Genomics of "Wild-Type" GIST: Domestication In Progress

Jason Sicklick, MD
Associate Professor of Surgery

GIST Support International

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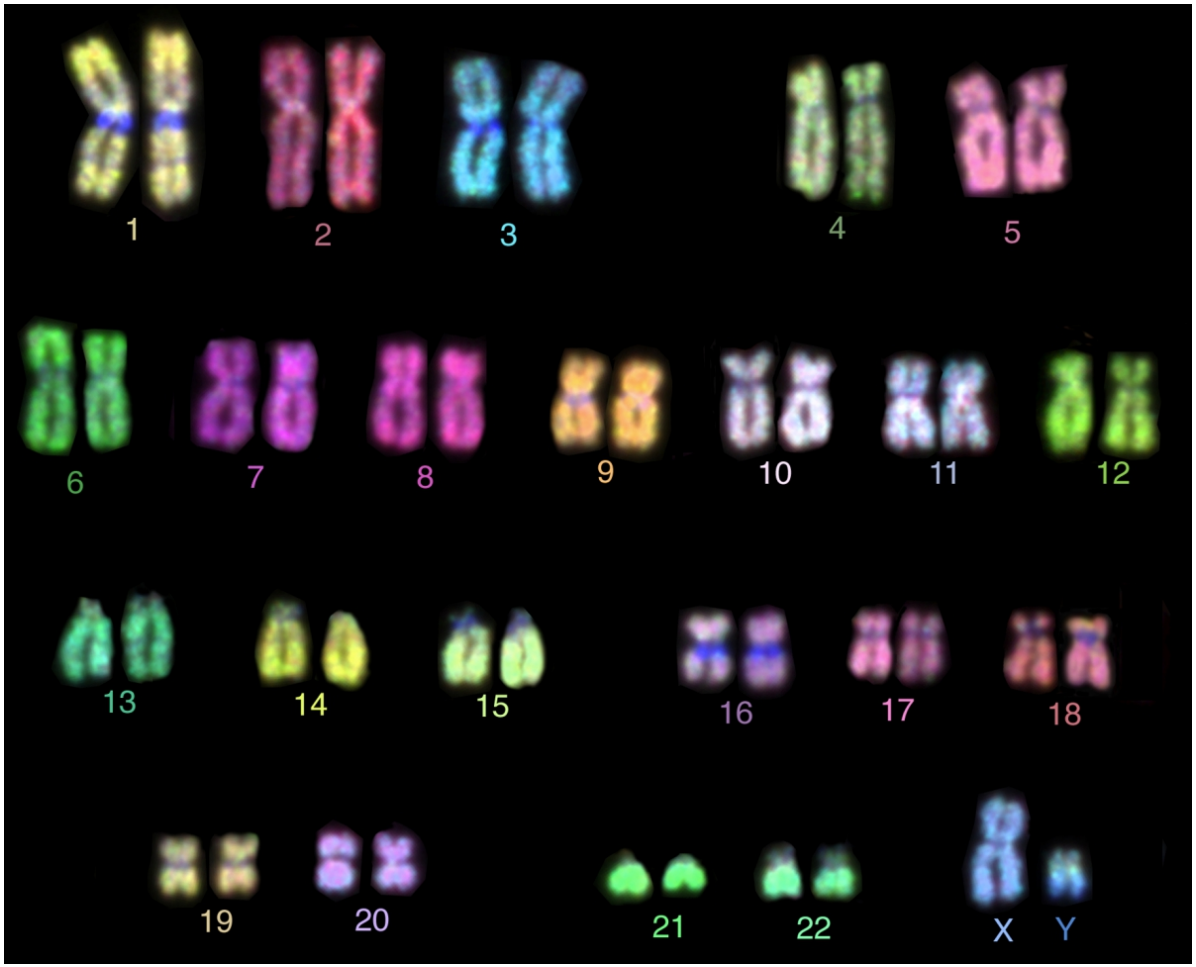
UC San Diego Health System

Genomics 101



23 + 23 = 46 chromosomes

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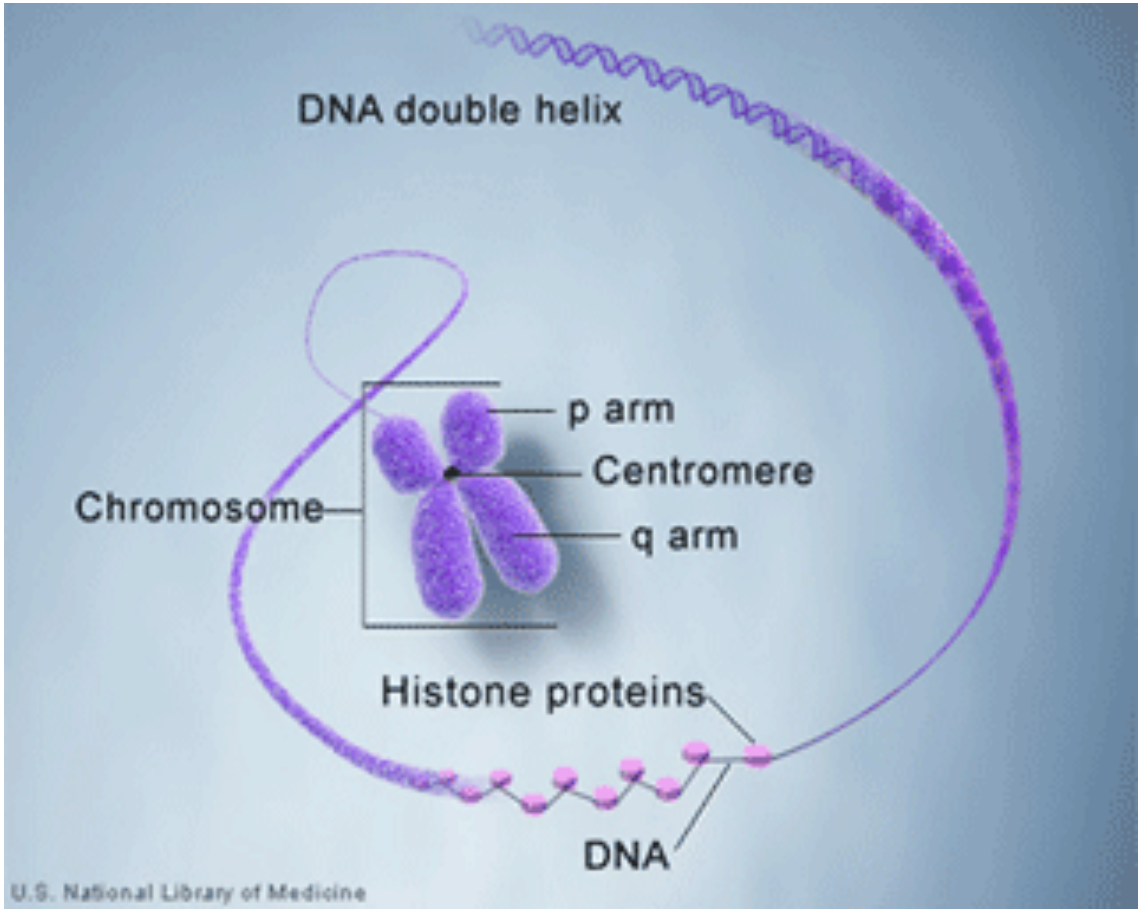
Genomics 101



A = T
C ≡ G

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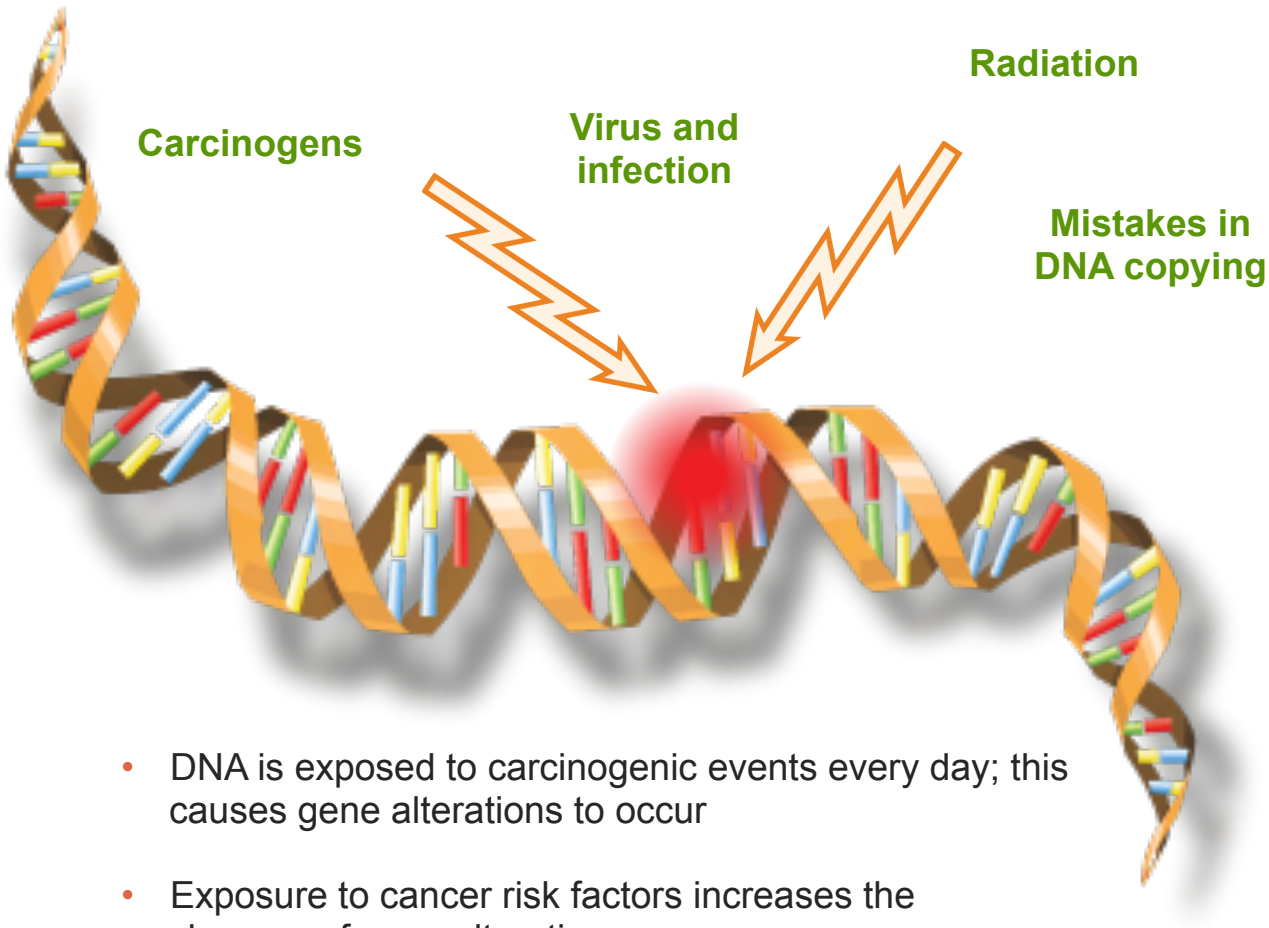
Cancer Is A Disease Of The Genome



- DNA is exposed to carcinogenic events every day; this causes gene alterations to occur
- Exposure to cancer risk factors increases the chances of gene alterations

