



# **GIST Research Update: What's New and Promising?**

## ***Location of Gastric GIST Predicts Mutation Profile***

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**UC San Diego**  
**MOORES CANCER CENTER**

# Disclosures



## Research Funding

Amgen  
Foundation Medicine

## Consultant

Deciphera

## Speaker

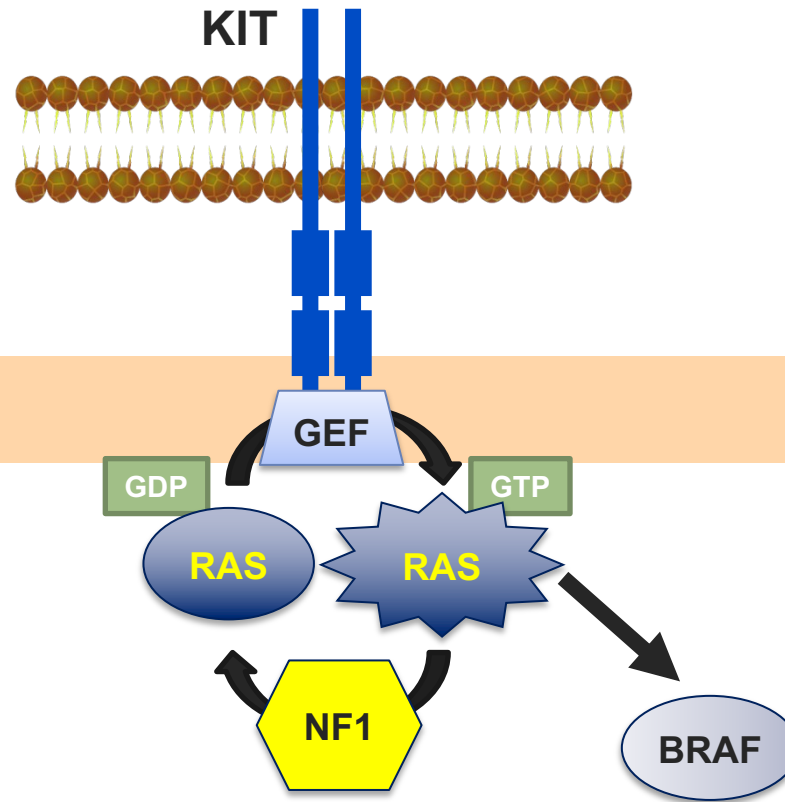
Bayer  
Deciphera  
Foundation Medicine  
La Hoffman-Roche  
Merck  
QED

# The evolution of GIST genomics

**KIT**

Gain-of-function mutations  
Hirota et al., *Science*.

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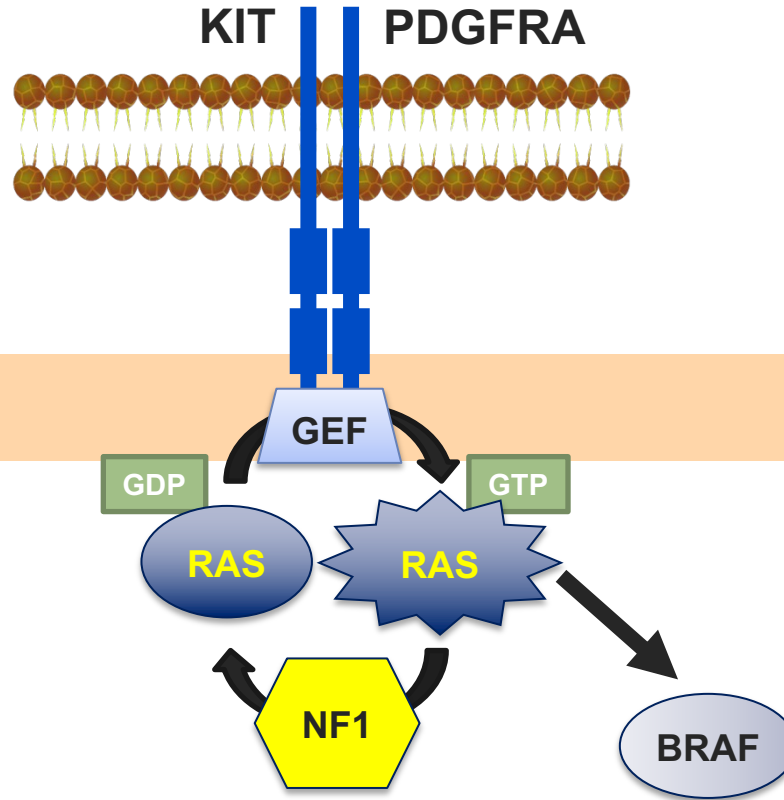
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Activating mutations in 35%  
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GIST in pts with NF-1  
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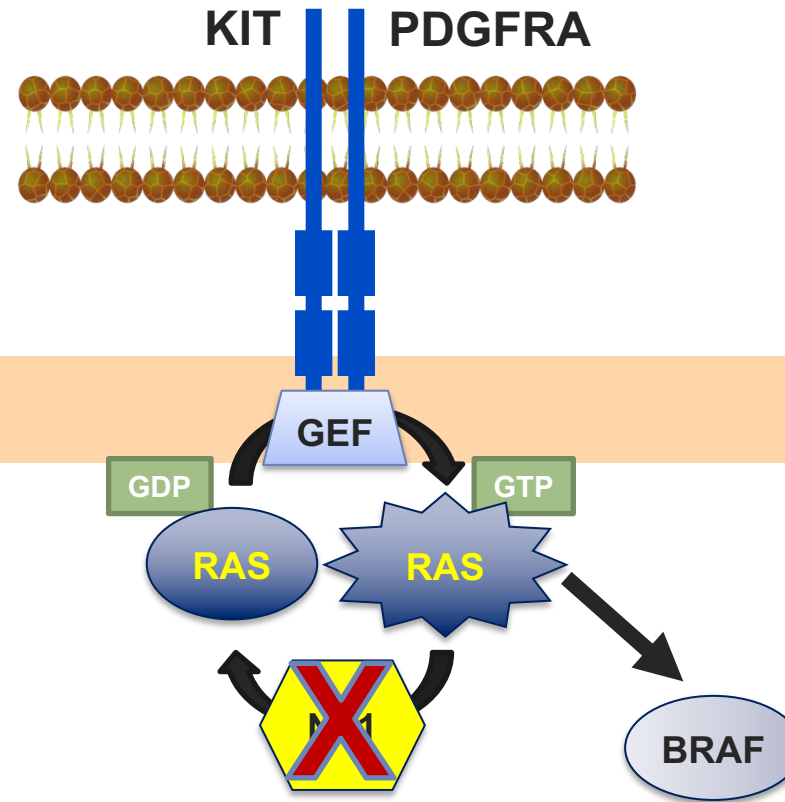
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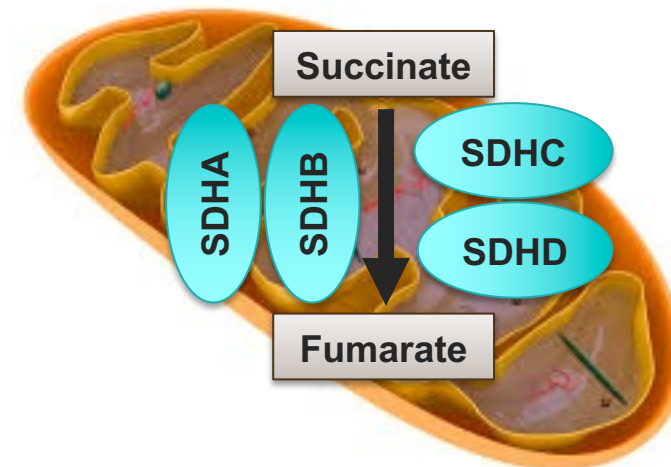
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7 families with *SDH*  
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McWhinney et al., *NEJM*.



