BIOBANK PPUKM-UMBI: PERANAN BERSAMA DEMI PEMBANGUNAN PENYELIDIKAN MASA HADAPAN

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UMBI

INSTITUT PERUBATAN MOLEKUL UKM

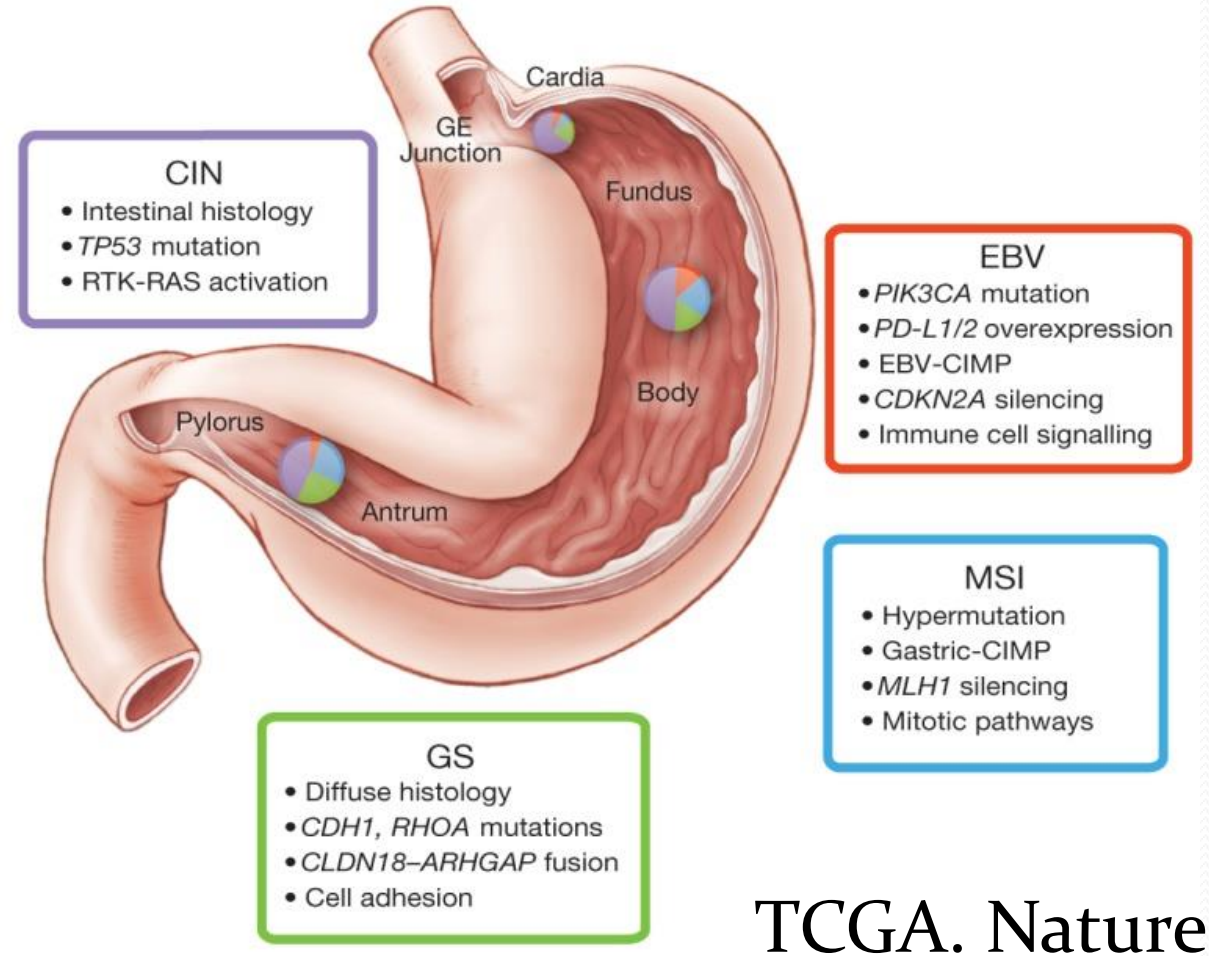
UKM MEDICAL MOLECULAR BIOLOGY INSTITUTE

Penyelidikan berkualiti memerlukan sampel berkualiti

BRCA1/BRCA2 dalam kanser payudara familial

Her2 +ve dan penggunaan herceptin

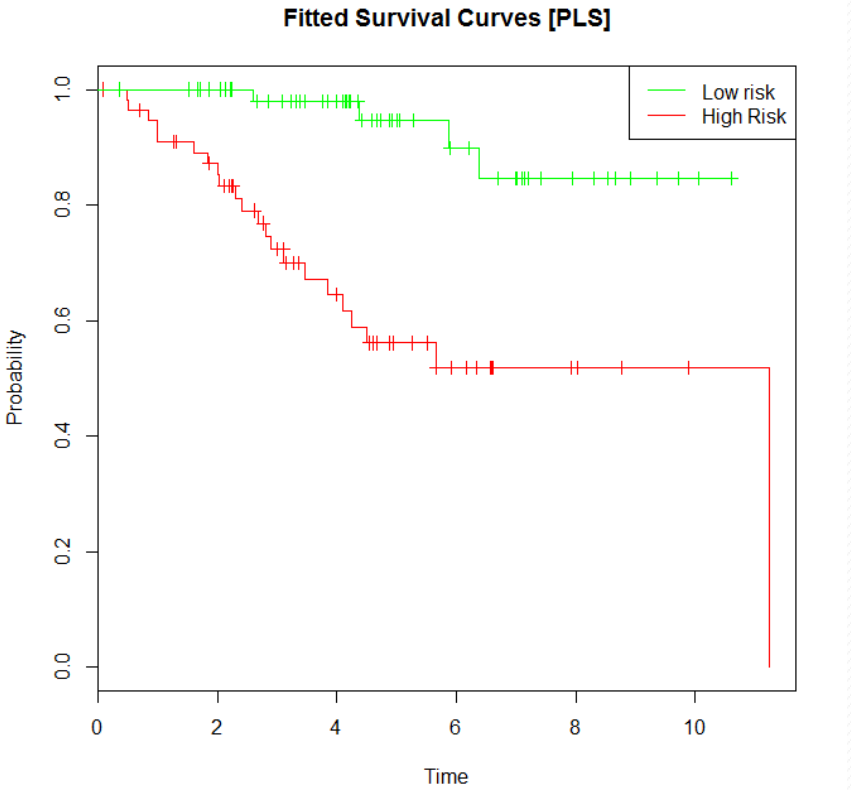
Whole Genome Sequencing ke atas 295 tisu kanser gaster: Klasifikasi baru



TCGA. Nature. 513:2014

Inovasi: Penemuan ColoPREDICT hasil penyelidikan dari Biobank

- Satu panel **19-gen** untuk menentukan prognosis pesakit kanser kolorektal
- Nombor Paten: PI2014702296