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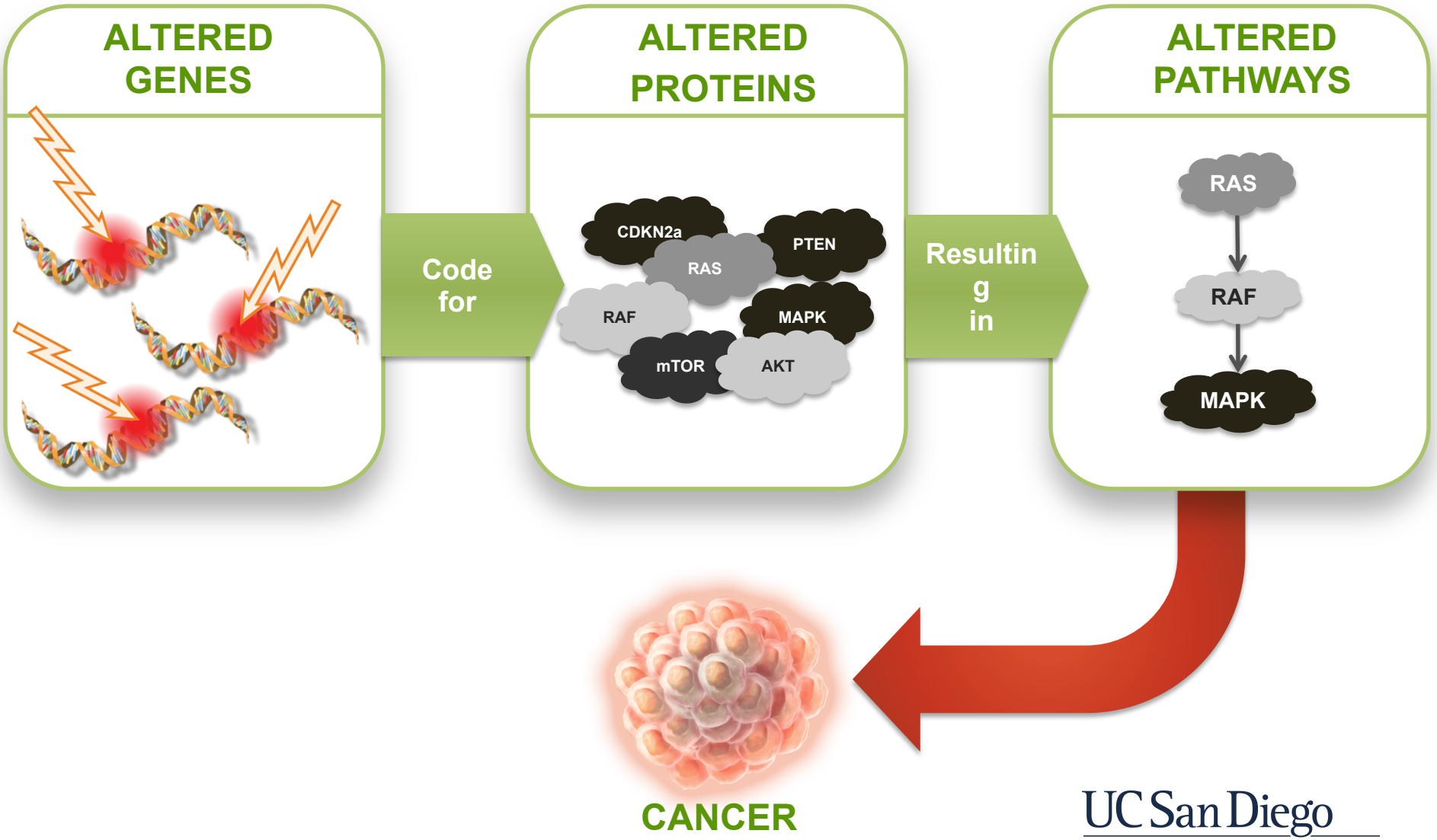
How Gene Alterations Can Cause Cancer



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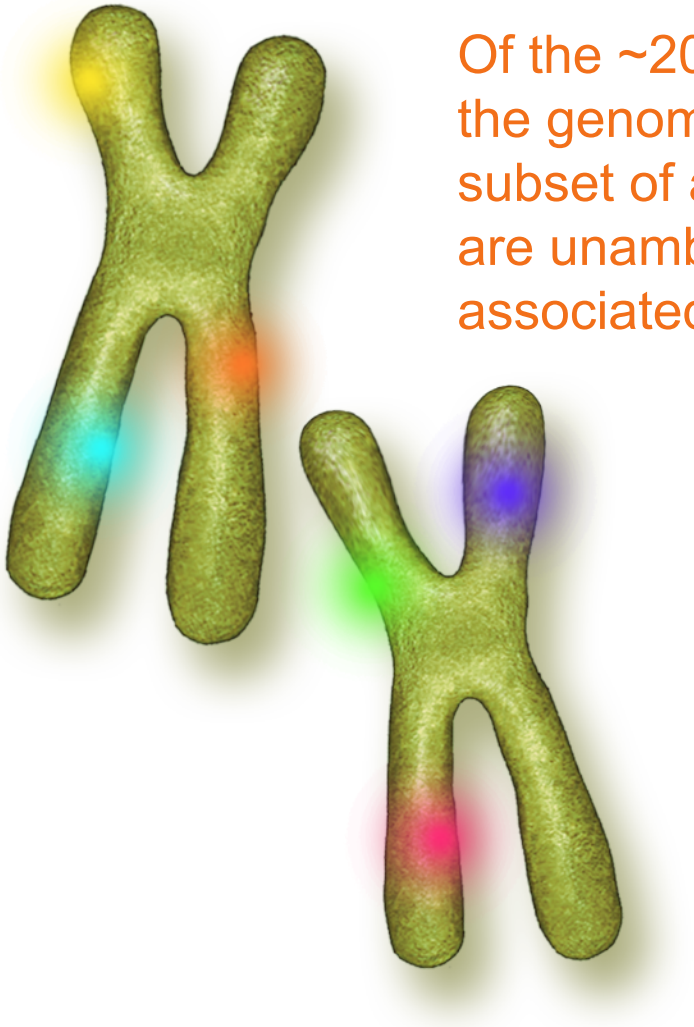
Cancer Related Genes



Of the ~20,000 genes in the genome, only a subset of a few hundred are unambiguously associated with cancer

Gene names
KIT
PDGFRA
BRAF
KRAS
HRAS
NRAS
FGFR1

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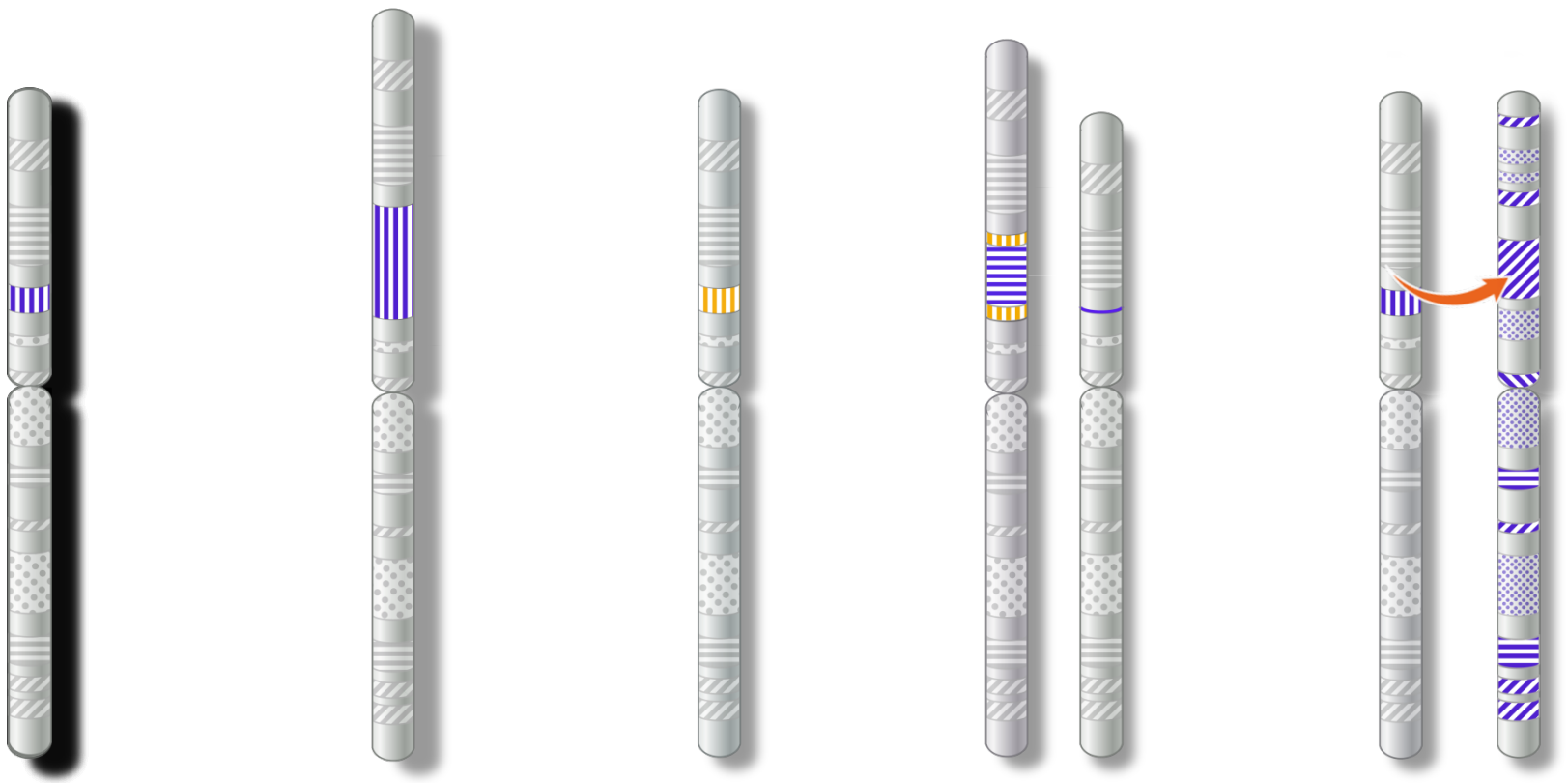
Types Of Alterations In Cancer Genes



Normal

Copy number alterations

Substitutions (Missense)

Insertions and deletions

Rearrangements Fusions

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The Shift Toward Targeted Therapy

Chemotherapy

- Anticancer drugs may be highly effective in some, but less effective in others
- Patients encounter side effects which are often significant

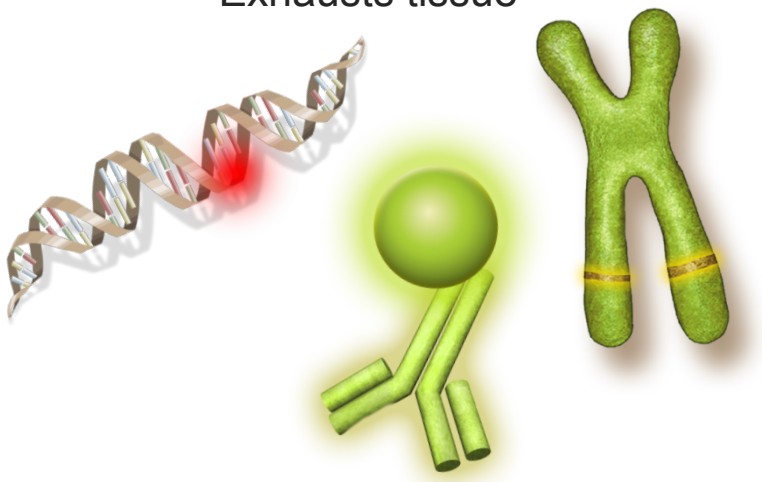
Targeted Therapy

- In personalized medicine, clinicians use biomarkers to predict a patient's response to therapy
- Patients are more likely to get therapies with the greatest impact which often have fewer side effects

