

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

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

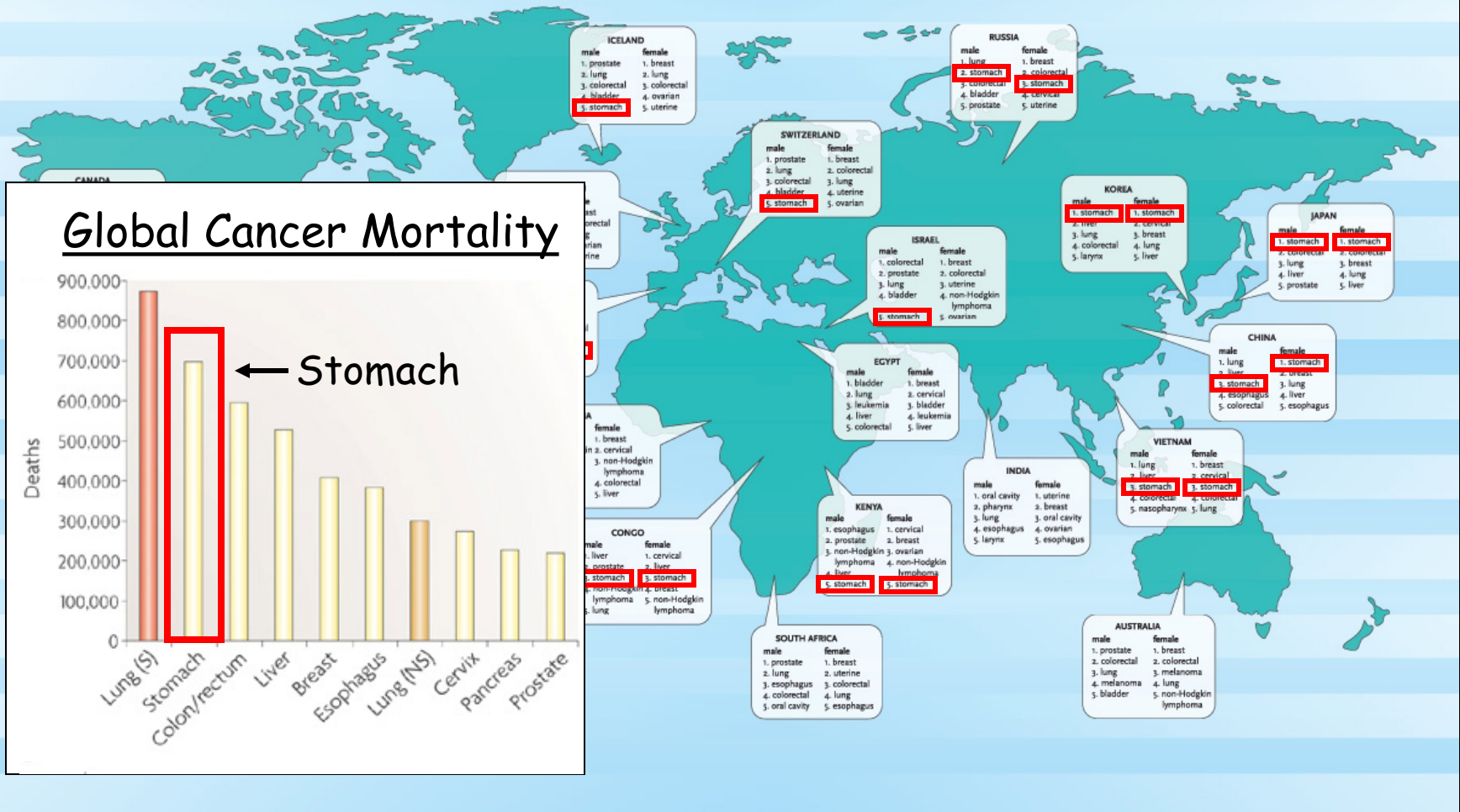
Significant and increasing BMS support from Singapore government

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

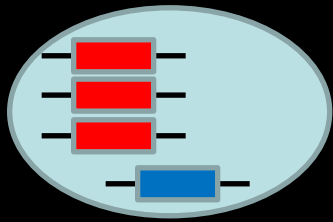
Multiple Research Institutes (eg Biopolis)
and Academic Medical Centres (eg
Singhealth, National University Hospital)

Focus Area : Asian Cancers (eg Gastric/Stomach)

