

Molecular Subtypes of Gastric Cancer and Therapeutic Implications

Patrick Tan, MD PhD

gmstanp@duke-nus.edu.sg

Duke-NUS Graduate Medical School Singapore

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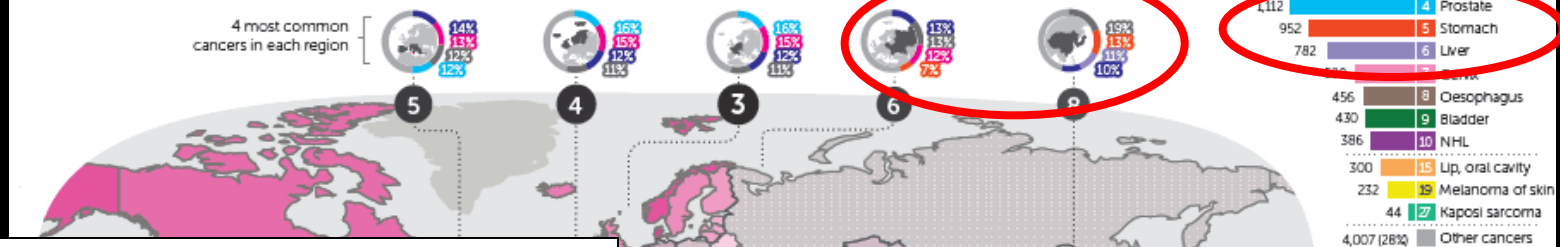
DISCLOSURE SLIDE

- ◆ No Financial Disclosures (Patrick Tan)

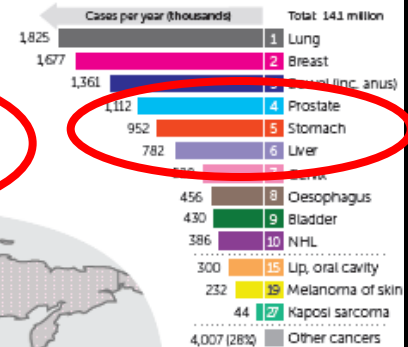
Gastric Cancer : World's 5th Most Common Cancer and 3rd Leading Cause of Cancer Death

Worldwide Cancer Incidence

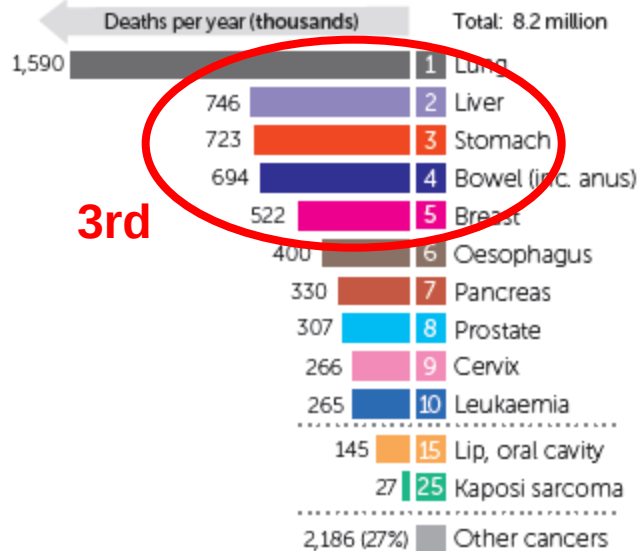
An estimated 14.1 million adults in the world were diagnosed with cancer in 2012. These cases were not spread evenly across the globe and the reliability of cancer statistics available for each country varies.



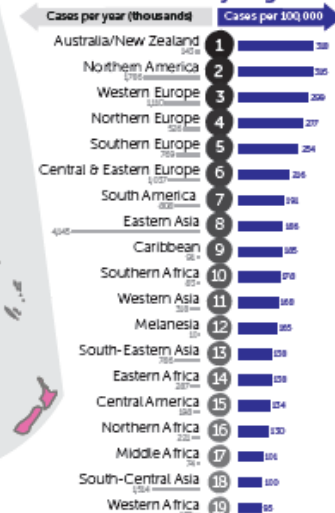
Most Common Cancers Worldwide



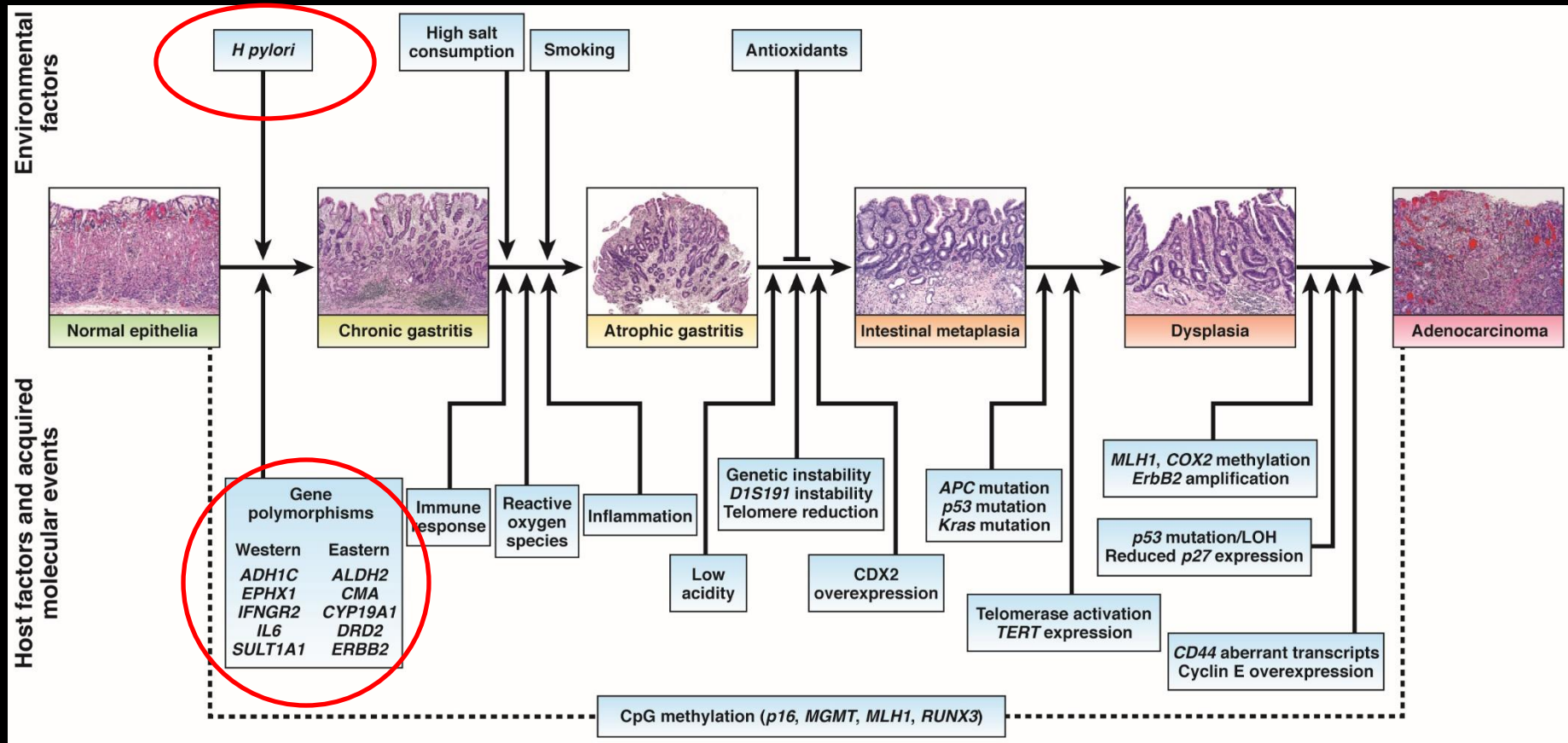
Most Common Causes of Cancer Death



Cancer Incidence by Region

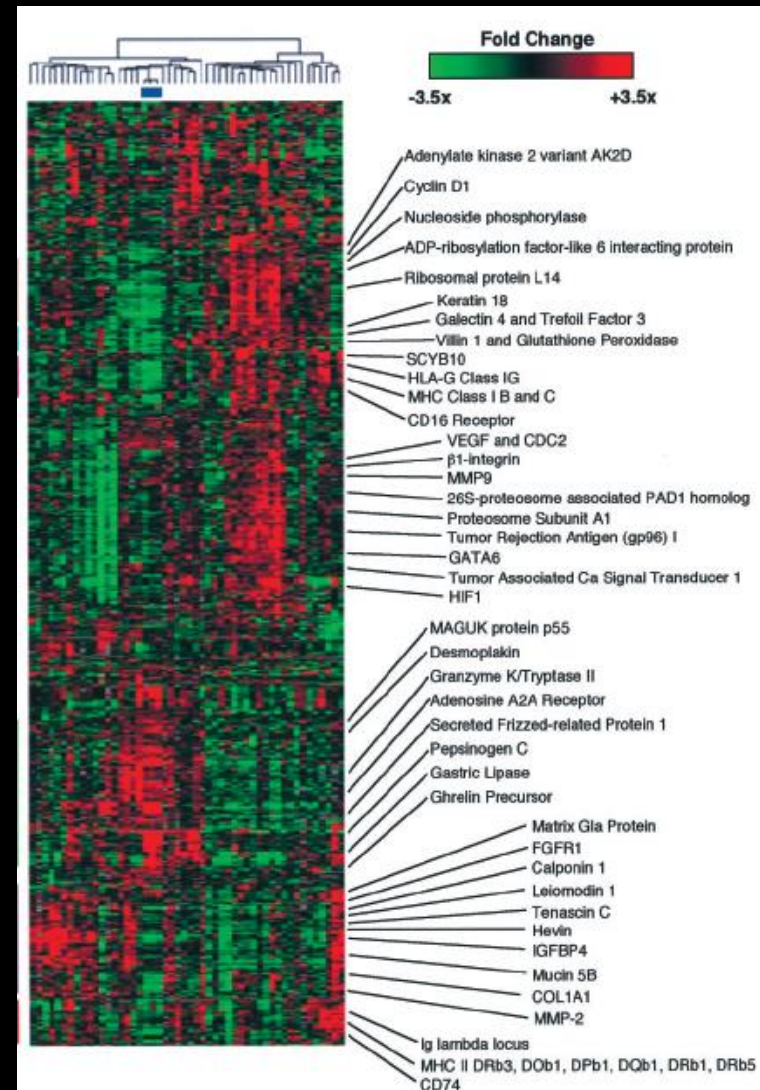
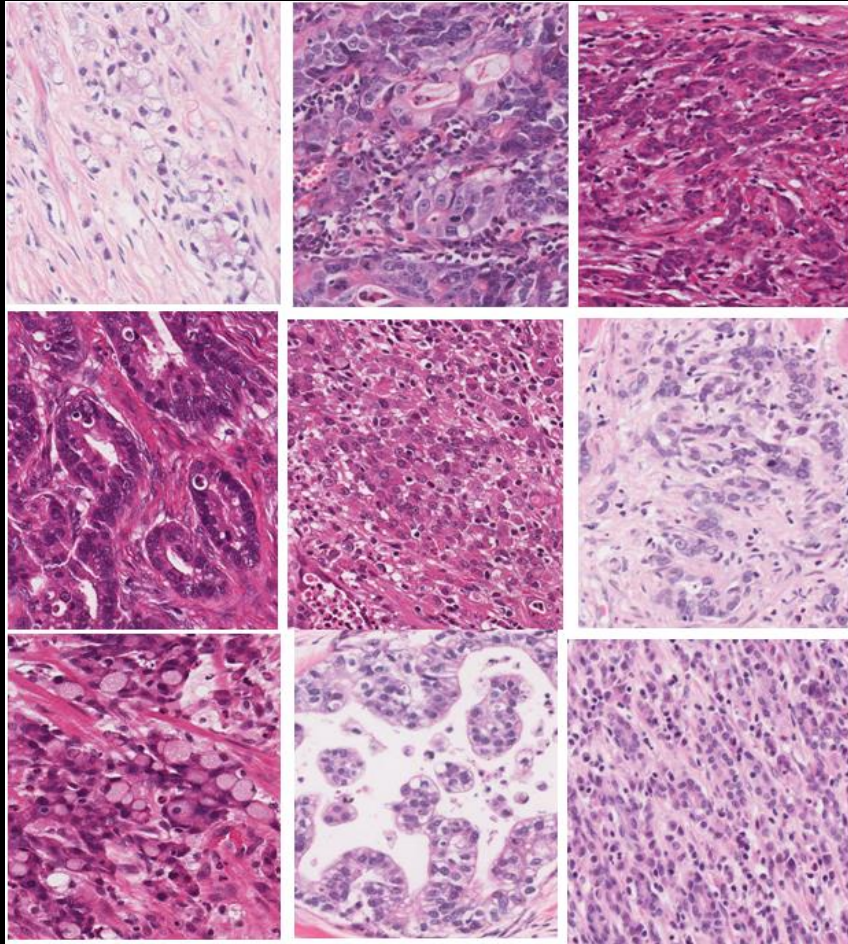