Advantages Of Comprehensive Genomic Profiling (CPG) vs. Traditional Hot Spot Testing

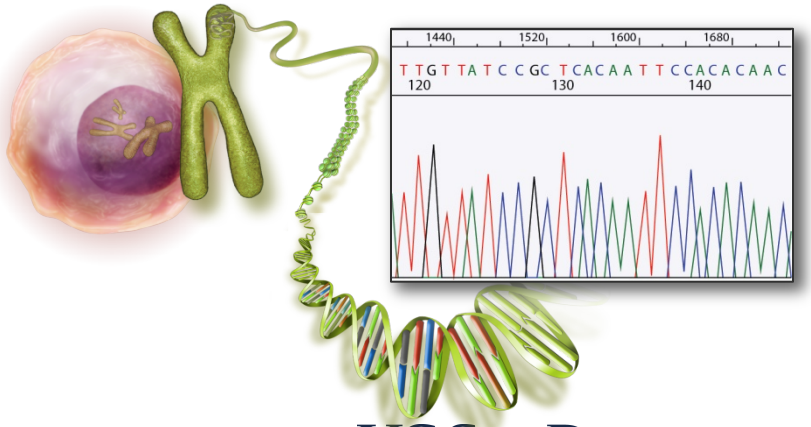
Hot Spot or Single-Marker Testing

- Misses some types of mutations (rearrangements/fusions, copy number alterations)
- Limited number of alterations screened at once
- Results are specific for the test used: need to know ahead of time what questions to ask
- Exhausts tissue



CGP

- Able to identify hundreds of clinically relevant mutations at once
- Allows the opportunity to identify all alterations
- Tissue sparing



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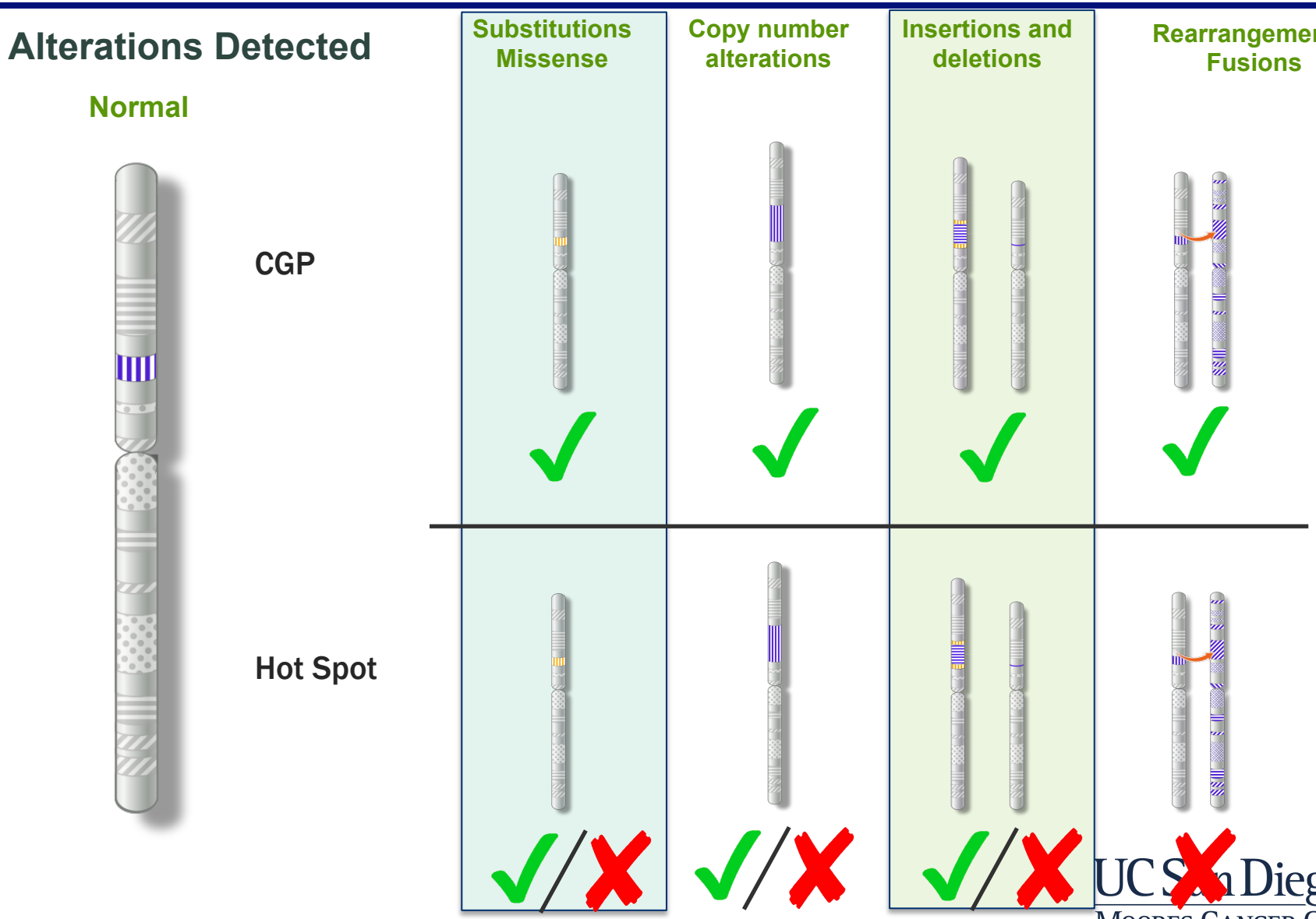
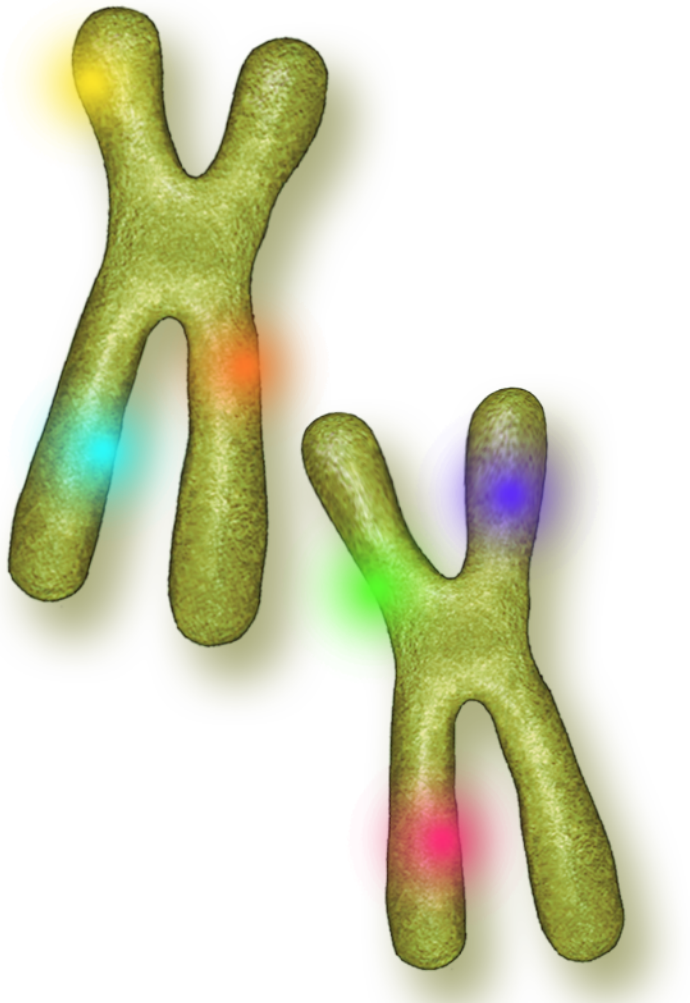
CPG vs. Hot Spot



Cancer Related Genes in GIST



Gene names
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HRAS
NRAS
FGFR1

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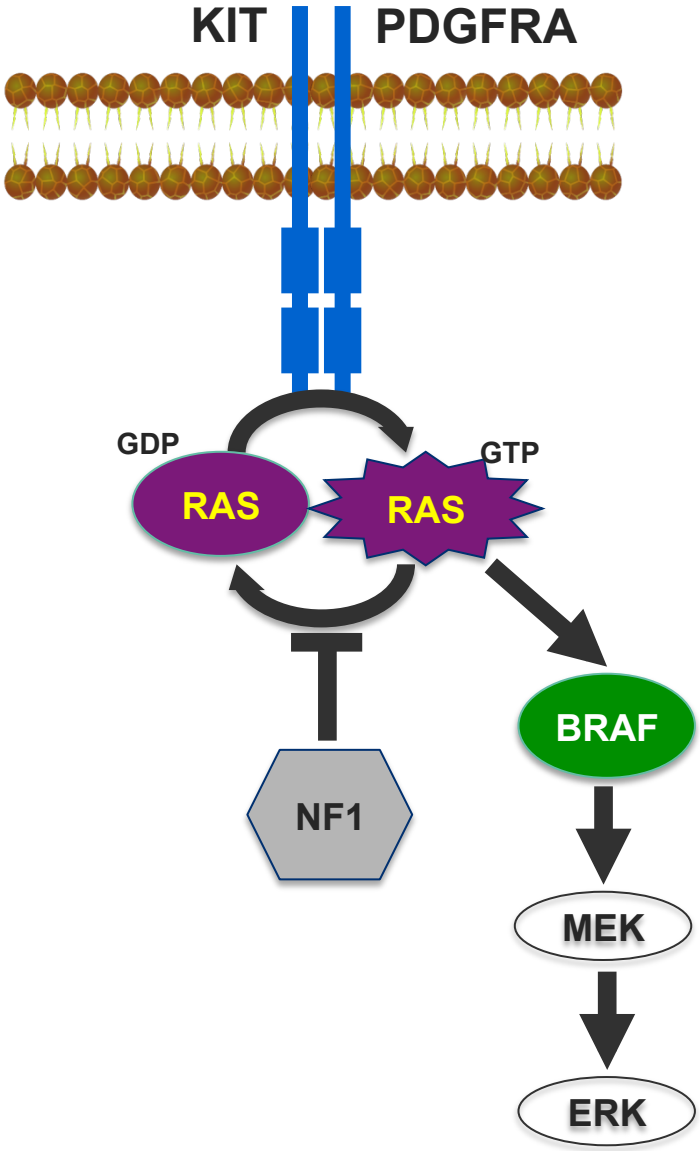
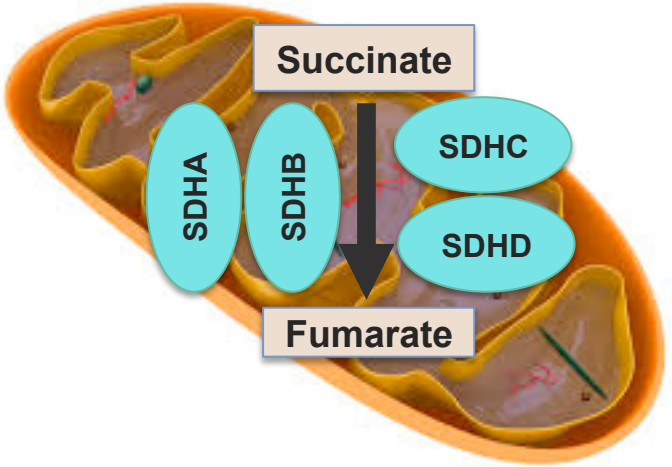
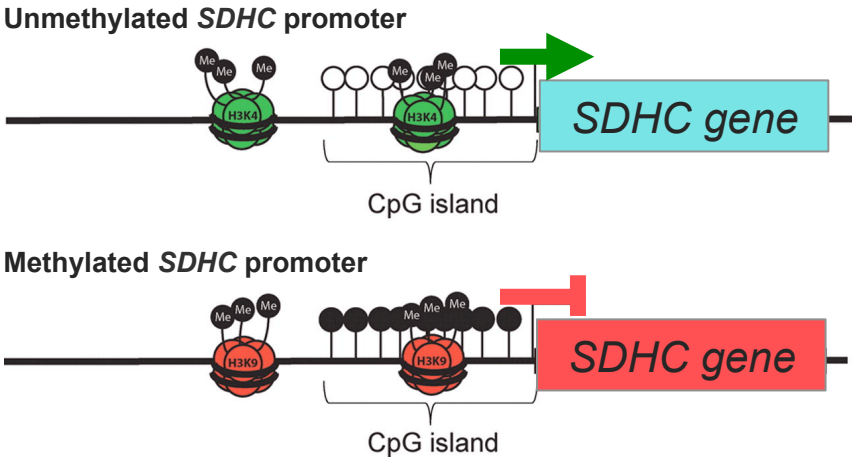
Known Driver Genes in 85-90% of GIST







Corless *et al.*, *Nature Reviews Cancer*. 2011.
Pantaleo *et al.*, *Cancer Medicine*. 2015.
Killian *et al., Sci Transl Medicine*. 2014.