Panel gen telah divalidasi menggunakan kohort pesakit kanser kolorektal USA

BIOBANK

Satu koleksi besar sampel tisu serta data biologi dan perubatan yang dikumpulkan untuk tujuan penyelidikan

Lonjakan paradigma pengumpulan tisu dan spesimen

Koleksi spesimen patologi

- Tisu atas slaid
- *Formalin-fixed paraffin embededed*

BIOBANK sebagai infrastruktur penyelidikan

- Pelbagai jenis sampel

Generasi baru -80oC freezer

NHS National Biosample Centre, Milton Keynes United Kingdom

Biobank:
Jenis sampel yang disimpan

Whole blood	Mono-nuclear cells	Plasma	Serum
RBC clot	Urine	Hair	Nails
Stools	Saliva	DNA	RNA

TUJUAN DAN PERANAN UTAMA

Koleksi biospesimen berkualiti

Penyelidikan berkualiti

BIOBANK di serata dunia

biobank uk

The New Hampshire Birth Cohort Study

臺灣 Taiwan Biobank

BIOBANK • 健康世代

中央研究院・臺灣人體生物資料庫

Iran Tumor Bank

NUH TISSUE REPOSITORY

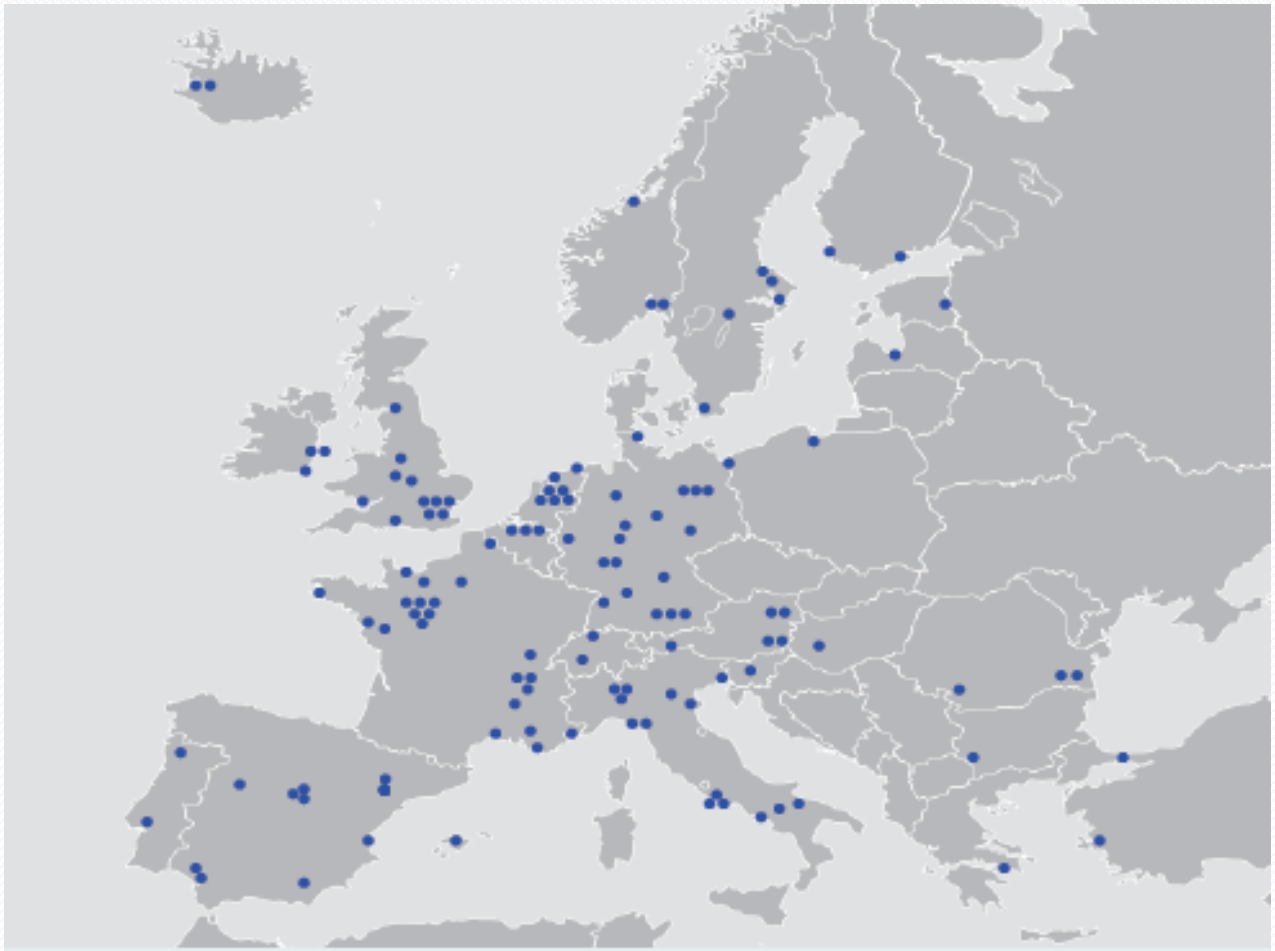
Banking Singapore's Future

قطر بيوبنك

qatarbiobank for medical research

Member of Qatar Foundation

Biobanks in Europe



The BBMRI Project: Representing Europe's Biobanks

The *Biobanking and Biomolecular Resources Research Infrastructure*

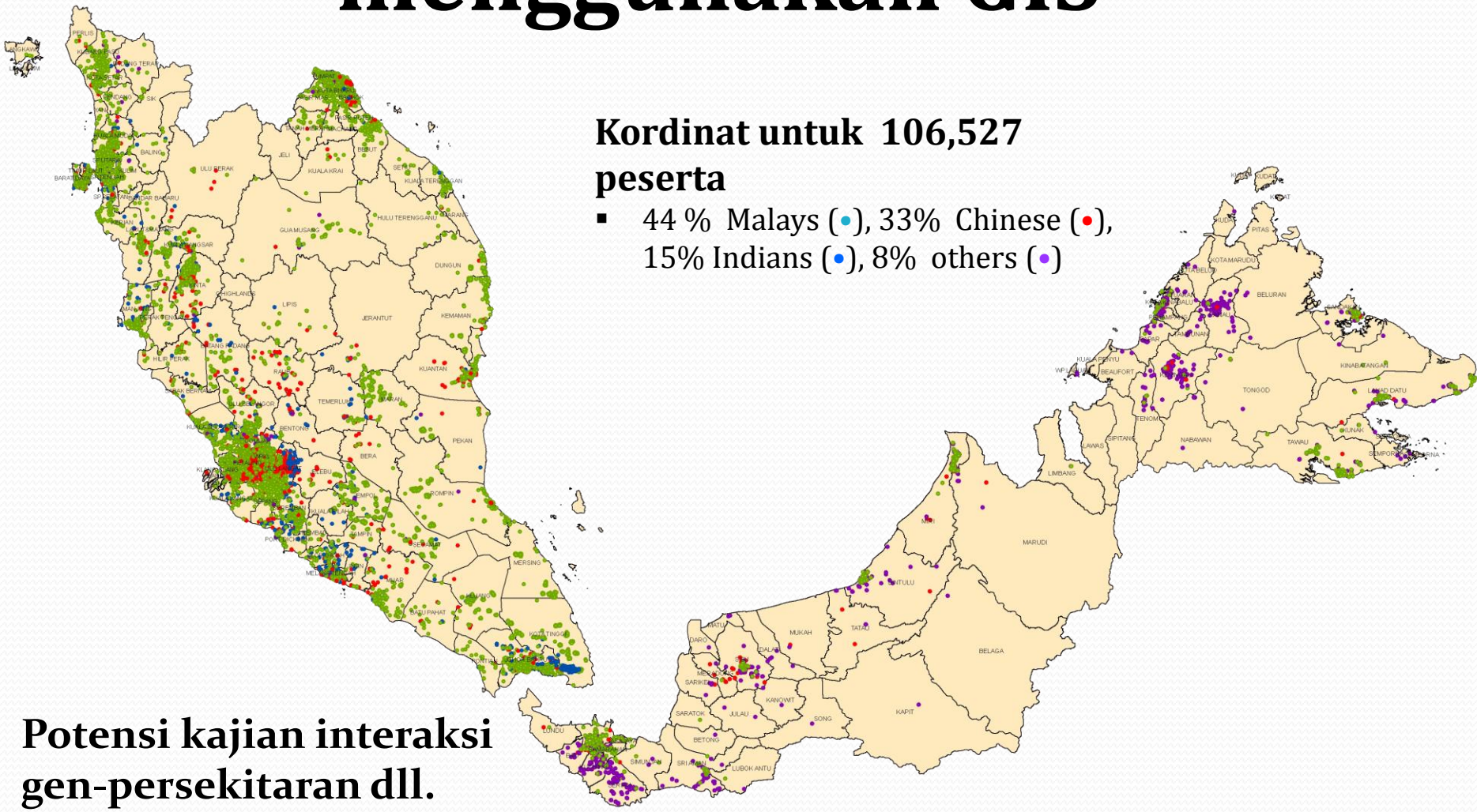
Malaysia pun BOLEH?

Biobank PPUKM-UMBI

Biobank Cohort:
Terbesar di Asia Tenggara

- Biobank Utama
- 2 Biobank Satelit (PPUKM & MTDC)

Pemetaan peserta Cohort menggunakan GIS



Kordinat untuk 106,527 peserta

- 44 % Malays (•), 33% Chinese (•), 15% Indians (•), 8% others (•)

Potensi kajian interaksi gen-persekitaran dll.

MS ISO 15189:2007: Akreditasi Makmal Bioanalitikal Cohort

STANDARDS MALAYSIA
ACCREDITED LABORATORY

MS ISO 15189

Certificate of Accreditation

No: SAMM 537 Valid until: 1 November 2014

This is to certify that

THE MALAYSIAN COHORT
INSTITUT PERUBATAN MOLEKUL, UKM (UMBI)
KUALA LUMPUR
MALAYSIA
(FIELDS OF MEDICAL TESTING: HAEMATOLOGY & CHEMICAL PATHOLOGY)

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Department of Standards Malaysia

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Director General
Department of Standards Malaysia

Date of issue: 1 November 2011

Issuance of this certificate is governed by Section 16 Subsection (2) and (3) of Standards of Malaysia Act 1996, (Act 549)