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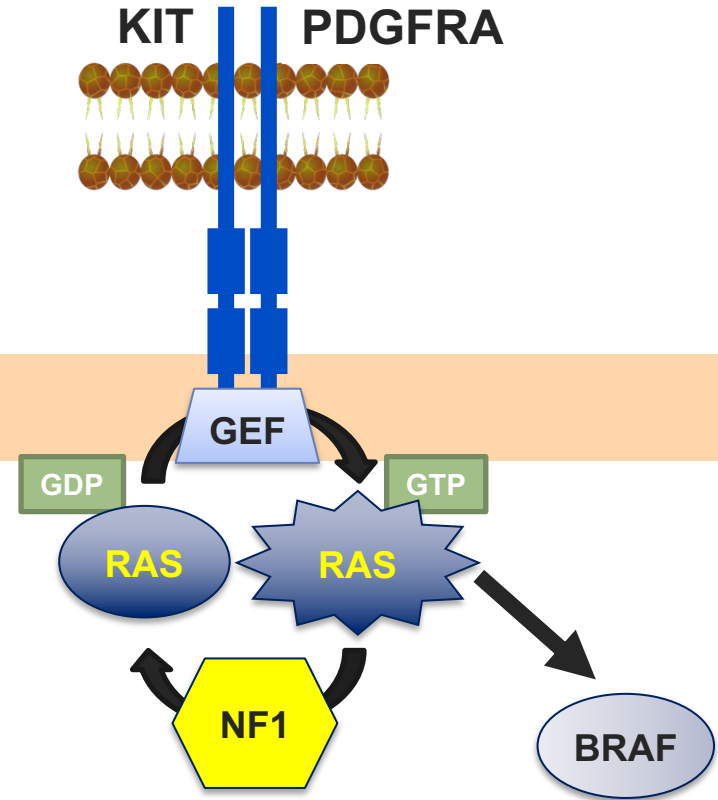
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Activating mutations in 7% of *non-KIT/PDGFRA* mutant  
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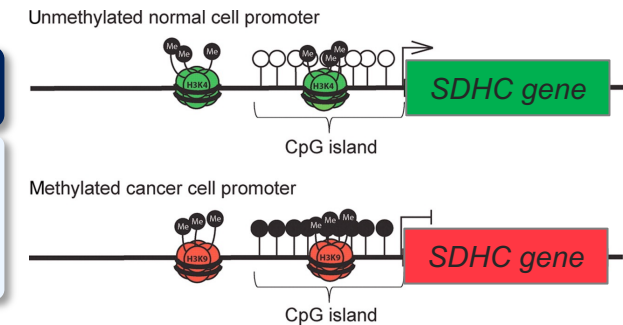
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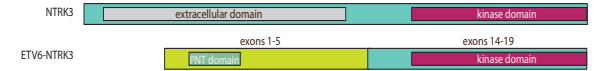
## ***SDHC* "Epimutation"**

*SDHC* promoter  
hypermethylation  
Killean et al., *Sci Trans Med*.





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## **BRAF V600E**

Activating mutations in 7% of *non-KIT/PDGFR*A mutant  
Agaram et al., *Genes Chrom Cancer*.

## **ETV6-NTRK3**

Quadruple WT (*KIT/PDGFR*A/*RAS-P/SDH*) have ETV6-NTRK3 fusion  
Brenca et al., *J Pathol*  
Shi et al., *JTM*.

