

NMRC Awards Ceremony and Research Symposium, 3 April 2019



# Singapore Gastric Cancer Consortium

*Bringing Discoveries to Patients*

**YEOH** Khay Guan, Patrick **TAN**

Yoshiaki **ITO**, Matthew **NG**, Jimmy **SO**, Melissa **TEO**, **YONG** Wei Peng



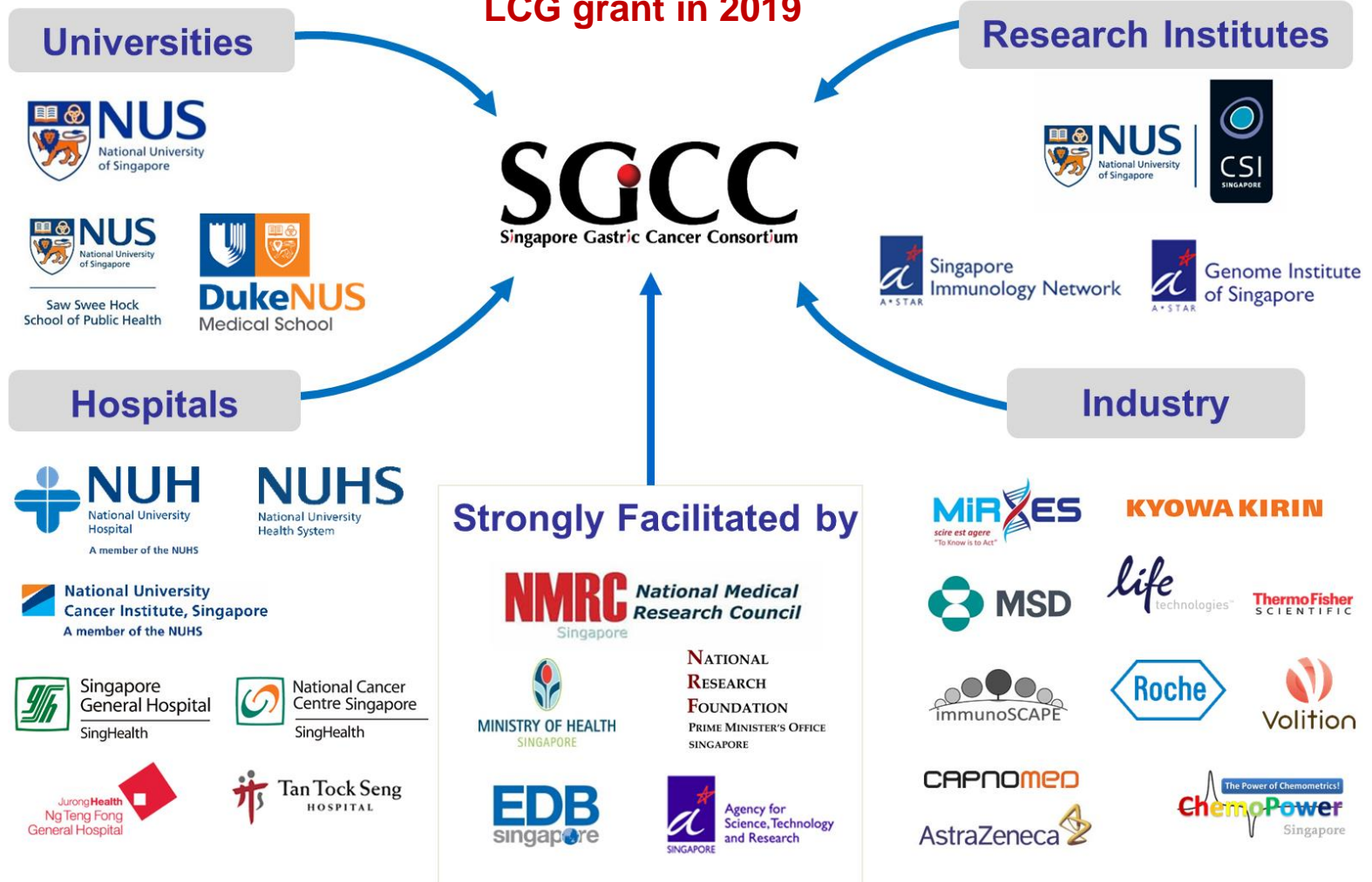
# Singapore Gastric Cancer Consortium

*a national flagship effort translating science to benefit patient care*

**1<sup>st</sup> TCR Flagship Grant in 2007**

**2<sup>nd</sup> TCR grant in 2013**

**LCG grant in 2019**



# Gastric Cancer: *total cases still increasing!*

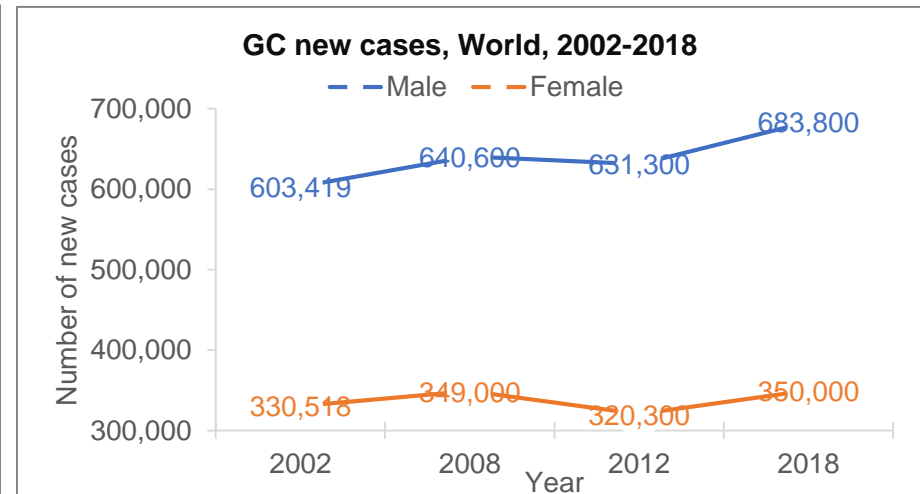
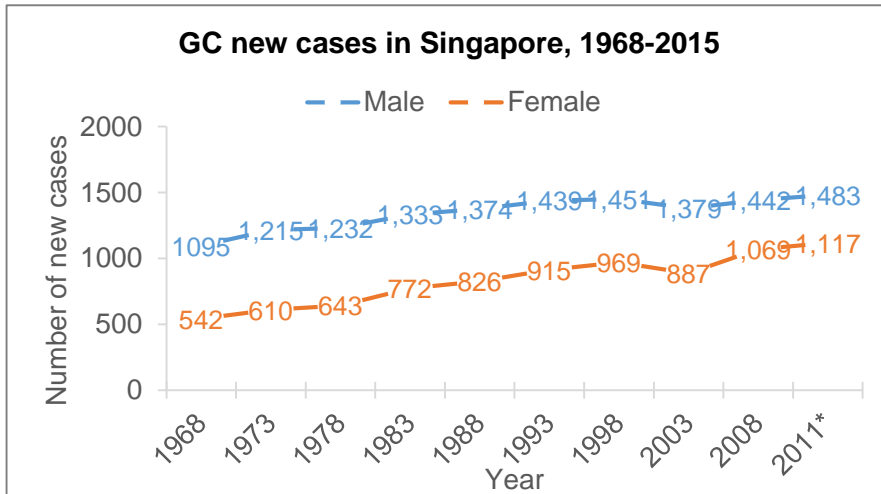
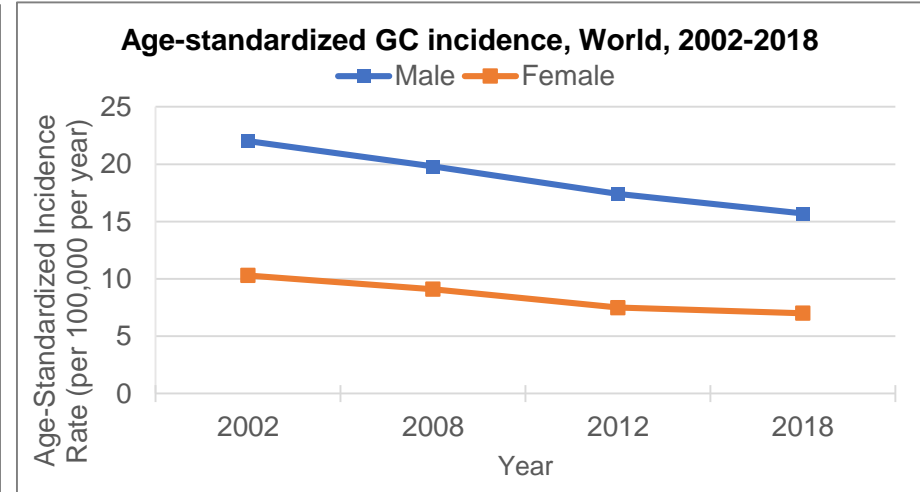
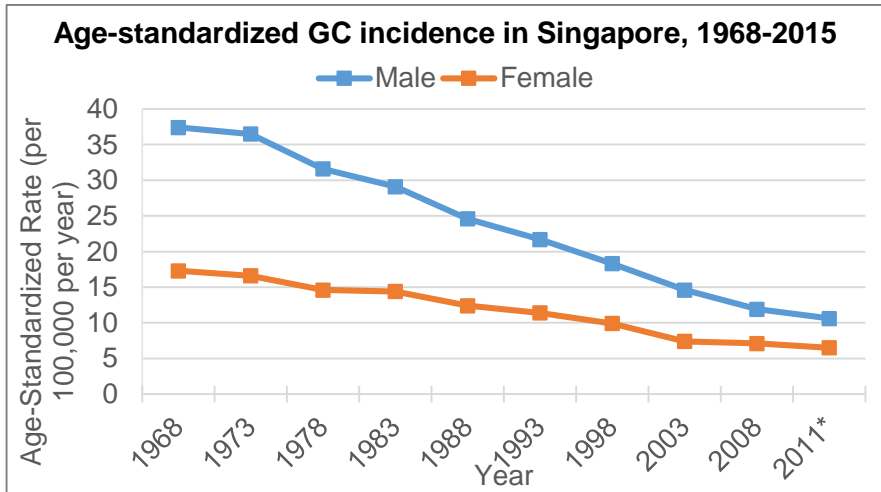


## Singapore

- 7<sup>th</sup> most common cancer in men; 9<sup>th</sup> in women
- 4<sup>th</sup> deadliest cancer in men; 5<sup>th</sup> in women

## World

- 5<sup>th</sup> most frequently diagnosed cancer
- 3<sup>rd</sup> leading cause of cancer death



