BioJapan 2014

World Business Forum

(October 15-17, 2014)

Future Perspectives of the National Center Biobank Network (NCBN) and Its Potential Impacts on Achieving Precision Medicine

がん患者コホート研究からみた個別化医療への期待

～ナショナルセンターバイオバンクネットワークの現状と展望～

中釜　斉

Hitoshi Nakagama

National Cancer Center Research Institute, Tokyo

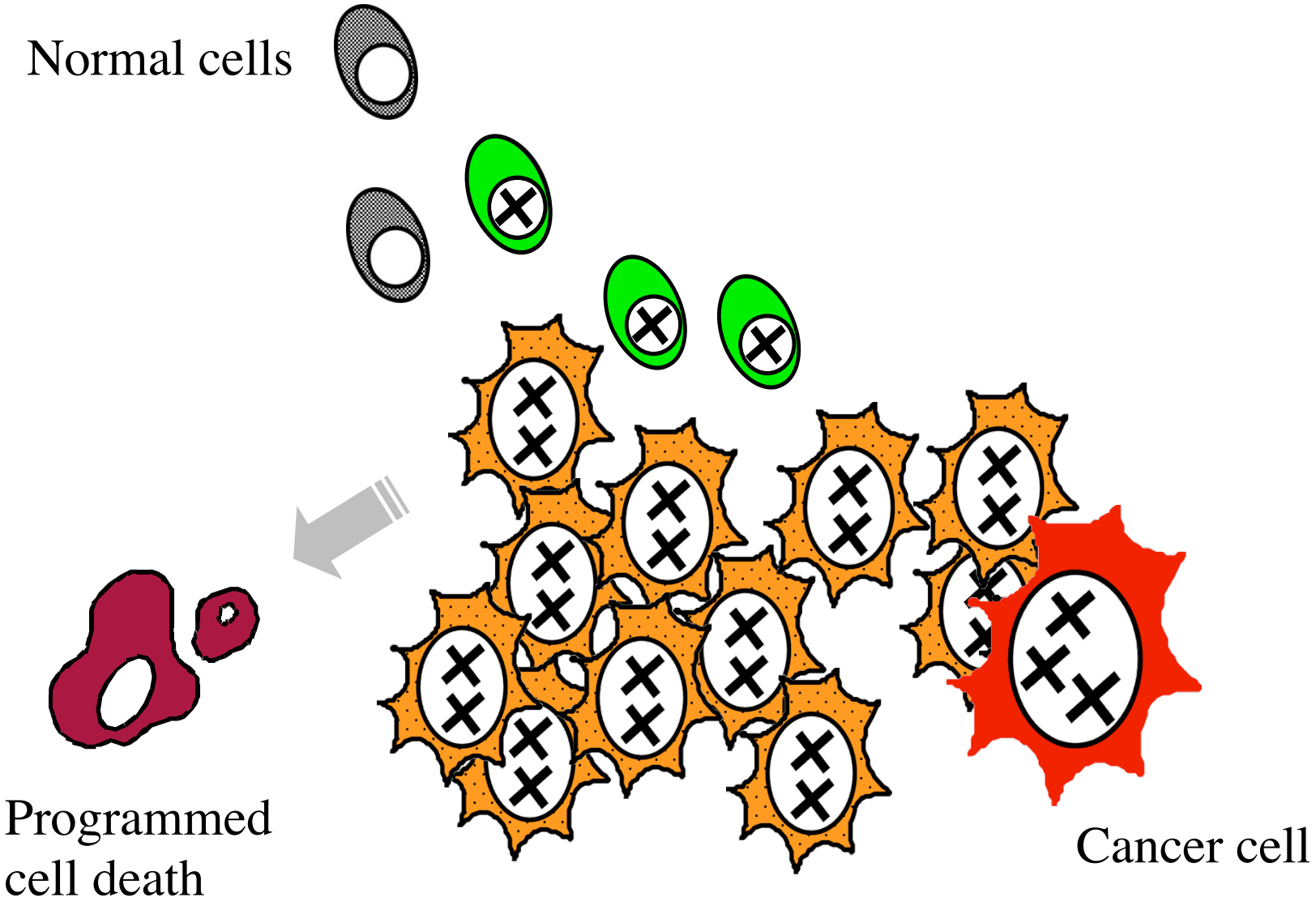
Causation of Human Diseases

- Hereditary (Genetic) factors
- Environmental factors

Environmental and Heritable Factors in the Causation of Cancer
- Analyses of Cohorts of Twins from Sweden, Denmark, and Finland -
(Lichtenstein P, et al., New Engl J Med, July, 2000)

Site and Type	Proportion of Variance	
	Heritable factor	Environmental factor
Stomach	0.28	0.72
Colorectum	0.35	0.65
Pancreas	0.36	0.64
Lung	0.26	0.74
Breast	0.27	0.73
Cervix uteri	0	1.00
Corpus uteri	0	1.00
Ovary	0.22	0.78
Prostate	0.42	0.58
Bladder	0.31	0.69
Leukemia	0.21	0.78

Cancer Develops after Accumulation of Multiple Genetic Changes



Causation of Human Diseases

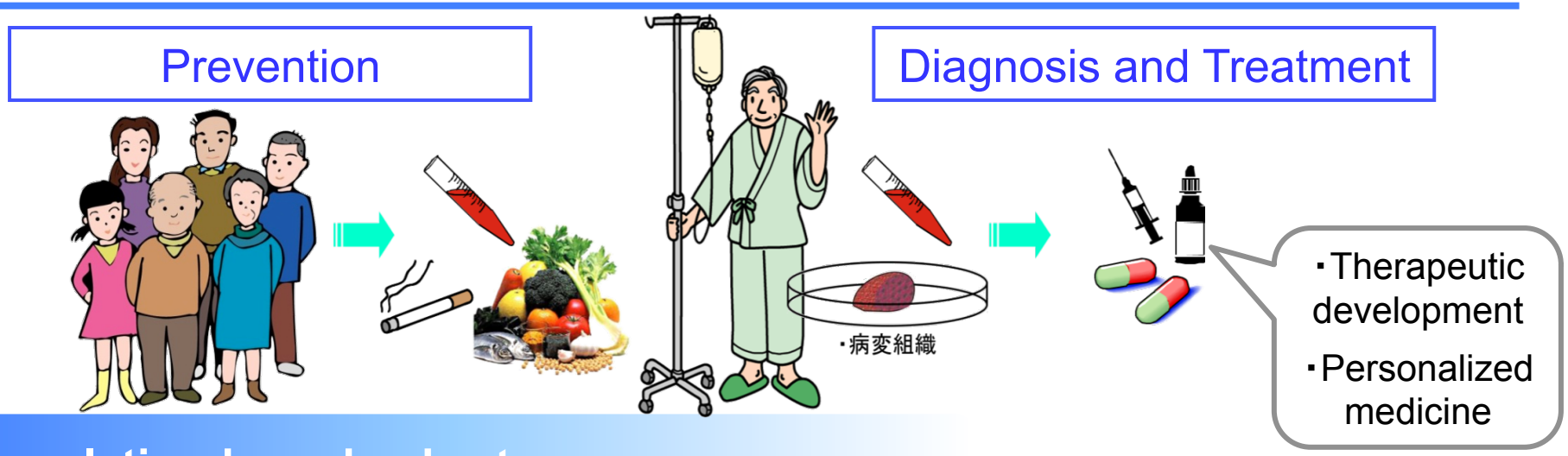
- Hereditary (Genetic) factors

  ← **Germ-line mutations/variations (SNPs; genetic susceptibility)**

- Environmental factors

  → **Somatic mutations Epigenetic alterations**

Current Major Cohort and/or Biobank Projects in Japan



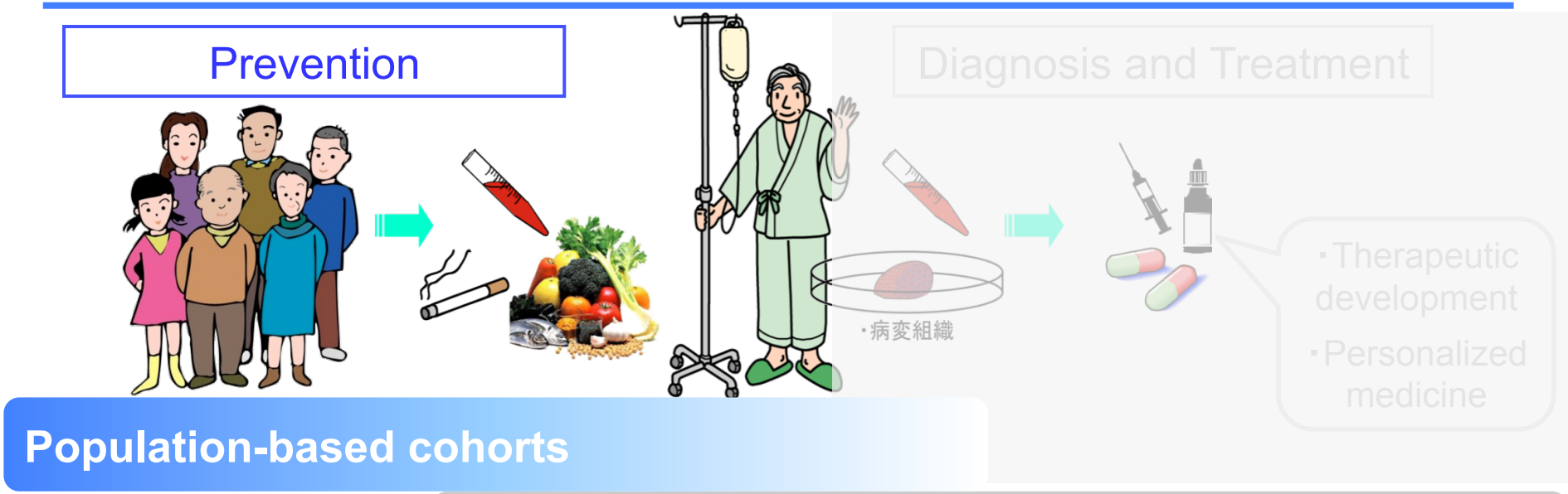
Population-based cohorts

Tohoku Medical Megabank (ToMMo)	・Stress cohort of the residents of the arch 2011 Quake and Tsunami area, incl. trio birth cohort ・approx. 150K (plan)
・JPHC ・J-MICC	・Nation-wide population-based cohorts ・approx. 100K
・Nagahama 0th prevention cohort ・Hisayama cohort	・Local community cohorts ・approx 10K

Patient cohorts

Biobank Japan (BBJ)	・Nation-wide community hospitals, university hospitals. ・47 diseases, approx 300K cases by approx 200K patients ・Blood samples, predetermined list of clinical information ・(Mostly) distribution-type biobank
National Center Biobank Network (NCBN)	・Centers for Highly Advanced and Specialized Medical Care ・Incl. diseases and subtypes relatively few in BBJ ・Blood and pathological tissue specimens with rich longitudinal clinical information ・(Mostly) collaboration/ contract-research biobank (cluster of the disease specialists, focused research and clinical trials)
Rare dis. bank	・Specific rare and intractable diseases

Current Major Cohort and/or Biobank Projects in Japan



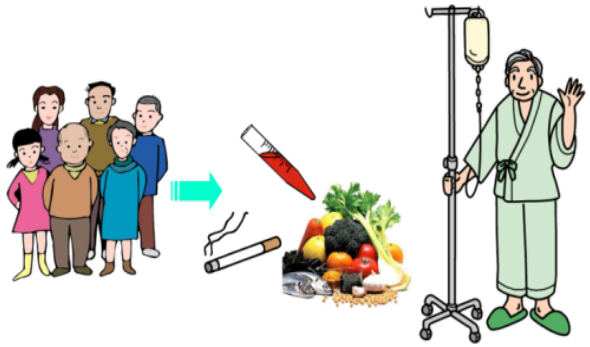
Population-based cohorts

Tohoku Medical Megabank (ToMMo)	・Stress cohort of the residents of the arch 2011 Quake and Tsunami area, incl. trio birth cohort ・approx. 150K (plan)
・JPHC ・J-MICC	・Nation-wide population-based cohorts ・approx. 100K
・Nagahama 0th prevention cohort ・Hisayama cohort	・Local community cohorts ・approx 10K

Patient cohorts

Biobank Japan (BBJ)	・Nation-wide community hospitals, university hospitals. ・47 diseases, approx 300K cases by approx 200K patients ・Blood samples, predetermined list of clinical information ・(Mostly) distribution-type biobank
National Center Biobank Network (NCBN)	・Centers for Highly Advanced and Specialized Medical Care ・Incl. diseases and subtypes relatively few in BBJ ・Blood and pathological tissue specimens with rich longitudinal clinical information ・(Mostly) collaboration/ contract-research biobank (cluster of the disease specialists, focused research and clinical trials)
Rare dis. bank	・Specific rare and intractable diseases

Follow-up Study among the 140,000 JPHC Participants



Disease A

Disease A

Decease

? (Untraceable)

Disease B

Disease C

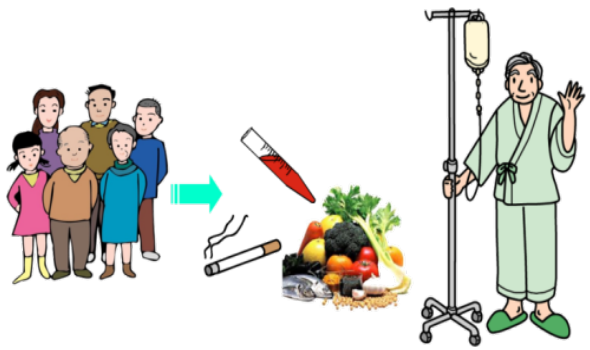
Decease

? (Untraceable)

Disease B

Disease A

Follow-up Study among the 140,000 JPHC Participants



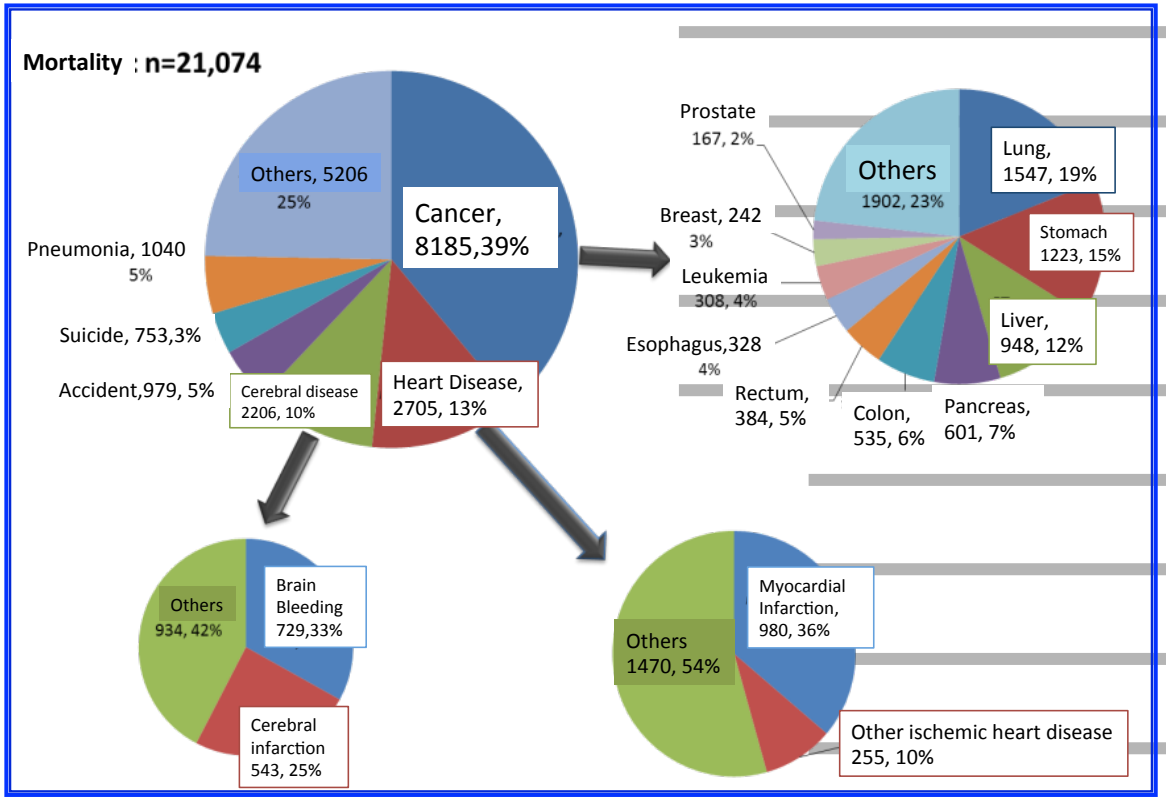
Disease A

Disease A

Decease

? (Untraceable)

＊ Follow up 140,000 people for 20 years



Disease B

Disease C

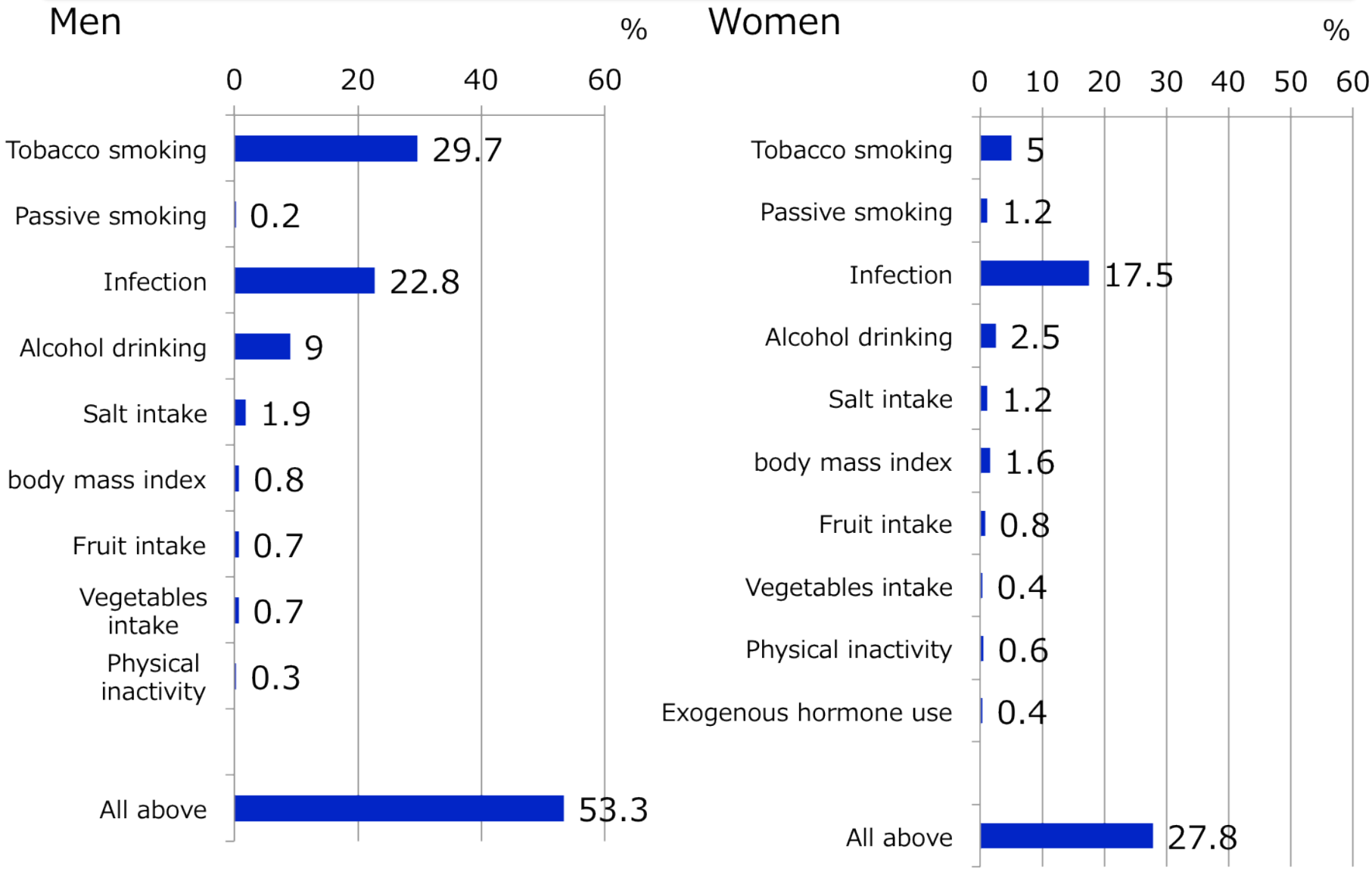
Decease

? (Untraceable)

