Unraveling the Taxonomy in Gastric Cancer

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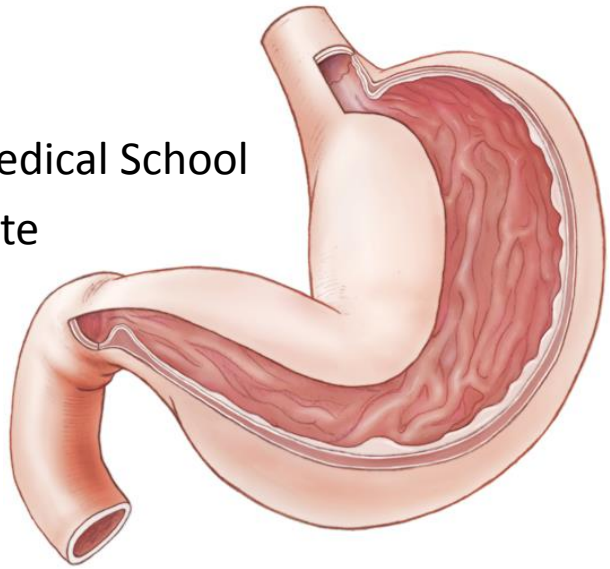

ESMO World Congress
On Gastrointestinal Cancer
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DANA-FARBER CANCER INSTITUTE

BROAD INSTITUTE

Disclosure

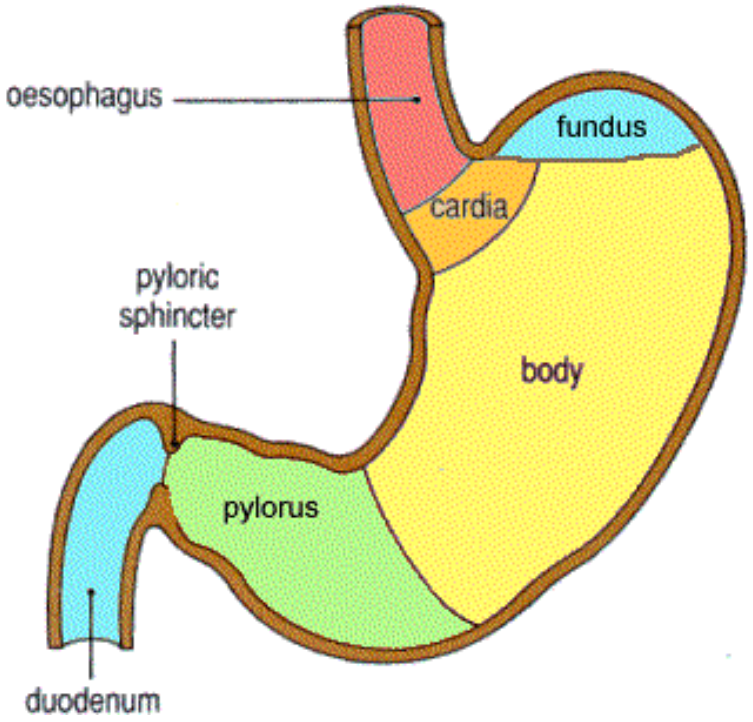
- Research Funding from Sanofi, Onkaido
- Member of SAB for Strand Life Sciences
- Consultant for Eli Lilly

Key Steps For Defining Targets/Strategies For Gastric and Gastroesophageal Cancer

- Definition of basic disease pathophysiology
  - Identifying rational subtypes
  - Finding candidate dependencies in these tumors
    - Linking dependencies with biomarkers
- Going beyond ‘The right drug for the right patient’
  - Ultimately, developing rational combination therapy for distinct classes of disease

Gastric Adenocarcinoma: What Disease are We Trying to Treat?

- Histologic
  - Intestinal vs Diffuse
- Anatomic
  - GEJ vs body vs pylorus
- Geographic
  - East vs West
- Molecular
  - MSI vs MSS, ERBB2+…..



Gastric Adenocarcinoma: What Disease are We Trying to Treat?

- Histologic
  - Intestinal vs Diffuse

A diseased recognized to be heterogeneous, but one were we have largely applied a ‘one-size fits all’ approach to therapy

  - MSI vs MSS, ERBB2+…..

Dealing with the Taxonomy of Gastric and Esophageal Cancer

- We have Esophageal SCC, Esophageal Adeno, 'GE Junction' Adeno, Gastric Adeno (with subtypes!)
- Debates include:
  - Are EAC and Gastric AdenoCA different or same?
  - Should we lump GEJ with Gastric or Esophageal?
  - Now that we have new Gastric Subgroups:
    - Does this explain East/West differences?
    - Does this inform the Esophagus vs. Stomach debate

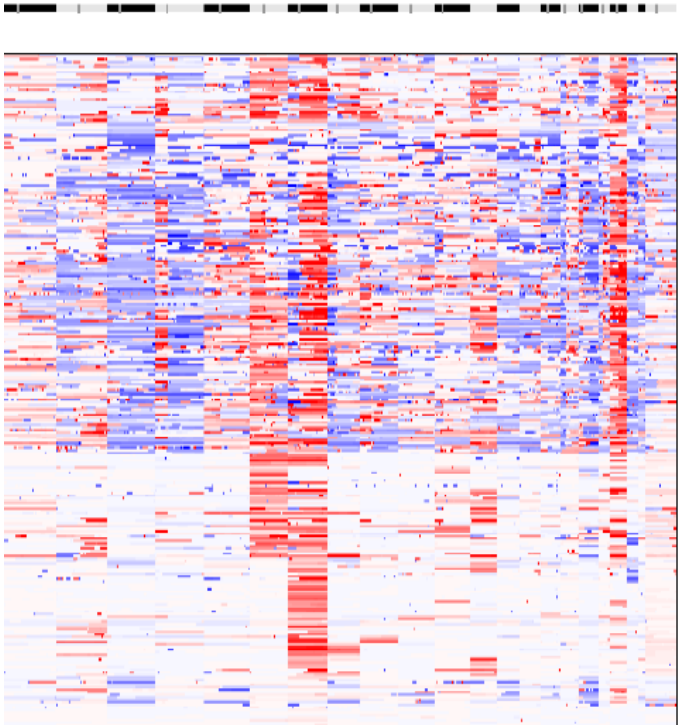
The Cancer Genome Atlas

- Comprehensive molecular/genomic annotation of high-quality frozen tumors without prior neoadjuvant care
  - Samples collected from lots of different hospitals across the world, so clinical data are imperfect and treatment is highly variable
  - We lack the numbers and key data for nuanced assessment of treatment and anatomic questions
  - So, this is primarily a means to understand molecular/genomic features of cancers.
- Phase I (published): 295 'gastric' cancers
- Phase II (unpublished): 559 gastroesophageal cancers

Rules Based Classification for Gastric Cancer

- A classification scheme that requires multi-dimensional data and complex analytics is not readily applied to cases outside TCGA
- We wanted a simple/usable classifier
- So we picked 'simple' features that could help stratify tumors in the clinical world
  - This was informed by our detailed molecular clustering, not directly using it.
    - Yes, we lose some information/discriminant ability with a rule-based approach

‘Cluster of Clusters’: Start with assessment of Platform-Level Clustering



TCGA, Nature 2014

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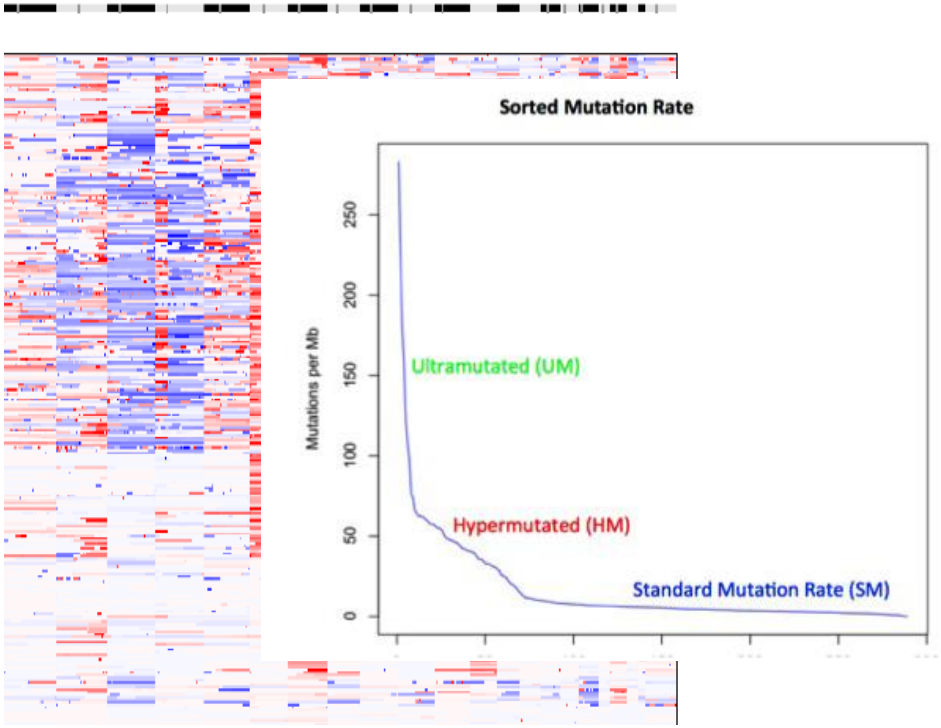

TCGA, Nature 2014

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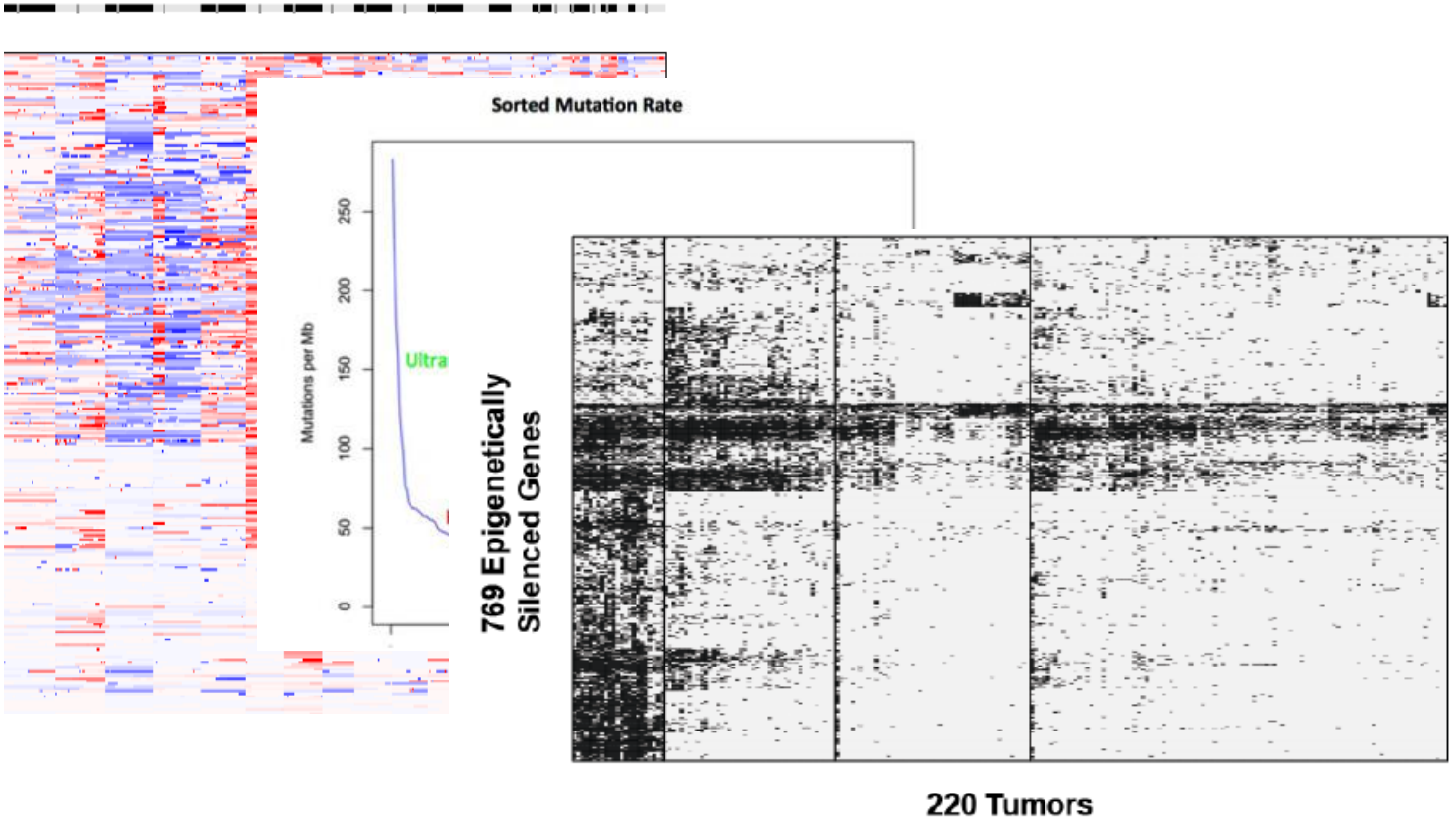

TCGA, Nature 2014

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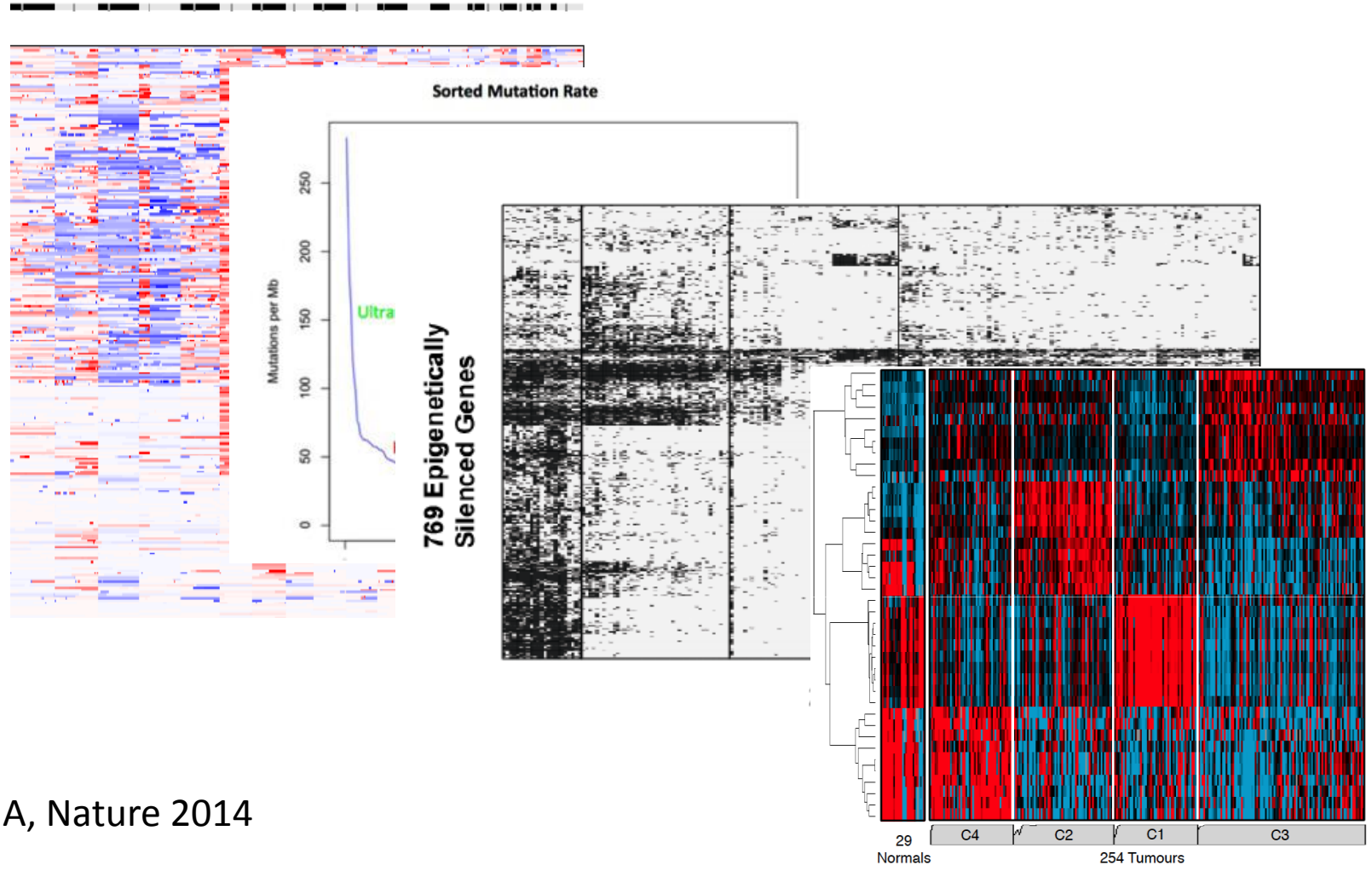
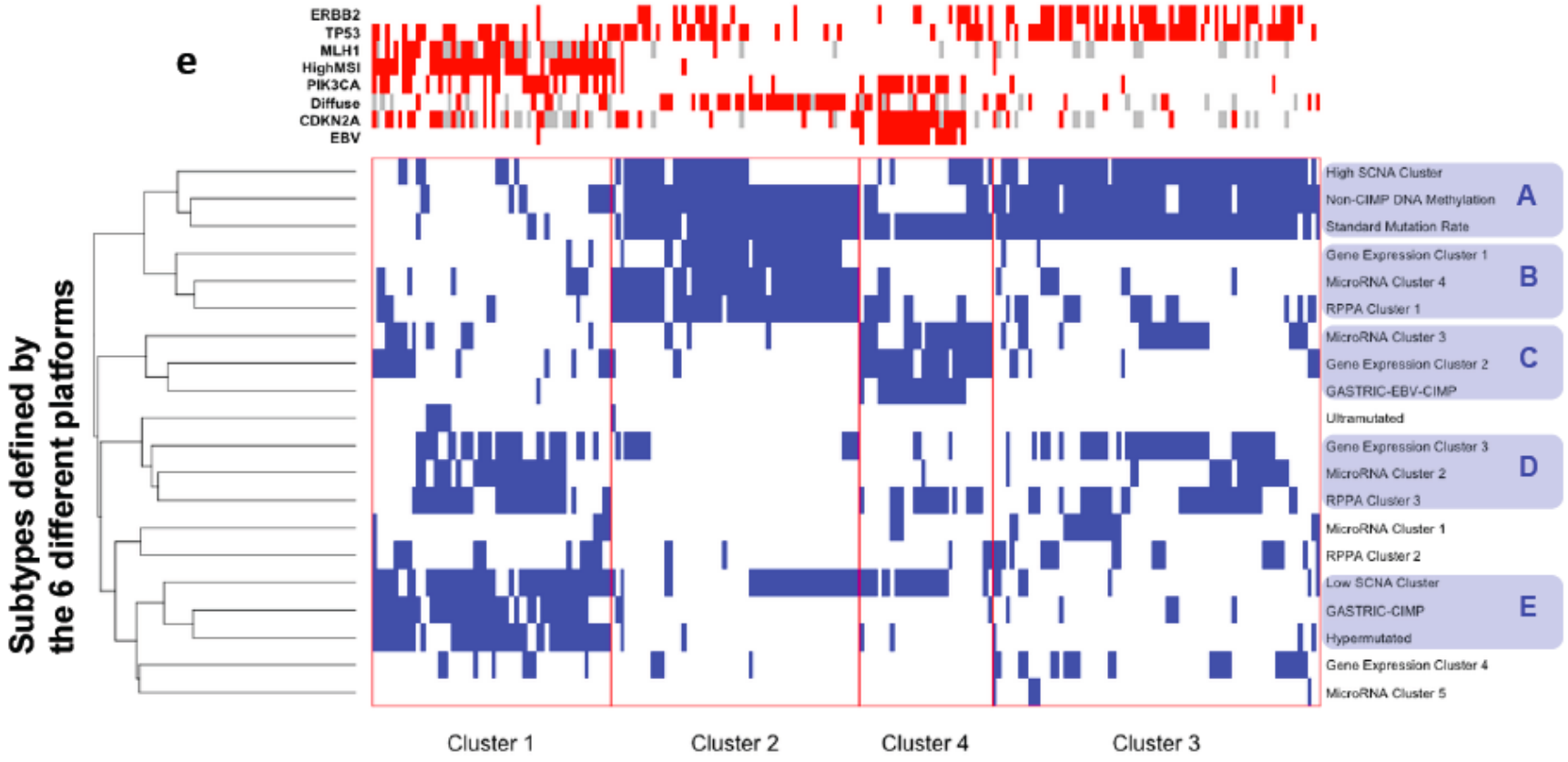


