National Biobank Consortium of Taiwan

Introduction of Cancer Precision Medicine and Biobank Consortium Collaboration Pilot Project

This is a **Public Private Partnerships (PPP) project** to build up **a real world data (RWD)** with comprehensive genetic testing and detailed medical records. This database is also **friendly** for industrial applications.

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National Biobank Consortium of Taiwan

The Biobank Management Act

was enforced in Taiwan in 2010

- Biobank can legally obtain **broad consent** from participants
- Biobanks are requested to have strict **data safety** managment.
- Business use of biobank specimens or data should give **commercial benefit feedback**, which is an important clause for industrial applications.

Above are the 3 most important niches of the Biobanks in Taiwan. The 35 biobanks should become big fortunes for biomedical researchers and industries in Taiwan.

National Biobank Consortium of Taiwan

The establishment of National Biobank Consortium of Taiwan (NBCT)

- To improve the performance and function of Biobanks in Taiwan, a National Biobanks was suggested.
- Through the cooperation of all biobanks in Taiwan, with **uniform quality and clinical data content,** a large and comprehensive human biobank network can be **quickly** established.
- Under such design, National Biobank Consortium of Taiwan (NBCT) was established through the **fund support and governance from Ministry of Health and Welfare.**
- All Alliance should follow the same SOP for the biomaterial collection and have the same quality of the biosamples and data when submitted to the applicants.

NBCT was formally established on 2019-10-30

國家級人體生物資料庫整合平台

National Biobank Consortium of Taiwan (NBCT)

NBCT is a **virtual biobank**, the specimens and data are stored in each biobank

(decentralized storage)

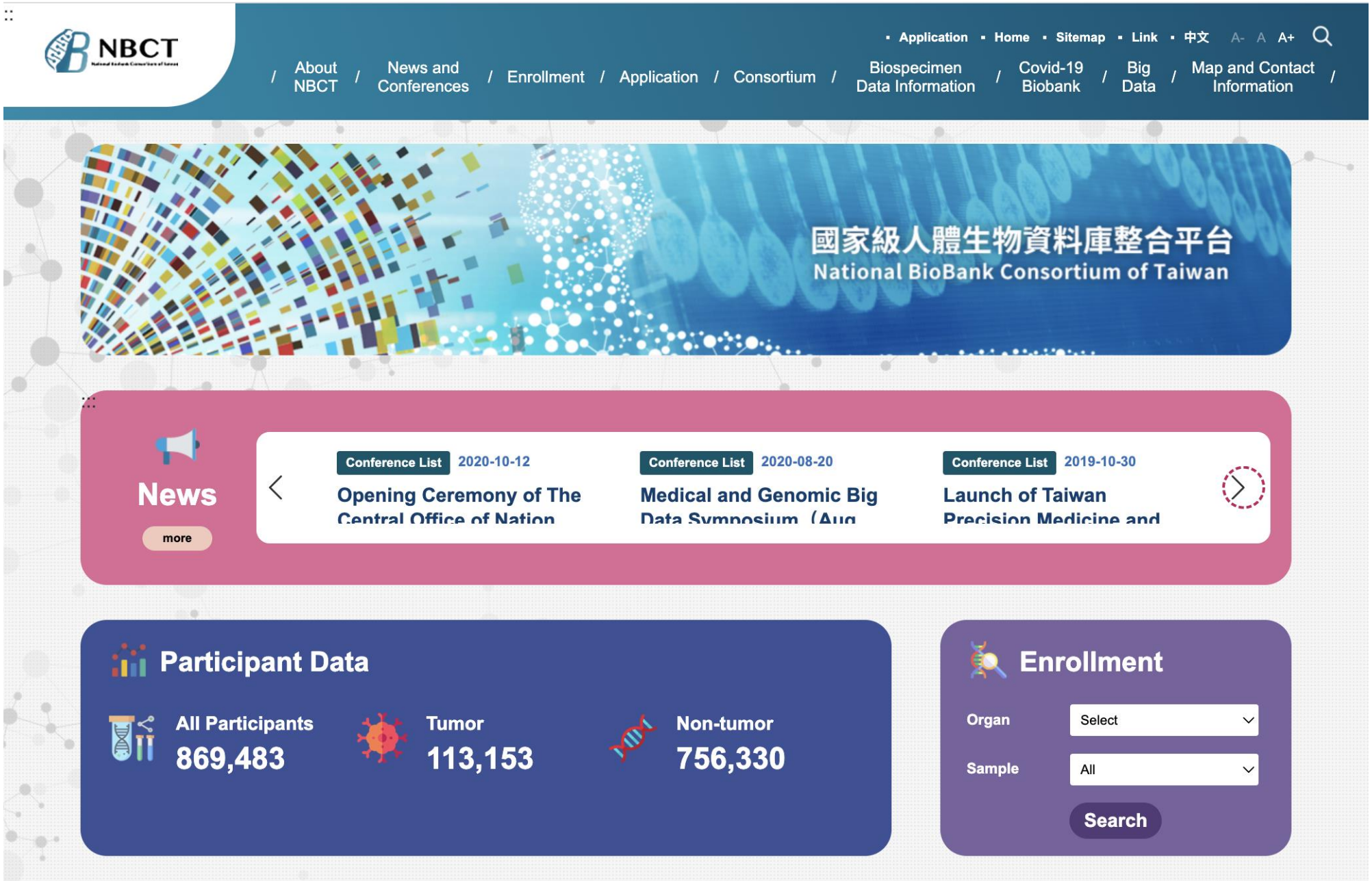
Researchers can applied the biospecimens and data from various biobanks though NBCT