# GC: Current Critical Clinical Problems



**Rate-limiting Problems >>**

Majority present late as advanced cancers

Chemotherapy results are poor

**Twin strategies to improve outcomes**

**Early Detection**

**Improve treatment**

**Biology**

# Innovations to address Critical Clinical Problems



Twin strategies  
to improve outcomes

microRNA test



Blood test for GC  
>90% accuracy

Molecular test



To identify v hi risk  
patients for  
surveillance

Early Detection

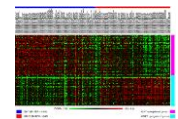
Improve treatment

Robot



First-in-the-world  
Endoscopic robot

Genomic classification



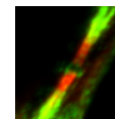
Guiding treatment,  
Right drug, right person

Raman Optical bx



Live, real-time,  
in-vivo feedback

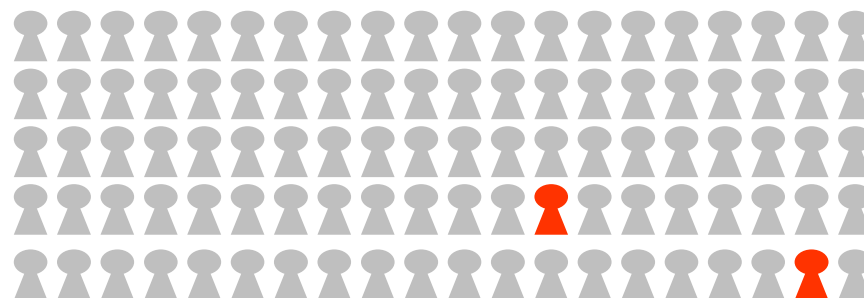
Gatekeeper Gene



Runx3 inactivation  
leads to cancer

Biology

# How do we identify people at High-Risk for Gastric Cancer?



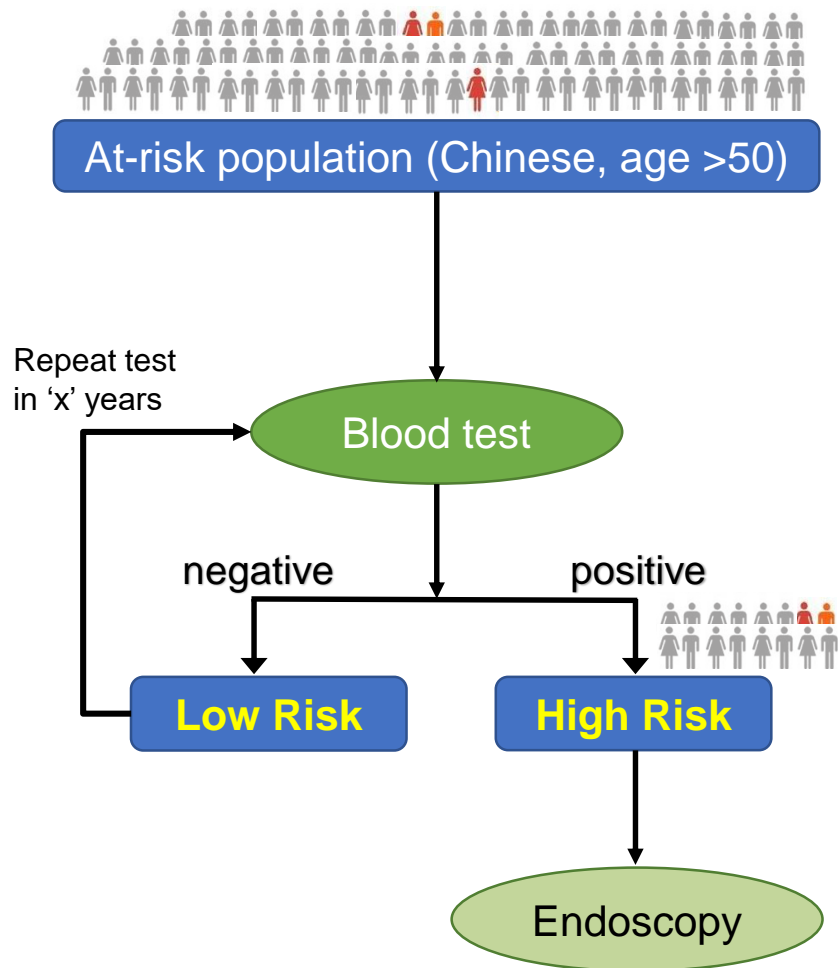
## Population Risk Stratification for Gastric Cancer

