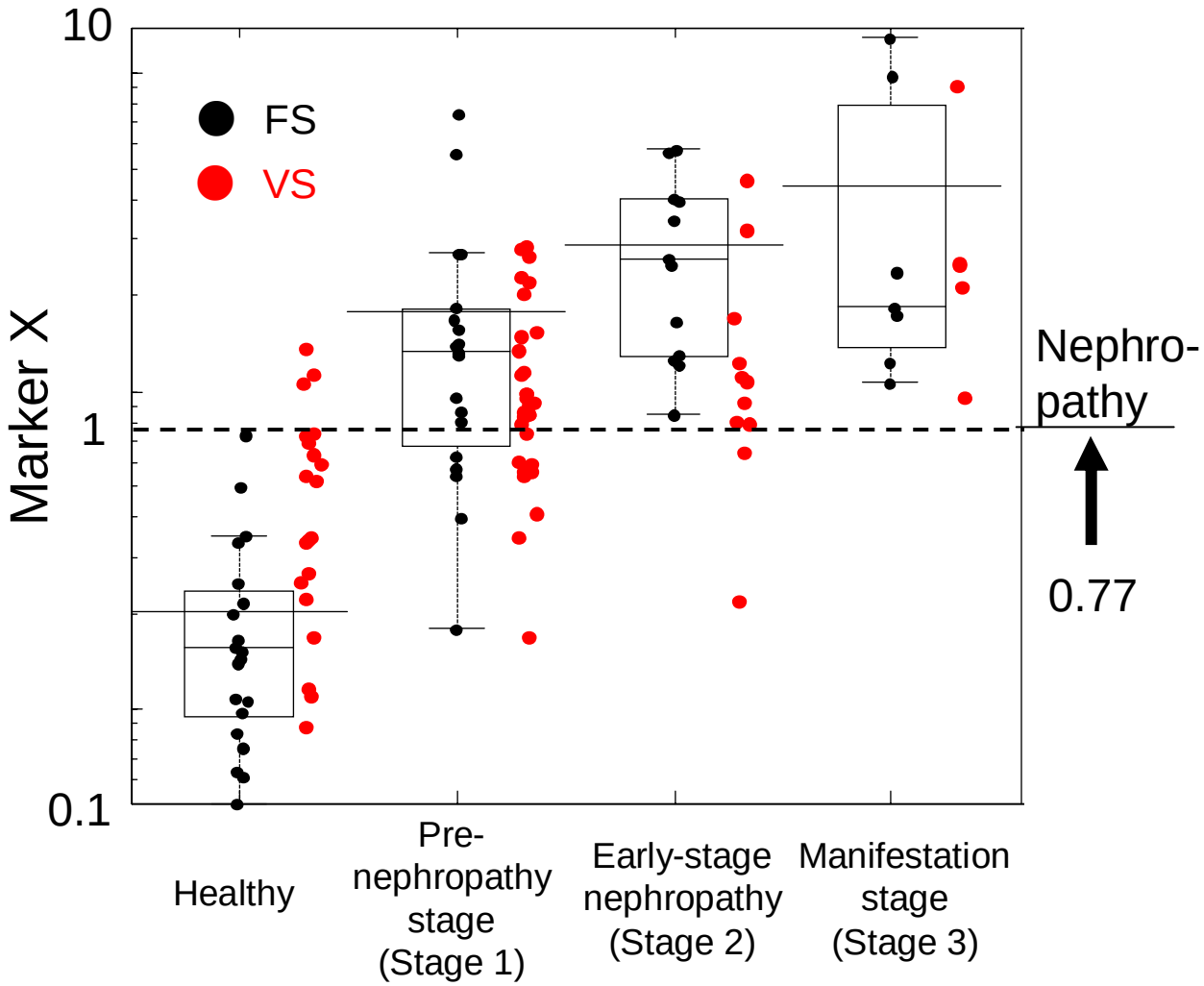
CE-MS measurement

Database search →

Selection of diagnostic marker candidates

Collaborative research: Human Metabolome Technologies

1) Early Detection of Diabetic Nephropathy: Clinical Value of Marker Candidates



Feasibility study (FS)
Sensitivity 100% / Specificity 100%

Validity study (VS)
Sensitivity 88% / Specificity 85%

Perform additional validation through retrospective and prospective studies, including for other marker candidates, to ascertain practical applications

