

# Precision Oncology Applications in Gastric Cancer

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# DECLARATION OF INTERESTS

First name Patrick Tan

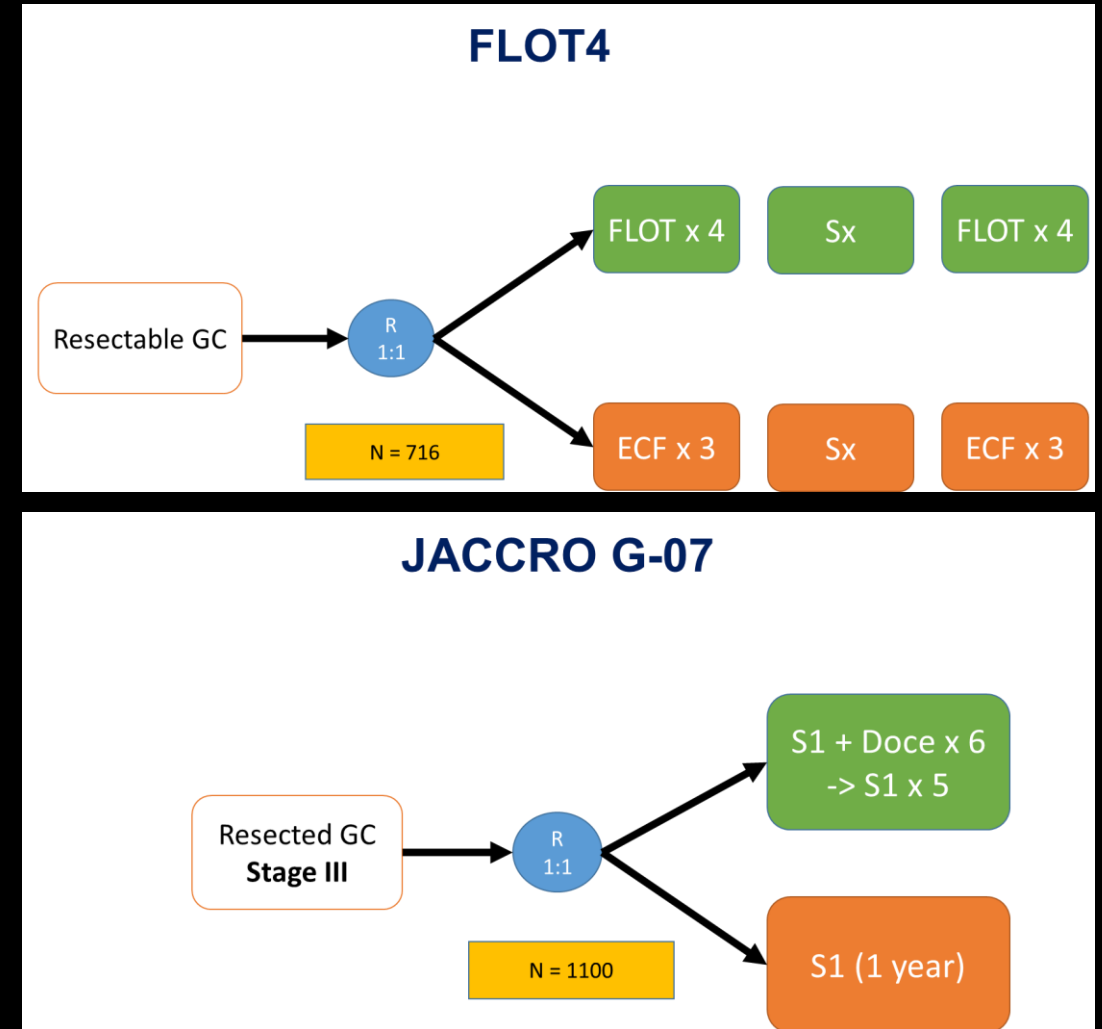
I am named on patent applications filed by A\*STAR (Agency for Science, Technology and Research) related to the use of alternate promoters in cancer

## Today's Topics

- 1) Predictive Biomarkers for Chemotherapy  
- Machine Learning and Taxane Sensitivity
- 2) Predictive Biomarkers for Immune Checkpoint Inhibitors  
- Epigenetic Use of Alternate Promoters

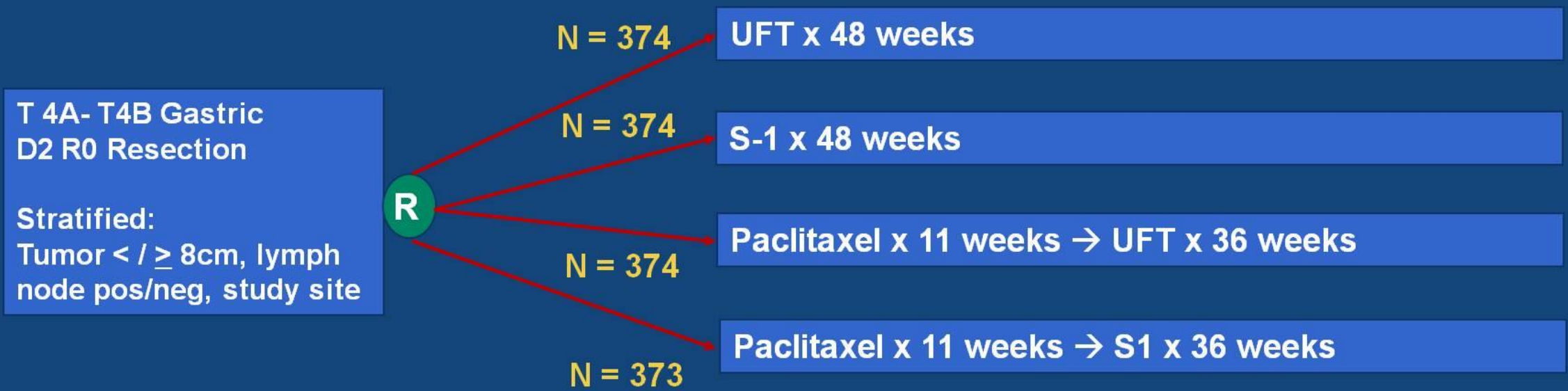
# Taxanes are Playing an Increasingly Prominent Role in Gastric Cancer

- FLOT4 – role of perioperative **docetaxel**
- JACCRO-G07 – role of adjuvant **docetaxel**
- PRODIGY – neoadjuvant **docetaxel**
- V325 – first-line **docetaxel** + platinum doublet
- RAINBOW – **Paclitaxel** + ramucirumab, second line GC
- KEYNOTE-061 – failure of immunotherapy vs **paclitaxel**