TCGA, Nature 2014

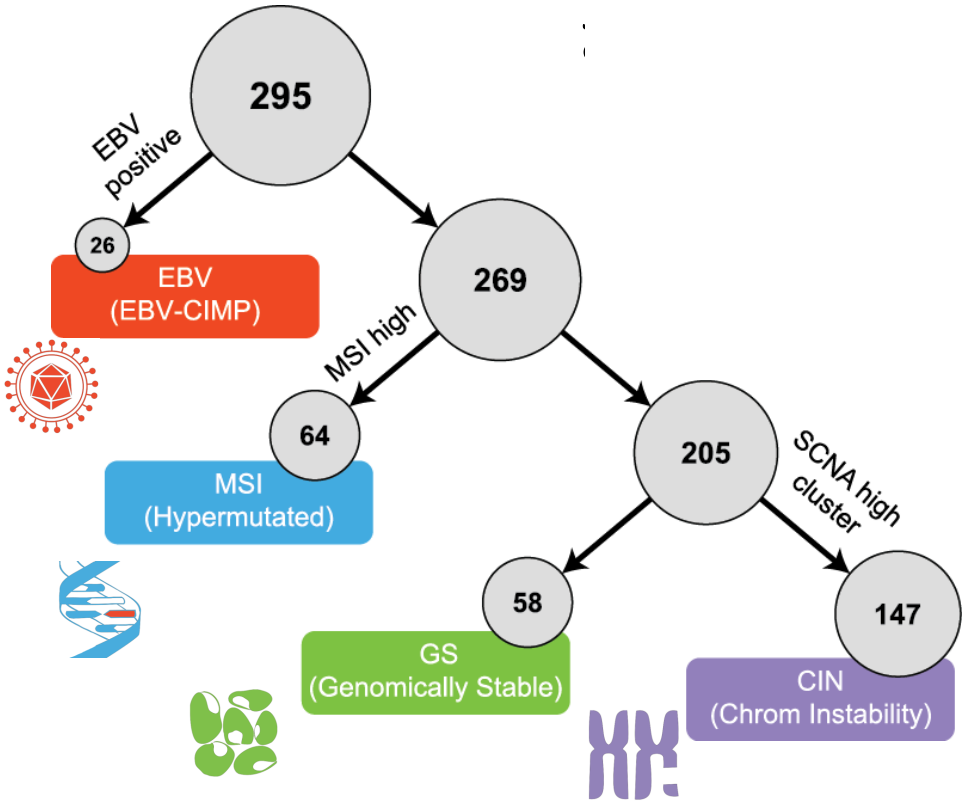
Developing a Gastric Classification: Learn from data. Then make it simple



MSI Diffuse EBV Aneuploid

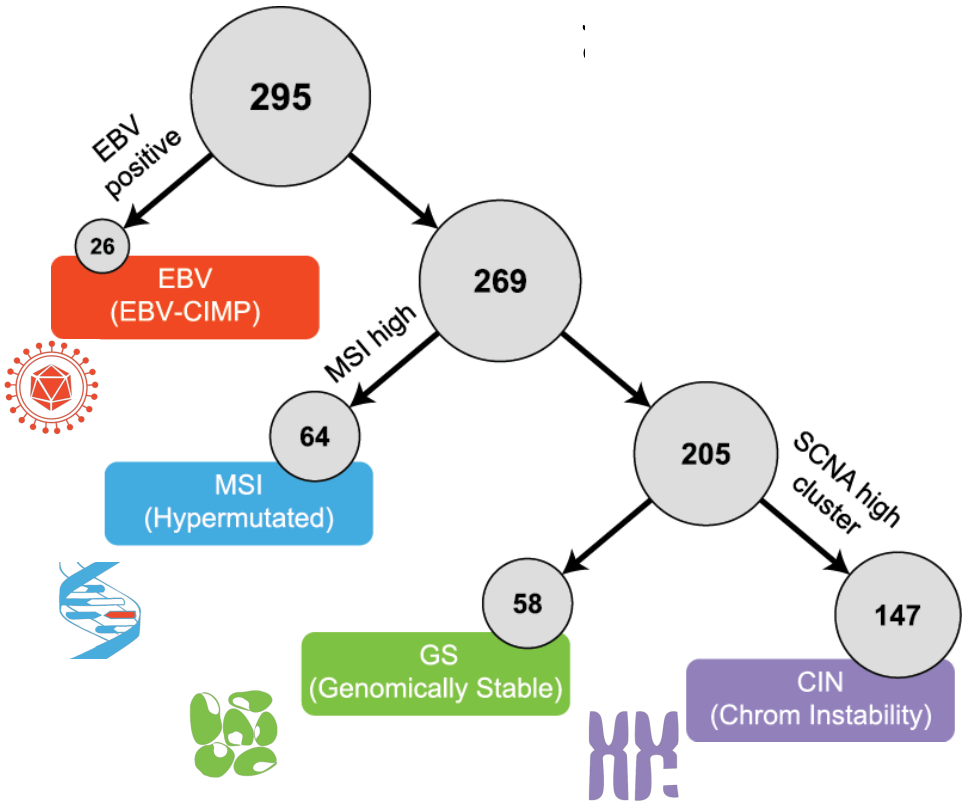
Vesteinn Thorsson

Molecular Classification Scheme for Gastric Cancer

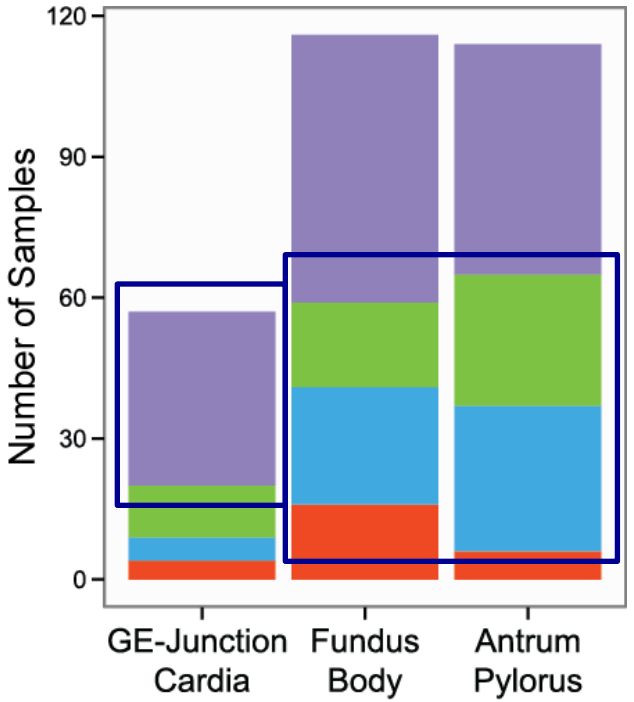


Nature 2014

Molecular Classification Scheme for Gastric Cancer



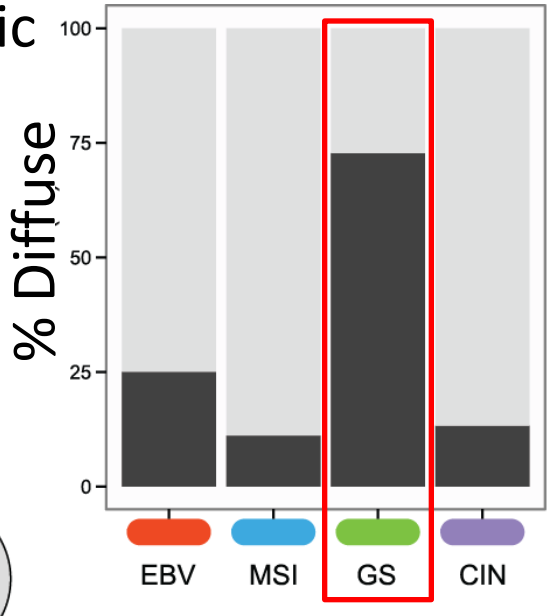
Anatomic

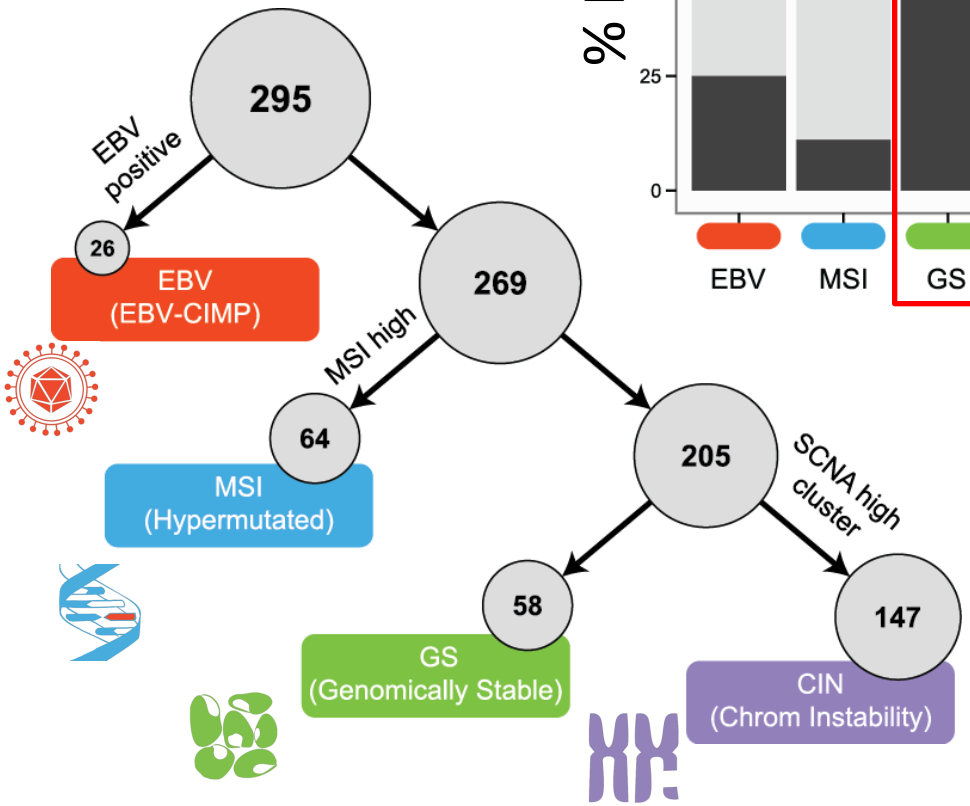


Nature 2014

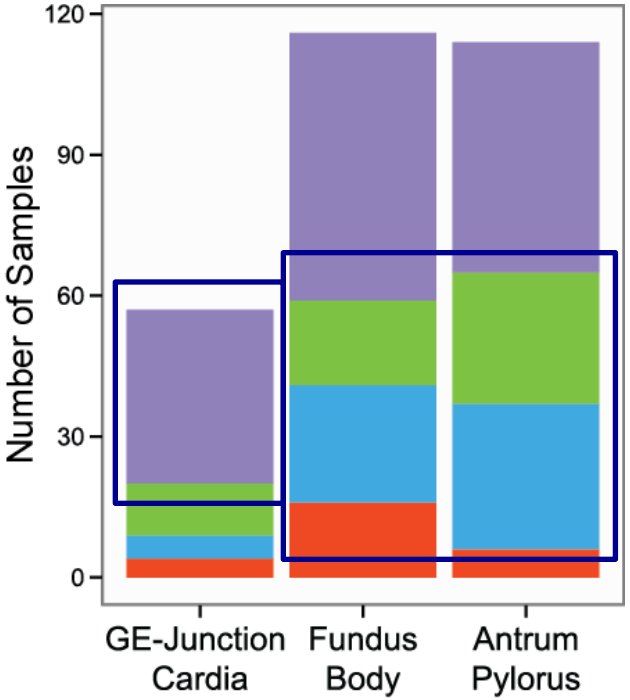
Molecular Classification Scheme for Gastric Cancer