2003

2007

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2016

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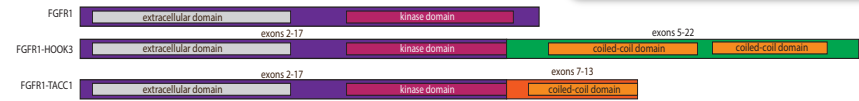
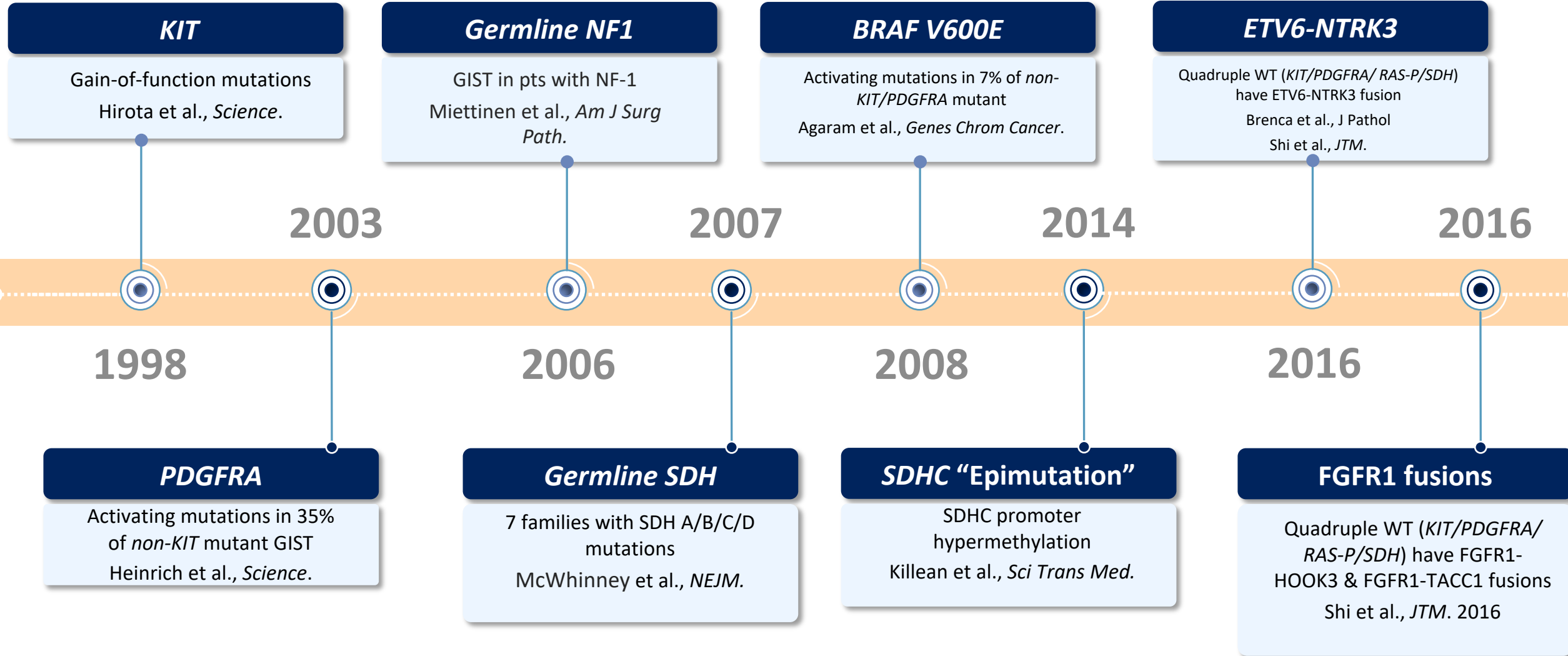
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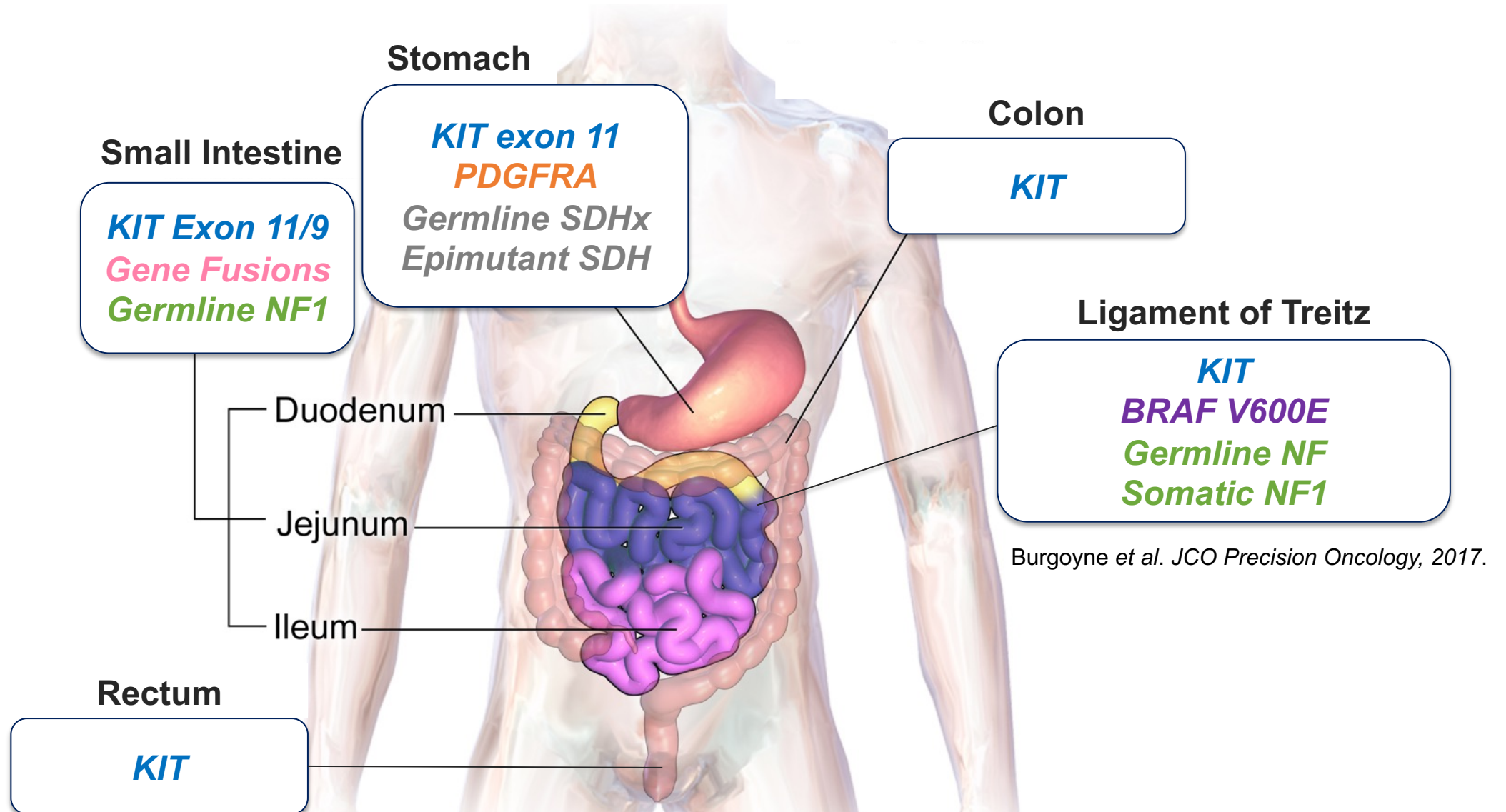
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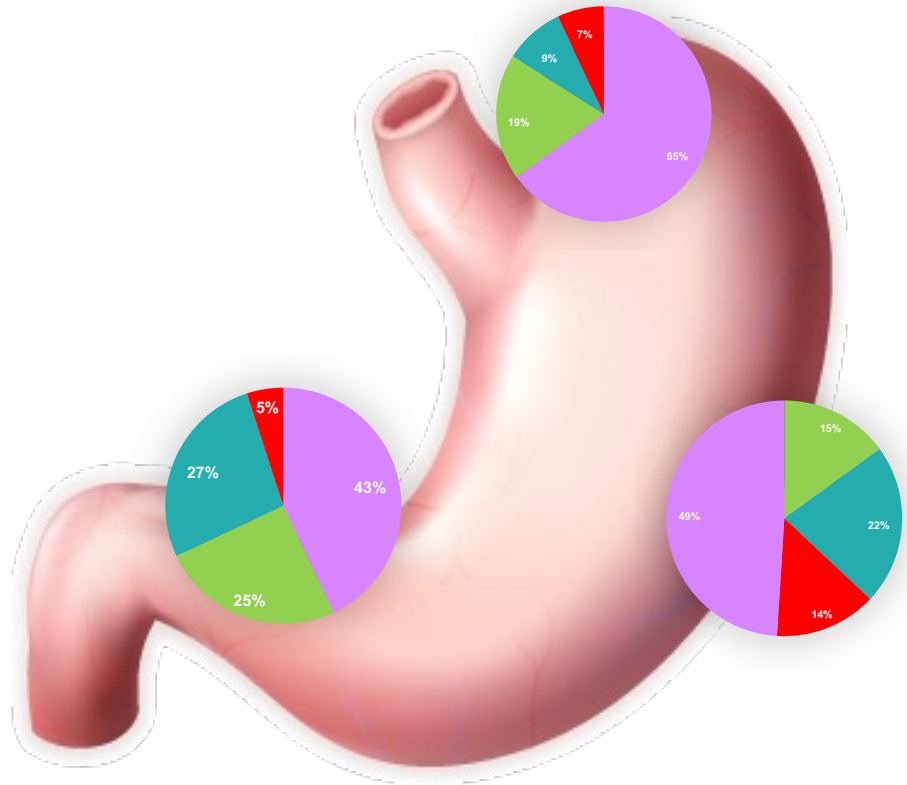
# The evolution of GIST genomics



# Mutation Profile Associated with Location



# Tumor Location within Organs Correlates with Mutation Profile



TCGA, *Nature*. 2014.  
 Caris Life Sciences. ASCO. 2017  
 Sohal *et al.*, *Crit Rev Onc/Hem*. 2016.

## CIN - Chromosomal Instability

- Intestinal histology
- TP53 mutation
- RTK-RAS activation

## GS - Genomically Stable

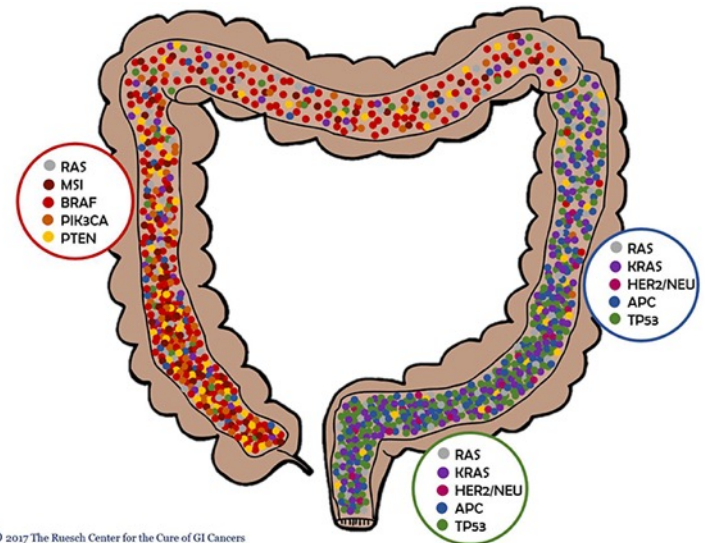
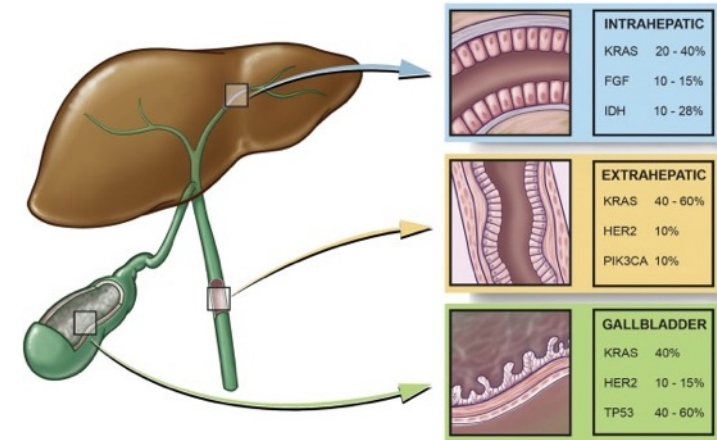
- Diffuse histology
- CDH1, RHOA mutations
- CLDN1S-ARHGAP fusion
- Cell adhesion