BIG data = BIG Paper: IF 9.7

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International Journal of Epidemiology, 2014, 1–9
doi: 10.1093/ije/dyu089
Cohort profile

Cohort profile

Cohort profile: The Malaysian Cohort (TMC) project: a prospective study of non-communicable diseases in a multi-ethnic population

Rahman Jamal,[1]* Syed Zulkifli Syed Zakaria,[2] Mohd Arman Kamaruddin,[1] Nazihah Abd Jalal,[1] Norliza Ismail,[1] Norkhamiwati Mohd Kamil,[1] Noraidatulakma Abdullah,[1] Norhafizah Baharudin,[1] Noor Hamidah Hussin,[3] Hanita Othman,[3] Nor Muhammad Mahadi[4] and the Malaysian Cohort Study Group

POTENSI PESAKIT PPUKM SEBAGAI SUMBER PENYELIDIKAN

382,086 pesakit luar

35,837 pesakit dalam

7,858 pesakit dalam surgeri

14,099 pesakit luar psikiatri

Data dari Jabatan Farmasi PPUKM 2014

RIBUAN SAMPEL PESAKIT PPUKM TIDAK DIKUMPUL

>2000 pembedahan tumor otak sejak 1997

- **Peluang keemasan** untuk membangunkan koleksi terbesar tumour otak

~150 tisu glioma dikumpul dan disimpan

- Projek penyelidikan glioma
- Memakan masa 3 tahun (2010-2013)

Pesakit psikiatri: Potensi tinggi untuk penyelidikan

3000 kes bipolar & schizophrenia

- Pesakit susulan

<50 spesimen terkumpul

- Projek validasi varian kes bipolar
- Sudah >2 tahun

7 sebab jadi begini

- Ini bukan penyelidikan saya
- Ini bukan skop kerja saya
- Apa yang saya dapat?
- Tak ada masa untuk ambil *informed consent*
- Kenapa harus saya bantu?
- Kenapa perlu tolong UMBI?
- Kalau saya beri sampel, nanti orang lain yang dapat guna untuk penyelidikan

HARUS KITA INGAT

UKM adalah universiti penyelidikan

HCTM adalah hospital pengajar

Penyelidikan memerlukan sampel

Kelebihan penyelidikan dengan sampel yang sudah lengkap

BIOBANK PPUKM-UMBI

Pertumbuhan pesat

- Kapasiti
- Kompetensi
- Kualiti
- Jaringan penyelidik

2003 MULA!!!

- Kertas Kerja Biobank
- Jawatankuasa PPUKM-UMBI

2005

- Diluluskan
- Pengumpulan sampel dimulakan
- Jabatan Surgeri: Kanser Payudara & Rektum
- Penyimpanan (-80°C) & tisu sahaja

2006

- Kapasiti kecil tangki LN (-190 °C)

2016

- Kapasiti besar tangki LN (-190)
- Pengumpulan sampel daripada pelbagai penyakit