(one stop service)

Currently NBCT is composed of 34 biobanks, 29 belonged to medical hospitals, 4 belonged to research institutes , 1 is in the University

Detailed Executive Plans

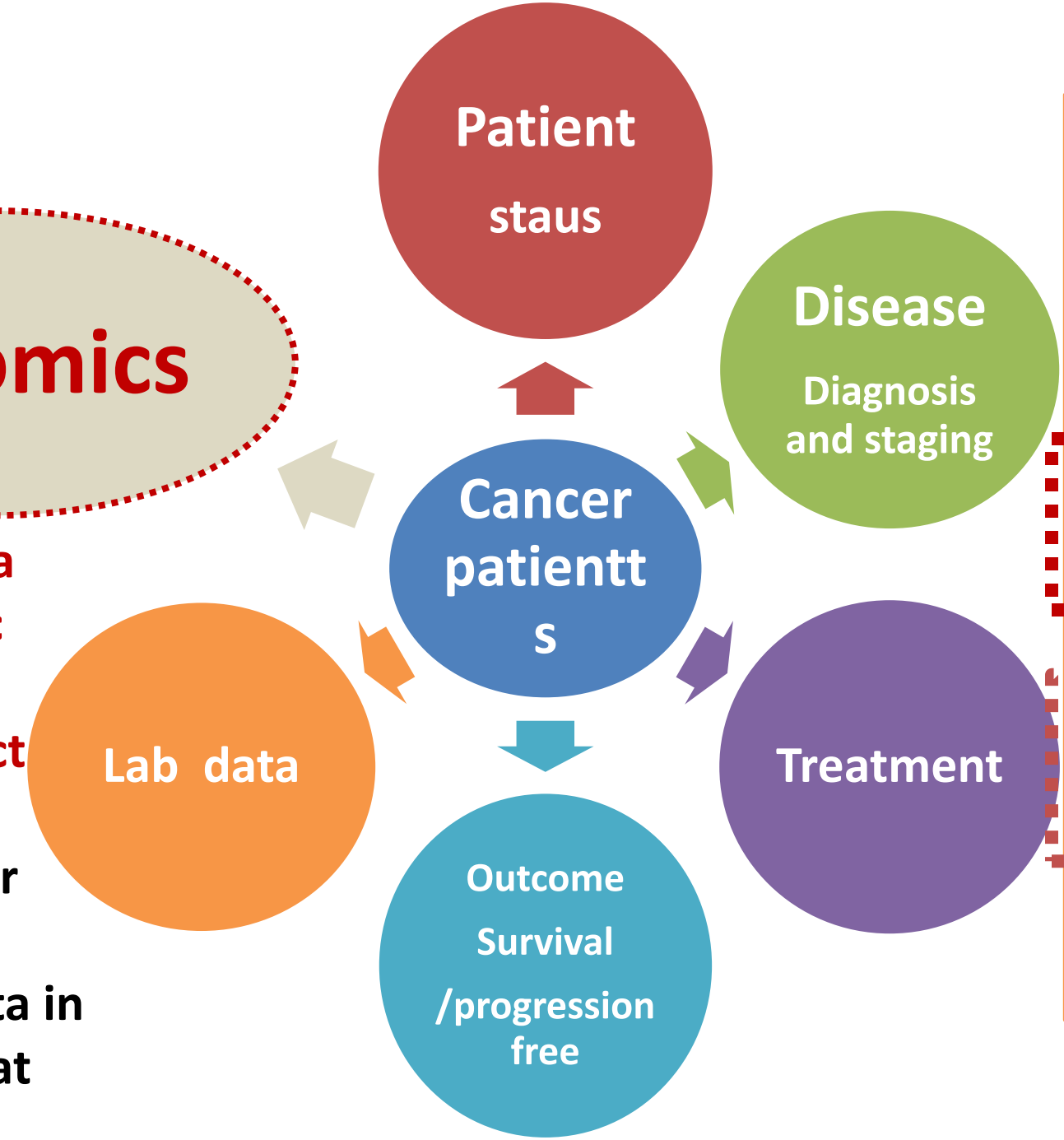
- Facilitate the cooperation of the nationwide biobanks to utilize the specimen and related information.
- Improve the management standards of all biobanks to promote the quality consistency of biobank specimens and related information.
- Combined with value-added services for all biobanks to increase the application incentives from all biomedical researchers.
- The goal is to become the most important resource for biotechnology medicine and the healthcare industry.