## MSI - Micro Satellite Instability

- Hypermutation
- Gastric-CIMP
- MLH1 silencing
- Mitotic pathways

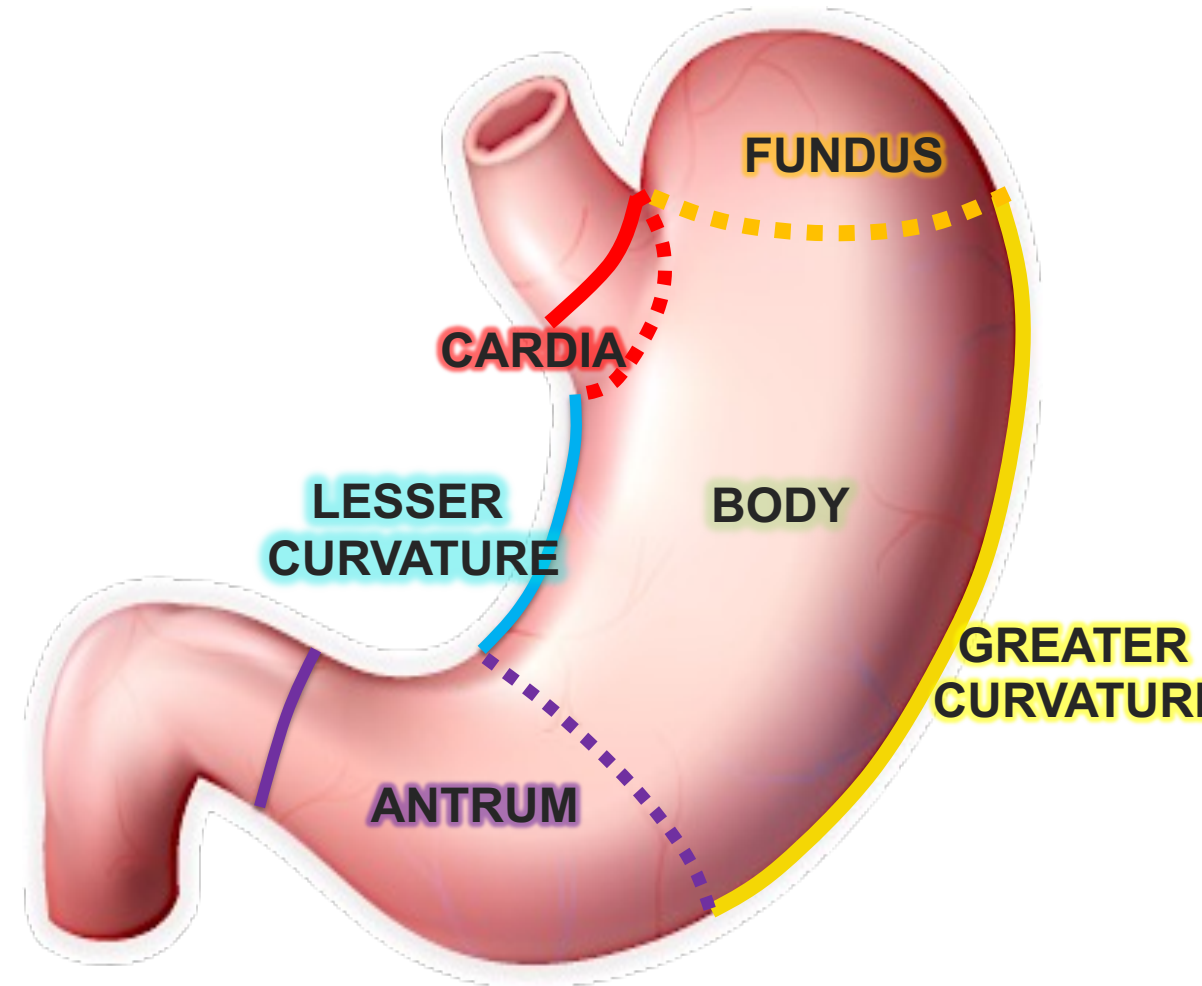
## EBV - Epstein Barr Virus

- PIK3CA mutation
- PD-L1/2 overexpression
- EBV-CIMP
- CDKN2A silencing
- Immune cell signaling



# Hypothesis

GIST arising from distinct regions within the stomach may possess unique genomic profiles.