Disease B

Disease A

Attributable cause of cancer in Japan, 2005 Incidence



(Inoue M et al. Ann Oncol 2012 May;23(5):1362-9)

Causation of Human Diseases

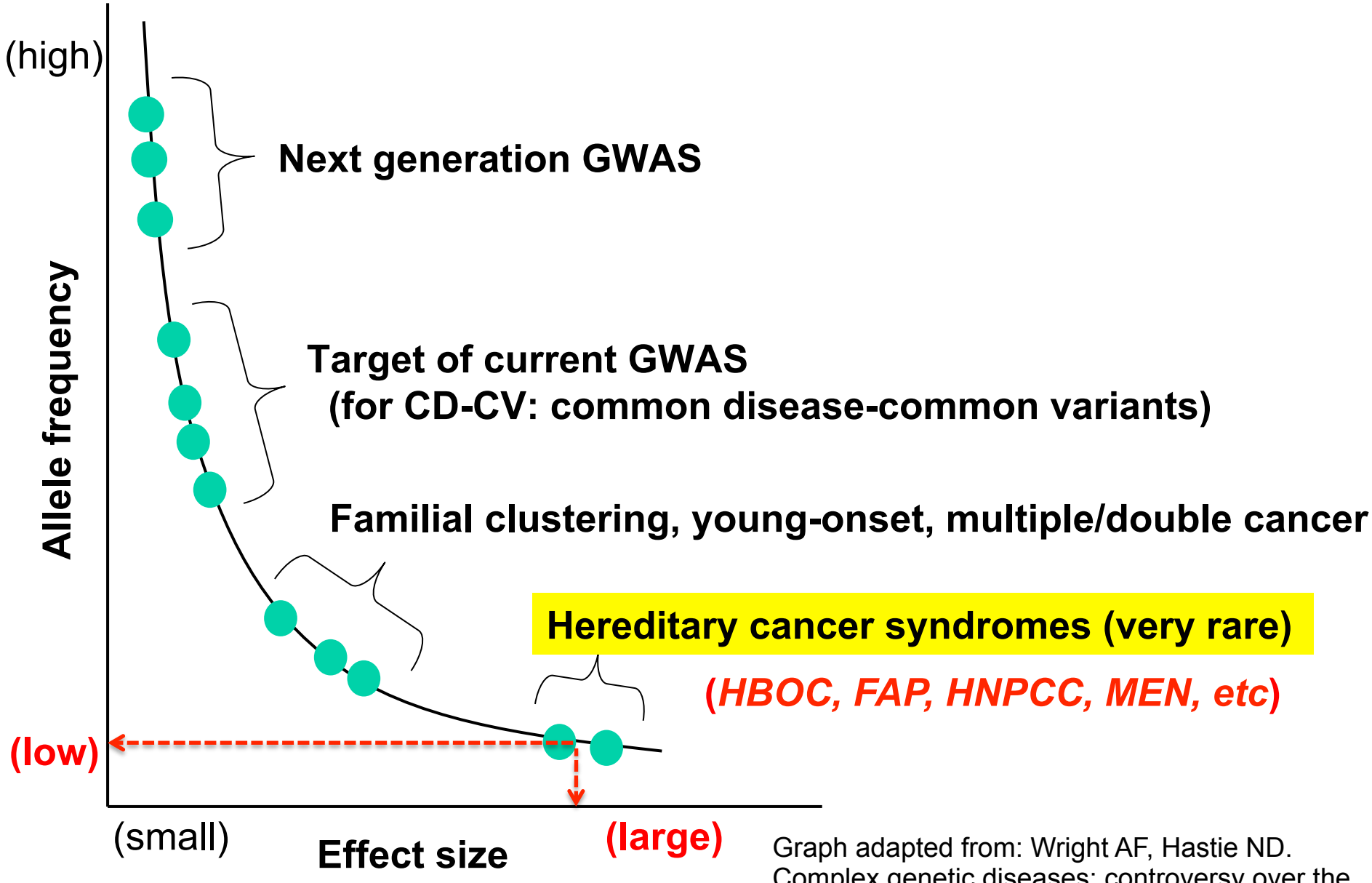
- Hereditary (Genetic) factors

  ← **Germ-line mutations/variations (SNPs)**

- Environmental factors

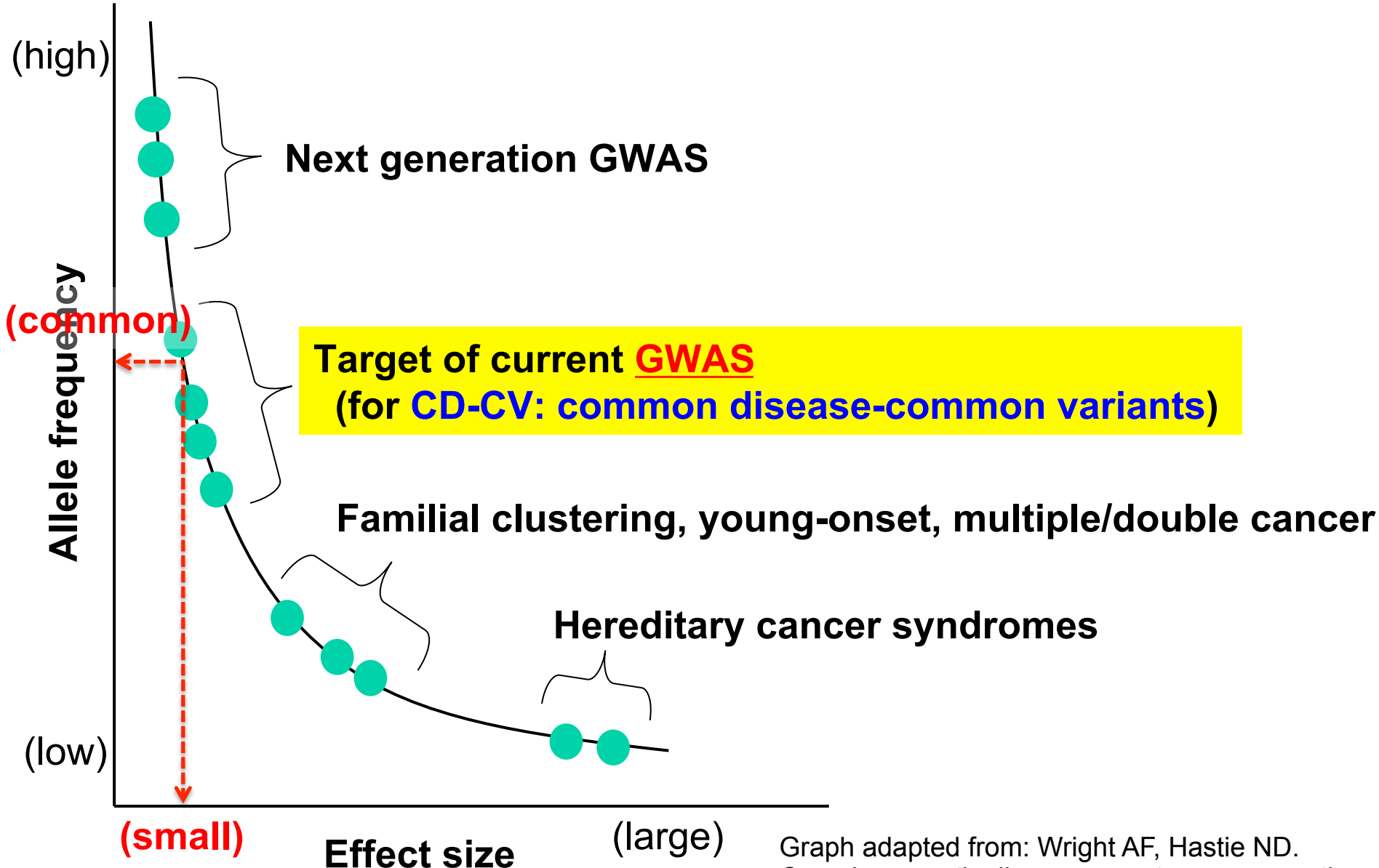
  → **Somatic mutations**
  Epigenetic alterations

Genetic Architecture of Disease Susceptibility



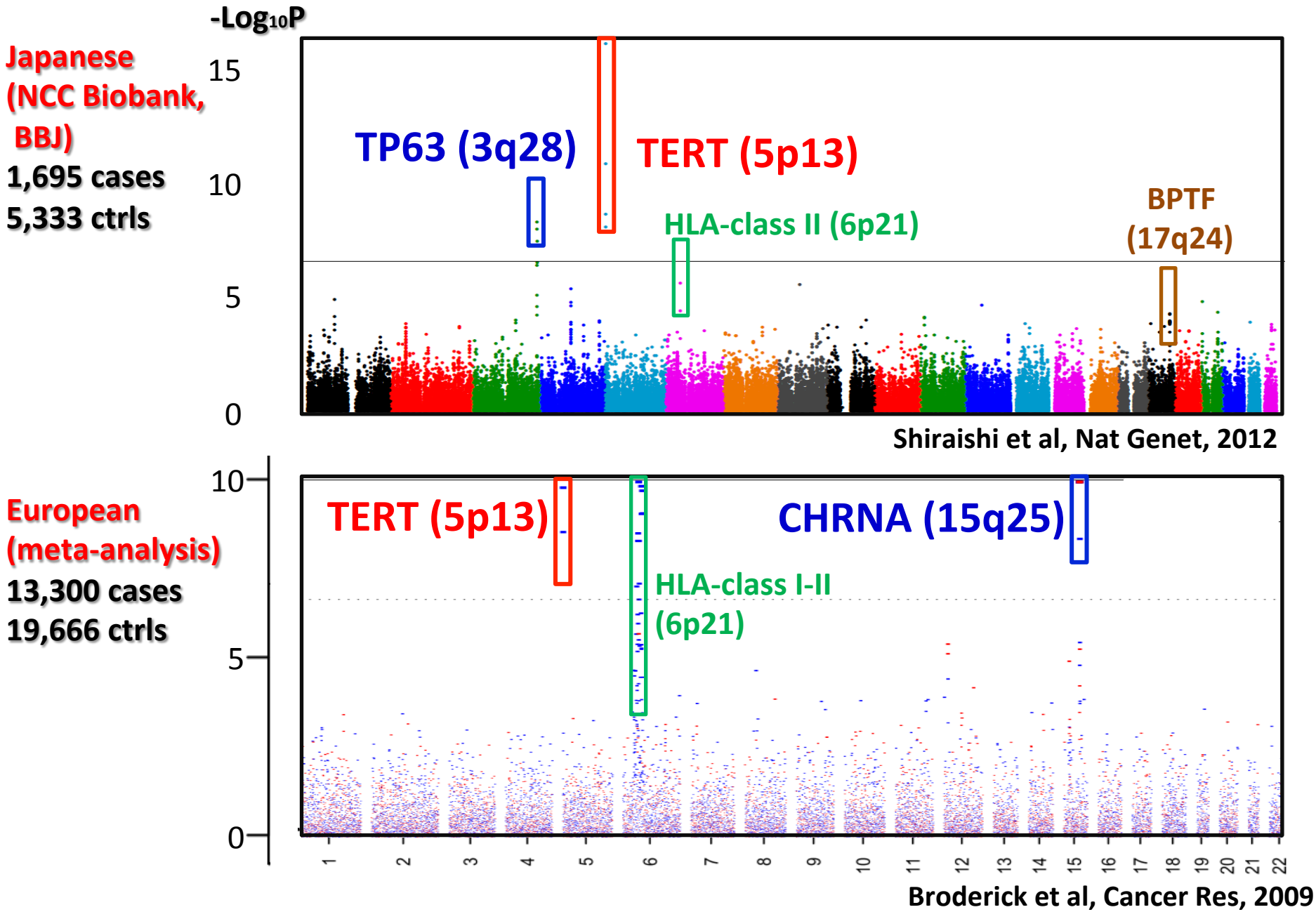
Graph adapted from: Wright AF, Hastie ND. Complex genetic diseases: controversy over the Croesus code. Genome Biol. 2001

Genetic Architecture of Disease Susceptibility



Graph adapted from: Wright AF, Hastie ND. Complex genetic diseases: controversy over the Croesus code. Genome Biol. 2001

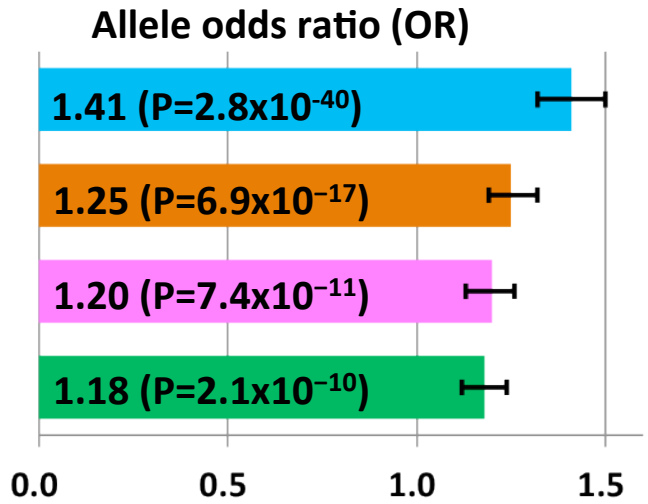
Genetic Factors for Lung Adenocarcinoma Risk by Ethnicity



Genome-wide Association Study (GWAS) on Lung ADC Risk

Japanese population (6,000 Lung ADC cases & 13,000 controls)

Gene	Product
TERT (rs2853677)	Telomerase
TP63 (10937405)	p53 homolog
BPTF (rs7216064)	Chromatin remodeler
BTNL2 (rs3817963)	Immune regulator



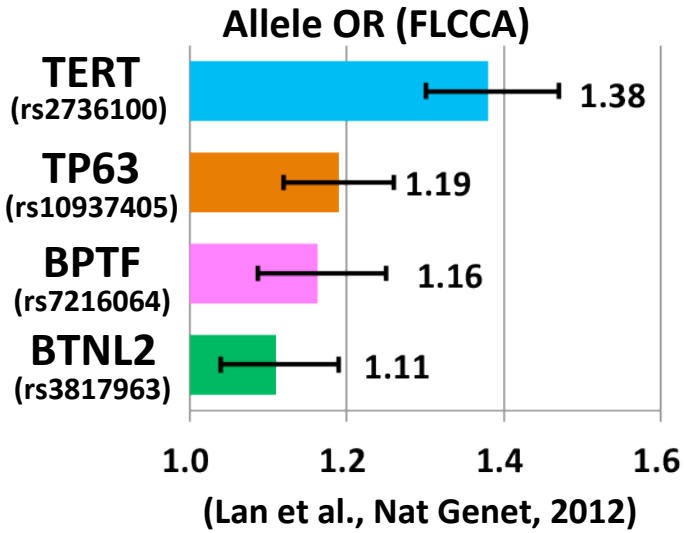
BPTF: bromodomain PHD finger transcription factor
BTNL2: butyrophilin-like 2

(Shiraishi et al., Nat Genet, 2012)

Meta analysis, difference by ethnicity & validation

ILCCO
(International lung Cancer Consortium)
IARC and European, US & Japan

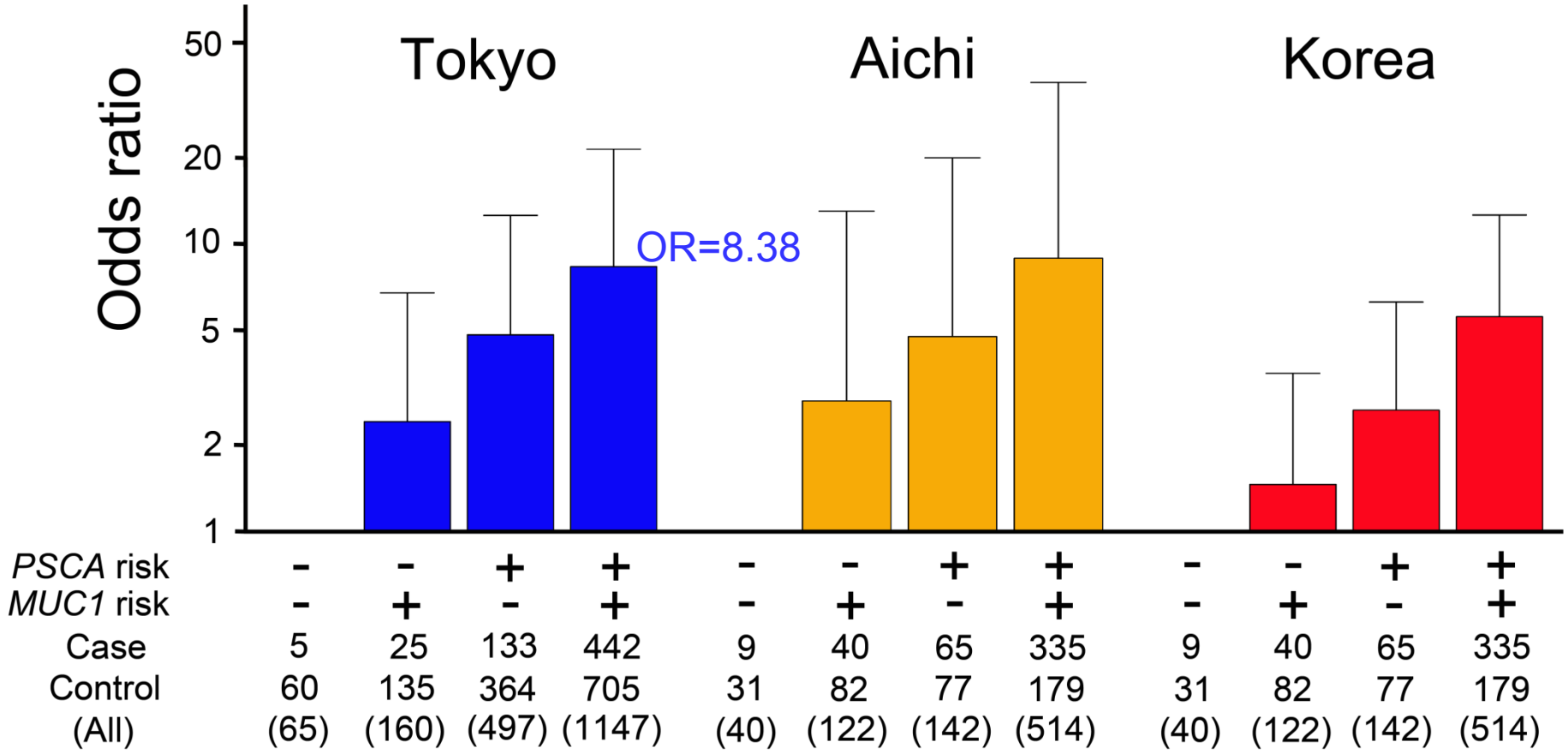
FLCCA
(Female Lung Cancer Consortium in Asia)
NCI, USA and 15 groups in Asia