Lack Mutations in *KIT*, *PDGFRA*, RAS Pathway (*NF1*, *RAS*, *BRAF*) and *SDH* Subunits

Quadruple Wild-type (qWT) GIST

SDHB+
IGF1R-

Any age?
Equal sex?
Site?
Multifocality?

- **Genomics?**
- **Epidemiology?**
- **Disease Biology?**

Pantaleo *et al.*, *Cancer Medicine*. 2015.

Hypothesis

Broad genomic profiling of “quadruple-WT (qWT)” GISTs would reveal insights into the genomic alterations and disease biology of this understudied patient population.

Methods

Patient Population and Data Collection

- Foundation Medicine, Inc. (FMI) database consisting of de-identified patients from across the U.S. (October 2012 – May 2015).
- Retrospectively analyzed this prospectively collected data.

Broad Genomic Profiling

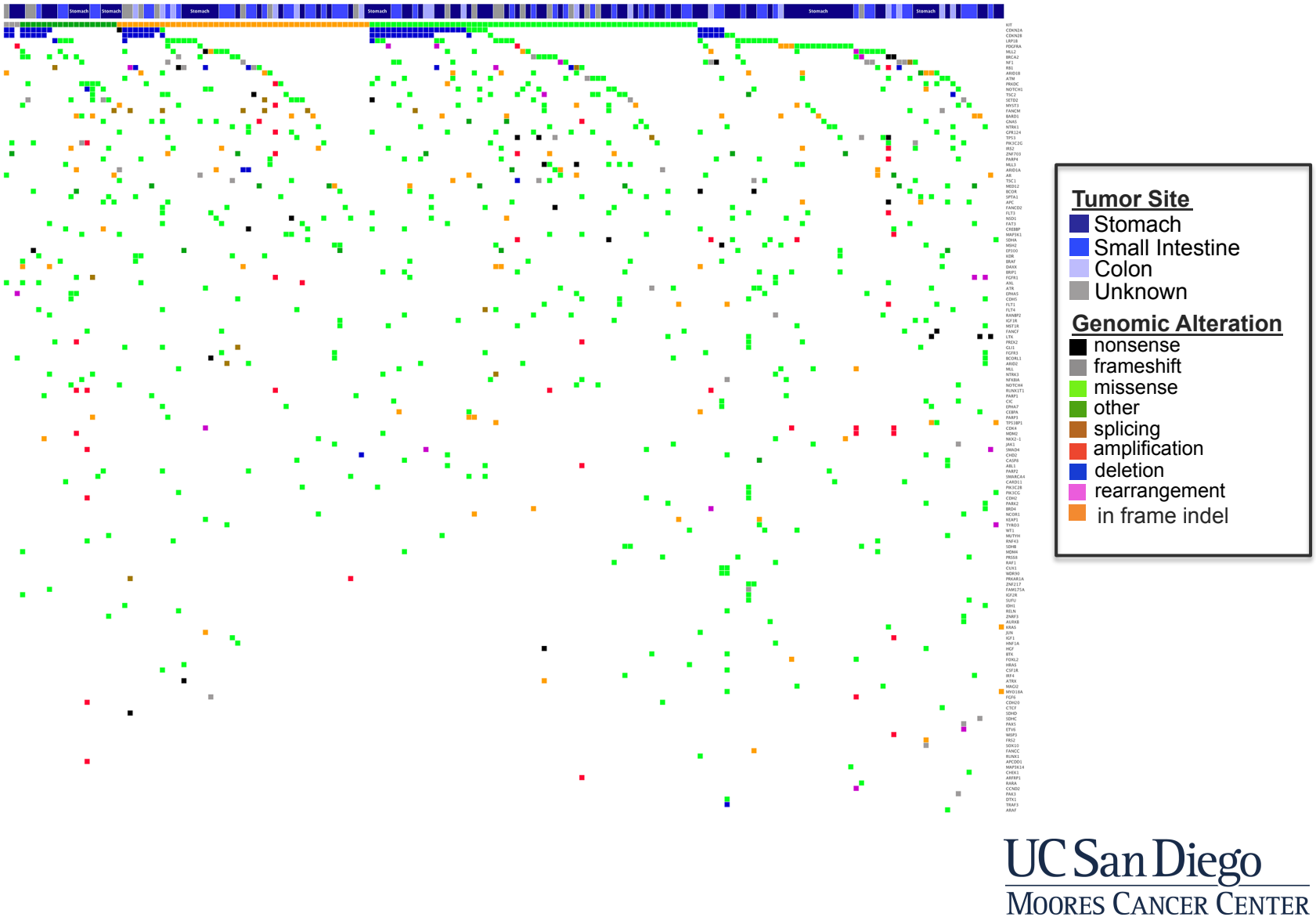
- DNA was extracted from FFPE tumor specimens.
- NGS assay utilizes the Illumina HiSeq 2500 instrument to sequence against hybridization-captured, adaptor ligation-based libraries for coding regions of 315 cancer-related genes plus introns from 28 genes frequently implicated in cancer transformation.

Methods (Continued)

Data Analysis

- Genomic alterations were further categorized:
  - Known somatic
  - Likely somatic
  - Variant of unknown significance (VUS).
- To understand of the potential deleterious effects of all missense VUS's, we analyzed them with 4 prediction modeling programs (SIFT, PolypPhen, MutationTaster, and MutationAssessor).
- Considered *potentially deleterious* if they were predicted deleterious by ≥50% tools. Of 1240 VUS's, we considered 325 (26.2%) potentially deleterious.
- Exome Aggregation Consortium (ExAC) Browser was used to exclude *missense variants* with a minor allele frequency >1% (*NOTCH2, FANCD2, MAP3K1, MSH3*, and *ZNF217*).

Somatic Genomic Landscape in 186 GIST



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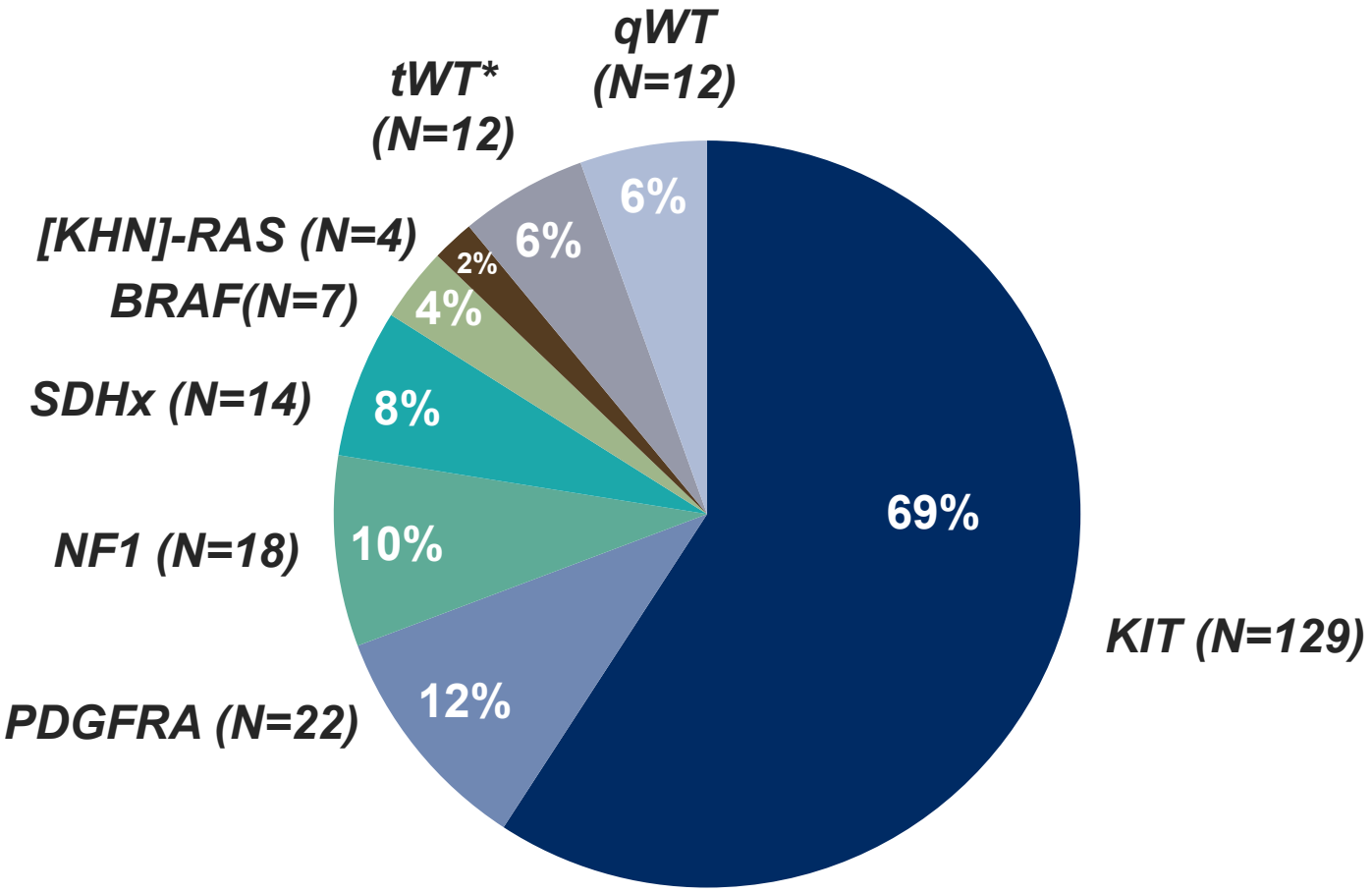
Driver Mutations in 186 GIST



tWT = sequencing performed before FMI testing of SDHx genes*

Demographics of GIST Patients

Variables		WT GIST N (%)	Non-WT GIST N (%)	P-value
Total Patients		24	162	
Age (years, mean ± SD)		44.4 ± 15.7	58.3 ± 14.1	<0.01
Sex	Female	12 (50.0)	66 (40.7)	0.51
	Male	12 (50.0)	94 (58.0)	
	Not Reported	-	2 (1.2)	
Primary GIST Site	Colon	2 (8.3)	15 (9.3)	0.26
	Small intestine	9 (37.5)	44 (27.2)	
	Stomach	13 (54.2)	83 (51.2)	
	Other	0 (0.0)	20 (12.3)	