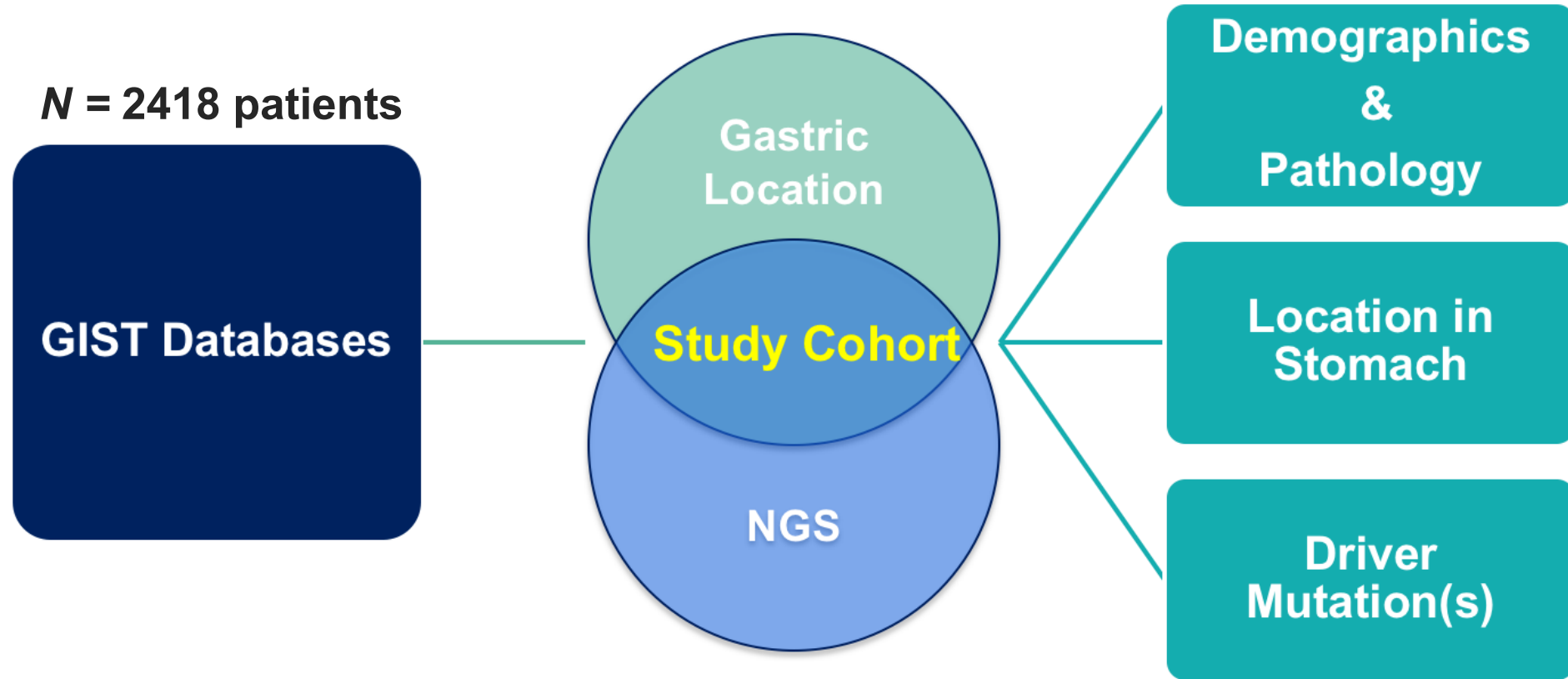




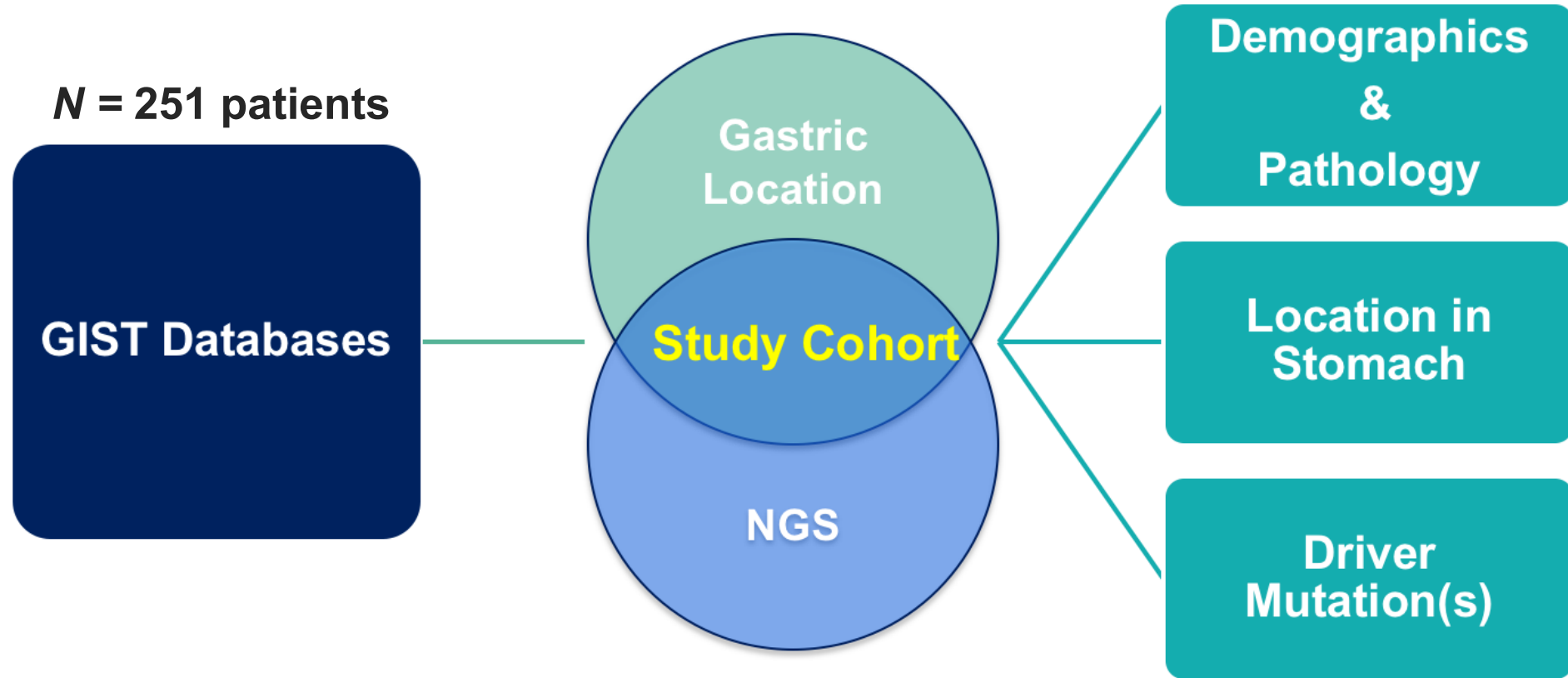
# Location of Gastrointestinal Stromal Tumor (GIST) in the Stomach Predicts Tumor Mutation Profile and Drug Sensitivity

Ashwyn K. Sharma<sup>1,2</sup>, Jorge de la Torre<sup>1,2</sup>, Nikki S. IJzerman<sup>3,4</sup>, Thomas L. Sutton<sup>5</sup>, Beiqun Zhao<sup>1,2</sup>, Tahsin M. Khan<sup>6</sup>, Sudeep Banerjee<sup>1,2,7</sup>, Christina Cui<sup>1</sup>, Vi Nguyen<sup>1</sup>, Maha Alkhuziem<sup>1,2</sup>, Petur Snaebjornsson<sup>8</sup>, Hester van Boven<sup>8</sup>, Annemarie Bruining<sup>9</sup>, Chih-Min Tang<sup>1,2</sup>, Hyunho Yoon<sup>1,2</sup>, Alexa De la Fuente<sup>1</sup>, Shumei Kato<sup>2,10</sup>, Hitendra Patel<sup>2,10</sup>, Michael C. Heinrich<sup>11</sup>, Christopher L. Corless<sup>12</sup>, Santiago Horgan<sup>13</sup>, Adam M. Burgoyne<sup>2,10</sup>, Paul Fanta<sup>2,10</sup>, Jill P. Mesirov<sup>2,14</sup>, Andrew M. Blakely<sup>6</sup>, Jeremy L. Davis<sup>6</sup>, Skye C. Mayo<sup>5</sup>, Winan J. van Houdt<sup>15</sup>, Neeltje Steeghs<sup>3</sup>, and Jason K. Sicklick<sup>1,2</sup>

# National Cancer Database (NCDB)



# TransAtlantic GIST Collaborative (TAGGC)





# NCDB & TAGC Cohorts

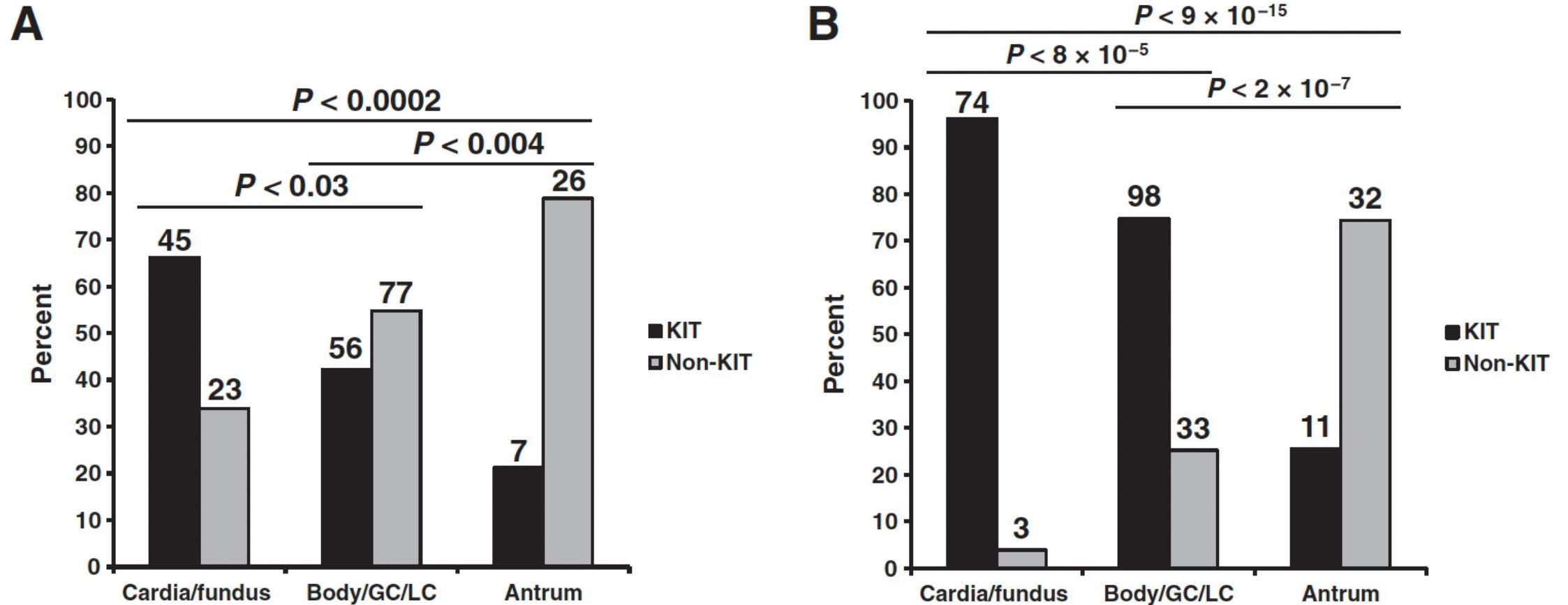
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## NCDB cohort