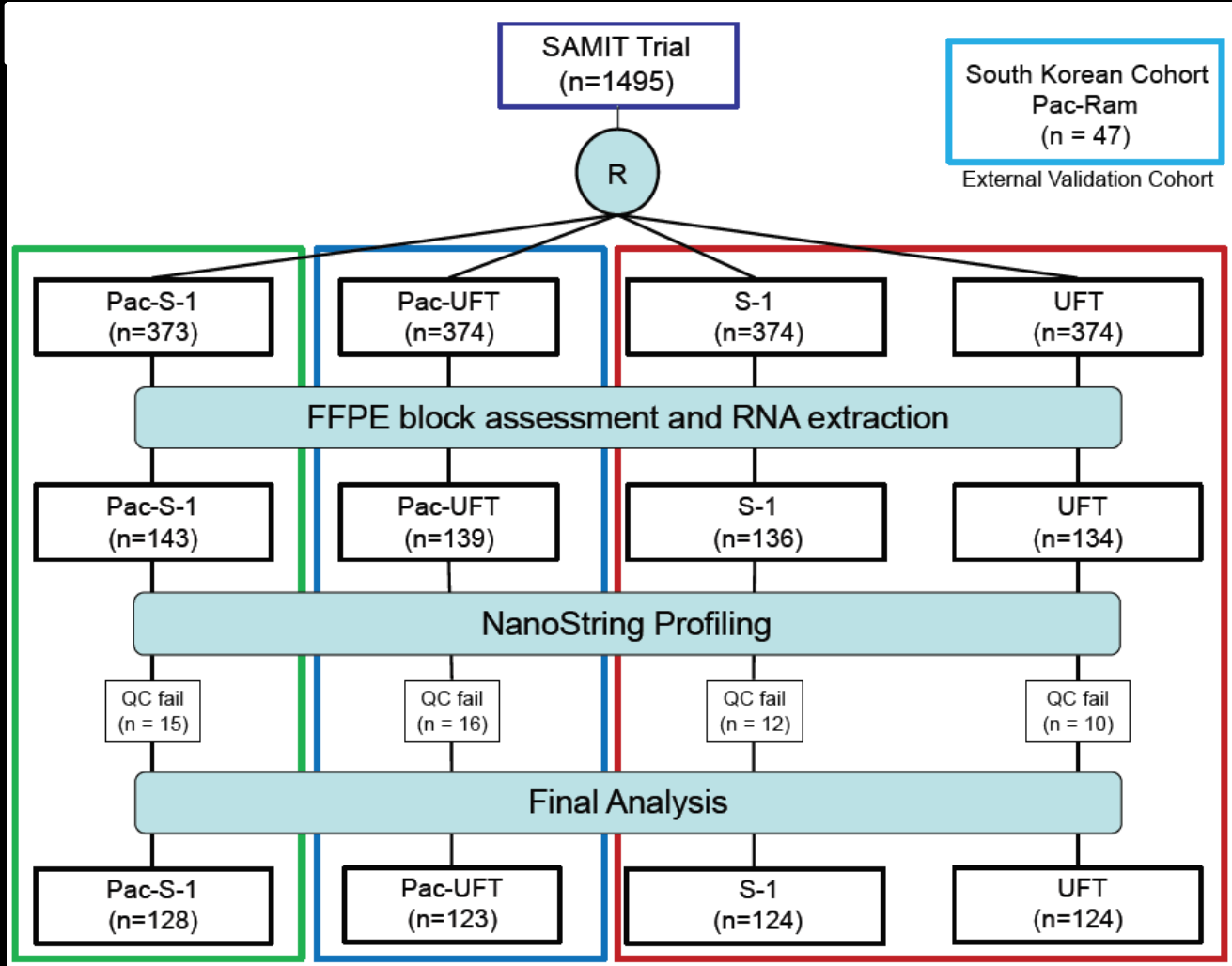
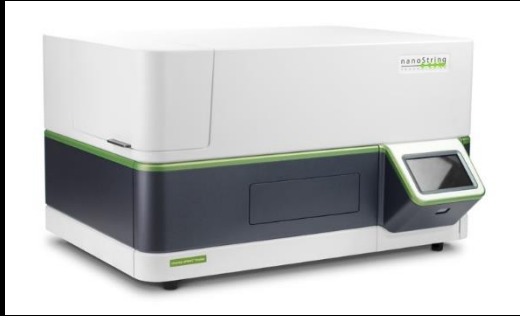
# SAMIT : One of the Largest Adjuvant Trials in Gastric Cancer

SAMIT: Adjuvant Paclitaxel → S1/UFT vs. S1/UFT alone  
Schema:



Primary endpoint: Disease-Free Survival

# SAMIT's 2x2 Design Enables Training, Validation and Treatment Interaction Analysis



**Training**

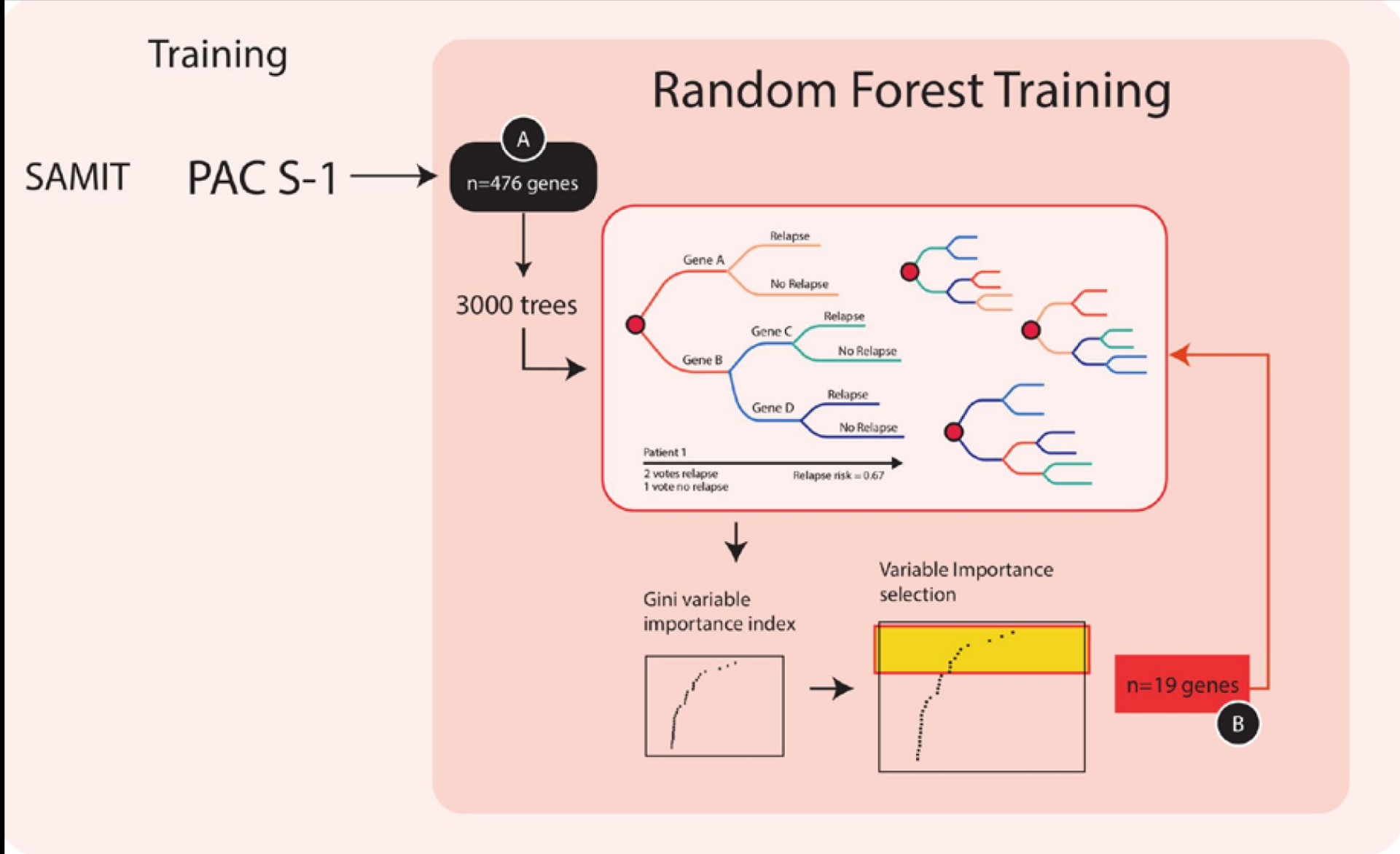
**Validation**

**Treatment Interaction**

## Nanostring Analysis of 500 Genes

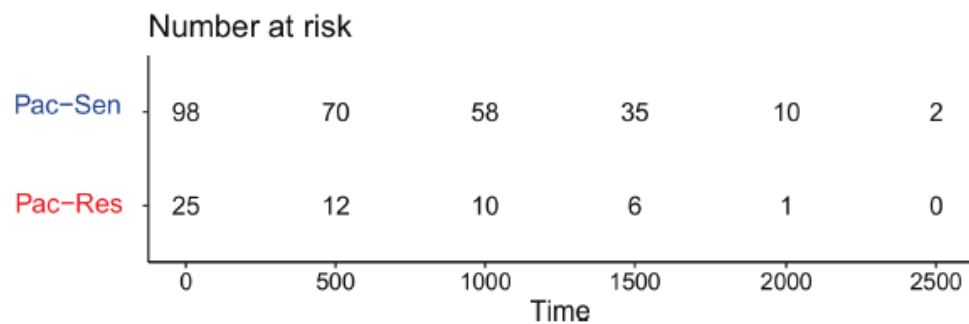
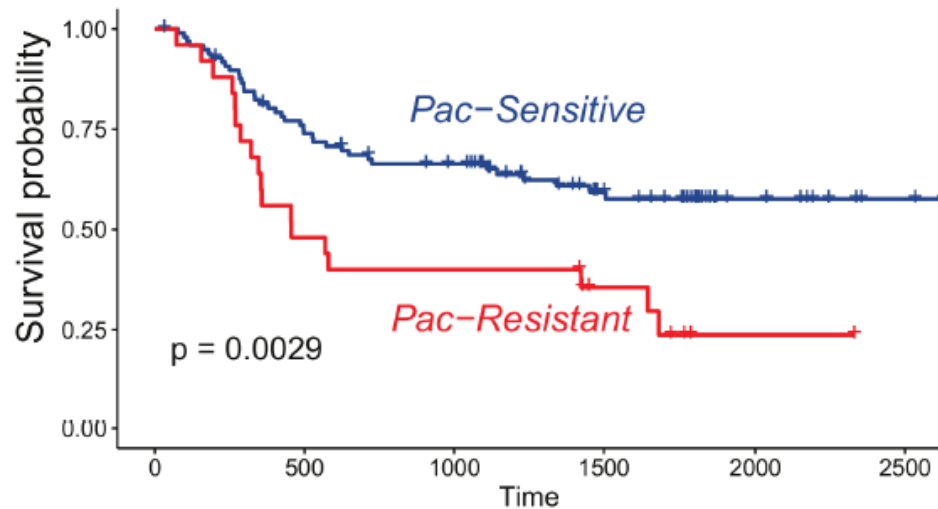
- Spindle assembly checkpoint
- Therapeutic targets in GC
- Tumour microenvironment
- Oncogenic signalling
- Frequent genomic alterations
- Immune-related
- DNA repair
- Chemotherapy benefit (from literature)

# A 19-gene Signature of Paclitaxel Response Identified by Random-Forest Machine Learning

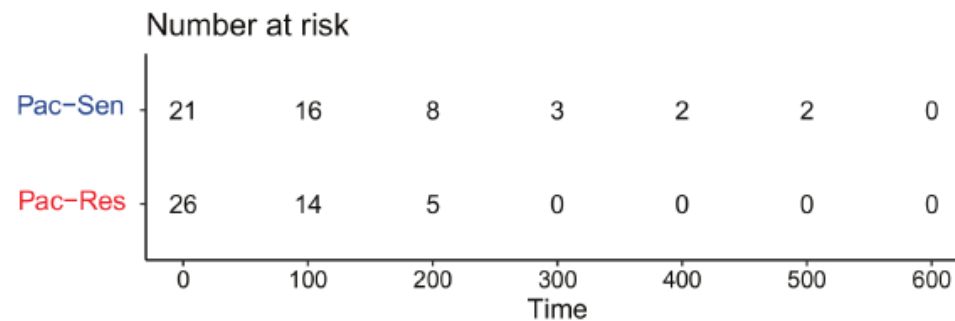
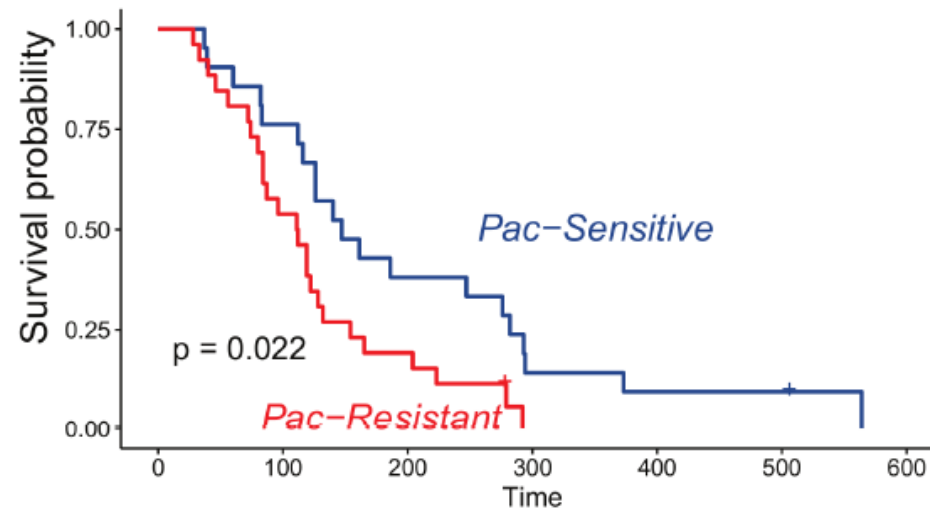