Sampel dari >30 jenis penyakit

	DISEASE
1	NORMAL SAMPLES (CONTROLS)
2	BETA THALASSEMIA
3	ACUTE LEUKEMIAS
4	GENETIC RARE DISEASES
5	LIVER CANCER
6	BREAST CANCER
7	OBSTRUCTIVE LUNG DISEASE
8	BRAIN TUMOR
9	CORONARY ARTERY DISEASE
10	FRAGILE X
11	LUNG CANCER
12	CYSTIC FIBRIOSIS
13	HUNTINGTON'S DISEASE
14	OVARIAN CANCER
15	BLADDER CANCER
16	HIRSCHSPRUNG'S DISEASE
17	ENDOMETRIUM CANCER

	DISEASE
18	GASTRITIS
19	IGM DEFICIENCY
20	PARKINSON'S DISEASE
21	BIPOLAR DISORDERS
22	EPILEPSY
23	MYELOPOLIFERATIVE NEOPLASIA
24	CERVICAL CANCER
25	PLACENTA PRAEVIA
26	HEMOPHILIA
27	PANCREATIC CANCER
28	CHILDHOOD OBESITY
29	GASTRIC CANCER
30	HERNIA
31	SLE
32	GOUT
33	PENDRED SYNDROME
34	SEPSIS

DARI MULA HINGGA KINI

Keperluan sampel untuk projek penyelidikan

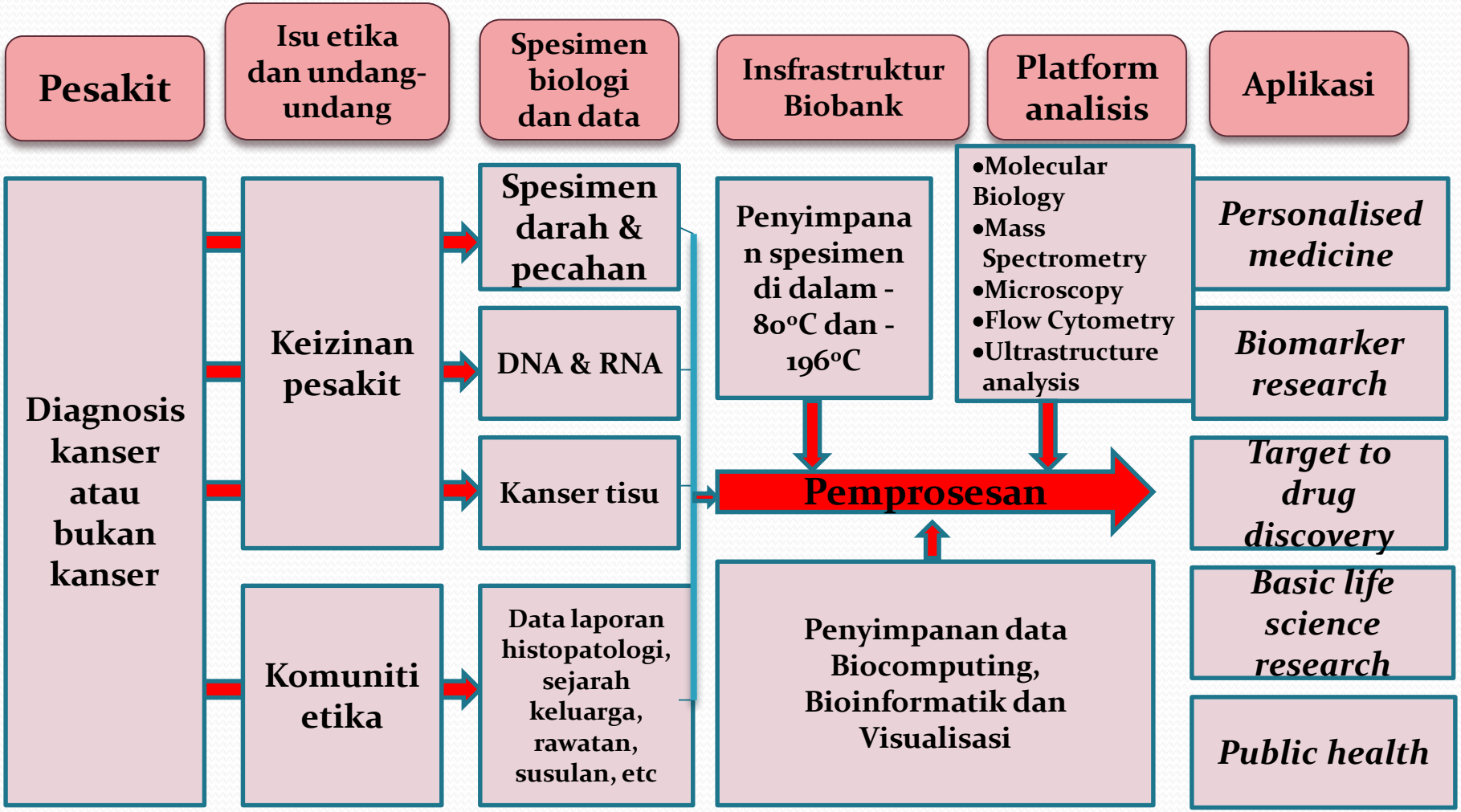
Permintaan dari penyelidik

Penyimpanan strategik untuk penyelidikan masa depan

FASILITI BIOBANK PPUKM-UMBI

- -80°C (12)
- -20°C (1)
- 4°C (1)
- Cryocyl (10)
- Tangki cecair nitrogen(12)
- Tangki penyimpanan sampel (9)

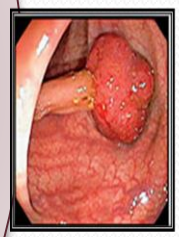
KOMPONEN UTAMA BIOBANK PPUKM-UMBI



APA YANG DISIMPAN?