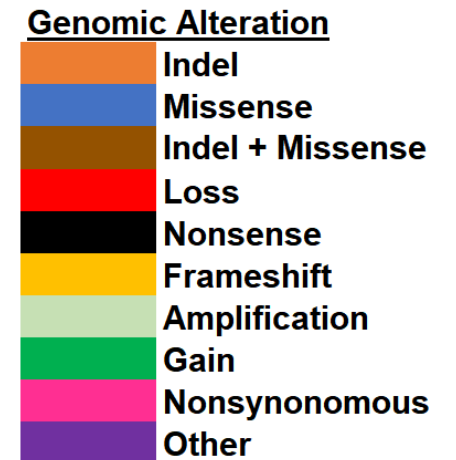
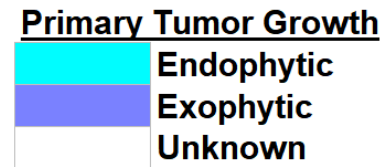
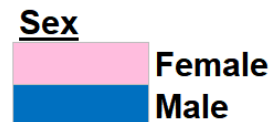
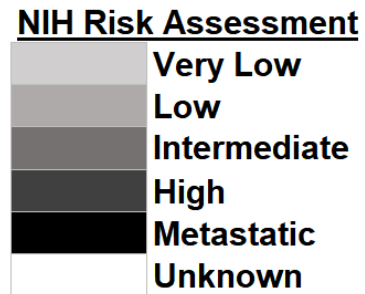
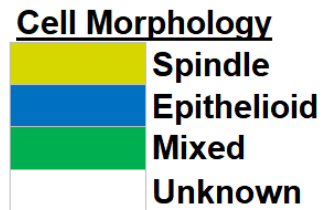
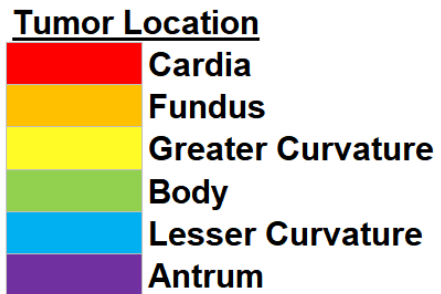
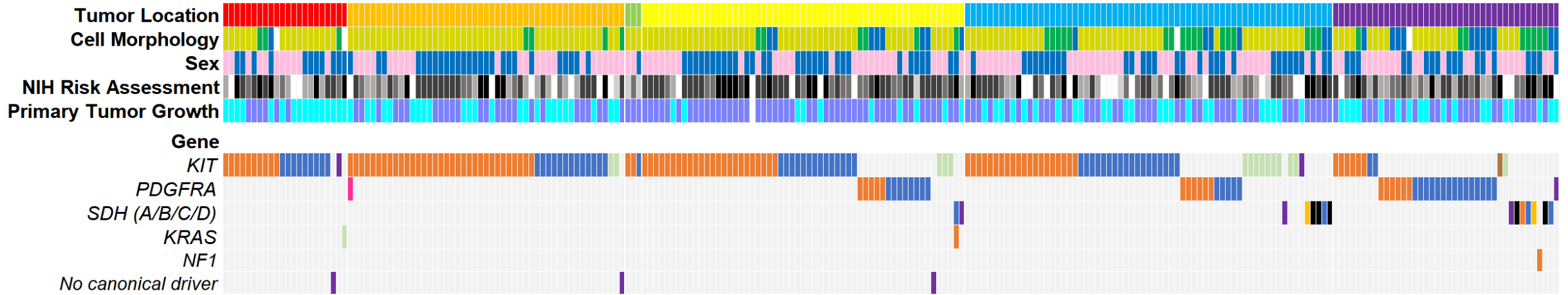
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<b>Characteristic</b>	<b>Number (%)</b>
<b>Age at diagnosis</b> Median [IQR]	64.5 [56-74]
<b>Tumor size</b>	
< 2 cm	222 (9.2)
2.1-5.0 cm	828 (34.3)
> 5 cm	934 (38.7)
Unknown	429 (17.8)
<b>Location within stomach</b>	
Cardia/fundus	785 (32.5)
Body/GC/LC	1,379 (57.0)
Antrum/pylorus	254 (10.5)
<b>Gene testing</b>	
<i>KIT</i> only	2,162 (89.4)
<i>PDGFRA</i> only	22 (0.9)
Multigene <sup>a</sup>	234 (9.7)
<b>Mutation status</b>	
<i>KIT</i>	2,270 (93.9)
<i>PDGFRA</i>	81 (3.3)
<i>KIT/PDGFRA</i> wild-type <sup>b</sup>	67 (2.8)
<b>Baseline mitotic rate</b>	
Low ( $\leq 5/5$ mm <sup>2</sup> )	1,770 (73.4)
High ( $> 5/5$ mm <sup>2</sup> )	440 (18.2)
Unknown	203 (8.41)