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

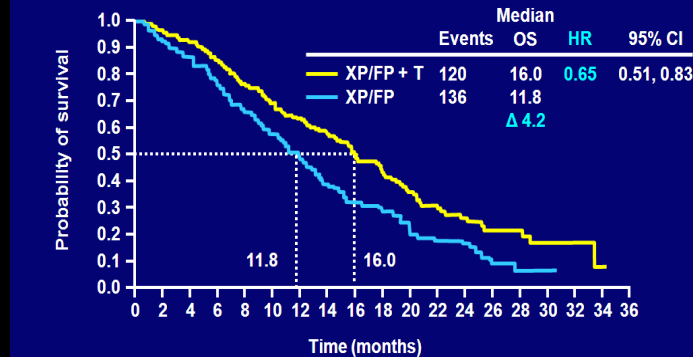


Genomic Amplifications Highlight GC Therapeutic Targets



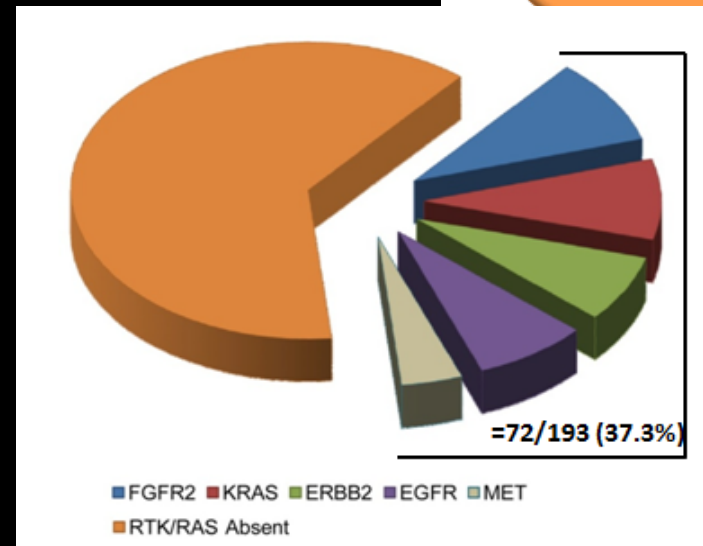
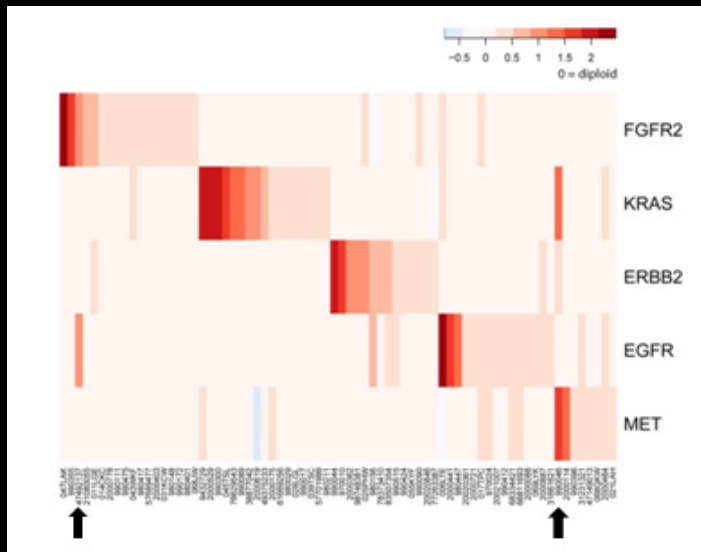
**ERBB2/HER2
Amplification**

