The 15th Technology Presentation

March 9, 2018

Sysmex Corporation

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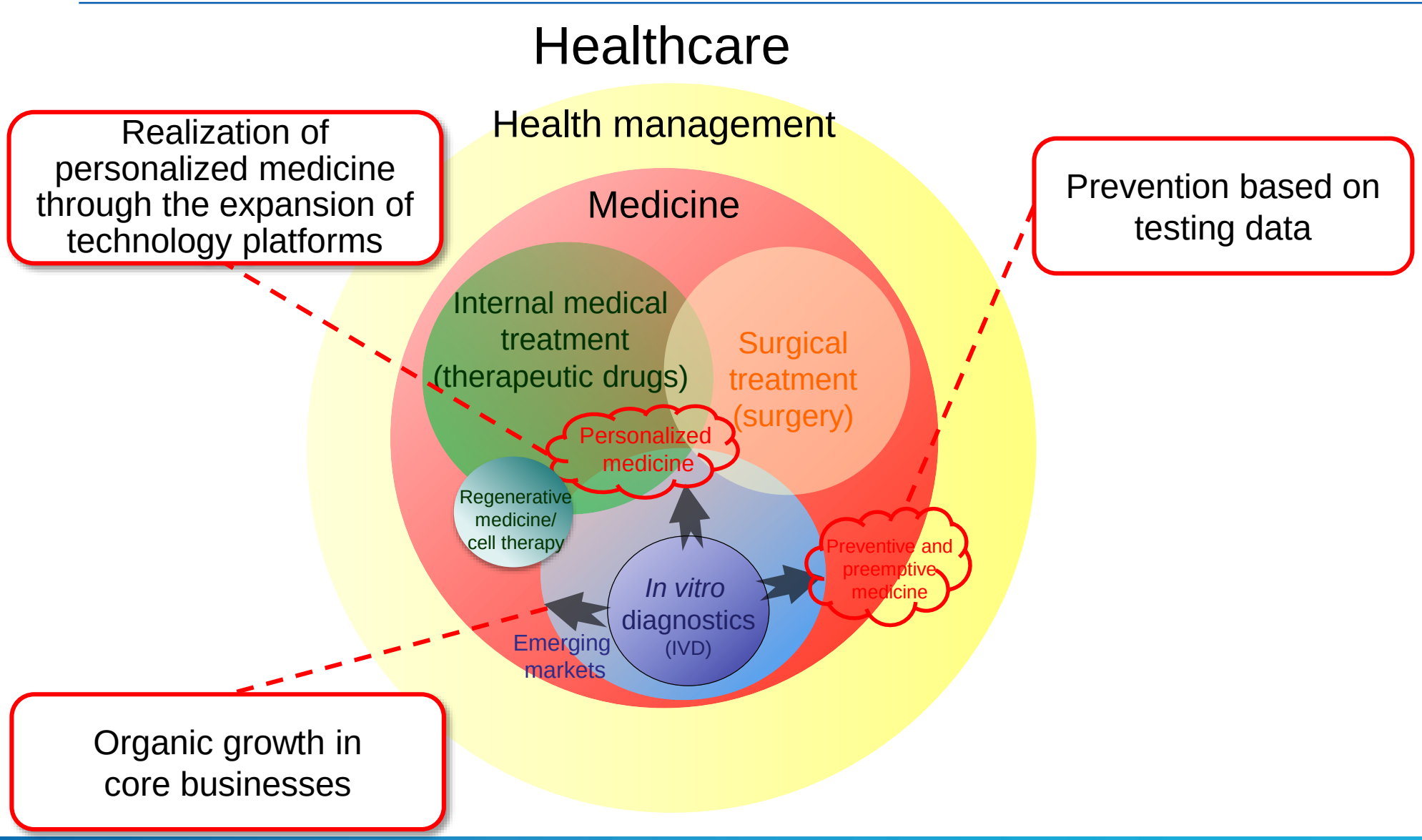
2. Technology Strategy Progress and Future Initiatives

Kaoru Asano,

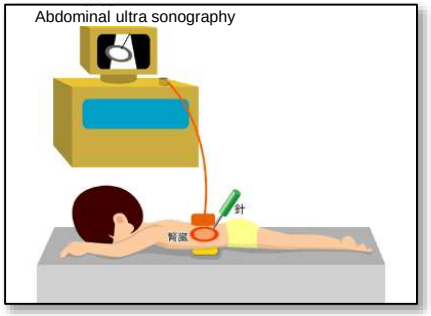
Member of the Managing Board and Senior Executive Officer,
Senior Managing Director

The Healthcare Market



Liquid Biopsy

Conventionally

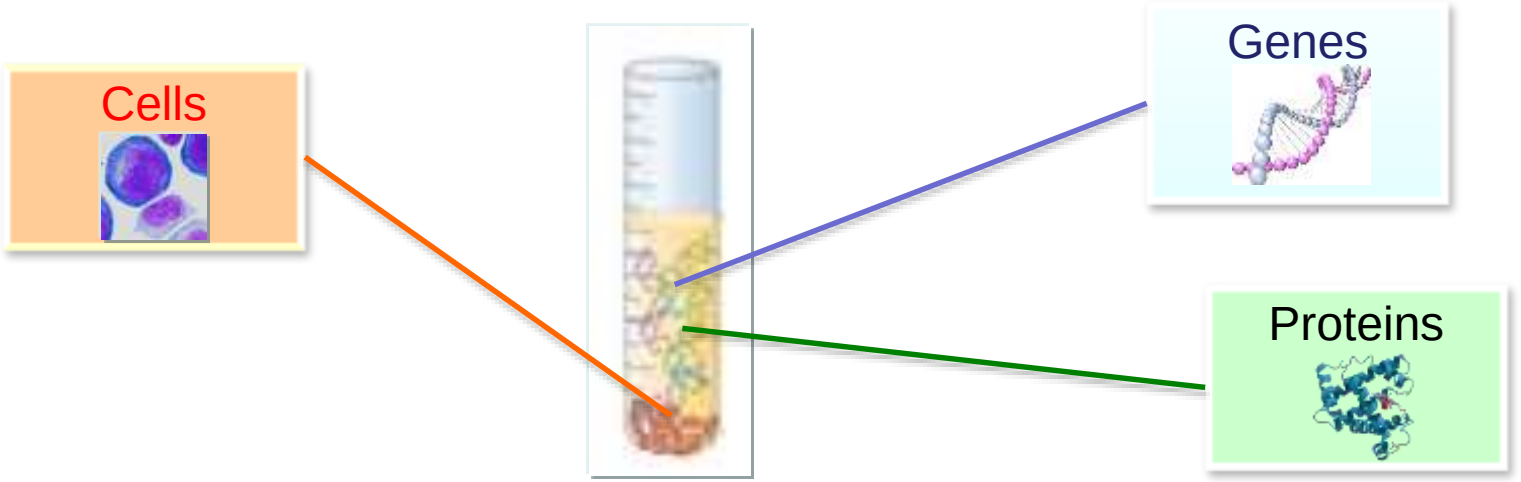


Invasive sample collection
of affected organ/tissue

From biopsy to liquid biopsy

Future

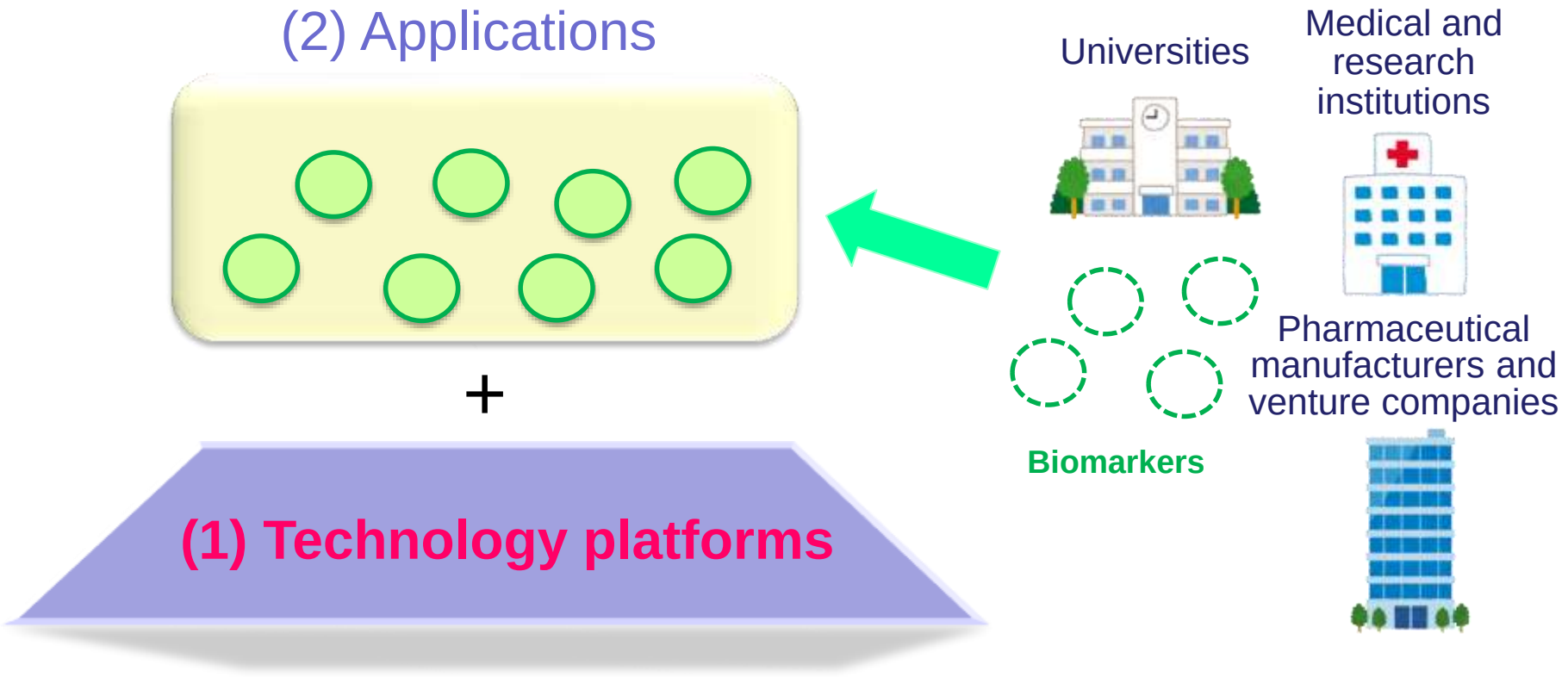
Minimally invasive sample collection
of disease-derived components in
the blood (bodily fluid)



