

# Genomic Predictors of Clinical Outcome in Gastric Cancer : The Singapore Experience

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# Biomedical Sciences (BMS) in Singapore (2003-2013)

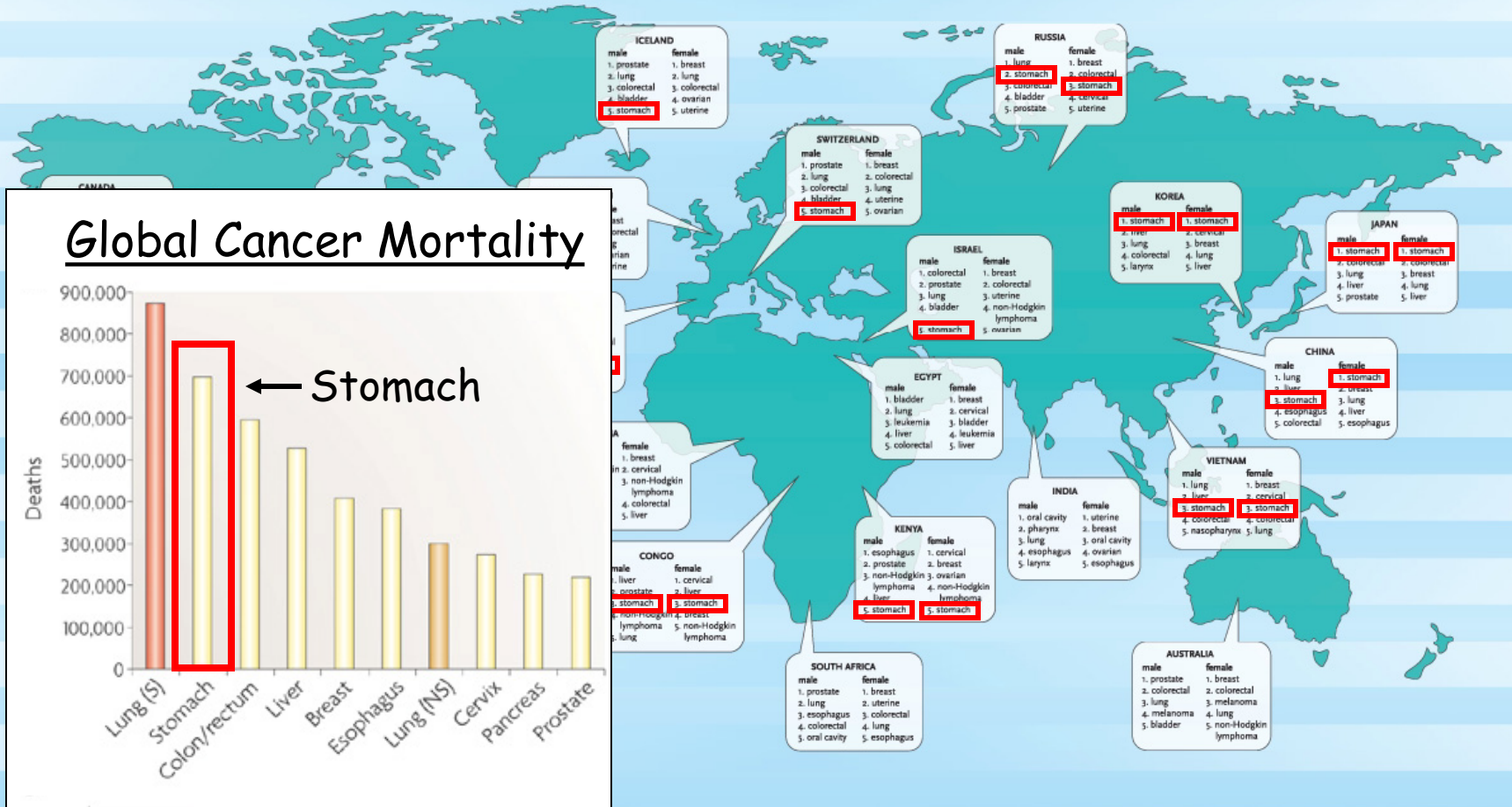
**Significant and increasing** BMS support from Singapore government

Funding from **Three Major Ministries**  
(Trade/Industry, Education, Health)