# Performance of 19-gene Paclitaxel Classifier in Validation Cohorts

Gene signature in Pac-UFT cohort



Gene signature in Pac-Ram cohort  
Kim et al, Genome Medicine 2021





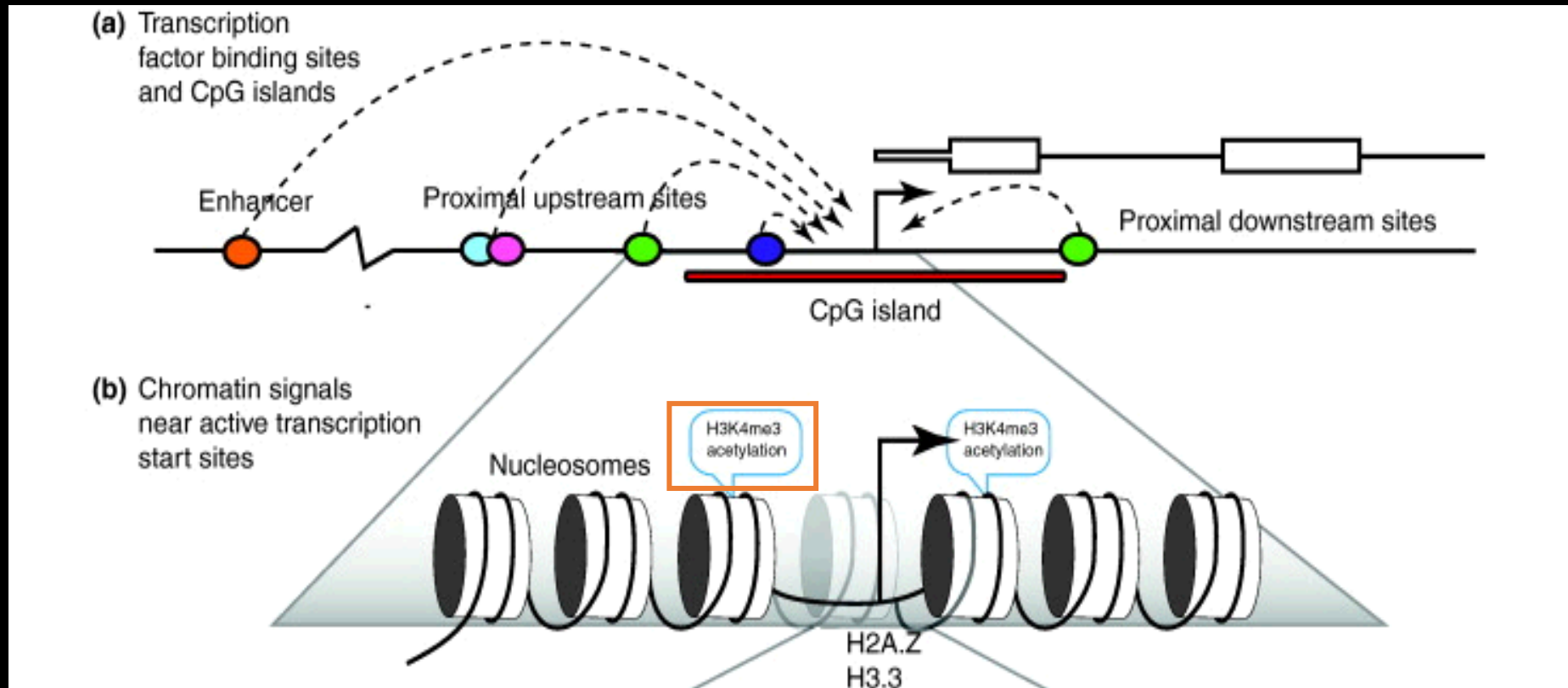
## Take-Home Messages

- Applying machine-learning to SAMIT, one of the largest adjuvant Phase III trials in GC, identifies a **19-gene expression signature of paclitaxel response**
- The signature was validated in **two independent cohorts**, thereby reflecting one of the first predictive biomarkers for taxanes in GC
- Given the increasing use of taxanes in GC in the adjuvant and perioperative setting, this biomarker may guide clinicians in identifying patients with GC who might benefit from taxane based therapy
- Further validation of the 19-gene biomarker is warranted

# Today's Topics

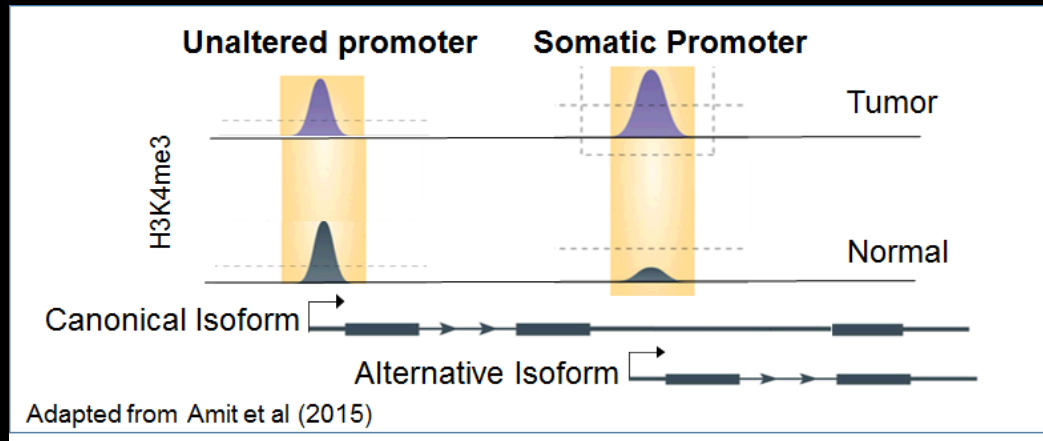
- 1) Predictive Biomarkers for Chemotherapy
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- 2) Predictive Biomarkers for Immune Checkpoint Inhibitors
  - Epigenetic Use of Alternate Promoters