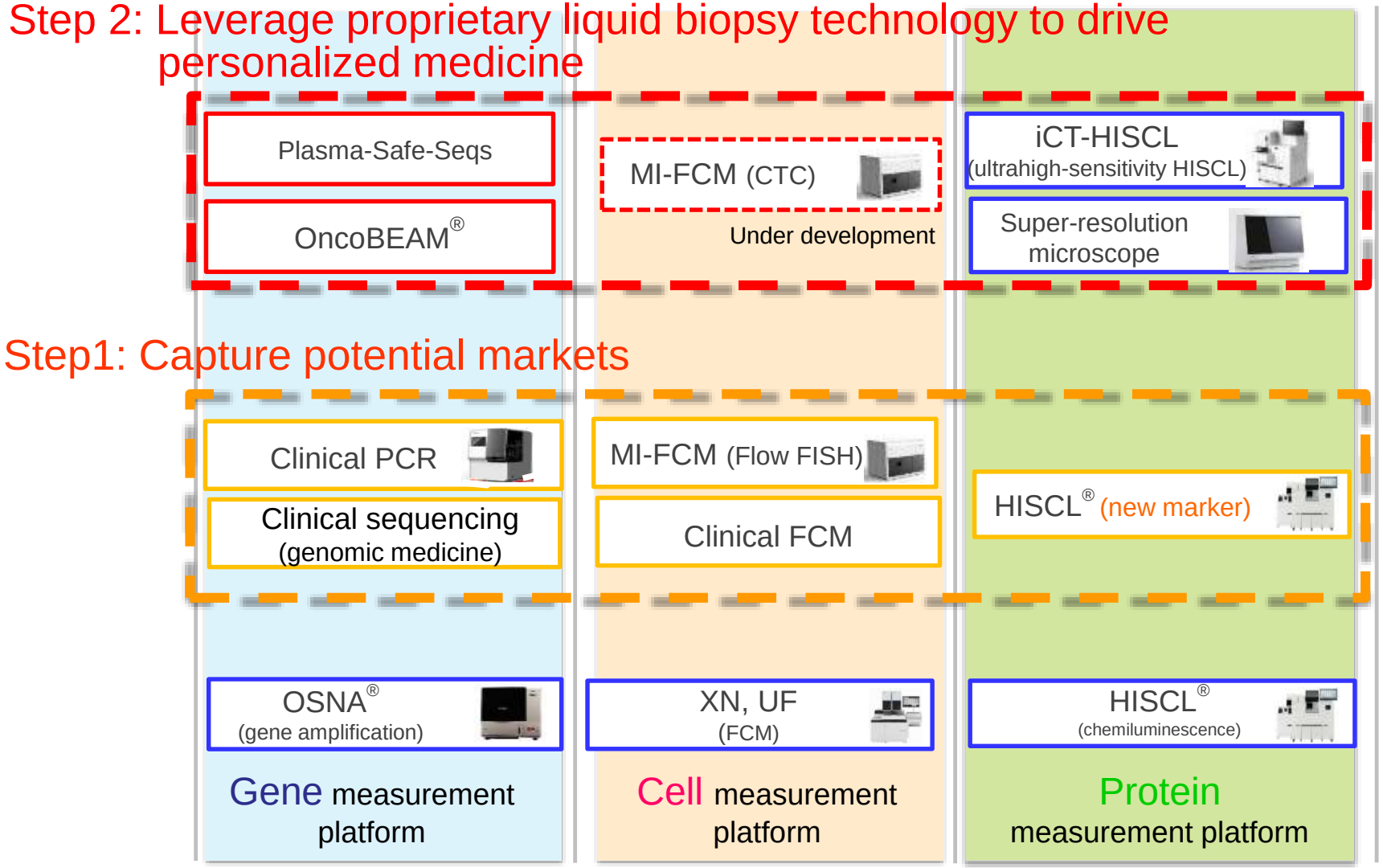
Detection sensitivity will need to be 100 to 1,000 times higher than conventional methods

Technology Strategy

First, establish technology platforms and promote open innovation to develop applications with high clinical value.

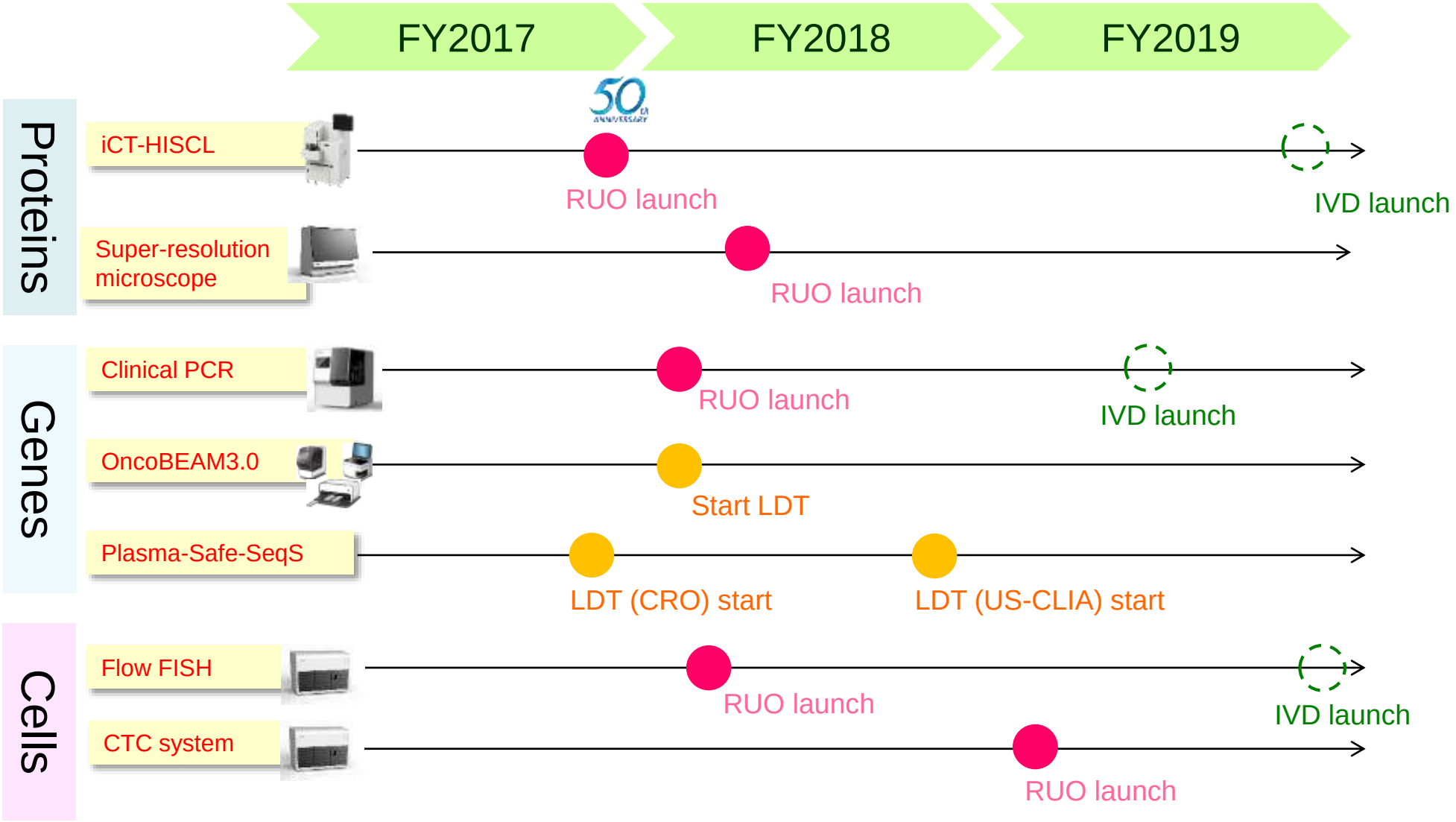


Expansion of Technology Platforms*



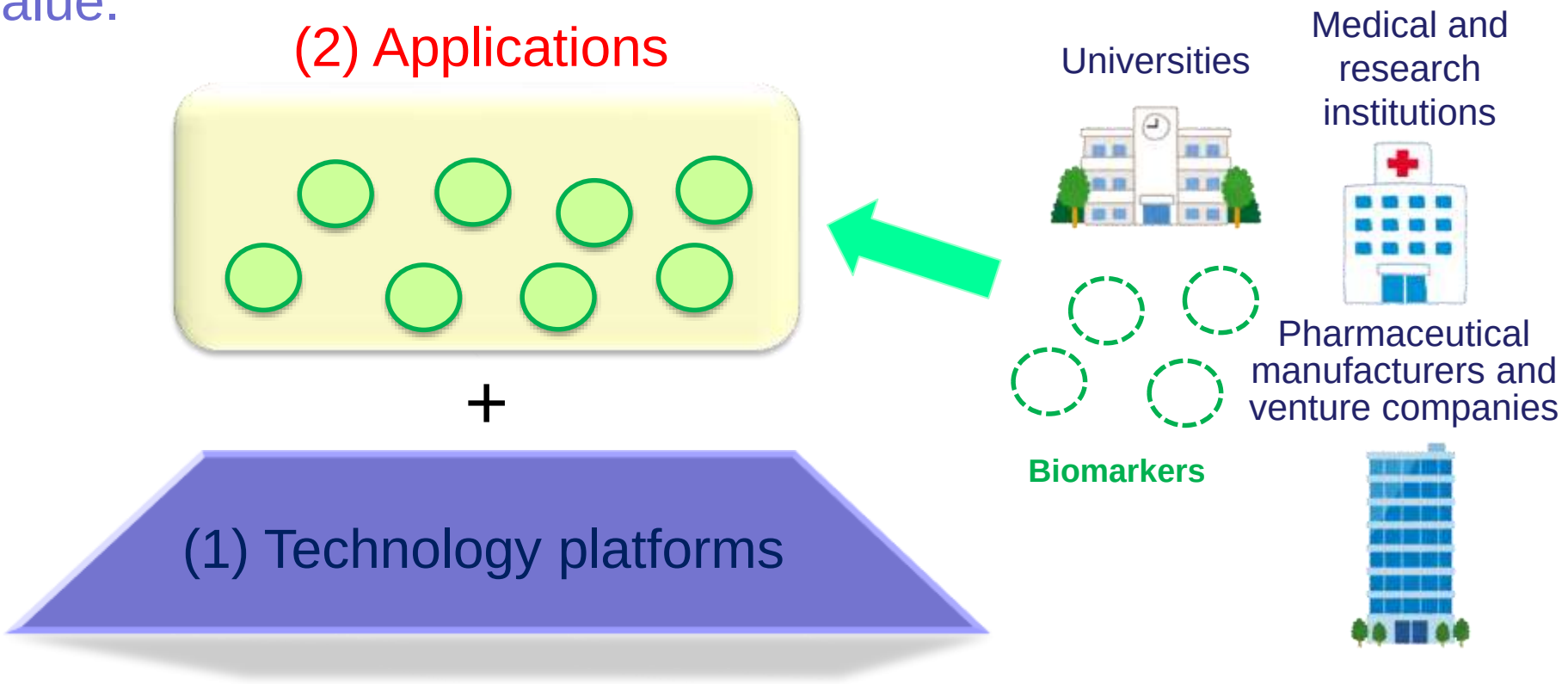
* Rearranged into commercialization steps

Technology Platform Launch Plans



Technology Strategy

After establishing technology platforms, promote a process of collaborative innovation with customers for the development and commercialization of applications with high medical value.