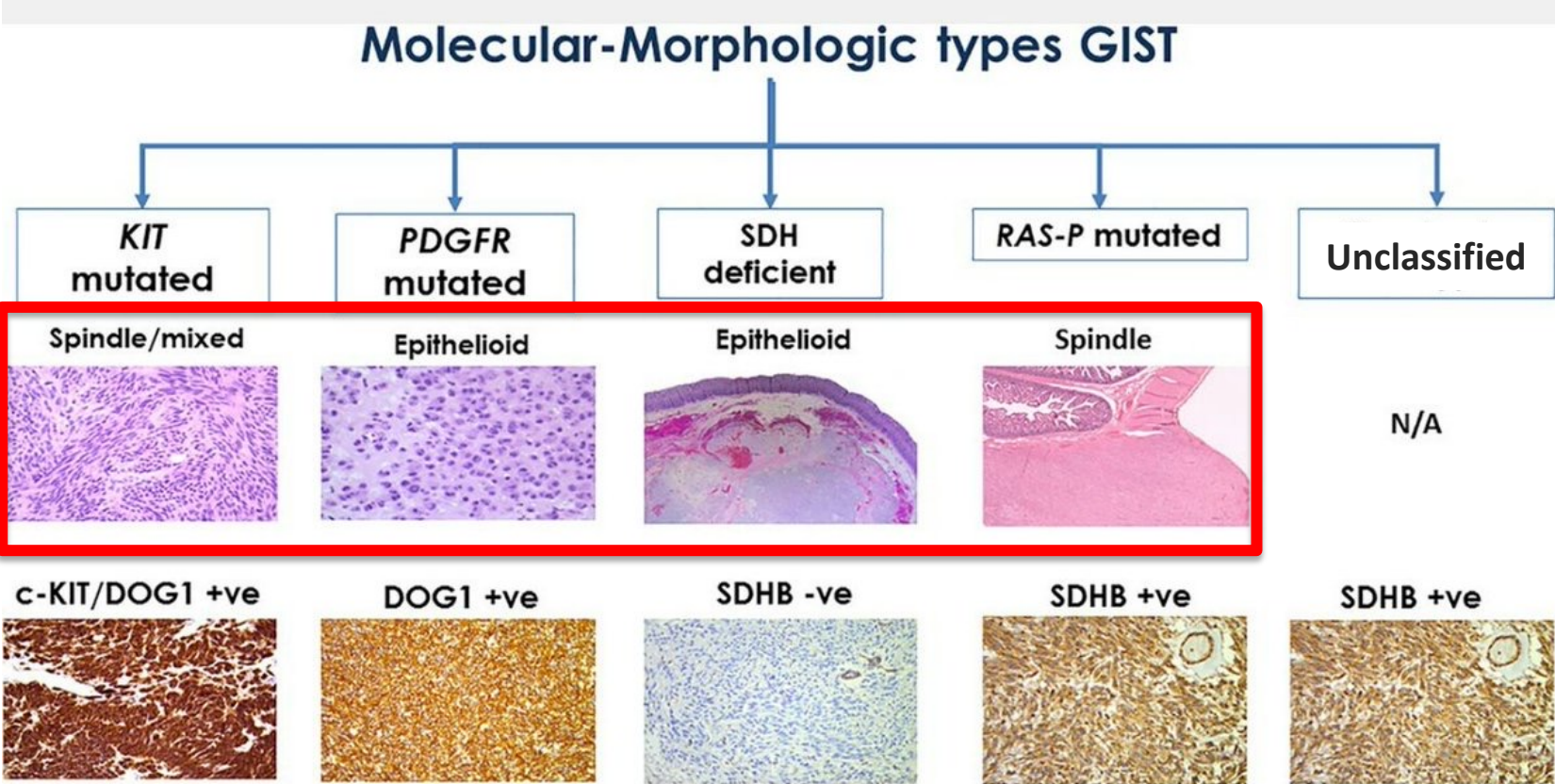
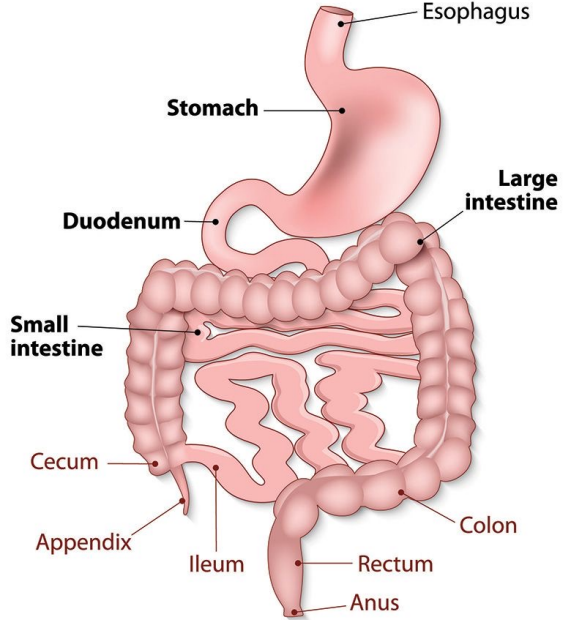
# Non-*KIT* Mutations are More Common in Distal Stomach



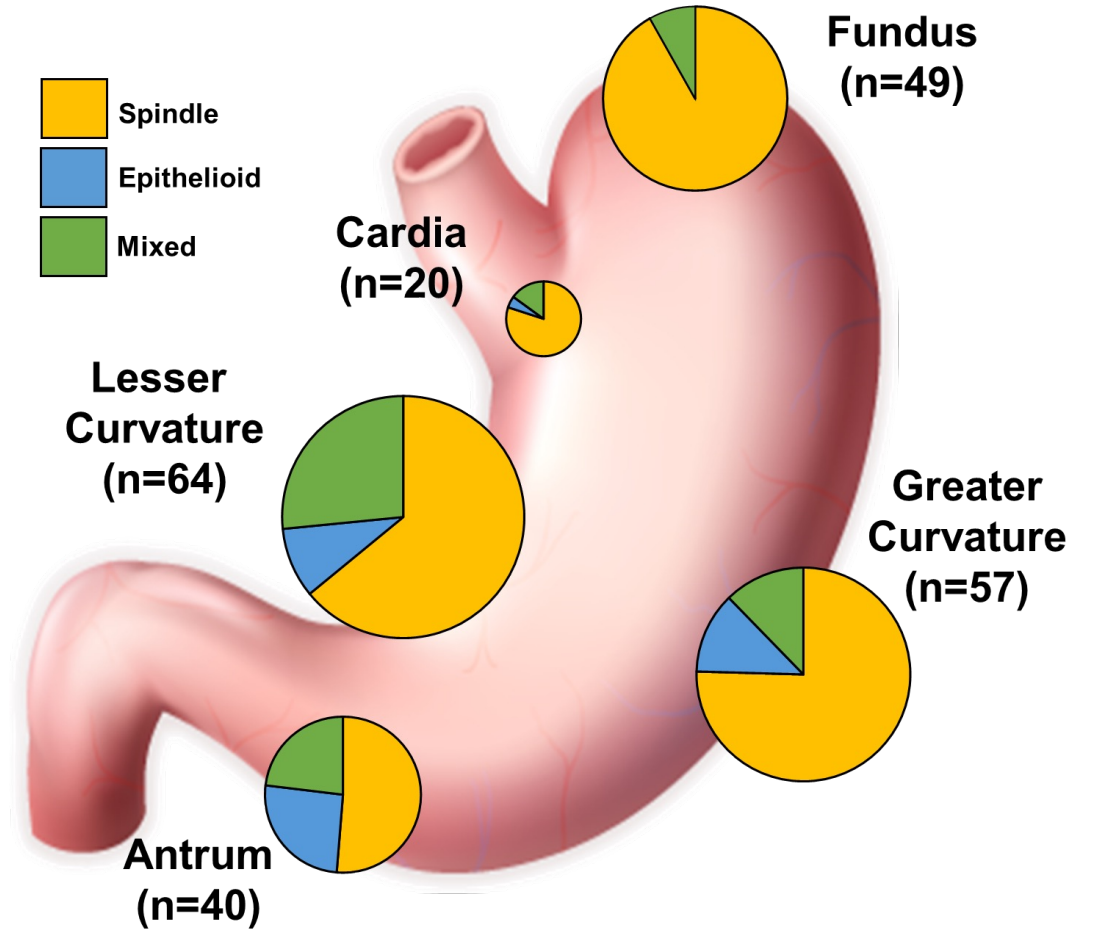
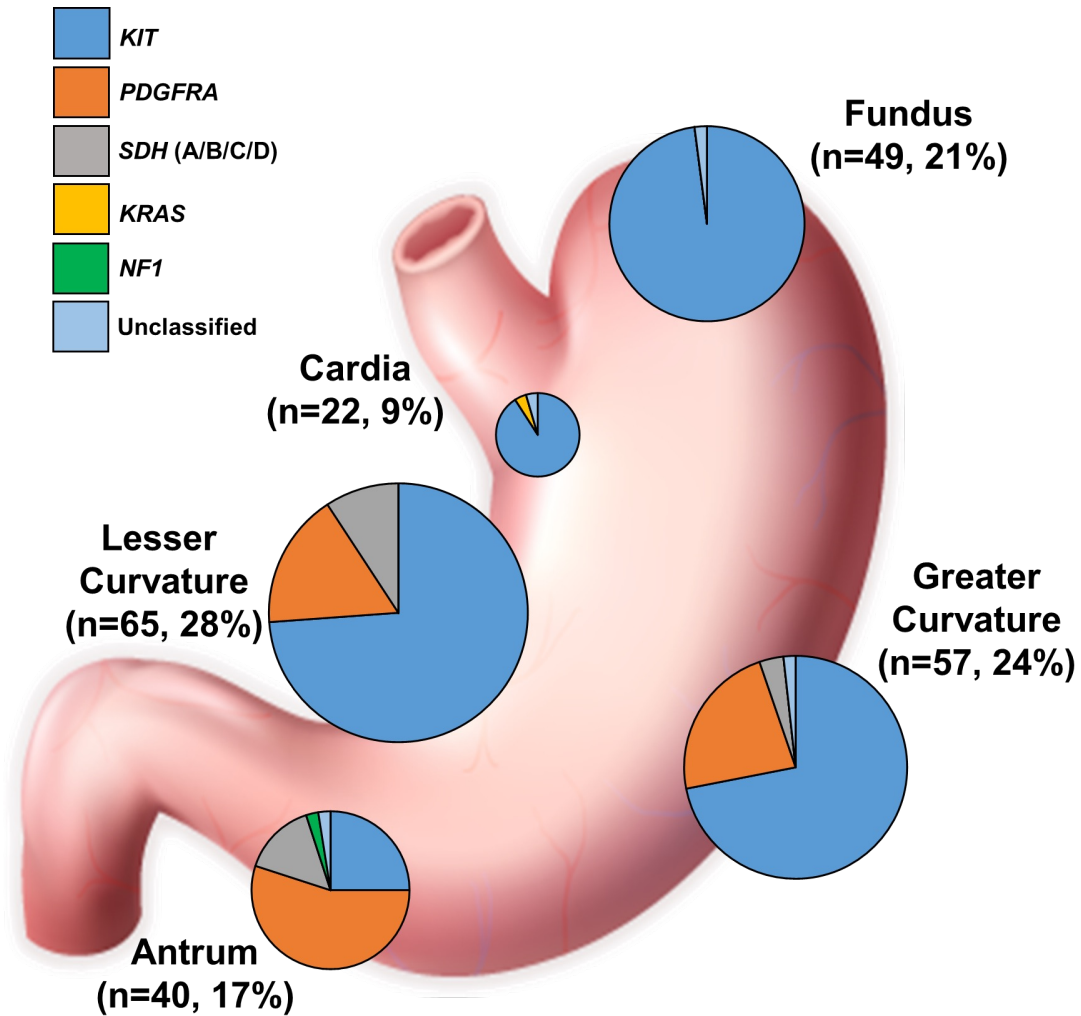
# TAGC Cohort