# Gene Promoters : Critical Integrators of Regulatory Inputs

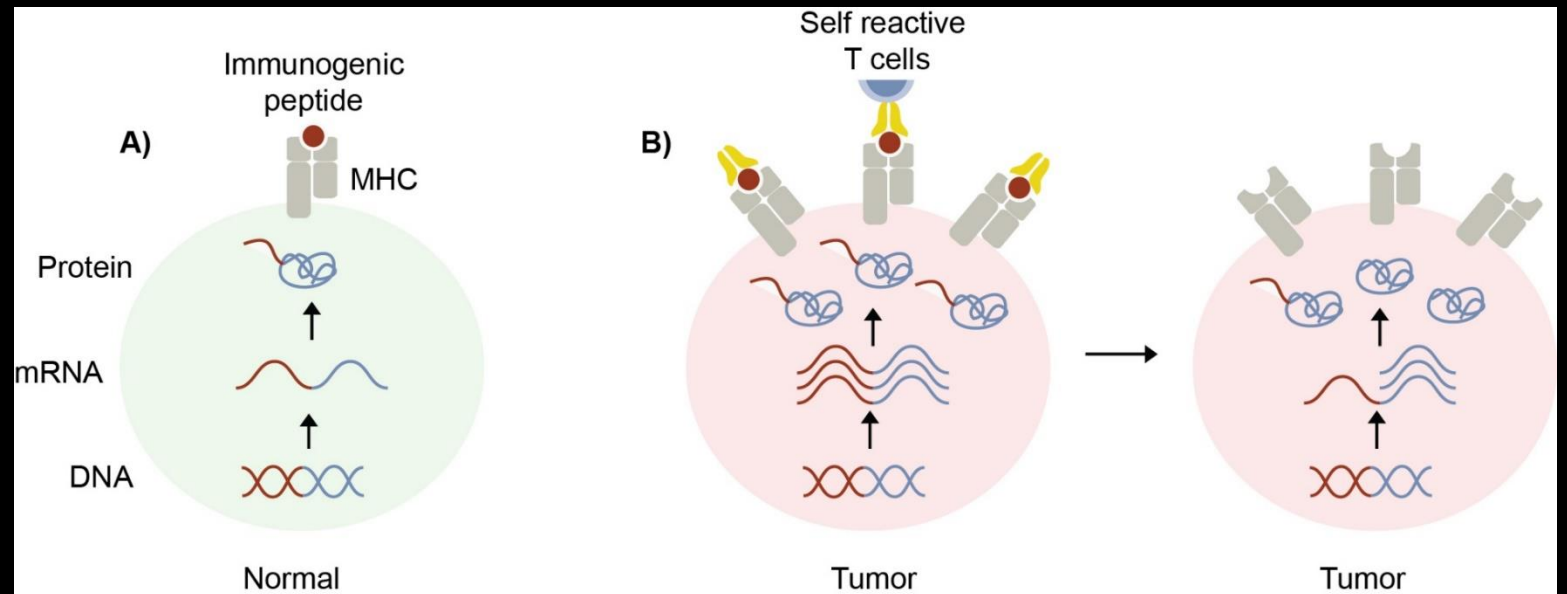
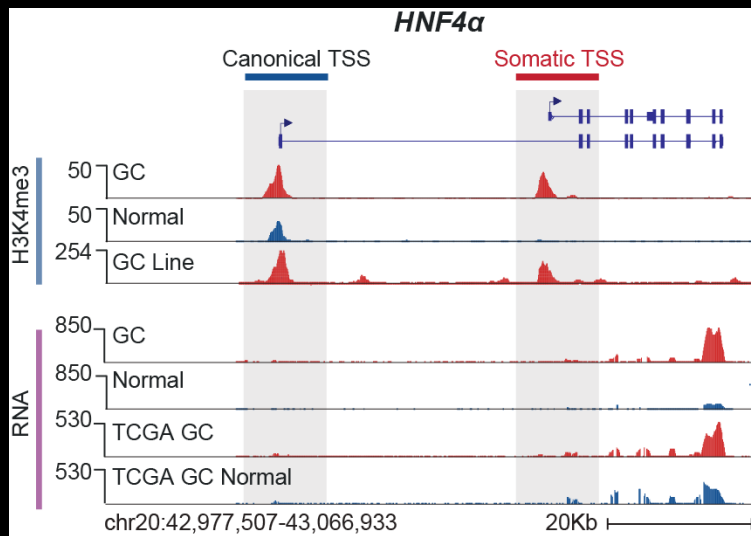
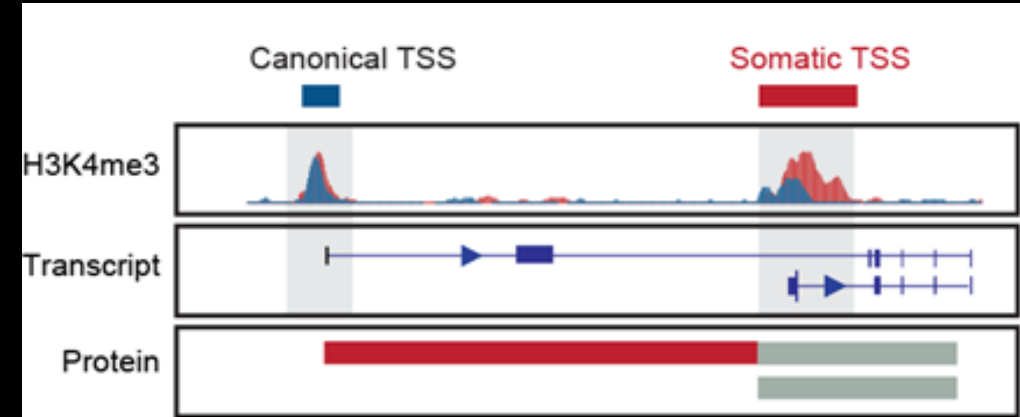