https://nbct.nhri.org.tw

Establish 12 Standard operation procedures (SOP) for the application procedures and specimen's Quality

1) Application for NBCT Specimens and Information
2) Review of NBCT Specimens and Information
3) Confidentiality and Conflict of Interest Avoidance
4) NBCT Specimens - Procedure of the Fresh Frozen Tissue Collection and DNA Extraction
5) NBCT Specimens - Procedure of the Tissue RNA Extraction
6) NBCT - Procedure of the Blood Specimens Processing
7) NBCT - Procedure of the Blood Specimens DNA Extraction
8) NBCT - Procedure of the Paraffin Blocks and Blank Section Specimens Making
9) NBCT - Procedure of the Pleural Fluid, Ascites, Spinal Fluid, and Cerebrospinal Fluid Specimens Collection and Processing
10) NBCT - Procedure of the Urine Specimens Collection and Processing
11) NBCT - Standard Operating Procedure of the Specimens Delivery Ⅰ - Refrigeration Shipping
12) NBCT - Standard Operating Procedure of the Specimens Delivery Ⅱ – Room Temperature Shipping



Genomics

aggregates data from electronic health records (EHRs) via direct feeds, with no requirement for the clinician to capture the data in a specific format

Electronic health records (EHR):

First stage

- Structured data

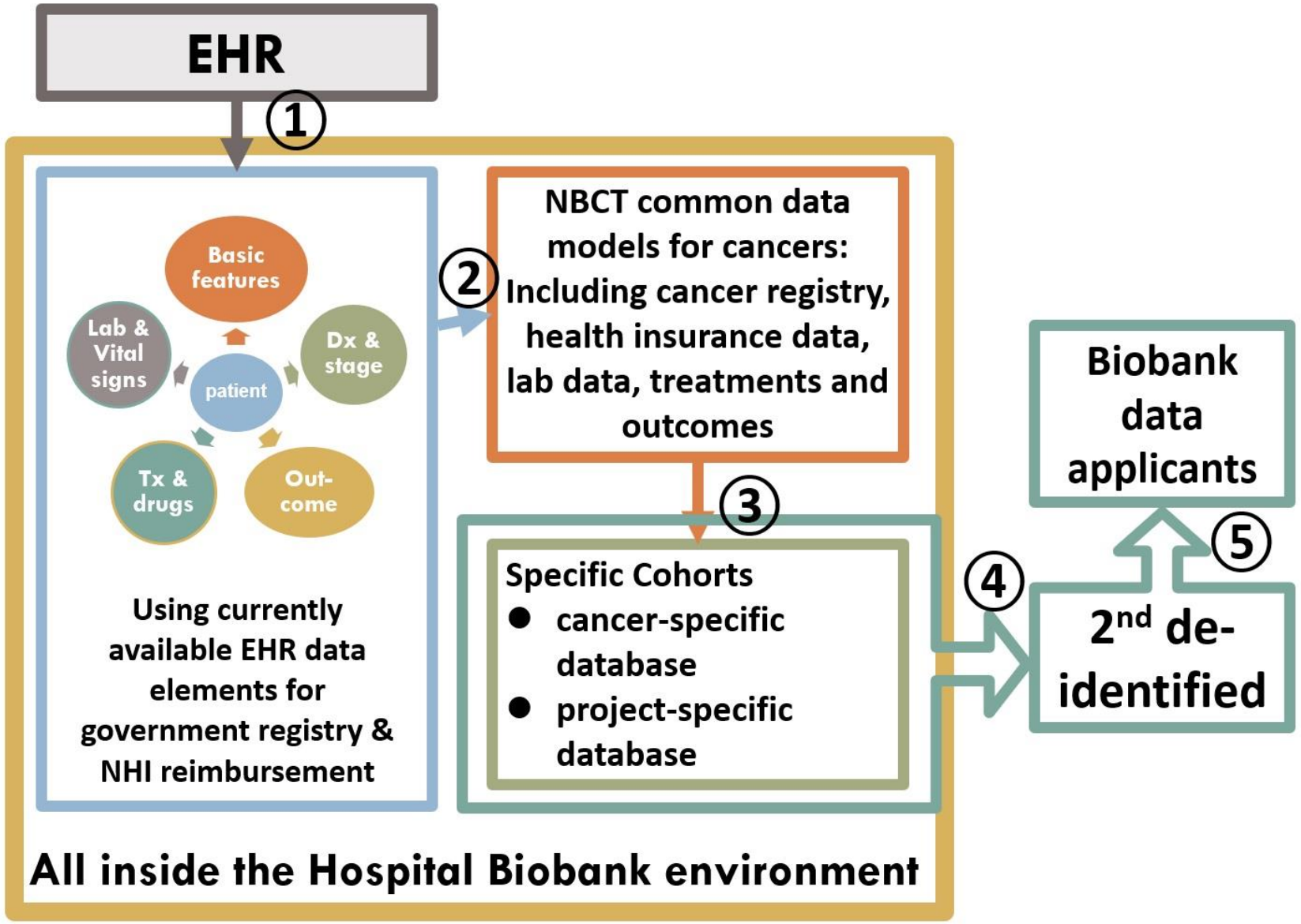
2nd stage

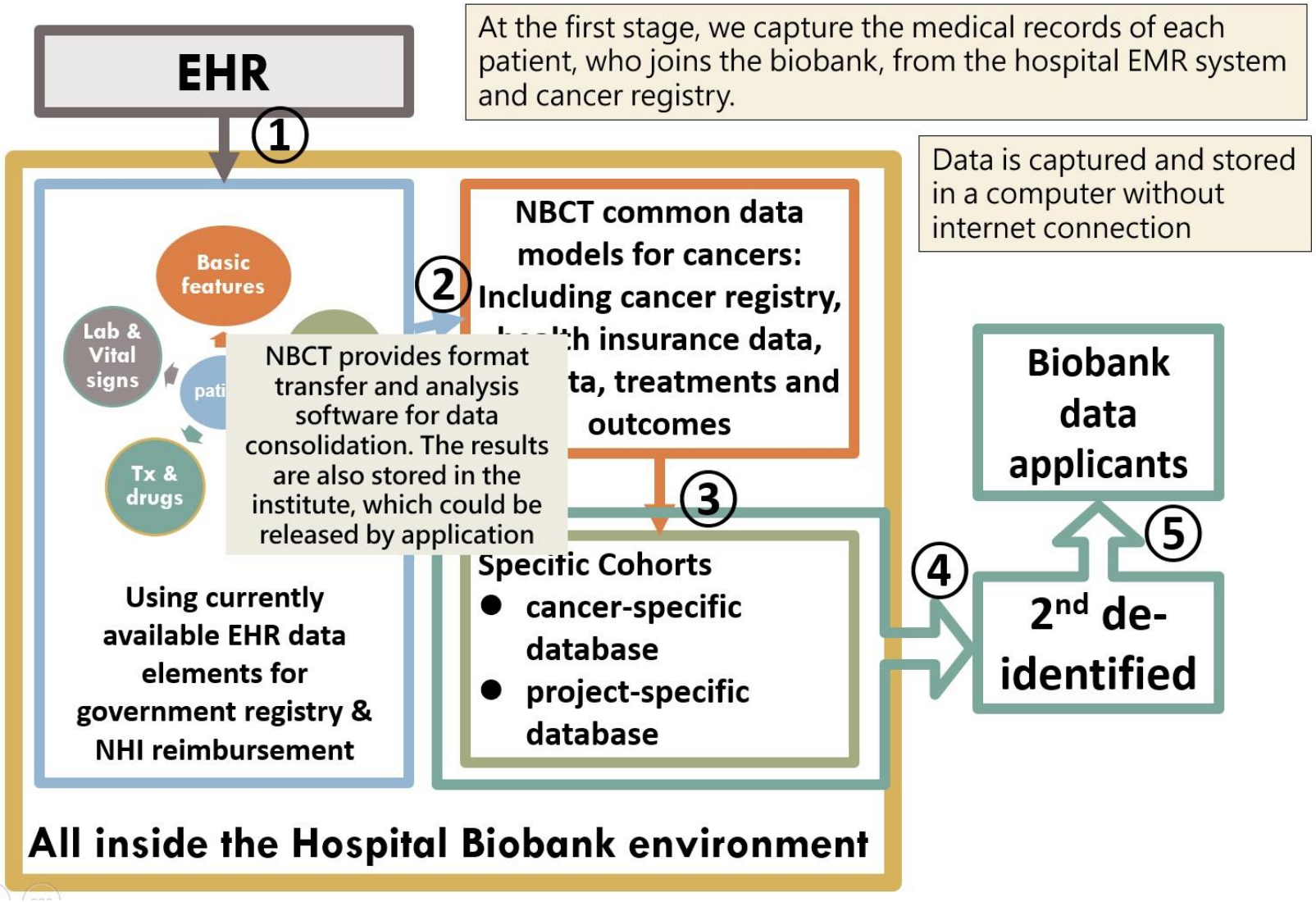
- Unstructured data
  - free text
  - image

Establish the Common Data Model in each hospital's biobank (NBCT CDM)

To build up **standardized medical big data** for future collaboration

Since Taiwan has only **one universal health insurance system**, it became a big niche to build up a CDM from the electronic health record (EHR).