3. Status of Progress at the Research Stage

(2) High-Performance Protein Recombination Technology

1) Sugar Chain Modification Technology

Application of Recombinant Silkworms

Recombinant silkworms

Development of raw materials for diagnostic reagents

- Immunochemistry reagents
- Coagulation reagents

Contract manufacturing for protein

ProCube

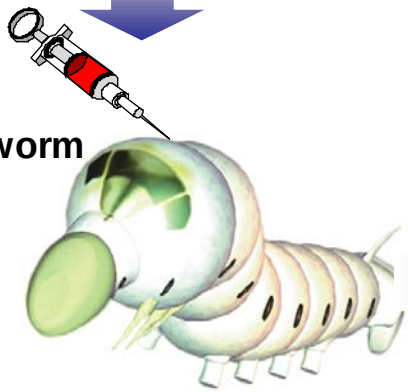
Highly functional protein creation technology

- Sugar chain modification

Protein Expression Using Recombinant Silkworms

Target gene

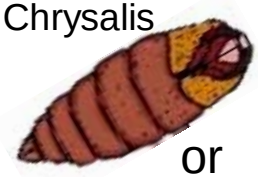
Introduce gene into larval virus



Infect with recombinant virus

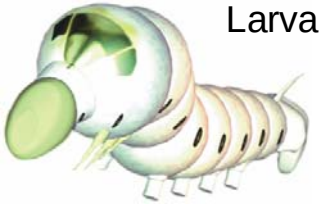
Recombinant virus produces protein in silkworm

Chrysalis



or

Larva



Preparation of chrysalides and larvae

Purification

Protein raw material

Production Characteristics of Various Recombinant Proteins

	Produc-tivity	Cost	Production Period	Nearness to Human Type	Sugar Chain Structure (N Type)
E. Coli	○	◎	○	×	(None)
Yeast	○	○	○	△	
Silkworm	○	○	○	○	
Animal	×	×	×	◎	

Acetyleglucosamine Mannose Galactose Sialic acid

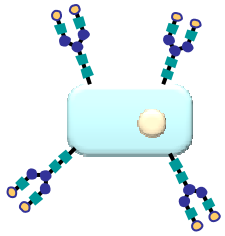
Expectations for Controlling the Sugar Chain Structure

* The sugar chain structure substantially impacts protein function (activity, stability, solubility)
  - High activity
  - High stability
  - Increased solubility

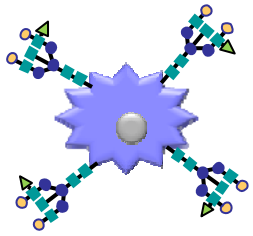
→ Improved product function

* Recognizing the sugar chain structure contributes to higher diagnostic agent functionality (qualitative alteration)
  - Development of antibodies that can recognize the sugar chain structure