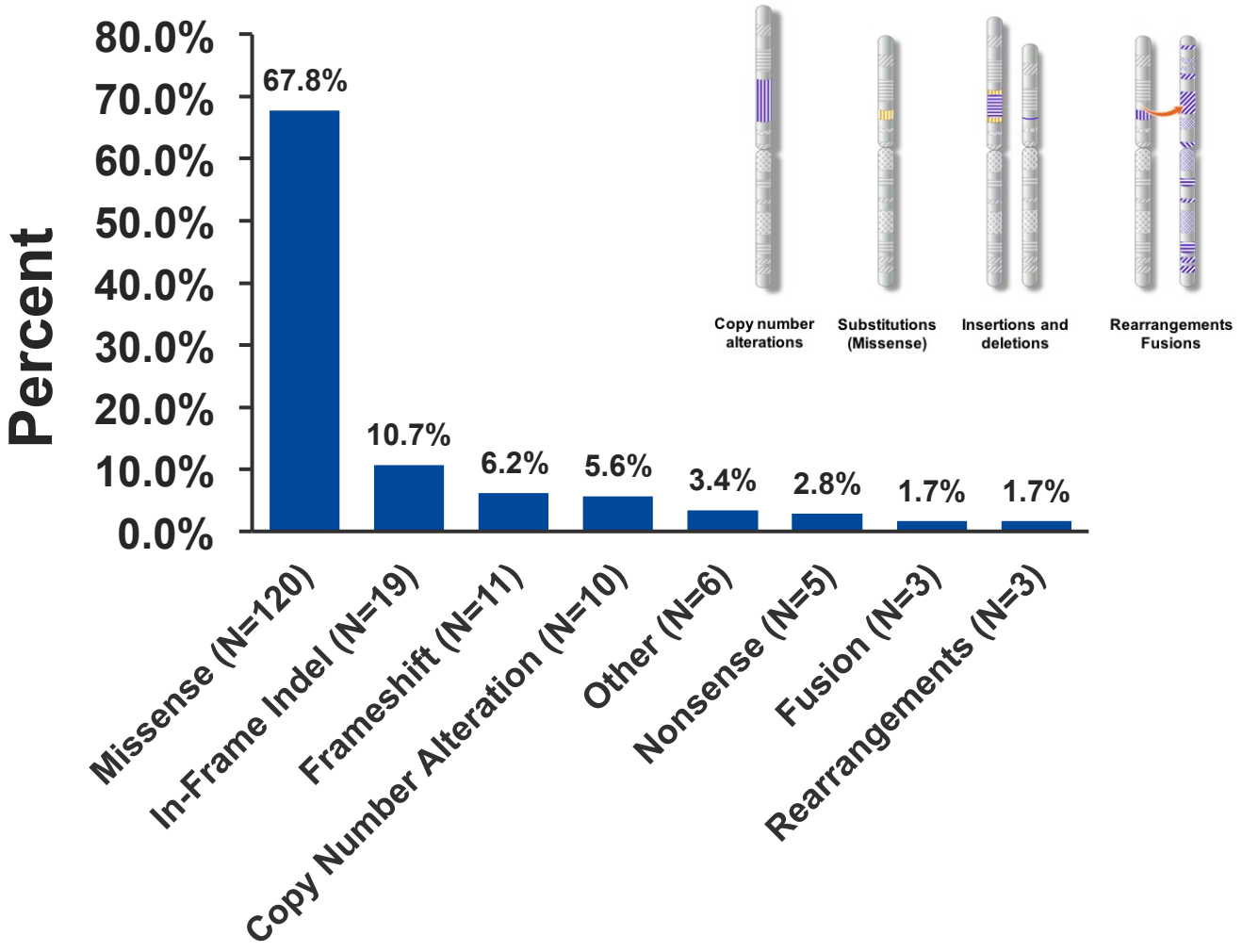
Demographics of GIST Patients

Variables		qWT GIST N (%)	tWT GIST N (%)	P-value
Total Patients		12	12	
Age (years, mean ± SD)		44.0 ± 14.9	44.8 ± 17.1	0.90
Sex	Female	5 (41.7)	7 (58.3)	0.68
	Male	7 (58.3)	5 (41.6)	
	Not Reported	-	-	
Primary GIST Site	Colon	0 (0.0)	2 (16.7)	0.36
	Small intestine	4 (33.3)	5 (41.6)	
	Stomach	8 (66.7)	5 (41.6)	

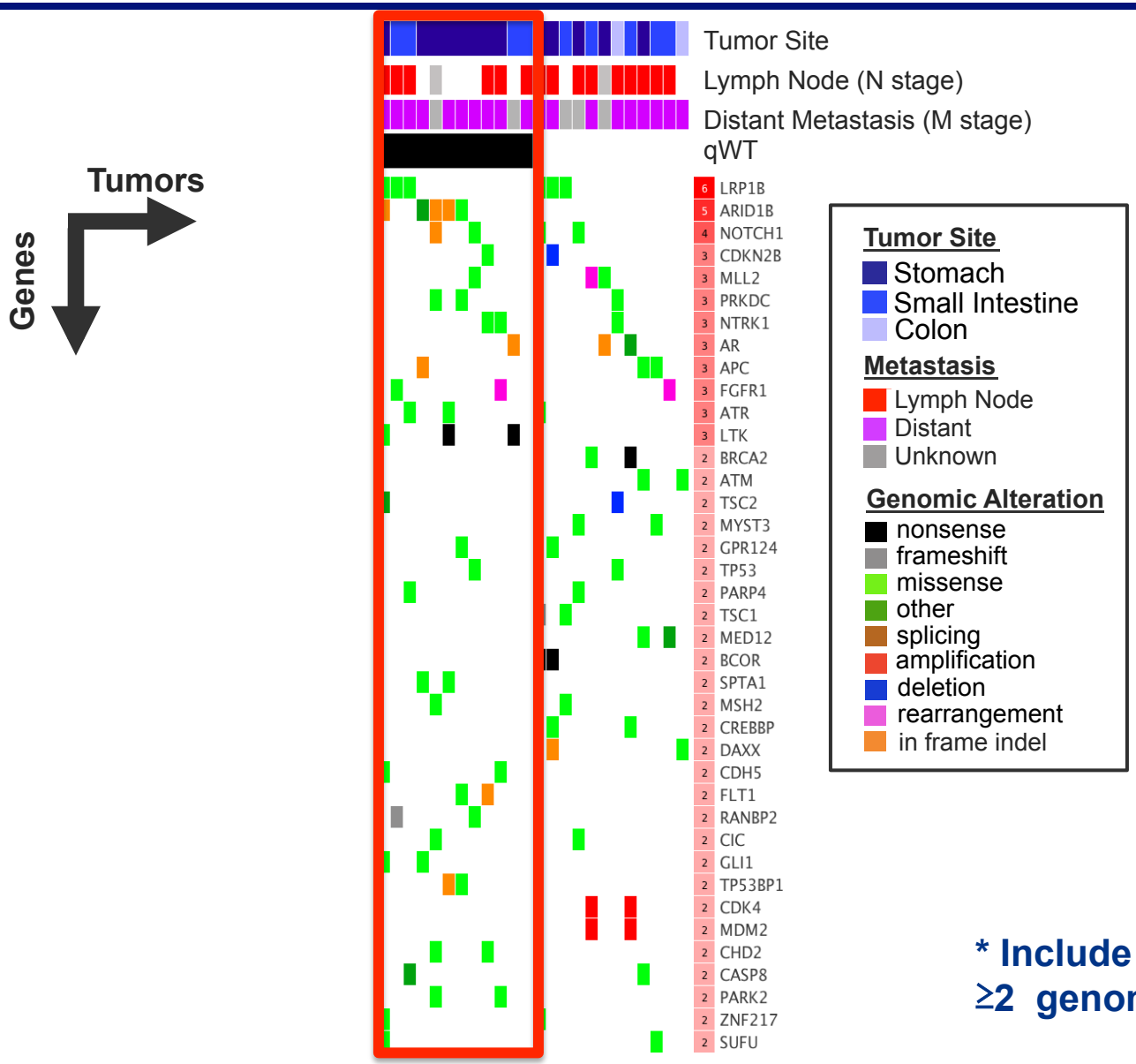
Demographics of GIST Patients

TNM Classification		qWT GIST N (%)	tWT GIST N (%)	P-value*
Tumor Size (T)	T1 (≤ 2 cm)	0 (0.0)	0 (0.0)	0.05
	T2 (>2, ≤5 cm)	0 (0.0)	2 (16.7)	
	T3 (>5, ≤10 cm)	11 (91.7)	5 (41.6)	
	T4 (>10 cm)	1 (8.3)	4 (33.3)	
	Tx	0 (0.0)	1 (8.3)	
Regional Lymph Nodes (N)	N0	6 (50.0)	2 (16.7)	0.14
	N1	3 (25.0)	8 (66.7)	
	Nx	3 (25.0)	2 (16.7)	
Distant Metastases (M)	M0	0 (0.0)	0 (0.0)	1.0
	M1	9 (75.0)	8 (66.7)	
	Mx	3 (25.0)	4 (33.3)	

Types of Genomic Alterations Detected



Heterogeneous Set of Genomic Alterations*
(Known/Likely + Potentially Deleterious VUS)

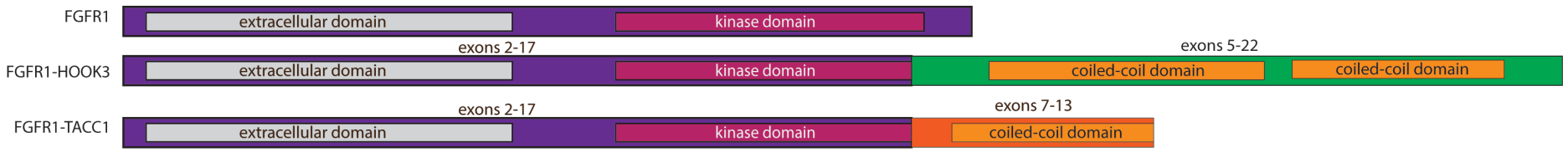


*** Include only genes with ≥2 genomic alterations**

7 Genes Significantly More Affected

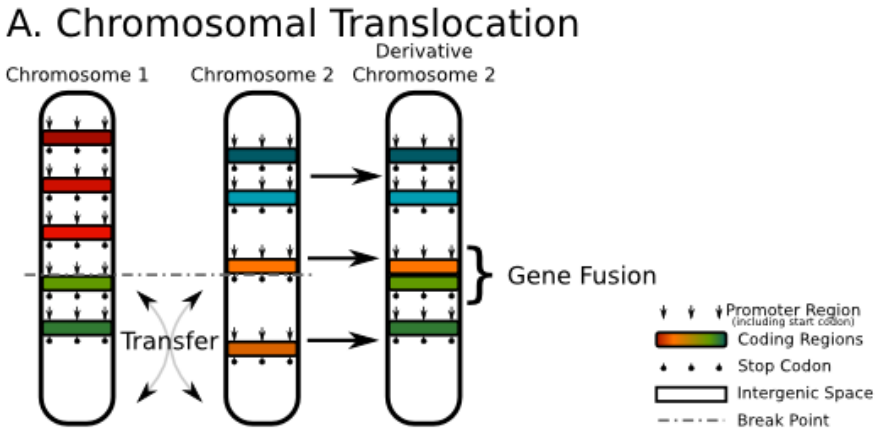
Gene	Aliases	Alterations in non-WT (%)	Alterations in WT (%)	P-value
ARID1B	AT Rich Interactive Domain 1B	11 (6.79%)	5 (20.83%)	0.04
FGFR1	Fibroblast growth factor receptor 1	4 (2.47%)	3 (12.5%)	0.047
ATR	Ataxia telangiectasia and Rad3 related	4 (2.47%)	3 (12.5%)	0.047
LTK	Lymphocyte receptor tyrosine kinase	2 (1.23%)	3 (12.5%)	0.02
SUFU	Suppressor of Fused	0 (0%)	2 (8.33%)	0.02
ZNF217	Zinc Finger 217	0 (0%)	2 (8.33%)	0.02
PARK2	Parkin RBR E3 Ubiquitin Protein Ligase	1 (0.62%)	2 (8.33%)	0.044