Gastric Cancer Pathogenesis : Interplay Between Environmental and Host Factors



Yeoh and Tan (2015) *Gastroenterology*
 Chia and Tan (2016) *Annals of Oncology*

Molecular and Clinical Heterogeneity in Gastric Cancer (GC)

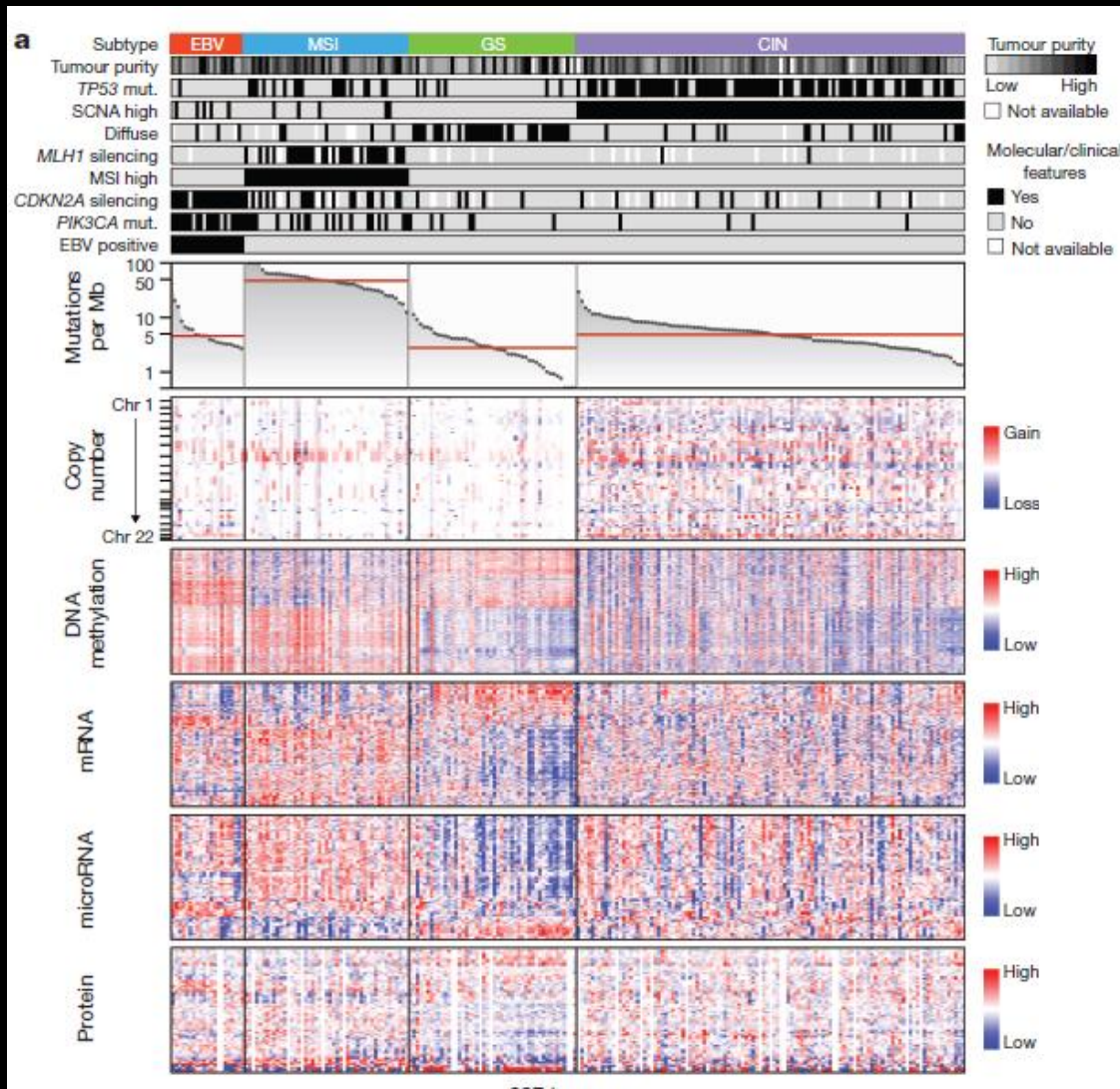


Tay et al., (2003) *Cancer Research*

Can Genomics Improve Gastric Cancer Patient Outcomes?

- 1) Recent Progress in Molecular Subtyping of GC
 - *TCGA and ACRG Studies*
- 2) Molecular factors driving treatment response/resistance?
 - *Gene Amplification*
 - *Within-Tumor Heterogeneity*

TCGA Study (~3-4 Major GC Genomic Subtypes)



A) Chromosomal Instability (CIN)

B) Microsatellite Instability (MSI)

C) Genome Stable (GS)

D) Epstein-Barr Virus (EBV)

GC Genomic Subtypes Show Distinct Molecular and Pathological Characteristics

Chromosomal Instability (CIN) (50%)

- Intestinal-type GCs
- *TP53* mutations
- Focal somatic gene amplifications in RTK/RAS genes

Microsatellite Instability (MSI) (20%)

- Intestinal-type GC ***ARID1A*, *CIMP***
- *TGFBR2*, *HLA-B* mutations

Genome Stable (GS) (20%)

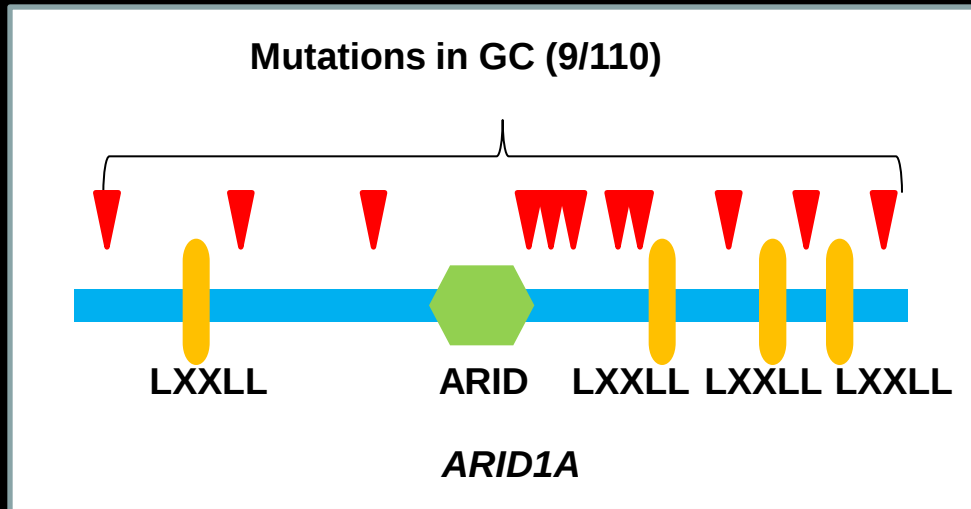
- Diffuse-type GC
- *CDH1*, *RHOA*** mutations

Epstein-Barr Virus (EBV) (10%)

- Global ***ARID1A*, *CIMP*** on
- *PDL-1/2* Gene Amplification**

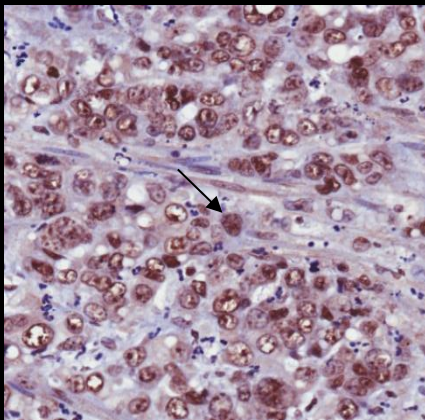
Matsusaka et al(2011)*Cancer Res*
Wang et al(2011) *Nat Genetics*
Zang et al (2012) *Nat Genetics*
Zouridis et al (2012) *Sci Trans Med.*
Wang et al (2014) *Nat Genetics*
Kakiuchi et al (2014)*Nat Genetics*
USA TCGA (2014) *Nature*

GC Somatic Mutations in *ARID1A*, a SWI/SNF-related chromatin remodeling gene

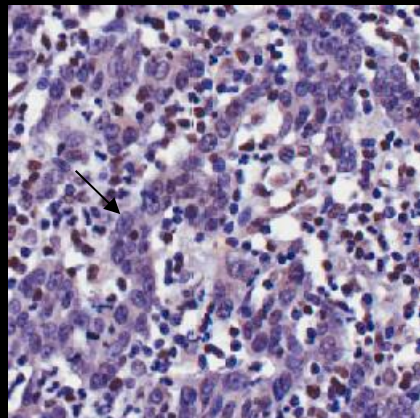


Associated with MSI
and EBV-positive GC

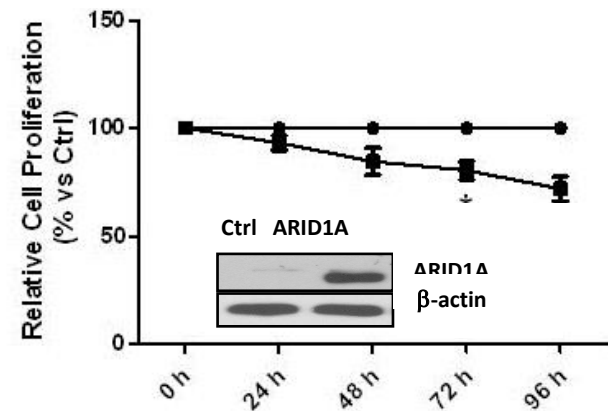
ARID1A (Wild-type)