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



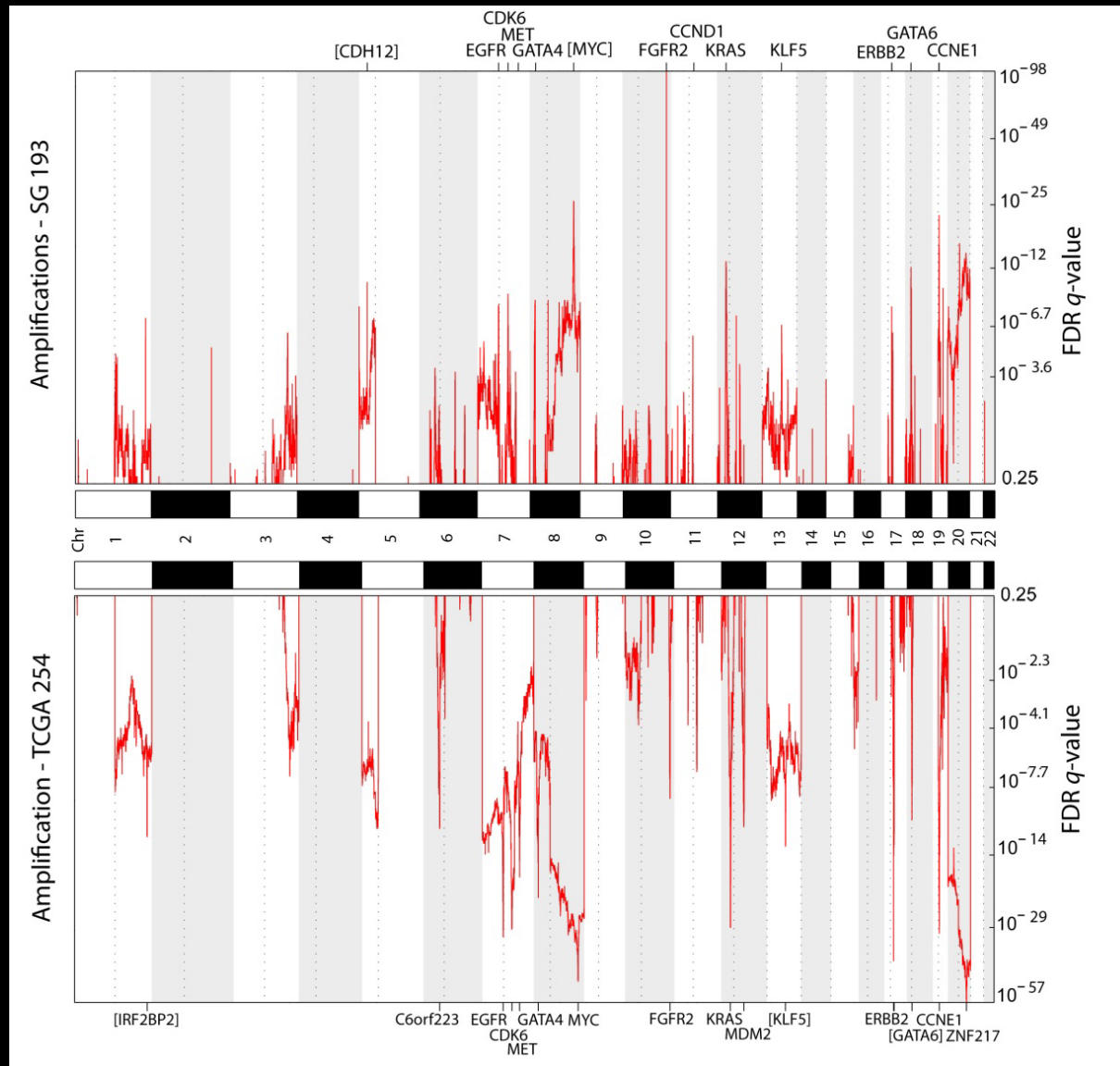
TOGA Trial, Lancet 2010

ERBB2 Positive
(8-10%)



Gut 2012

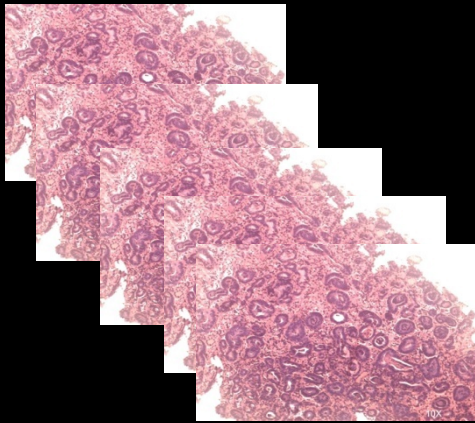
Genomic Amplifications in Asian and Caucasian GCs - Concordant and Largely Similar