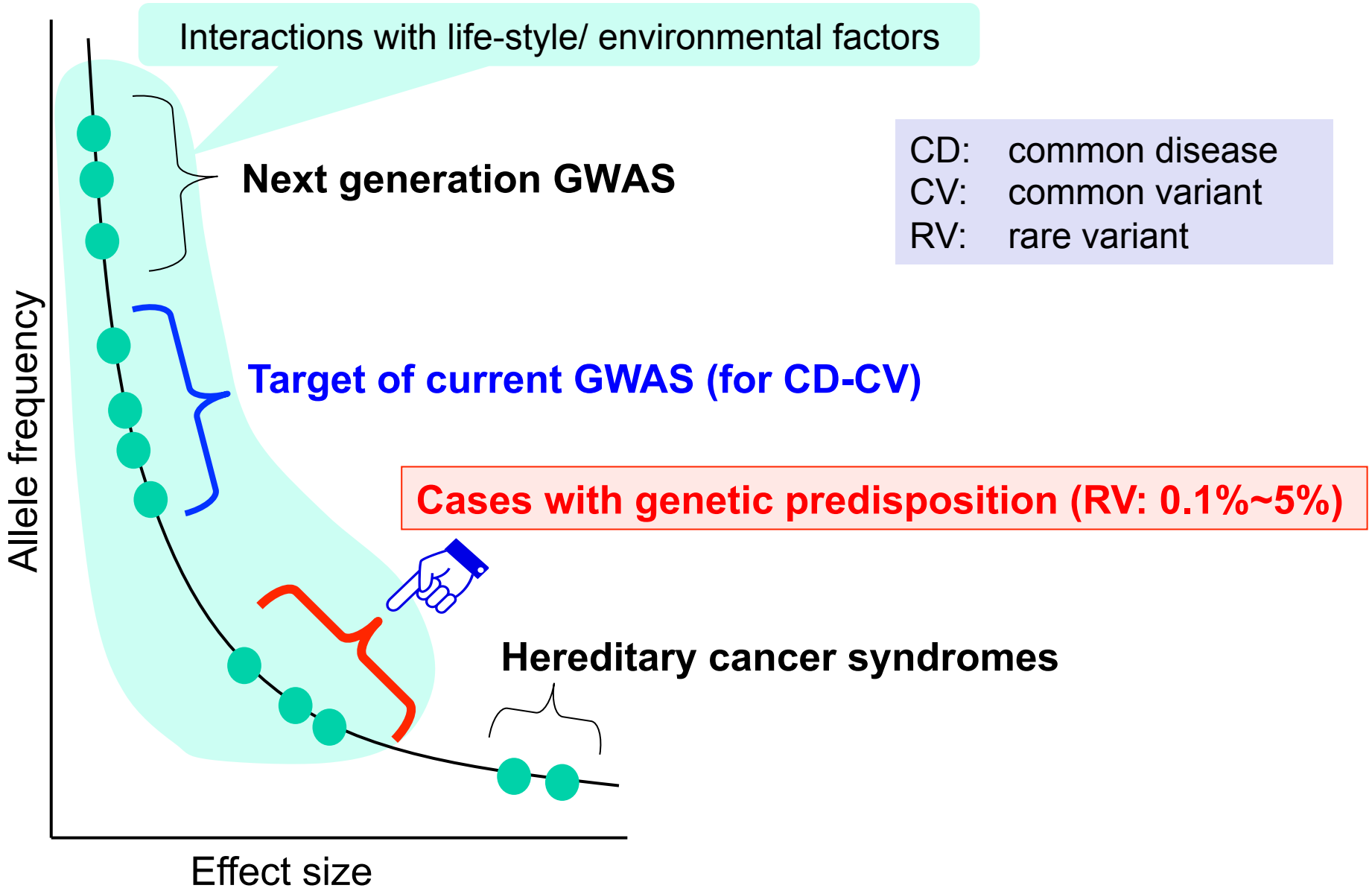
(Lan et al., Nat Genet, 2012)

Accumulation of Common Risk Variants for Gastric Cancer

Risk Genotype of
***PSCA* (rs2294008 T/C) and *MUC1*(rs4072037 A/G)**

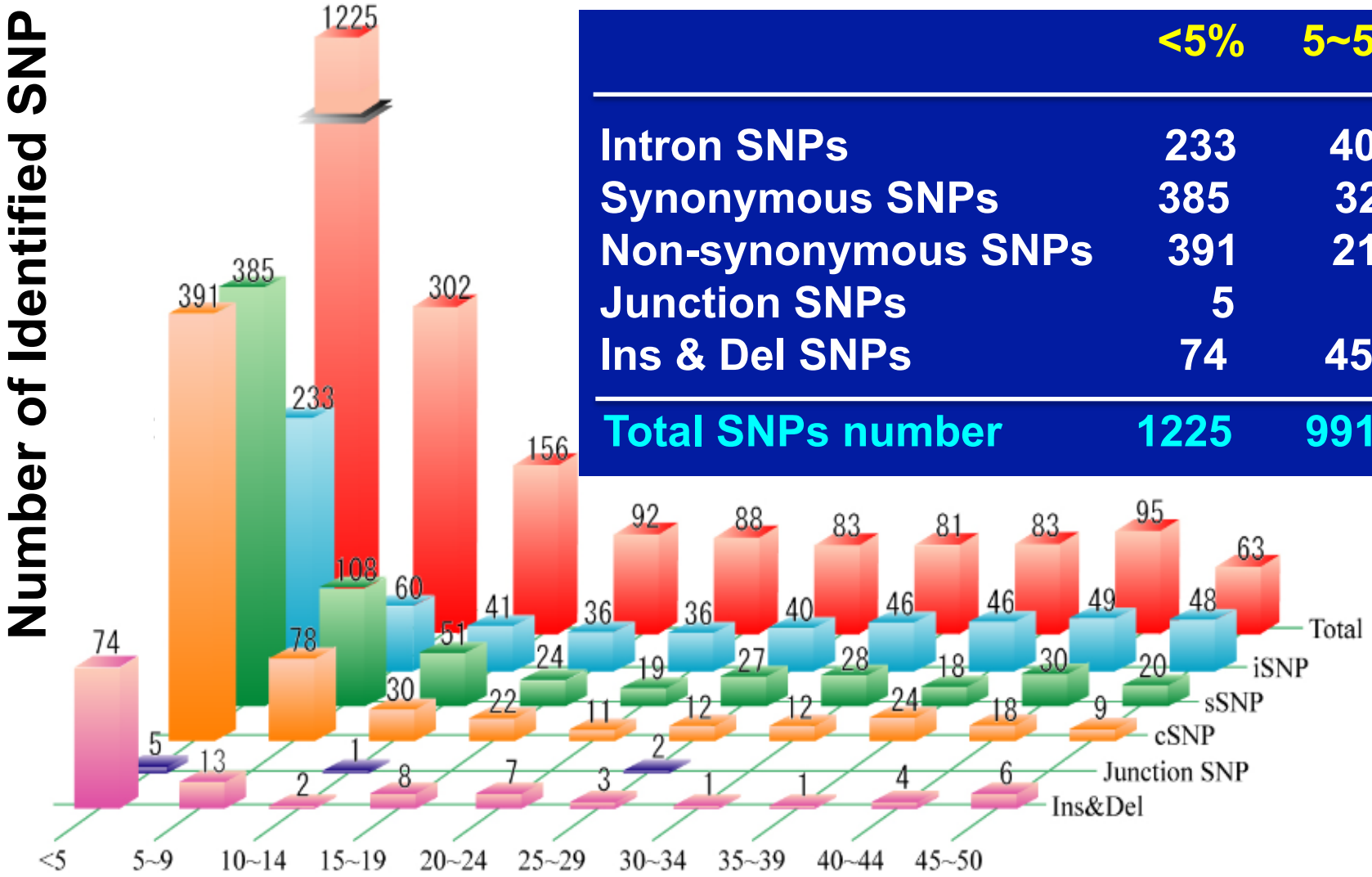


Genetic Architecture of Cancer Susceptibility



Graph adapted from: Yoshida T, et al. Genome-wide germline analyses on cancer susceptibility and GeMDBJ database: Gastric cancer as an example. *Cancer Sci* 101:1582-9, 2010.

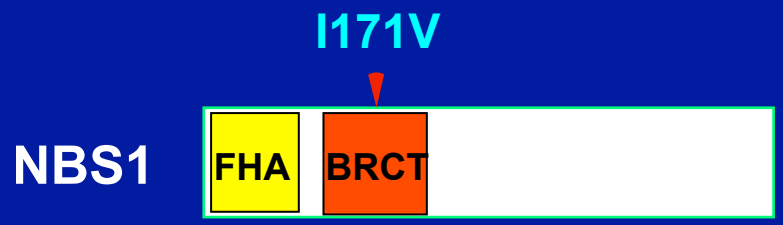
Distribution of Allele Frequency of SNPs in DNA Repair Genes in Japanese



	<5%	5~50%
Intron SNPs	233	402
Synonymous SNPs	385	325
Non-synonymous SNPs	391	216
Junction SNPs	5	3
Ins & Del SNPs	74	45
Total SNPs number	1225	991

(Yamamoto Y, et al. *Cancer Res*, 74:3707-3715, 2014)

Association of *NBS1* Variation with Breast Cancer in Japanese




```
                    I171V
                      ▼
Human   : ALICGRPIVKPEYFT
Mouse   : ALICGRPIIKPEYFS
Rat     : ALICGRPIVKPEYFS
Chicken : ALICGRPIVKPEFFT
```

Type	Normal(%)	Patient(%)	OR	P-val
I / I	1455(99.5)	1501(98.5)		
I / V	7(0.5)	23(1.5)	3.19	0.0048
V / V	0(0)	0(0)		

Source: BioBank Japan

(Yamamoto Y, et al. *Cancer Res*, 74:3707-3715, 2014)

Causation of Human Diseases

- Hereditary (Genetic) factors

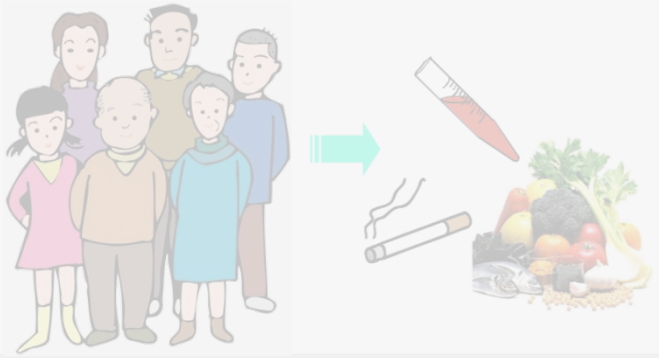
  ← **Germ-line mutations/variations (SNPs; genetic susceptibility)**

- Environmental factors

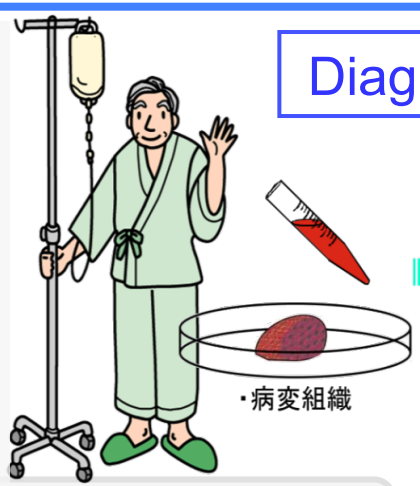
  → **Somatic mutations**
  Epigenetic alterations

Current Major Cohort and/or Biobank Projects in Japan

Prevention



Diagnosis and Treatment



・Therapeutic development
・Personalized medicine

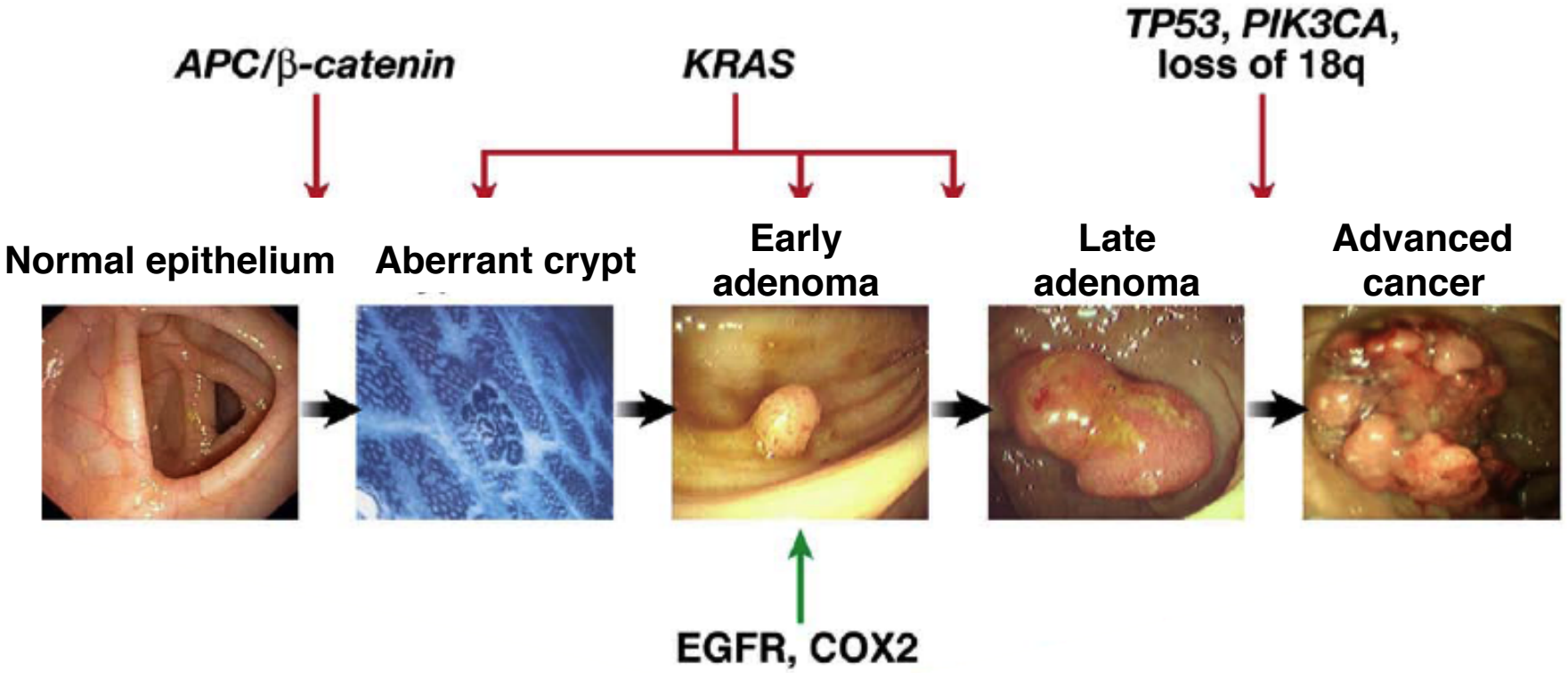
Population-based cohorts

Patient cohorts

Tohoku Medical Megabank (ToMMo)	・Stress cohort of the residents of the arch 2011 Quake and Tsunami area, incl. trio birth cohort ・approx. 150K (plan)
・JPHC、 ・J-MICC	・Nation-wide population-based cohorts ・approx. 100K
・Nagahama 0th prevention cohort ・Hisayama cohort	・Local community cohorts ・approx 10K

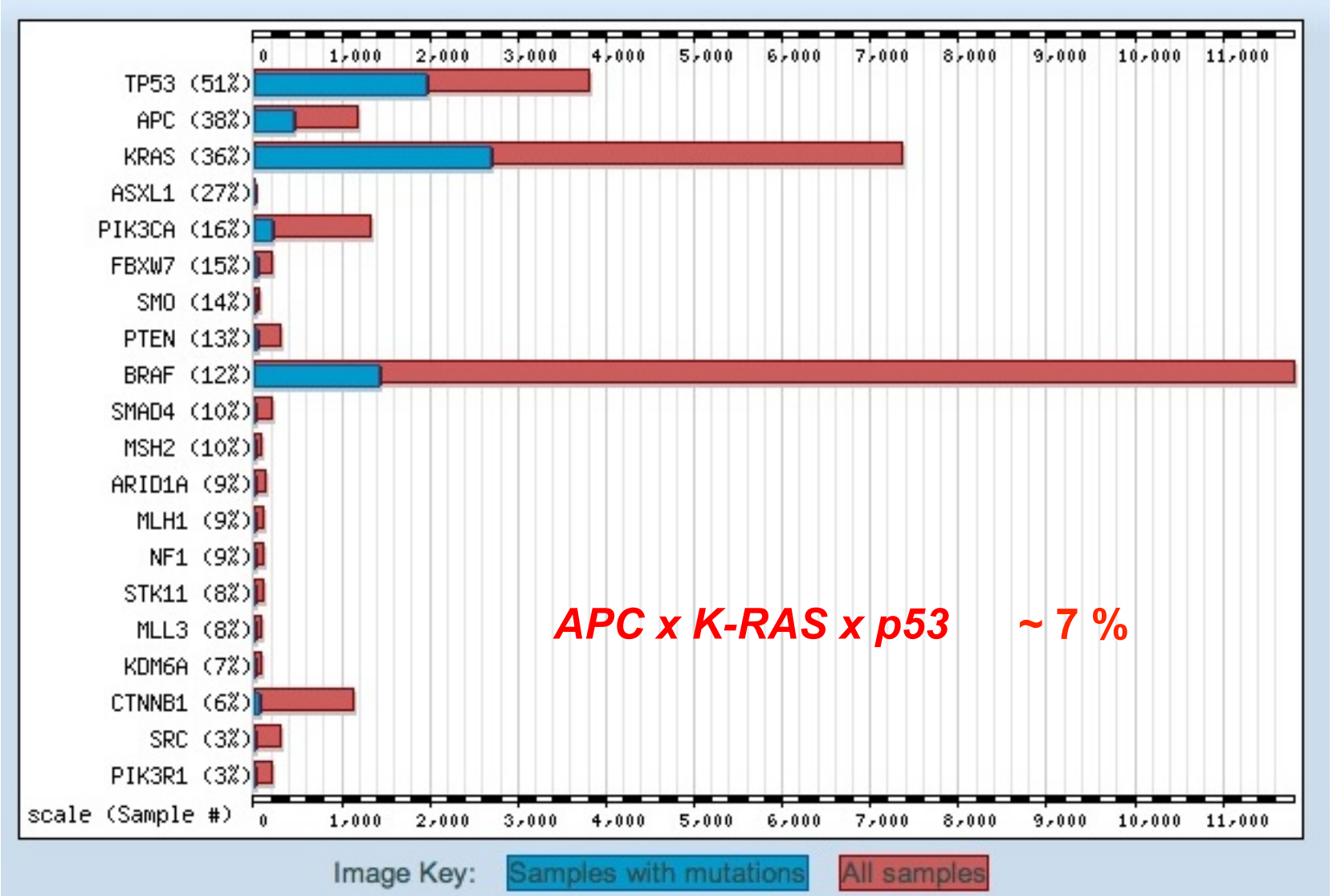
Biobank Japan (BBJ)	・Nation-wide community hospitals, university hospitals. ・47 diseases, approx 300K cases by approx 200K patients ・Blood samples, predetermined list of clinical information ・(Mostly) distribution-type biobank
National Center Biobank Network (NCC & NCBN)	・Centers for Highly Advanced and Specialized Medical Care ・Incl. diseases and subtypes relatively few in BBJ ・Blood and pathological tissue specimens with rich longitudinal clinical information ・(Mostly) collaboration/ contract-research biobank (cluster of the disease specialists, focused research and clinical trials)
Rare dis. bank	・Specific rare and intractable diseases