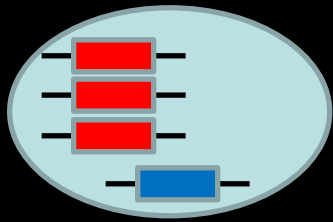
**Multiple Research Institutes** (eg Biopolis)  
and **Academic Medical Centres** (eg Singhealth, National University Hospital)

# Focus Area : Asian Cancers (eg Gastric/Stomach)

Frequency of Cancers Around the World  
Top Five Cancers (# of cases, not deaths)

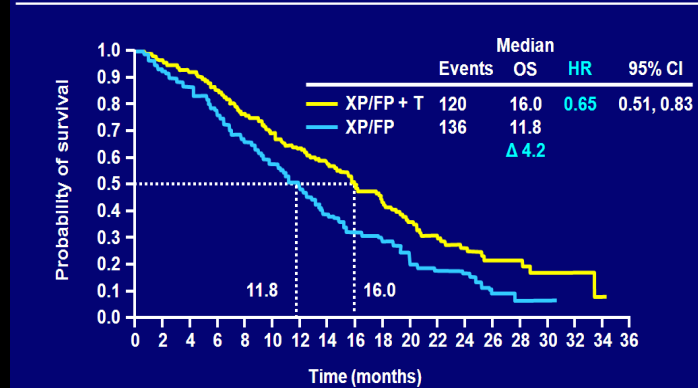


# Genomic Amplifications Highlight GC Therapeutic Targets



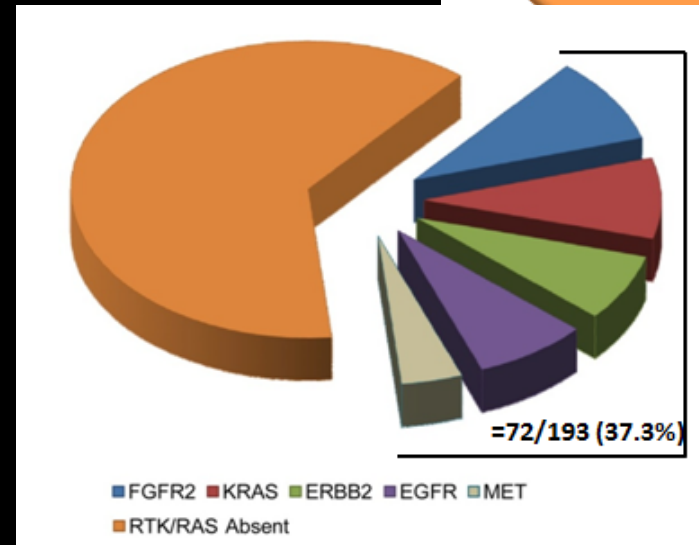
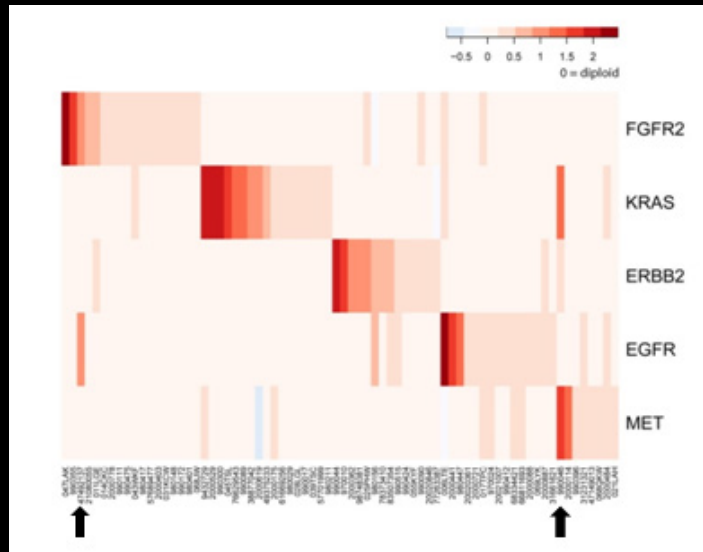
**ERBB2/HER2  
Amplification**