# Mutation and Histology

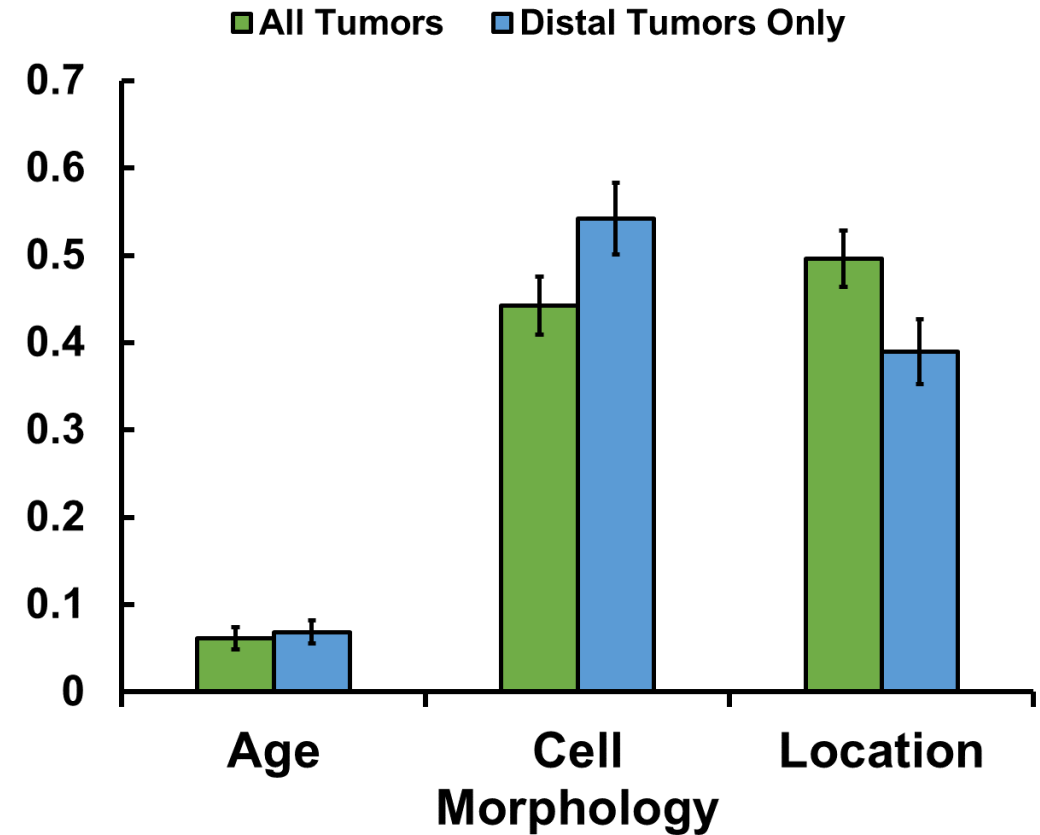


# Location Matters



# Morphology & Location More Important than Age

Characteristic	Univariable regression	95% CI	p-value	Multivariable regression	95% CI	p-value
<b>Age at diagnosis</b>						
≤65 years	Reference					
>65 years	<b>1.500</b>	0.822 - 2.737	<b>0.186*</b>	<b>2.343</b>	1.065 - 5.157	<b>0.034**</b>
<b>Tumor size</b>						
≤7 cm	Reference					
>7 cm	1.029	0.581 - 1.821	0.923			
<b>Gender</b>						
Male	Reference					
Female	1.048	0.594 - 1.851	0.871			
<b>Location</b>						
Proximal	<b>14.000</b>	4.244 - 46.397	<b>&lt;0.001*</b>	<b>17.735</b>	3.905 - 80.550	<b>&lt;0.001**</b>
Distal	Reference					
<b>Growth pattern</b>						
Endophytic	Reference					
Exophytic	0.756	0.419 - 1.367	0.355			
<b>Mitotic rate</b>						
Low (≤5/5 mm <sup>2</sup> )	Reference					
High (>5/5 mm <sup>2</sup> )	1.320	0.657 - 2.649	0.435			
<b>Cell morphology</b>						
Spindle	Reference		<b>&lt;0.001*</b>			<b>&lt;0.001**</b>
Epithelioid	<b>0.029</b>	0.009 - 0.092		<b>0.038</b>	0.011 - 0.134	
Mixed	<b>0.106</b>	0.049 - 0.229		<b>0.111</b>	0.047 - 0.261	



83% accurate when including all tumors



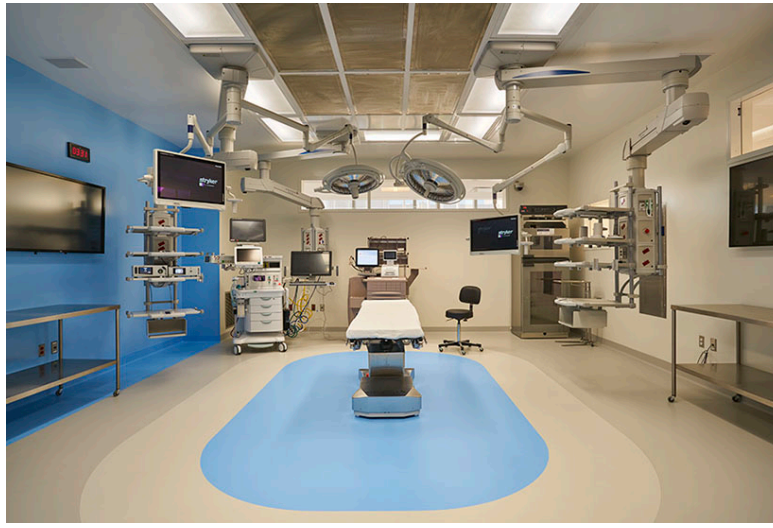
# New and Promising

## Summary

- Gastric GISTs are not homogenous and possess somatic mutations that correlate with tumor location.

## Clinical Implications

- In resource limited settings where mutation profiling is not widely available, or when time is of the essence to start treatment before profiling, **knowing the tumor location & cell morphology may be predictive of *KIT* vs non-*KIT* mutations and in turn, potential TKI sensitivity or resistance.**



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**#11  
GASTROENTEROLOGY  
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# THANK YOU!

## Jason Sicklick, MD



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