*“Combining established clinical parameters & emerging molecular information to create preventive, diagnostic & therapeutic solutions tailored to individual patient requirements”*

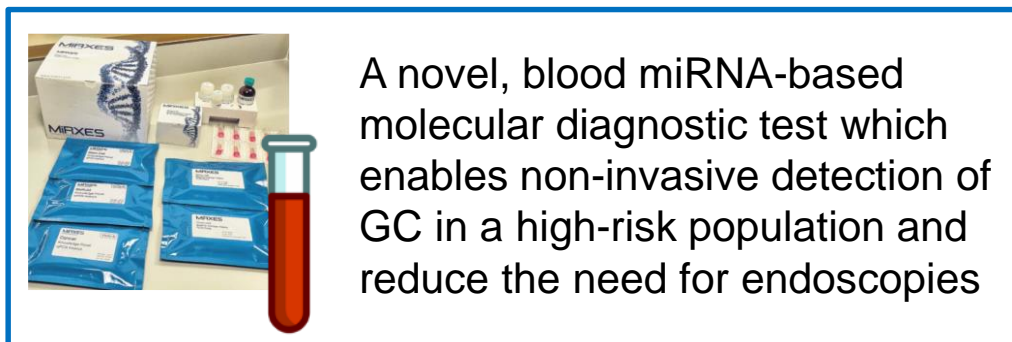
Global Agenda Council on Personalized & Precision  
Medicine 2012-2014, World Economic Forum

# Can a Screening Blood test Detect GC?

## A) Screening

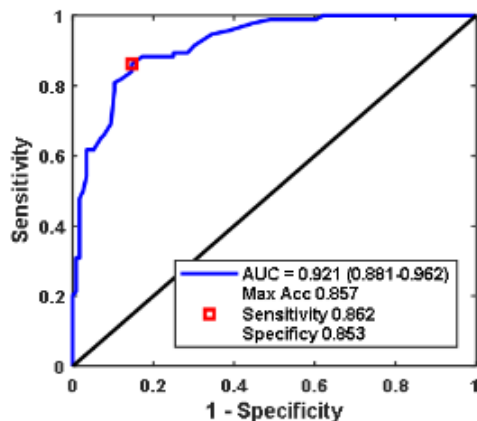


# Serum miRNA test



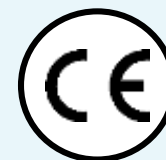
TOO Heng-Phon Jimmy SO KG Yeoh Chia CK

- Validated in multi-centre blinded case-control cohort (n=218, incl 94 cancers)



AUC = 0.92  
Sensitivity = 0.86  
Specificity = 0.85

- Validation underway in large, real patient population of n=5,000 at NUH and TTSH



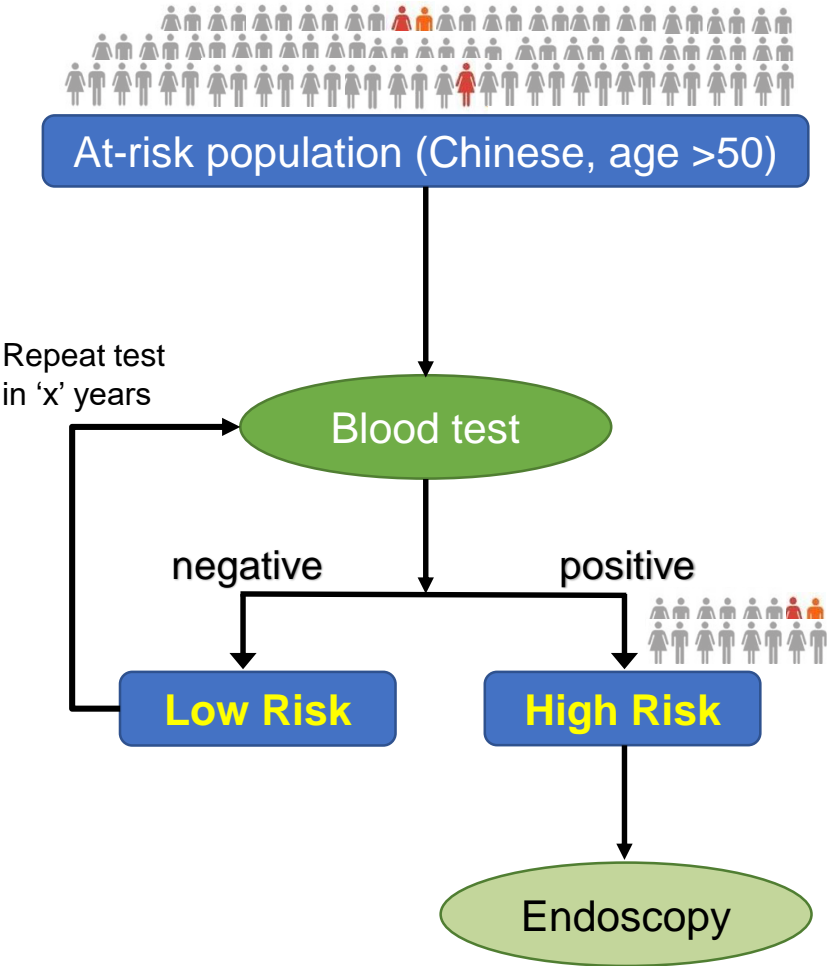
- Achieved CE-mark in Nov 2017, marketed as GASTROClear™ in Europe
- Currently under HSA review, results expected Q3 2019