Multistep Carcinogenesis Model of the Colon



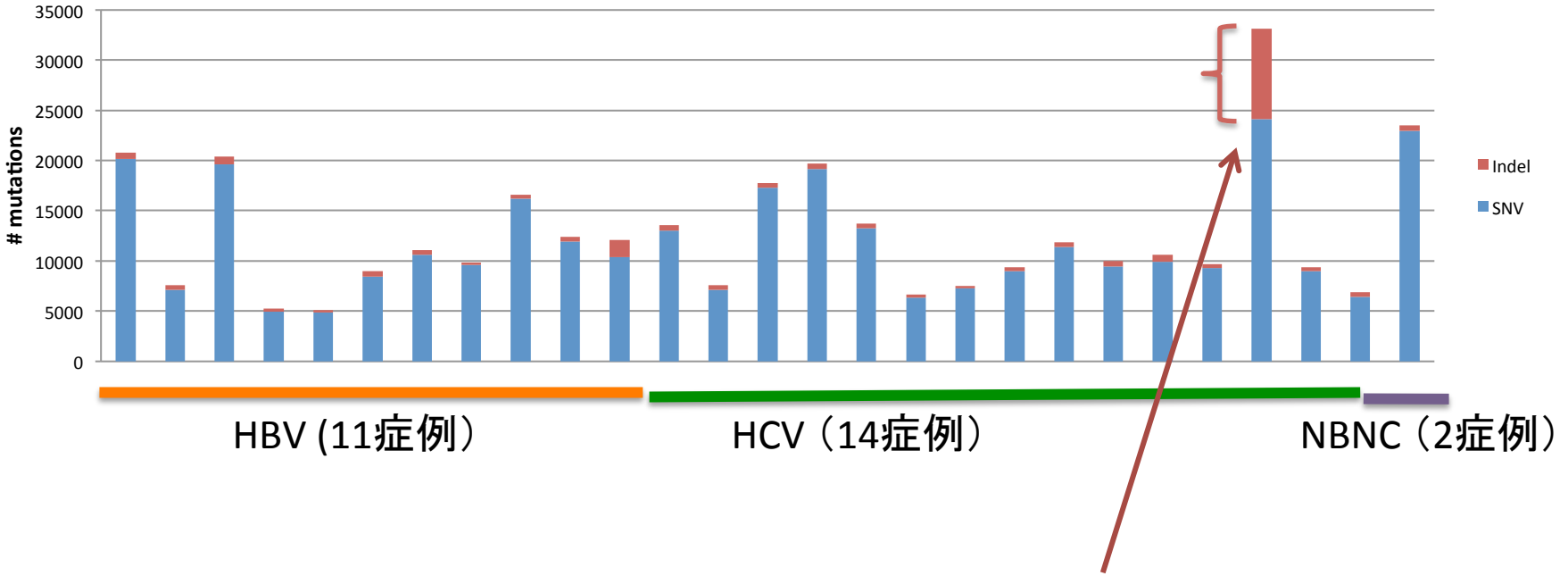
Pino MS & Chung DC, 2010

Genetic Alterations Frequently Observed in Human CRC



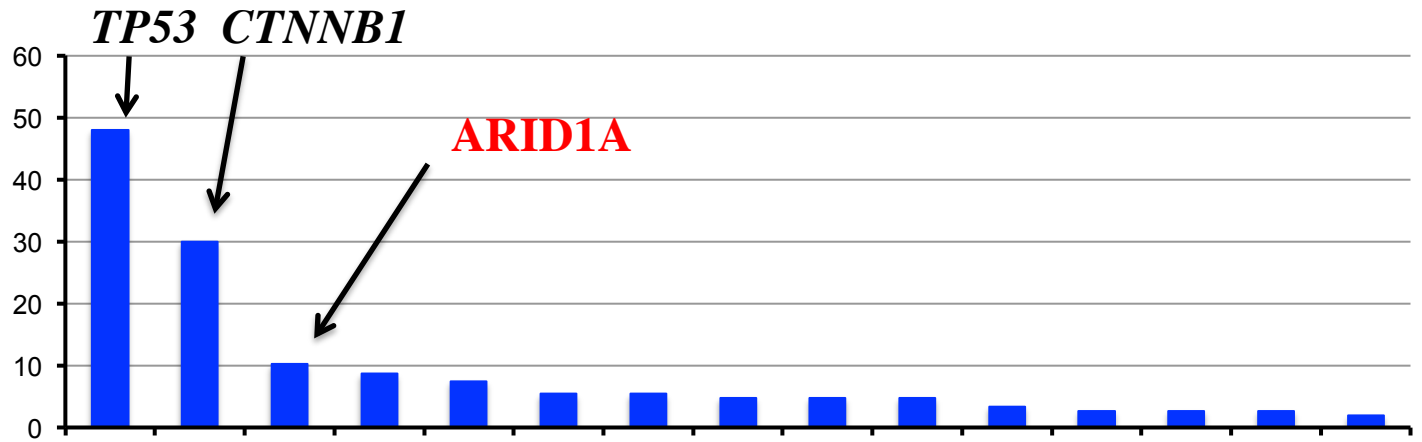
Somatic Substitution Patterns of 27 HCC Genomes

Average no. of mutation is ~4.2/Mb



This case has a nonsense mutation of the *MLH1* gene.

Heterogeneity (Diversity) in Genetic Alteration In HCV-induced Liver Cancers



Pathway analysis revealed "chromatic regulator" as significant in these mutation set.

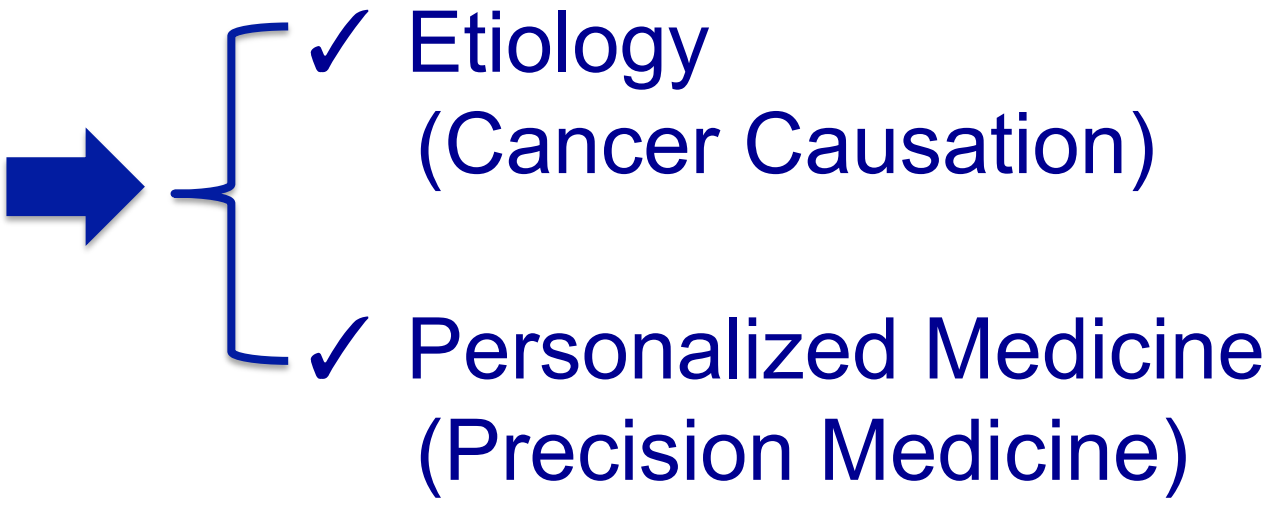
Category	Term	Count	%	*P-value*	List Total	Pop Hits	Pop Total	Fold Enrichment	*q-value*
SP_PIR_KEYWORDS	phosphoprotein	162	55.1	6.92E-10	292	7263	19235	1.469292662	0.00000023
INTERPRO	IPR013032:EGF-like region, conserved site	19	6.5	8.02E-07	260	293	16659	4.154909425	0.00049
INTERPRO	IPR000742:EGF-like, type 3	15	5.1	2.14E-06	260	194	16659	4.954103886	0.0006
INTERPRO	IPR006210:EGF-like	15	5.1	3.25E-06	260	201	16659	4.781572905	0.0007
SP_PIR_KEYWORDS	egf-like domain	15	5.1	1.15E-05	292	230	19235	4.296083979	0.0019
UP_SEQ_FEATURE	domain:EGF-like 1	12	4.1	2.25E-06	292	120	19113	6.545547945	0.0039
SMART	SM00181:EGF	15	5.1	3.00E-05	175	201	9079	3.871641791	0.0043
SP_PIR_KEYWORDS	polymorphism	208	70.7	4.75E-05	292	11550	19235	1.18628951	0.0052
SP_PIR_KEYWORDS	calcium	28	9.5	9.42E-05	292	803	19235	2.2969515	0.0078
UP_SEQ_FEATURE	sequence variant	218	74.1	1.06E-05	292	11992	19113	1.189901144	0.0092
SP_PIR_KEYWORDS	**bromodomain**	6	2.0	2.89E-04	292	39	19235	10.13435195	0.019
SP_PIR_KEYWORDS	**chromatin regulator**	12	4.1	4.17E-04	292	213	19235	3.711171136	0.023
INTERPRO	IPR006209:EGF	10	3.4	1.66E-04	260	127	16659	5.045124167	0.025
SP_PIR_KEYWORDS	disease mutation	42	14.3	5.45E-04	292	1591	19235	1.738955426	0.026
INTERPRO	**IPR001487:Bromodomain**	6	2.0	3.69E-04	260	40	16659	9.610961538	0.044
SP_PIR_KEYWORDS	tumor suppressor	9	3.1	0.001157126	292	137	19235	4.327442256	0.047

q-value was obtained by Benjamini and Hochberg's FDR method

(Fujimoto A, et al. *Nature Genet*, 2012)

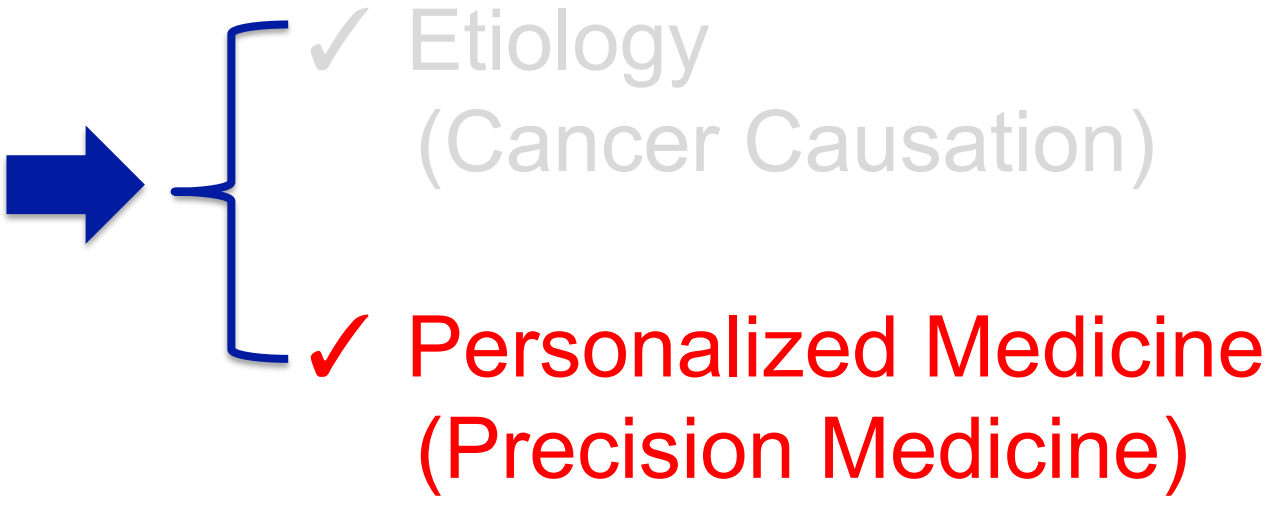
Heterogeneous Nature of Individual Cancers

- **Somatic/genetic mutations**
- **Epigenetic alterations**

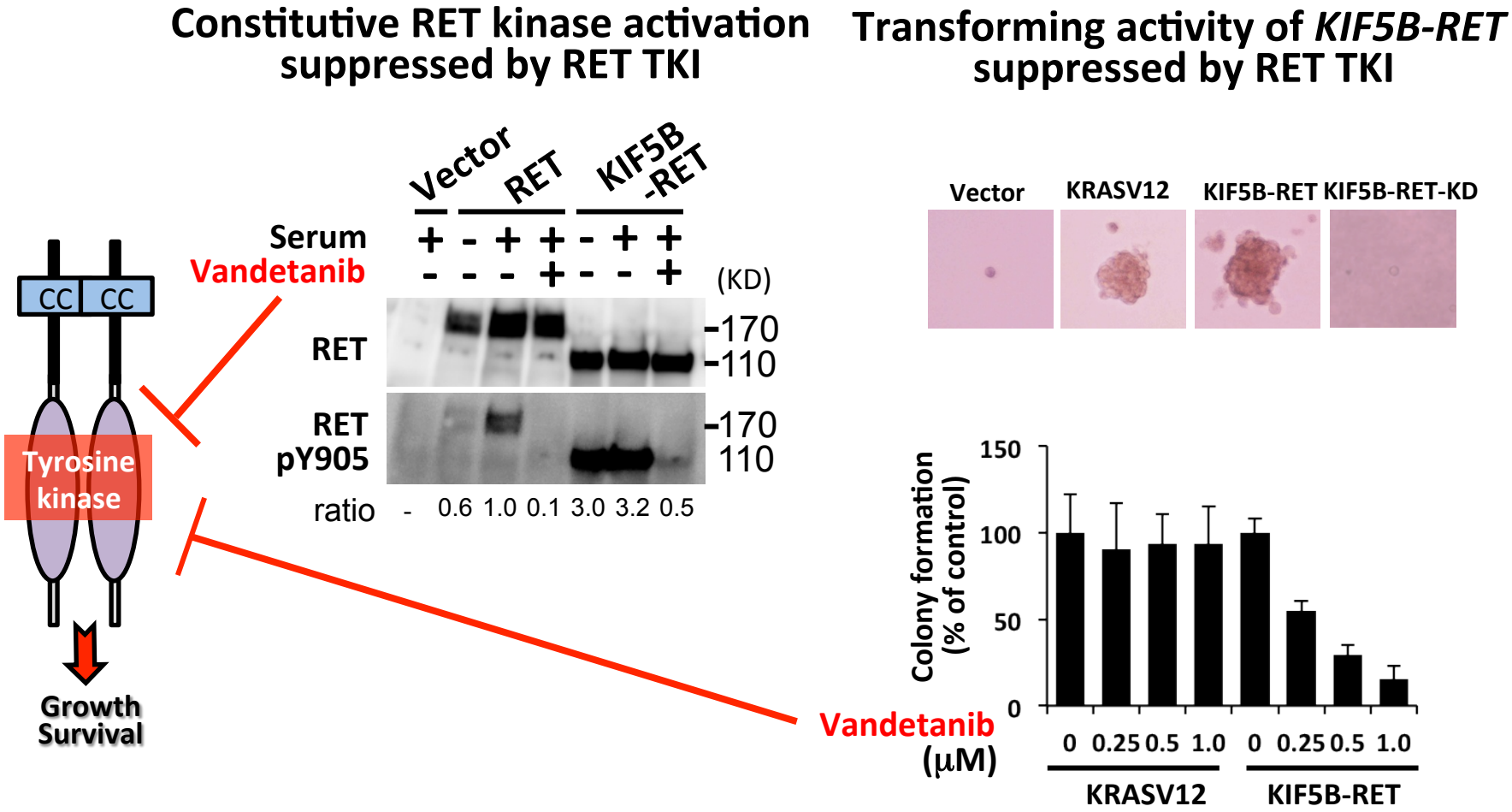


Heterogeneous Nature of Individual Cancers

- **Somatic/genetic mutations**
- **Epigenetic alterations**



RET Fusion: A New Driver Aberration & Therapeutic Target



(Kohno et al, Nat Med, 2012)

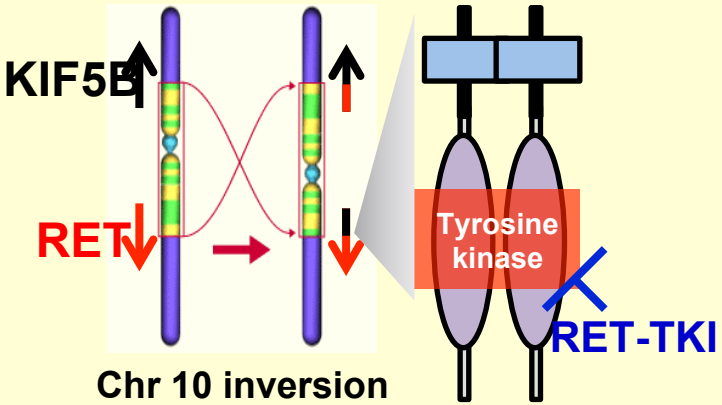
RET Fusion Gene: Discovery & Translation to Lung Cancer Therapy

Discovery

(Kohno, Ichikawa, ….. Shibata, *Nat Med*, 2012)

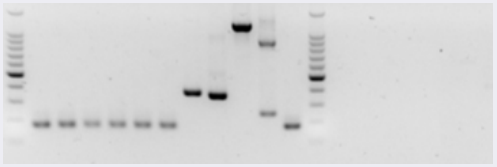
Whole transcriptome sequencing of
30 lung adenocarcinoma specimens
(NCC biobank)

KIF5B-RET fusion
Japan 6/319 (1.9%) & US 1/80 (1.3%)