→ Improved sensitivity/specificity

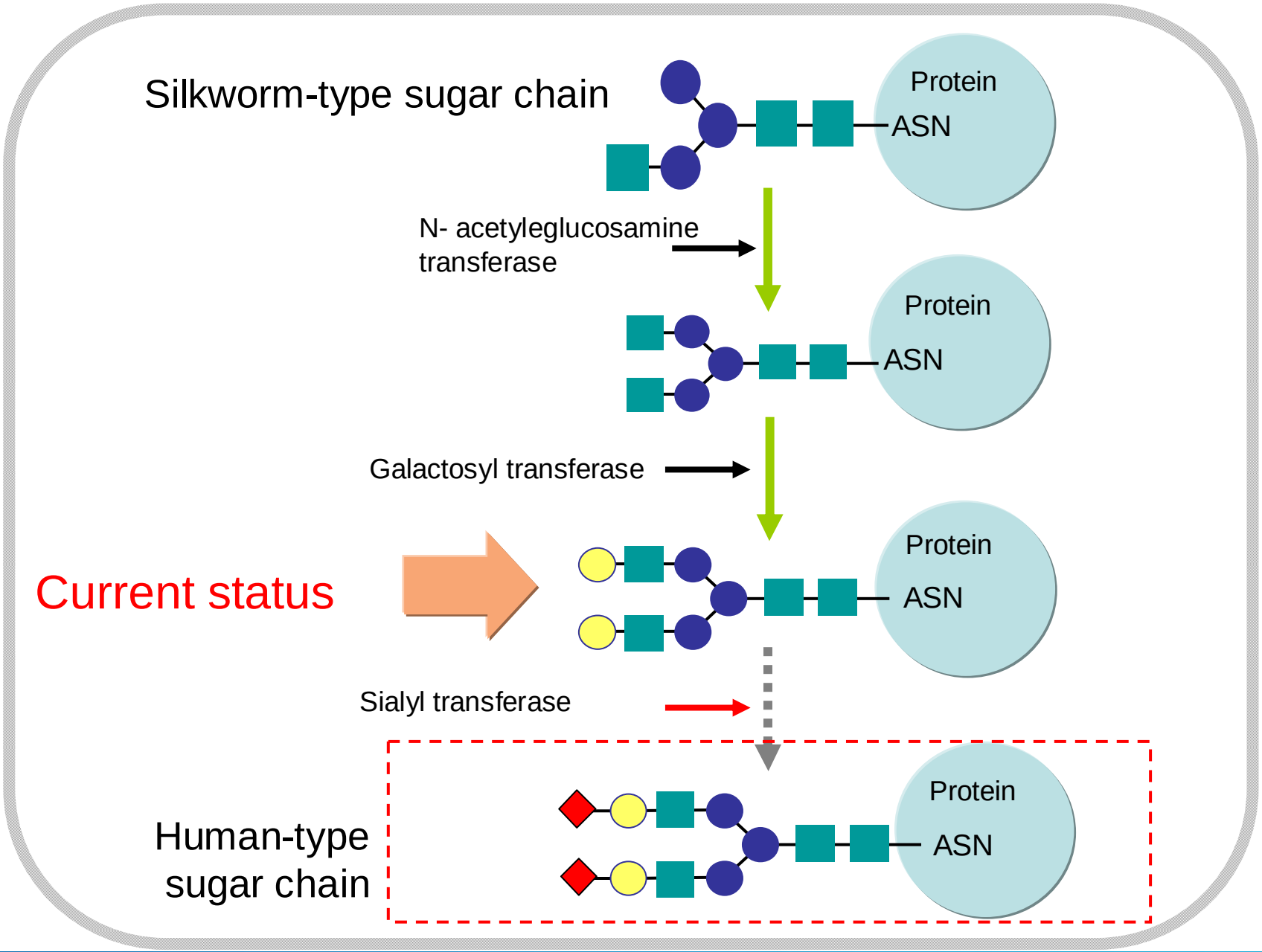


Normal cell



Cancer cell

Status of Sugar Chain Structure Control



3. Status of Progress at the Research Stage

(3) Approach toward e-Health

1) Genetic Diagnosis Support System Using Secret Sharing Scheme

The Era of Personal Genomes

Cost of Genome Analysis

- 2003 International Human Genome Project
  up to ¥100 billion
- Currently
  10 days, ¥500,000
- In two years
  5 days, ¥100,000
- 2020
  Within 1 hour, ¥10,0000