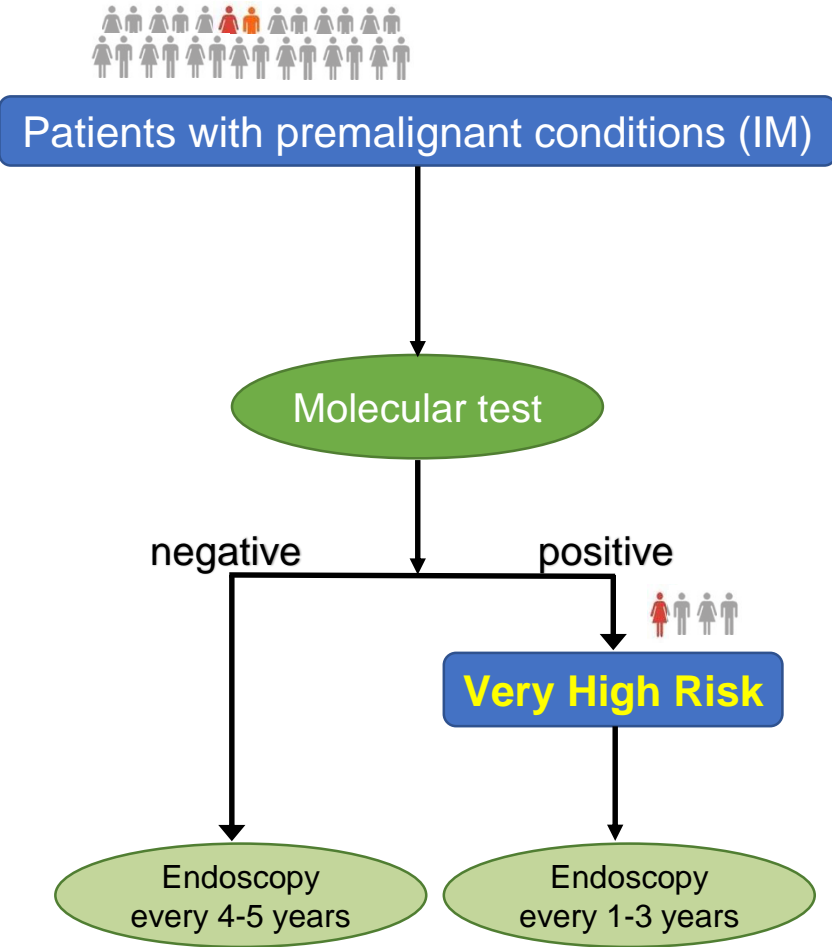


# Proposed Clinical Screening Algorithm

## A) Screening



## B) Surveillance



# Molecular test

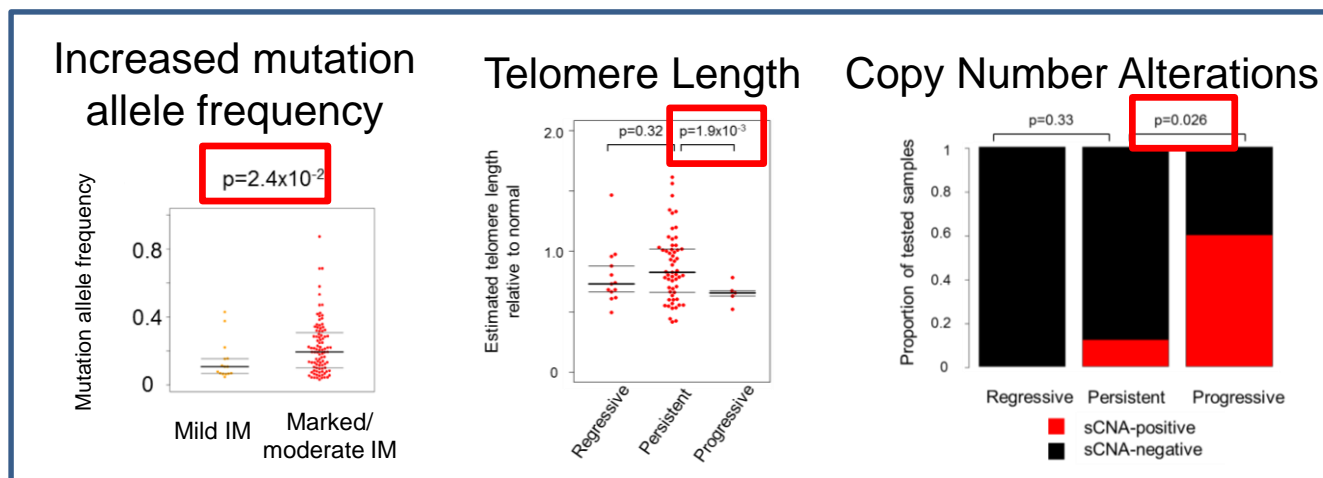
- Intestinal metaplasia (IM) is a pre-cancerous lesion, and the single most influential risk factor for GC
- Extensive genomic profiling of IM revealed 3 main genomic alterations associated with progression to GC:



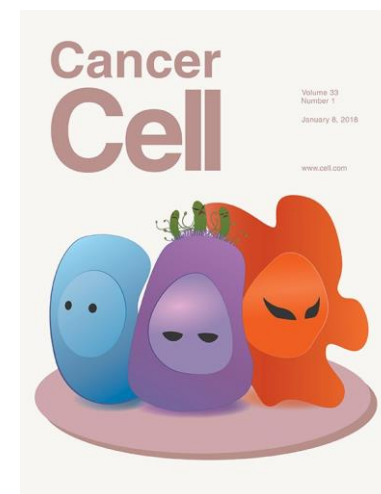
Patrick TAN



KG Yeoh



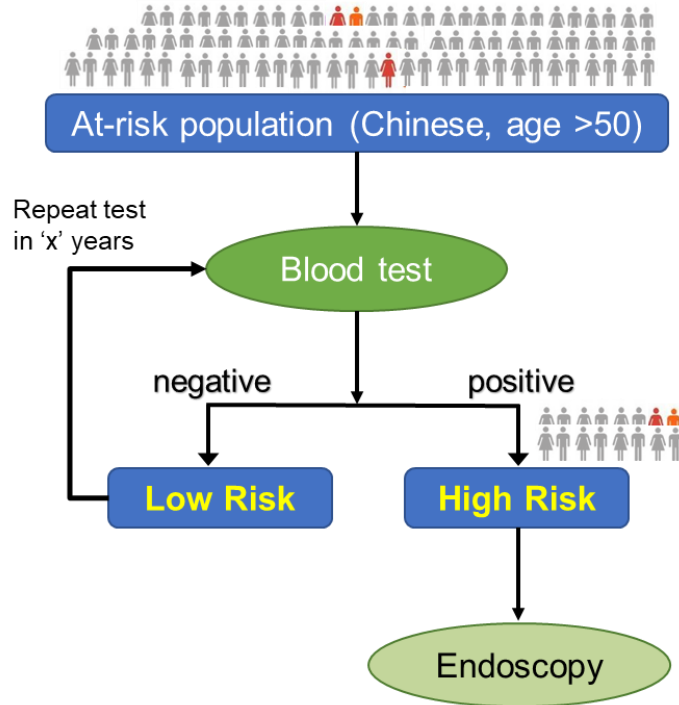
- These genomic markers may be applied in a molecular test to identify subset of IM patients at very high risk of GC
- Potentially guide clinical management of IM and endoscopic surveillance to enable early detection



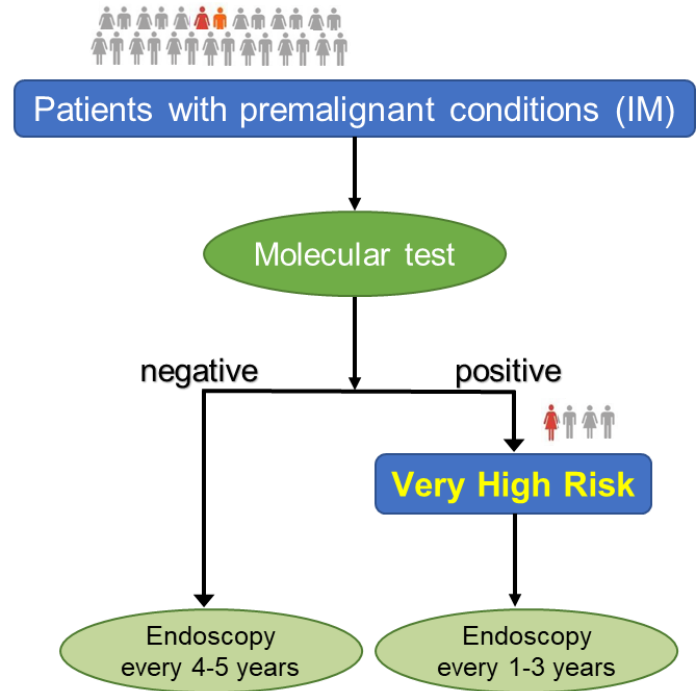
Huang et al. *Cancer Cell* 2018;33(1):137-150.e5.