ARID1A (Mutated)

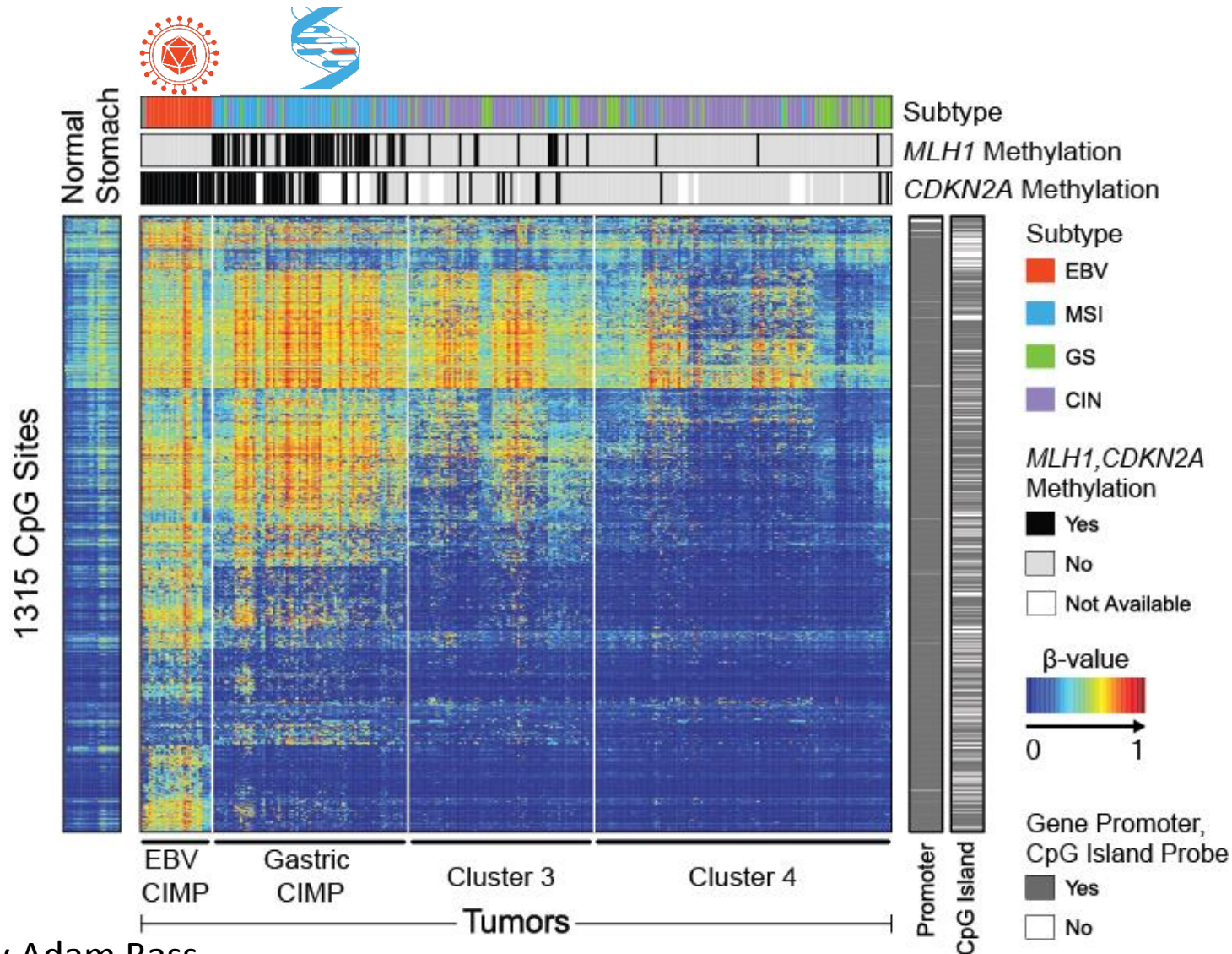


SNU5 (*ARID1A* Deletion)

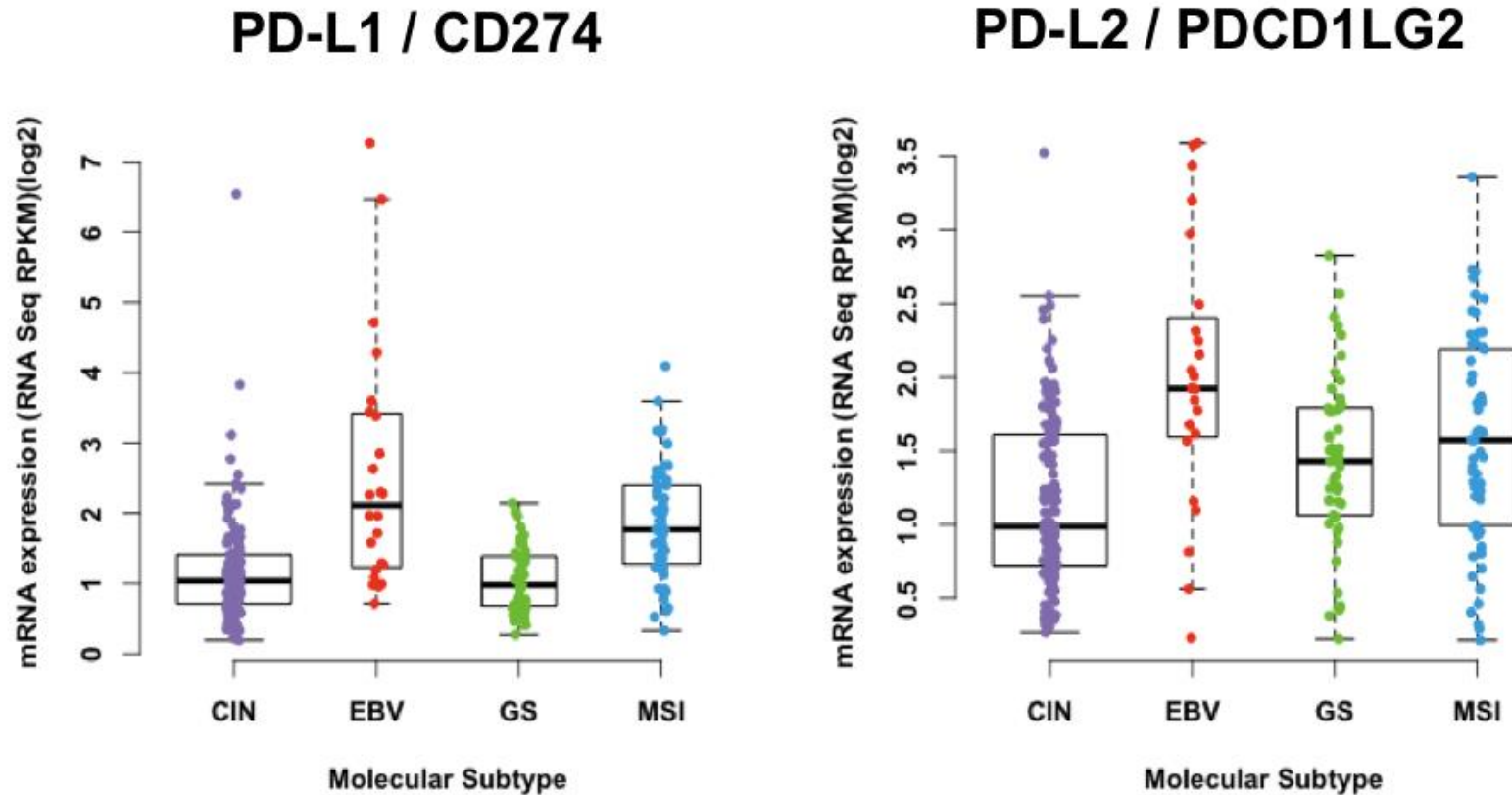


Wang et al., 2011 *Nature Genetics*
Zang et al., 2012 *Nature Genetics*

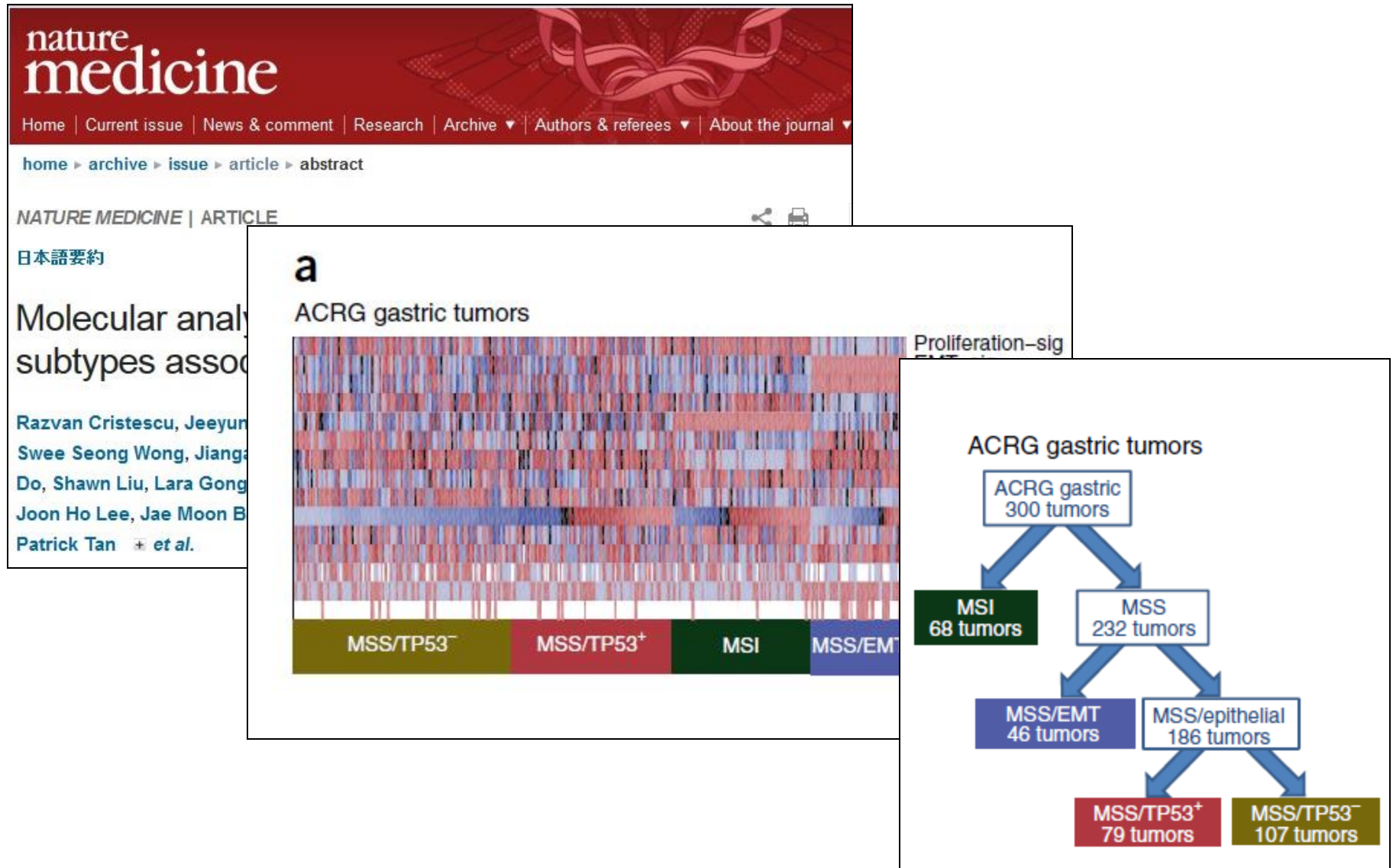
Distinct CIMP Profiles Differentiate EBV+ and MSI+ Gastric Cancer