**OS in IHC 2+ / FISH+ or IHC 3+  
(exploratory analysis)**



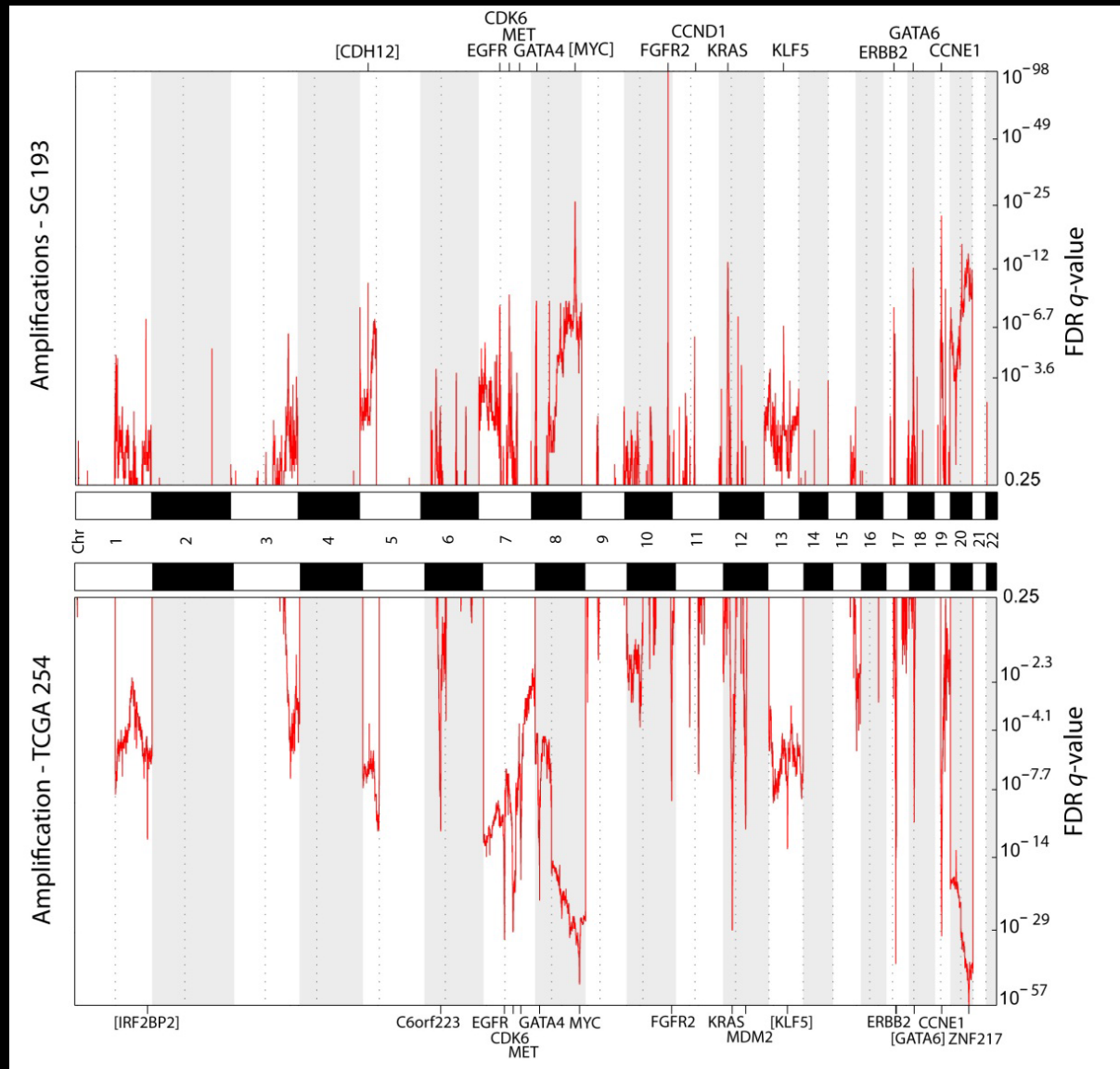
**TOGA Trial, Lancet 2010**

**ERBB2 Positive  
(8-10%)**



**Gut 2012**

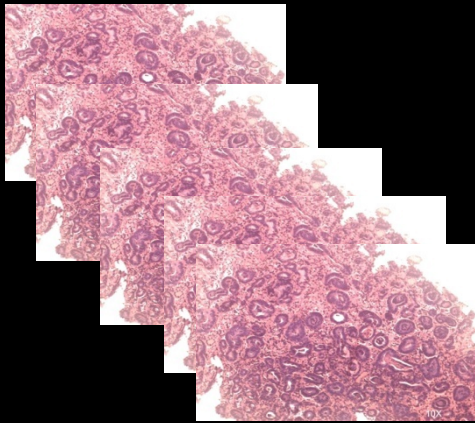
# Genomic Amplifications in Asian and Caucasian GCs - Concordant and Largely Similar