R&D Strategies Leading to Commercialization

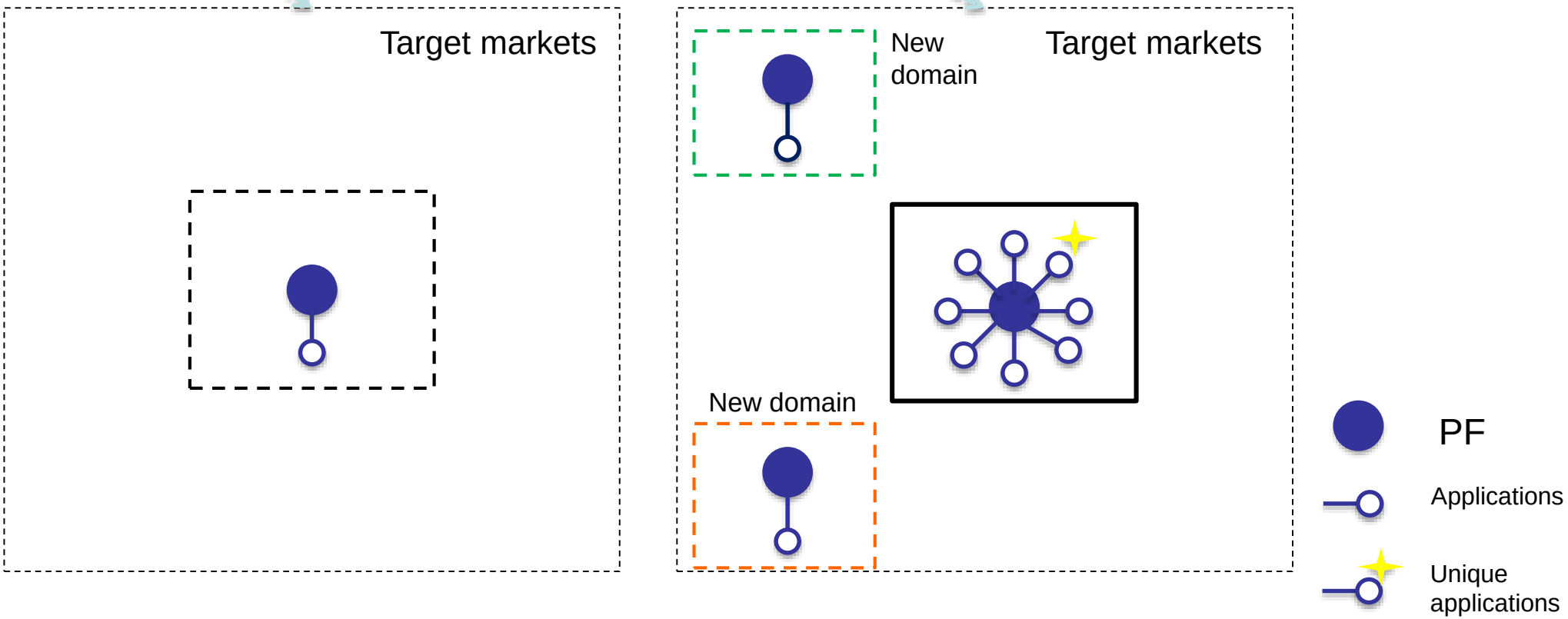
Strategy (1) Develop applications with customers in a process of collaborative innovation

Market recognition and manifestation process
(process of collaborative innovation with customers)

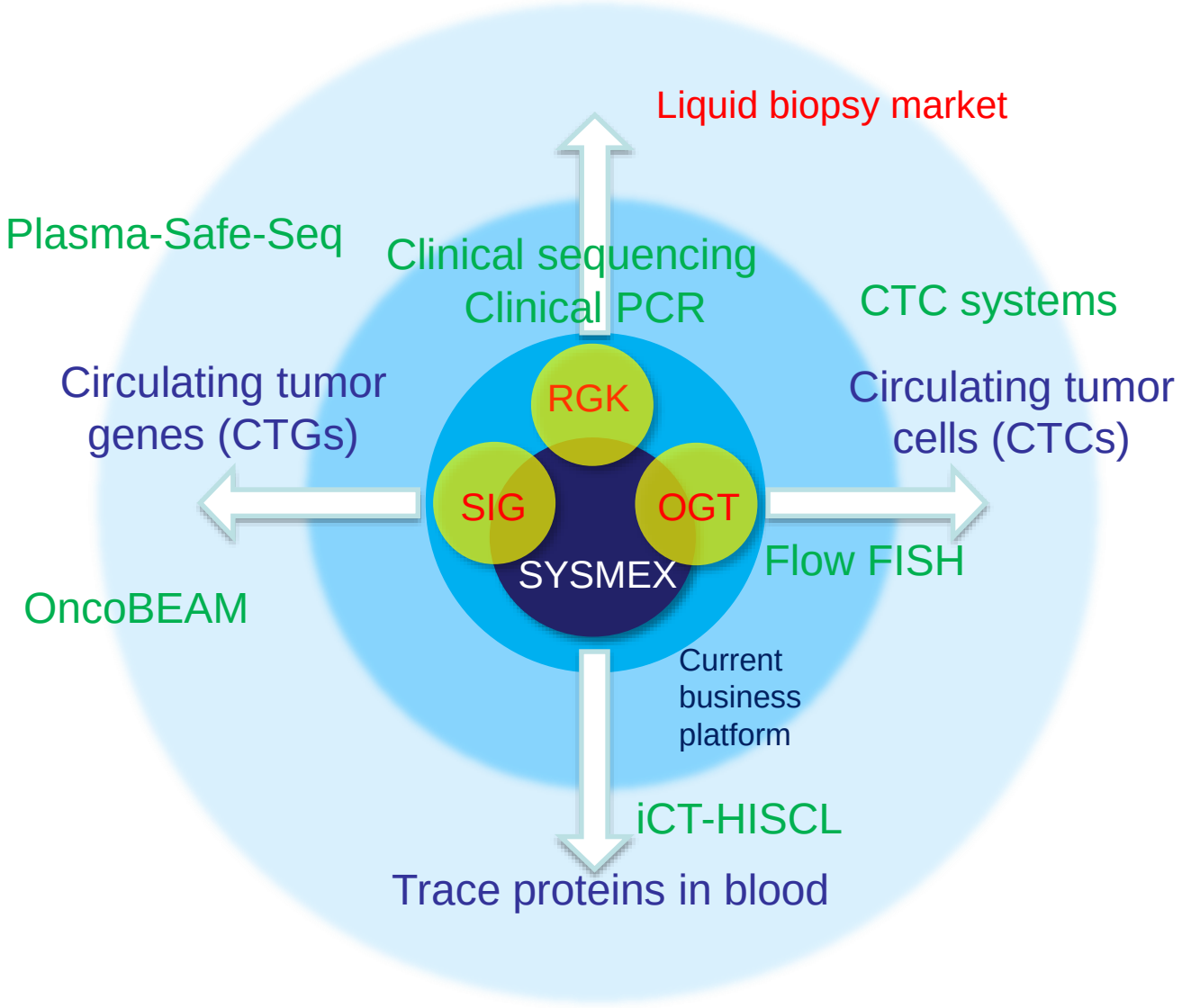
Bearing process

RUO
LDT (CRO)