Valen and Sandelin (2011) *Trends in Genetics*

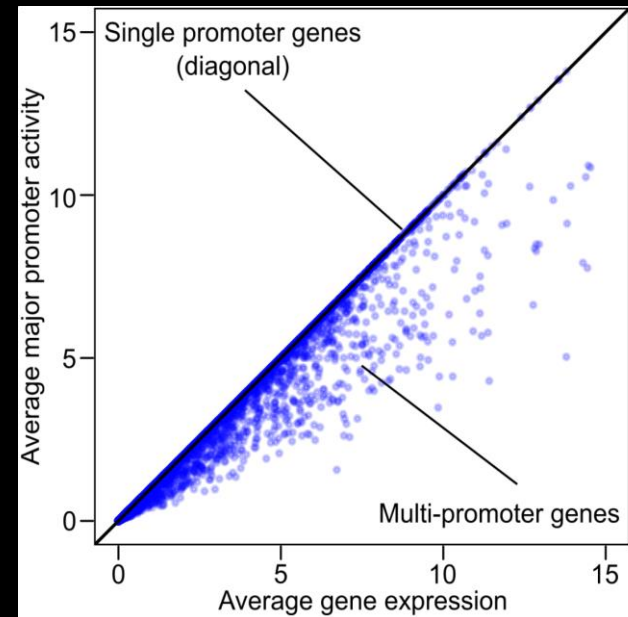
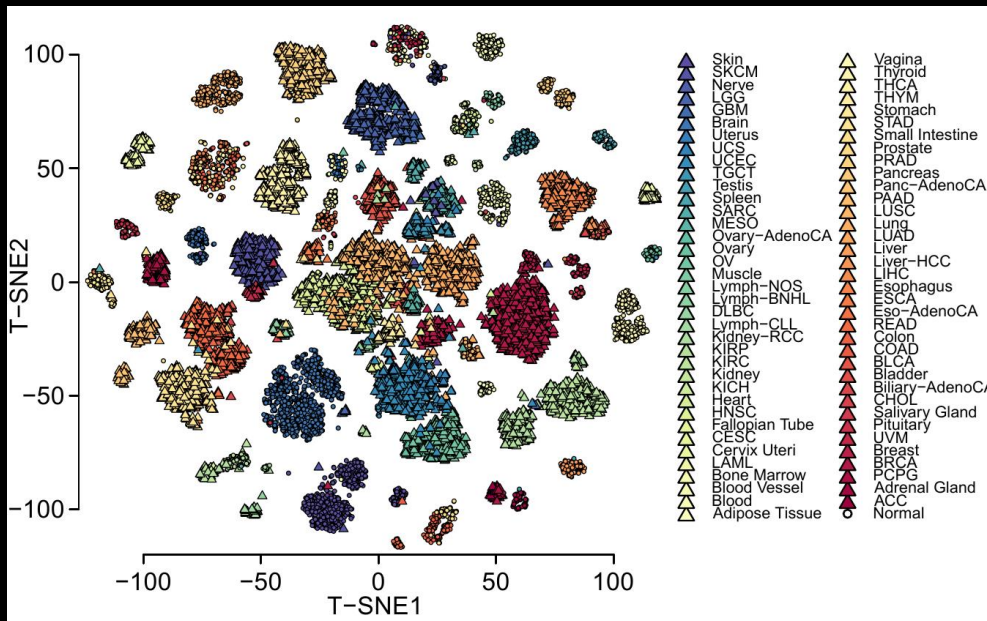
# Many GC Promoters Comprise Alternative Promoters



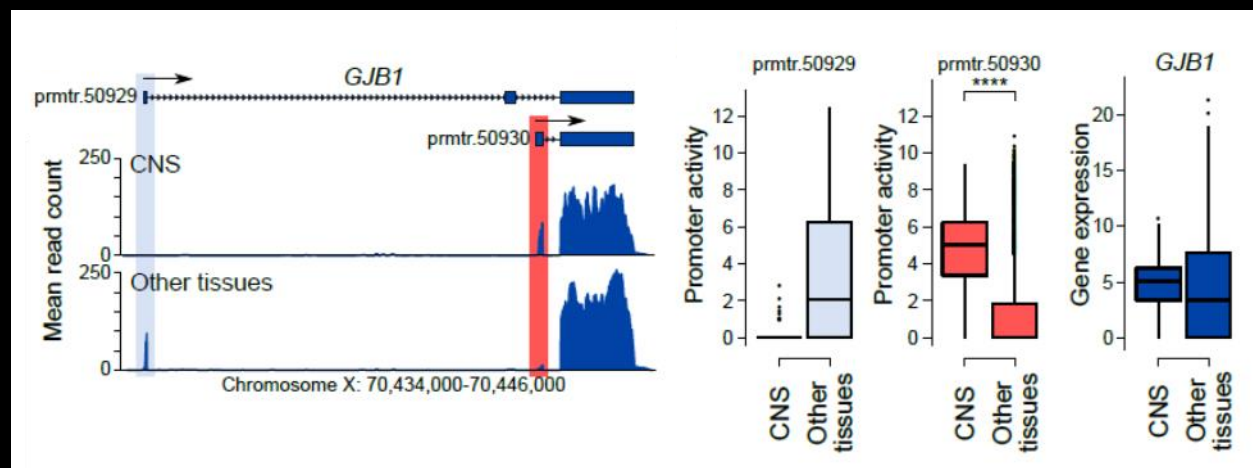
# Alternative Promoters cause Loss of 5' Immunogenic Regions