Singapore Cohort

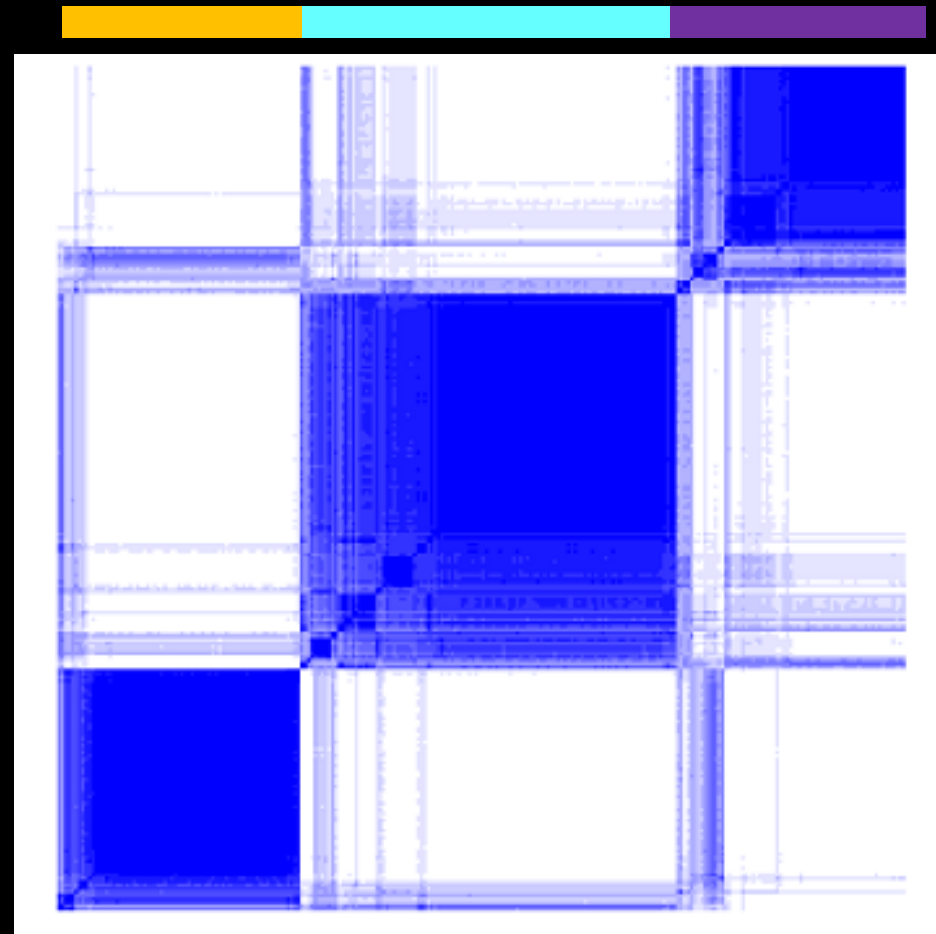
TCGA Cohort (USA)

# Transcriptome Clustering Identifies THREE GC Subtypes : Integration with Pathology



250 Gastric Tumors

Consensus Clustering



Consensus Subtype Matrix

# GC Genomic Subtypes : Mesenchymal, Proliferative, and Metabolic

EMT Pathways  
CSC Pathways  
TGFβ and Signaling

Genomic Subtype	Histological Features	Associated Genes/Pathways	Drug sensitivity (Preclinical)
Mesenchymal	<ul style="list-style-type: none"> <li>Diffuse subtype</li> </ul>	<ul style="list-style-type: none"> <li>EMT pathways</li> <li>CSC pathways</li> <li>TGFβ</li> <li>mTOR signalling</li> </ul>	<ul style="list-style-type: none"> <li>Sensitive to PI3K/AKT/mTOR inhibitors</li> </ul>
Proliferative	<ul style="list-style-type: none"> <li>Intestinal subtype</li> </ul>	<ul style="list-style-type: none"> <li>Genomic instability</li> <li>TP53 mutations</li> <li>Cell cycle</li> <li>DNA replication</li> <li>Mitosis</li> <li>Copy number alterations (ERBB2/HER2 and KRAS)</li> </ul>	<ul style="list-style-type: none"> <li>Unresponsive to 5-FU</li> </ul>
Metabolic	<ul style="list-style-type: none"> <li>Gastric subtype</li> </ul>	<ul style="list-style-type: none"> <li>Metabolic processes</li> <li>Digestion</li> <li>Secretion</li> <li>SPEM</li> </ul>	<ul style="list-style-type: none"> <li>Increased sensitivity to 5-FU</li> </ul>