Cancer Genome

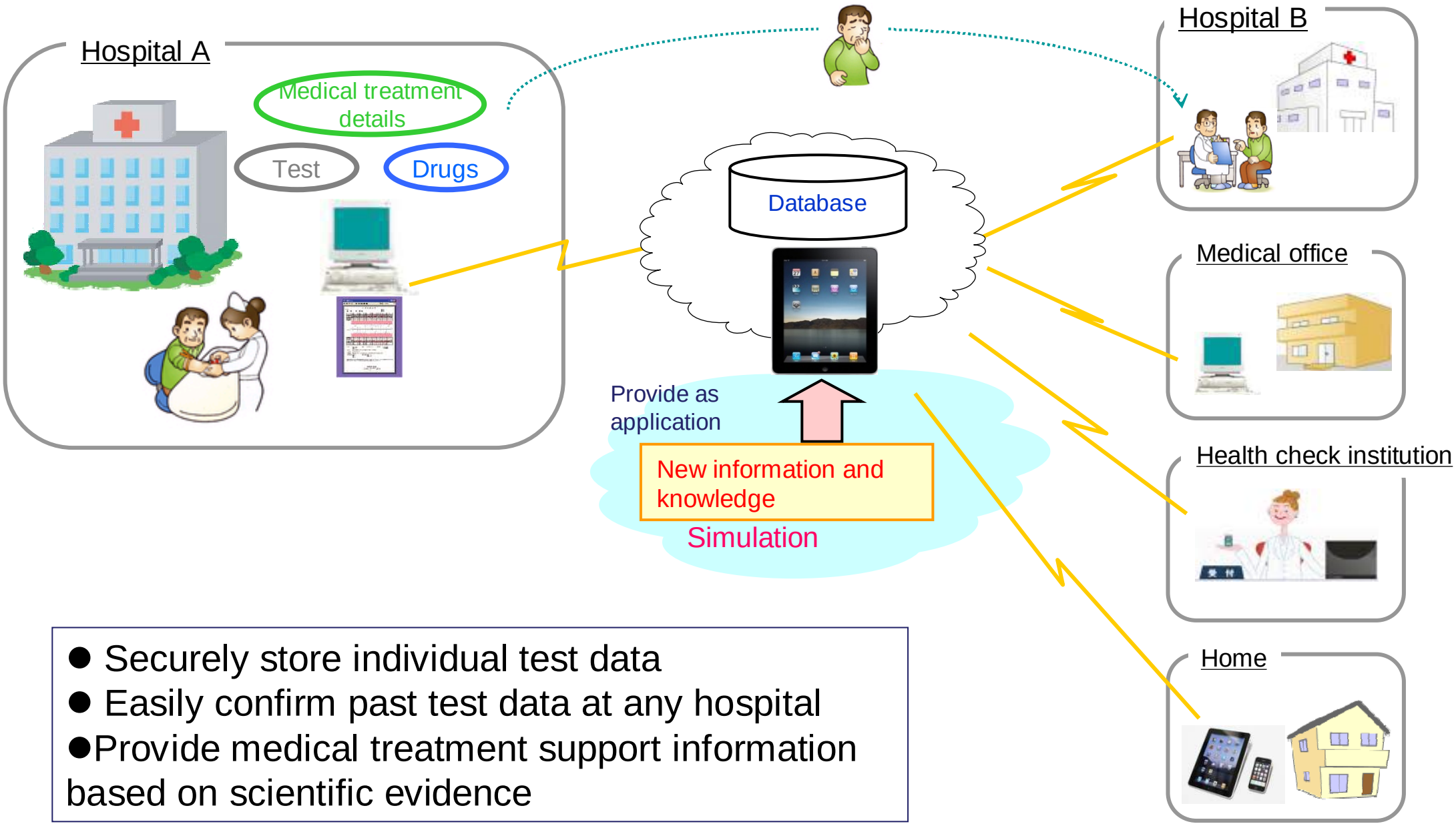
- International Cancer Genome Consortium
  - Creating catalog of major cancer genome abnormalities
  - Includes information on all genomes for 50,000 people, including 25,000 cancer samples

Supercomputer “K”

•The use of a supercomputer for analysis leads to the generation of new knowledge related to cancer