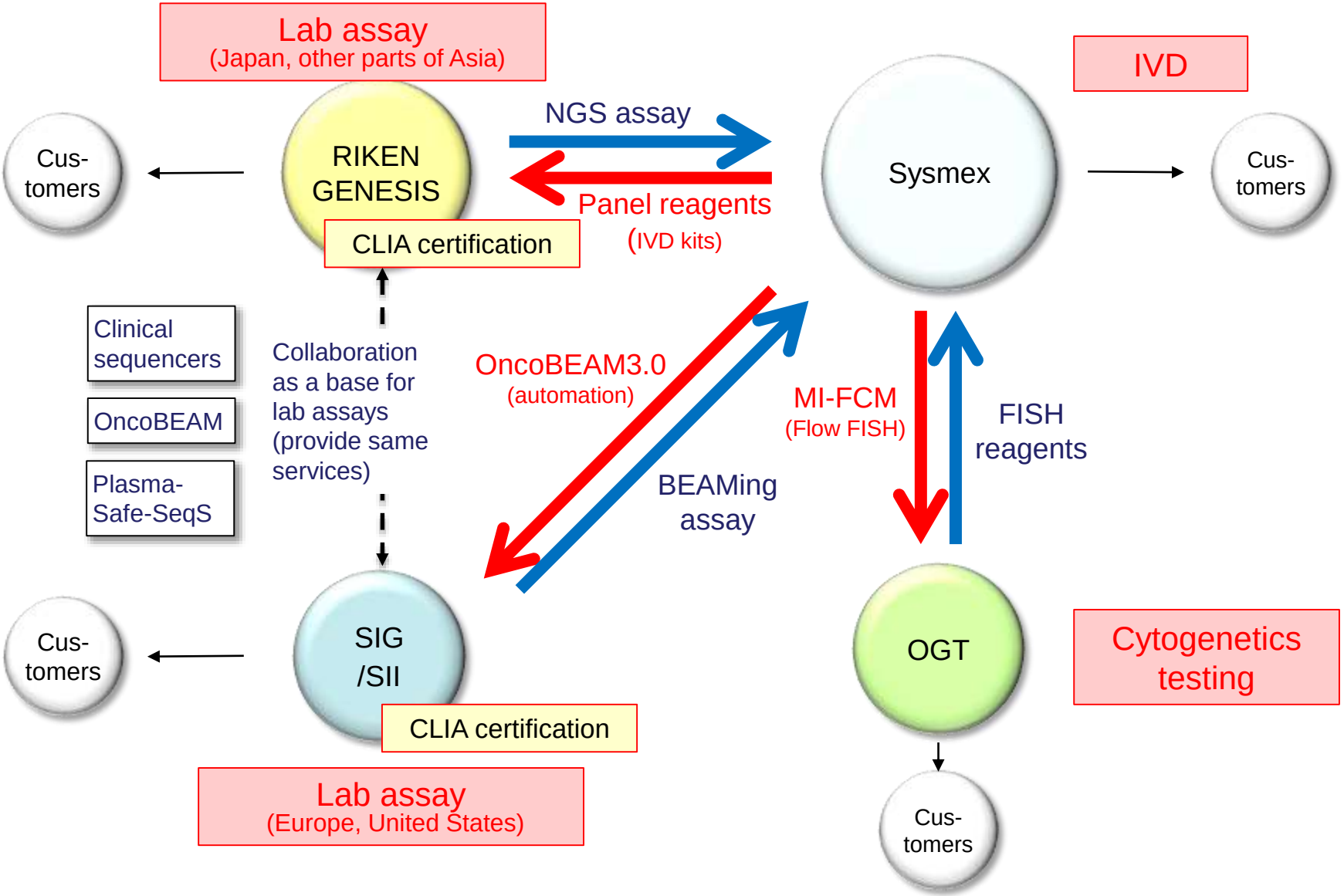
IVD



Strategy (2) Leverage Synergies with Group Companies

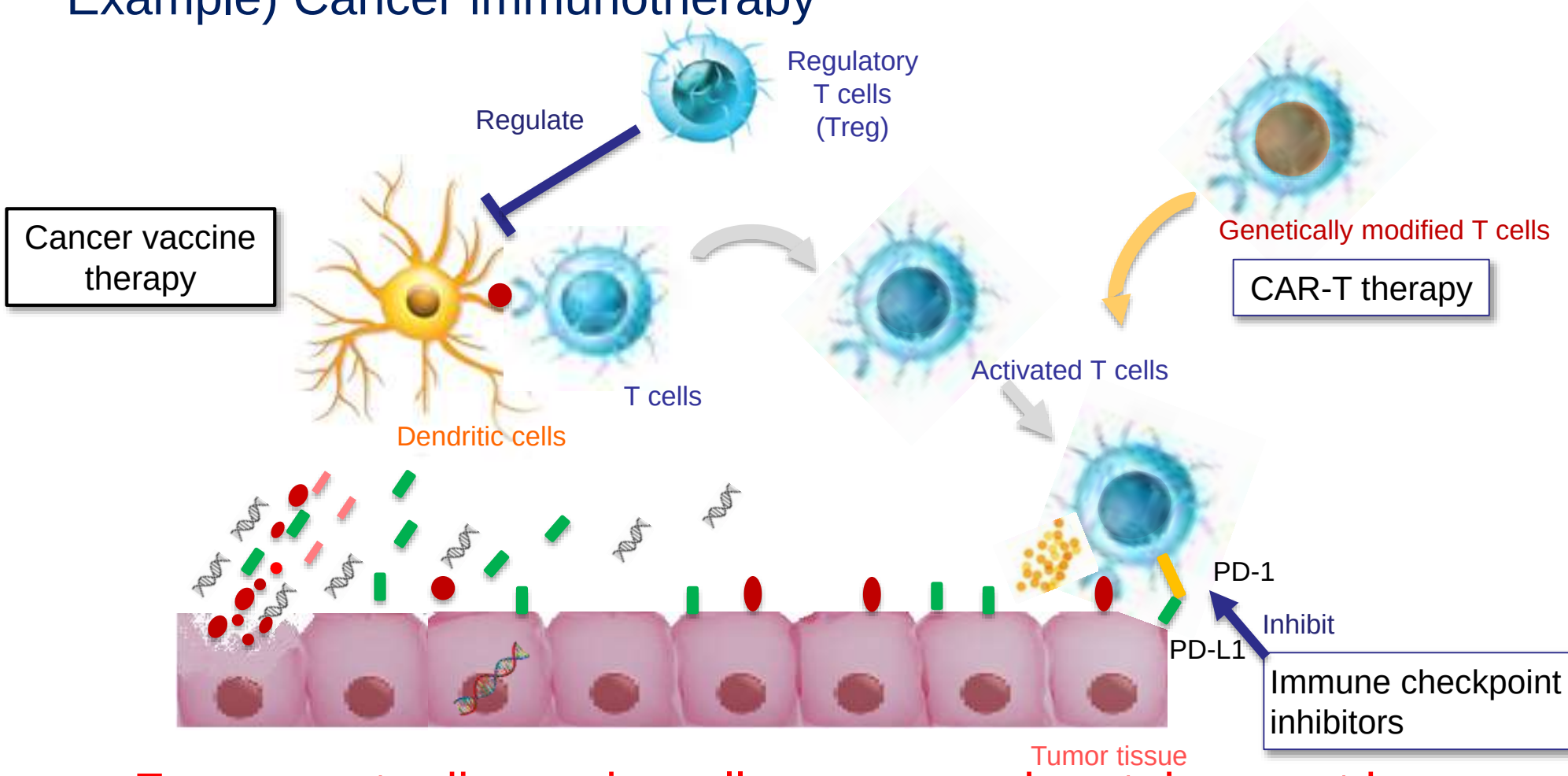


Strategy (2) Leverage Synergies with Group Companies



Strategy (3) Leverage Strengths of the Gene, Cell and Protein Platforms

Example) Cancer immunotherapy



For accurate diagnosis, cells, genes and proteins must be analyzed in an integrated manner

Development of Applications toward Commercialization

Gene measurement platform

- Solid tumor
  - RAS
  - BRAF
  - EGFR
- OncoBEAM®

- Solid tumor
  - RAS
  - BRAF
  - EGFR
- Clinical PCR

Cell measurement platform

- MI-FCM
  (CTC system)

- Transplant testing
  - Bone-marrow transplant
- Leukemia
  - BCR-ABL
  - PML-RARα
  - • •
- MI-FCM
  (Flow FISH)

Protein measurement platform

- HDL function
- Alzheimer's disease
  - Tau
  - Aβ
- iCT-HISCL
  (Ultrahigh-sensitivity HISCL)

- Immune checkpoint inhibitors
  PD-1/PD-l1/CTLA-4
- Hepatic cancer recurrence
  AFP/PIVKAII/GPC3
- HISCL® (New marker)

Looking to the Future

- New testing methods
  - ✓ Exosome measurement technology (jointly developed with JVCK)

- Preventive and preemptive medicine
  - ✓ Development of compact immunochemistry instruments
  - ✓ Development of disease prediction methods using artificial intelligence (SFRC Lab)

- Regenerative medicine, cell therapy
  - ✓ Investment in Megakaryon
  - ✓ Joint R&D related to pre-transplant histocompatibility testing method for retinal pigment epithelial cells (RPE cells) derived from allogeneic iPS cells (Healios, Sumitomo Dainippon Pharma)

3. Progress Report on Technology Development

Kenji Tsujimoto,
Executive Vice President of Technology Strategy Division

(1) Progress in genomic medicine and Sysmex's initiatives

(2) Progress in technology development

(1) Technology for automating BEAMing technology (OncoBEAM 3.0)

(2) Plasma-Safe-SeqS technology

(3) Clinical PCR

(4) MI-FCM

(5) Initiatives targeting Alzheimer's disease

(1) Progress in Genomic Medicine and Sysmex's Initiatives For Genomic Medicine

■ Conventional testing (CDx)

Specific gene mutations

Specific treatment drugs

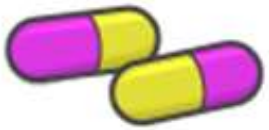
■ Panel testing

```
ATGATGATACTGGGTAAAGCCGGG
AATACCATTCGGAATAATTTAAGT
TCATTAGCAAAGGTGCTGCAACAA
AAGAGAGATGCAGTAAAAACTGGG
CACGGCTTATTCGGTAACAAGCTC
TTGGGAAGAGACGTGTATCTGCTG
GTCCATAACTACGAAGTCATGTCG
AACACCAATGGAGGCCCTATTATA
```

Gene profile

Provide information useful in the selection of treatment method (not Multi CDx)

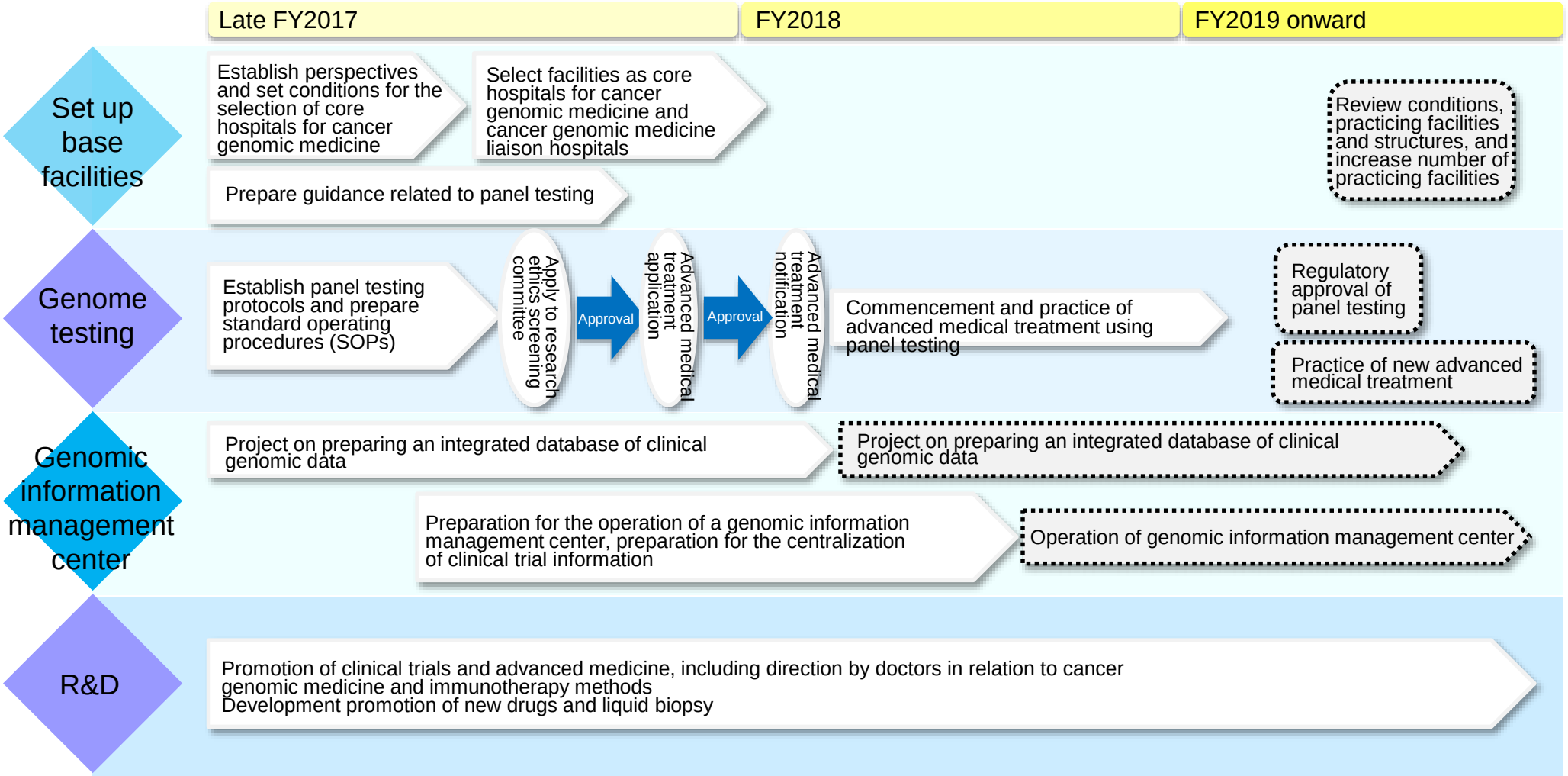
Expert panel



Selection of therapeutic drugs (including use off-label drugs)