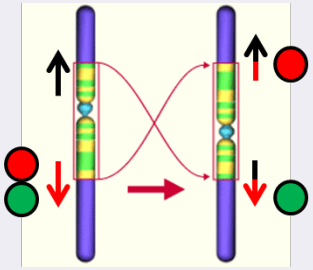


Diagnosis: LC-SCRUM

Multiplex RT-PCR



Fluorescence *in situ* hybridization



Screening includes
>100
hospitals in Japan

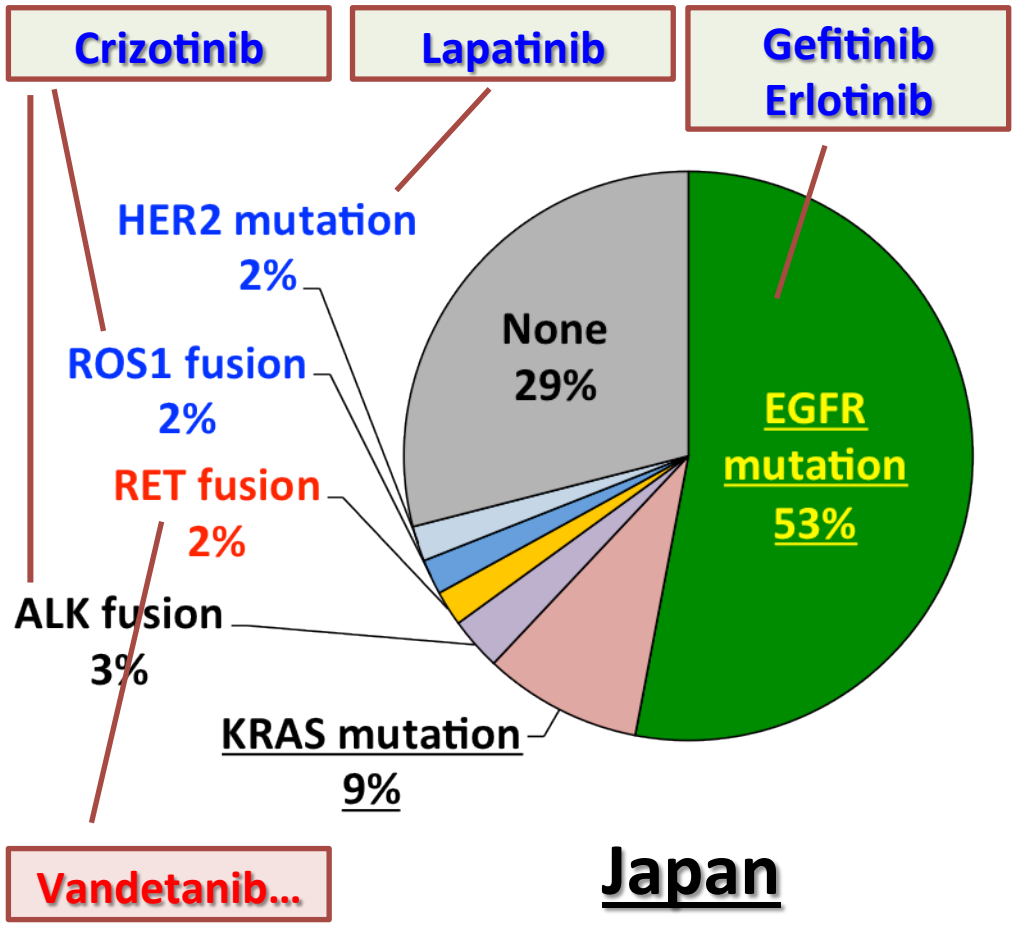
Clinical trial: LURET study PI: Dr. Goto K

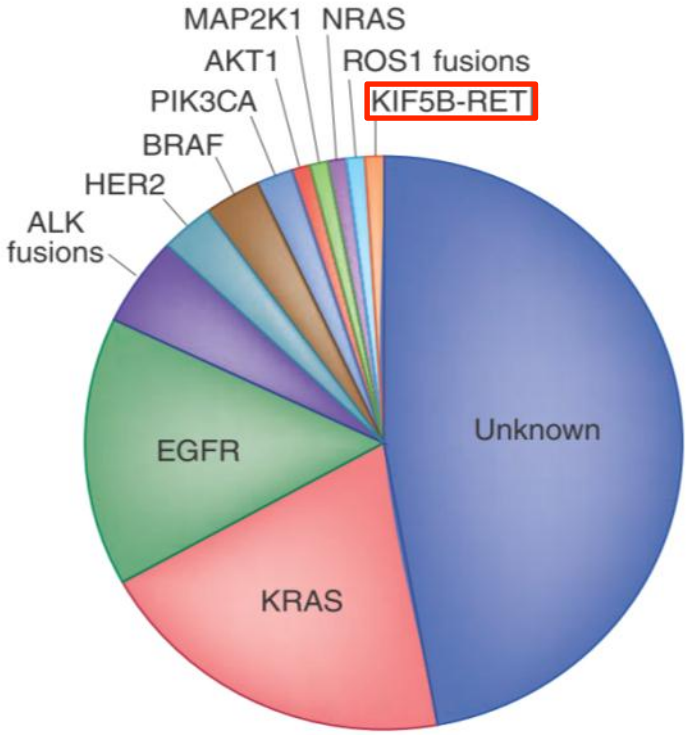
Phase II study of vandetanib (AZ6474) on RET fusion-positive advanced non-small cell lung cancer
Primary endpoint: Overall response rate
Enrollment: 17 patients in 2 years
Follow-up: 1 year
Treatment: 7 hospitals

NCC EPOC

Molecular Basis of Adenocarcinoma of the Lung

>60% of patients in Japan
>30% of patients in USA/Europe
will benefit from therapy using existing tyrosine kinase inhibitors (TKIs).





Japan

NCC: Stage I-II cases

USA/Europe

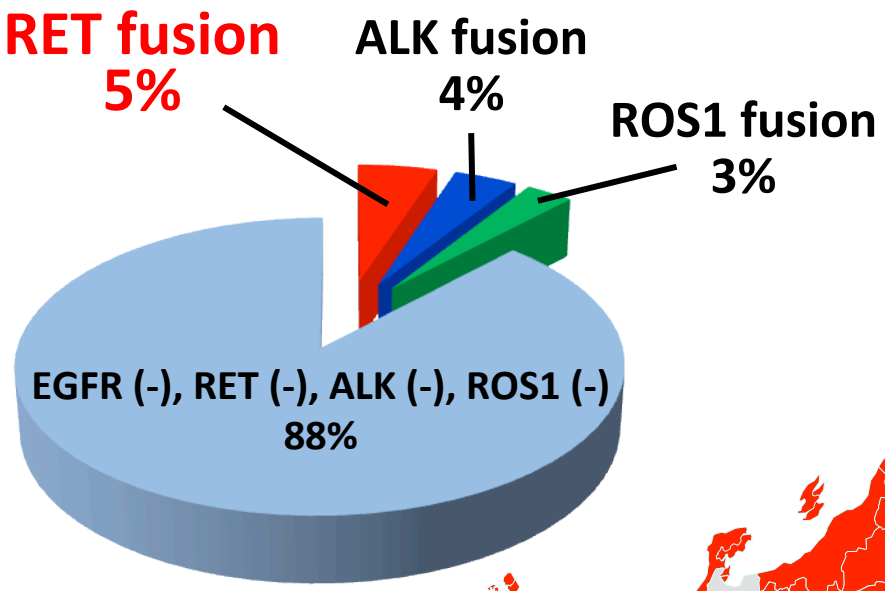
Nat Med, N & V (2012)

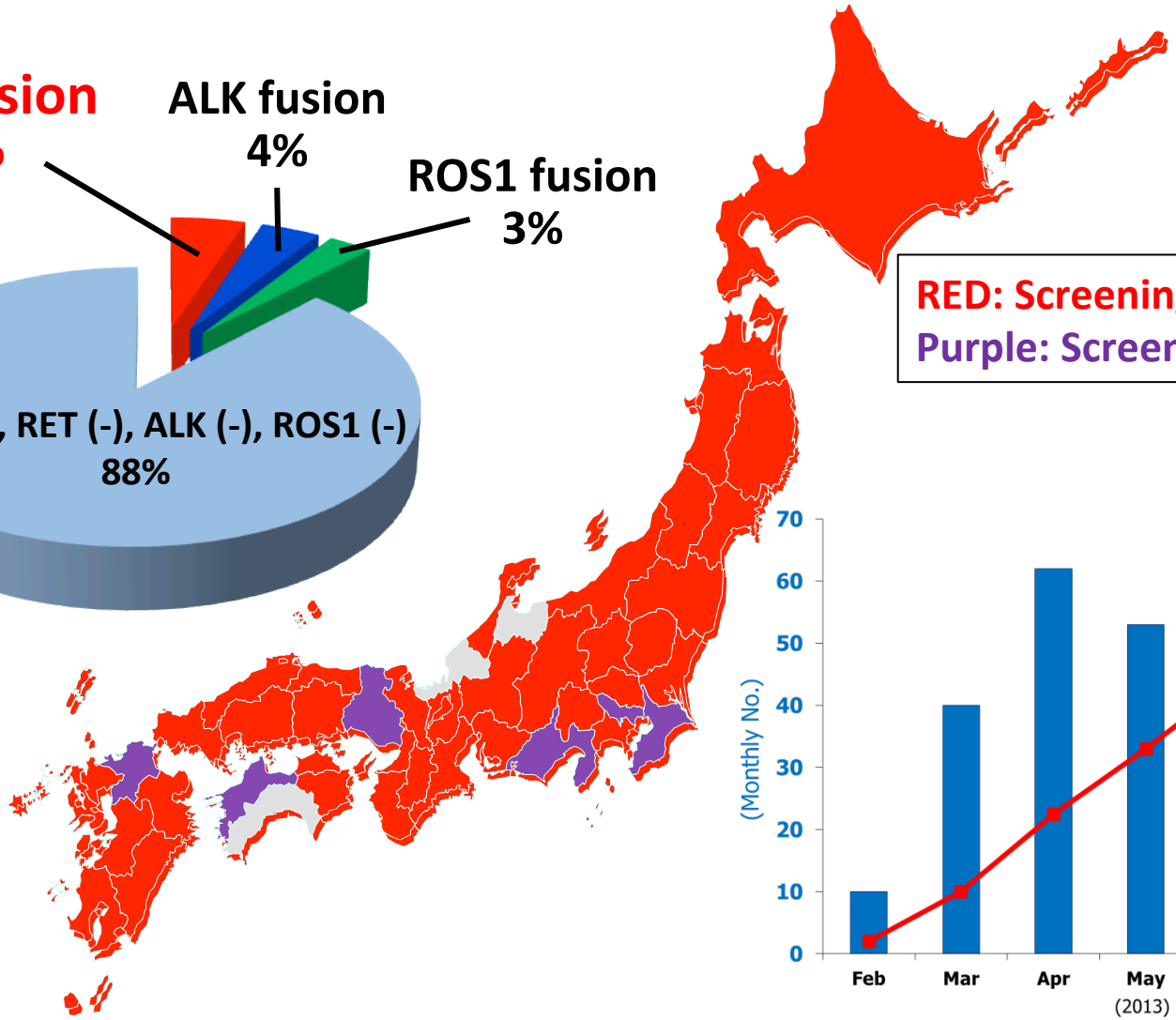
LC-SCRUM-Japan

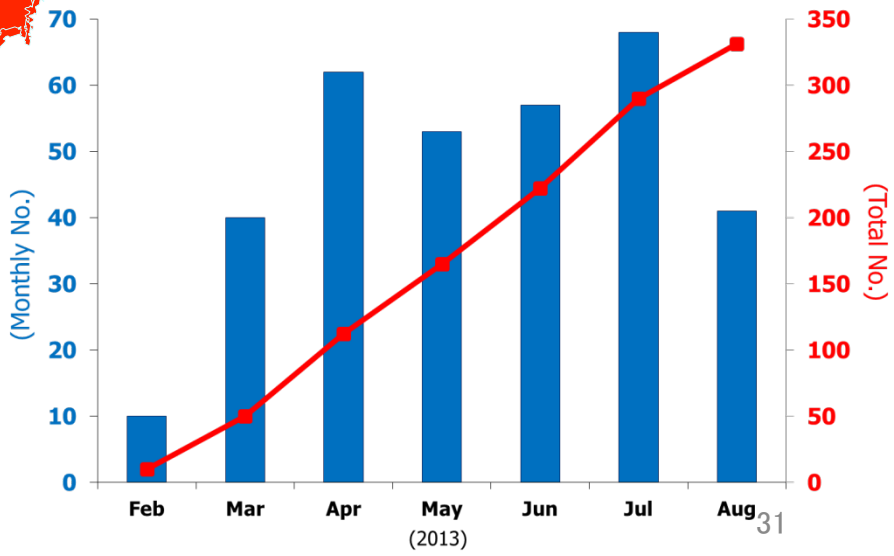
Lung Cancer Genomic Screening Project for Individualized Medicine in Japan

NCC NATIONAL CANCER CENTER JAPAN
EPOC
Exploratory Oncology Research & Clinical Trial Center
早期・探索臨床研究センター

136 institutes in 44 prefectures are participating, and 324 patients have been examined (Nov. 15th 2013). 5% of patients are positive for *RET*-fusion.





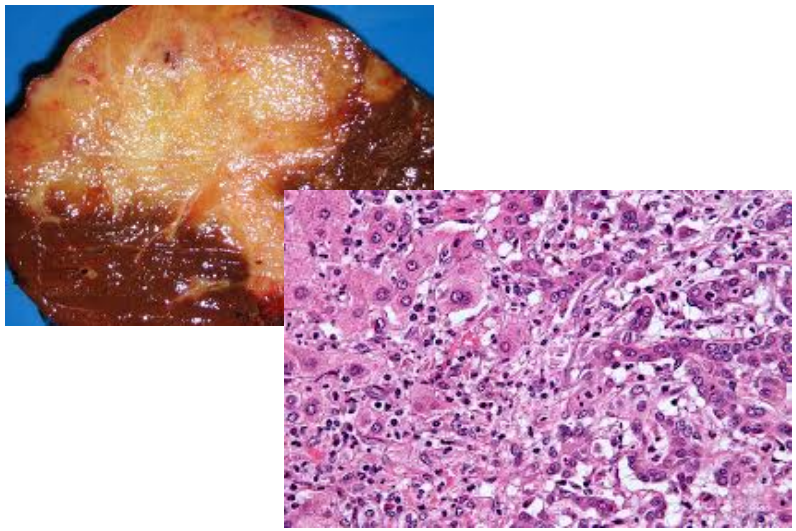


Biliary tract cancer

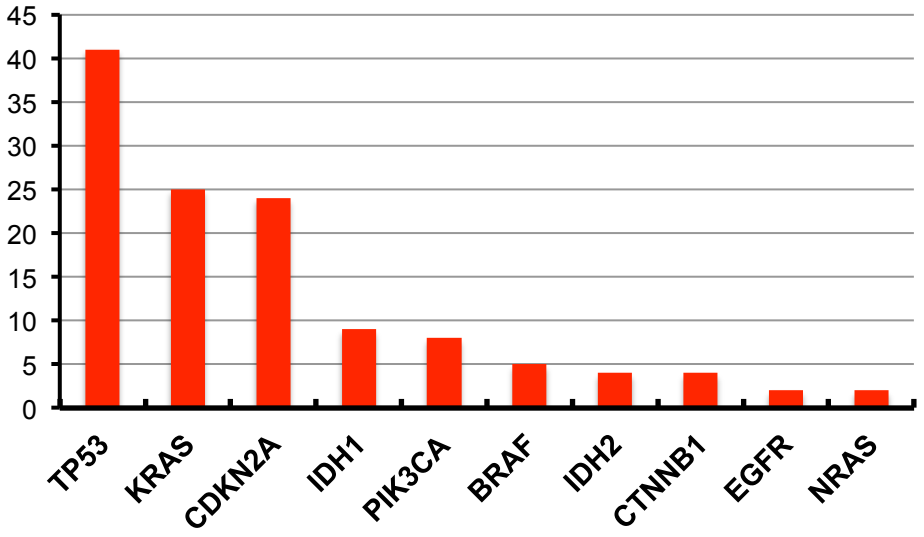
1. The incidence of biliary tract cancer is particularly high in Chile and Asian countries (Thailand, Japan, China and Korea).

2. Five year survival rate is ~20% (next to pancreatic cancer (7%)).

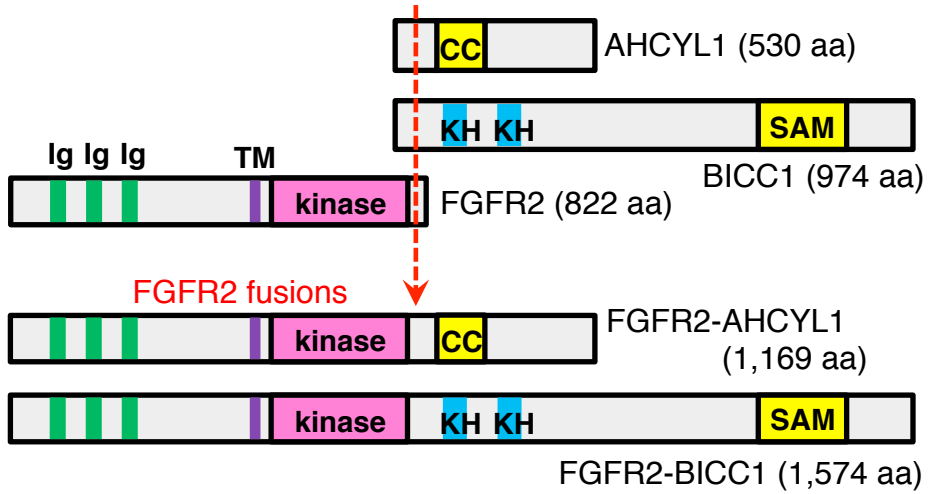
3. Surgical resection is the only curable therapy.