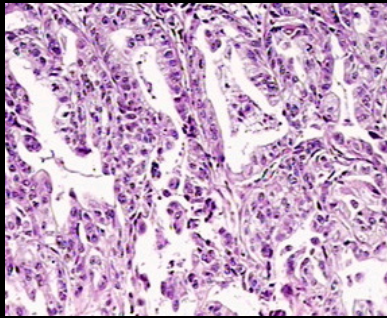
Cell replication

Metabolic processes  
Digestion, Secretion

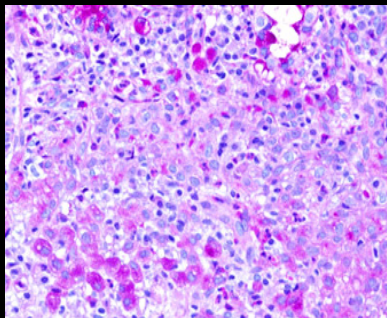
# Genomic Subtyping May Drive Improved Pathology

Lauren's Classification  
(1960)

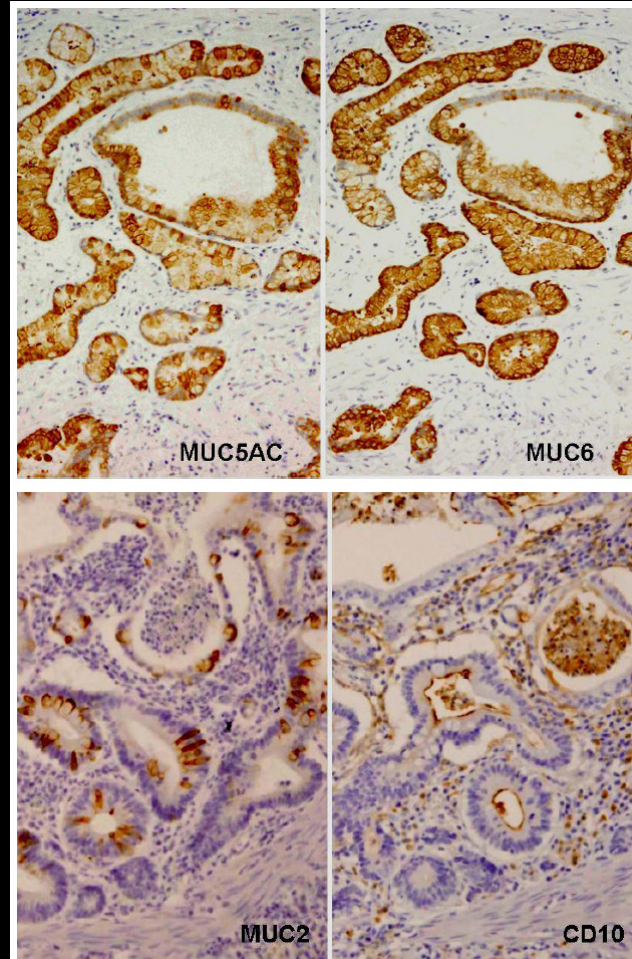
**Intestinal**



**Diffuse**



WHO Classification  
(2010)