Histologic



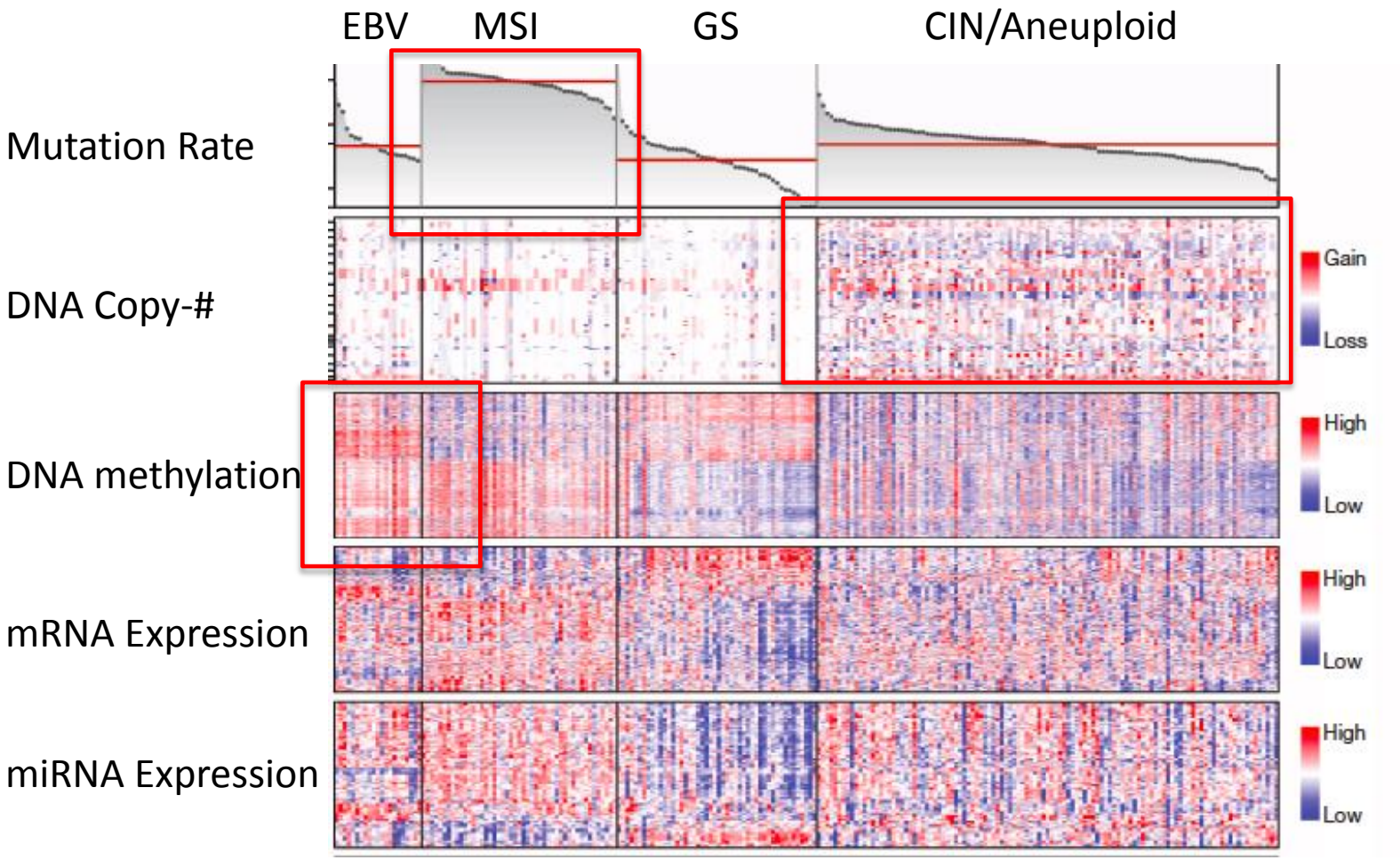


Anatomic



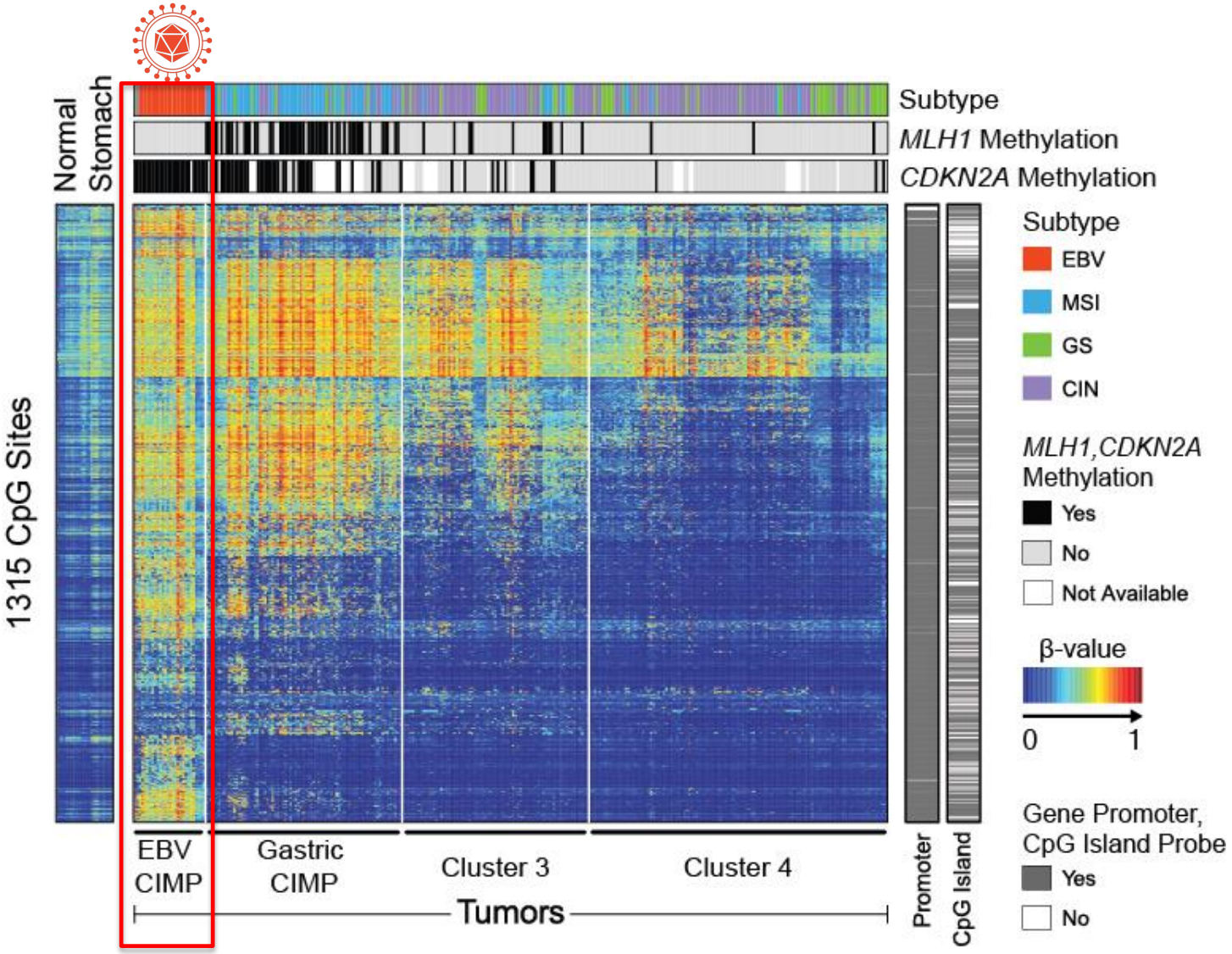
Nature 2014

Four Molecular Classes of Gastric Cancer

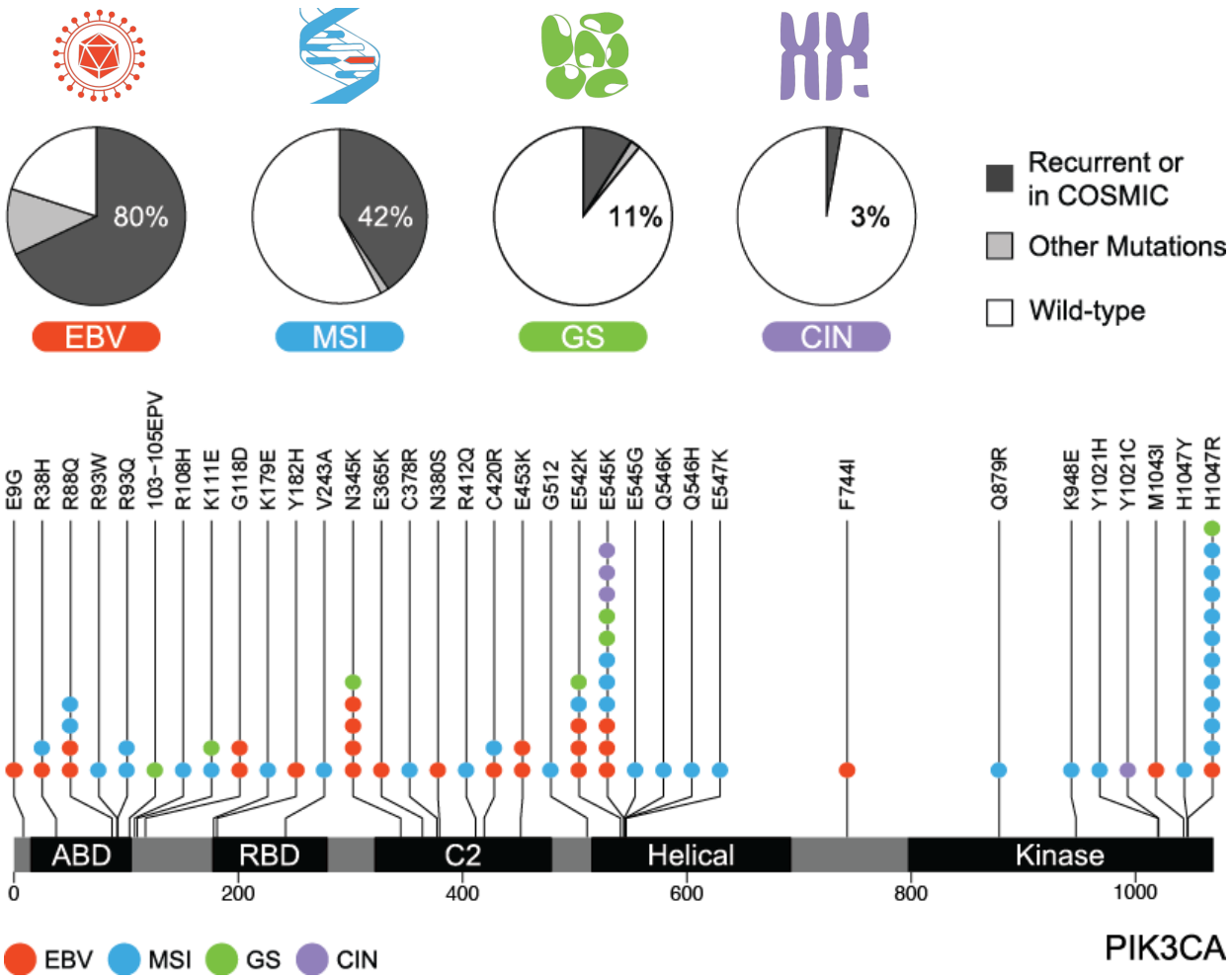


Nature 2014

Distinct CIMP Profiles Differentiate EBV+ and MSI+ Gastric Cancer

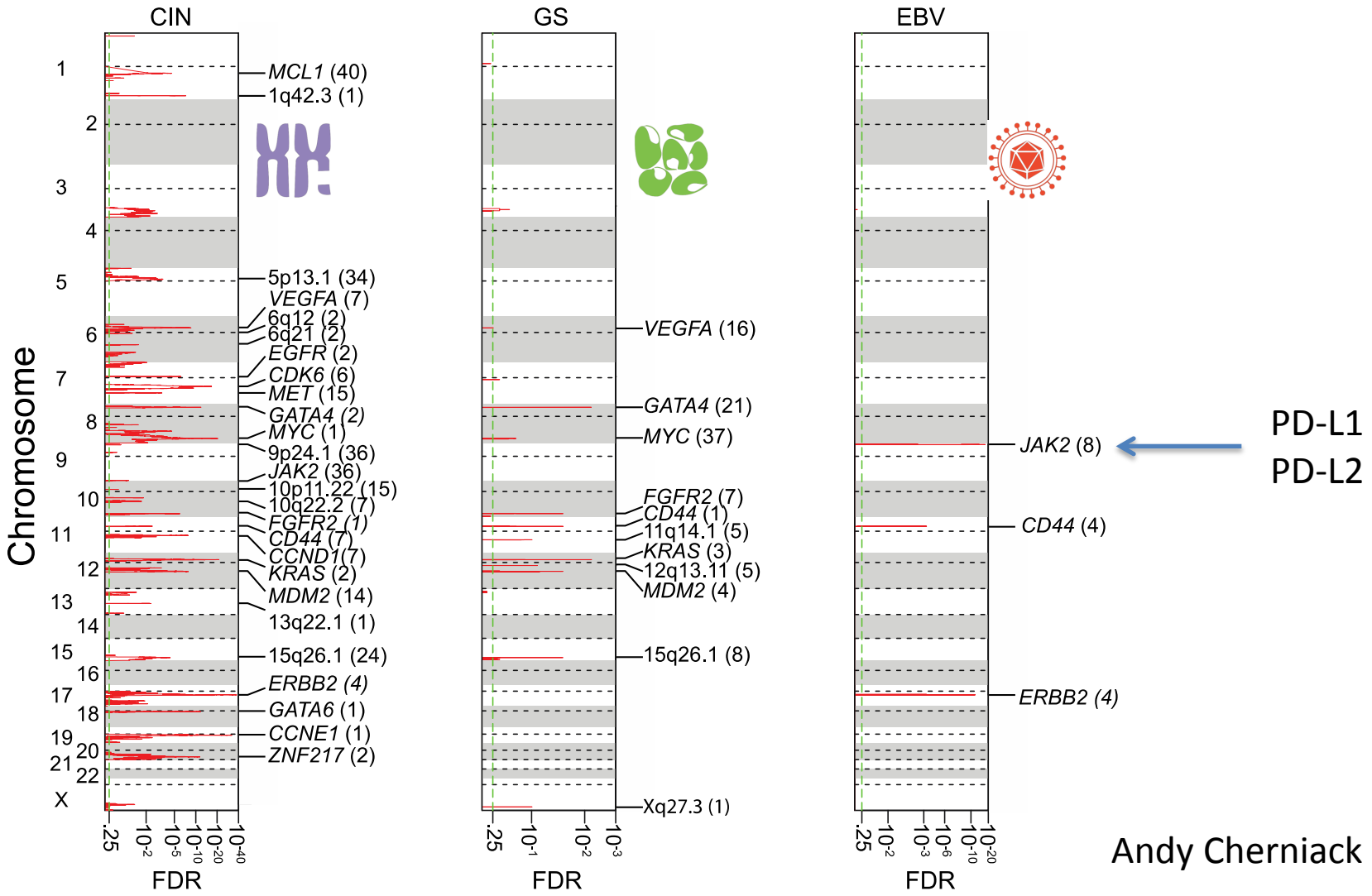


Dramatic Rates of *PIK3CA* Mutation in EBV+ GC



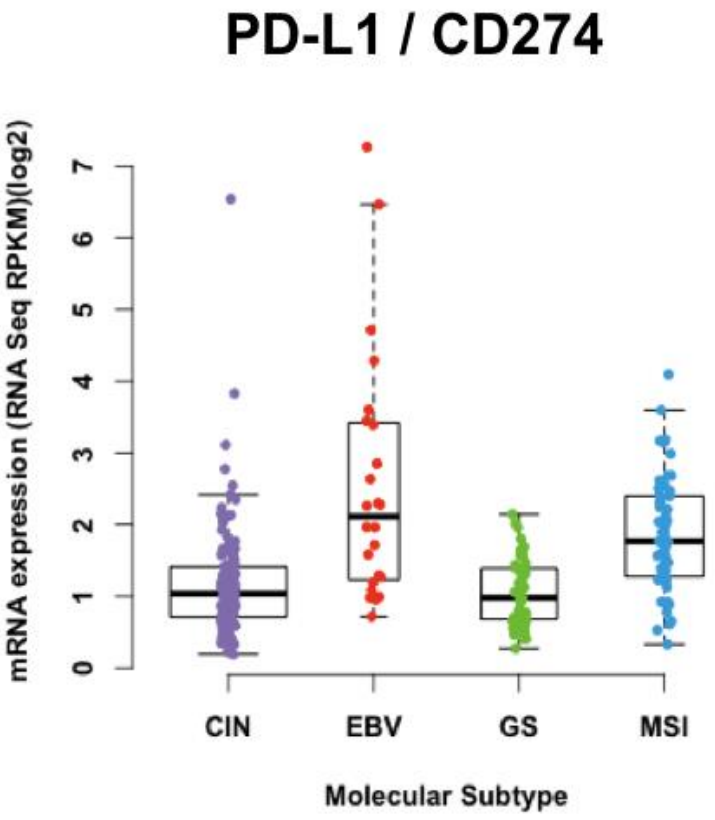
Amaro Taylor-Weiner

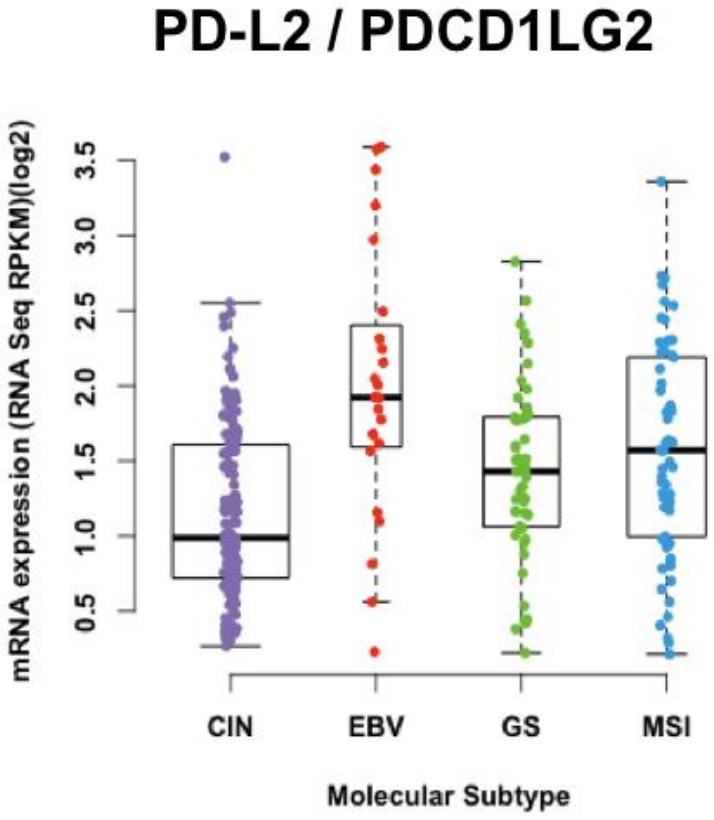
Focal Amplification Peaks Across Molecular Subtypes