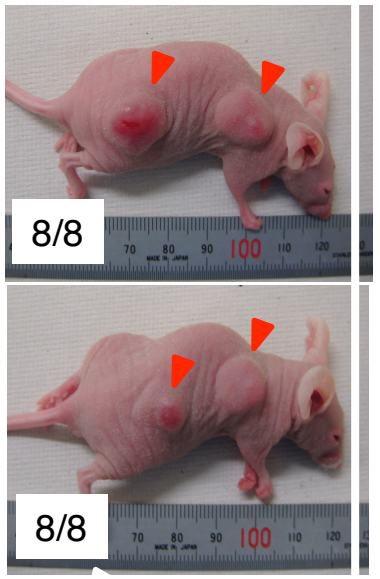


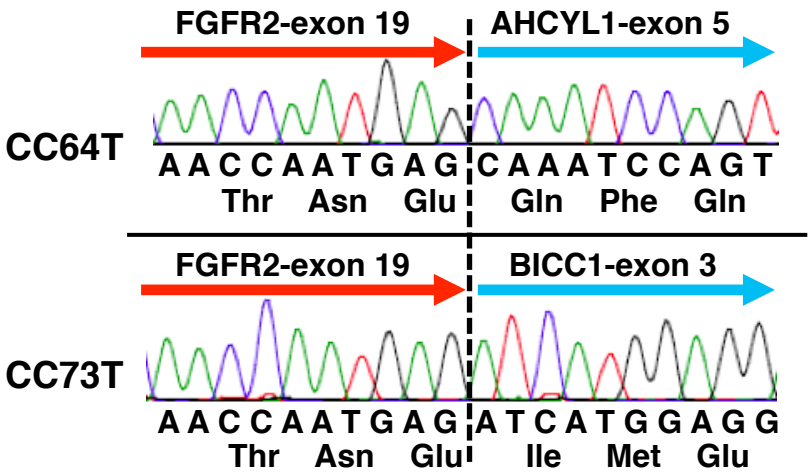
Reported mutation profile
(by COSMIC, only genes analyzed in >200 cases)

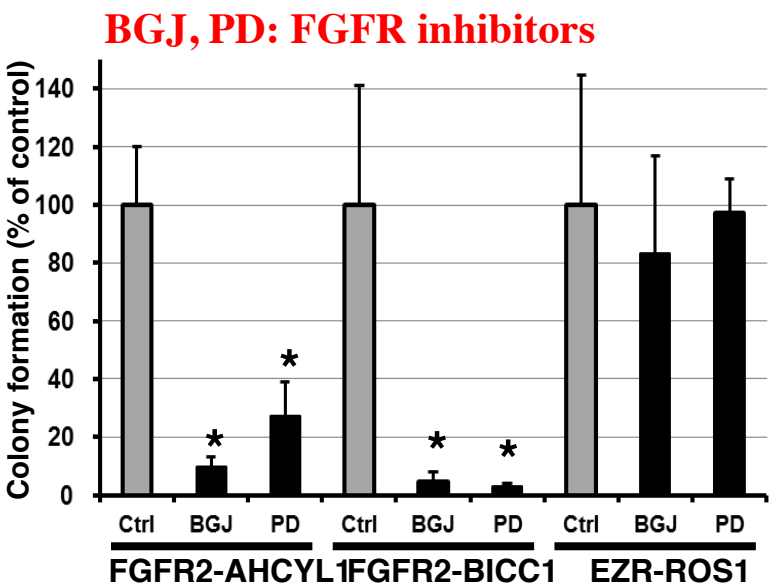


Discovery of novel FGFR fusion genes in cholangiocarcinoma









(Arai et al, Hepatology, 2014)

Translational Development of Genomic Biomarker-driven Targeted Therapy by NCC-(multi) Pharma Consortium

① Systematic survey and validation of driver mutations in each cancer case

IC on whole ① +②scheme to the patients w/o standard therapeutic option

Image-guided research biopsy, etc.

Genome screen followed by validation on minute clinical materials

Multidisciplinary Sequencing Tumor Board

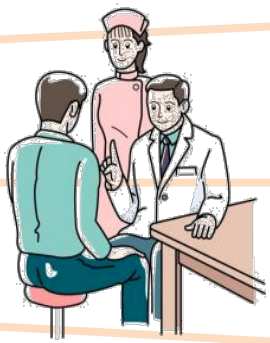
Report of results

② Clinical trial targeted to the identified driver mutation

②A : Gene A alteration

②B : Gene B alteration

②C : Gene C alteration



IC of available clinical trial

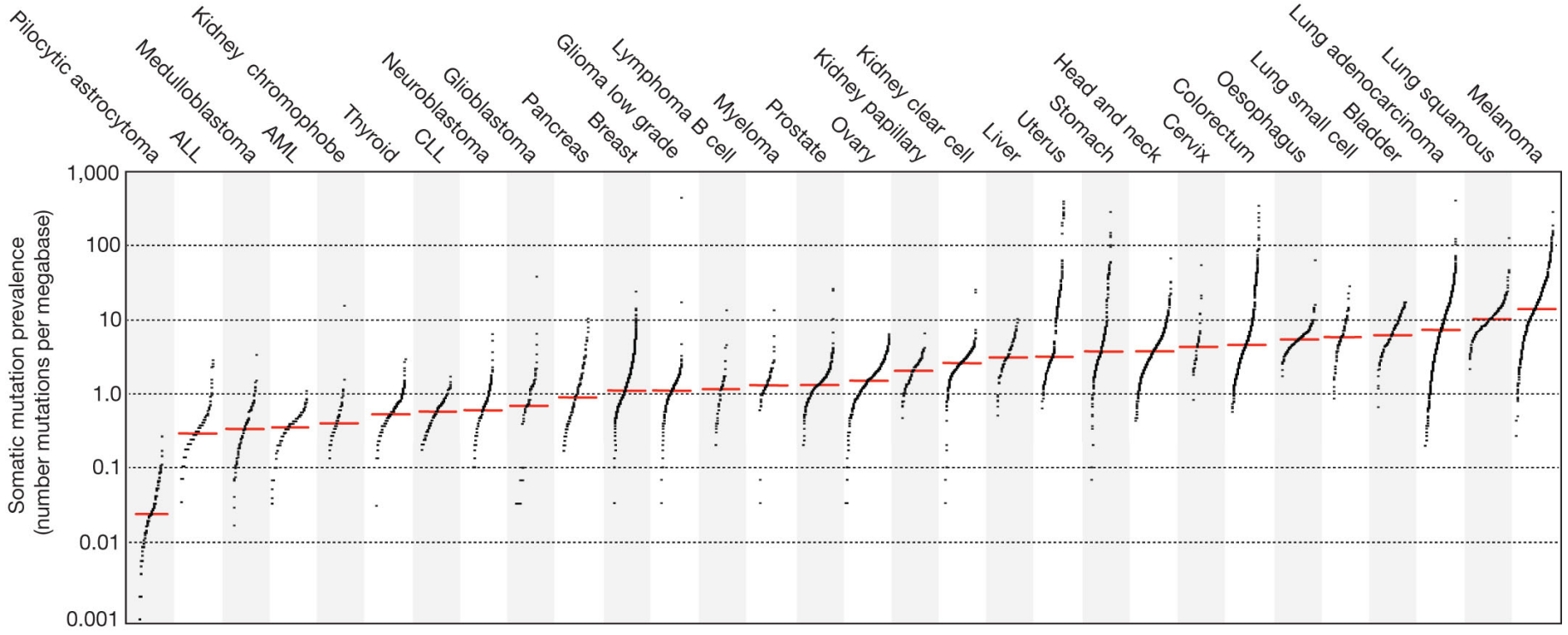
On-going clinical trials at NCC

- Industry-sponsored clinical trial on Compound X (Phase I, II, III)
- IIT or "Highly Advanced Medical Technology Assessment System" on Compound Y (Phase I, II)
- Clinical trial for indication expansion of Drug Z

- **Somatic/genetic mutations**
- **Epigenetic alterations**

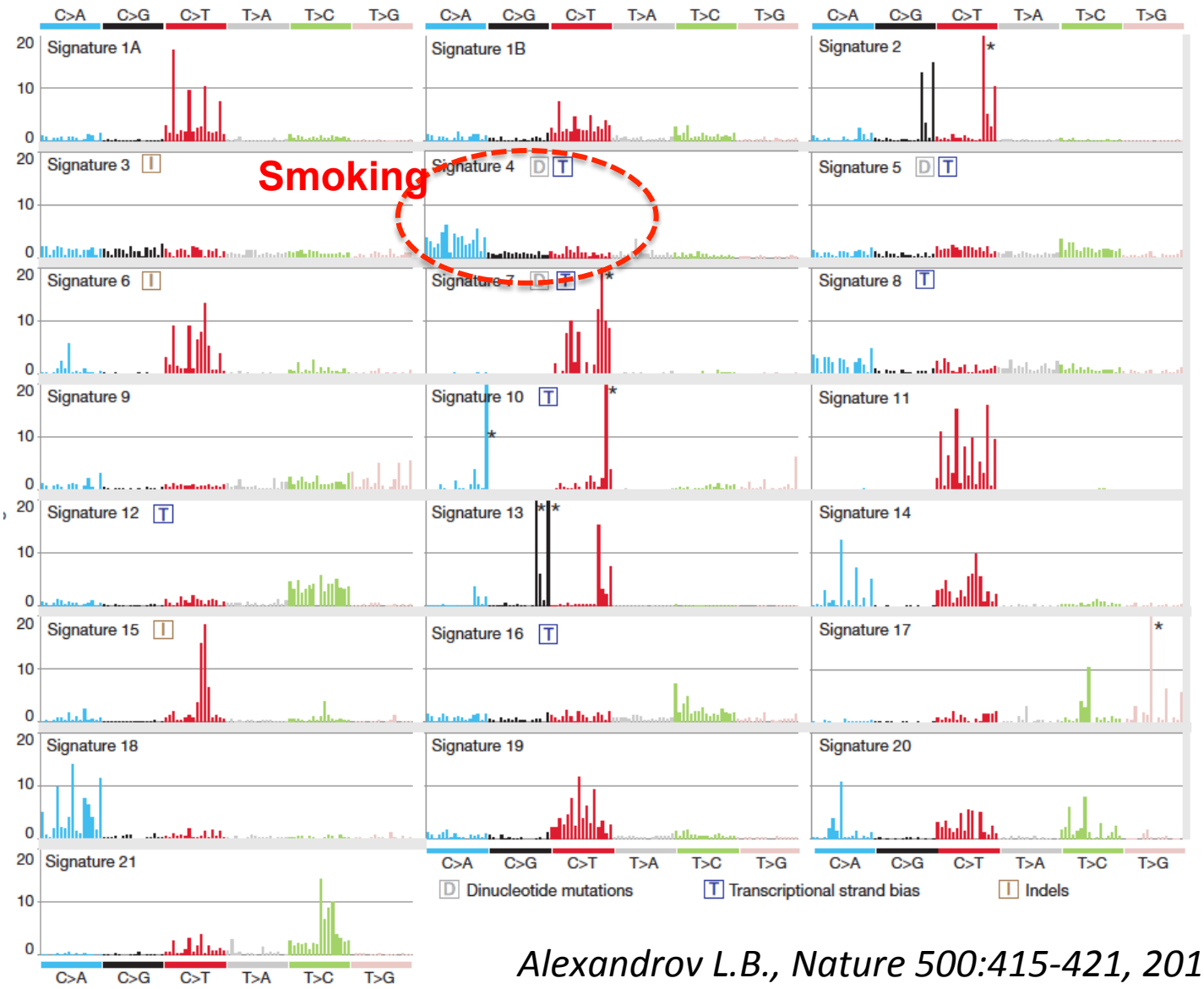
The Prevalence of Somatic Mutations Across Human Cancer Types

(7,042 primary cancers of 30 different classes)



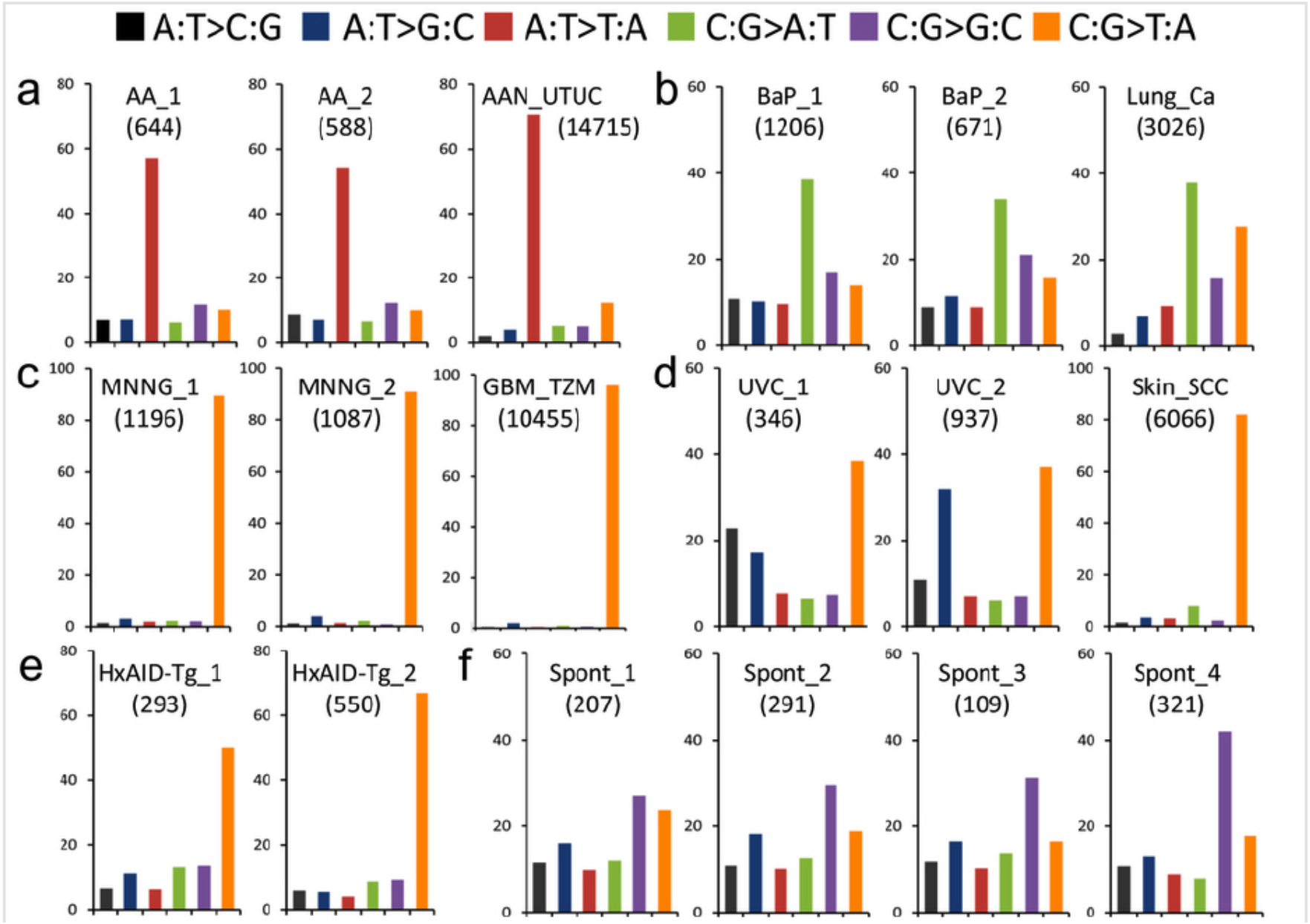
"Signatures of mutational processes in human cancer"
Alexandrov L.B., Nature 500:415-421, 2013

Validated Mutational Signatures Found in Human Cancer



Alexandrov L.B., Nature 500:415-421, 2013

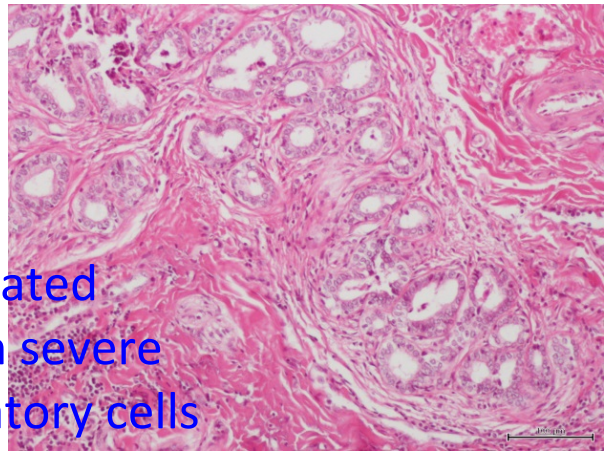
Mutation Patterns derived from Exome Data obtained from MEF



(Oliver M, et al. *Scientific Reports* 4:4482, 2014)

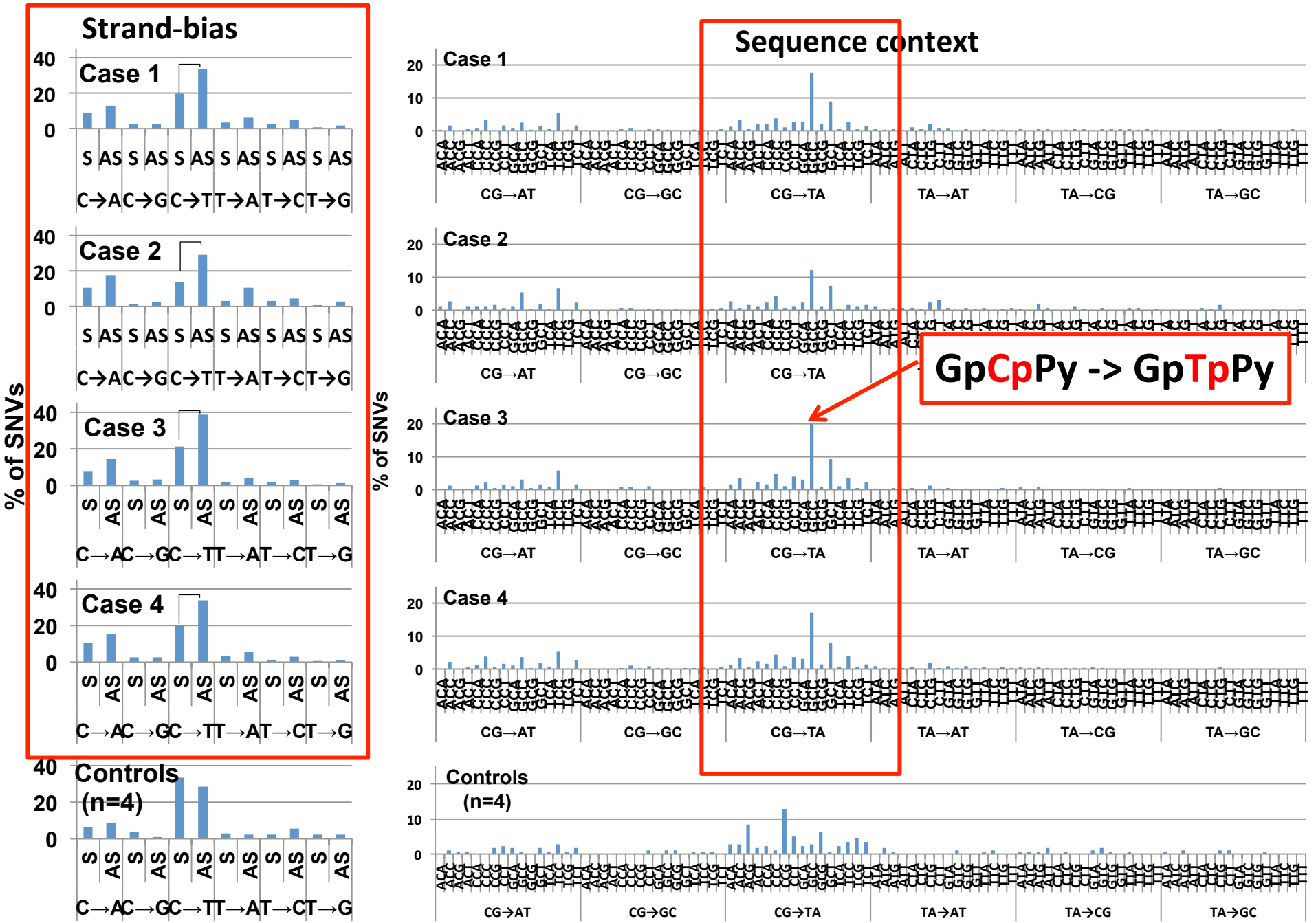
Cholangiocarcinoma Case of an Offset Color Proof-printing Worker

- Male, 40s
- History of chemical exposure:
  1,2-DCP/ DCM for several years
- Chief complaint:
  Increased γ-GTP at medical checkup
- Lab data
  AST 66, ALT 107, γ-GTP 679, CRP 0.05
  CEA 1.0, CA19-9 34, Span-1 21,
  Dupan-2 85