PENGUMPULAN

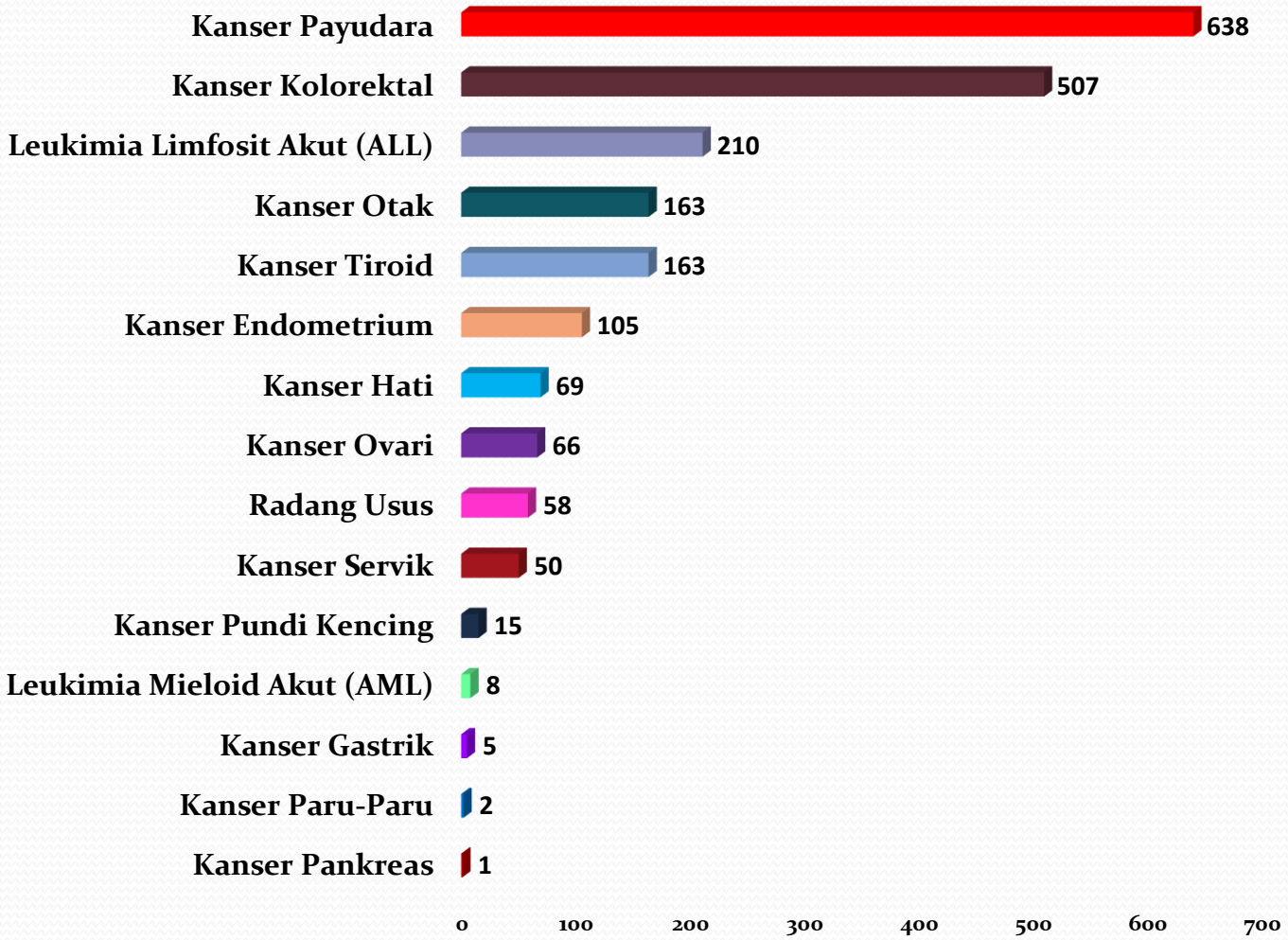
- ✓ Tisu Biopsi
- ✓ Darah (plasma, serum, sel darah merah dan sel darah putih)
- ✓ Tisu kanser dan tisu normal
- ✓ DNA



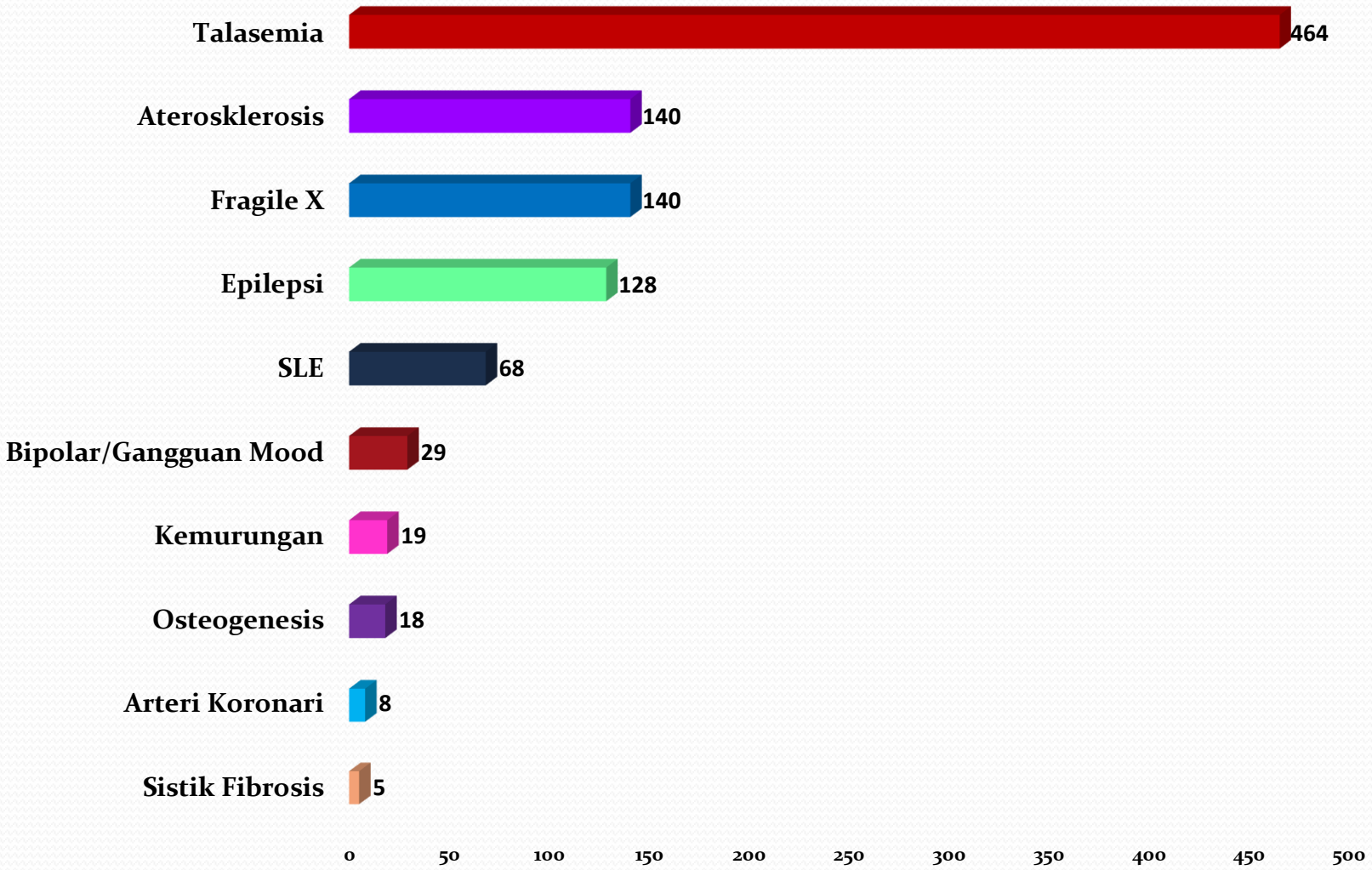
BANK DATA

- ✓ Data peribadi dengan mematuhi peraturan-peraturan perlindungan data
- ✓ Diluluskan oleh Jawatankuasa etika