FGFR1 Gene Fusions Identified in 2/3rd GISTs

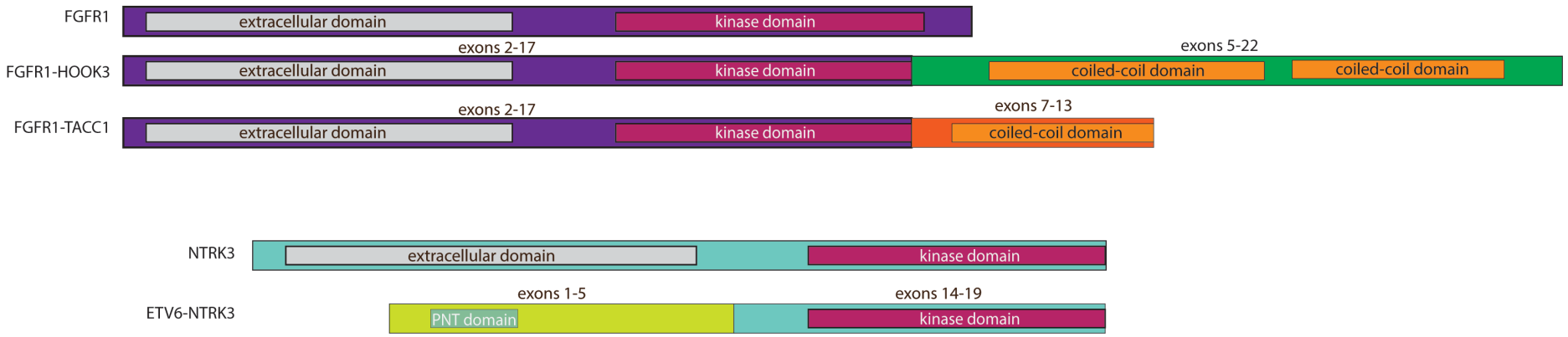


Gene Fusions

- Hybrid gene formed from 2 previously separate genes
- It can occur as a result of 3 mechanisms:



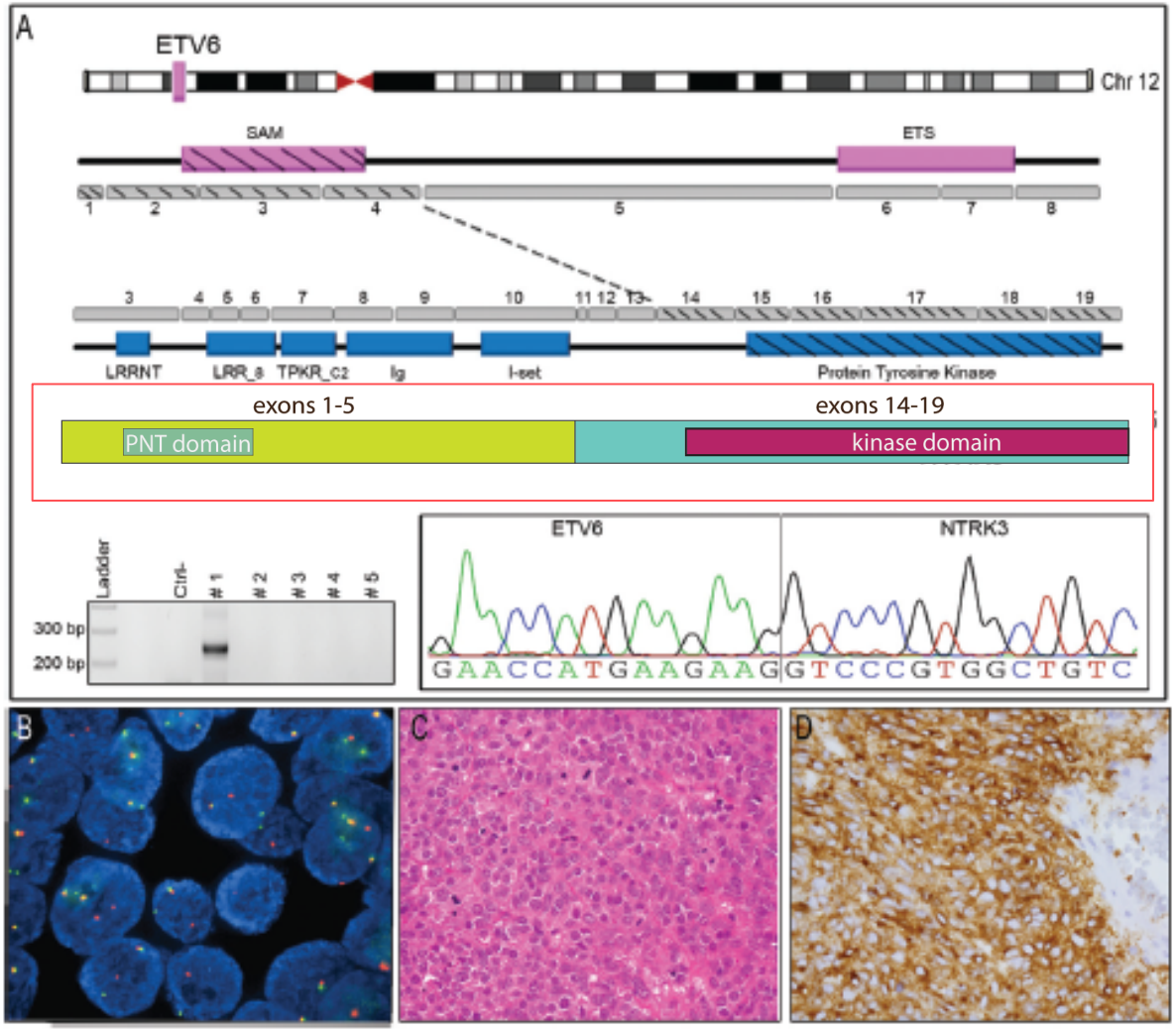
CTOS in November 2015



Gene	Fusion	Previously Reports
FGFR1	*FGFR1-TACC1*	Glioblastoma multiforme
	FGFR1-HOOK3	RET-HOOK3 fusion in papillary thyroid cancer
ETV6	*ETV6-NTRK3*	Infantile fibrosarcoma secretory breast carcinoma salivary gland tumors

Shaw *et al.*, Nature Reviews *Cancer*. 2013.

ETV6-NTRK3 in qWT GIST



Brenca *et al., J Pathology*. March 2016.

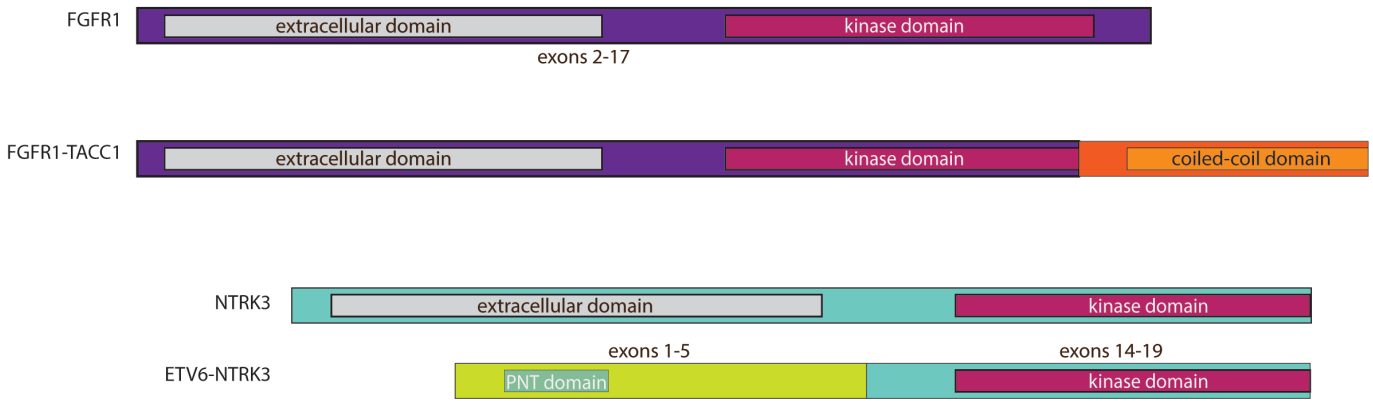
OHSU Validation in 2nd Study Population

Target Kinase	Fusion Partners
AKT3	*MAGI3*
ALK	*ATIC, C2orf44, CARS, CLTC, EML4, FN1, KIF5B, KLC1, MSN, NPM1, PPFIBP1, PTPN3, SEC31A, SQSTM1, STRN, TFG, TPM3, TPM4, TRAF1, VCL*
BRAF	*AGK, AGTRAP, AKAP9, CLCN6, FAM131B, FCHSD1, GNAI1, KCTD7, KIAA1549, MAD1L1, MKRN1, NUDCD3, PLIN3, RNF130, SLC45A3, SOX6, TRIM24, ZKSCAN5*
EGFR	*EGFR variant III, CAND1, PSPH, SEPT14, SLC12A9*
ERBB4	*EZR*
ERG	*TMPRSS2*
FGFR1	*BAG4, CPSF6, ERLIN2, PLAG1, TACC1, ZNF703*
FGFR2	*AFF3, AHCYL1, BICC1, CASP7, CCDC6, CIT, KIAA1967, OFD1, SLC45A3*
FGFR3	*BAIAP2L1, TACC3*
MET	*MIR548F1, TPR*
NTRK1	*BCAN, CD74, MIR548F1, MPRIP, NFASC, TFG, TPM3, TPR*
NTRK2	*NACC2, QKI*
NTRK3	*ETV6*
NRG1	*CD74, SLC3A2*
PDGFRA	*KDR, SCAF11*
PDGFRB	*NIN*
RAF1	*DAZL, ESRP1, MSS51, SRGAP3*
RET	*AFAP1, CCDC6, ERC1, HOOK3, KIAA1468, KIF5B, NCOA4, PARG, PCM1, PRKAR1A, TRIM27, TRIM33*
ROS1	*CCDC6, CD74, CEP85L, EZR, GOPC, KDELR2, LRIG3, SDC4, SLC34A2, TFG, TPM3*

Compliments of M. Heinrich and C. Corless, OHSU.