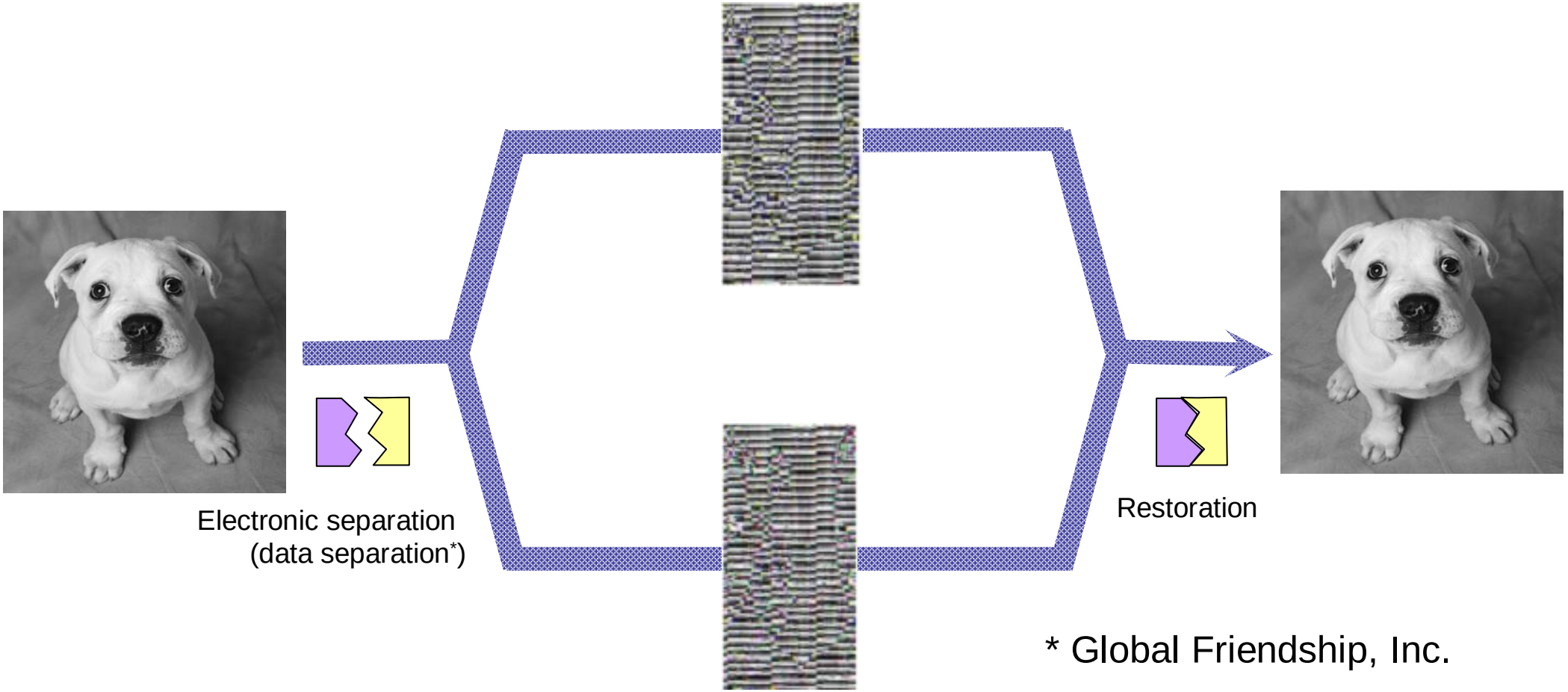
Personalized medicine based on DNA information:
The time is nearing when anyone will be able to present their DNA when obtaining medical care, as with medical insurance cards today

Using ICT to Realize Personalized Medicine



- Securely store individual test data
- Easily confirm past test data at any hospital
- Provide medical treatment support information based on scientific evidence

Secret Sharing Scheme (Data Separation*)