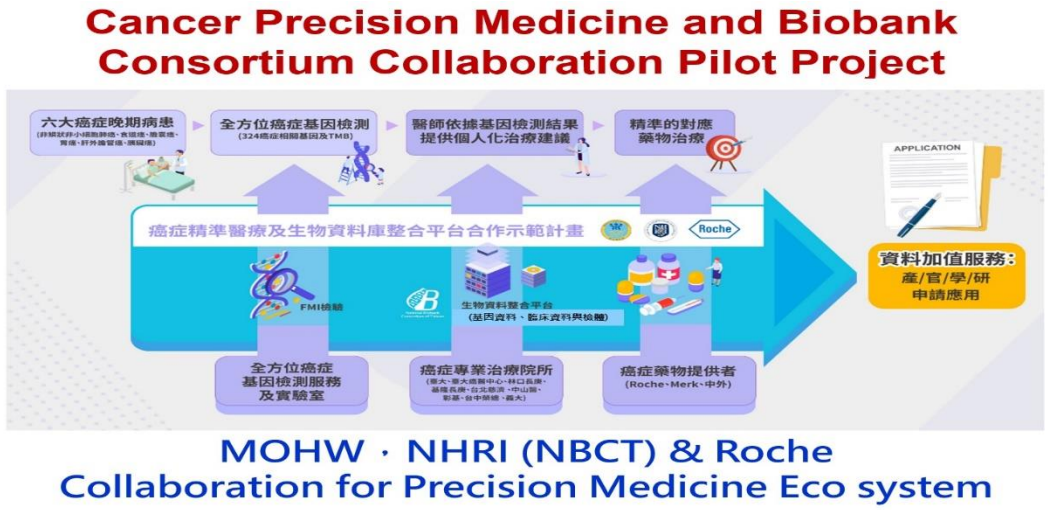
The establishment of CDM has been successful in more than 15 hospitals.
This becomes **one big achievement** of NBCT and **the important base for RWD**

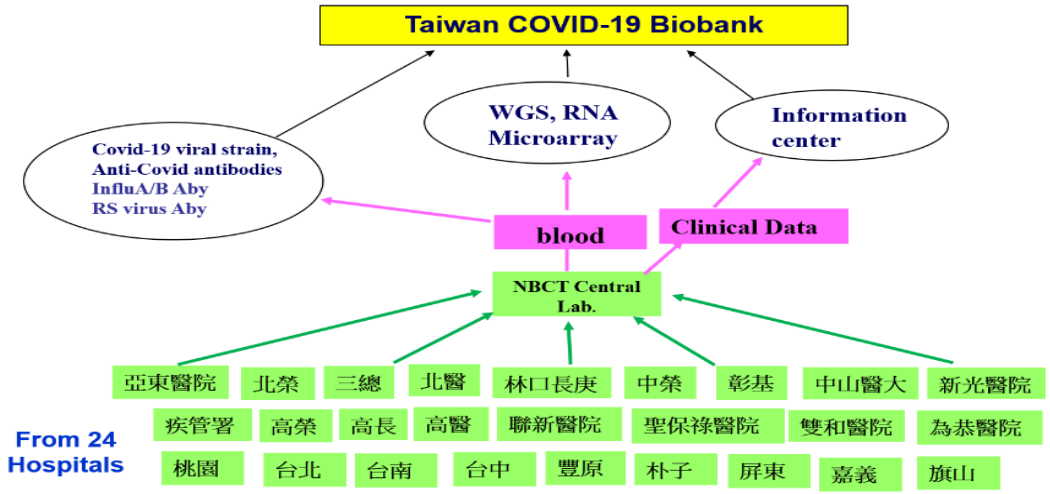
National Biobank Consortium of Taiwan

Success in promoting the precision medicine ecosystem Unleash the Potential of the Epidemic Prevention Industry

By the end of August. 2023：

34	869,000	12	142	26
Biobanks	participants	SOP	Academic applications	Industrial applications





Cancer Precision Medicine and Biobank Consortium Collaboration Pilot Project

MOHW · NHRI (NBCT) & Roche Collaboration for Precision Medicine Eco system

Recruitment of 2000 participants with late stage cancers

- Patients of late stage cancer patients with no prior systemic anti-cancer treatment
- Patients with recurrence of cancer disease who received prior neo-adjuvant, adjuvant or CCRT at least 12 months ago
- only adults older than 18 years can be recruited.
- All participants need to agree for medical data collection and stored in the Hospital biobanks

Cancer types	Stage
Non-small cell carcinoma（needs to be EGFR、ALK and ROS1 negative）	IIIB以上
Esophageal carcinoma	IIIB以上
Gall bladder carcinoma	IIIB以上
Gastric carcinoma	IIIB以上
cholangiocarcinoma	IIIB以上
Pancreatic carcinoma	III以上

All participant can get one free comprehensive genetic test composed of 324 genes (FoundationOne® CDx) for their tumor tissue.

FoundationOne® CDx has been approved by FDA of USA for diagnostic practice.