Singapore Cohort

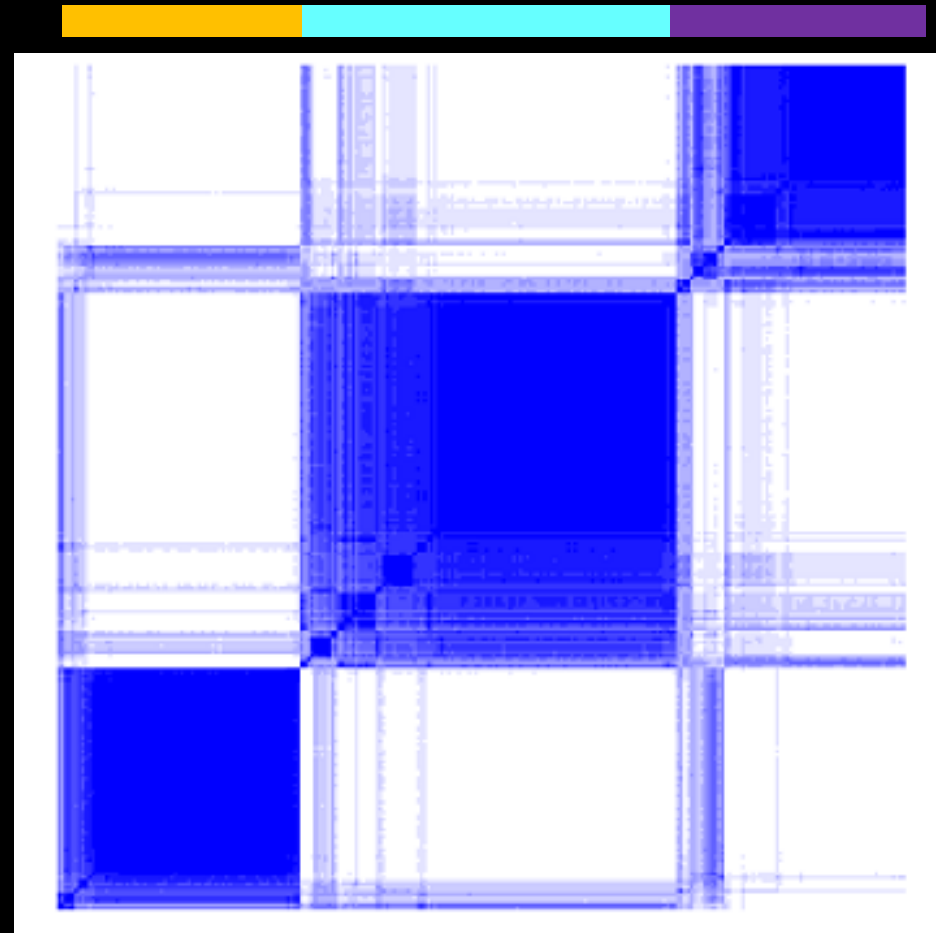
TCGA Cohort (USA)

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
TGF β and
Signaling

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

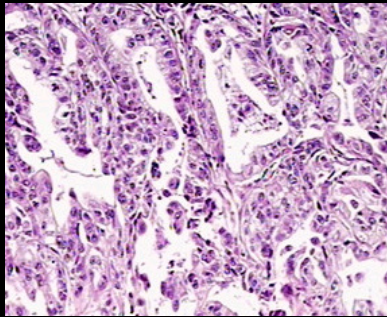
Cell
replication
s

Metabolic processes
ion, Secretion

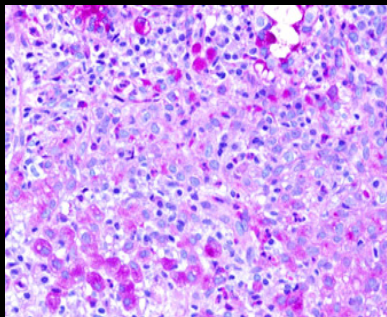
Genomic Subtyping May Drive Improved Pathology

Lauren's Classification
(1960)