Elevated PD-L1 and PD-L2 Expression in EBV+ Gastric Cancer



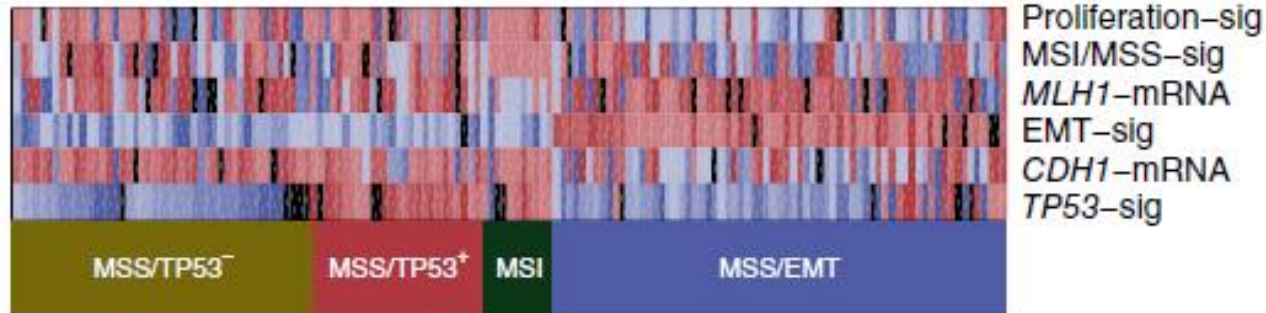
ACRG GC Classification (Samsung, Eli Lilly, Merck, BGI)



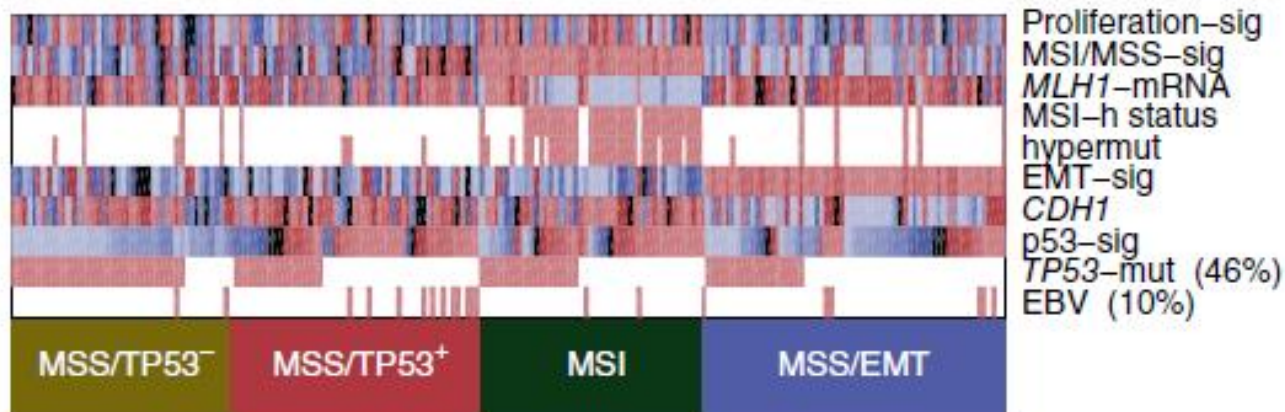
Cristescu, Lee et al., (2015) *Nature Medicine*

ACRG Classification is Applicable to GC datasets where Expression Data is Available

Singapore gastric tumors

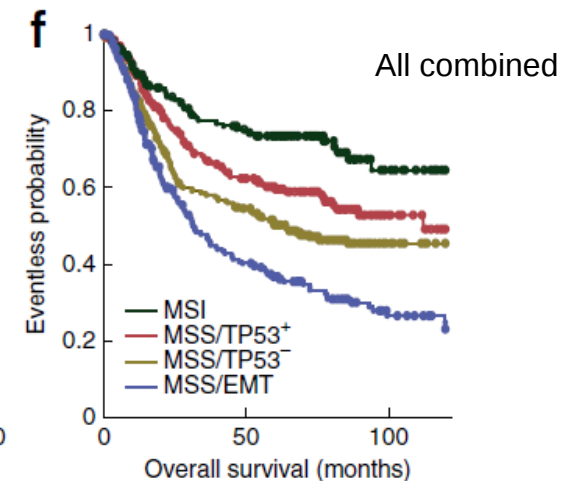
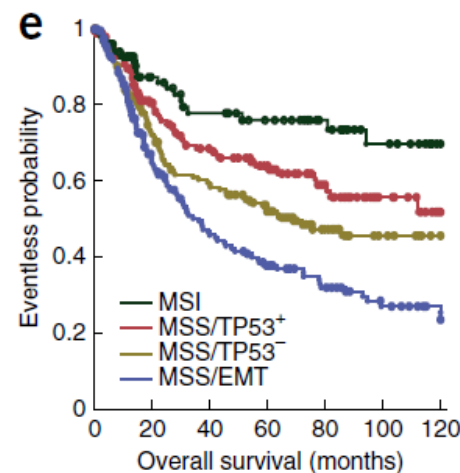
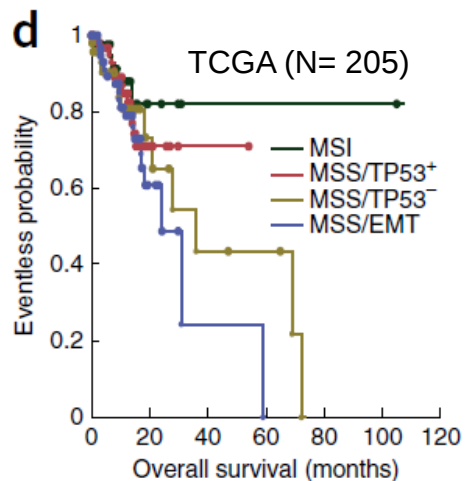
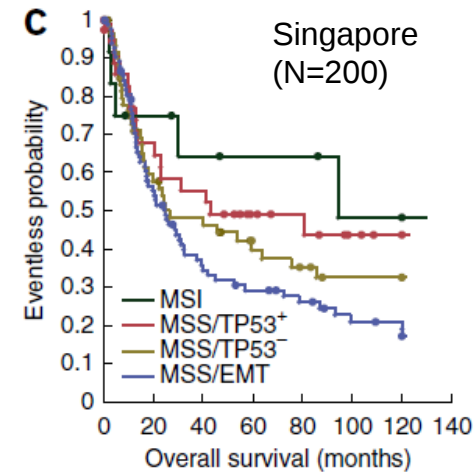
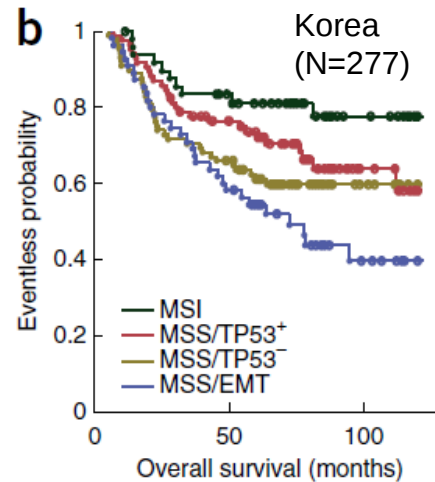
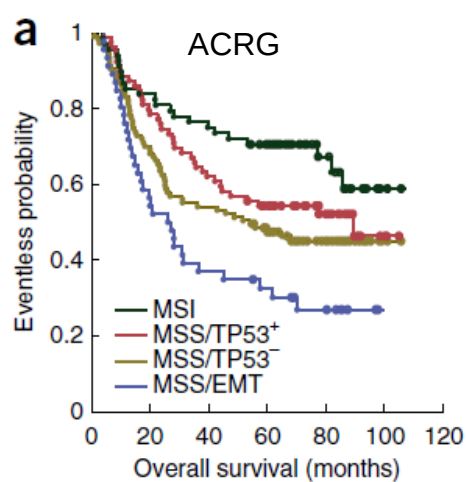


TCGA gastric tumors



Prevalence of ACRG subtypes varies across datasets

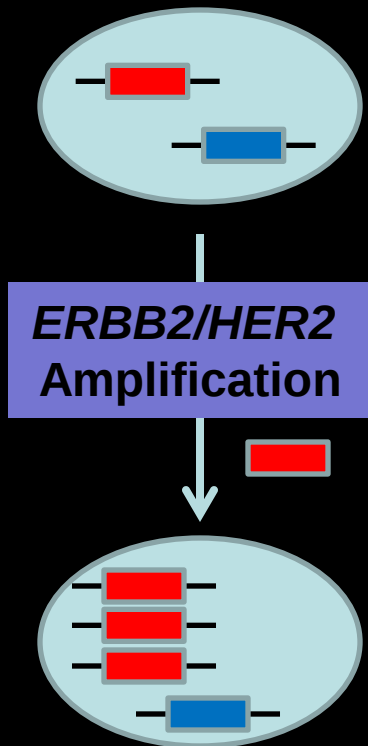
Best prognosis → Worst prognosis
MSI → MSS/TP53⁺ → MSS/TP53⁻ → MSS/EMT



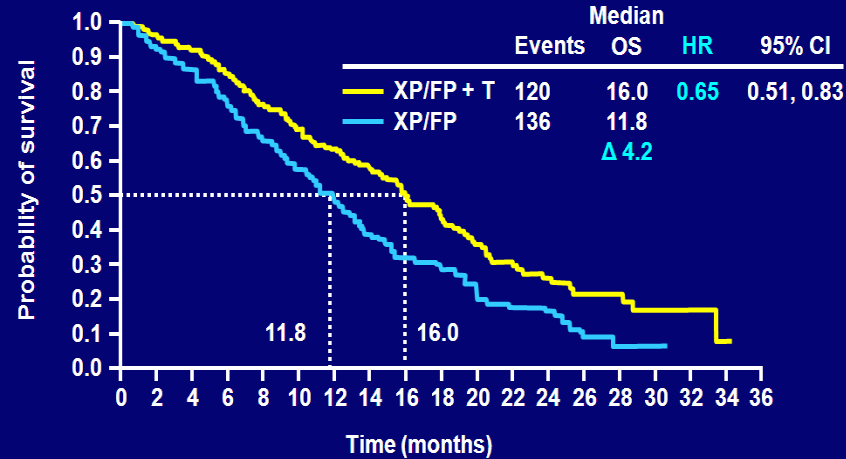
Can Genomics Improve Gastric Cancer Patient Outcomes?