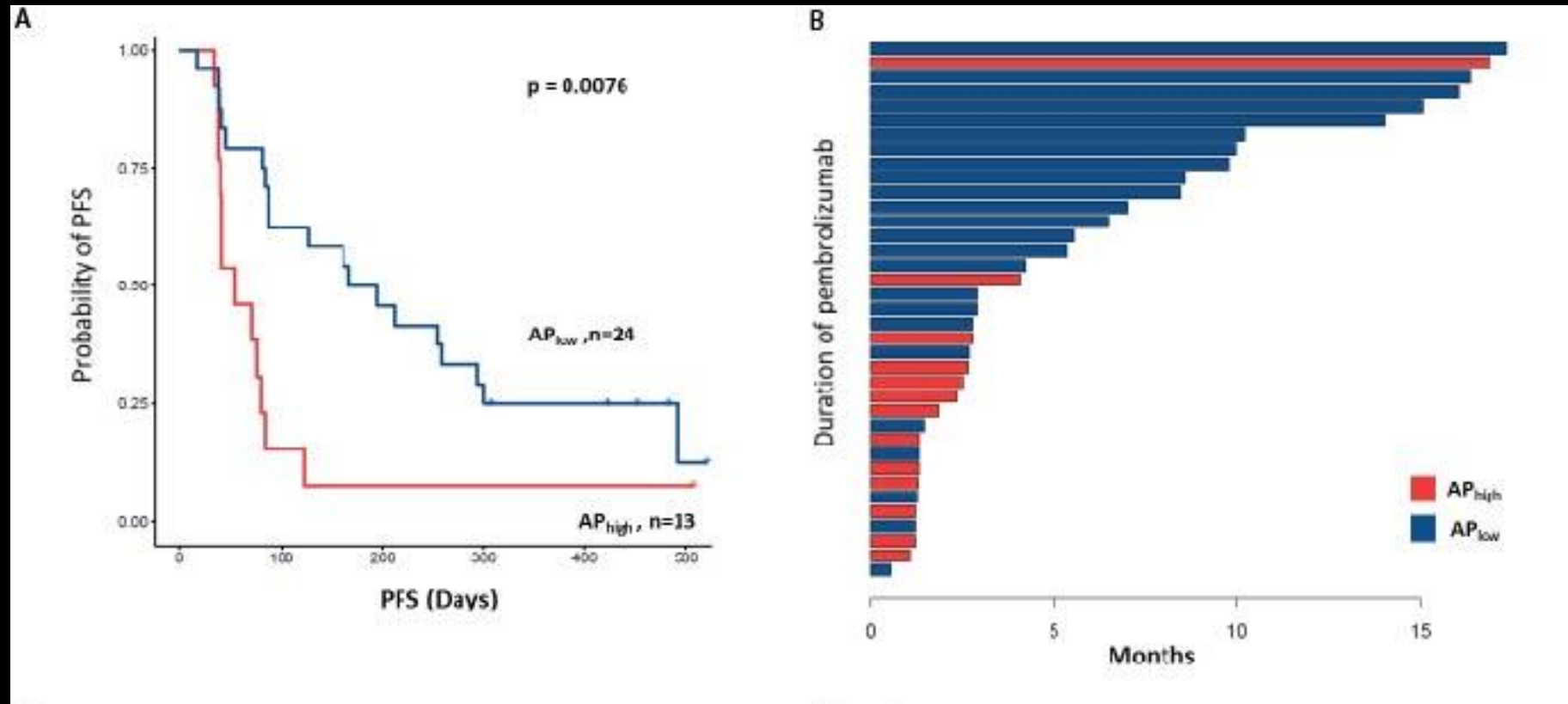
# Alternate Promoter Usage is Widespread across Tumor Types (18,468 samples, 33 tumor types)



Several genes have Multiple Promoters



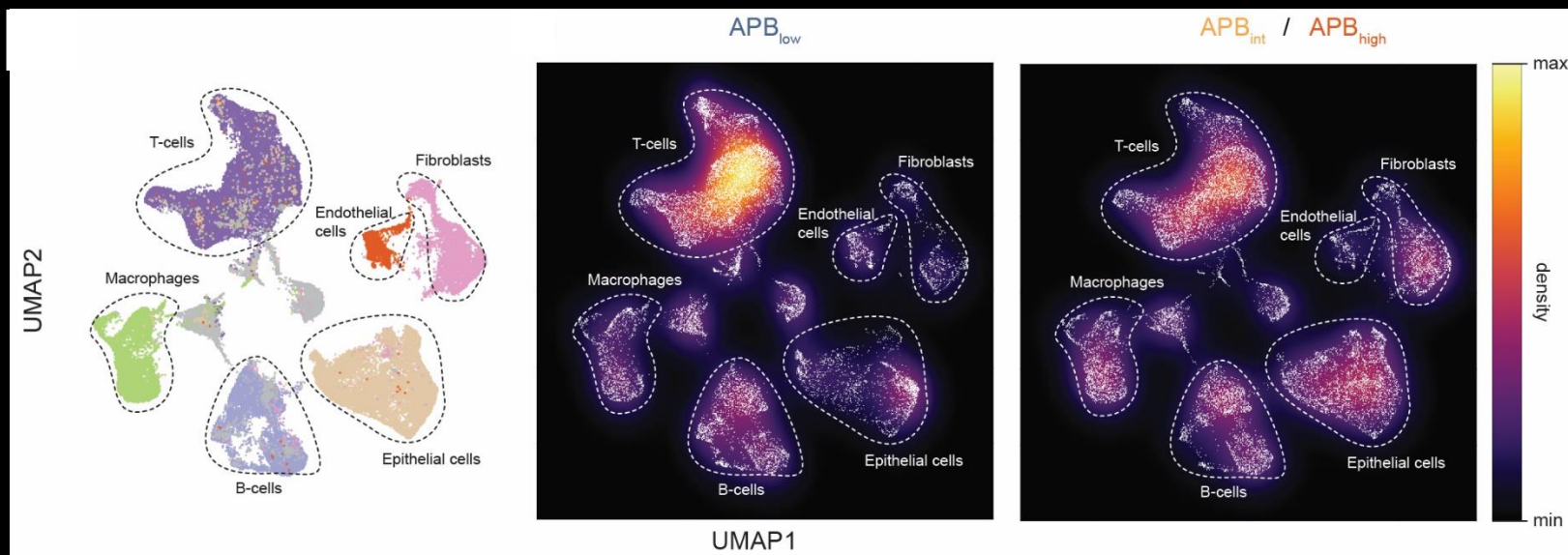
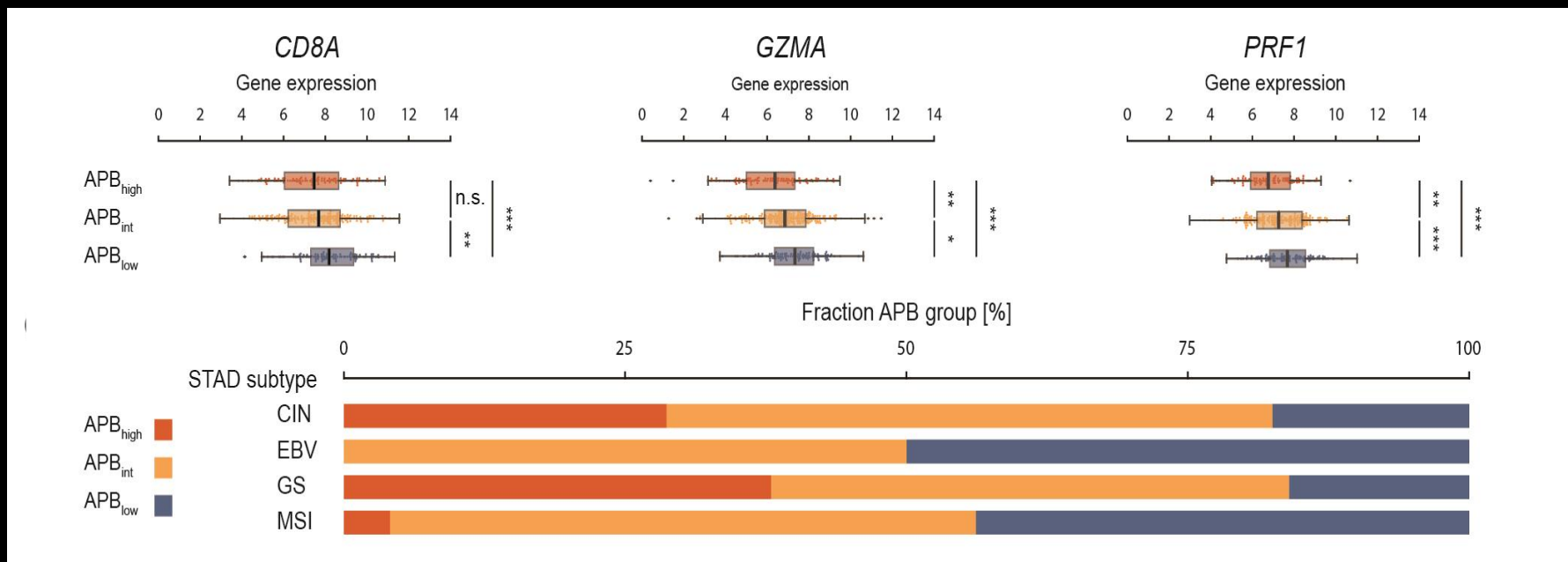
# Alternative Promoter Burden (APBscore) is a Candidate Negative Predictive Biomarker of I/O Response