5 qWT GIST in OHSU Study Population

Age (Years)	Gender	Primary Tumor Location	Tumor Stage	SDHB Immunostaining	Fusion Panel Result
54	Male	Pelvic mass	Unknown	Unknown	***FGFR1-TACC1***
54	Male	Colon	Unknown	**Positive**	***ETV6-NTRK3***
49	Male	Small intestine	T3NxMx	Positive	None detected
51	Female	Unknown	TxN1Mx	Positive	None detected
53	Male	Stomach	Unknown	Unknown	None detected



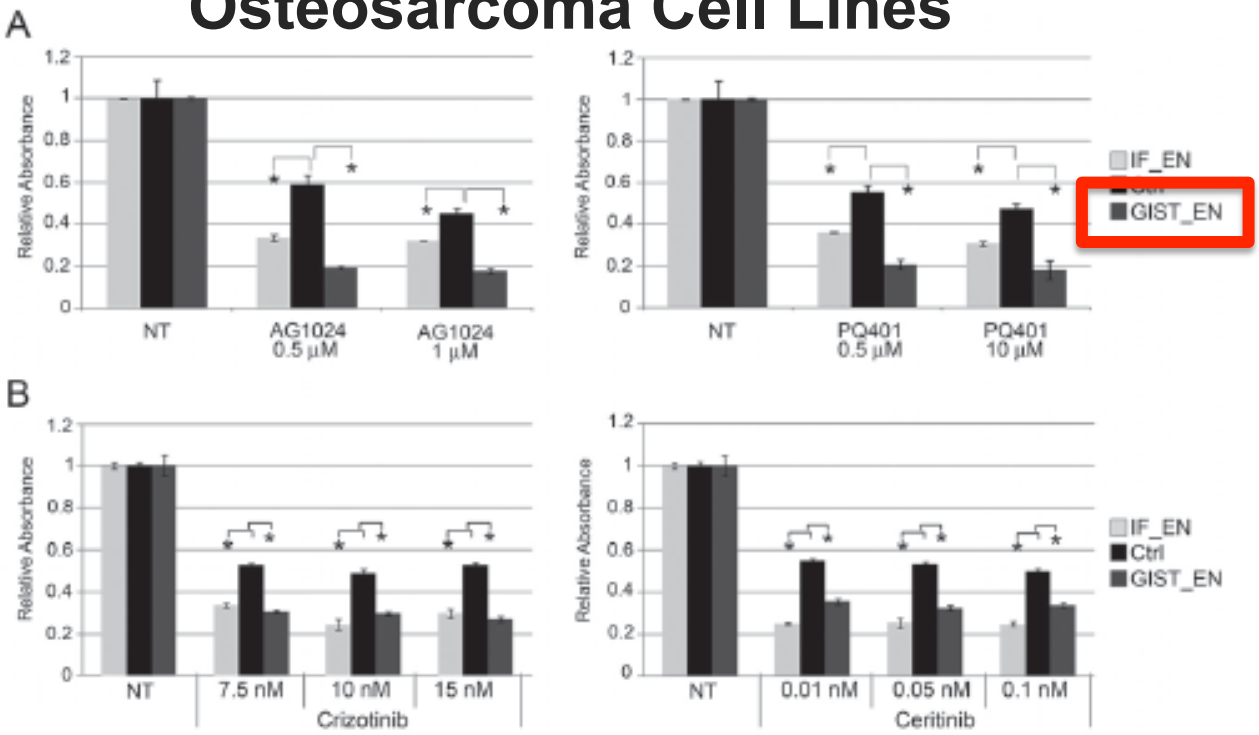
Compliments of M. Heinrich and C. Corless, OHSU.

ETV6-NTRK3 Sensitizes Cells to IGF1R and ALK Inhibitors

IGF-1R inhibitors

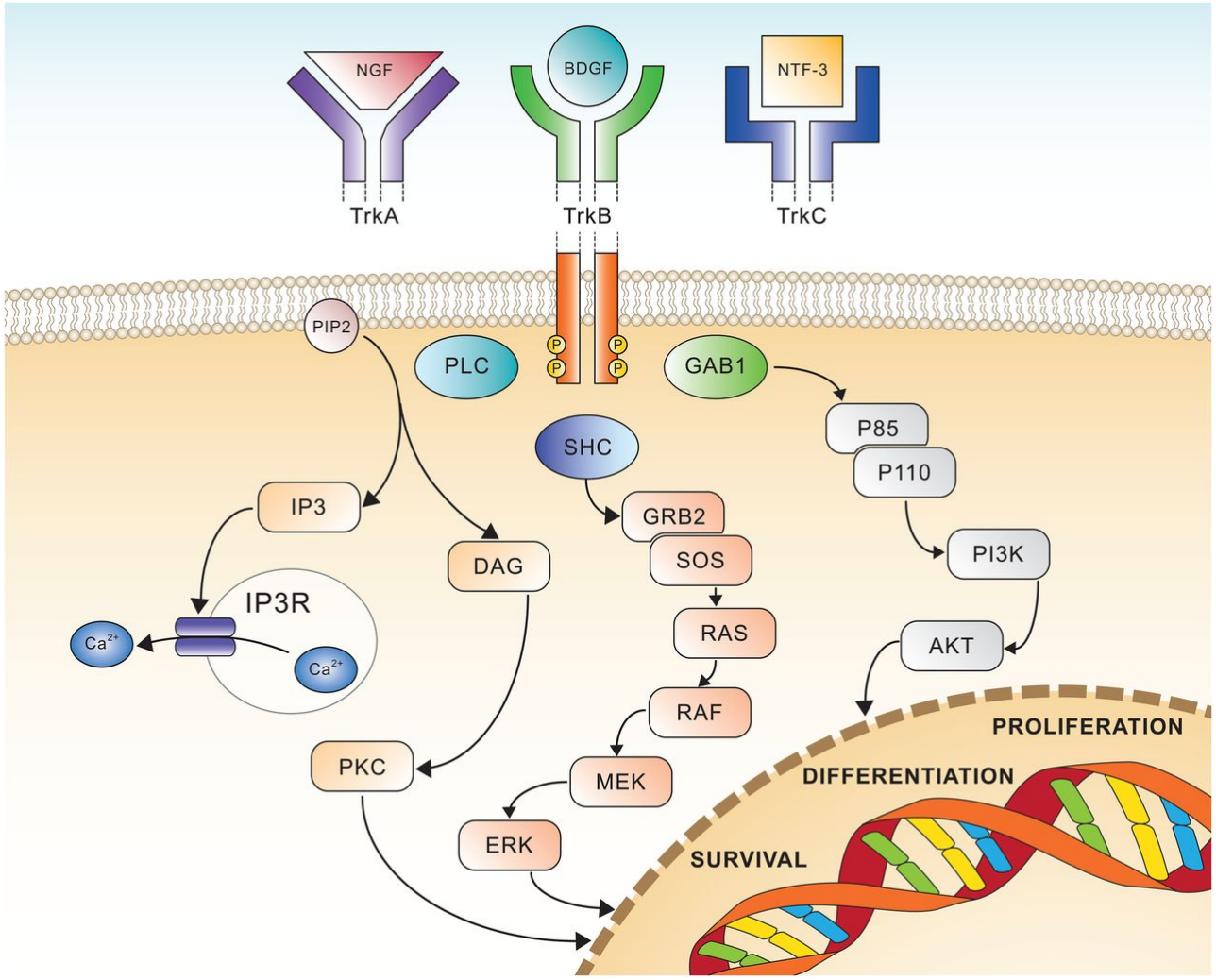
ALK inhibitors

Infantile Fibrosarcoma & Osteosarcoma Cell Lines



Brenca *et al., J Pathology*. March 2016.

Neurotrophic tropomyosin receptor kinase (*NTRK*)



Amatu *et al., ESMO Open*. 2016.

NTRK Inhibitors

Table 2 Ongoing phase I/II trials involving drugs with known inhibitory activity of NTRK-related kinases

NCT/EudraCT number	Title	Drug	Targets	Phases	Patients	Start date
NCT02219711	Phase 1/1b study of MGCD516 in patients with advanced cancer	MGCD516	MET, AXL, c-kit, MER, DDR2, VEGFR, PDGFR, RET, Trk, Eph	1	120	August 2014
NCT02568267	Basket study of entrectinib (RXDX-101) for the treatment of patients with solid tumors harboring NTRK1/2/3, ROS1, or ALK gene rearrangements (fusions)	Entrectinib (RXDX-101)	TrkA, TrkB, TrkC, ROS1, ALK	2	300	October 2015
NCT02097810	Study of oral RXDX-101 in adult patients with locally advanced or metastatic cancer targeting NTRK1, NTRK2, NTRK3, ROS1, or ALK molecular alterations			1/2	175	June 2014
NCT02650401	Study of RXDX-101 in children with recurrent or refractory solid tumors and primary CNS tumors			1	80	December 2015
NCT02048488/ 2013–000686–37	A phase I/IIa open-label, dose escalation and cohort expansion trial of oral TSR-011 in patients with [illegible] lymphomas	TSR-011	TrkA, ALK	1/2	150	October 2012
NCT02637687	Oral TRK inhibitor LOXO-101 for treatment of advanced pediatric solid or primary central nervous system tumors	LOXO-101	TrkA, TrkB, TrkC	1	36	December 2015
NCT02122913	Oral TRK inhibitor LOXO-101 for treatment of advanced adult solid tumors			1	108	April 2014
NCT02576431	Study of LOXO-101 in subjects with NTRK fusion positive solid tumors			2	151	October 2015
	fusion-positive advanced non-small cell lung cancer and those with other genotypes: ROS1 or NTRK fusions or increased MET or AXL activity	(XL184)	ROS1, MET, AXL			
NCT01804530	Phase 1 study of PLX7486 as single agent and with gemcitabine plus nab-paclitaxel in patients with advanced solid tumors	PLX7486	TrkA, TrkB, TrkC, FMS	1	160	August 2013
NCT02279433	A first-in-human study to evaluate the safety, tolerability and pharmacokinetics of DS-6051b	DS-6051b	TrkA,TrkB, TrkC, ROS1	1	70	September 2014
2013–003009–24	Phase I-II study of F17752 in patients with advanced solid tumours	F17752	ALK, ROS1, Trk	1/2	112	September 2015
NCT02228811	A study of DCC-2701 in participants with advanced solid tumors	Altiratinib (DCC-2701)	TrkA, TrkB, TrkC, MET, TIE2, VEGFR	1	48	June 2014

ALK, anaplastic lymphoma receptor tyrosine kinase; AXL, AXL receptor tyrosine kinase; c-kit, mast/stem cell growth factor receptor; CNS, central nervous system; DDR2, discoidin domain receptor 2; Eph, ephrin receptor tyrosine kinases; FMS, McDonough Feline Sarcoma Viral; MER, MER receptor tyrosine kinase; MET, hepatocyte growth factor receptor; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1; TIE2, TEK receptor tyrosine kinase; TRK, tropomyosin-related kinases (also known as TrkA,B,C for kinase A, B and C); VEGFR, vascular endothelial growth factor receptor.

Amatu *et al., ESMO Open*. 2016.