Moves by the Japanese Government to Implement Genomic Medicine

■ Putting a system into place in FY2018 with a view to clinical practice

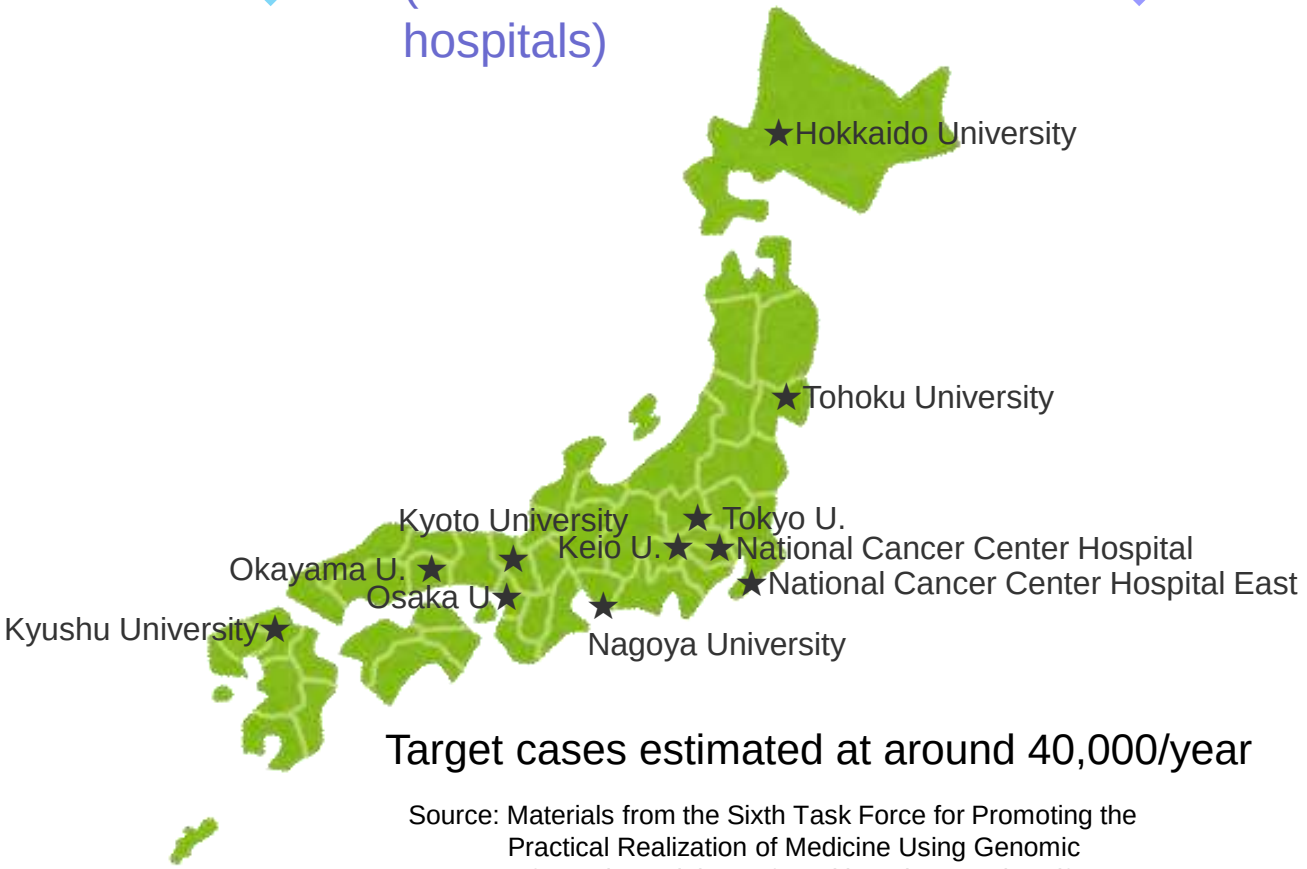


Source: “Overview of Report by the Roundtable Consortium on the Promotion of Cancer Genomic Medicine,” Ministry of Health, Labour and Welfare, partially revised

Recent Update

Set up base facilities

Eleven facilities selected as core hospitals for cancer genomic medicine (around 100 as liaison hospitals)



Target cases estimated at around 40,000/year

Source: Materials from the Sixth Task Force for Promoting the Practical Realization of Medicine Using Genomic Information, Ministry of Health, Labour and Welfare

Genome testing

From Q1 of 2018, the National Cancer Center is expected to begin applying advanced medical treatment

Subjects:

- 16 years or older
- Non-resectable or recurrent
  - Carcinoma of unknown origin
  - Solid tumor for which standard treatment has been concluded or is expected to conclude

Gene analysis using NCC Oncopanel

Expected number of cases: 205 to 350

About the NCC Oncopanel

Cancer diagnostic panel developed by the National Cancer Center

114 mutated and amplified genes (all exons)								12 fusion genes
ABL1	CRKL	ENO1	GNAS	MAP2K2/ MEK2	NOTCH2	POLD1	SMAD4	AKT2
ACTN4	BCL2L11/BIM	EP300	HRAS	MAP2K4	NOTCH3	POLE	SMARCA4/ BRG1	ALK
AKT1	BRAF	ERBB2/HER2	IDH1	MAP3K1	NRAS	PRKCI	SMARCB1	BRAF
AKT2	BRCA1	ERBB3	IDH2	MAP3K4	NRG1	PTCH1	SMO	ERBB4
AKT3	BRCA2	ERBB4	IGF1R	MDM2	NTRK1	PTEN	STAT3	FGFR2
ALK	CCND1	ESR1/ER	IGF2	MDM4	NTRK2	RAC1	STK11/LKB1	FGFR3
APC	CD274/PD-L1	EZH2	IL7R	MET	NTRK3	RAC2	TP53	NRG1
ARAF	CDK4	FBXW7	JAK1	MLH1	NT5C2	RAD51C	TSC1	NTRK1
ARIDIA	CDKN2A	FGFR1	JAK2	MTOR	PALB2	RAF1/CRAF	VHL	NTRK2
ARID2	CHEK2	FGFR2	JAK3	MSH2	PBRM1	RB1		PDGFRA
ATM	CREBBP	FGFR3	KDM6A/UTX	MYC	PDGFRA	RET		RET
AXIN1	CTNNB1/ b-catenin	FGFR4	KEAP1	MYCN	PDGFRB	RHOA		ROS1
AXL	CUL3	FLT3	KIT	NF1	PIK3CA	ROS1		
BAP1	DDR2	GNA11	KRAS	NFE2L2/Nrf2	PIK3R1	SETBP1		
BARD1	EGFR	GNAQ	MAP2K1/ MEK1	NOTCH1	PIK3R2	SETD2		

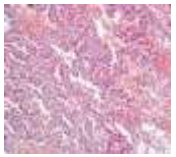
Use FFPE tissue DNA to detect gene mutation, amplification and fusion

Clinical Sequence Testing

Clinical sequencing in genomic medicine: comprehensive analysis of disease-related genes for diagnosis, treatment and prevention of cancer and similar diseases

Guaranteed accuracy

Tissue



Gene panel

Amplification of disease-related genetic domains for screening

DNA sequencer

AGAAGCACCTGGAGA
ACTCATG.....

TGCACACATTGACTT
ACCCACT.....

Detection of genetic mutations

Analytical programs

Database

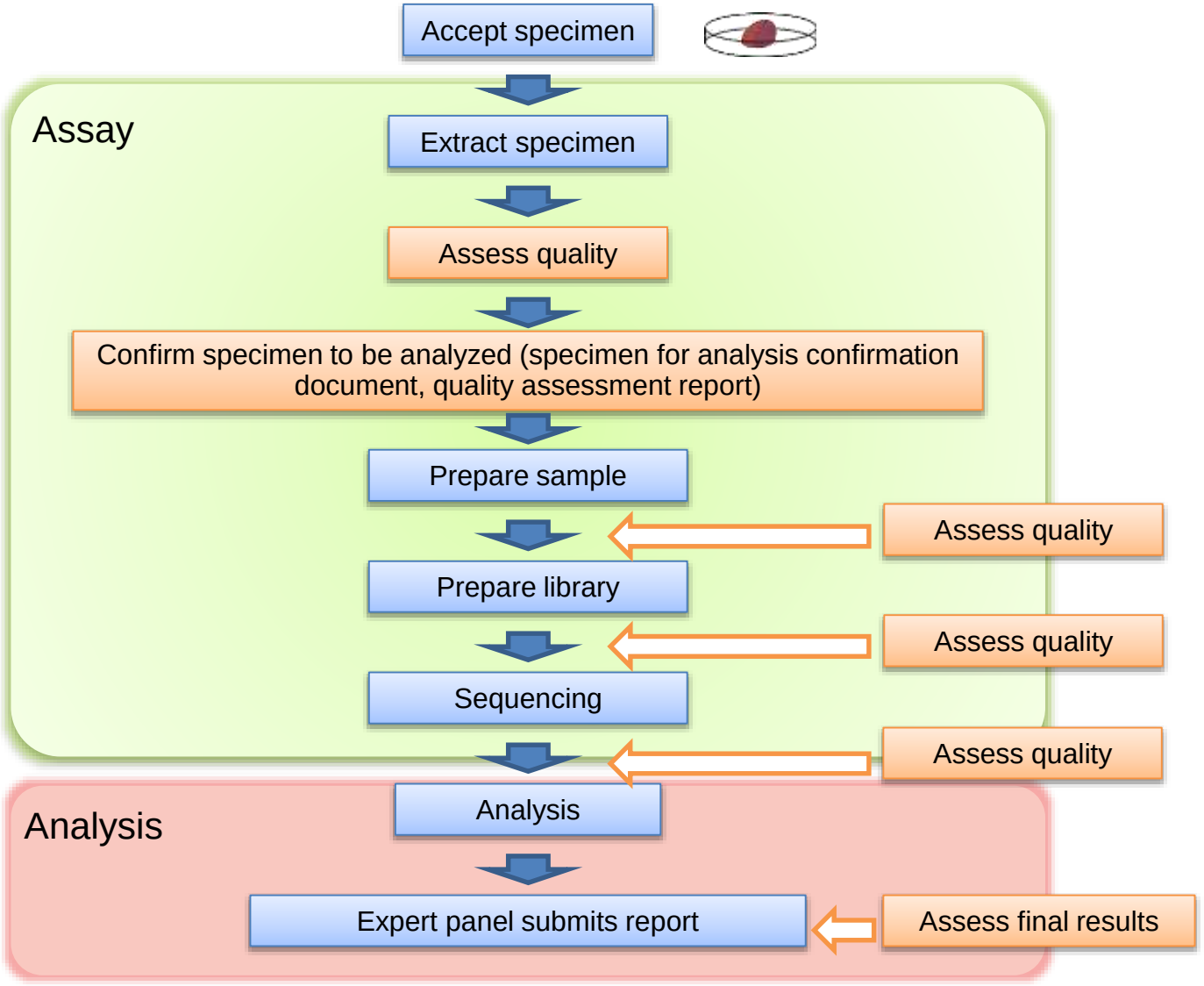
Reference/evaluation

Disease-related genetic abnormalities detected, and results output in report form