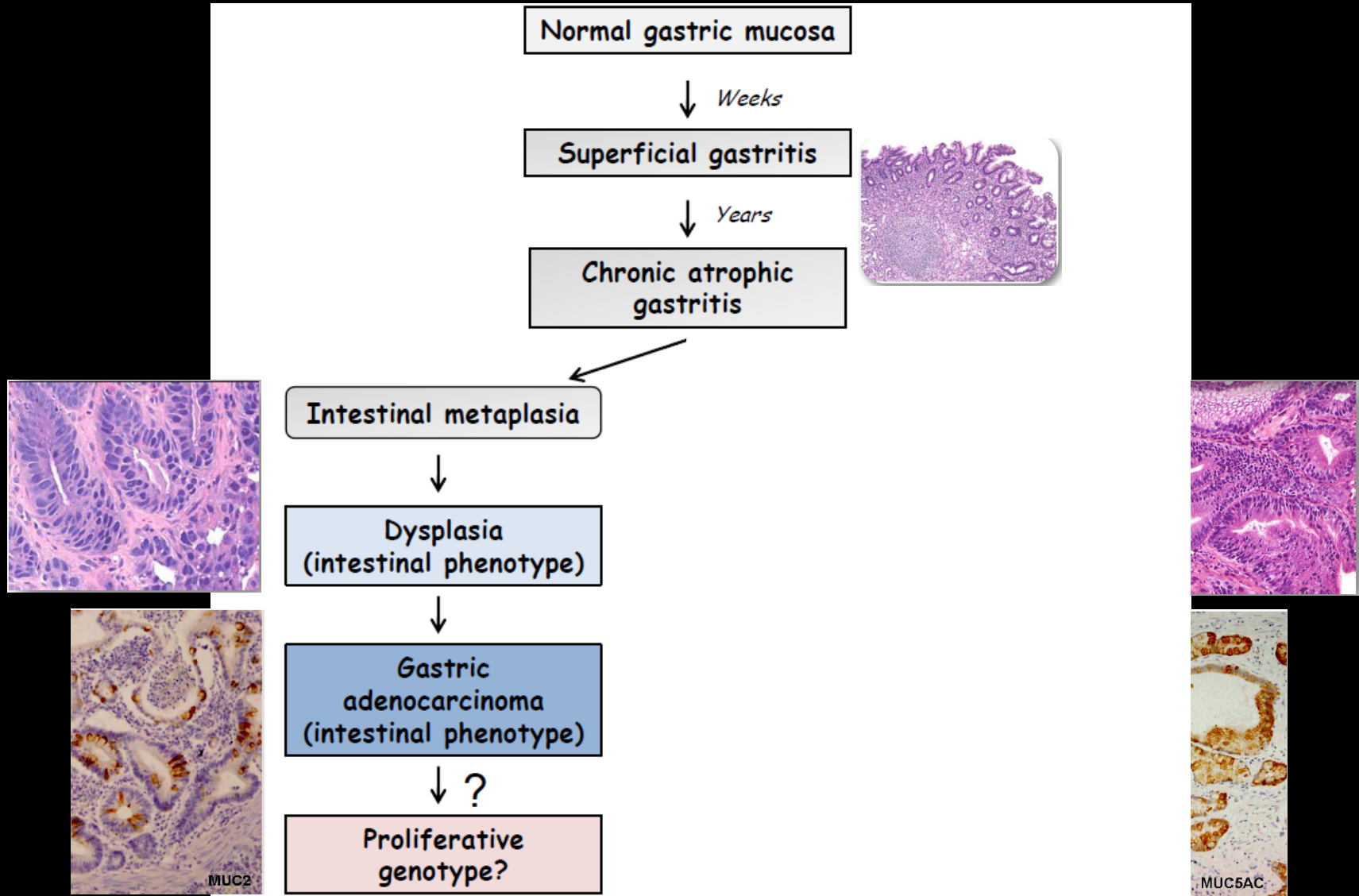


**Gastric  
Phenotype  
Aka Metabolic**

**Intestinal  
Phenotype  
Aka Proliferative**



# Working Roadmap for GC Carcinogenesis



Courtesy Fatima Carneiro, IPATIMUP

# Dissecting Asian Cancers - Some Contributions from Singapore

Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes

Nature Genetics (2012)

A common *BIM* deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer

Nature Medicine (2012)

Oncofetal Gene *SALL4* in Aggressive Hepatocellular Carcinoma

N Engl J Med (2013)

# The POLARIS Program - Enabling Genomic Medicine in a City-State

Funded by A-STAR (Agency for Science, Technology and Research) for 3 years

Pilot clinical use of genomic testing (cancer and genetic diseases)

National network of CAP-certified laboratories at hospitals and research institutes



# Some POLARIS Operating Principles

Genomic medicine labs should be deployed  
**WITHIN** existing clinical frameworks