# Precision Prevention in Gastric Cancer

## A) Screening



## B) Surveillance



Relative risk of GC	1X	?	?	6X	20X
Absolute lifetime risk of GC	1 in 100	?	?	1 in 16	1 in 5
Population Size (Singapore)	1.1 mil	?	?	220,000	22,000

# Innovations to enable early detection

## miRNA



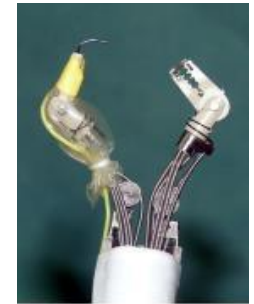
## Mol test



## Raman



## robot



TOO Heng-Phon Jimmy SO KG Yeoh Chia CK

**Screening blood test**

**T3:** translation to practice

Spinoff company  
**MiRXES**



Patrick TAN KG Yeoh

**Identify very high risk**

**T1:** translation to humans (early-phase clinical trials)



Zhi-Wei HUANG Lawrence HO

**Improved imaging for real-time diagnosis**

**T2:** translation to patients (late-phase clinical trials)

Spinoff company  
**Endofotonics**



Louis PHEE Lawrence HO

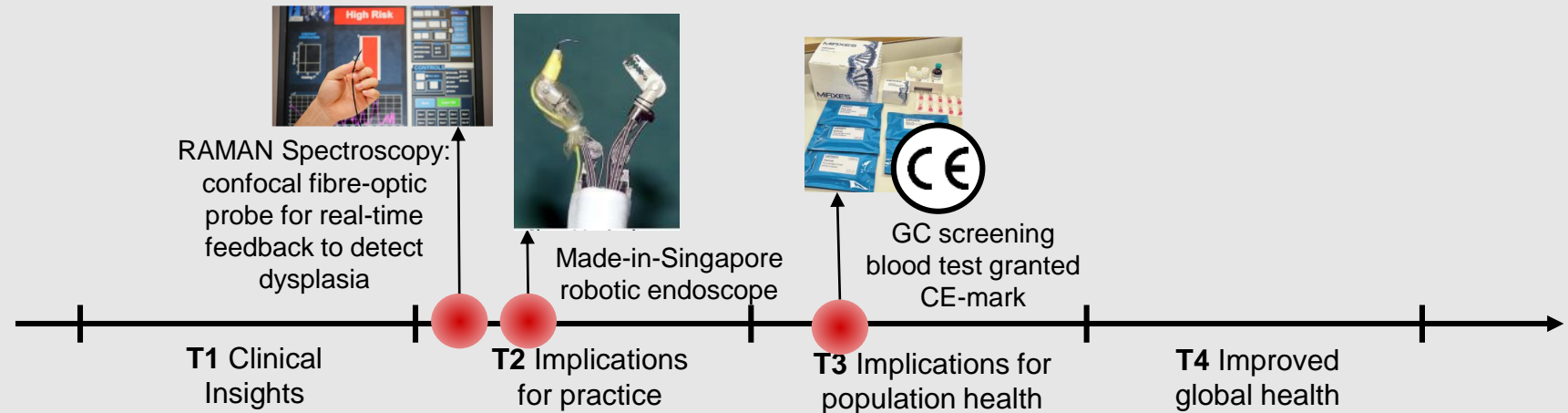
**Endoscopic resection**

**T2:** translation to patients (late-phase clinical trials)

Spinoff company  
**Endomaster**

# Research highlights in the past 10 years

## Inventions and products of translation



## International recognition as thought leaders

1<sup>st</sup> Asian recipient of the AACR Team Science Award as Team Leader (P Tan)

KG Yeoh gave the IGCC Plenary lecture in 2011

Invited review in *Gastroenterology*

## Unique studies

GCEP - world's largest endoscopic surveillance cohort  
 "3G" trial – Guided by Genomics in Gastric Cancer

## High impact publications

>230 publications (h-index of 48 as at Dec 2018)

Study on molecular determinants of GC progression was a cover article on *Cancer Cell* (*IF=22*) in Jan 2018



## Economic Value

47 patents and invention disclosures

**4 Spin-offs:** EndoMaster Pte Ltd, Endofotonics Pte Ltd, Signomax, MiRXES Pte Ltd

**>\$24million** in industry funding from >20 companies across >30 projects;  
**\$81million** raised by SGCC start-ups

# Key Publications (>230 since 2007)

H-index = 48 as of Dec 2018 *excluding self-citations*



**Journal Impact Factor**  
(at time of publication)



Genomic and Epigenomic Profiling of High-Risk Intestinal Metaplasia Reveals Molecular Determinants of Progression to Gastric Cancer. *Cancer Cell* 2018; 33(1):137-150.e5

**22.84**

Real-Time Tumor Gene Expression Profiling to Direct Gastric Cancer Chemotherapy: Proof-of-Concept "3G" Trial. *Clinical Cancer Research* 2018;24(21):5272-5281.

**10.20**

Epigenomic Promoter Alterations Amplify Gene Isoform and Immunogenic Diversity in Gastric Adenocarcinoma. *Cancer Discovery* 2017;7(6):630-51.

**24.37**

Identification of Stem Cells in the Epithelium of the Stomach Corpus and Antrum of Mice. *Gastroenterology* 2017;152(1):218-231.e14.

**20.77**

Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nature Medicine* 2015;21(5):449-56.

**30.36**

Fiberoptic Confocal Raman Spectroscopy for Real-Time In Vivo Diagnosis of Dysplasia in Barrett's Esophagus. *Gastroenterology* 2014;146(1):27-32.

**16.72**

Identification of molecular subtypes of gastric cancer with different responses to PI3-kinase inhibitors and 5-fluorouracil. *Gastroenterology* 2013;145(3):554-65

**13.93**

Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion & chromatin remodeling genes. *Nature Genetics* 2012; 44(5):570-4.

**35.21**

STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis independent of tumor inflammation. *Cancer Cell* 2012; 22(4):466-78.

**24.76**

Loss of Runx3 is a key event in inducing precancerous state of the stomach. *Gastroenterology* 2011;140(5):1536-1546.