Report analysis by specialists (e.g., physicians/bioethicists/gene counselors)

Selection of optimal therapy and treatment plan for each individual patient

Quality Assurance with Clinical Sequence Testing



Quality assurance in a host of processes is required to use gene diagnoses results in treatment

Sysmex Group's Strengths

Develop for IVD

- In charge of gene panel and analysis program quality (IVD quality)

Assay service

- In charge of measurement protocol quality
- Provide testing in accordance with regulatory approval

Realize high-quality clinical sequence testing

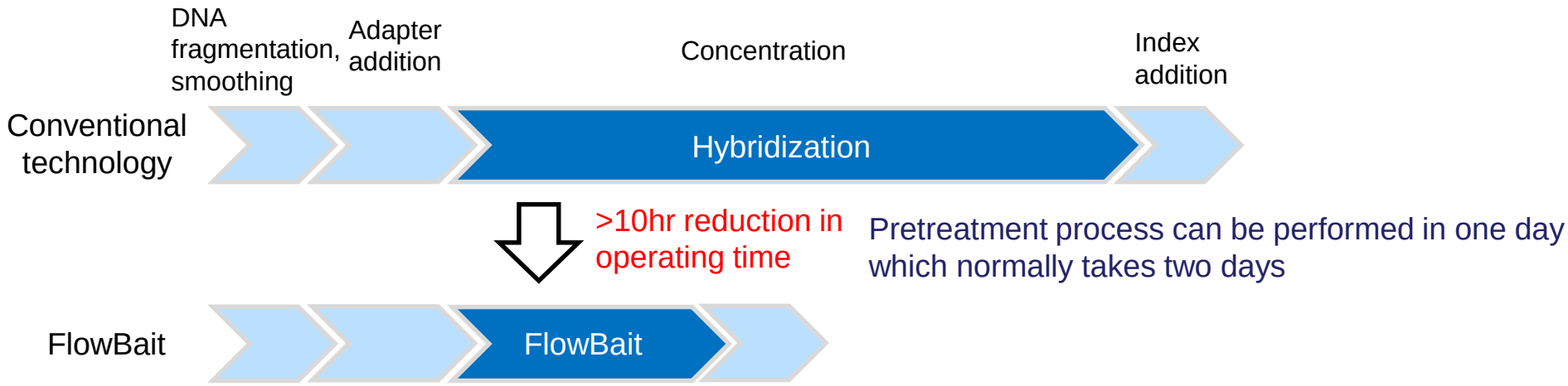
R&D toward Future Genomic Medicine

Promoting the development of liquid biopsy technologies by leveraging synergies with affiliated companies

- Plasma-Safes-SeqS (Sysmex Inostics)

  Explained in detail later

- Pretreatment technology: FlowBait (Oxford Gene Technology)

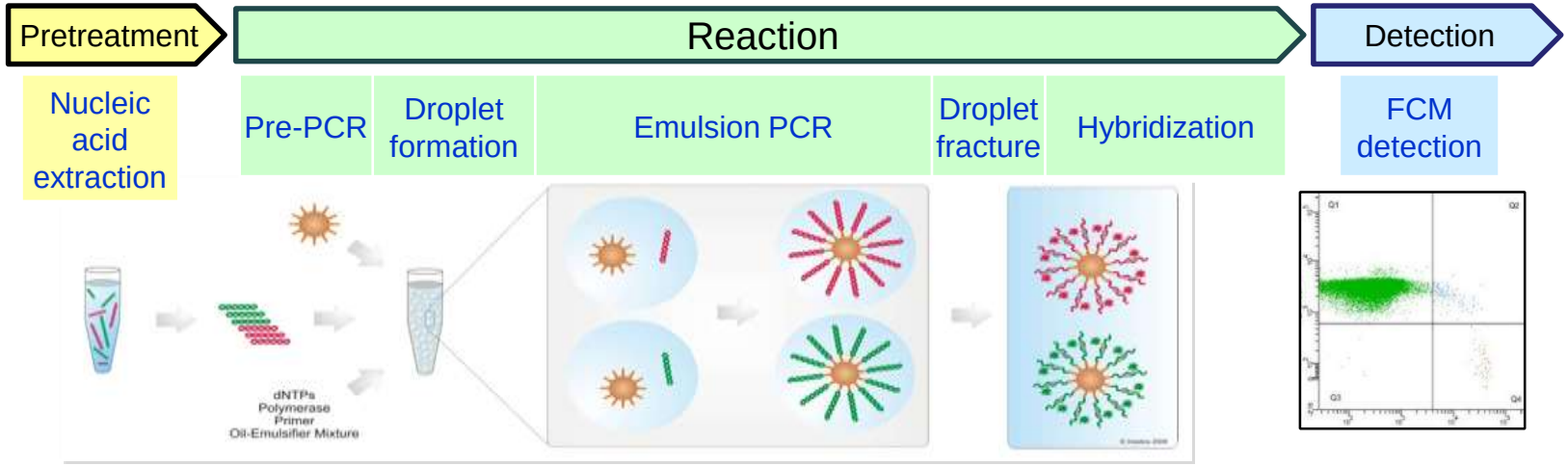


Technology for concentrating target nucleic acid in next-generation sequencer pretreatment ⇒ Achieve rapid and accurate reactions

(2) Progress in Technology Development

(1) Technology for Automating BEAMing Technology (OncoBEAM3.0)

<Manual method>



Nucleic acid extraction module

Pre-PCR module

Droplet formulation to hybridization module

Detection module

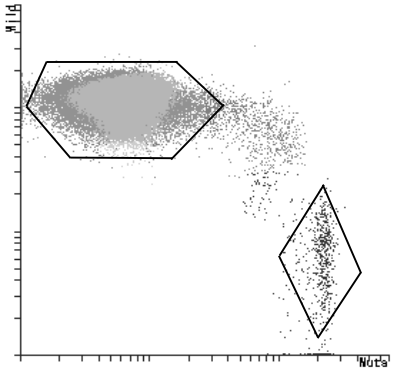
<Automation>

Development complete

(1) Technology for Automating BEAMing Technology (OncoBEAM3.0)

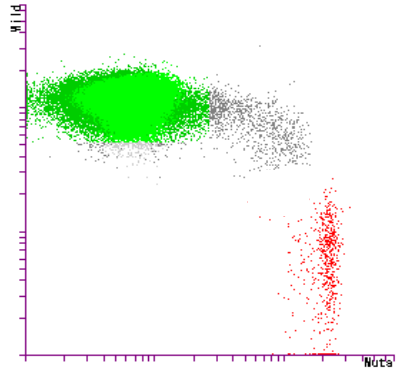
■ Development of automatic analysis software

＜Manual＞



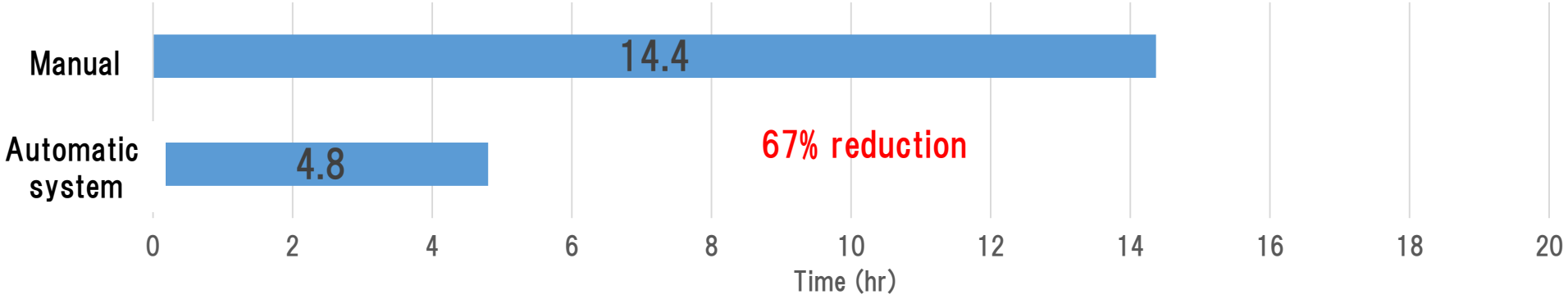
Must be analyzed and gated by professional technician

＜Automatic analysis＞



Automatic analysis by unique clustering technology

■ Comparison of Hands-on time



Realize simplification and streamlining by implementing automated system in own laboratory

OncoBEAM ctDNA monitoring tests capable of detecting recurrence at an earlier stage than diagnostic imaging

Targets: EGFR T790M mutation positive cases (7 cases)

Diagnostic imaging:
CT imaging every eight weeks until the sixth month, and every 12 weeks thereafter

Confirmation of cancer progression using diagnostic imaging

Avg. 31.7th week

EGFR-TKI treatment

4th week 8th week ...