Sundar et al, *Annals of Oncology* 2019



# APB(High) GCs Show Decreased T-cell Markers and Infiltrate

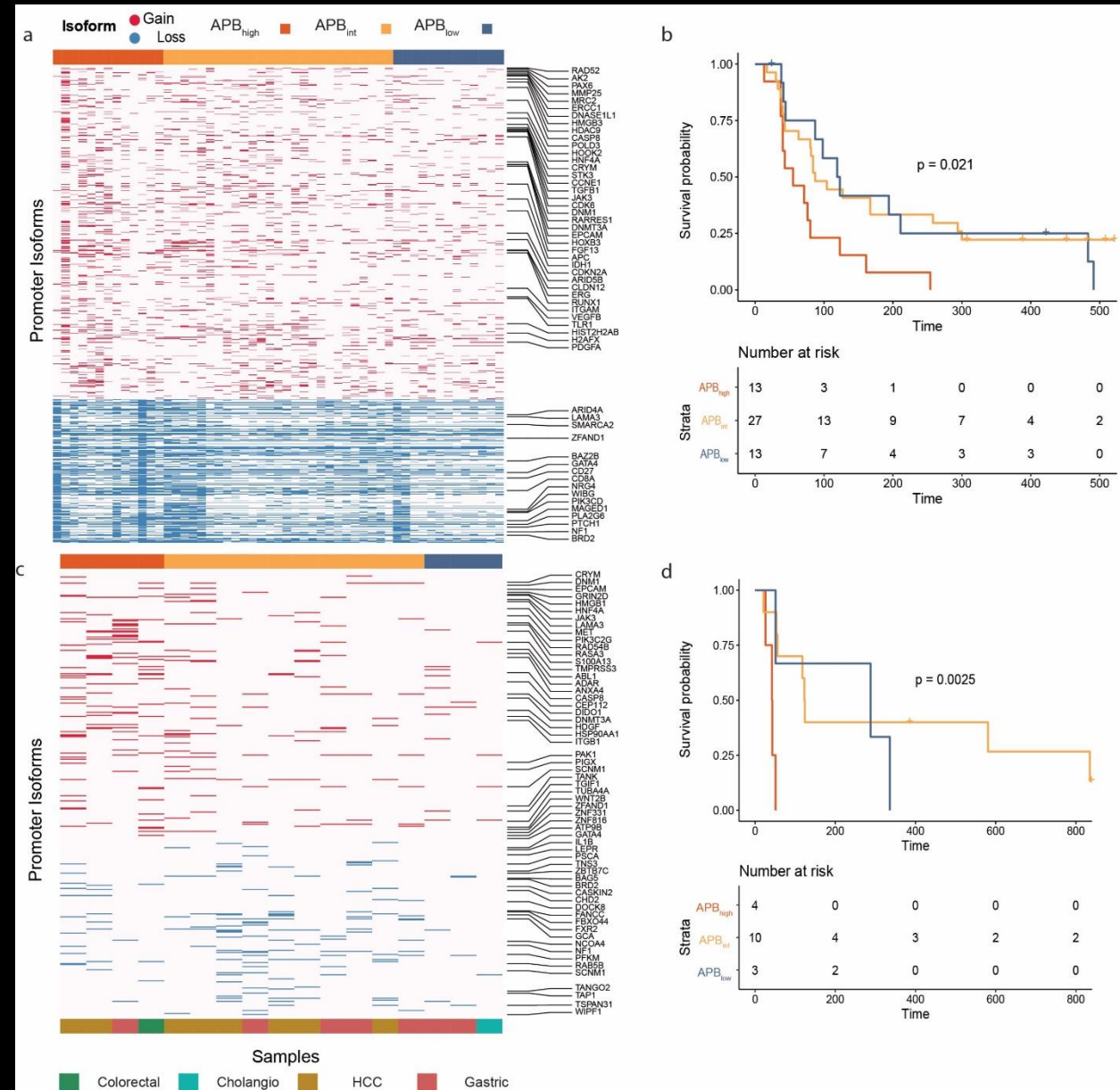


# APB(High) Gastrointestinal Tumors Exhibit Resistance to ICIs

## ICI-Treated Cohorts from

National Cancer Centre/National University Hospital (Singapore)  
 Samsung Medical Centre (S. Korea)  
 Yonsei Cancer Centre (S. Korea)  
 Pharmaceutical Company (Intl)  
 University of Milan (Europe)  
 Aichi Cancer Centre (Japan)

Treated with nivolumab,  
 pembrolizumab, durvalumab





## Take-Home Messages

- Alternate promoter utilization is an epigenetic phenomenon associated with immune-editing and immune-evasion
- Tumors with high alternate promoter burden (APB) are depleted of T-cells in the tumor microenvironment and tend to be resistant to immune checkpoint inhibition
- This phenomenon, initially identified in gastric cancer, appears to occur in multiple tumor types
- **APB is a potential predictive biomarker for immunotherapy**

# Acknowledgements

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- Raghav Sundar – Lead fellow
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- Thaleia Ong – cell lines

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- Takashi Oshima

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