JUMLAH SAMPEL KANSER TERKUMPUL 2004-2015



JUMLAH PENYAKIT BUKAN KANSER



PENYELIDIKAN YANG BOLEH DILAKUKAN

Spesimen Biorepositori

Analisis Saintifik

Genomik

Transkriptomik

Epigenomik

Proteomik

Metabolomik

Rawatan/ Ujian Diagnostik

CABARAN

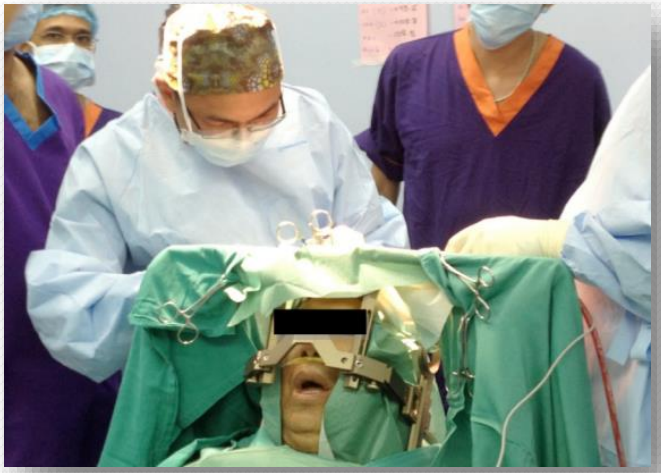
- Sistem C-Hets yang kurang dikemaskini
- Sukar melakukan pengambilan sampel bagi kes kecemasan dan kes pada hujung minggu.
- Sampel yang diperolehi kurang berkualiti
- Cabaran untuk mendapat kerjasama daripada pegawai perubatan
- Cabaran untuk mendapat kerjasama daripada kakitangan hospital

PERANAN PESAKIT DAN WARGA PPUKM/HCTM

- Kesedaran peranan Biobank
- Lobi dan kempen
- Anggap sampel amat berharga
- Penyelidikan memberi manfaat besar

Pesanan untuk para doktor

Hargai sampel pesakit untuk tujuan penyelidikan



Bantu mendapatkan ‘informed consent’

Aktiviti utama BIOBANK: Semua dengan SOPs

Keizinan bermaklumat	Pengumpulan & Pengangkutan	Proses & Simpan
Dokumentasi & Maklumat Klinikal	Kawalan kualiti	Pembekalan sampel & Analisa

BEBERAPA ISU PENTING

Konsep *Colder is Better*

-20°C

- DNA

-80°C

- RNA, Serum & plasma

Waspada akan enzim degradatif pada suhu rendah

-196°C

- RNA, serum, plasma, cells

Faktor yang boleh menjejaskan kualiti samples

Time to separate cells from plasma/serum	*Tissue hypoxia from arterial clamping*	*Temperature for transportation*
Medication and anaesthesia regime	*Length of time at room temperature before storage*	*Time to fixate and type of fixative*

Biobank Cohort: Penghantaran & pemprosesan dalam masa 24 jam

Tisu segar diperlukan untuk penyelidikan 'omik' berkualiti

- Tisu akan lemas dalam *fixative*
- Sel mula mati apabila tumor dibedah – hypoxia menyebabkan degradasi RNA dan protein
- Formalin merosakkan protein, DNA dan RNA
- Tisu segar yang TERBAIK

Formalin-fixed paraffin-embedded (FFPE)

Isu penting

Consent	*Privacy and data protection*	*Legal & Technical*
Re-identification	*Ownership, benefits, rights*	*Access to resources*
Representation and bias	*Governance*	*Standardisation*

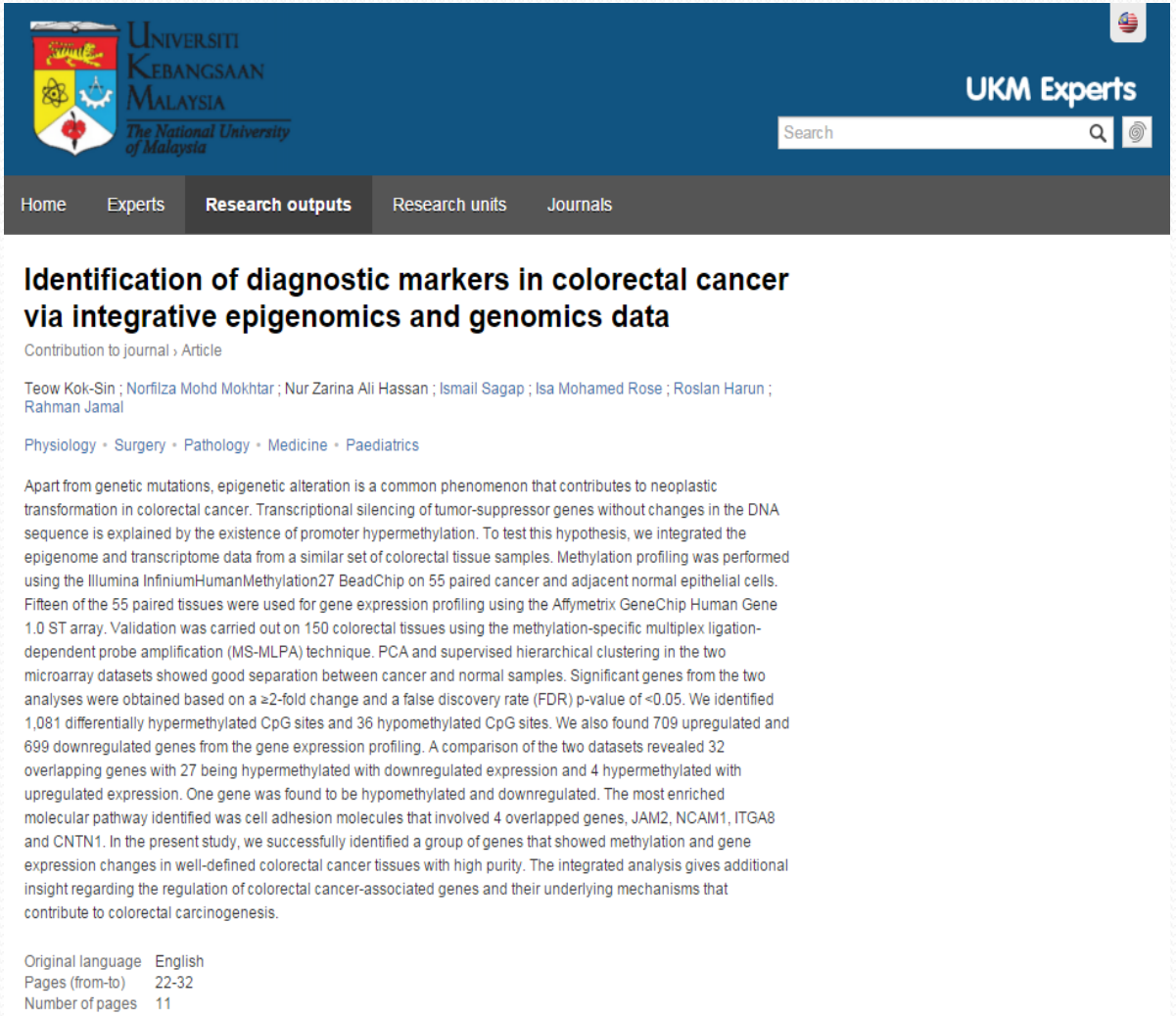
SIAPA PEMILIK SPESIMEN?