Avg. 23.6rd week

OncoBEAM:
Blood sampling every four weeks
(Base on EGFR-TKI treatment)

EGFR T790M gene mutation detected in the blood plasma

OncoBEAM EGFR T790M gene mutation testing detects recurrence by an average of around eight weeks earlier than diagnostic imaging

Image modified from “LungBEAM: A prospective multicenter trial to monitor EGFR mutations using BEAMing technology in Stage IV NSCLC EGFR + patients,” presented by Garrido P at the 18th World Conference on Lung Cancer (IASLC) in October 2017

(2) Plasma-Safe-SeqS Technology

Plasma-Safe-SeqS technology for detection of rare genes in blood

riken genesis

Conducted at the RIKEN GENESIS Innovation Genome Center

Sample preparation	Pretreatment		Measurement	Analysis
DNA extraction	1st PCR	2nd PCR	NGS	Software

Blood

Analysis results of circulating tumor DNA mutations

Specialized reagent supplied by Sysmex Inostics

(2) Plasma-Safe-SeqS Technology

Video

◆Website location:

Sysmex Website > Research & Development > Sysmex's Technologies >

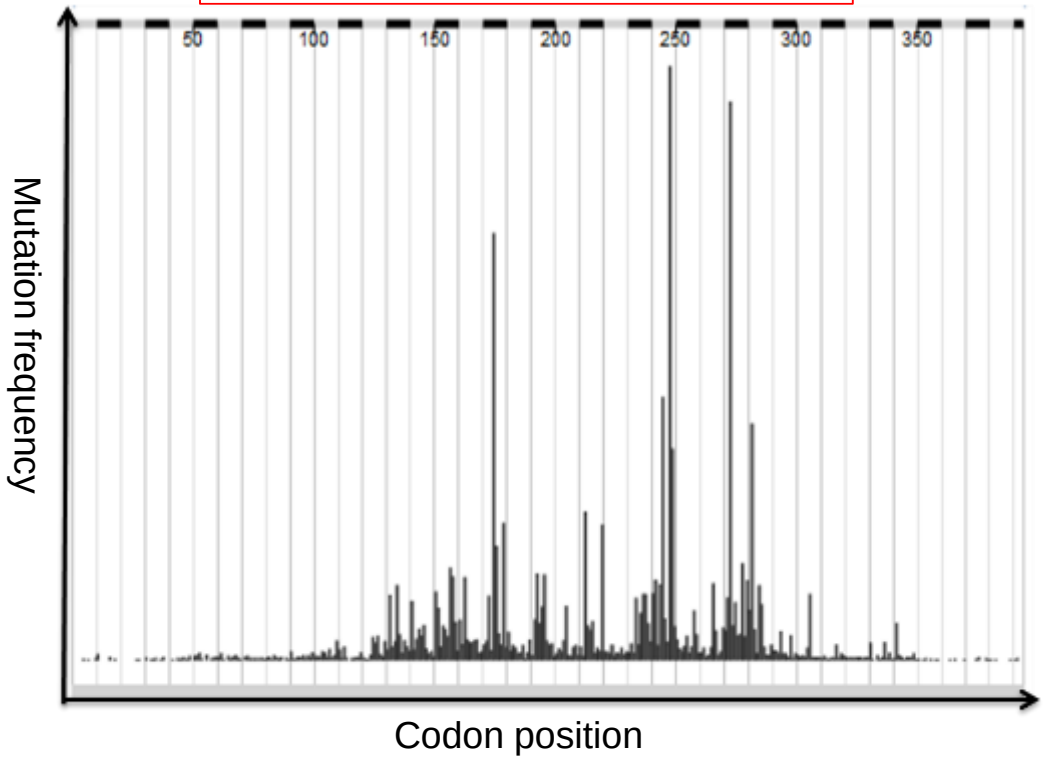
Gene Measurement Technologies

http://www.sysmex.co.jp/en/rd/technologies/gene.html

(2) Plasma-Safe-SeqS Technology

Starting a lab assay business (for research) realizing 0.06% ultrahigh sensitive measurement

P53 Tumor-suppressor gene



Plasma-Safe-SeqS technology is effective at identifying mutations by conducting an exhaustive search in cases where mutations are generated on multiple codons as with the P53 gene, and expression patterns of gene mutations are multiple.

We have begun a service to test for the TP53 gene, which is seen in many types of cancer, and we are receiving orders from university and other research institutions.

(2) Plasma-Safe-SeqS Technology

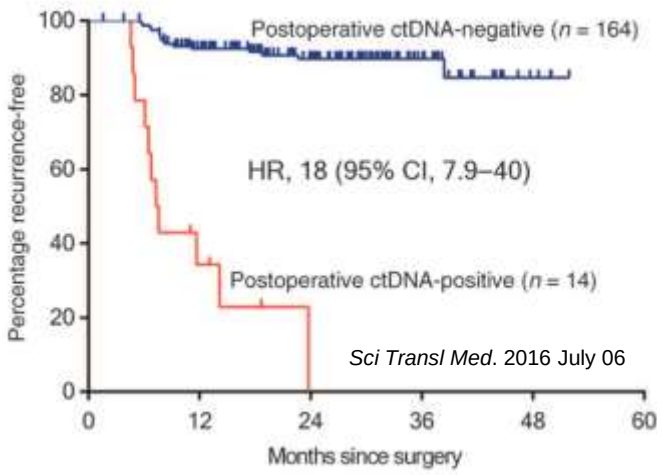
Developing a panel for prognosis and detection of minimum residual disease

■ Flow of treatment following tumor excision

Screening → **Diagnosis prognosis, Detection of minimum residual disease** → Drug selection (CDx) → Monitoring

sysmex

■ Evidence in colorectal cancer



ctDNA(-)
3y Relapse-Free Survival 90%

ctDNA(+)
3y Relapse-Free Survival 0%

Targets:
178 patients with Stage II colorectal cancer who have undergone surgery but not yet undergone adjuvant chemotherapy

Results:
(1) No ctDNA mutations (164 people), mutations (14 people)
(2) Of those having no mutations, 90% had no recurrence three years post-surgery; those with mutations were 0%

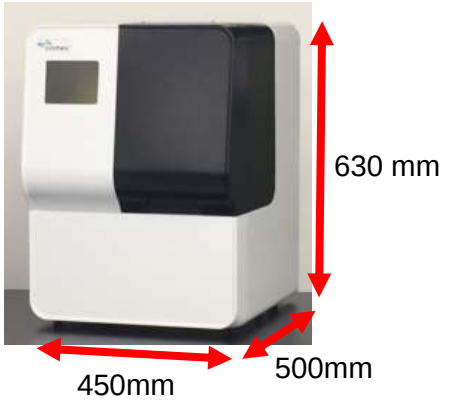
Using PSS technology for the highly sensitive detection of ctDNA mutations enables prognoses for stage II patients.

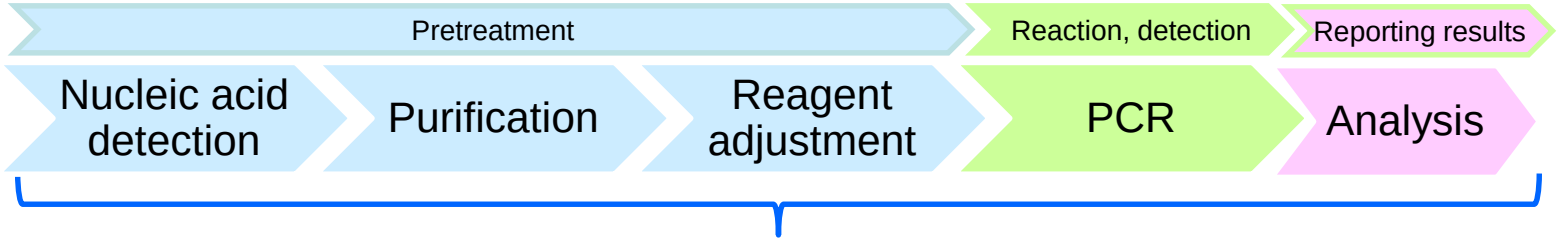
(3) Clinical PCR

[Issues with gene testing]
Operations are complex (many manual operations), so difficult to handle at hospital labs

[The concept of clinical PCR]
A gene testing system that can be used in hospital labs

- Fully automated, from pretreatment to detection to the reporting of results
- Highly sensitive detection (0.1% Mut for 10^6 copies of WT)
- Quality assurance
- Clinically useful marker sets
- Multiplex assay
- Compact





To be launched as an RUO product in Q1 of FY2018

(3) Clinical PCR

Video

◆Website location:

Sysmex Website > Research & Development > Sysmex's Technologies >

Gene Measurement Technologies

http://www.sysmex.co.jp/en/rd/technologies/gene.html

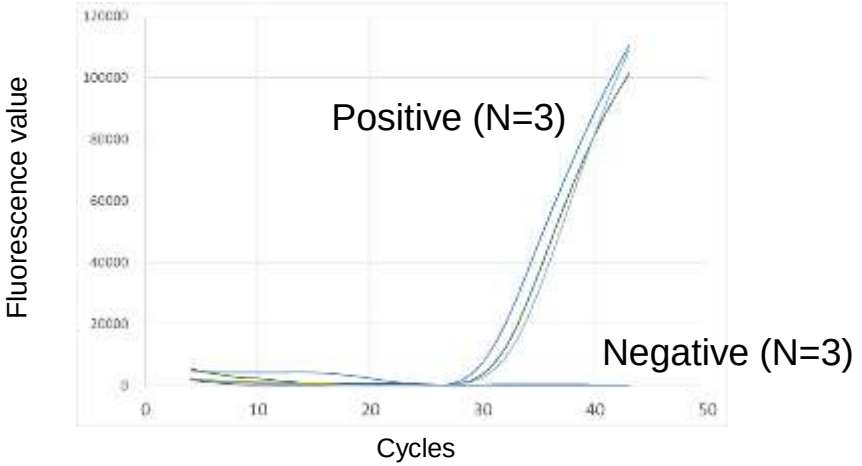
(3) Clinical PCR
Performance Evaluation Results

Development of EGFR panel complete

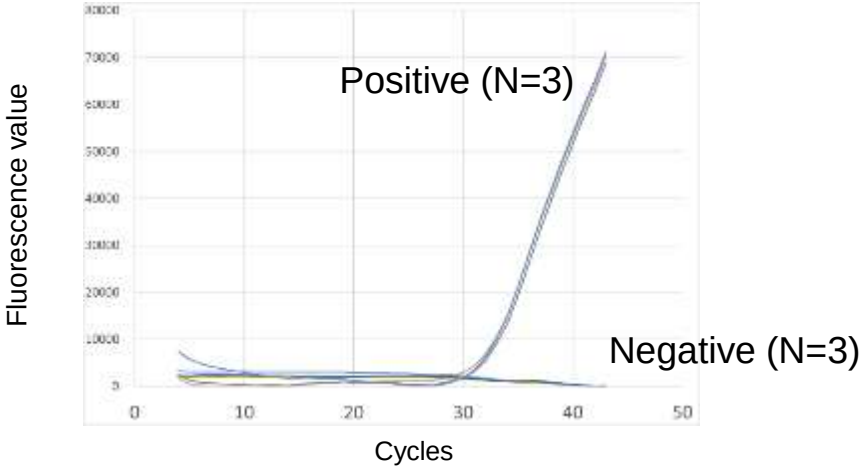
EGFR panel

Exon	Mutations
18	G719X
19	Deletions
20	S768I
20	Insertions
20	T790M
21	L858R
21	L861Q