- 1) Recent Progress in Molecular Subtyping of GC
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Targeted Therapies in Gastric Cancer

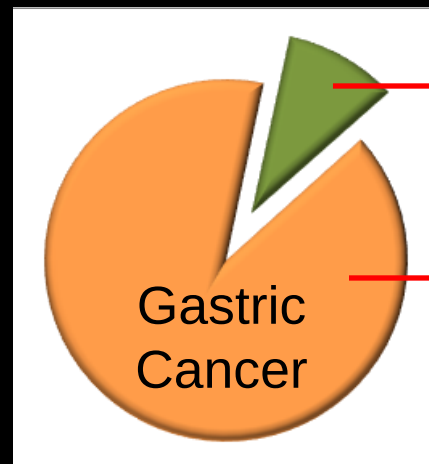


OS in IHC 2+ / FISH+ or IHC 3+
(exploratory analysis)



The TOGA Trial

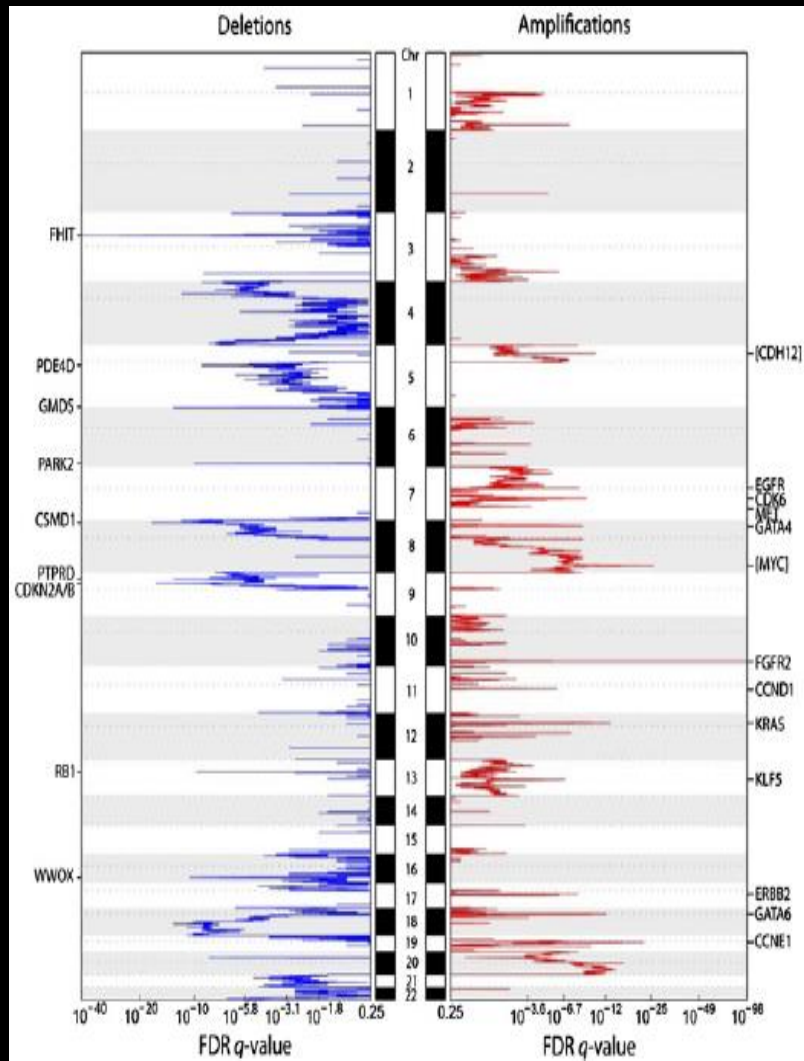
Bang et al (2011) *Lancet*



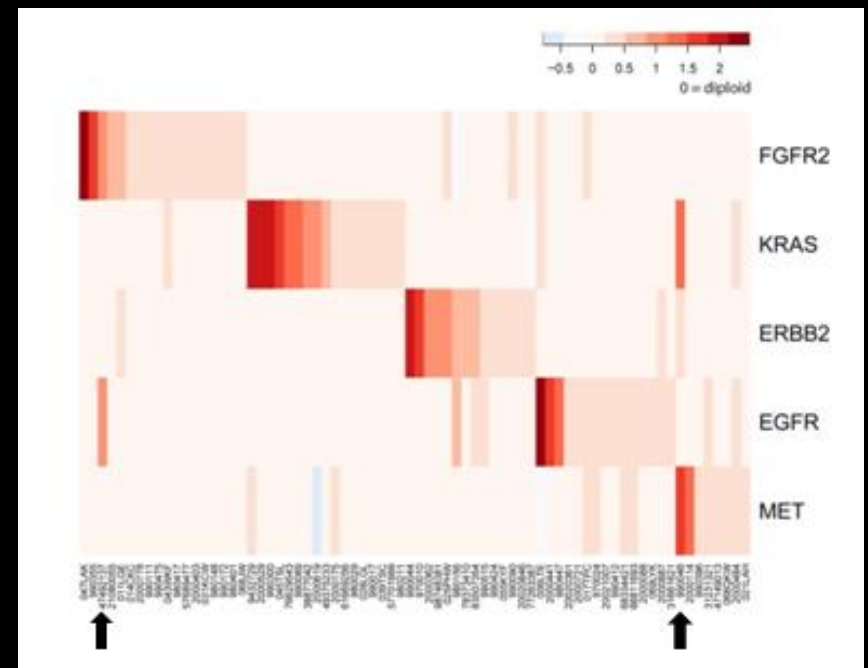
ERBB2 Positive
(8-10%)

?????

Focal Genomic Alterations Highlight Therapeutic Opportunities in GC

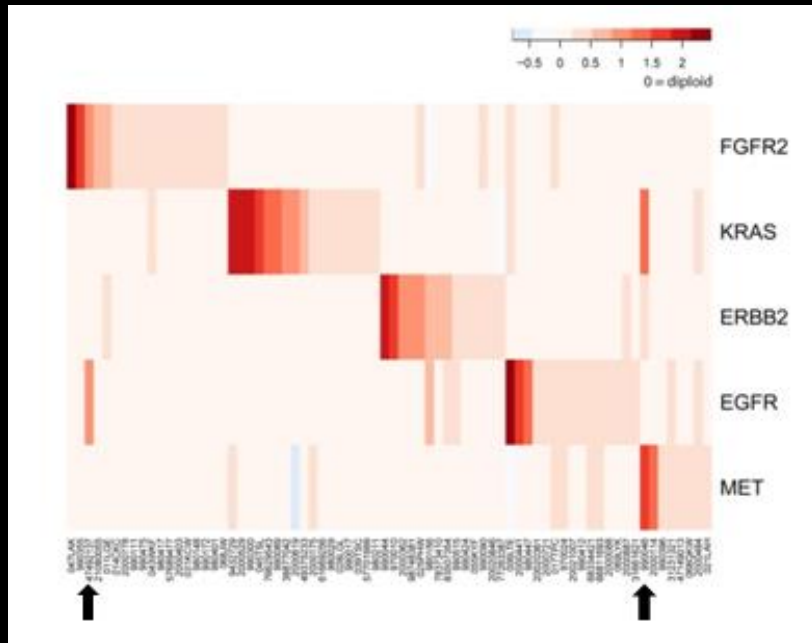


RTK/KRAS Amplifications

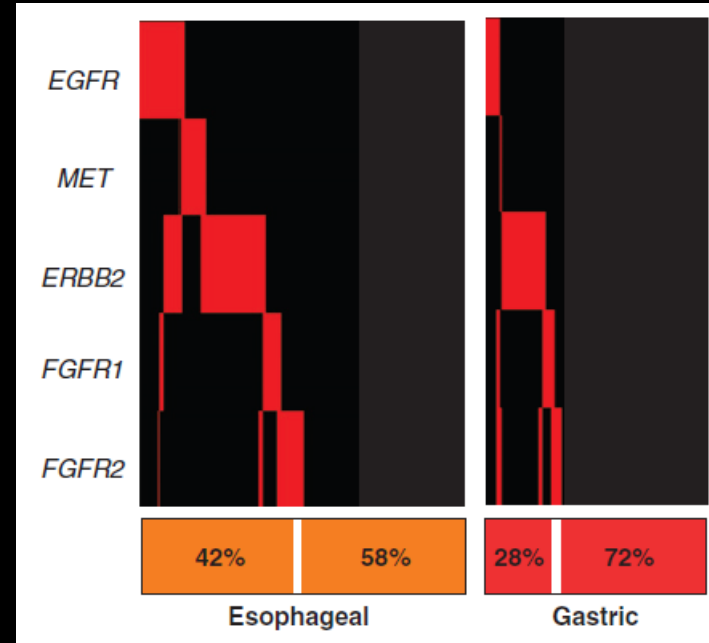


Deng et al., 2012 *Gut*

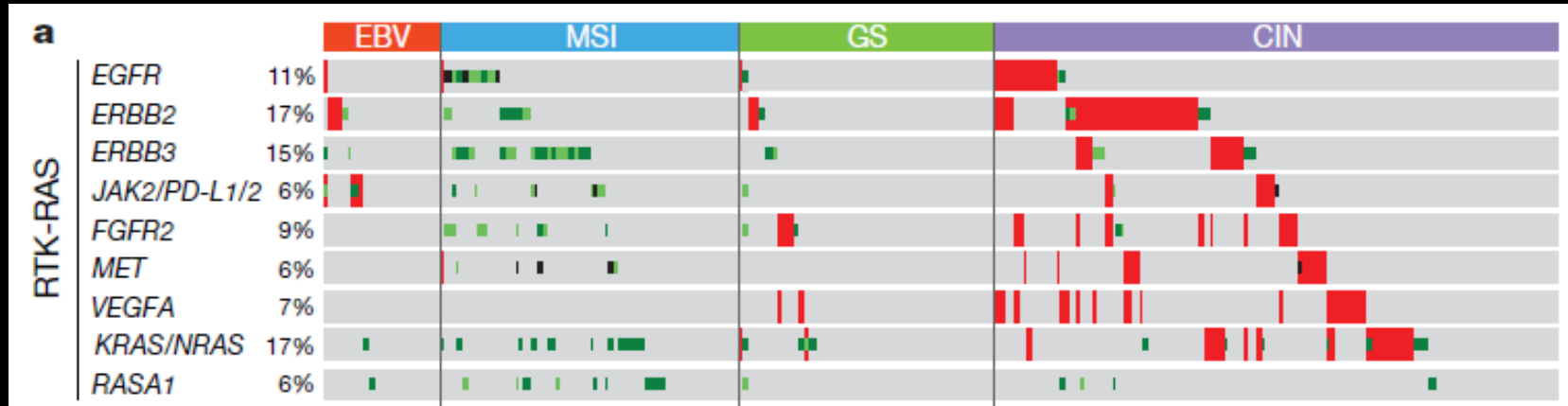
Relationships Between RTK Drivers?