The first project of NBCT combined with Precision Medicine

- This project will collect the genetic data and clinical medical data **(real world data)** of the 2000 participants.
- The comprehensive genetic testing reports and detailed medical records will be stored and managed in each hospitals' biobank.
- The EHR data in each biobank after transformed into **NBCT CDM,** will be combined with the XML data of FoundationOne® CDx report, and build up a cancer genetic and medical dataset of each patient.
- Through one stop service of NBCT, researchers can apply all of the 2000 patients' data together. Hereinafter referred to as **the large cancer genetic and medical database.**

The goal of this first pilot project of NBCT combined with Precision Medicine

- This large database will help strengthen Taiwan's medical quality and provide clinicians with more reference for **decision-making.**
- This large database can be applied by the industrial researchers **directly** to accelerate industrial upgrading.
- In addition, through this project, the use of **real-world evidence (RWE)** can be promoted in the future as a mechanism for drug research and development, drug marketing registration and **health insurance reimbursement** evaluation.

The medical records collected in this pilot project

(Red words mean the data are collected directly from EHR)

1 Patient demographic

2-1 Cancer characteristic (newly diagnosis)

2-2 Cancer characteristic (recurrence)

3 Performance status

4. Co-morbidities

5. Laboratory results

6. Biomarker test

7. Cancer related medication

7-1 Stopping reason for cancer related medication (inpatient)

7-2 Stopping reason for cancer related medication (outpatient)

8. Co-medication

9. Cancer related radiotherapy

10 Cancer related surgery

11. Cancer treatment outcome

12. Follow-ups

13. Death data

14. Value indicator of the project

Establishment of Molecular Tumor Board (MTB)

Molecular guided treatment options for personalized medicine by **comprehensive** genetic testing has become **a new trend**. The drugs may be **matched with the gene targets,** but not in the approved condition by TFDA (**off-label use**).

- Set up a MTB becomes necessary to help for the **best treatment decision.**
- MTB needs to be a **multidisciplinary Practice.**

The responsibility of MTB in this pilot project

- Provide consultation service for attending doctors in this project
- **Decide the feasibility of the compassionate use of the free drugs** matched with the gene targets

- This pilot project has successfully established in-house Molecular Tumor Board in each participating hospital, and a **central molecular tumor board.**

- This is a **big step forward** in the promotion of cancer precision medicine in Taiwan.

Compassionate use of the drugs matched with the gene targets

Roche、Merk、Chugai, and Lily also join the pilot project，will give free drugs for patients according to their genetic testing results in this project and after approval by MTB.

Roche 羅氏藥廠贈藥品項	對應基因
賀癌寧®凍晶注射劑/ Kadcyla® Vial 100mg/ 160mg	HER2
賀癌平®凍晶注射劑/ Herceptin® Vial 440mg	HER2
得舒緩®膜衣錠/ Tarceva® Film-coated Tablets 150mg/100mg	EGFR
日沛樂®膜衣錠/ Zelboraf® Film-coated 240mg	BRAF
可泰利®膜衣錠/ Cotellic® Film-coated tablets 20mg	BRAF
羅思克®膠囊/ Rozlytrek® hard capsules 200mg	ROS1
羅思克®膠囊/ Rozlytrek® hard capsules 200mg	NTRK

Lilly

禮來公司之贈藥	對應基因
Selpercatinib	RET

MERCK

默克藥廠之贈藥	對應基因
Tepotinib	MET

CHUGAI

中外製藥之贈藥	對應基因
ALECENSA®	ALK

Through the comprehensive genetic testing, and the decision of the molecular tumor board (MTB), the compassionate use of these drugs matched with the gene targets has been successful in practice. It becomes a win-win–win strategy for cancer patients, attending doctors, and the pharma.

Lung adenocarcinoma, 86yr, male, ECOG=2

Sensitivity for the detection of copy number alterations is reduced due to sample quality.

Biomarker Findings

Microsatellite status - MS-Stable

Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

MET **exon 14 splice site (2888-32_2891del36)**

7 Disease relevant genes with no reportable alterations: *ALK, BRAF, EGFR, ERBB2, KRAS, RET, ROS1*

Lung adenocarcinoma, 62 yr male ECOG=1

Biomarker Findings

Microsatellite status - MS-Stable

Tumor Mutational Burden - 7 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

MET amplification `copy-number="29"`

NF1 I679fs*21

FBXW7 K326*

HGF amplification - equivocal†

KEAP1 deletion exons 4-5

TP53 Q144fs*26 (VAF 26%)

7 Disease relevant genes with no reportable alterations: ***ALK, BRAF, EGFR, ERBB2, KRAS, RET, ROS1***

Gastric adenocarcinoma, 73 yr male, ECOG=1

Biomarker Findings

Microsatellite status - MS-Stable

Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

MET amplification

CCNE1 amplification

RAF1 amplification - equivocal†

TP53 E286*

1 Disease relevant genes with no reportable alterations: *ERBB2*

† See About the Test in appendix for details.