Deletion



L858R

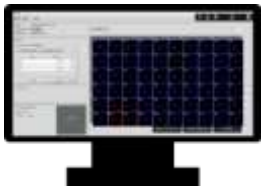


(4) MI-FCM Technology

➢ FISH testing

FISH reagent

MI-FCM



Flow FISH software

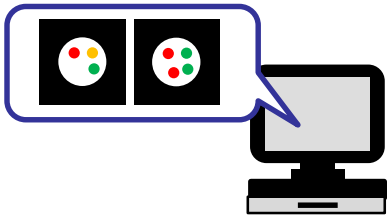
A game-changer in the FISH testing market → Launch of RUO products in Q1 of 2018

➢ CTC testing

Cell separation and concentration instrument

FISH reagent (for CTCs)

MI-FCM



CTC software

Cultivate the liquid biopsy market with CTC measurement

(4) MI-FCM Technology

Video

◆Website location:

Sysmex Website > Research & Development > Sysmex's Technologies >

Cell Measurement Technologies

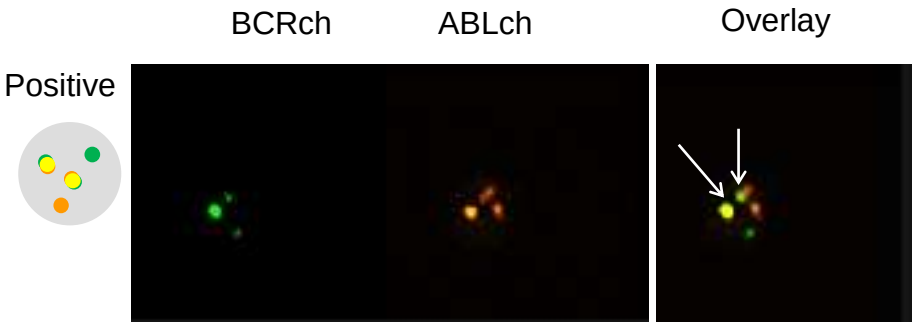
http://www.sysmex.co.jp/en/rd/technologies/cell.html

(4) MI-FCM Technology (Flow FISH System) Application Example

Rapid market launch, replacing existing FISH testing

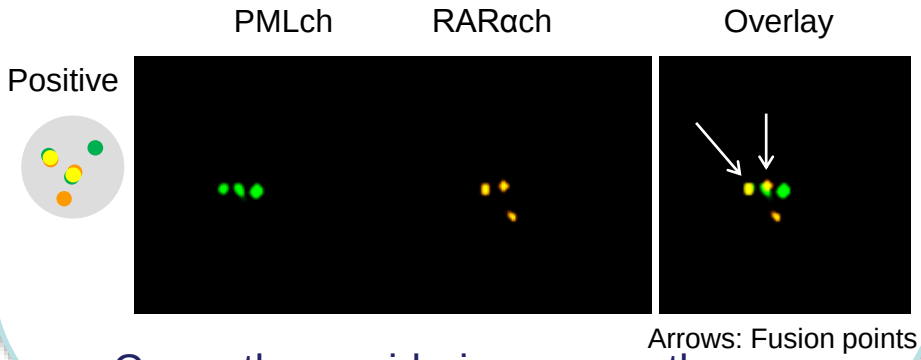
Leukemia domain

BCR-ABL



Arrows: Fusion points

PML-RARα

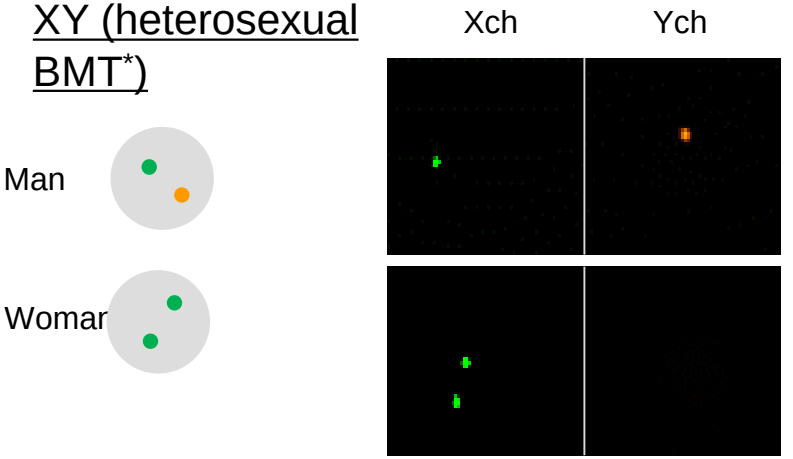


Arrows: Fusion points

Currently considering many other leukemia-related parameters

Bone-marrow transplant

XY (heterosexual BMT*)



* Testing for engraftment of donor cells and the early detection of recipient cells by recurrence, after a bone-marrow transplant between different genders,

Use OGT's FISH probes to simplify and increase the precision of existing FISH testing

(4) MI-FCM Technology (Flow FISH System) Application Example

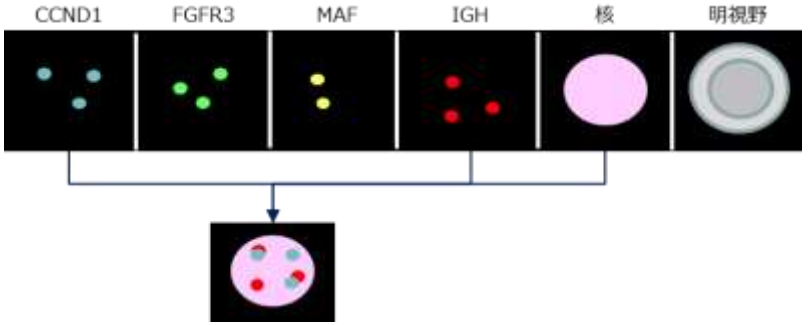
Developing proprietary applications leveraging Flow FISH characteristics

■ Using FISH testing to diagnose multiple myeloma

- ✓ Making simultaneous judgements on multiple gene abnormalities is complex, and multiple tests needed to obtain a confirmed diagnosis
- ✓ Specialized technology necessary for diagnosis
- ✓ Large burden on the person performing tests

Flow FISH system and specialized reagent for simultaneous measurement

- ✓ Enables multiple gene abnormalities to be tested at once
- ✓ Allows for standardization of testing
- ✓ Reduces the burden on the person performing tests



Conducting assessments with a university by using clinical specimens

(5) Initiatives Targeting Alzheimer's Disease

Alzheimer's screening by liquid biopsy

Principal pathologies of Alzheimer's disease

- Senile plaques due to accumulation of Aβ (Amyloid-β)
- Neurofibrillary tangle due to tau protein

[Issues]

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

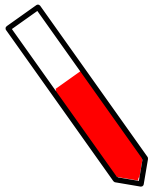
Quantitative analysis

Structural analysis

✓High cost
✓Limited facilities

<Spinal fluid test>

<Blood test>



Aβ quantity in blood: Aβ quantity in spinal fluid = **1:50**
(National Center for Geriatrics and Gerontology, Proc. Jpn. Acad., Ser. B, 2014)

✓Highly invasive

iCT-HISCL

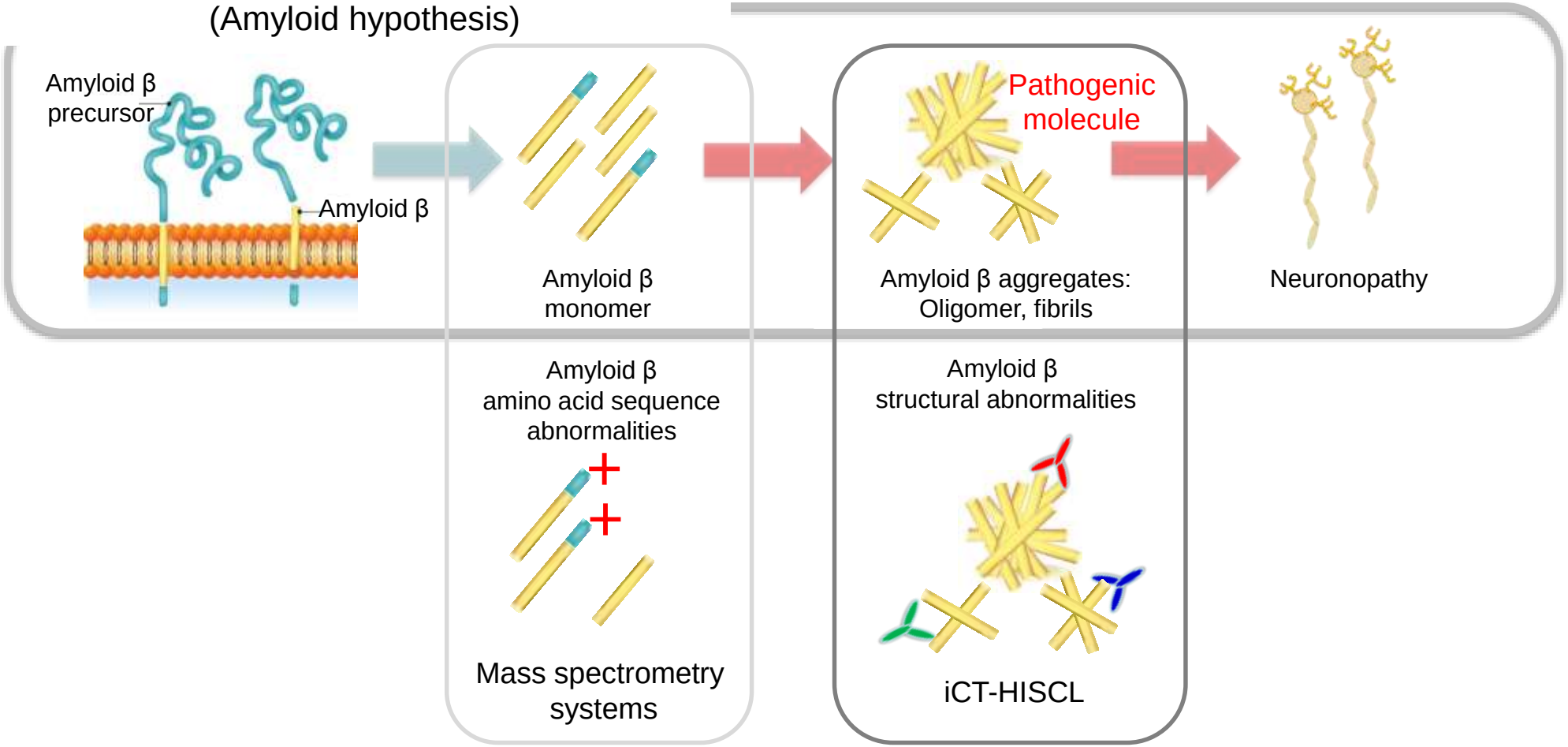
Super-resolution microscope

Good Design Award recipient

Used in joint development with Eisai Co., Ltd.

(5) Initiatives Targeting Alzheimer's Disease
Comparison with Other Technologies

Pathogenic mechanism of Alzheimer's disease
(Amyloid hypothesis)



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