Deng et al., 2012 *Gut*

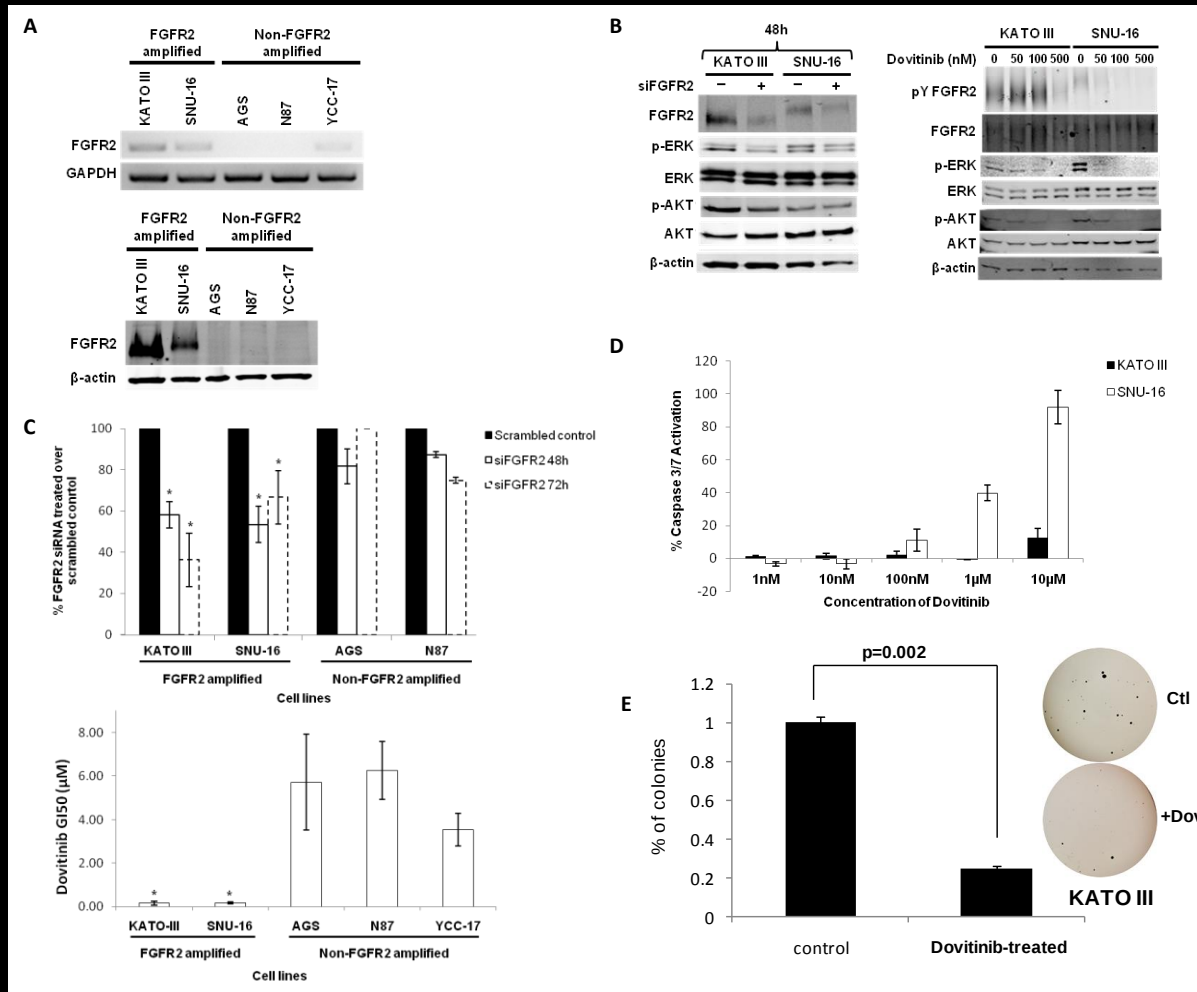


Dulak et al., 2012 *Cancer Research*



USA TCGA, 2014 *Nature*

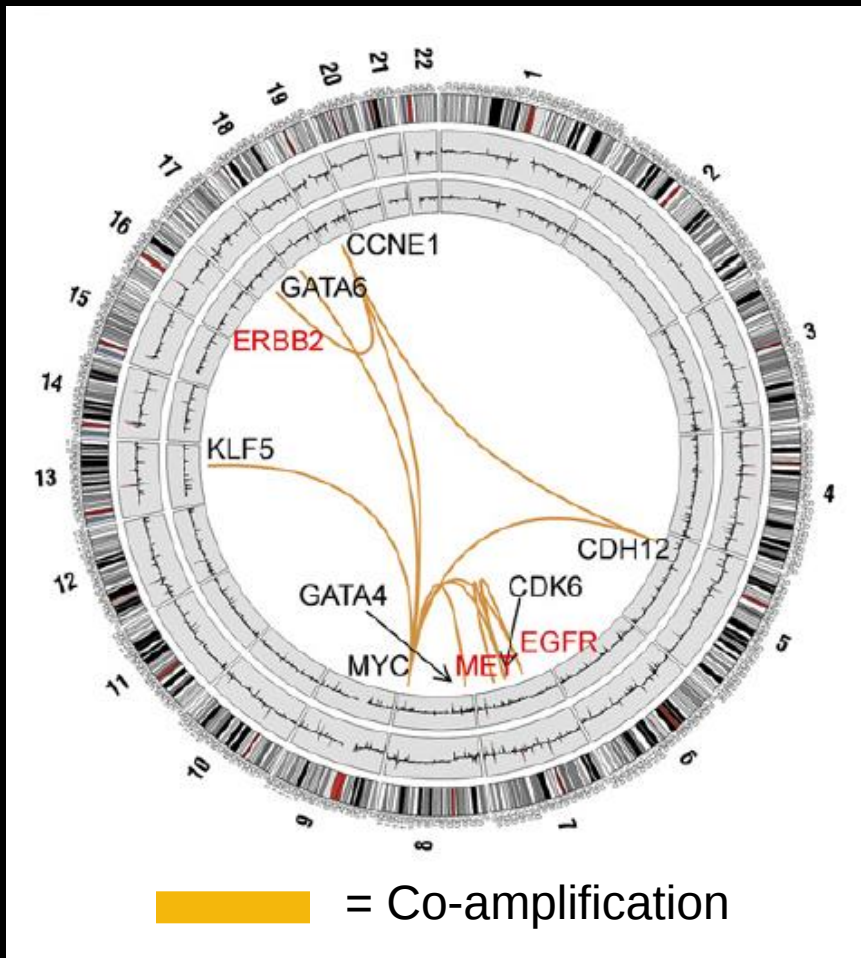
Dovitinib (TKI258) is a Subtype-Specific Therapy for FGFR2-Amplified GCs (Collaboration with Novartis)



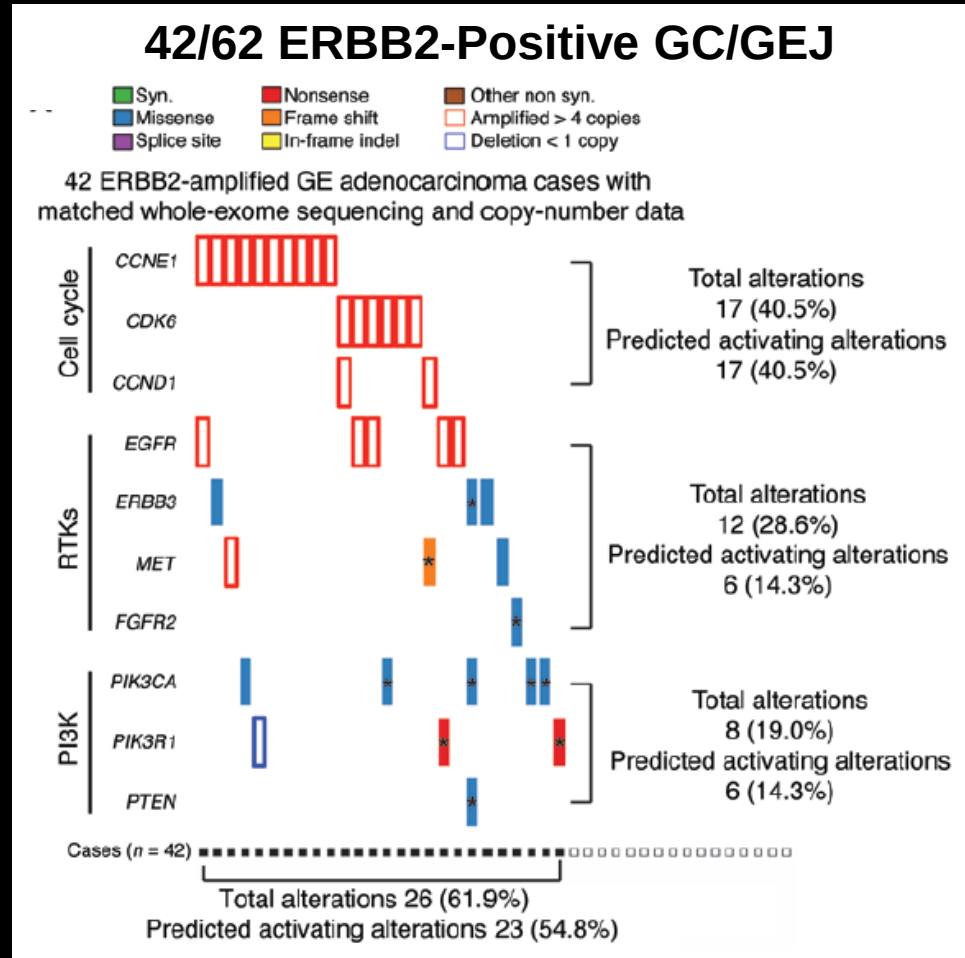
Disappointing Results from Recent RTK-Targeting Trials in GC

RTK	Drug	Result	Reference
HER2/ERBB2	Trastuzumab	Positive	Bang et al., (2011) Lancet
HER2/ERBB2	Lapatinib	Negative	Hecht et al., (2015) JCO
HER2/ERBB2	Trastuzumab Emtansine (TDM1)	Negative	Roche Oct 22 nd 2015
FGFR2	AZD5457	Negative	ASCO 2015
MET	Rilotinumab	Negative	ASCO 2015
MET	Onatuzumab	Negative	ASCO 2015