- **Pesakit atau Penderma** Tisu/Spesimen
  - Mempunyai hak untuk menarik diri serta memohon untuk tisu/spesimen dikeluarkan dari BIOBANK

- Ketua Institusi sebagai PENJAGA (*Custodian*)

KOLABORASI PENYELIDIKAN

- Kolaborasi dengan penyelidik dari:
  - Jabatan Perubatan
  - Jabatan Patologi
  - Jabatan Surgeri
  - Jabatan Psikiatri
  - Jabatan O&G
  - Jabatan Pediatrik
  - Jabatan Kesihatan Masyarakat
  - Fakulti Sains Kesihatan



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Identification of diagnostic markers in colorectal cancer via integrative epigenomics and genomics data

Contribution to journal › Article

Teow Kok-Sin ; Norfilza Mohd Mokhtar ; Nur Zarina Ali Hassan ; Ismail Sagap ; Isa Mohamed Rose ; Roslan Harun ; Rahman Jamal

Physiology • Surgery • Pathology • Medicine • Paediatrics

Apart from genetic mutations, epigenetic alteration is a common phenomenon that contributes to neoplastic transformation in colorectal cancer. Transcriptional silencing of tumor-suppressor genes without changes in the DNA sequence is explained by the existence of promoter hypermethylation. To test this hypothesis, we integrated the epigenome and transcriptome data from a similar set of colorectal tissue samples. Methylation profiling was performed using the Illumina InfiniumHumanMethylation27 BeadChip on 55 paired cancer and adjacent normal epithelial cells. Fifteen of the 55 paired tissues were used for gene expression profiling using the Affymetrix GeneChip Human Gene 1.0 ST array. Validation was carried out on 150 colorectal tissues using the methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) technique. PCA and supervised hierarchical clustering in the two microarray datasets showed good separation between cancer and normal samples. Significant genes from the two analyses were obtained based on a ≥2-fold change and a false discovery rate (FDR) p-value of <0.05. We identified 1,081 differentially hypermethylated CpG sites and 36 hypomethylated CpG sites. We also found 709 upregulated and 699 downregulated genes from the gene expression profiling. A comparison of the two datasets revealed 32 overlapping genes with 27 being hypermethylated with downregulated expression and 4 hypermethylated with upregulated expression. One gene was found to be hypomethylated and downregulated. The most enriched molecular pathway identified was cell adhesion molecules that involved 4 overlapped genes, JAM2, NCAM1, ITGA8 and CNTN1. In the present study, we successfully identified a group of genes that showed methylation and gene expression changes in well-defined colorectal cancer tissues with high purity. The integrated analysis gives additional insight regarding the regulation of colorectal cancer-associated genes and their underlying mechanisms that contribute to colorectal carcinogenesis.

Original language English
Pages (from-to) 22-32
Number of pages 11

KOLABORASI PENYELIDIKAN GENOMIK-JABATAN SURGERI DAN PATOLOGI

OPEN ACCESS Freely available online

PLOS ONE

Integrated Analysis of Copy Numbe Genome-Wide Expression Profiling i Cancer Tissues

Nur Zarina Ali Hassan[1], Norfilza Mohd Mokhtar[1,4]*, Teow Kok Sin
Roslan Harun[1,5], Rahman Jamal[1]*

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Kebangsaan Malaysia, Kuala Lumpur, Malaysia, 3 Department of Surgery, Faculty of Medicine, Universiti Ke
Physiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, 5 Department of M
Kuala Lumpur, Malaysia

Abstract

Integrative analyses of multiple genomic datasets for selected samples can pro
can enhance our knowledge of cancer. The objective of this study was to elucid
variation (CNV) and gene expression in colorectal cancer (CRC) samples and t
Sixty-four paired CRC samples from the same patients were subjected to CNV
Quad assay, and validation was performed using multiplex ligation probe ampl
profiling was performed on 15 paired samples from the same group of patient
array. Significant genes obtained from both array results were then overlappe
were mapped to the KEGG database. Whole genome CNV analysis that con
epithelium revealed gains in 1638 genes and losses in 36 genes. Significant gai
position 20q12 with a frequency of 45.31% in tumor samples. Examples of genes
PTPRT, *EMILIN3* and *CHD6*. The highest number of losses was detected at ch
occurrence in all tumor samples. Among the genes found at this cytoband were
profiling showed 709 genes to be up-regulated and 699 genes to be down-reg
samples. Integration of these two datasets identified 56 overlapping genes, whi
22. MLPA confirmed that the CRC samples had the highest gains in chromoso
Interpretation of the CNV data in the context of the transcriptome via integr
knowledge of the genomic landscape of CRC.

Citation: Ali Hassan NZ, Mokhtar NM, Kok Sin T, Mohamed Rose I, Sagap I, et al. (2014) Integrated
Expression Profiling in Colorectal Cancer Tissues. PLoS ONE 9(4): e92553. doi:10.1371/journal.pone.0092

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Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Colorectal cancer is a major health concern, with more than a million individuals diagnosed every year worldwide [1]. This cancer is among the top three of all cancers that lead to death worldwide [2]. In Malaysia, it ranks as the second most common cancer in both sexes [3].