Andy Cherniack

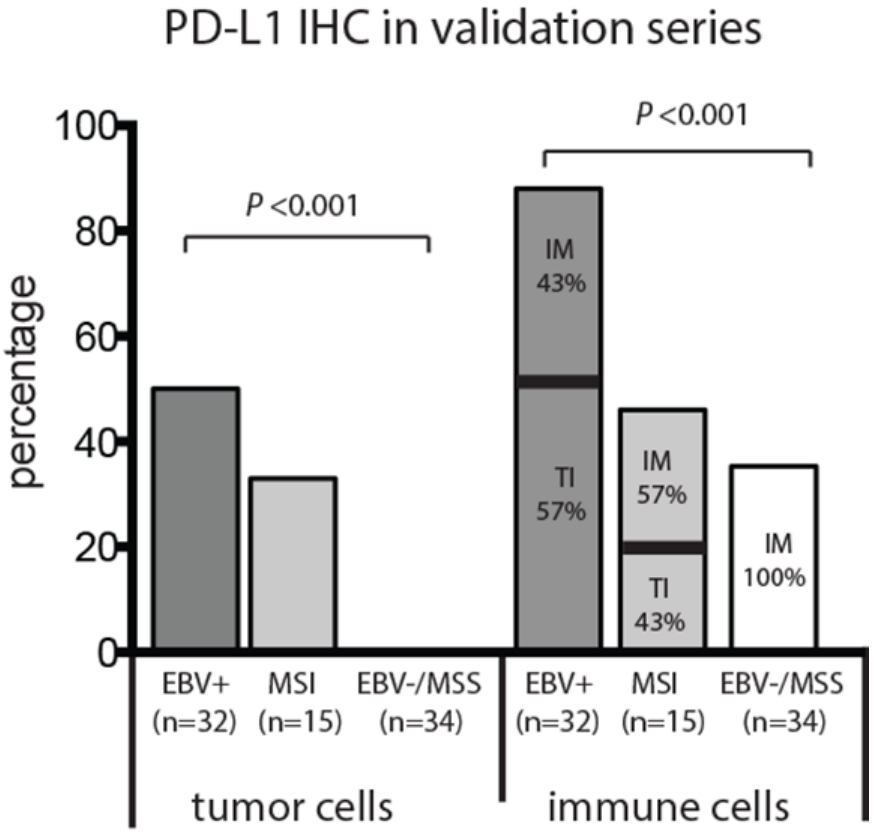
Elevated PD-L1 and PD-L2 Expression in EBV+ Gastric Cancer

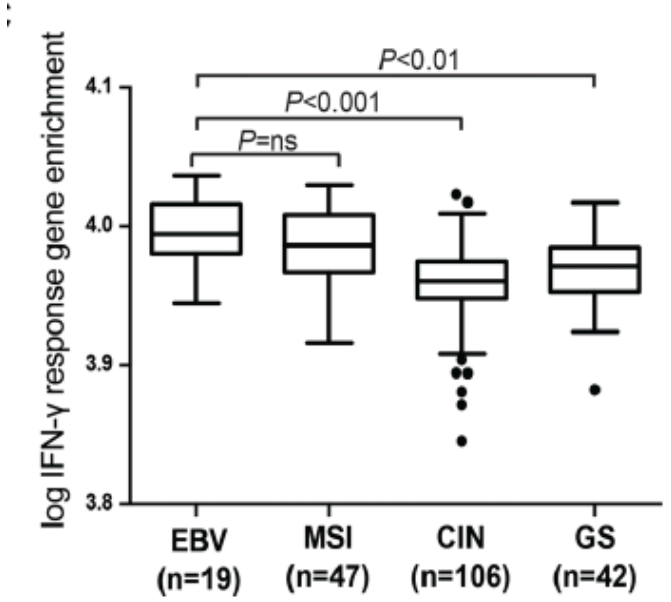




Andy Cherniack
Vesteinn Thorsson

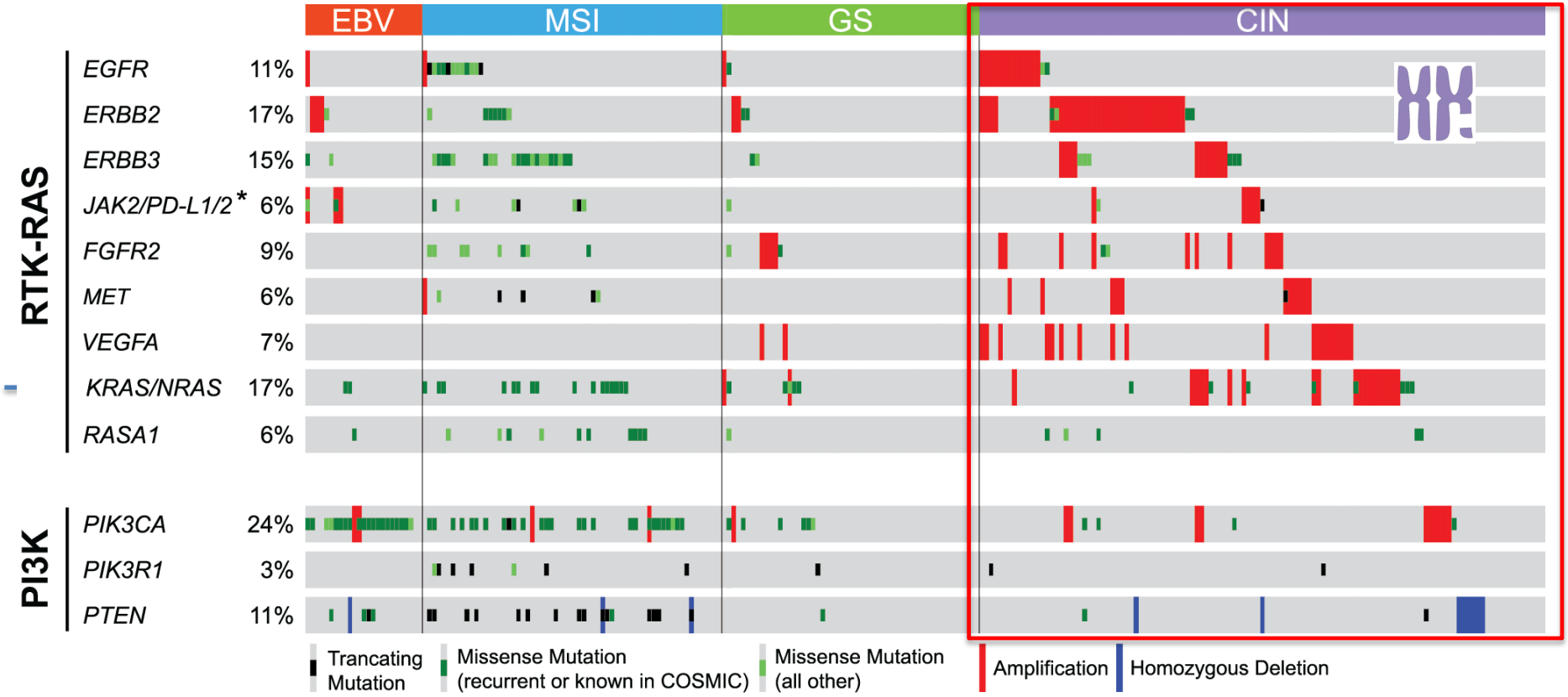
Potential Importance of Subgroups Regarding PD-1 Therapy