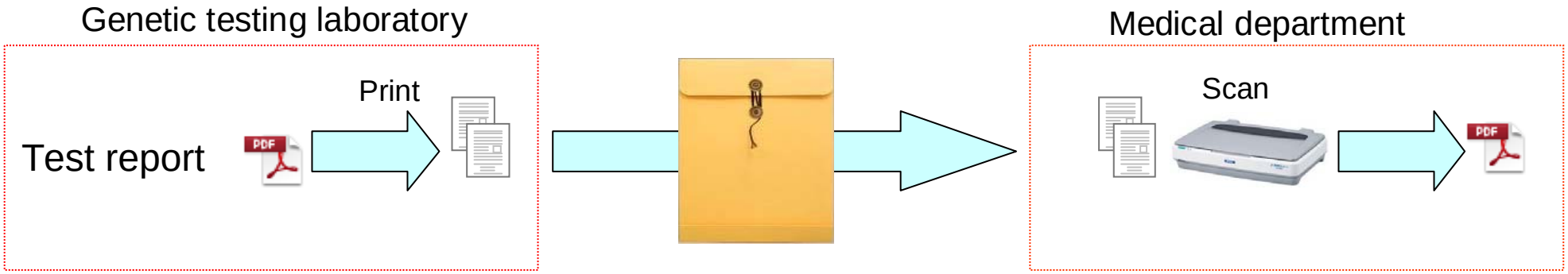


* Global Friendship, Inc.

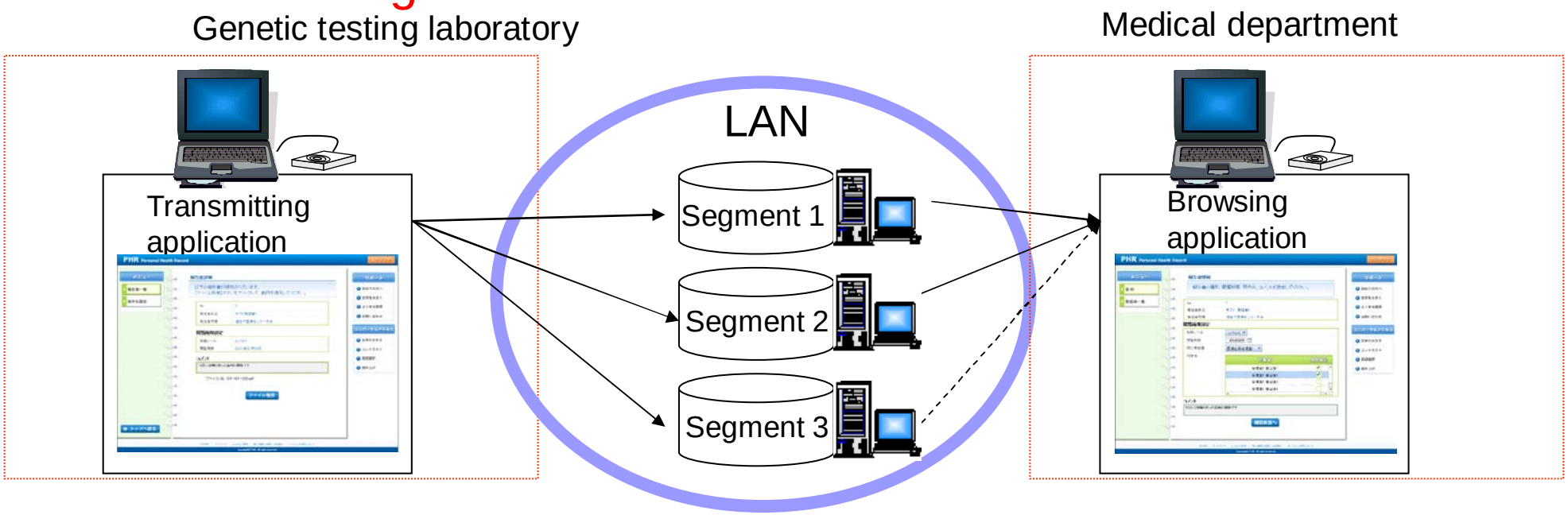
Key point: Even if personal data is included in the original data, data that is separated at the bit level does not constitute personal information.

Demonstration Experiments of Gene Diagnosis Support System Using Secret Sharing Scheme

Now



Verification testing



We Believe the Possibilities.

Sysmex Corporation

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