GENE

MET

ALTERATION

amplification

copy-number="15"

GENE

CCNE1

ALTERATION

amplification

copy-number="8"

GENE

TP53

ALTERATION

E286*

TRANSCRIPT ID

NM_000546.4

CODING SEQUENCE EFFECT

856G>T

VARIANT CHROMOSOMAL POSITION

chr17:7577082

VARIANT ALLELE FREQUENCY (% VAF)

26.5%

Esophageal carcinoma 62 male., ECOG=1

Sensitivity for the detection of copy number alterations is reduced due to sample quality.

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

MET amplification
CCND1 amplification
FGFR1 amplification
MTAP loss exons 2-8
MYC amplification
SOX2 amplification
CDKN2A/B CDKN2B loss, CDKN2A loss
FGF19 amplification
FGF3 amplification
FGF4 amplification
MLL2 M5280fs*6
NSD3 (WHSC1L1) amplification
TBX3 R269W - subclonal†
TP53 K132R
ZNF703 amplification

1 Disease relevant genes with no reportable alterations: ***ERBB2***

† See About the Test in appendix for details.

GENE
MET

ALTERATION
amplification

copy-number ="8"

GENE
TP53

ALTERATION
K132R

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
395A>G

VARIANT CHROMOSOMAL POSITION
chr17:7578535

VARIANT ALLELE FREQUENCY (% VAF)
65.5%

Lung adenocarcinoma, 80 yr male ECOG=1

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported.

Biomarker Findings

Microsatellite status - Cannot Be Determined [α]
Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

BRAF **V600E**
PIK3CA **H1047R**
DNMT3A **splice site 2408+2T>C**
TP53 **S261fs*84**

7 Disease relevant genes with no reportable alterations: *ALK, EGFR, ERBB2, KRAS, MET, RET, ROS1*

† See About the Test in appendix for details.
α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Dabrafenib** (p. 9), **Dabrafenib + Trametinib** (p. 8), **Vemurafenib** (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 14)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A*** **splice site 2408+2T>C** (p. 6)

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRAF - V600E	Dabrafenib + Trametinib 2A	Dabrafenib 2A
		Vemurafenib 2A
		Encorafenib + Binimetinib
		Selumetinib
		Trametinib
10 Trials *see p. 14*		Vemurafenib + Cobimetinib
PIK3CA - H1047R	none	Everolimus
10 Trials *see p. 16*		Temsirolimus

☐ *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

DNMT3A - splice site 2408+2T>C p. 6

Adenocarcinoma of pancreas, 75 yr female, ECOG=0

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

BRAF G469S
PIK3CA M1043I
ARID1A Q1452fs*39
MTAP loss exons 2-8
ACVR1B loss
CDKN2A/B CDKN2B loss, CDKN2A loss
NSD3 (WHSC1L1) amplification - equivocal†
TP53 E336*
ZNF703 amplification - equivocal†

2 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2***

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Everolimus** (p. 10), **Selumetinib** (p. 10), **Temsirolimus** (p. 11), **Trametinib** (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)

GENE
BRAF

ALTERATION
G469S

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1405_1406GG>TC

VARIANT ALLELE FREQUENCY (% VAF)
36.9%

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 1 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***BRAF* -** G469S	none	Selumetinib
10 Trials see p. 15		Trametinib
***PIK3CA* -** M1043I	none	Everolimus
10 Trials see p. 18		Temsirolimus
***ARID1A* -** Q1452fs*39	none	none
8 Trials see p. 13		
***MTAP* -** loss exons 2-8	none	none
1 Trial see p. 17		

Esophagus, SCC, 52 yr. male ECOG=1

Biomarker Findings

Tumor Mutational Burden - 12 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

BRCA2 K944* - subclonal†
ERBB2 amplification - equivocal†
CCND1 amplification
CASP8 deletion exons 4-9
CDKN2A/B CDKN2B loss, p14ARF loss exon 1
FGF12 amplification - equivocal†
FGF19 amplification
FGF3 amplification
FGF4 amplification
TP53 E285V - subclonal, R248_I251>L, Y205C†

† See About the Test in appendix for details.