**11.68**

Clinical

Research

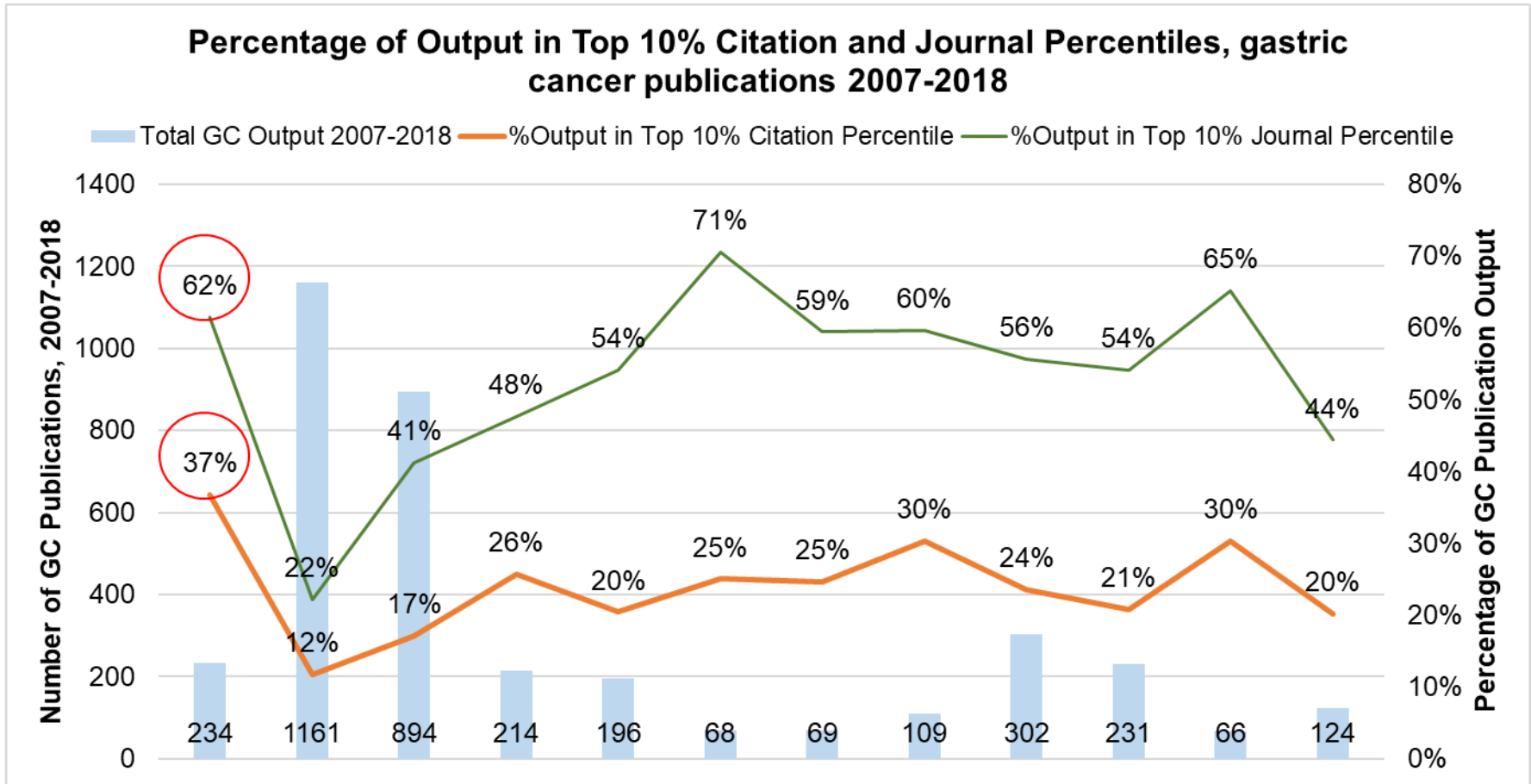
CANCER DISCOVERY

Gastroenterology

nature medicine



# Top 10% Citation & Top 10% Journal Percentiles



**SGCC**  
 Shanghai JT Univ  
 Seoul National Univ  
 Nat Ca Center Tokyo  
 Chinese Univ of HK

Oxford  
 Cambridge  
 Erasmus Univ MC  
 MD Anderson  
 Vanderbilt  
 Stanford  
 Harvard



Scopus®


SciVal




# Industry Collaborations

SGCC has completed >30 academic-industry projects with >20 companies, totaling \$24million over 10 years (\$13million in cash, \$11million in kind)


## Phase I-III Clinical Trials

 TAIHO PHARMA SINGAPORE \$750K-1.5mil

 OncoTherapy Science, Inc. \$1.5mil

 Roche \$230K-600K

 BAYER \$560K


 NOVARTIS \$300K-500K


 ASLAN PHARMACEUTICALS  MSD  Bristol-Myers Squibb

## Preclinical evaluation

- Cell lines
- Xenografts
- Organoids

**KYOWA KIRIN** \$1.0mil


 BAYER \$130K-\$140K

 siamab therapeutics \$20K

## Target discovery

 illumina® \$7.3mil

 life technologies®  ThermoFisher SCIENTIFIC \$900K

 BAYER \$630K

 Volition \$520K

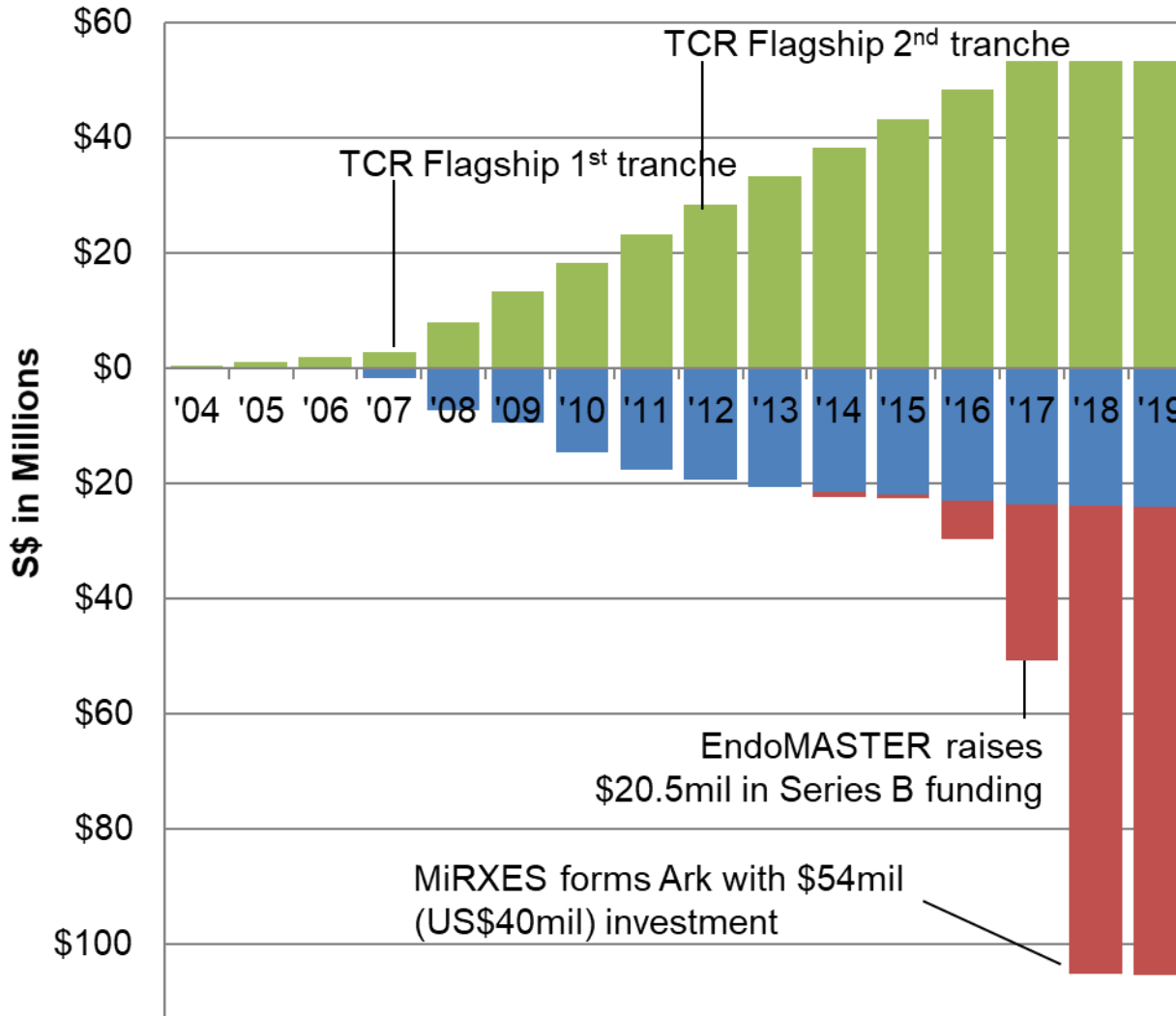
 MIRXES scire est agere "To Know is to Act" \$240K