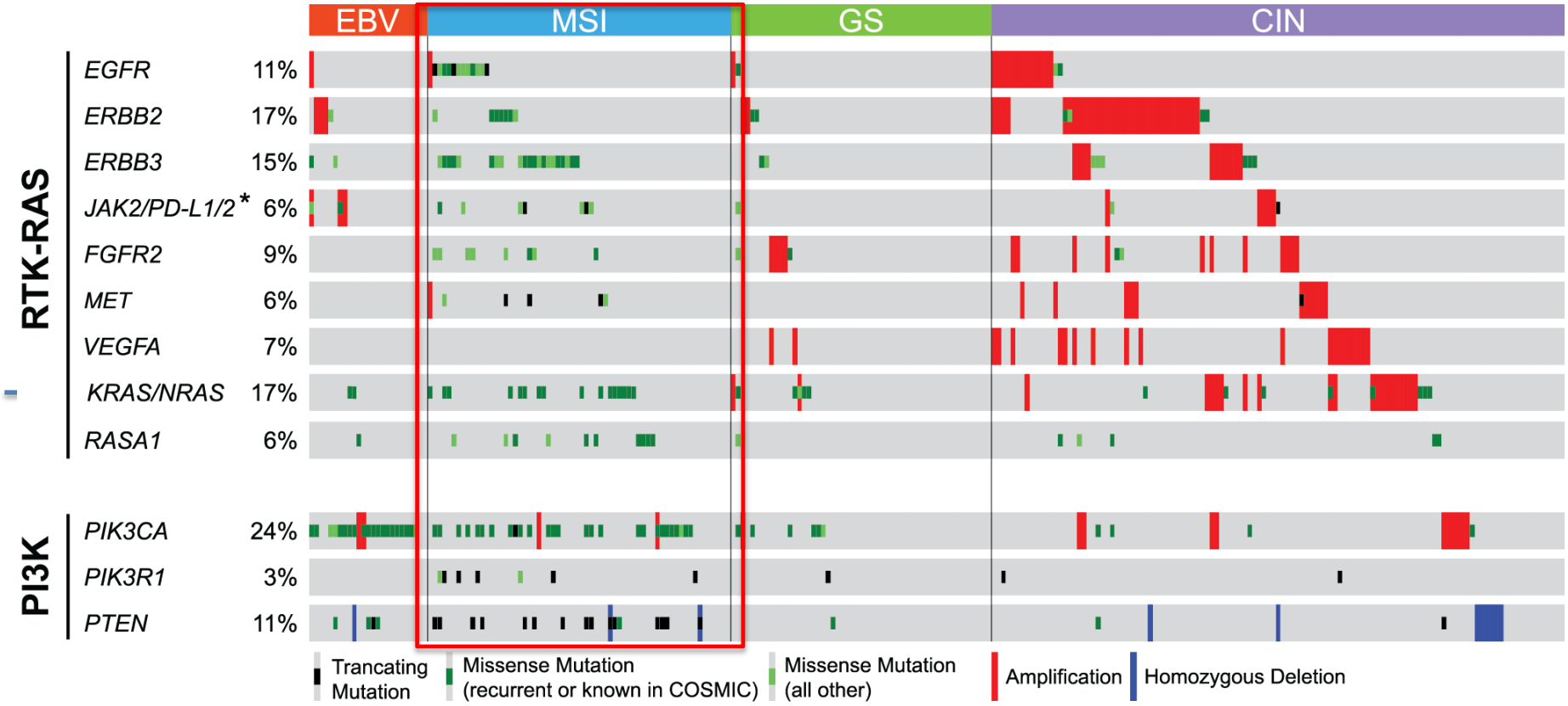
Derks et al, Oncotarget 2016

CIN Tumors: Highly Recurrent Amplification of Oncogenes



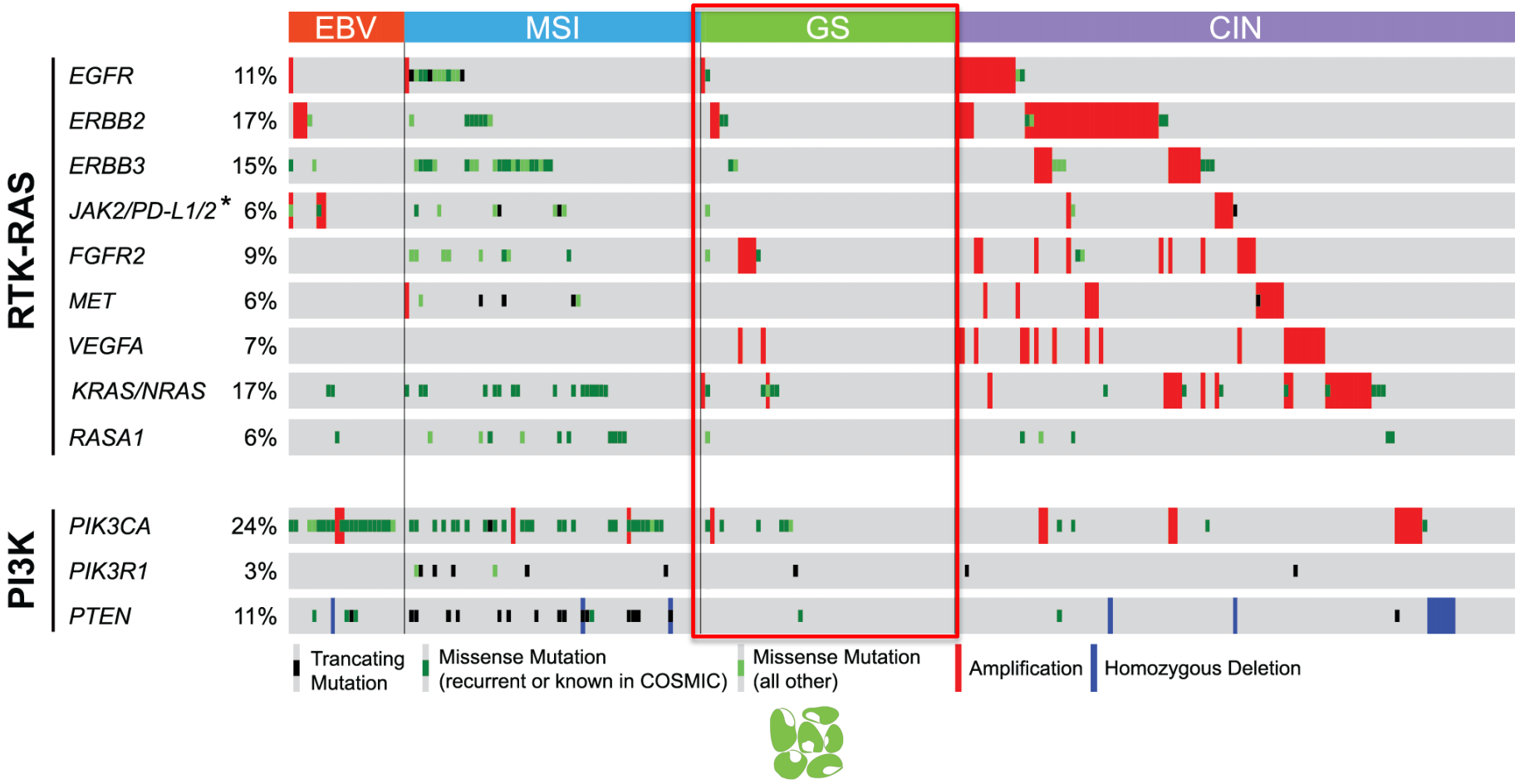
Nils Wilheim

MSI Tumors: Recurrent Mutations of Oncogenes

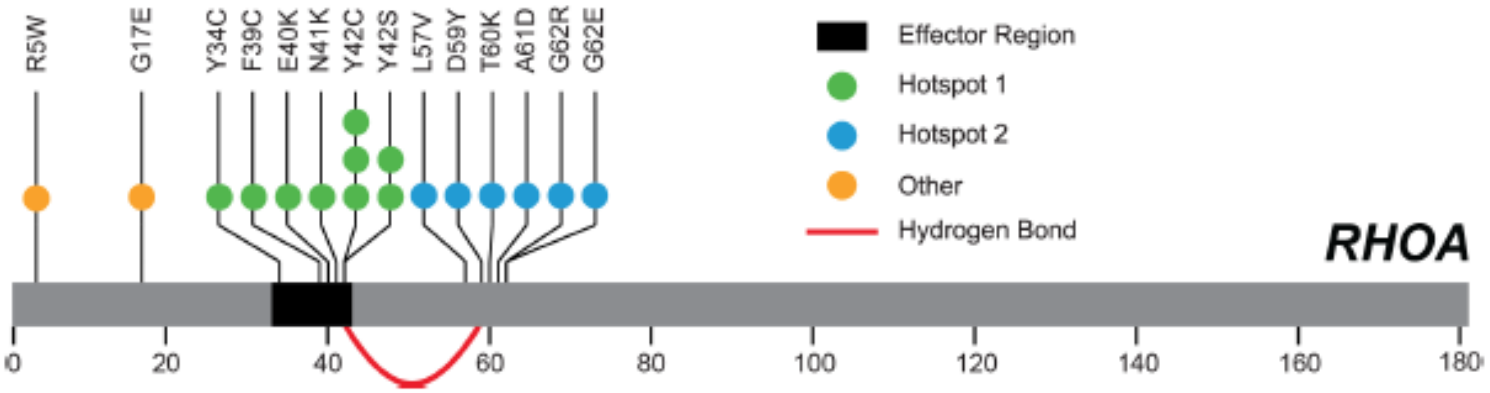


Nils Wilheim

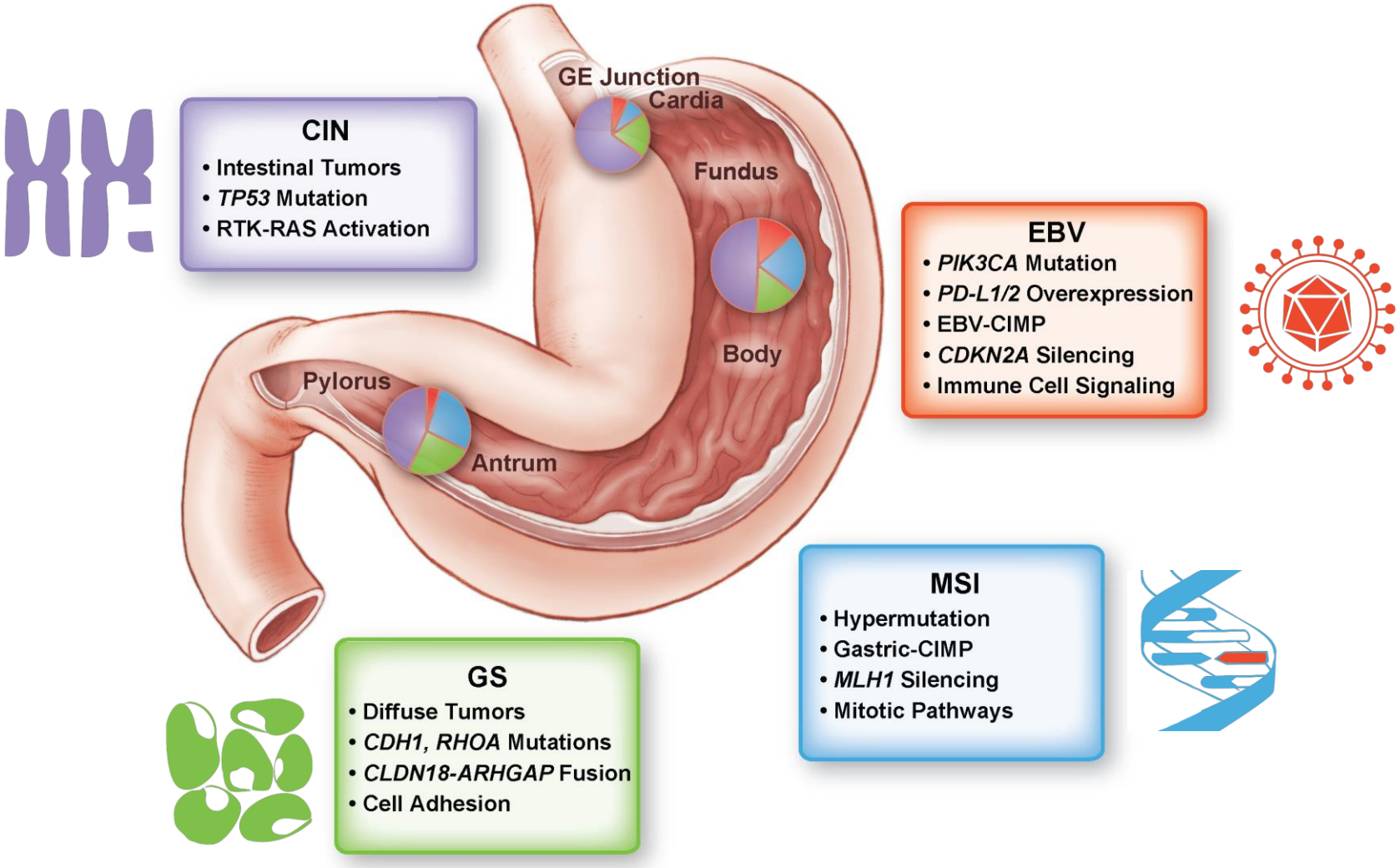
What About Genomically-Stable (i.e. Diffuse) Gastric Cancer



Highly Recurrent *RHOA* GTPAse Mutations in Diffuse/Genomically Stable GC



Molecular Subtypes of GC and Key Features



Nature 2014

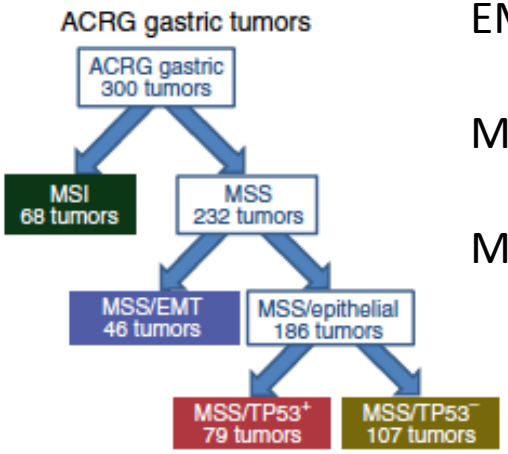
Summary of TCGA Results

- Distinct Subgroups of Gastric Adenocarcinomas
  - CIN Group– most common (especially more proximal)
    - Lots of candidate amplified targets (more on this later)
  - EBV: PD-1 pathway promising, consider testing *PIK3CA* pathway agents
  - MSI: promising candidates for PD-1, several common hotspot mutations: *ERBB3, ERBB2, PIK3CA*…
  - GS/Diffuse: A major mystery/problem
    - Perhaps RHOA pathway will lead to new targets… (someday, I hope…)?
    - Less classic targets, still some FGFR2, ERBB2

Complementary Classification: Asian Cancer Research Group

Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes

Razvan Cristescu[1,12], Jeeyun Lee[2,12], Michael Nebozhyn[1,12], Kyoung-Mee Kim[3,12], Jason C Ting[4], Swee Seong Wong[4], Jiangang Liu[4], Yong Gang Yue[4], Jian Wang[4], Kun Yu[4,11], Xiang S Ye[4], In-Gu Do[3], Shawn Liu[5], Lara Gong[5], Jake Fu[6], Jason Gang Jin[6], Min Gew Choi[7], Tae Sung Sohn[7], Joon Ho Lee[7], Jae Moon Bae[7], Seung Tae Kim[2], Se Hoon Park[2], Insuk Sohn[8], Sin-Ho Jung[8], Patrick Tan[9,10], Ronghua Chen[1], James Hardwick[1,11], Won Ki Kang[2], Mark Ayers[1], Dai Hongyue[1,11], Christoph Reinhard[4], Andrey Loboda[1], Sung Kim[7] & Amit Aggarwal[4]

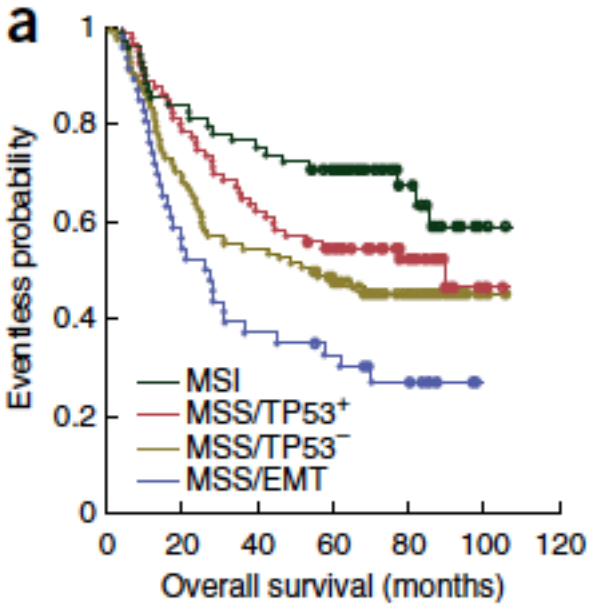


MSI

EMT Group- (largely diffuse)

MSS-TP53- (similar to CIN)

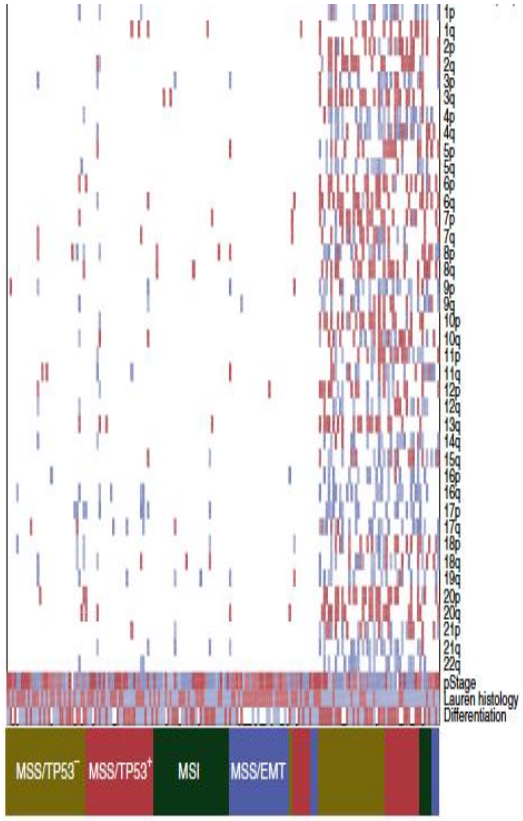
MSS-TP53+



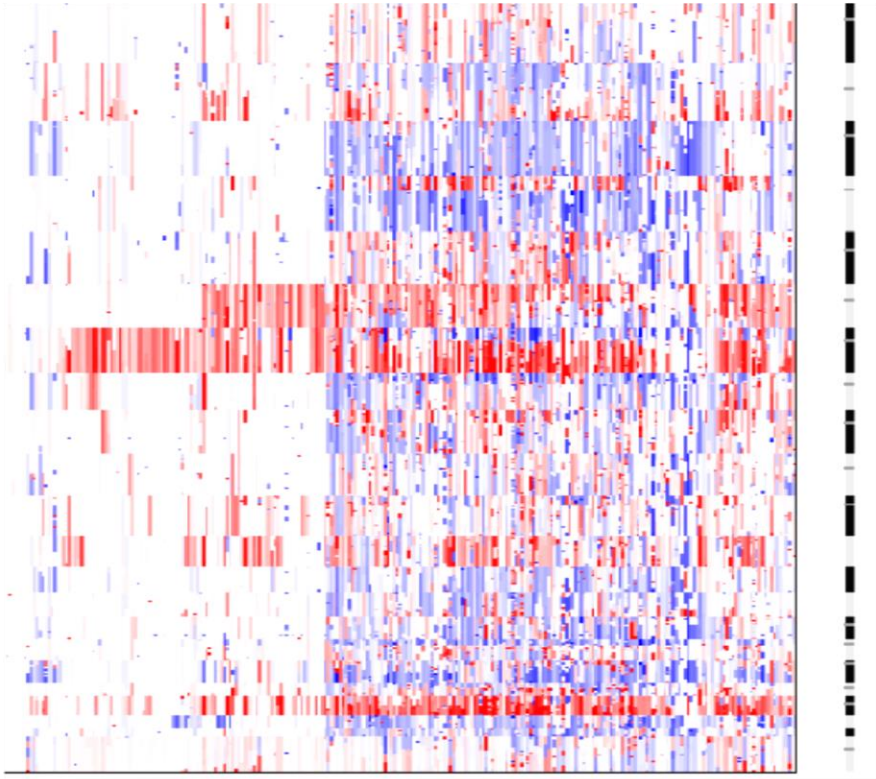
Comparative Features of TCGA and ACRG Datasets

	TCGA	ACRG
Ethnicity	25% East Asian	100% Korean
Histology	23% Diffuse	45% Diffuse
Stage	31% III/IV	57% III/IV
Location	19% GEJ	11% GEJ

Comparative Copy-Number Analysis: Greater Aneuploidy in TCGA Data Set Vs. ACRG



ACRG



TCGA

Simple ways to compare these classifiers…

- TCGA approach: includes gene mutations, methylation status, aneuploidy levels relating to mechanisms of tumor initiation….
  - This point to underlying molecular drivers and targets for therapy
  - But does not indicate the way that tumors with similar initiation may evolve and how present state may differ between 'like' tumors
- ACRG: greater focus on gene expression tells more about the tumor state at the time of diagnosis….
  - Allows for convergence to shared states from distinct starting points
    - For example, distinct classes of tumors may co-evolve towards a more mesenchymal, de-differentiated state
  - These classifiers may help us understand how not all tumors with the same driver act the same.

Back to the old question:

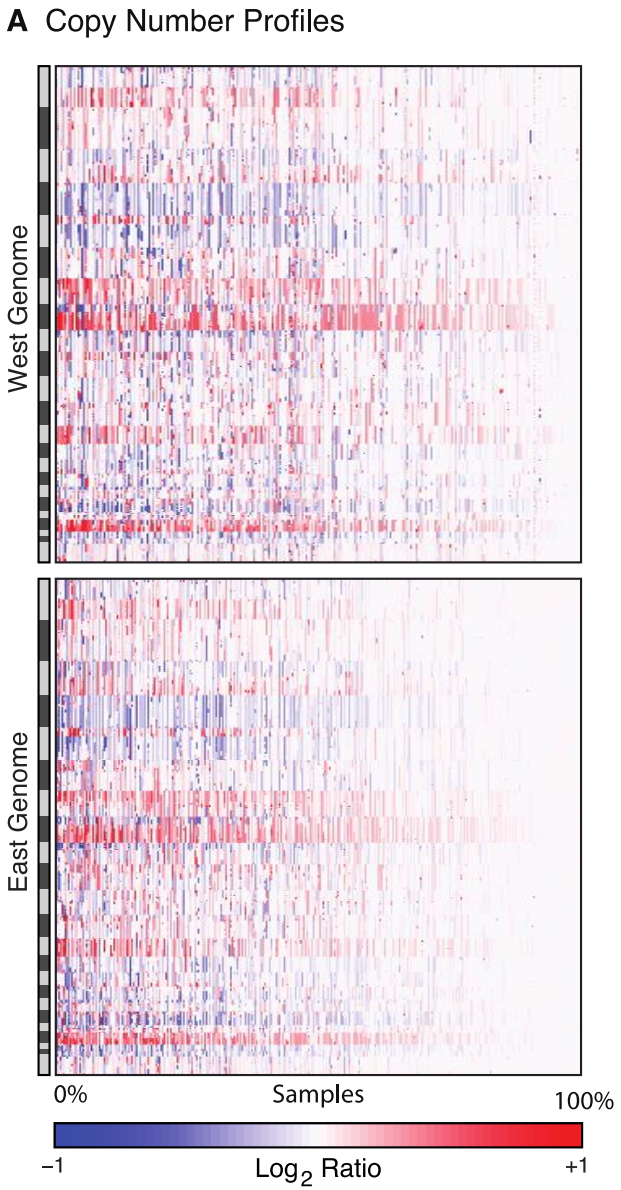
What about Asian vs. Western Gastric Cancer?

An Initial Comparison of Somatic Copy-Number of Eastern and Western Gastric Cancer

- Combined together ~700 fresh frozen gastric cancers which had been profiled on Affymetrix SNP6 arrays
  - Uniformly reprocessed at Broad Institute
- Samples from TCGA, collection of Italian GC, published collection from Singapore, and new collection from Korea