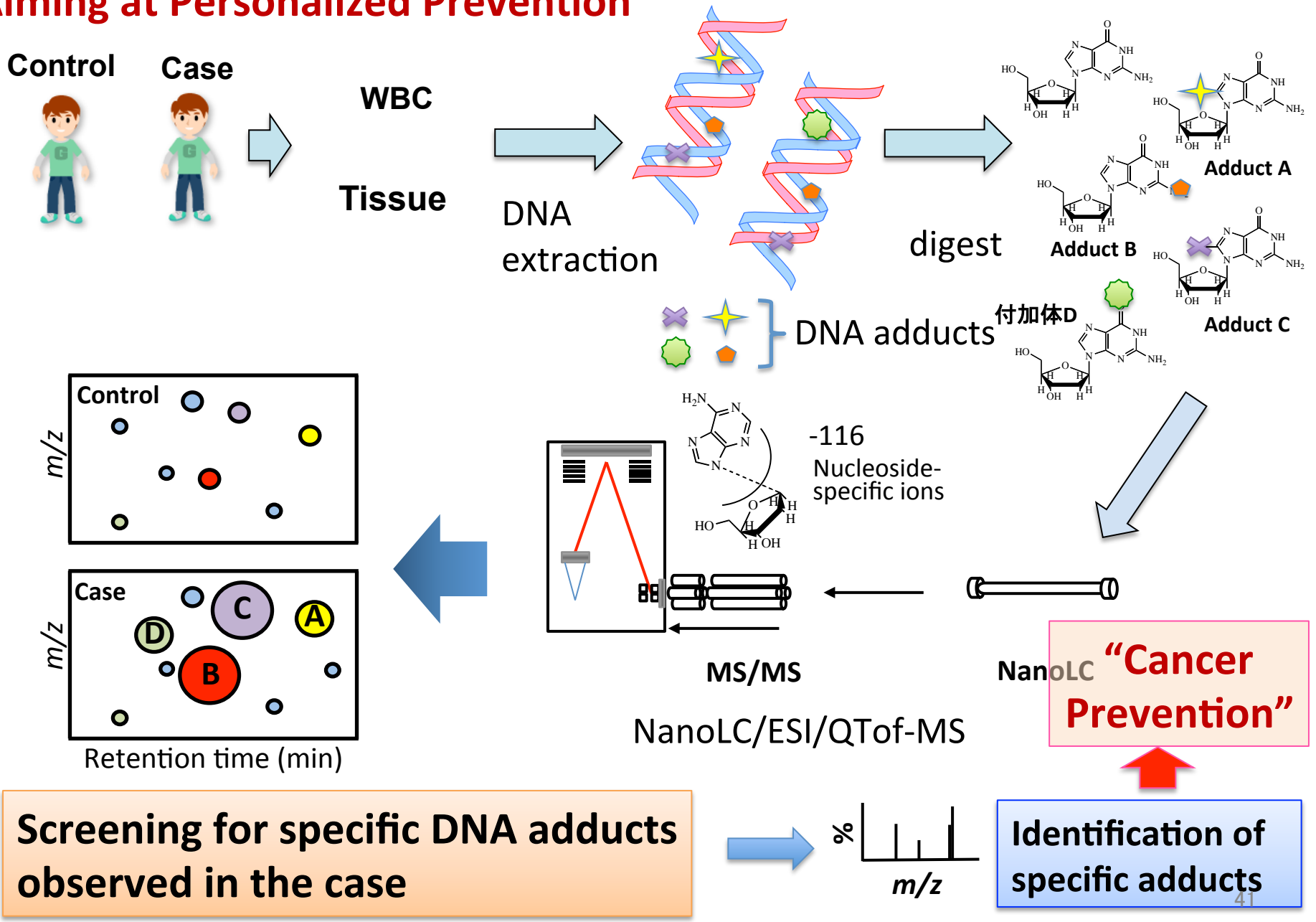


moderately differentiated adenocarcinoma with severe fibrosis and inflammatory cells

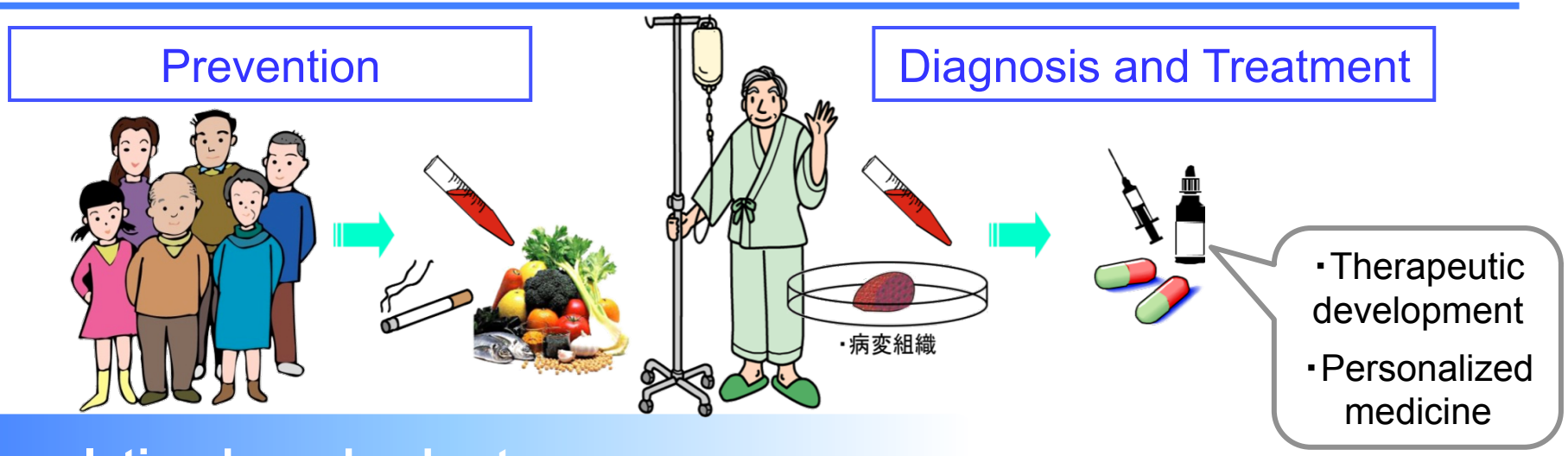
Exome Analysis Revealed Strand-baiased and Context-dependent Mutations



Blood-based and Tissue-based Profiles of DNA Adduct (Adductome) Aiming at Personalized Prevention



Current Major Cohort and/or Biobank Projects in Japan



Population-based cohorts

Tohoku Medical Megabank (ToMMo)	・Stress cohort of the residents of the arch 2011 Quake and Tsunami area, incl. trio birth cohort ・approx. 150K (plan)
・JPHC ・J-MICC	・Nation-wide population-based cohorts ・approx. 100K
・Nagahama 0th prevention cohort ・Hisayama cohort	・Local community cohorts ・approx 10K

Patient cohorts

Biobank Japan (BBJ)	・Nation-wide community hospitals, university hospitals. ・47 diseases, approx 300K cases by approx 200K patients ・Blood samples, predetermined list of clinical information ・(Mostly) distribution-type biobank
National Center Biobank Network (NCBN)	・Centers for Highly Advanced and Specialized Medical Care ・Incl. diseases and subtypes relatively few in BBJ ・Blood and pathological tissue specimens with rich longitudinal clinical information ・(Mostly) collaboration/ contract-research biobank (cluster of the disease specialists, focused research and clinical trials)
Rare dis. bank	・Specific rare and intractable diseases

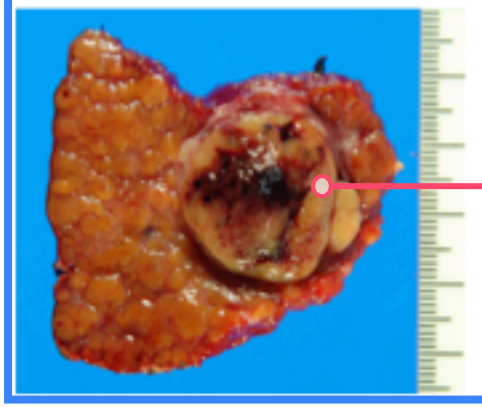
National Cancer Center Biobank (NCC-Biobank)

✓ Tumor tissue for somatic aberration research

Pathology Division

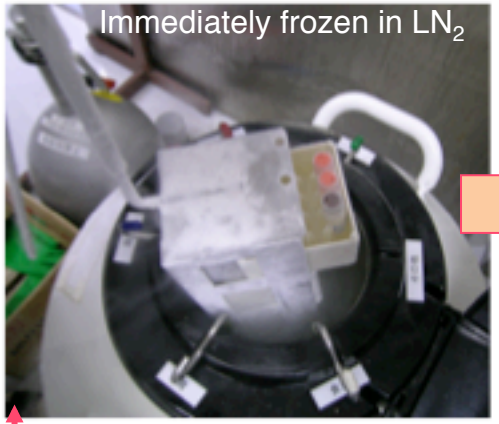
Routine work by pathologists
–macroscopic examination

Surgically resected specimen

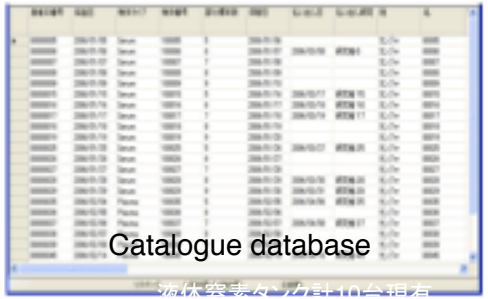


Biobank

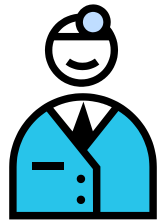
As of March, 2014
16,322 cases
66,282 vials



Viable tissue is taken by pathologists avoiding disadvantage for pathological diagnosis



Research Group



Pathologists, clinicians

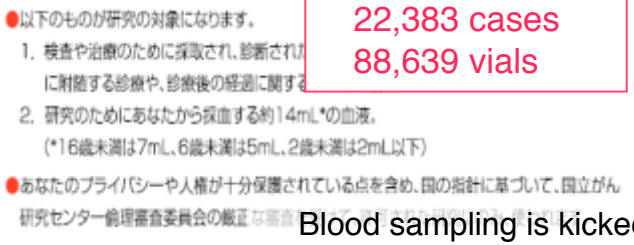
Researchers

Institutional review board

✓ Blood sample for germline research

As of March, 2014
22,383 cases
88,639 vials

Informed consent



●以下のものが研究の対象になります。
1. 検査や治療のために採取され、診断され
に附随する診療や、診療後の経過に関する
2. 研究のためにあなたから採血する約14mL*の血液。
(*16歳未満は7mL、6歳未満は5mL、2歳未満は2mL以下)
●あなたのプライバシーや人権が十分保護されている点を含め、国の指針に基づいて、国立がん研究センター倫理審査委員会の厳正な審査

国立がん研究センター中央病院で診療を受けられる患者さんへ
検査に使われた血液や組織、手術等で摘出された組織などの医学研究への利用、及び研究のための採血に関するお願い

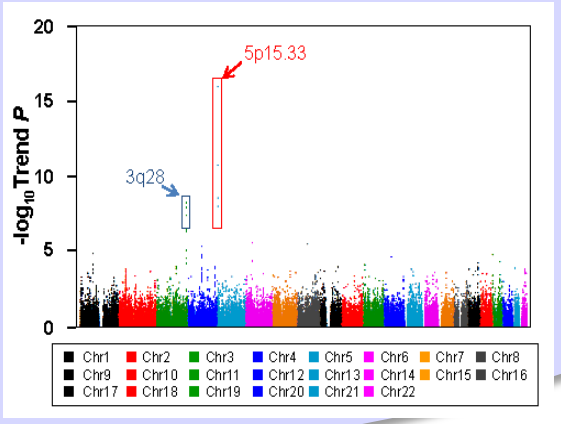
Blood sampling is kicked off in May 2011.

BBJ and NCBN：Connect Each Strength in Parallel

●**BBJ**：A powerful genome-wide screen based on its large sample size

Disease A

OR=1.2

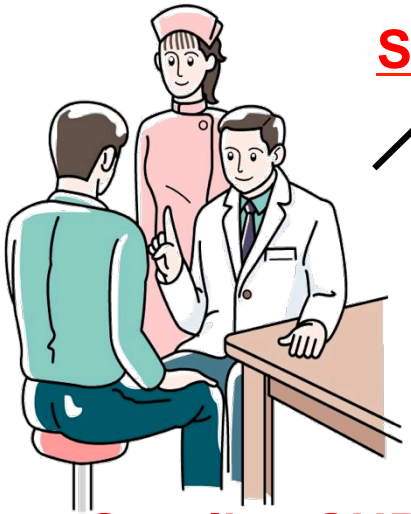


●**NCBN**：In-depth personalization based on detailed clinico-pathological information

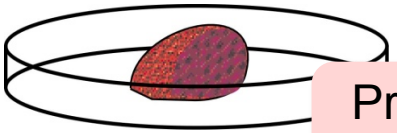
Sub type A1	Subtype A2	Subtype A3	Subtype A4
OR=1.0	OR=2.5	OR=1.1	OR=0.9

BBJ and NCBN: Connect Each Strength in Parallel

IC to Patient A



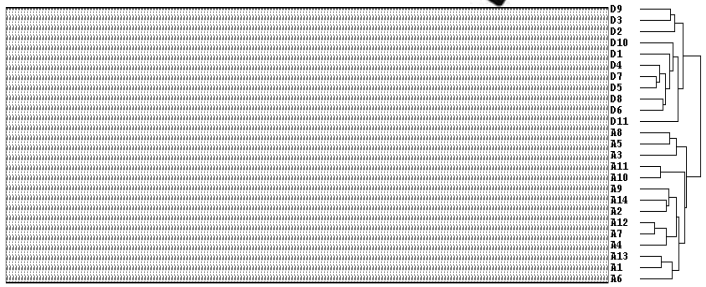
Biopsy



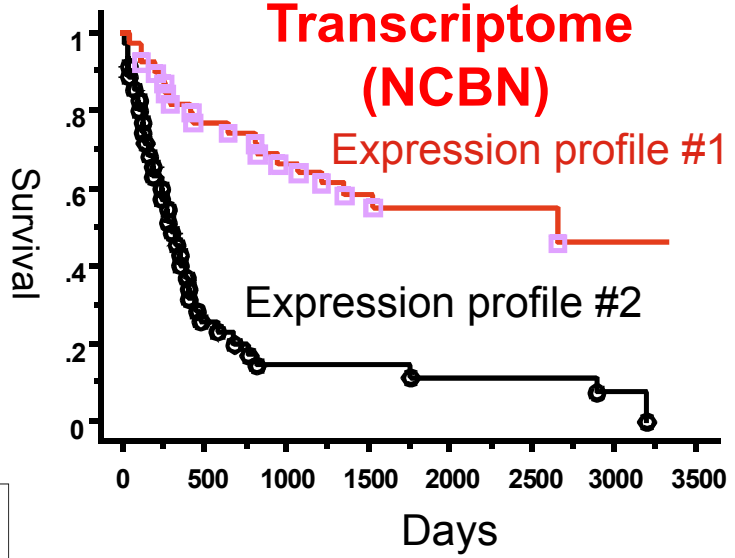
Somatic SNVs (NCBN)

Prediction of Response

e.g. Transcriptome analysis of cancer tissue



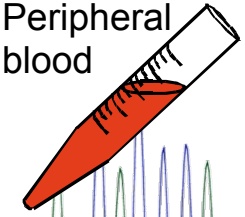
Transcriptome (NCBN)



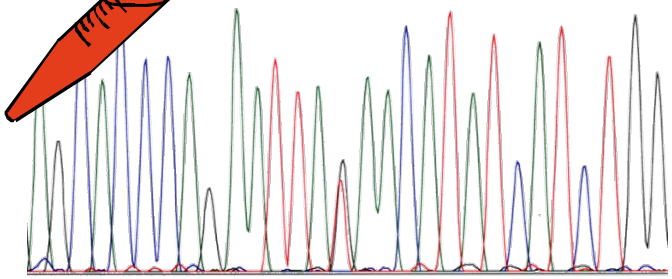
Gernline SNPs (BBJ)

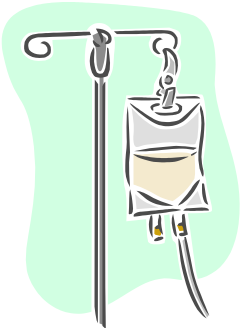
Prediction of ADR/ side effect

Peripheral blood



e.g. Germline polymorphisms





Biomarker-based prediction to maximize therapeutic response and minimize ADR for Patient A

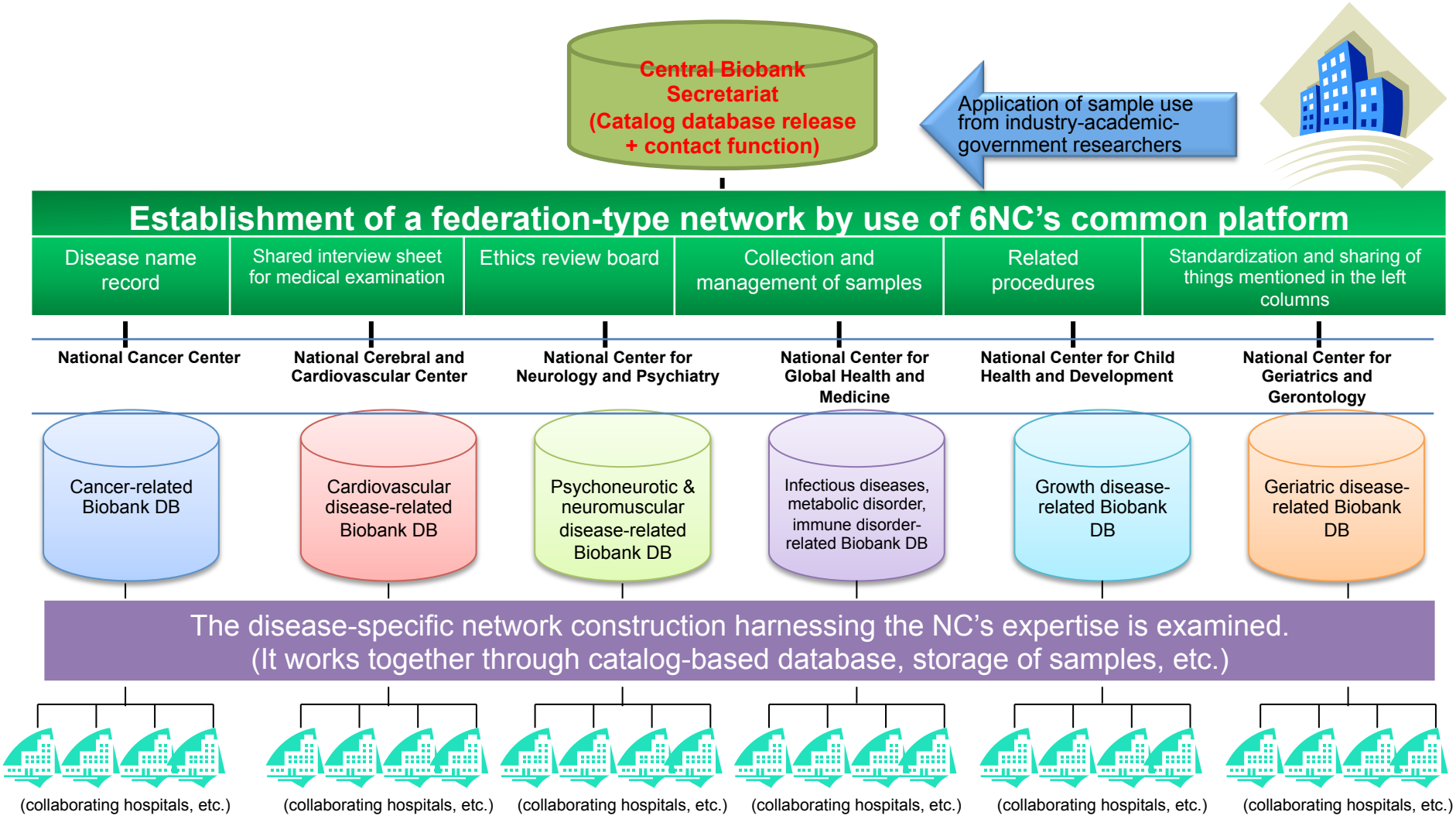
Choose this!