Frameworks for GENETIC testing should exist  
**PRIOR** to GENOMIC testing

Genomic tests should leverage on **EXISTING  
RESEARCH COMPETENCIES**

Tests providing **CLINICAL UTILITY** will lead to  
clinician buy-in

# POLARIS - Current Status (2013)

First POLARIS Test - **TGFBI Eye Test** (early 2014)

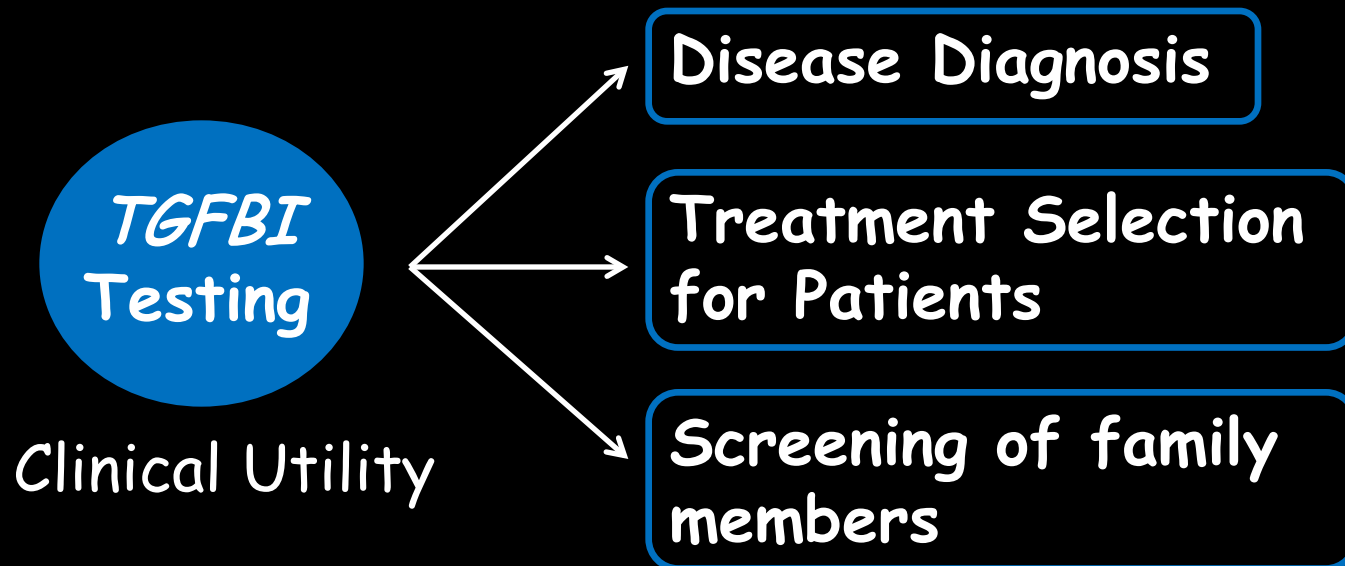
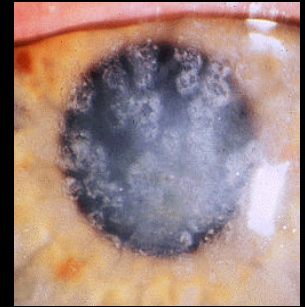
Genomic labs targeting **national certification** in mid 2014 (Illumina + Reflex Validation)

Test revenues are **distributed** among network partners on cost-recovery basis

Second POLARIS Test - **90 gene GI Panel** (3<sup>rd</sup> quarter 2014)

# Stromal Corneal Dystrophies (SCDs) and TGFBI Testing

- Inherited disorders leading to loss of corneal transparency.
- *TGFBI* mutations underline the majority of stromal CDs.



# PARTIES INVOLVED IN POLARIS™ TGFB1 TEST



## GIS/SERI

- Project Management
- Mutation Database

## SNEC/SGH

- Patients & Consultation
- Test Ordering
- Blood Collection

## NUHS

- Sequencing
- Mutation Rpt

POLARIS™  
TGFB1 Test



# Challenges in Developing a Singapore Framework for Genetic/Genomic Testing

**Legal and licensing agreements** across institutions and ministries are often complex

**Reimbursement options** for genetic assays that cross medical centres

**General lack** of genetic counsellors and advisors

**Official policies** on patient consent, incidental findings and aggregation of genetic/genomic data



# Thanks and Questions

Prof John Wong  
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