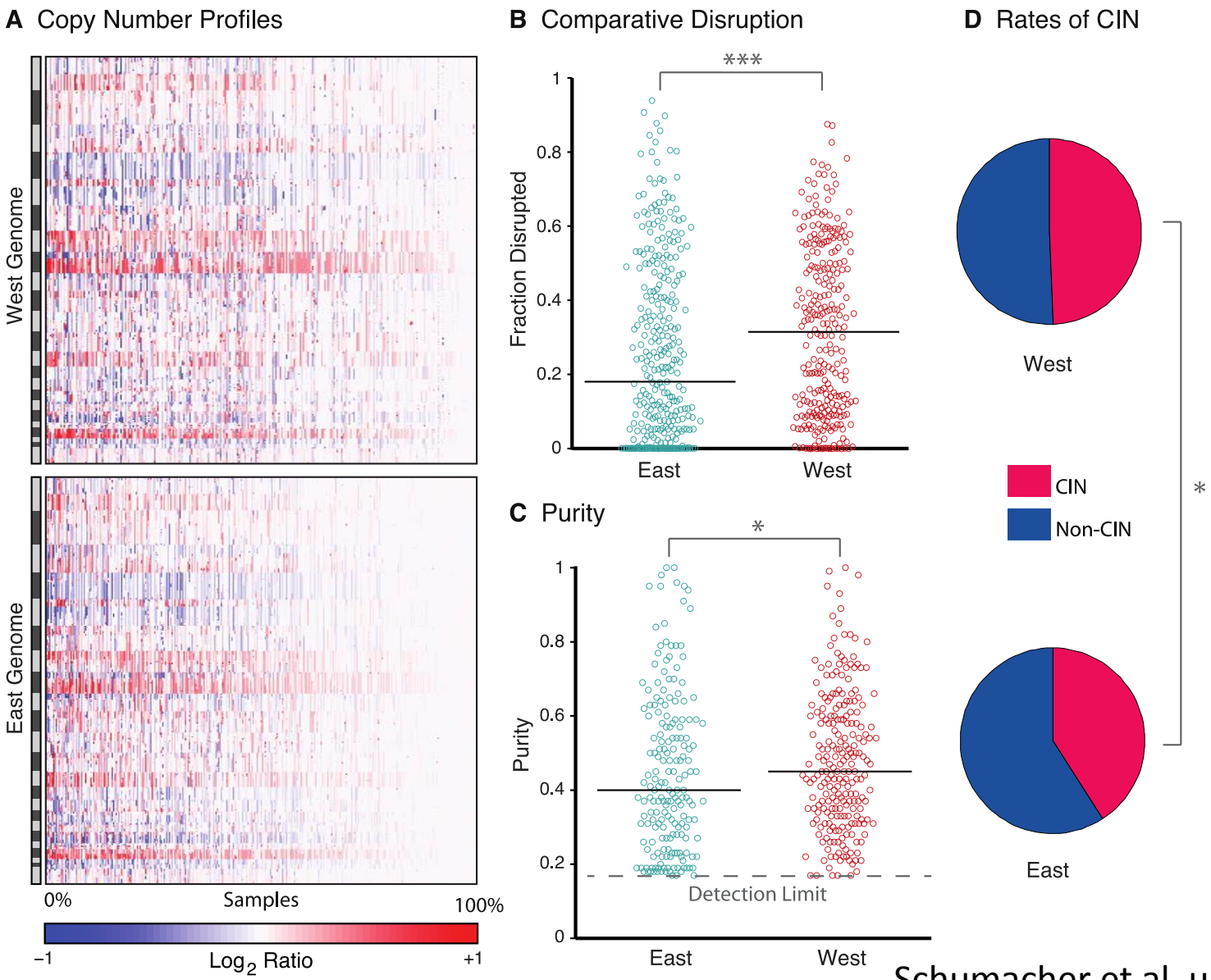
Schumacher et al, under revision

An Initial Look at the Data Suggests Differences

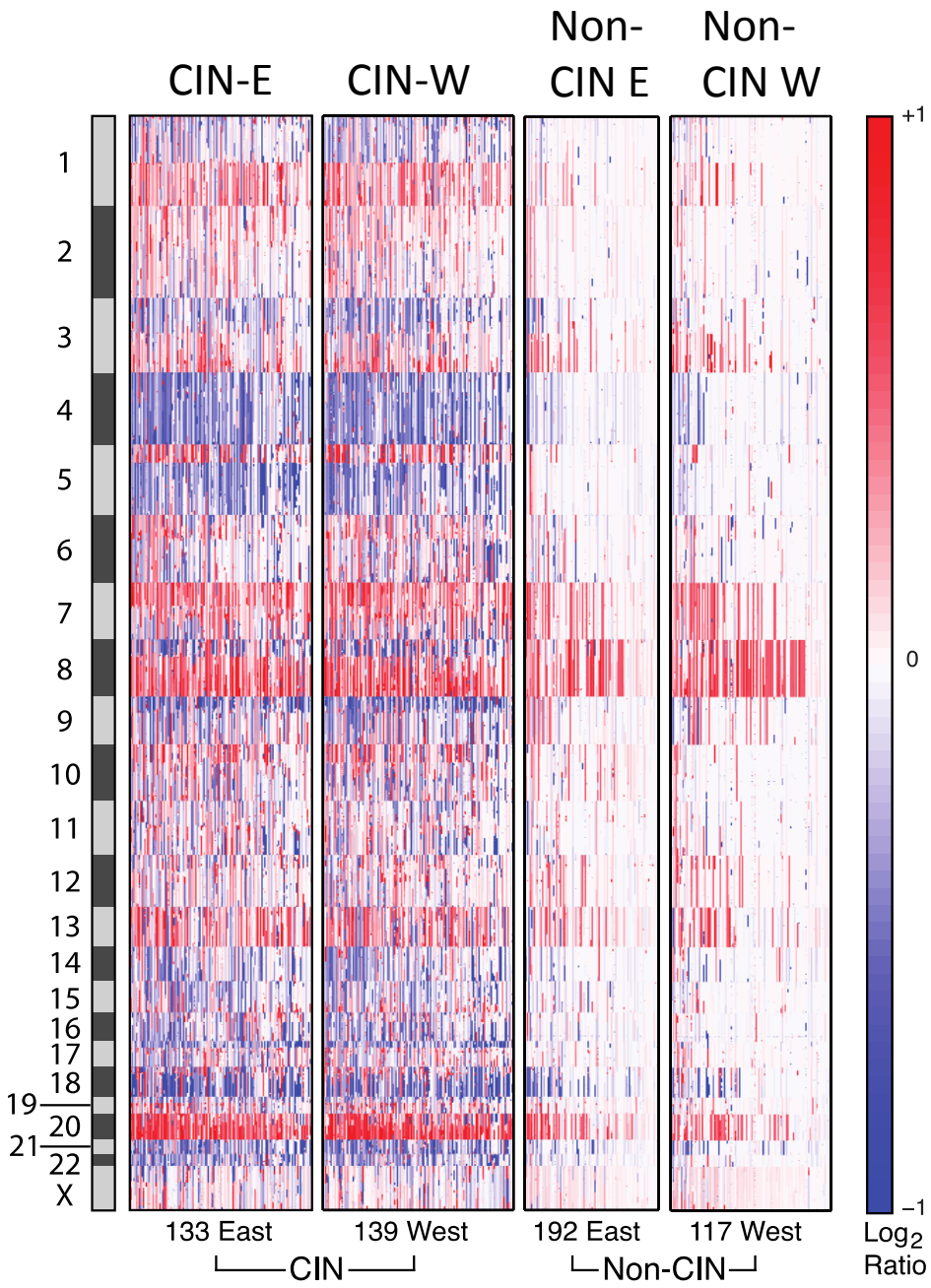


Schumacher et al, under review

An Initial Look at the Data Suggests Differences



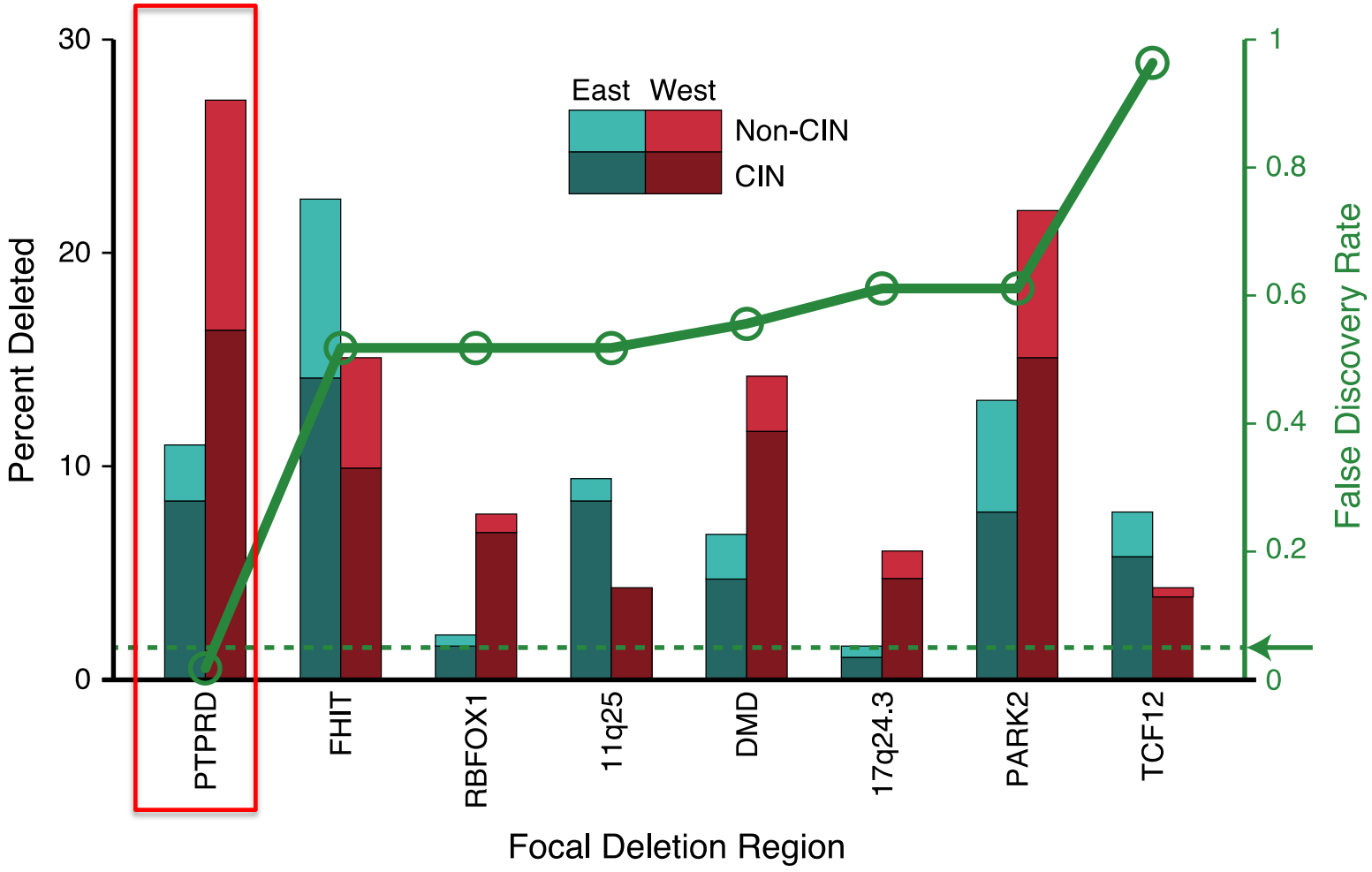
Schumacher et al, under review



Comparison of E/W Stratified by CIN:

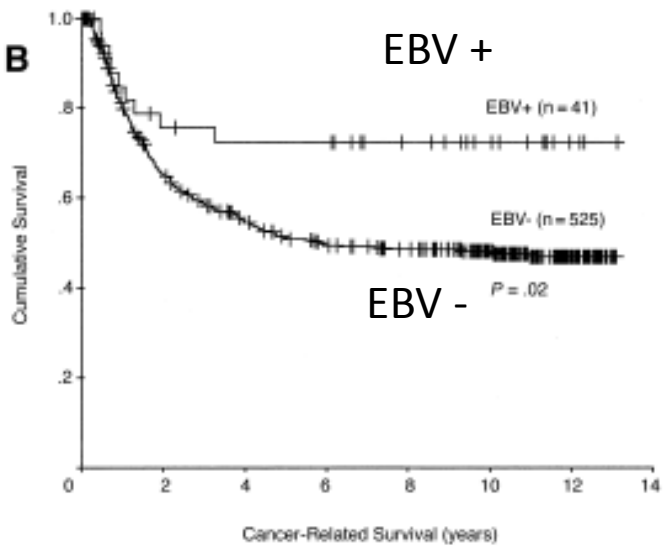
Tumor Subtype Appears to be a Stronger Discriminator Compared to Geography

Comparative East/West Analysis of Peaks Following CIN Correction: Only *PTPRD* Found



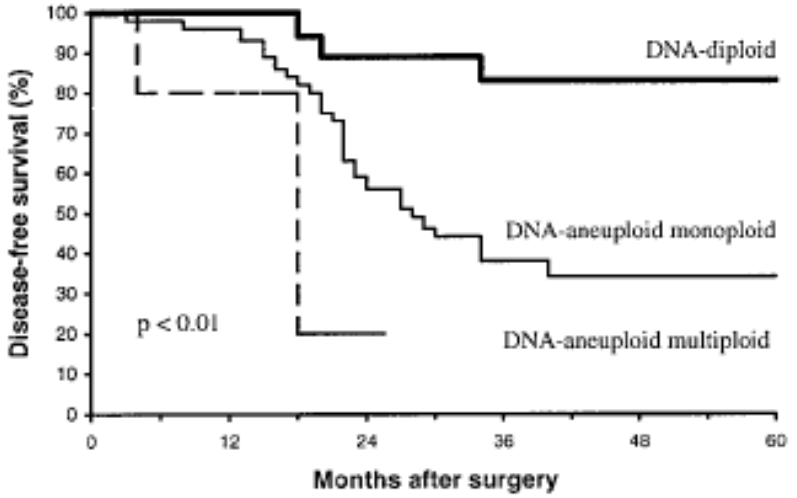
Distinct Subtypes Can Also Influence Survival in Gastric Cancer

EBV Influence



Van Beek et al, JCO 2004

Aneuploidy Influence



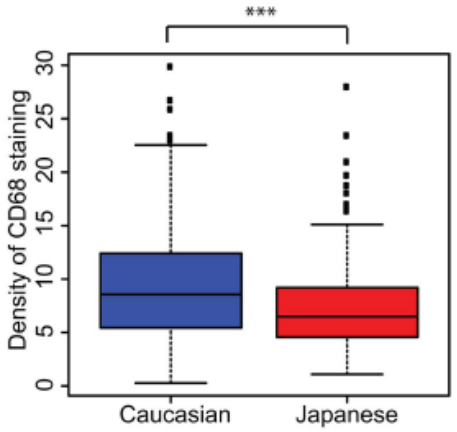
Russo et al, Cancer 2001

Raises Question of How Much Confounding by Subtype Influences East/West Survival Differences

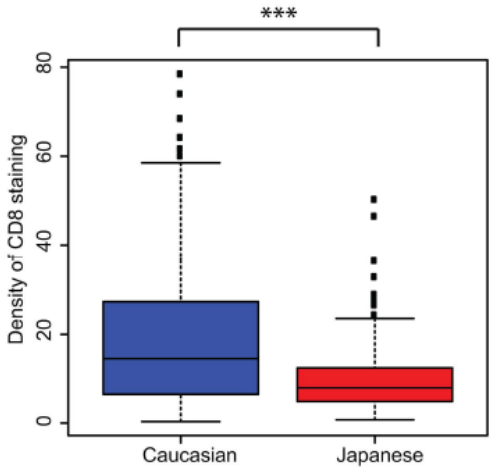
However, there remain other possible differences between E/W gastric cancer (even when you correct for subtype)

East vs. West: epidemiologic differences, e.g. higher rates of H. Pylori in the East.
-Potential for differences in tumor biology outside of what may be appreciated by somatic genomic analysis?

CD 68 Cells



CD 8 Cells



Distinct immune cell compositions seen (even when correct for MSI/EBV)

Lin et al, Gut 2014

Summary

- There is likely confounding of any East/West gastric cancer comparison due to different subtypes
  - CIN tumors are more common proximally and are over-represented in the Western patients.
- Remaining question is what additional differences remain, including those differences that may not be appreciated by TCGA or ACRG classifications
  - Among these, potential distinctions in the inflammatory environment are intriguing and, perhaps, increasingly relevant in the CIO era…

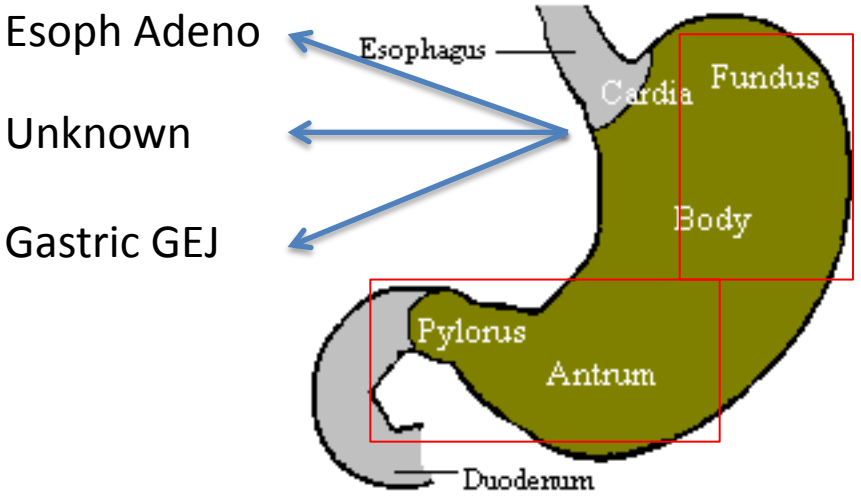
Revisiting Esophageal Adeno Vs. Gastric Adeno

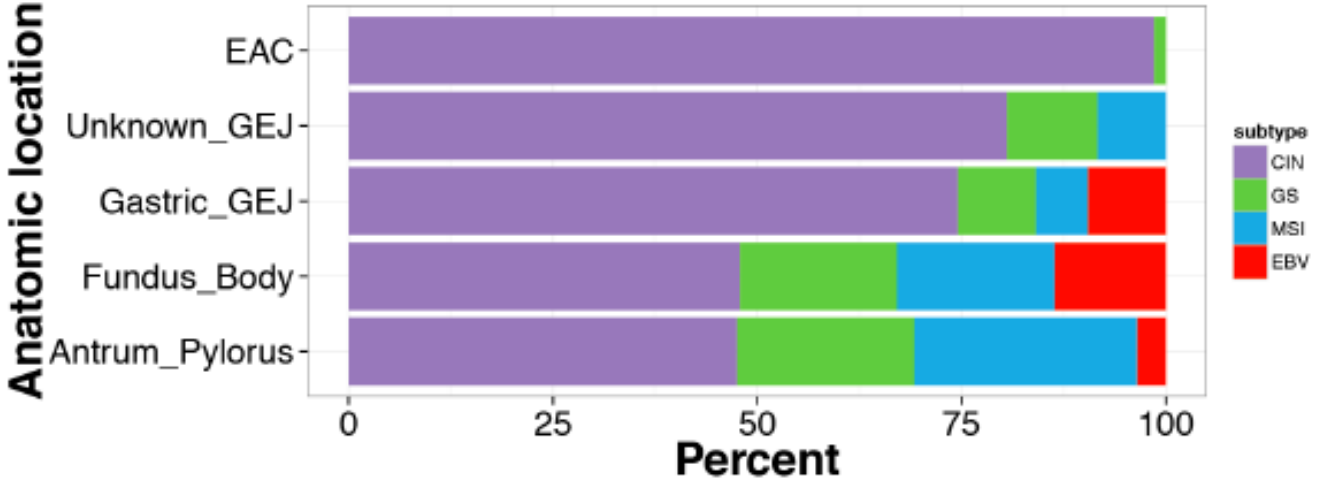
TCGA Marches On….To The Esophagus

- Clear uncertainty over where the draw the line between gastric and esophageal cancers (especially adenocarcinomas)
- We have transitioned the original TCGA stomach cancer working group to a joint stomach-esophageal group
  - Now actively working on analyzing esophageal cancer data (using stomach as comparator).