**KYOWA KIRIN** \$200K



# Industry Relevance

SGCC Cumulative Funding, 2004-2019



- Grant Funding (Programme)  
Total: \$53mil
- Industry Funding  
Total: \$24mil
- Spin-off Funding  
Total: \$81mil

## THE BUSINESS TIMES

**Medtech firm Ark launched with US\$40m Series A funding**

The company is formed through the merger of VC firm Venturecraft and medtech startup Mirxes

© TUE, NOV 27, 2018 - 9:00 AM

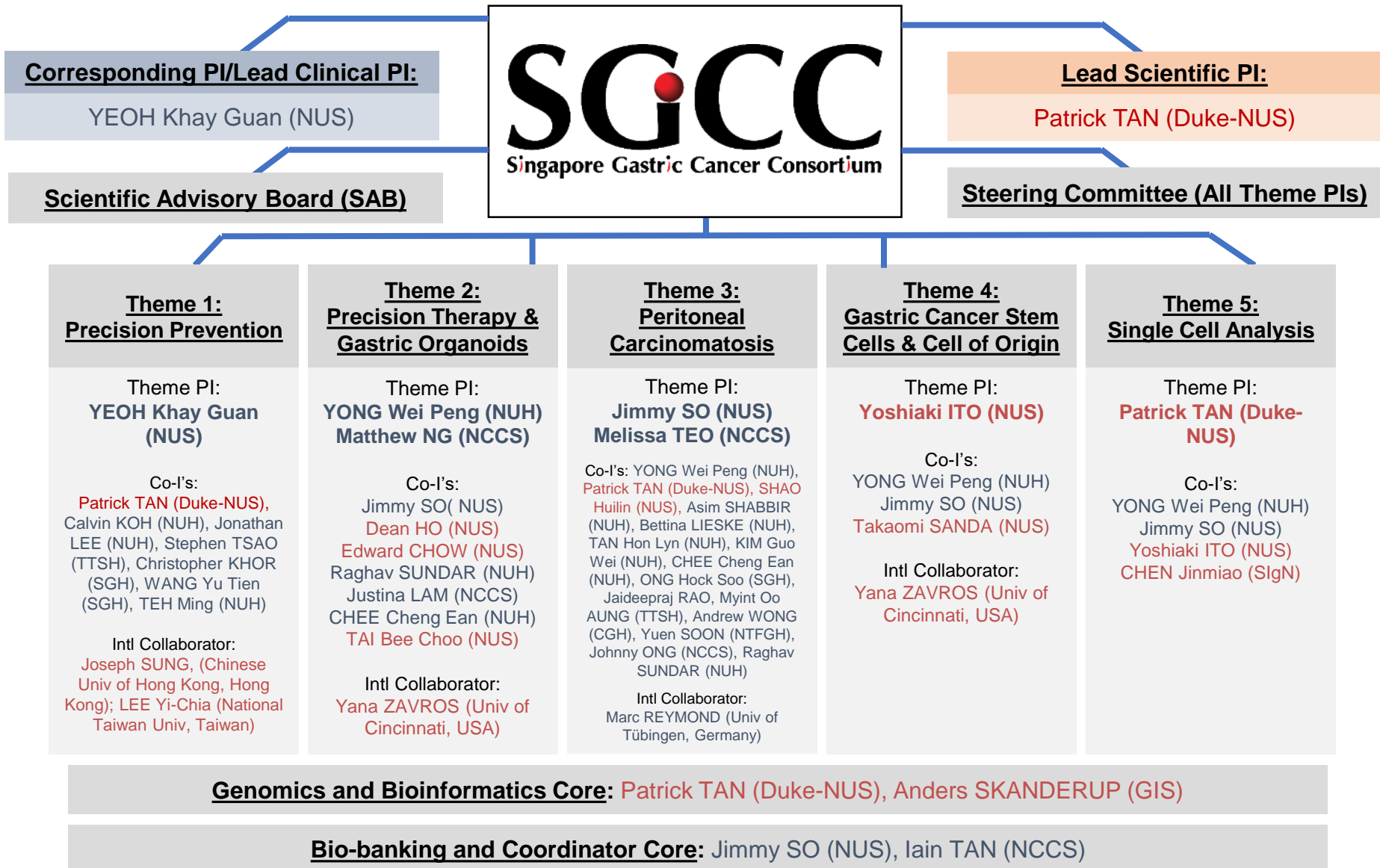
CLAUDIA CHONG ✉ chong.mc@sph.com.sg 🐦 @ClaudiaChongBT