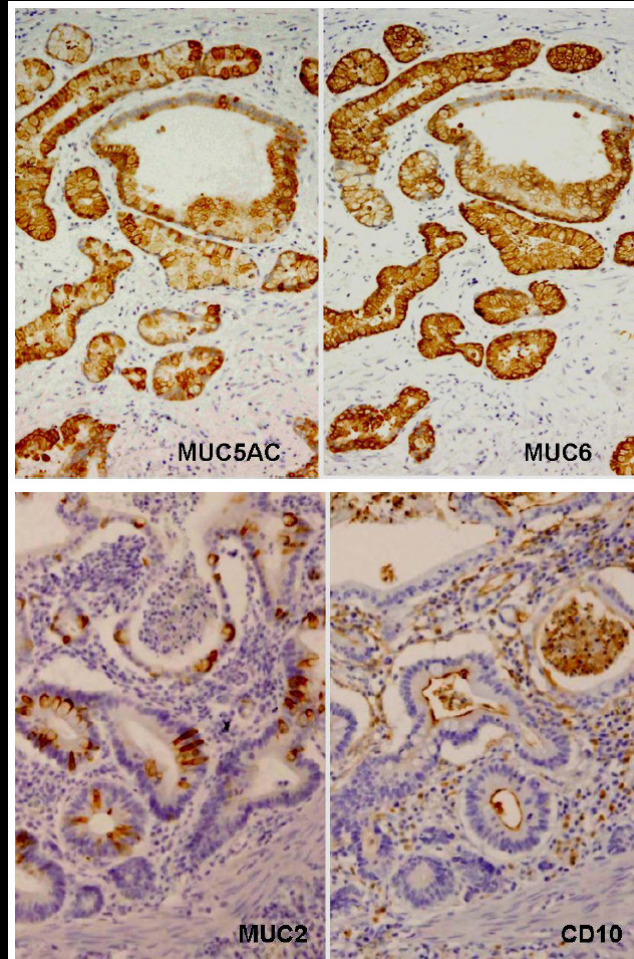
Intestinal



Diffuse



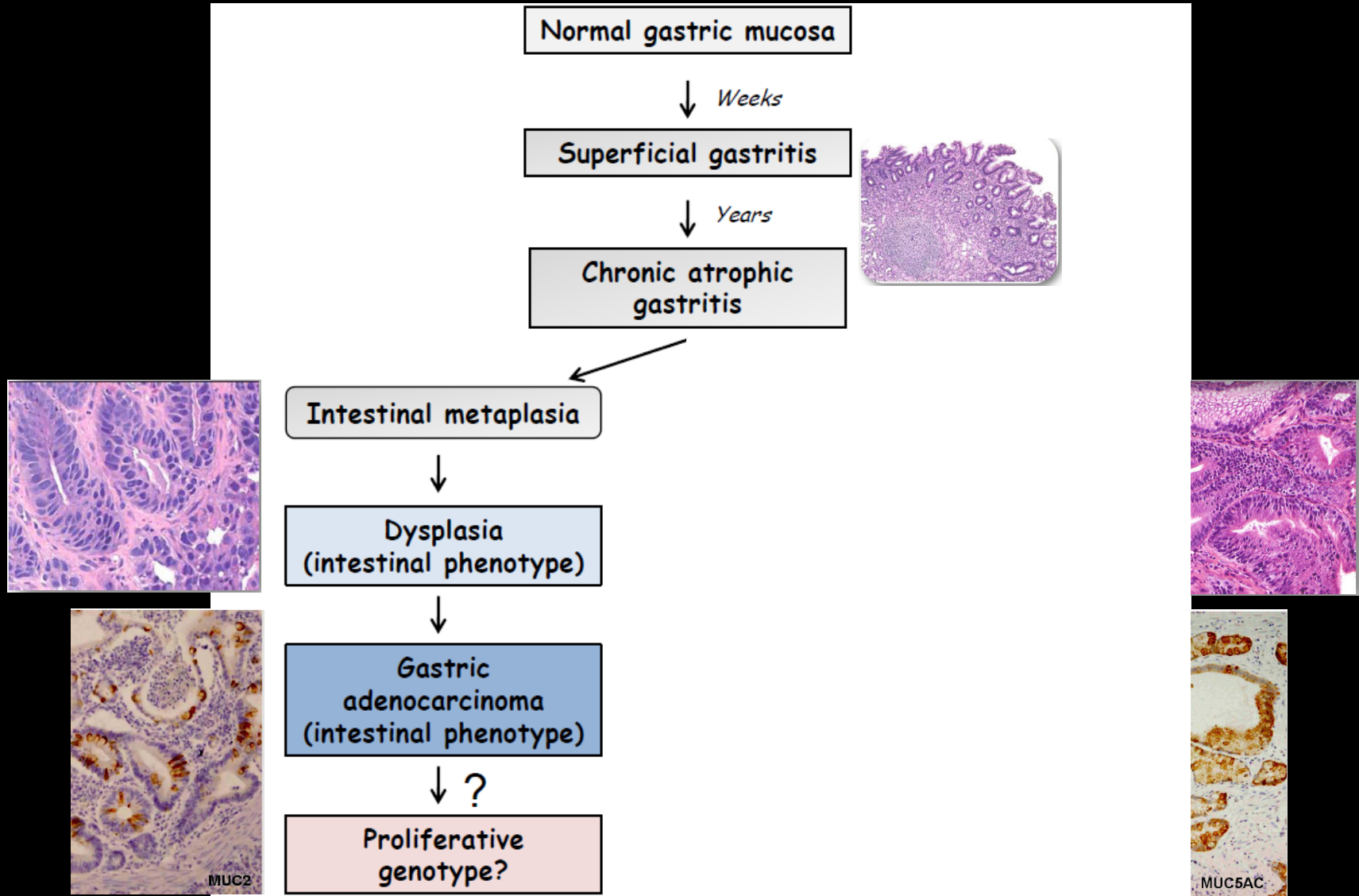
WHO Classification
(2010)