Applying ‘Stomach’ Groups Across GE Adenos

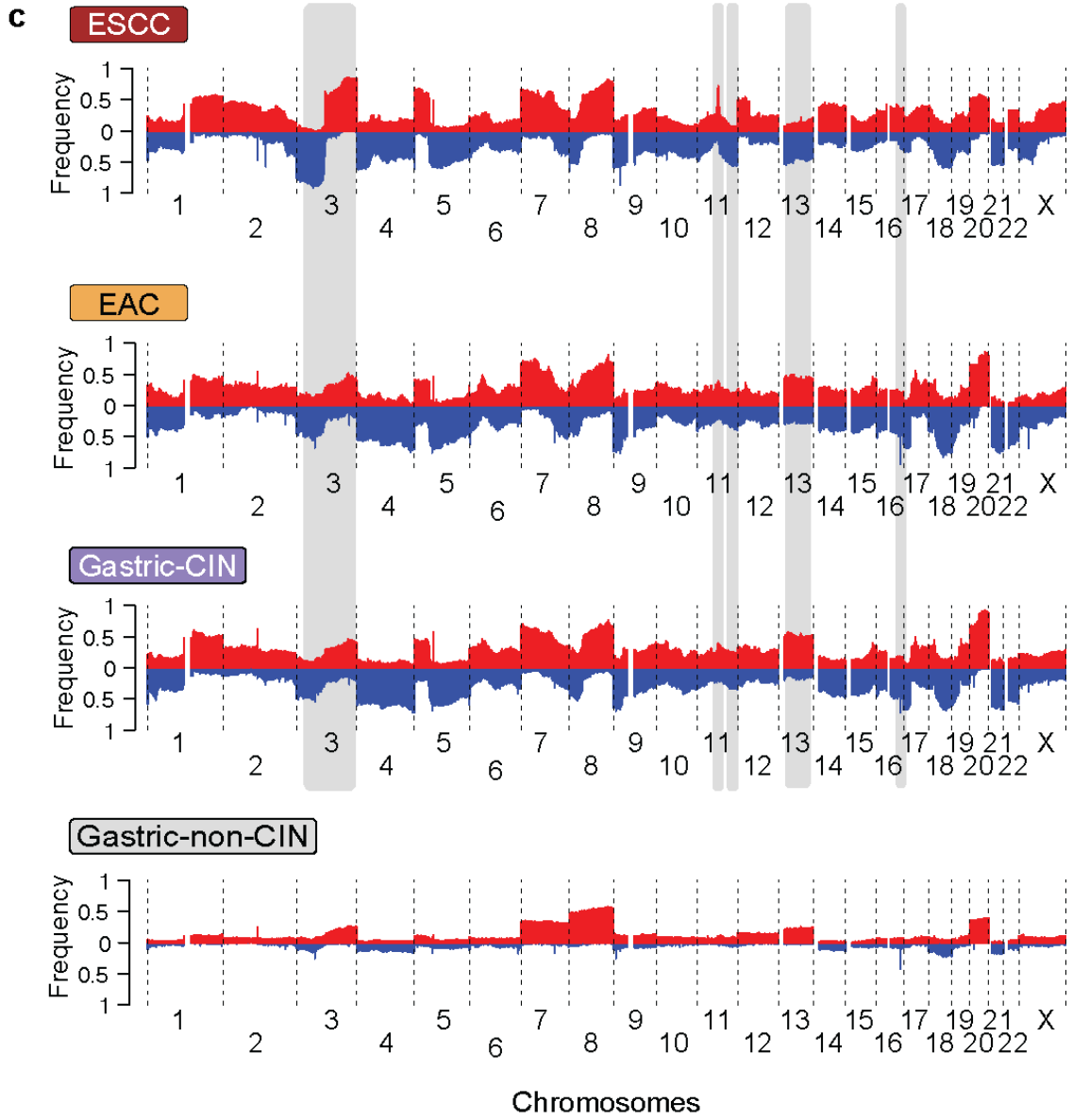
First, careful re-assignment of anatomic location by the Clinical-Pathology Review Team





Vesteinn Thorsson, Toshi Hinoue

So, How Similar are EAC and CIN Gastric Cancer?



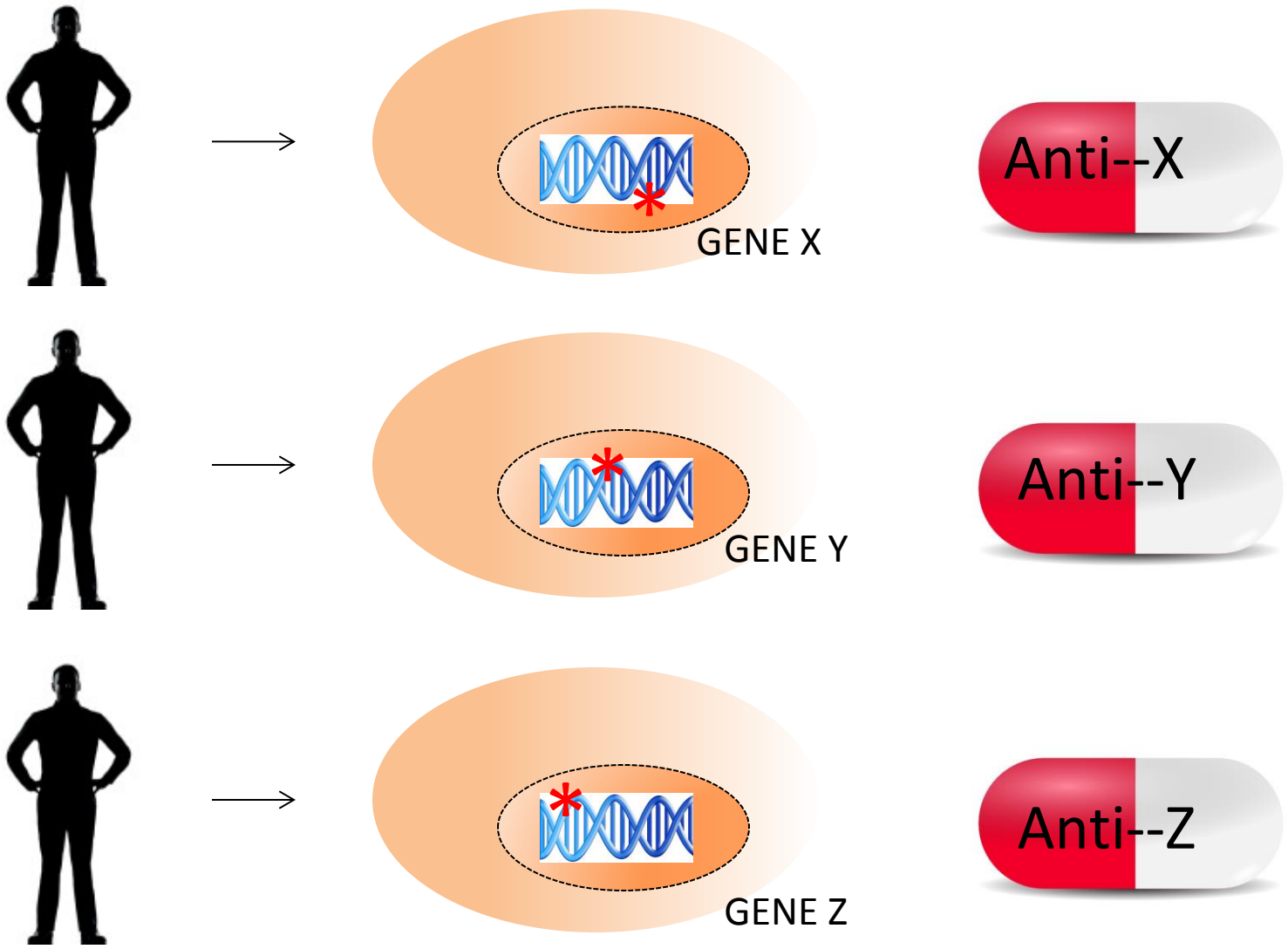
Andy Cherniack

Summary of Esopahgus vs. Stomach

- Like in the East/West debate, there is clear confounding by subtype…
  - There appear to be more subtypes of gastric cancer than of esophageal adenocarcinoma
  - Of these, EAC appears closest to the CIN class of gastric cancer
    - Emerging analysis is looking at the ‘apples to apples’ comparison of EAC and CIN-Gastric
      - More to come….

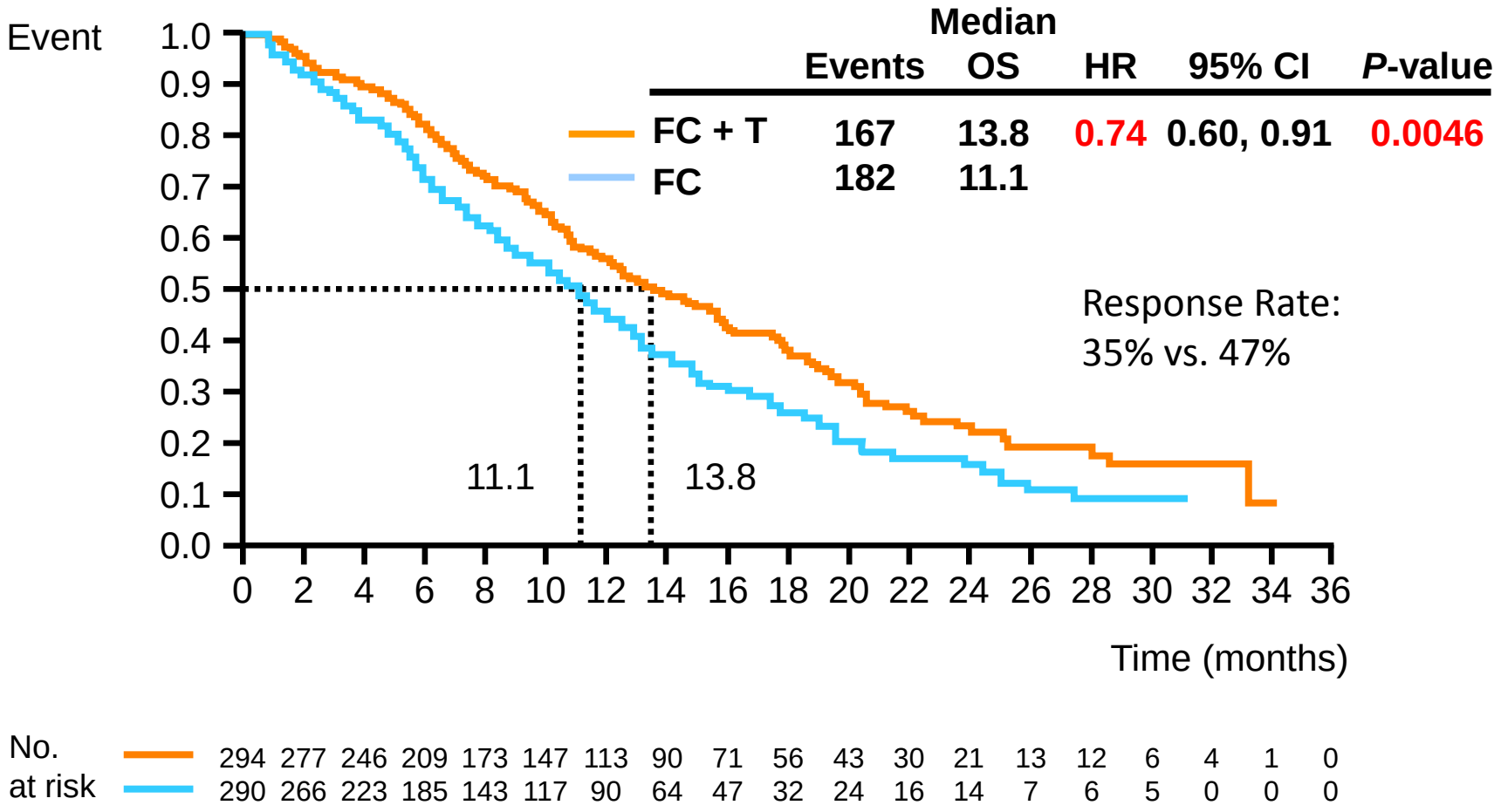
Now that we know subgroups and targets, developing therapy should be easy, right?

What I hoped (10 years ago)….



ToGA: Genomic biomarker 'success':

A single beats striking out (but is not good enough)

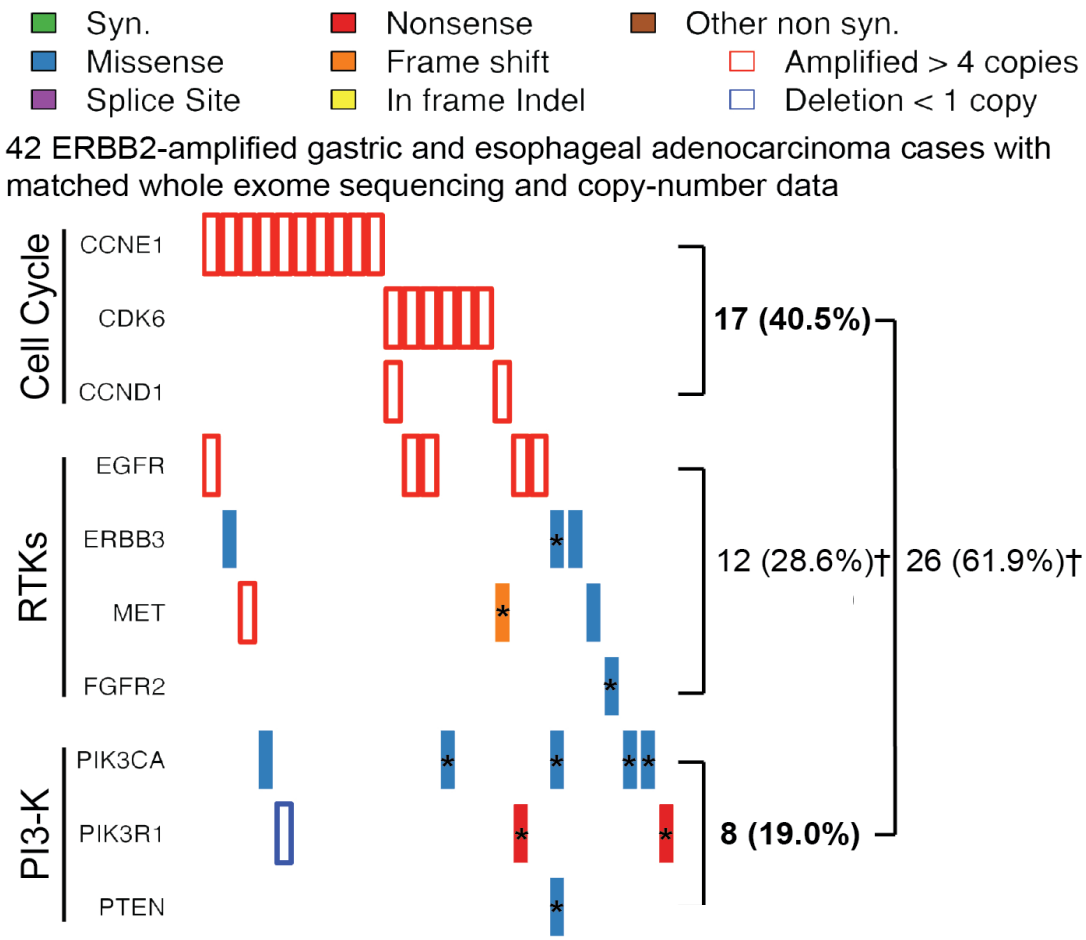


Bang, Y-J et al. Lancet 2010; 376:687

Genome Guided Therapy is Not a Panacea

- Gastroesophageal cancer is not CML!
  - Moving beyond 'The Right Drug for the Right Patient'!
- We are confronting the problem of resistance to therapies against promising targets
    - We often think about resistance as an acquired phenomena. (E.G. T790M *EGFR* mutations after initial response to EGFR TKI in lung adenocarcinoma)
  - A bigger problem is many gastroesophageal tumors is de novo resistance to therapy
    - Genomic etiologies of failure
    - Non-genomic etiologies