National Center Biobank Network

(NCBN)

National Center Biobank Network (NCBN)

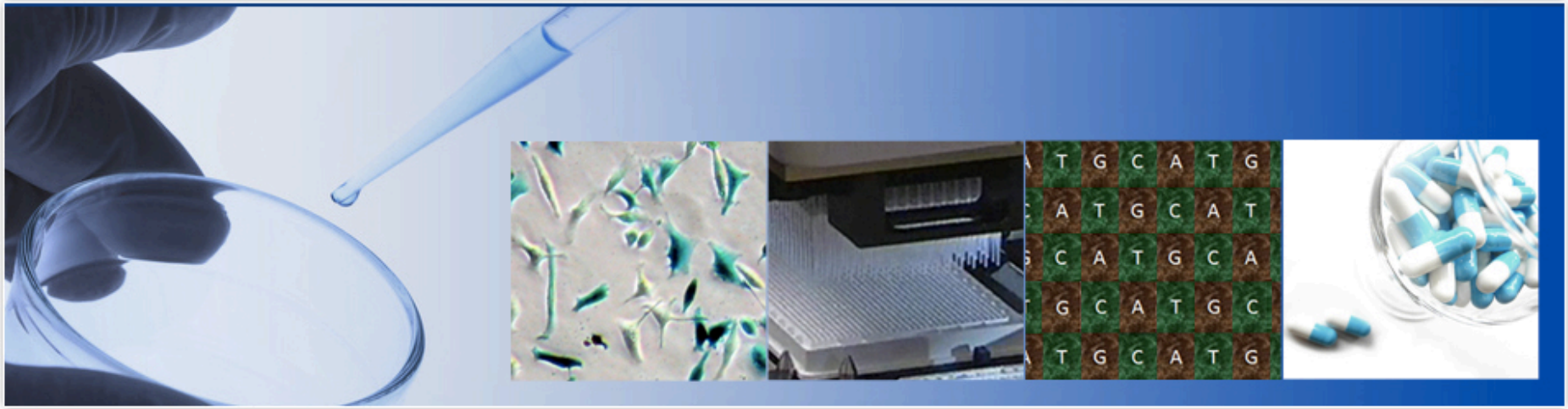
Enterprise of clinical-platform improvement for next-generation medical treatment



It is planned that the biobank network with collaborating organizations is extended step by step.

National Center Biobank Network: NCBN Project

National Center Biobank Network



NEWS & TOPICS

- Sept. 29, 2014 English pages were launched.
- Sept. 11, 2014 The NCBN will host a booth at the "BioJapan 2014 World Business Forum", to be held at the Pacifico Yokohama convention center from October 15th to October 17th. In addition, Dr. Nakagama, Director-General of the Research Institute of the National Cancer Center and President of the National Center Biobank Management Conference will make a presentation at the "organizer's seminar". The NCBN looks forward to welcoming many visitors.

  *Visitor registration is required to attend the seminars. Please apply to attend the seminar by clicking the "registration" button on the website:
  http://www.ics-expo.jp/biojapan/main/index.html.

Towards a Realization of the Concept of Personalized Medicine

NCBN Electronic-Catalogue-based Database

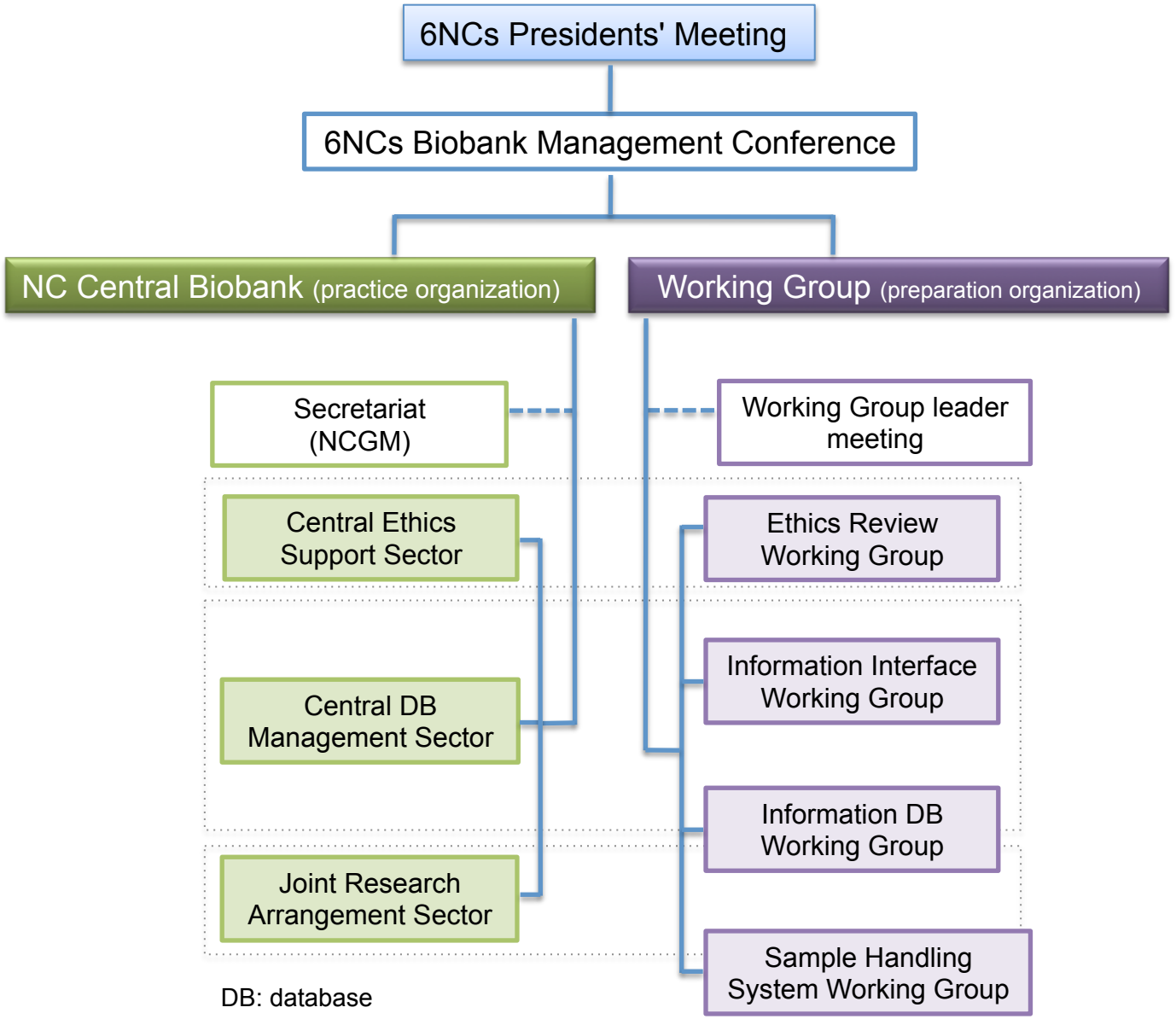
Public Information

Links

NCC NCVC MCRP NCGM NCCHD NCGG

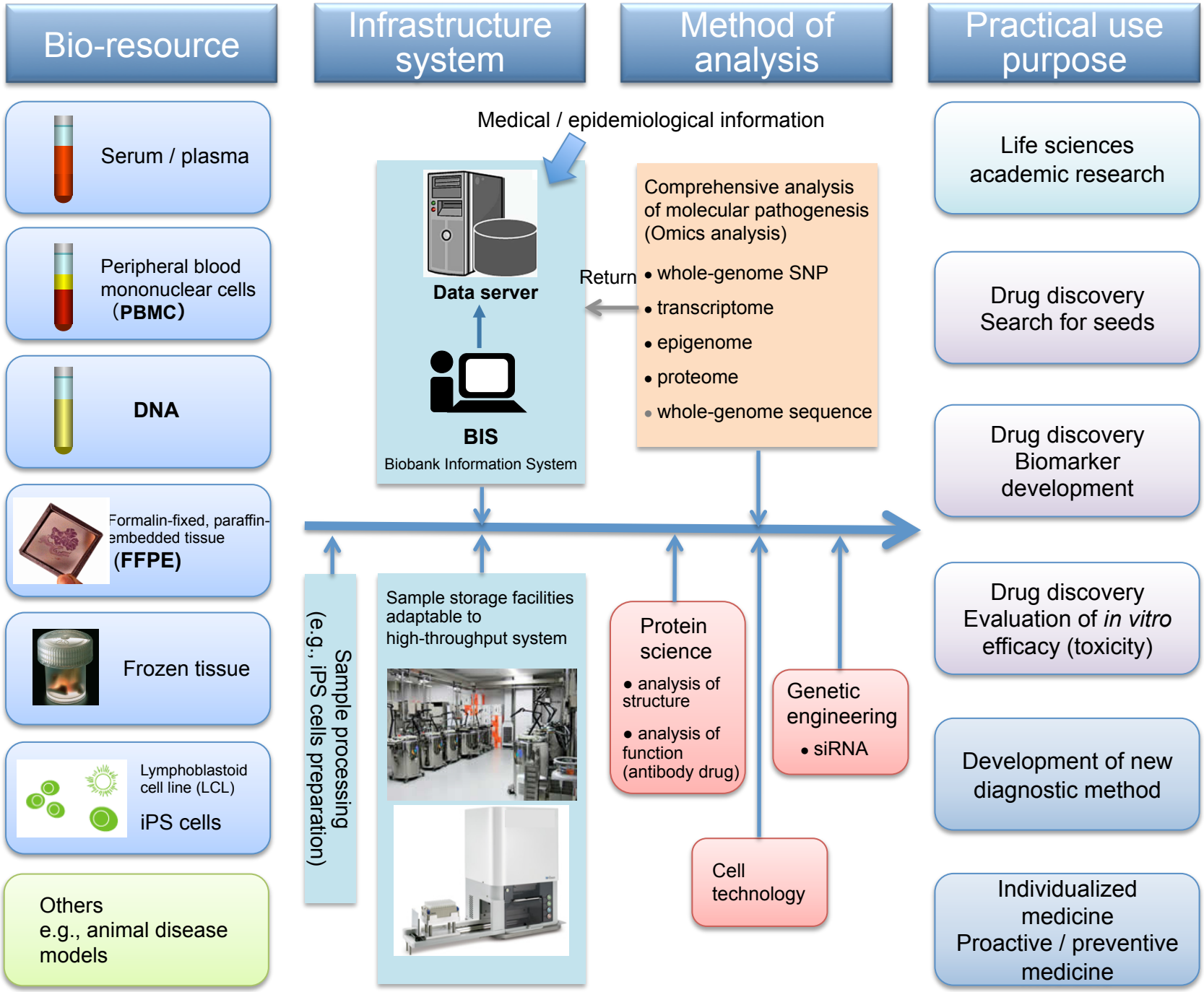
http://www.ncbiobank.org/index-e.html

Management Structure of the NCBN



Agenda and Outline of Each Working Group

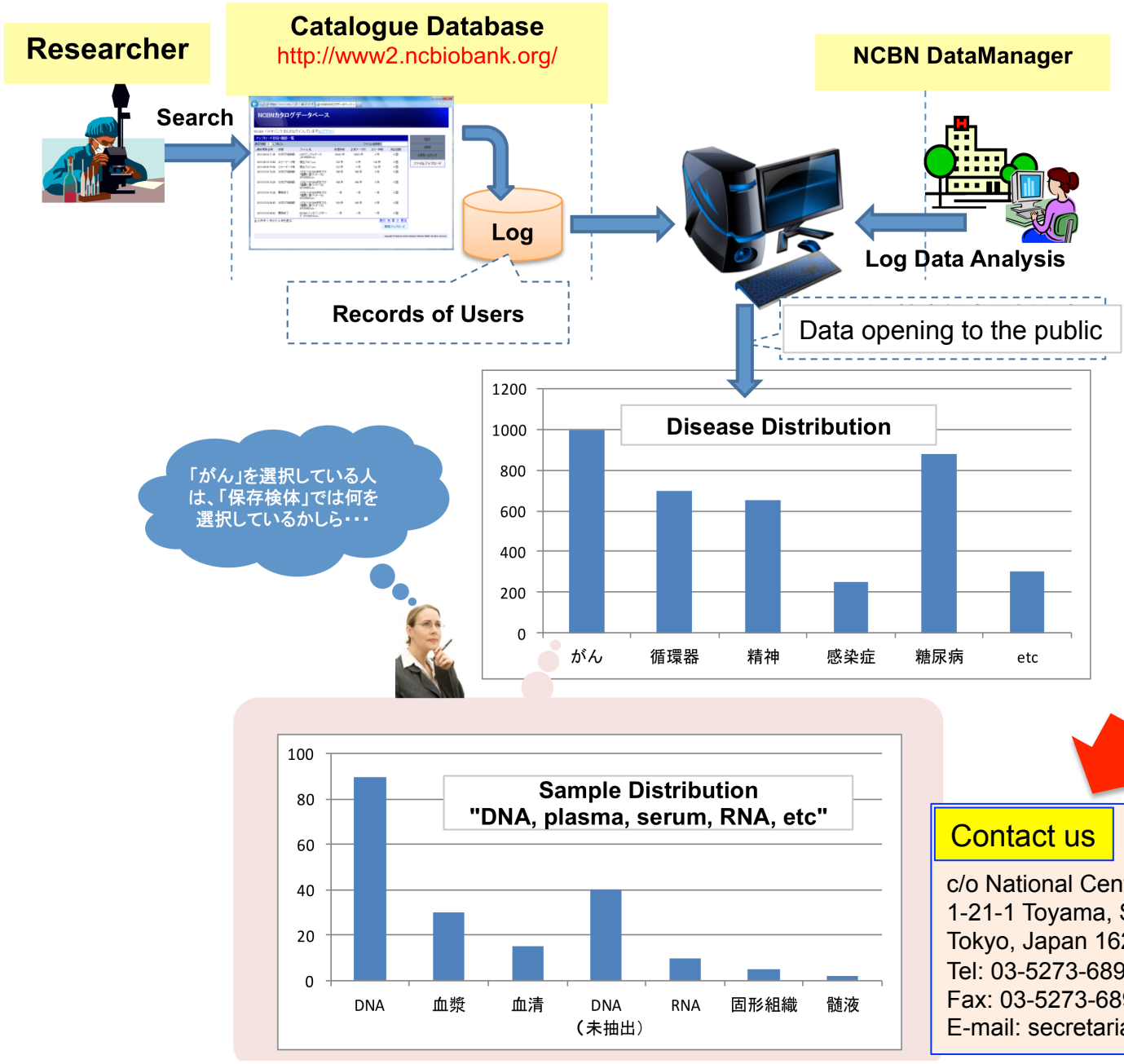
WG name	Agenda	Outline
Ethics Review WG	Creating the shared explanation / IC document model, etc.	To aim for bio-resource collection in a common format, 6NC work together to make consistent explanations & IC documents for the participants, and research proposal documents for ethics review.
Information Interface WG	6NC Information Network Structure	Review the global picture towards the networking structure among 6NC members.
	Shared interview sheet / Disease name registry	Make the idea for the shared interview sheet and the registration of disease name in common use by 6NC members.
	Review of an anonymization system	Review the state of the anonymization system based on the joint research and distribution of samples, etc. among several institutions, and review the way of handling bio-resource analytical data and accompanying medical information (whether the methods linking medical information to bio-resource should be changed according to the anonymization level, etc.)
	Review of catamnestic follow-up system	Review the state of catamnestic follow-up with time
Sample Handling System WG	Standardization of sample collection and storage	Review the standardization of bio-resource collection and management system by 6NC members.
	Review of the state of a shared platform	Review the appropriate way to make the processing and analysis of collected bio-resources, and to outsource them.
	Review of sample transfer procedure	Review the procedure of bio-resource transfer between Centers, etc.
Information DB WG	Survey of samples held by each NC.	Make the draft of the whereabouts of each information catalogue by examining the content of acquired IC and the possibility of opening to the public, etc. of bio-resources existing at each NC.
	Maintenance procedures for joint research agreement	Consider the framework of using bio-resource (for joint research agreement, etc.), and prepare the common procedures.
	Database and homepage construction	To facilitate visualization to the public, construct a catalogue of collected bio-resources, etc., and release it on our website.


Bio-resource
Infrastructure system
Method of analysis
Practical use purpose
Serum / plasma
Peripheral blood mononuclear cells (PBMC)
DNA
Formalin-fixed, paraffin-embedded tissue (FFPE)
Frozen tissue
Lymphoblastoid cell line (LCL)
iPS cells
Others
e.g., animal disease models
Medical / epidemiological information
Data server
BIS
Biobank Information System
Return
Comprehensive analysis of molecular pathogenesis (Omics analysis)
• whole-genome SNP
• transcriptome
• epigenome
• proteome
• whole-genome sequence
Sample processing (e.g., iPS cells preparation)
Sample storage facilities adaptable to high-throughput system
Protein science
• analysis of structure
• analysis of function (antibody drug)
Genetic engineering
• siRNA
Cell technology
Life sciences academic research
Drug discovery Search for seeds
Drug discovery Biomarker development
Drug discovery Evaluation of in vitro efficacy (toxicity)
Development of new diagnostic method
Individualized medicine Proactive / preventive medicine

Number of Samples Stored in Six National Center Biobanks (as of July, 2014)

Approximate Number of Samples Stored in Six National Center Biobanks (as of July, 2014)							
Six National Centers	Enrollment	Total Samples	Number of Samples by Type				
			DNA	Plasma	Serum	Tissue	Other
Newly Obtained Samples/Materials (with Broad Consent)	27,570	69,457	19,047	19,020	5,609	11,316	14,465
Existing Samples/Materials / Newly Obtained Samples without Broad Consent	34,139	69,660	12,142	4,017	1,251	15,556	36,694

Outline and Use of NCBN Electronic-Catalogue-based Database



Contact us

NCBN Central Biobank Secretariat

c/o National Center for Global Health and Medicine
1-21-1 Toyama, Shinzuku-ku
Tokyo, Japan 162-8655
Tel: 03-5273-6891
Fax: 03-5273-6892
E-mail: secretariat@ncbiobank.org

Medical Omics Analyses Alliance toward Achievement of Precision Medicine at National Centers using NCBN