Co-Occurring Genomic Alterations May Contribute to RTK Resistance

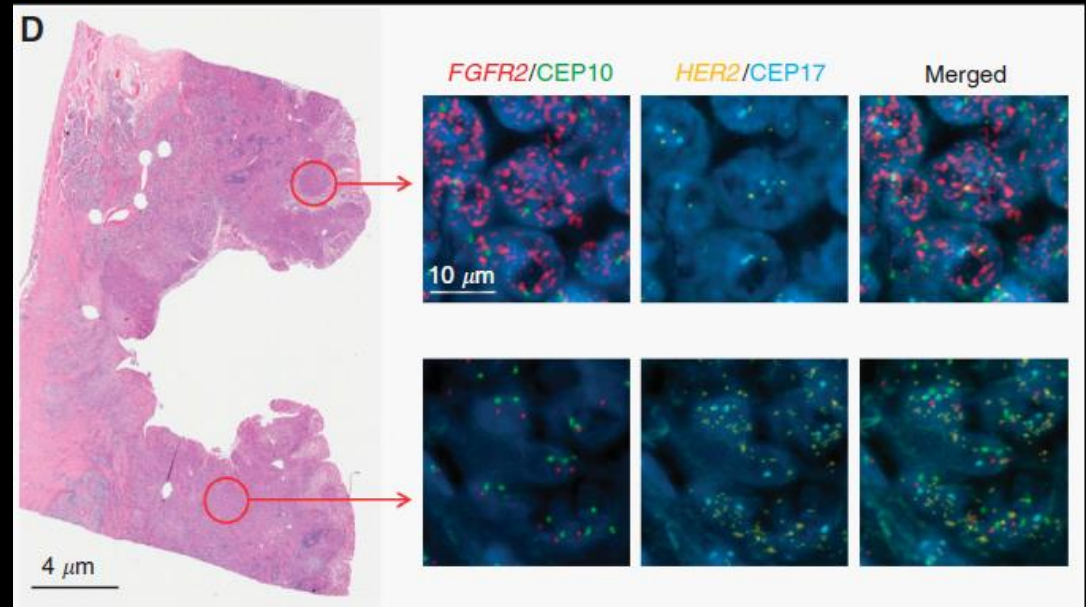
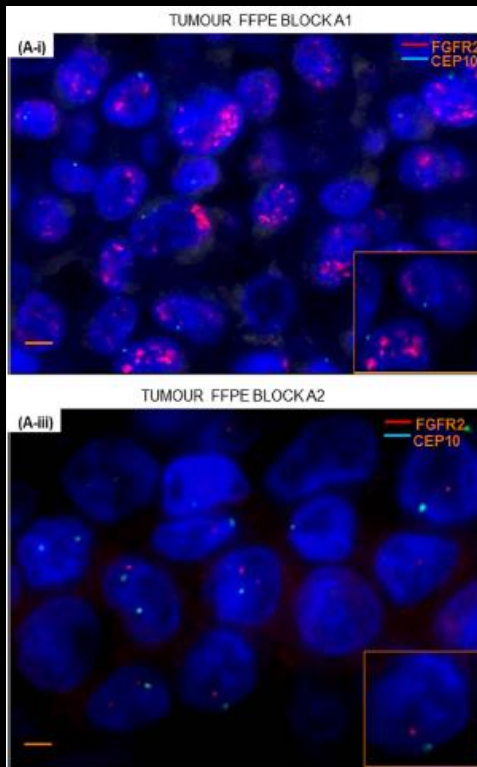


Deng et al., 2012 *Gut*



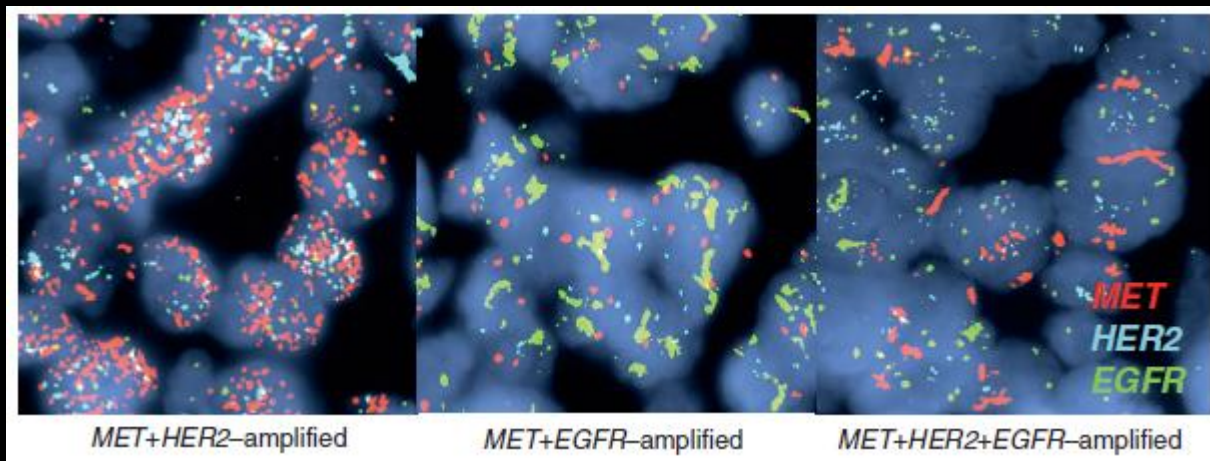
Kim et al., 2014 *JCI*

Intra-Tumoral RTK Heterogeneity in GC



Kilgour et al., 2014 BJC

Das et al., 2015 Cancer Letters

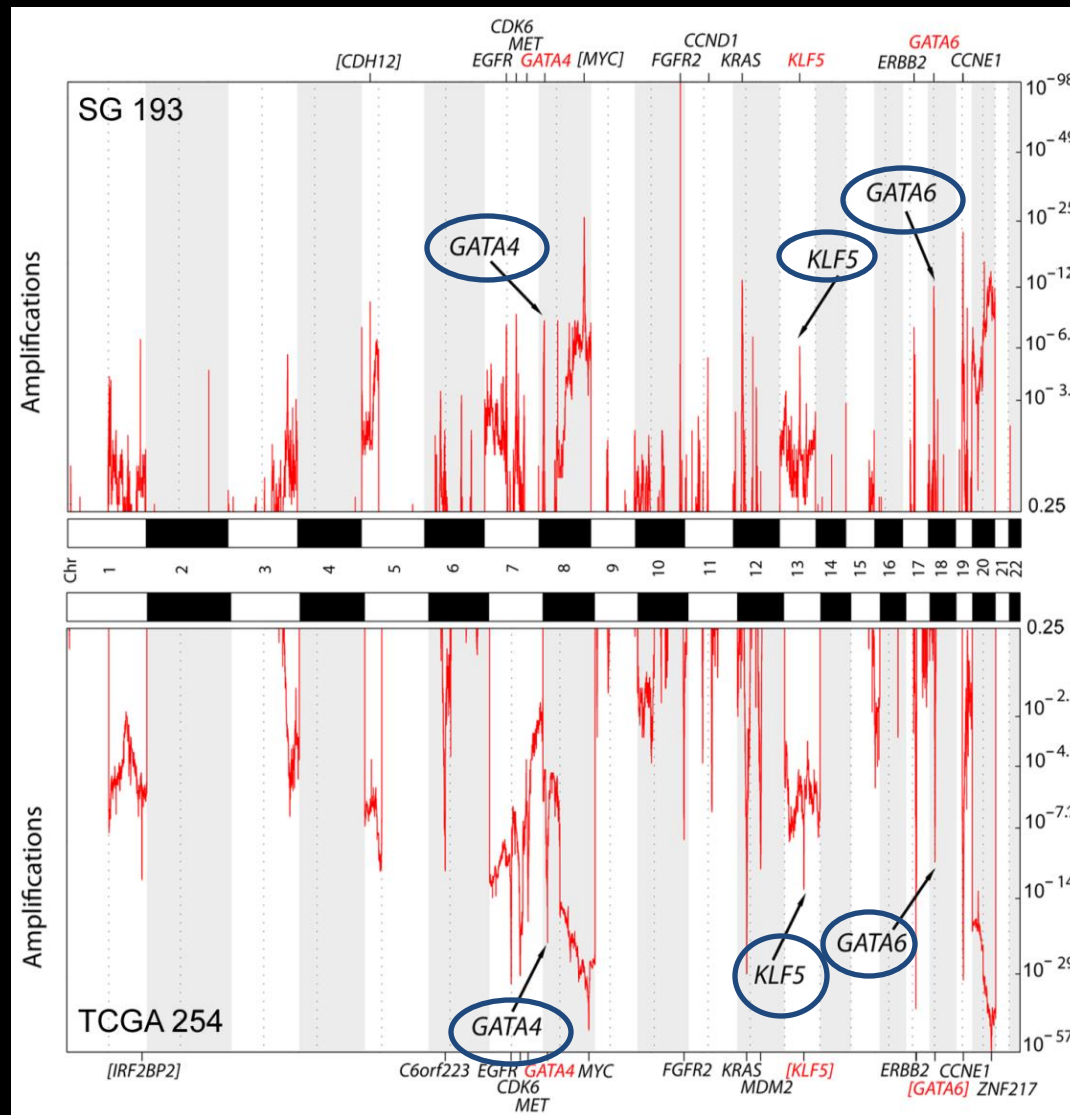


MET-therapy resistant
GC

Kwak et al., 2015
Cancer Discovery

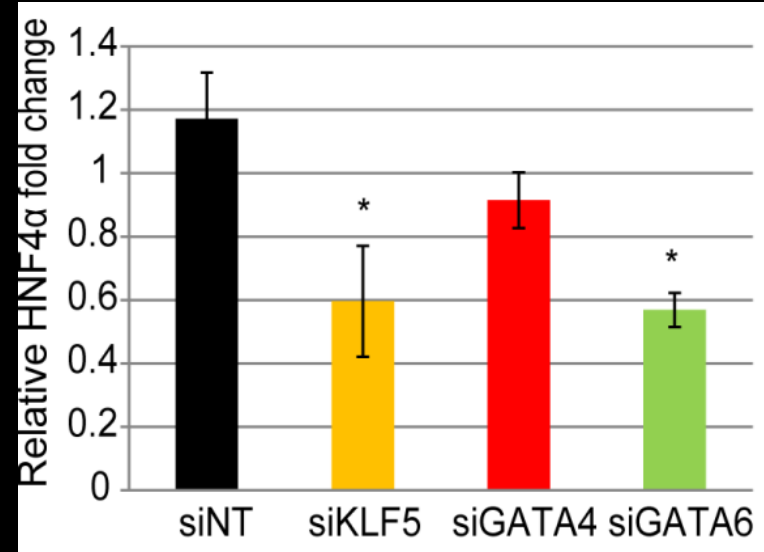
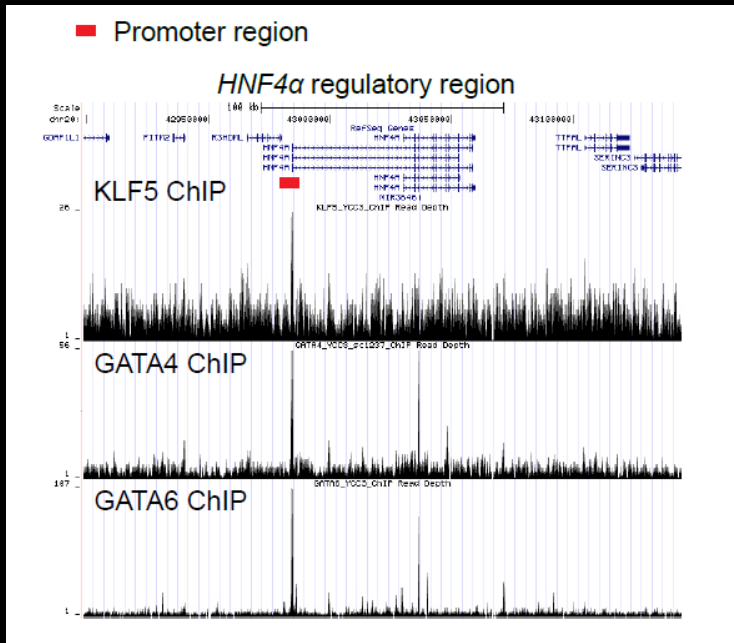
Transcription factors *KLF5*, *GATA4* and *GATA6* are amplified in GC samples