GENE
BRCA2

ALTERATION
K944* - subclonal

HGVS VARIANT
NM_000059.3:c.2830A>T (p.K944*)

VARIANT CHROMOSOMAL POSITION
chr13:32911322

VARIANT ALLELE FREQUENCY (% VAF)
6.0%

GENE
TP53

ALTERATION
E285V - subclonal, R248_I251>L, Y205C

HGVS VARIANT
NM_000546.4:c.854A>T (p.E285V),
NM_000546.4:c.743_751del (p.R248_I251delinsL),
NM_000546.4:c.614A>G (p.Y205C)

VARIANT CHROMOSOMAL POSITION
chr17:7577084, chr17:7577529-7577538, chr17:7578235

VARIANT ALLELE FREQUENCY (% VAF)
1.3%, 33.2%, 15.8%

GENE
ERBB2

ALTERATION
amplification - equivocal
copy-number="7"

GENE
CCND1

ALTERATION
amplification
copy-number="25"

GENE
FGF4

ALTERATION
amplification
copy-number="29"

GENE
FGF3

ALTERATION
amplification
copy-number="29"

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 12 Muts/Mb	Nivolumab [1]	Atezolizumab
	Pembrolizumab [1]	Avelumab
	Nivolumab + Ipilimumab [2A]	Cemiplimab
	Dostarlimab	Durvalumab
		Retifanlimab
10 Trials see p. 22		
Microsatellite status - MS-Stable	No therapies or clinical trials. See Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRCA2 - K944* - subclonal	none	Niraparib
		Olaparib
		Rucaparib
		Talazoparib
10 Trials see p. 24		
ERBB2 - amplification - equivocal	none	Ado-trastuzumab emtansine
		Fam-trastuzumab deruxtecan
		Lapatinib
		Margetuximab
		Neratinib
		Trastuzumab
		Trastuzumab + Pertuzumab
10 Trials see p. 27		
CCND1 - amplification	none	none
5 Trials see p. 26		

Esophageal cancers

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section
Tumor Mutational Burden - 5 Muts/Mb	No therapies or clinical trials. see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***ERBB2* -** A775_G776insYVMA	Afatinib	Ado-trastuzumab emtansine 2A
		Fam-trastuzumab deruxtecan 2A
		Trastuzumab
		Trastuzumab + Pertuzumab
		Lapatinib ⊗
10 Trials *see p. 10*		

Gastric cancer

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ERBB2 **-** amplification - equivocal	Trastuzumab	1	Ado-trastuzumab emtansine
	Fam-trastuzumab deruxtecan	2A	Afatinib
	Trastuzumab + Pembrolizumab		Dacomitinib
			Lapatinib
			Margetuximab
			Neratinib
10 Trials *see p. 20*			Trastuzumab + Pertuzumab
FBXW7 **-** Y545C - subclonal	none		Everolimus
9 Trials *see p. 22*			Temsirolimus
MET **-** amplification	none		Cabozantinib
			Capmatinib
			Crizotinib
10 Trials *see p. 24*			Tepotinib

Adenocarcinoma of stomach
67 year male, ECOG=1

Biomarker Findings

Microsatellite status - MSI-High

Tumor Mutational Burden - 74 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ERBB2 L755S

APC K1182fs*83, R1463fs*6

ARID1A D1850fs*33, G285fs*78

EZH2 R213H - subclonal†

PIK3CB D1067Y

PIK3R1 I287fs*10 - subclonal†

STK11 N109fs*20

CD70 G78fs*33 - subclonal†

CREBBP R1664C - subclonal†

GNAS R201C, R160C - subclonal†

HNF1A P291fs*51

MAP3K1 N1305fs*31

MLH1 loss exons 1-13

MLL2 A3552fs*4

MSH3 K383fs*32

PBRM1 R534*, I279fs*4

QKI K134fs*14

SETD2 T305fs*4

SNCAIP E852K

SPEN K943fs*31

TGFBR2 K128fs*3

TNFAIP3 C559* - subclonal†

TP53 K382fs*40 - subclonal, R273C†

WT1 R462Q - subclonal†

National Biobank Consortium of Taiwan

Summary

Cancer Precision Medicine and Biobank Consortium Collaboration Pilot Project has become the most successful example of **private public partnership (PPP)** model in Taiwan. It includes the participants of Ministry of Health and Welfare (MOHW), NBCT /NHRI, 14 medical hospitals, and 4 pharmaceutical companies.

The important achievement of the Pilot project -1

- ✓ The program has successfully recruited 1164 participants by the end of August, 2023 and established the MTB of in 12 hospitals and a central MTB of **clinical function level**.

- ✓ More than 10% of the patients have found gene targets for free drugs. So far, 90 patients/times have applied for the drugs.

- ✓ This project has recruited a large number of GI cancer patients (224 pancreatic cancers, 158 esophageal cancers, 193 gastric cancers), which is not just beneficial for the patients, but also become precious domestic genetic & medical data, since quite few comprehensive genetic studies performed in these GI cancers due to lack of drug targets.

The important achievement of the Pilot project -2

- ✓ This project also demonstrated that comprehensive NGS genetic testing can not only discover more gene variations, but also has future development, including **new drug targets** and analysis and identify of **efficacy indicators**.

- ✓ Through the establishment of CDM by NBCT, this pilot project have successfully integrated the genetic and medical data in each biobank.

- ✓ Integration of the genetic-medical big data of 500 patients from 7 cooperative hospitals has been achieved for the first time in Taiwan and have been sent to the applicant .

National Biobank
Consortium of Taiwan

The working team of the NBCT Central Office

THANKS

For your attentions