One form of genetic instability that is observed in at least 85% of sporadic CRC cases is chromosomal instability (CIN) [4]. Aneuploidy is a consequence of CIN that leads to the gain or loss of whole or parts of chromosomal regions [5], and it may cause structural complexity that leads to genomic instability. One common form of structural variants due to CIN is known as copy number variations (CNVs), which is defined as a gain or loss of copies of DNA segments that are larger than 1 kb in length when compared to a reference genome [6]. CNVs can affect gene expression and have been associated with disease susceptibility. It has been suggested that transcriptional changes correspond to

CNVs and alte
changes in expr

Thousands o
microarray tech
have revealed g
chromosome 8p
lead to the dele
oncogenes, or ne
aberrant expres
processes [13,14

A gene that h
higher level of e
gene that has or
lower level of exp
that expression l
genes were relat
gain of the *MYC*

ONCOLOGY REPORTS 34: 22-32, 2015

Identification of diagnostic markers in colorectal car via integrative epigenomics and genomics data

TEOW KOK-SIN[1], NORFILZA MOHD MOKHTAR[1,2], NUR ZARINA ALI HASSAN[1], ISMAIL SAGAP[3], ISA MOHAMED ROSE[4], ROSLAN HARUN[5] and RAHMAN JAMAL

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Abstract. Apart from genetic mutations, epigenetic alteration is a common phenomenon that contributes to neoplastic transformation in colorectal cancer. Transcriptional silencing of tumor-suppressor genes without changes in the DNA sequence is explained by the existence of promoter hypermethylation. To test this hypothesis, we integrated the epigenome and transcriptome data from a similar set of colorectal tissue samples. Methylation profiling was performed using the Illumina InfiniumHumanMethylation27 BeadChip on 55 paired cancer and adjacent normal epithelial cells. Fifteen of the 55 paired tissues were used for gene expression profiling using the Affymetrix GeneChip Human Gene 1.0 ST array. Validation was carried out on 150 colorectal tissues using the methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) technique. PCA and supervised hierarchical clustering in the two microarray datasets showed good separation between cancer and normal samples. Significant genes from the two analyses were obtained based on a ≥2-fold change and a false discovery rate (FDR) P-value of <0.05. We identified 1,081 differentially hypermethylated CpG sites and 36 hypomethylated CpG sites. We also found 709 upregulated and 699 downregulated genes from the gene expression profiling. A comparison of the two datasets revealed 32 with 27 being hypermethylated with downr sion and 4 hypermethylated with upregulate gene was found to be hypomethylated and do most enriched molecular pathway identified molecules that involved 4 overlapped genes *ITGA8* and *CNTN1*. In the present study, identified a group of genes that showed met expression changes in well-defined colorect with high purity. The integrated analysis insight regarding the regulation of colorect ated genes and their underlying mechanisms colorectal carcinogenesis.

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E-mail: rahmanj@ppukm.ukm.edu.my

Abbreviations: ANOVA, analysis of variance; CAMs, cell adhesion molecules; CEA, carcinoembryonic antigen; CGI, CpG islands; CIMP, CpG island methylator phenotype; ES, enrichment score; FDR, false discovery rate; GO, Gene Ontology; KEGG, Kyoto encyclopedia of genes and genomes; lncRNA, long non-coding RNAs; MBDs, methyl-CpG binding proteins; MS-MLPA, methylation specific-multiple ligation probe amplification; MSP, methylation-specific PCR; PCA, principal component analysis; PCR, polymerase chain reaction; qPCR, quantitative PCR; RIN, RNA integrity number

Key words: colorectal cancer, epigenetics, DNA methylation, CpG loci, gene expression

Introduction

In recent decades, the incidence of colorectal increased by 2- to 4-fold in many Eastern A as China, Japan, South Korea and Singapor risk of CRC among the Asian population, in is associated with a low fiber diet and high t tion (3). One of the screening methods to de CRC is by measuring the level of carcinoe (CEA) in the serum, however, the sensitivity reported to be <80% (4-6). Therefore, the ide biological markers for CRC is crucial.

Epigenetic markers such as methylation were first reported 10 years ago in DNA fro samples (7). DNA methylation is an epigen that involves the enzymatic process of ad group to the 5-carbon position of the cytosin ylcytosine (8-10). This modification mostly enriched site known as CpG islands (CGI), wh 70% of the annotated gene promoter regions DNA methylation patterns, global hypomet hypermethylation, have emerged as potential cancer genome (12). Hypermethylation is g the promoter CGI region, whereas global frequently occurs in CpG dinucleotides that are located in the repetitive sequences of DNA (satellite repeats or retrotransposon) (13).

CGI hypermethylation in the promoter region is thought to be linked with the transcriptional inactivation of

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ORIGINAL ARTICLE

Identification of Differentially Expressed Proteins in the Serum of Colorectal Cancer Patients Using 2D-DIGE Proteomics Analysis

Lay Cheng Lim[1] · Mee Lee Looi[2] · Syed Zulkifli Syed Zakaria[1] · Ismail Sagap[3] · Isa Mohammed Rose[4] · Siok-Fong Chin[1] · Rahman Jamal[1]

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Abstract Early detection of colorectal cancer (CRC) is vital for the improvement of disease prognosis. However to date there are no blood-based biomarkers sensitive and specific enough for early diagnosis. We analysed the differences in serum protein expression of early stage CRC (Dukes' A and B) and late stage CRC (Dukes' C and D) against normal controls using 2D Fluorescence Difference Gel Electrophoresis (2D-DIGE). Analysis of the 2D maps showed that 23 proteins were differentially expressed between groups ($p \leq 0.05$) and these proteins were identified with LC-MS/MS. Eight proteins were up-regulated and 2 down-regulated in patients with early CRC, whereas 14 proteins were up-regulated and 4 down-regulated in those with late CRC compared to normal controls ($p \leq 0.05$). Five proteins, namely apolipoprotein A1 (APOA1), apolipoprotein E (APOE), complement factor H (CFH), galectin-7 (GAL7) and synaptojanin-2 (SYNJ2) were validated using ELISA and only APOA1 and GAL-7 showed consistent findings. Further validation using immunohistochemistry showed negative immunoreactivity for GAL-7 in CRC tissues, suggesting that GAL-7 detected in the serum did not originate from the CRC tumour. APOA1 showed positive immunoreactivity but its expression did not correlate with Dukes' staging (p=0.314), tumour grading (p=0.880) and lymph node involvement (p=0.108). Differences in APOA1 isoforms and/or conformation between serum and tissue samples as well as tumour heterogeneity may explain for the discrepancies between DIGE and ELISA when compared to immunohistochemistry. Structural and functional studies of APOA1 in future would best describe the role of APOA1 in CRC.

Keywords Colorectal cancer · Proteomics · 2D-DIGE · LC-MS/MS · Apolipoprotein A1

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide [1]. In Peninsular Malaysia, it was ranked in 2006 as the most common cancer in men (16.2 % of the total cancer cases) and the second most common cancer in women (10.6 % of the total cancer cases) [2]. CRC is curable when detected at an early stage. It was reported that the 5-year survival rate is 90 % when CRC is detected at an early, localized stage; however, only 39 % of CRC are diagnosed at this stage due to the lack of specific and sensitive screening tests for early detection and monitoring of disease progression [3].

Current common screening tests for CRC include colonoscopy, flexible sigmoidoscopy, fecal occult blood test (FOBT) and double contrast barium enema [4]. Colonoscopy is the gold standard for CRC screening with 97 % sensitivity and 98 % specificity. However, it is not applicable to the general population due to its invasiveness, high cost, requires uncomfortable bowel preparation and highly trained medical personnel which leads to the reluctance of the general population at

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