Singapore Cohort
(193 patients)

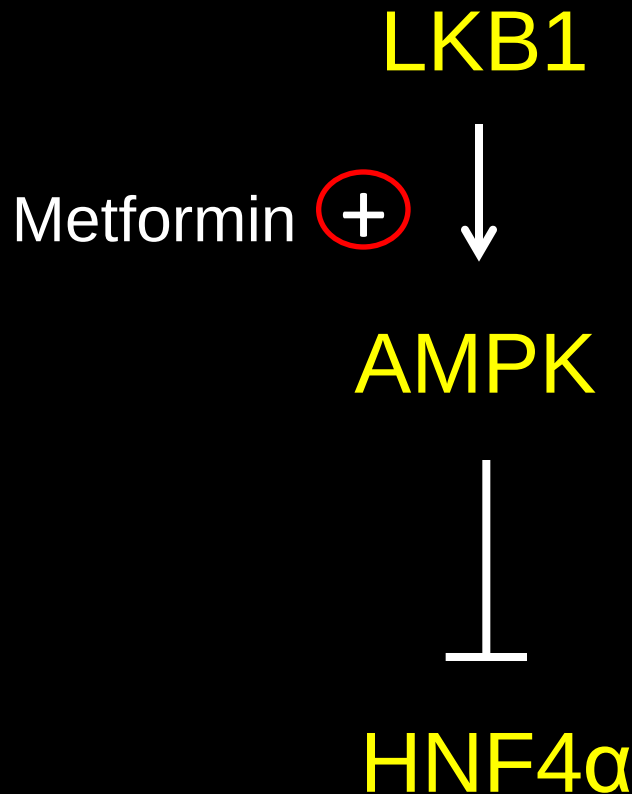


TCGA Cohort
(254 patients)

***HNF4 α* is a Common Downstream Target of KLF5 and GATA Factors**

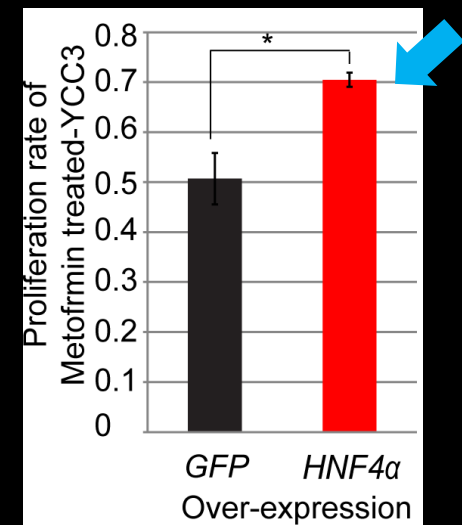
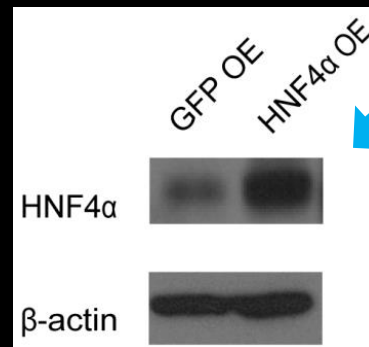
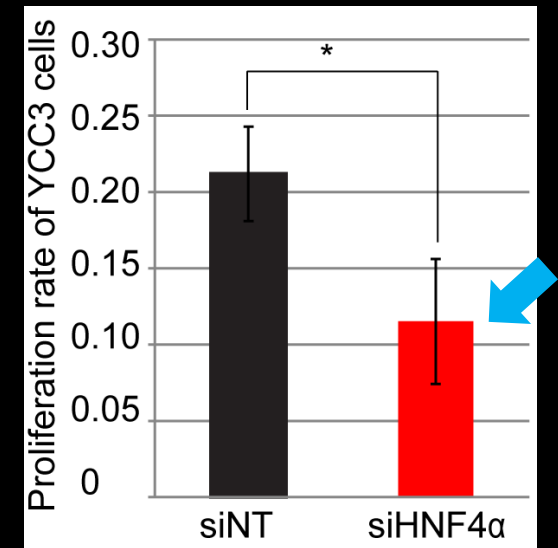
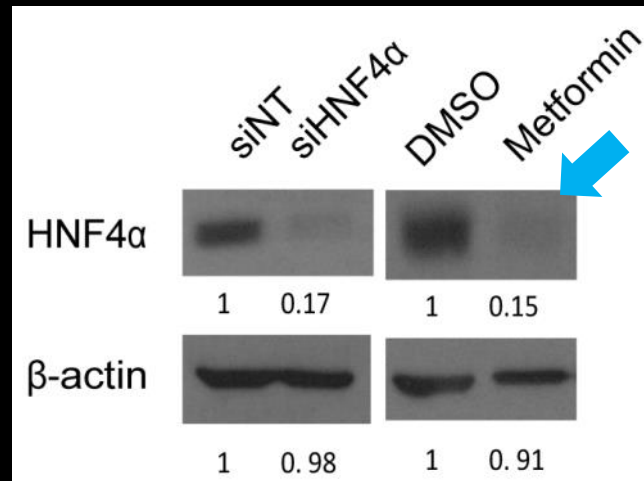
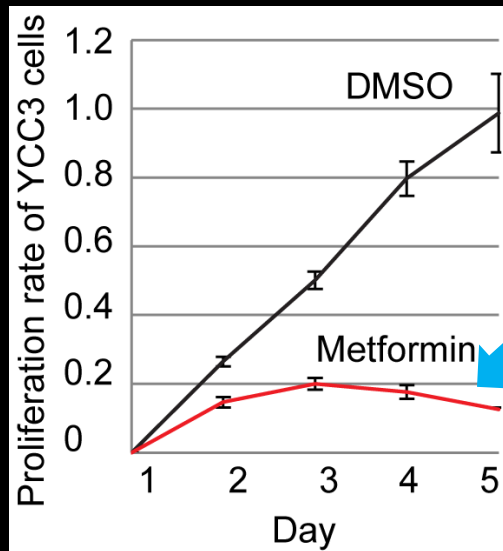


The Anti-diabetic Drug Metformin is a Potential HNF4 α Therapeutic



1. Treatment of type 2 diabetes
2. Poly Cystic Ovarian syndrome.

HNF4α is a potential predictor of Metformin response in GC

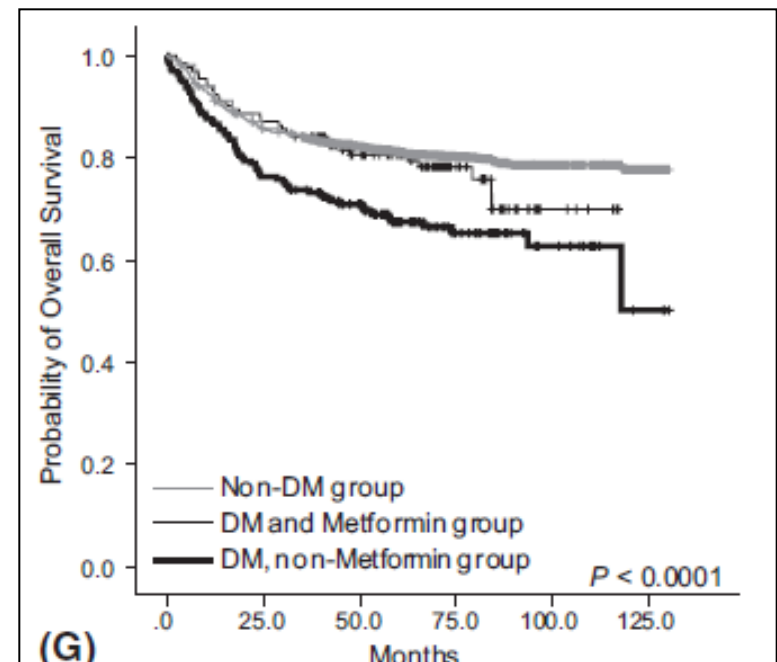
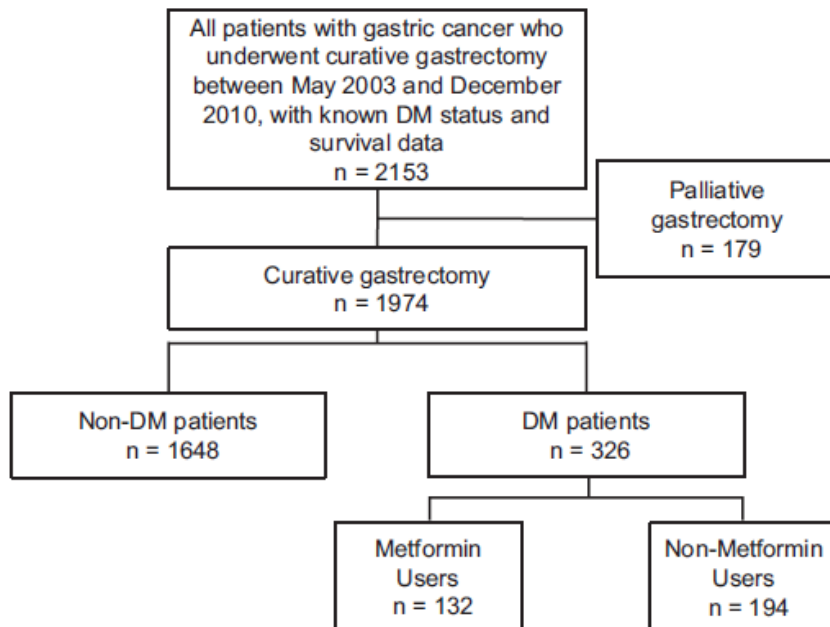


Metformin and GC Recurrence

Cumulative Metformin Use and Its Impact on Survival in Gastric Cancer Patients After Gastrectomy

Choong-kun Lee, MD, Minkyu Jung, MD,* Inkyung Jung, PhD,† Su Jin Heo, MD,* Yong Hyu Jeong, MD,‡
Ji Yeong An, MD, PhD,§ Hyoung-Il Kim, MD,§ Jae-Ho Cheong, MD, PhD,§ Woo Jin Hyung, MD, PhD,§
Sung Hoon Noh, MD, PhD,§ Hyo Song Kim, MD,* Sun Young Rha, MD, PhD,* and
Hyun Cheol Chung, MD, PhD**

Lee et al., 2016 *Annals of Surgery*



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Gek San Tan

Wei Keat Wan

Willie Yu

Anna Gan

Angie Lay Keng Tan

Su-Ting Tay

Masafumi Muratani

Wen Fong Ooi

Manjie Xing

Chang Xu

Aditi Qamra

Simeen Malik

Huihoon Chua

Wai Keong Wong

London Lucien Ooi

Pierce Chow

Khee Chee Soo

Liang Kee Goh

Qiang Yu

Huck Hui Ng

Liang Kee Goh

Qiang Yu

Huck Hui Ng

Teh Bin Tean

Steve Rozen

Yong Wei Peng

Yoshiaki Ito

Yeoh Khay Guan