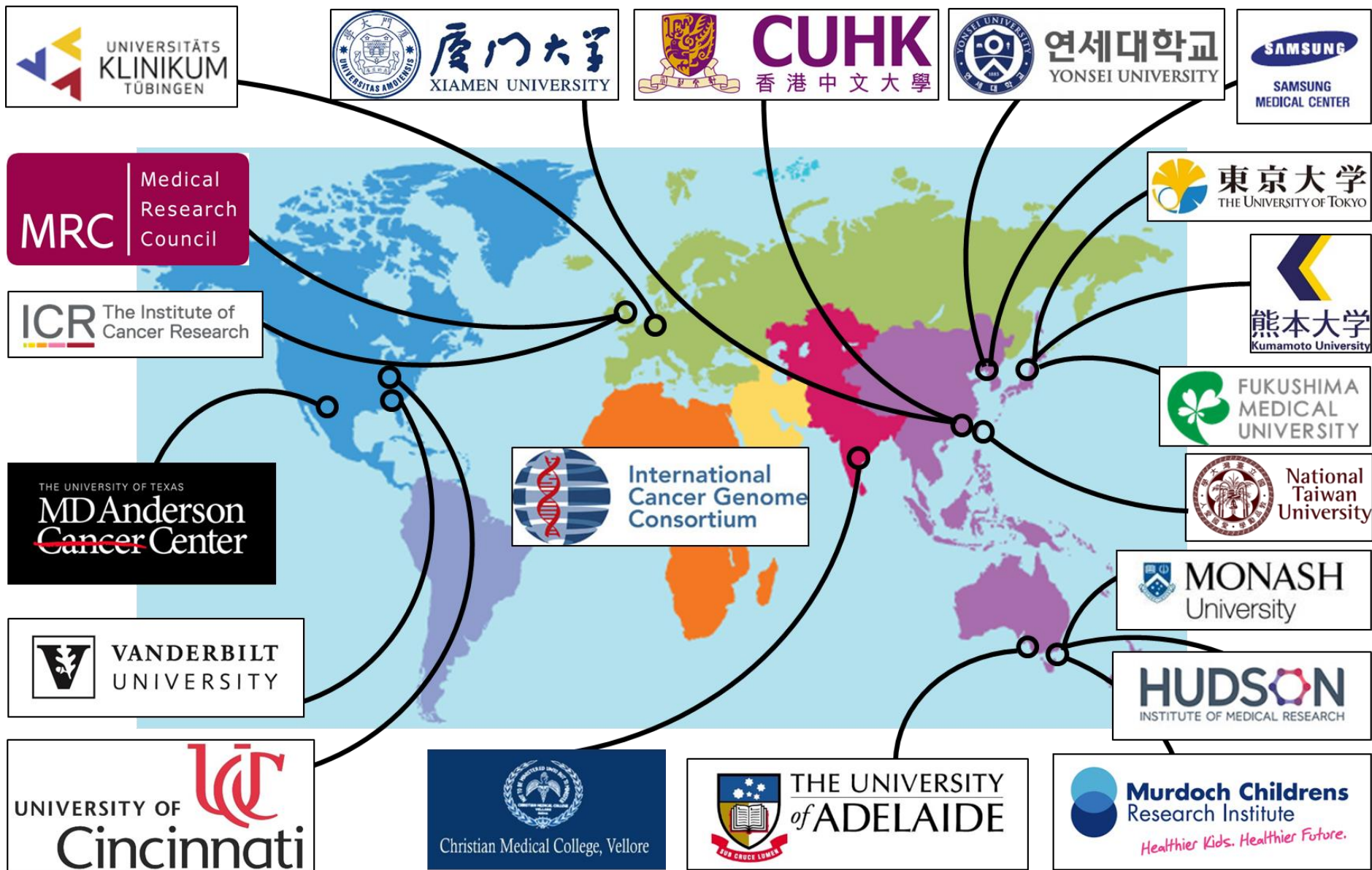
The Business Times, 27 Nov 2018

**Industry+Spin-off Funding to Programmatic Grant Funding ratio = 2:1**

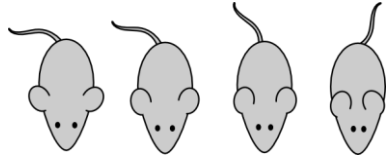
# Combined Clinical and Scientific Leadership



# Academic Collaborators Worldwide



# Unique Resources for Translation



- **Unique animal models** (RUNX3 knock-out mice)
- Xenograft lines



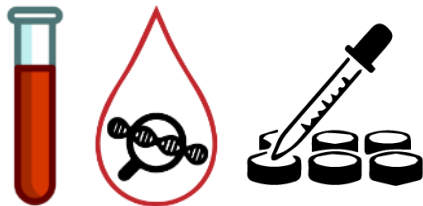
- **Genomics expertise** in Genome Institute of Singapore (GIS)



- Initiated 7 different **clinical trials** since 2012, combined recruitment of 550
- Evaluate treatment response, novel imaging systems etc



- Completed **large scale cohort studies** (n=3,000) and **cross-sectional studies** (n=12,000)
- Strong support from collaborating hospitals (NUH, TTSH, SGH, CGH, NTFGH)



- **Large volume of banked biospecimens**
  - 44,000 gastric tissue specimens, 10,000 sets of blood, sera and DNA

# Next Steps for 2019-2024

## Precision Prevention

How do we achieve early detection of GC in Singapore?

### Theme 1

1. Novel serum screening test
2. Molecular panel for identifying patients at highest risk for developing GC

## Precision Therapy

Most drugs don't work in GC as monotherapy

### Theme 2

- Use AI to find the best combinations

Peritoneal disease has the worst prognosis

### Theme 3

- Run clinical trials specifically in the PC setting

## Dissecting Tumour Heterogeneity

What is the cell of origin of gastric cancer?

### Theme 4

- Dissect mechanism of RUNX3(R122C) which phenocopies metaplasia (without external agents)

How does tumor heterogeneity and its evolution contribute to resistance?

### Theme 5

- Single-cell analysis on pre/post treated samples, drawn from other Themes



# Acknowledgements



## GCEP

Jonathan Lee, NUH  
Zhu Feng, NUS  
Chia Chung King, TTSH  
Christopher Khor, SGH  
Choon-Jin Ooi, SGH  
Kwong Ming Fock, CGH  
Jimmy So, NUS  
Wee Chian Lim, TTSH  
Khoon Lin Ling, SGH  
Tiing Leong Ang, CGH  
Andrew Wong, CGH  
Jaideep Raj Rao, TTSH  
Andrea Rajnakova, NUH  
Lee Guan Lim, NUH  
Wai Ming Yap, TTSH  
and all investigators from NUHS,  
TTSH, SGH and CGH

## miRNA

Too Heng-Phon, NUS  
Zhou Lihan, MiRXES  
Zou Ruiyang, MiRXES  
Jimmy So, NUS  
Yong Wei Peng, NUHS  
Celestial Yap, NUS  
Calvin Koh, NUHS  
Patrick Goo, A\*STAR  
Teo Yik Ying, NUS  
Joanne Yoong, NUS  
Ritika Kapoor, NUS  
Sun Young Rha, Yonsei  
Hyun Cheol Chung, Yonsei  
Jaideep Raj Rao, TTSH  
Chia Chung King, TTSH  
Stephen Tsao, TTSH  
Asim Shabbir, NUHS  
Lam Kong Peng, BTI  
Mikael Hartman, NUS

## Molecular test

Patrick Tan, Duke-NUS  
Teh Ming, NUH  
Kie Kyon Huang, Duke-NUS  
Kalpana Ramnarayanan, Duke-NUS  
Feng Zhu, NUS  
Supriya Srivastava, NUHS  
Chang Xu, Duke-NUS  
Angie Lay Keng Tan, Duke-NUS  
Minghui Lee, Duke-NUS  
Suting Tay, Duke-NUS  
Kakoli Das, Duke-NUS  
Manjie Xing, Duke-NUS  
Aliya Fatehullah, IMB  
Syed M. Fahmy Alkaff, SGH  
Tony Kiat Hon Lim, SGH  
Jonathan Lee, NUHS  
Steven George Rozen, Duke-NUS  
Bin Tean Teh, NCCS  
Nick Barker, IMB

**and all SGCC  
Principal Investigators,  
Co-Investigators and  
Collaborators**

**Visit us at [www.sgcc.sg](http://www.sgcc.sg)  
Singapore Gastric Cancer Consortium**