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)

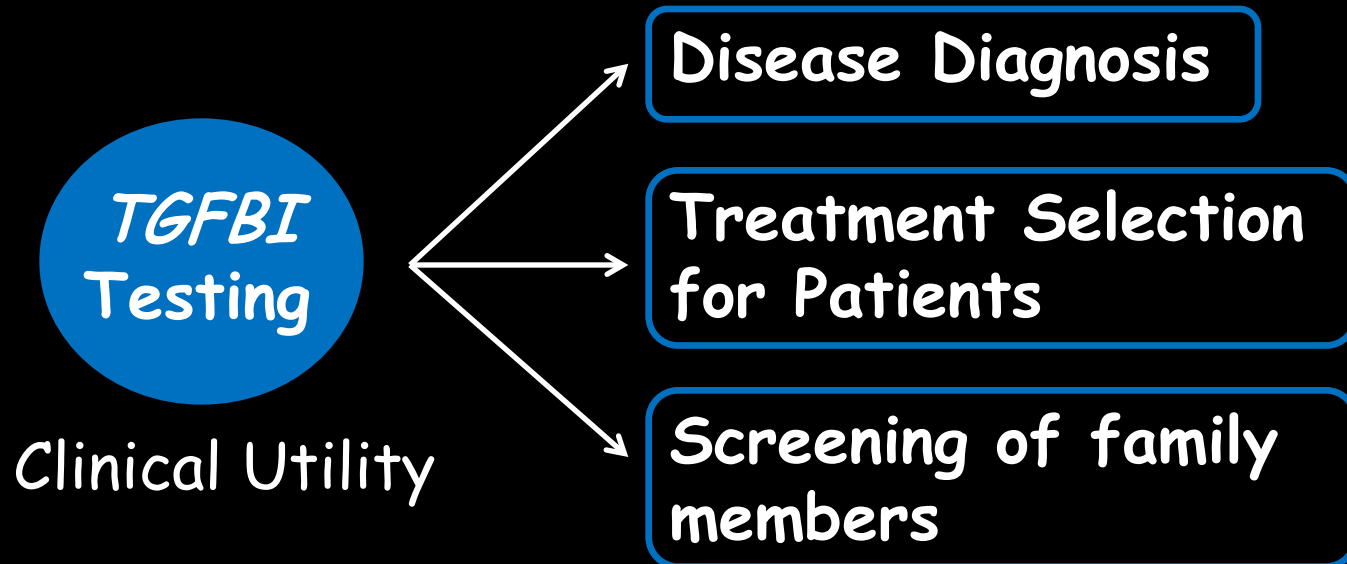
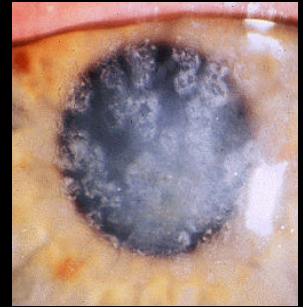
Genomic labs targeting **national certification** in mid 2014 (Illumina + Reflex Validation)

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

Second POLARIS Test - **90 gene GI Panel** (3rd 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



SINGAPORE EYE RESEARCH INSTITUTE



SNEC/SGH

- Patients & Consultation
- Test Ordering
- Blood Collection

GIS/SERI

- Project Management
- Mutation Database

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

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