Genomic Complexity: Tumors Can Have Multiple Targets

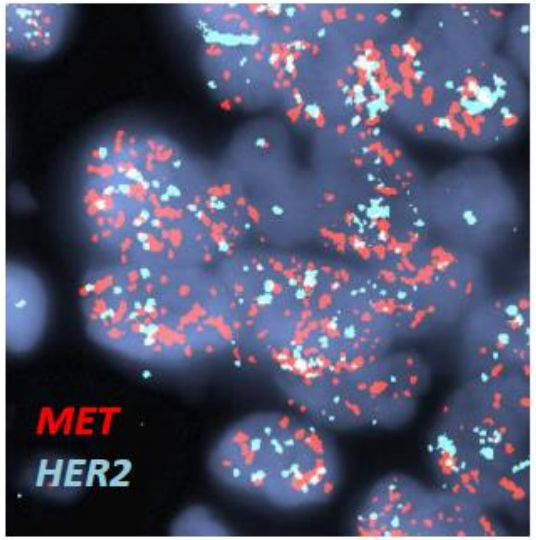


Genomic Landscape of ERBB2-Amplified GE Cancer:
Most tumors have a second 'actionable' oncogenic event…

Kim et al, JCI 2014

Demonstration of Co-Targeting of ERBB2 and MET

E



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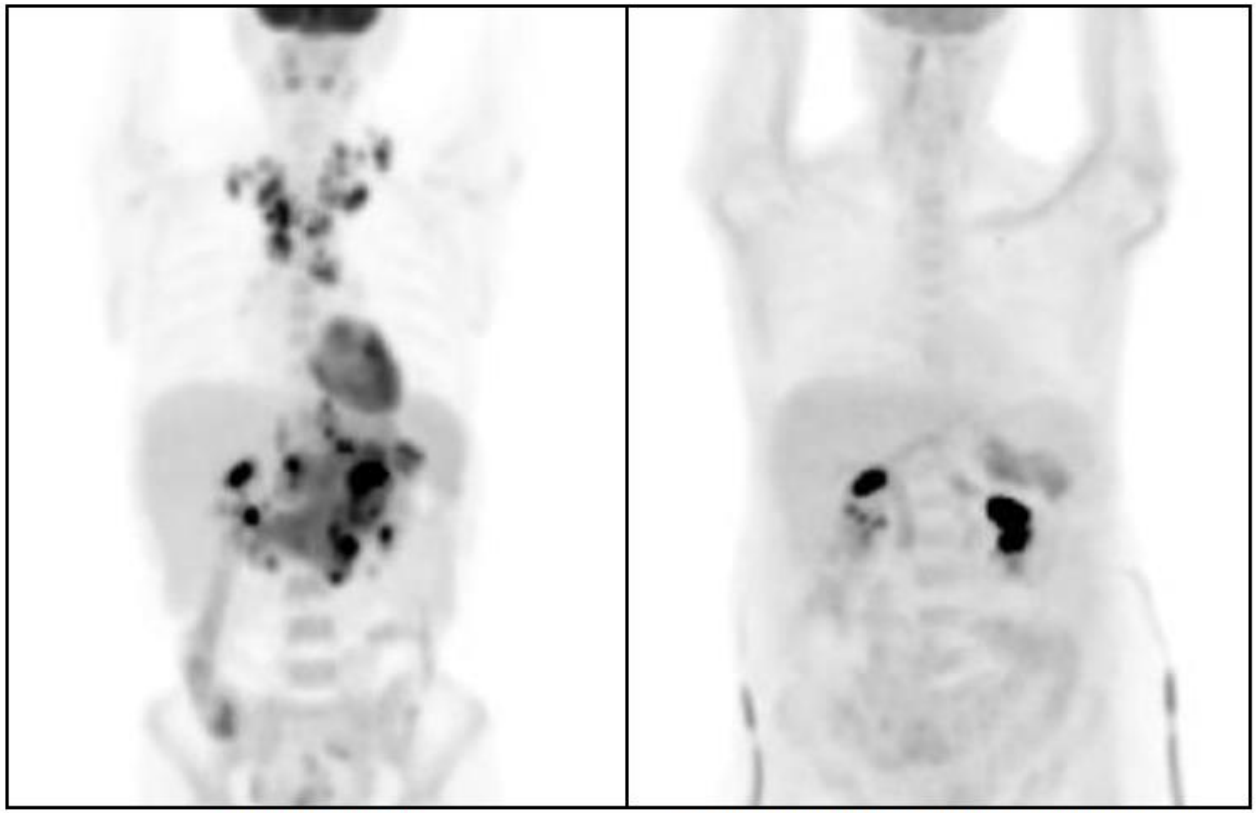
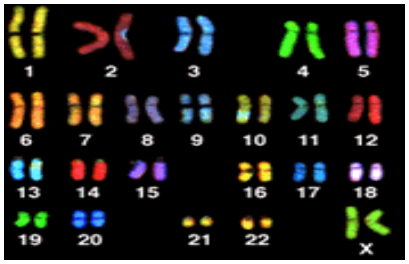
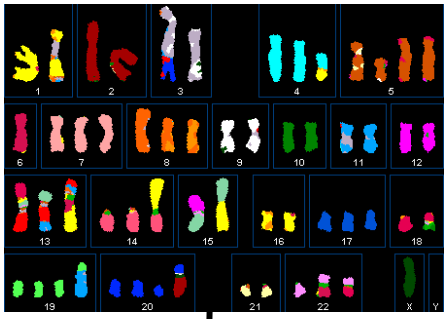


Kwak et al, Cancer Discovery 2015

Genomic Heterogeneity in Cancer: Barrier to Therapy





Initiating 'driver' event

'driver' events

Last clonal 'driver' events

Primary

Met

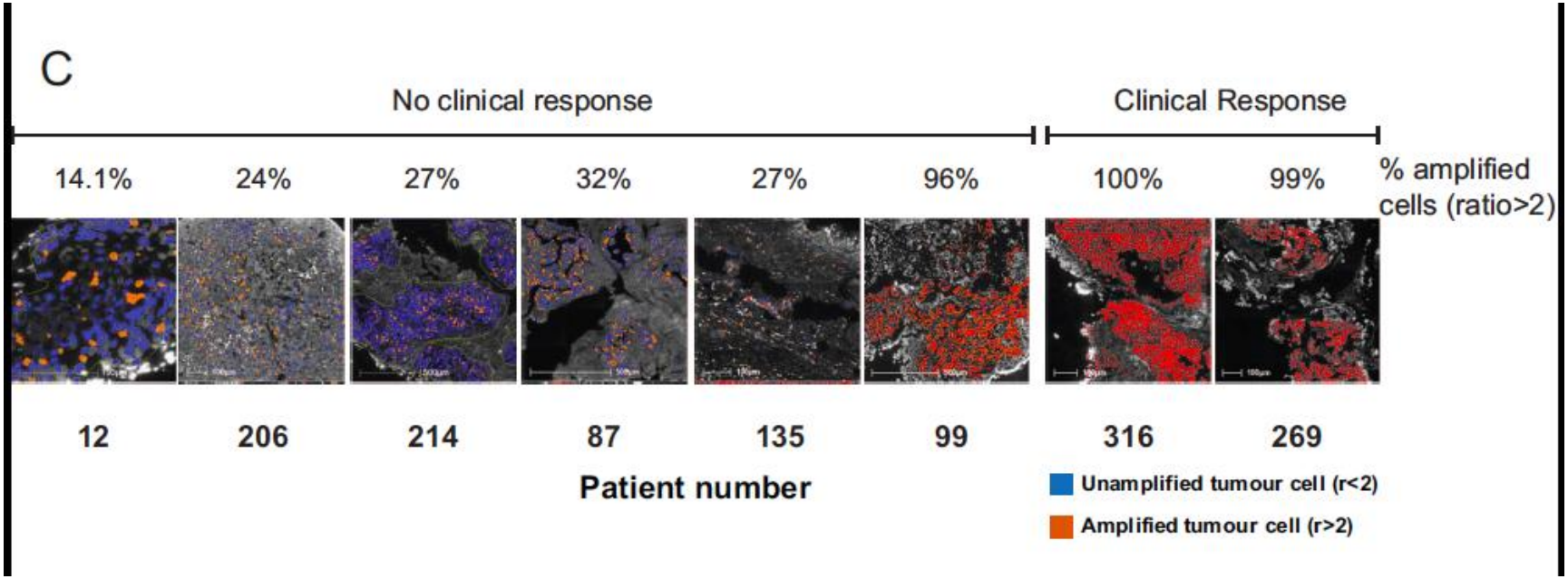
'passenger' events

time

Fitness

Slide adapted from Gad Getz

Heterogeneity and Responses to FGFR Inhibitors in Gastric Cancer



Additionally, saw +cfDNA signal in responders…..

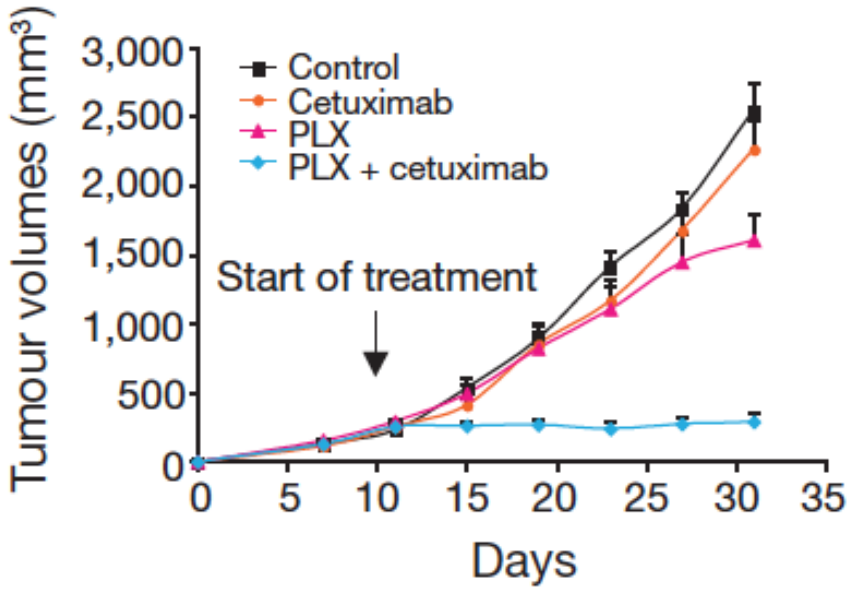
Pearson et al, *Cancer Discovery* 2016

BRAF and CRC: Reminder About the Studying Target Engagement and Non-Genetic Etiologies of Failure

-BRAF V600E mutant melanoma → great responses against vemurafanib (anti-BRAF)
-Colon cancers often have the exact same BRAF mutation!!
-So, they should respond to the same drug!
-But they don't….

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Anirudh Prahallad[1]*, Chong Sun[1]*, Sidong Huang[1]*, Federica Di Nicolantonio[2,3]*, Ramon Salazar[4], Davide Zecchin[2], Roderick L. Beijersbergen[1], Alberto Bardelli[2,3] & René Bernards[1]



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PD Biopsies Demonstrate Lack of Engagement: pERK

Unresponsiveness of colon canc
inhibition through feedback acti

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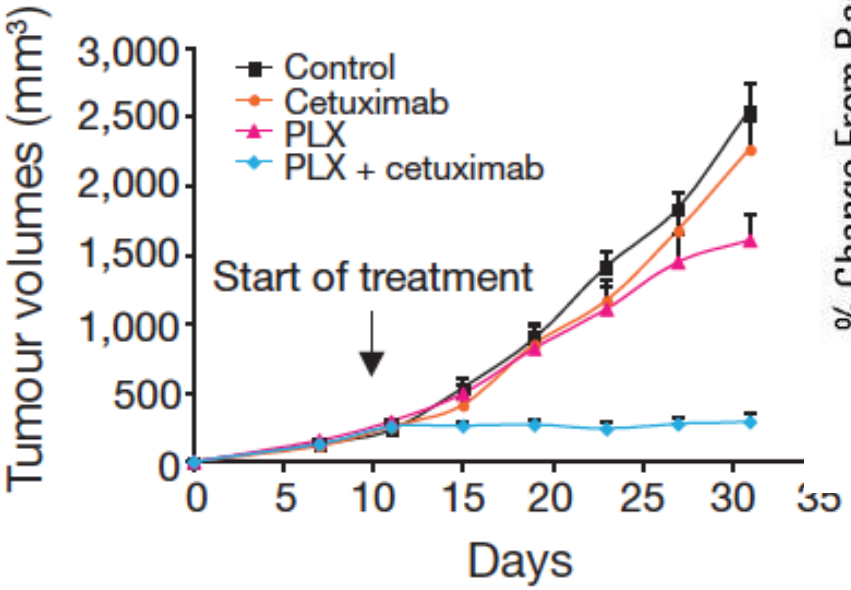

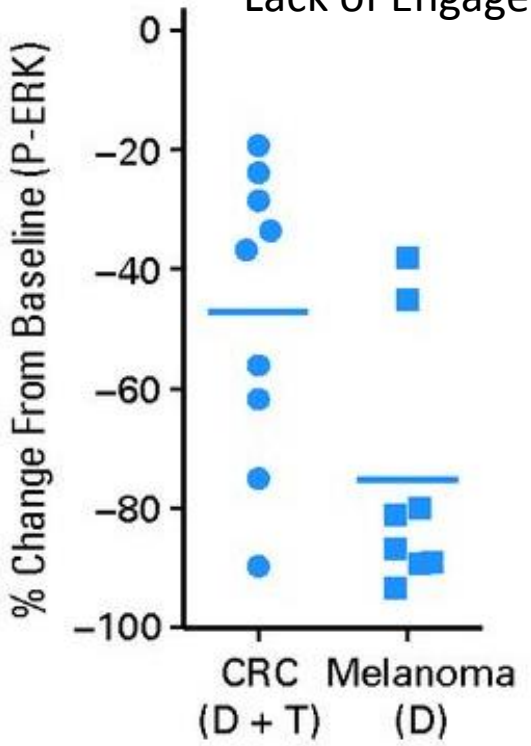

Corcoran et al JCO 2015

Re-thinking cancer therapy in the genomic era…

Conclusions

- Genomic-based therapies have little role (so far) in gastroesophageal and other GI cancers. However, genomic data allow us to better categorize these cancers and identify candidate therapeutic targets and identify biomarkers to guide how we can best apply current therapies
  - Many possibly actionable amplifications (with more as you move proximal, especially at GEJ)
  - Intriguing mutation in MSI cancers (e.g. ERBB2, ERBB3, PIK3CA)
  - PI3-K and PD-1 pathway emerge as targets in EBV (and MSI)
  - ??What to do about diffuse type gastric cancer??
  - Correcting for confounding by subtype will allow us to address debates such as East/West and esophagus/stomach.
- As we move forward, we have great opportunities to leverage these data to develop new therapies
  - But we should not over-simplify the challenge at hand
  - Key moving forward will be to combine our knowledge of the genome with tumor biology to learn how to 'play chess' with cancer. That is to develop effective rationale combination strategies to target key cancer genes and pathways.

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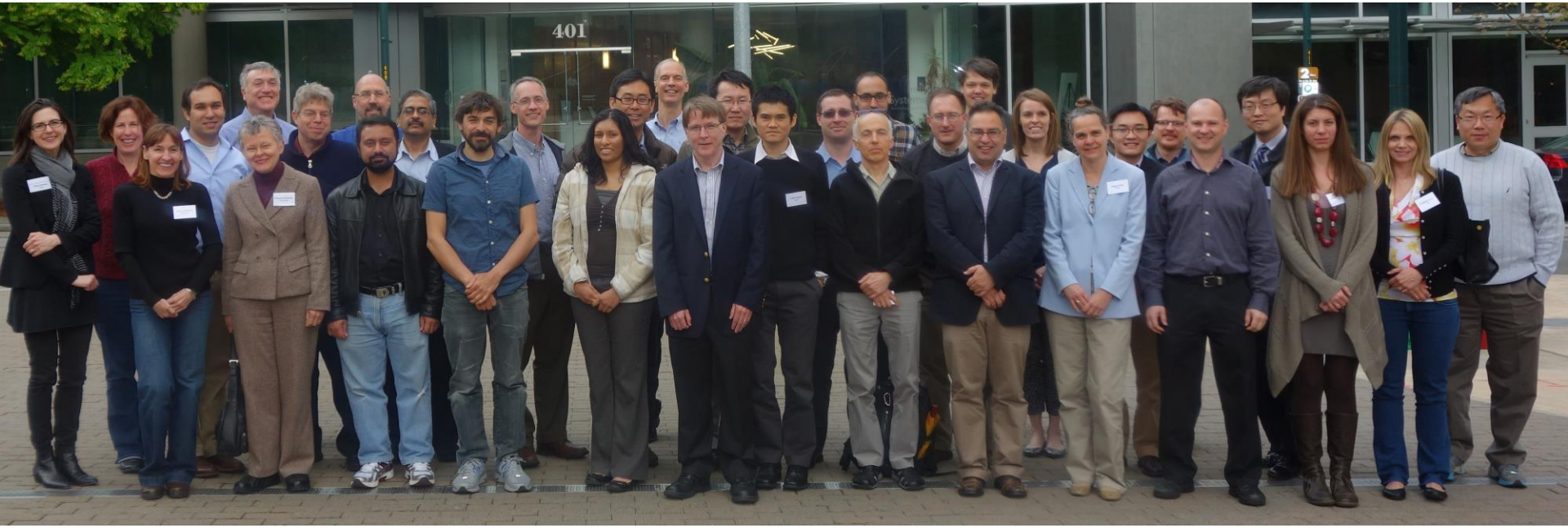

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