The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers

Hyman DM,[1] Laetsch TW,[2] Kummar S,[3] DuBois SG,[4] Farago AF,[5] Pappo AS,[6] Demetri GD,[7] El-Deiry WS,[8] Lassen UN,[9] Dowlati A,[10] Brose MS,[11] Boni V,[12] Turpin B,[13] Nagasubramanian R,[14] Cruickshank S,[15] Cox MC,[15] Ku NC,[15] Hawkins DS,[16] Hong DS,[17] Drilon AE[1]

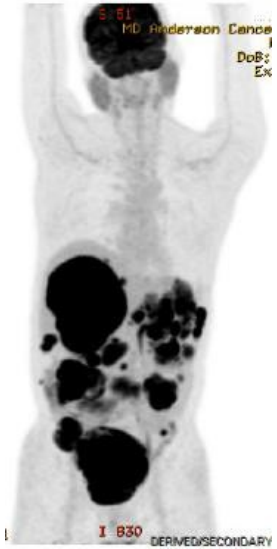
[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]University of Texas Southwestern, Dallas, TX; [3]Stanford University School of Medicine, Palo Alto, CA; [4]Dana-Farber Cancer Institute/Boston Children's Cancer and Blood Disorders Center, Boston, MA; [5]Massachusetts General Hospital, Boston, MA; [6]St. Jude Children's Research Hospital, Memphis, TN; [7]Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; [8]Fox Chase Cancer Center, Philadelphia, PA; [9]Rigshospitalet, Copenhagen, Denmark; [10]UH Cleveland Medical Center, Cleveland, OH; [11]Department of Otorhinolaryngology: Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; [12]START Madrid CIOCC, Hospital HM Universitario Sanchinarro, Madrid, Spain; [13]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [14]Nemour's Children's Hospital, Orlando, FL; [15]Loxo Oncology, Inc., San Francisco, CA; [16]Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; [17]The University of Texas MD Anderson Cancer Center, Houston, TX

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17
Hyman, LBA2501

LOXO ONCOLOGY

Treatment Refractory *ETV6-NTRK3* GIST

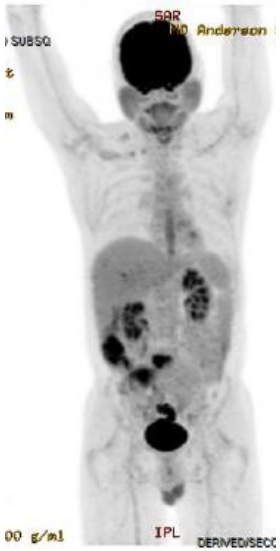
Baseline

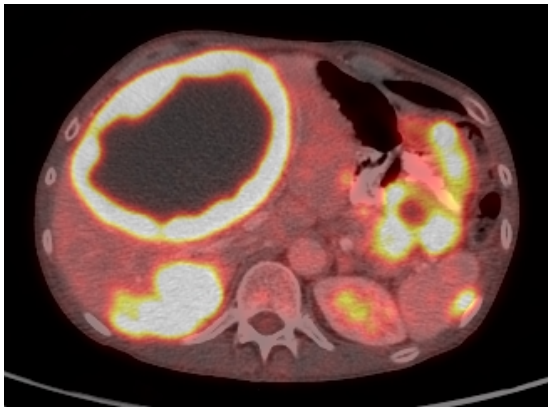


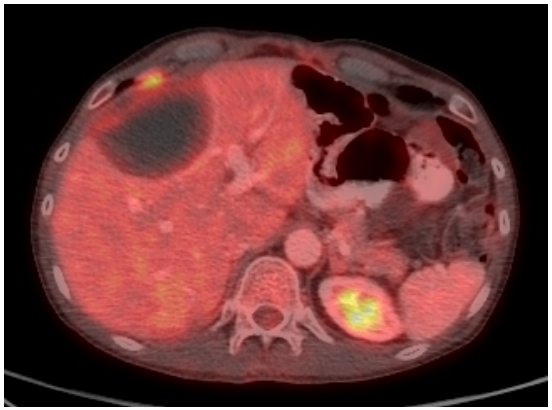
LOXO-101

Larotrectinib

Week 8

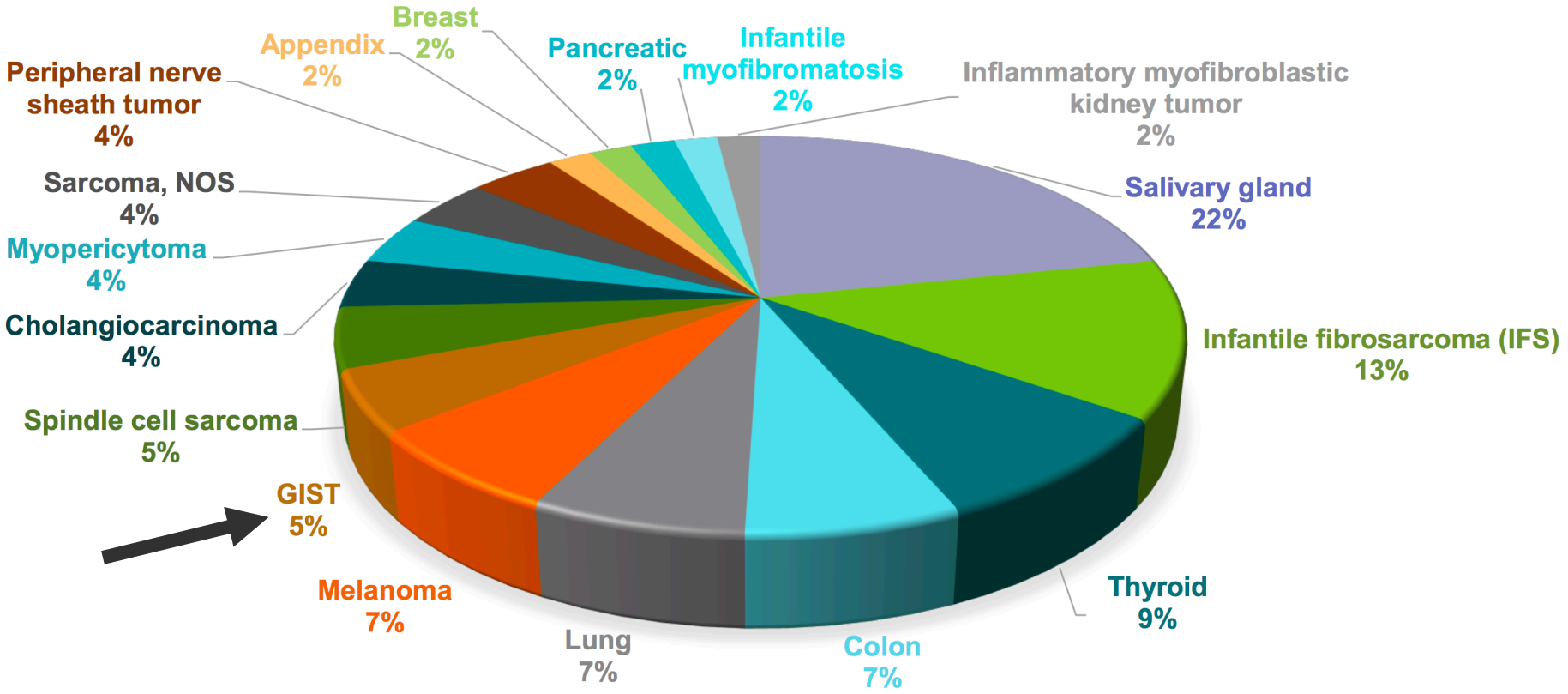






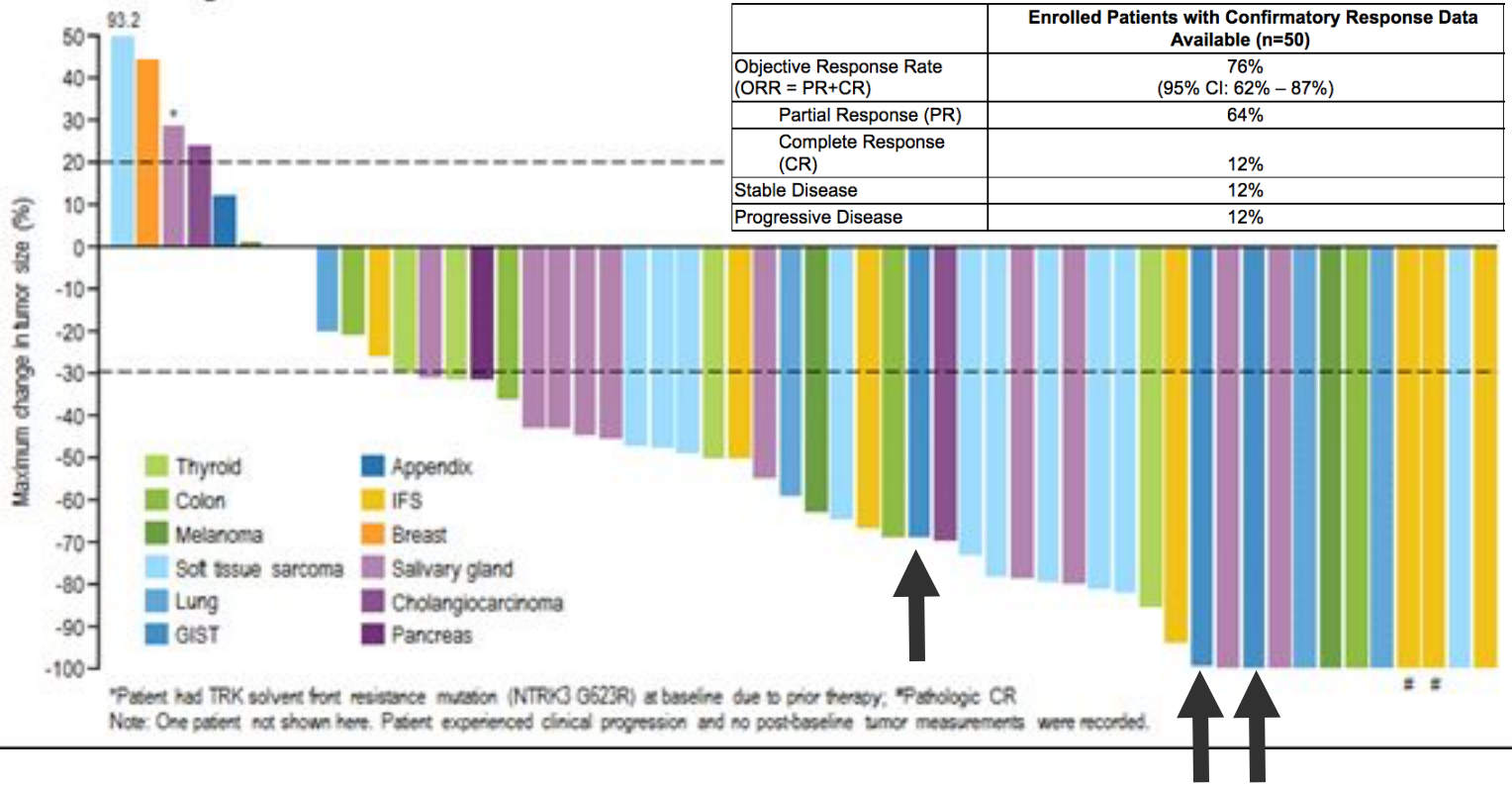
Shi et al,, *JTM* 2016.

Diversity of cancers treated - 17 unique types

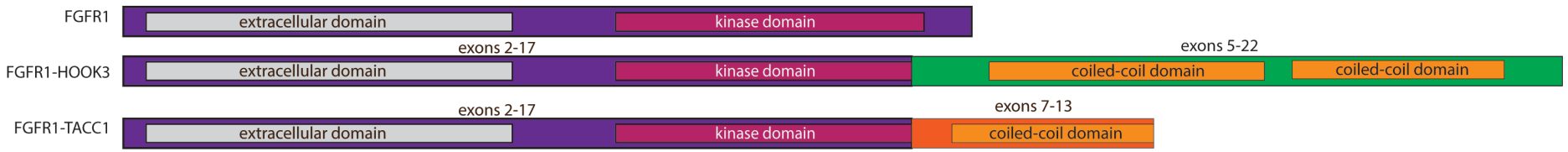


Efficacy of larotrectinib in TRK fusion cancers

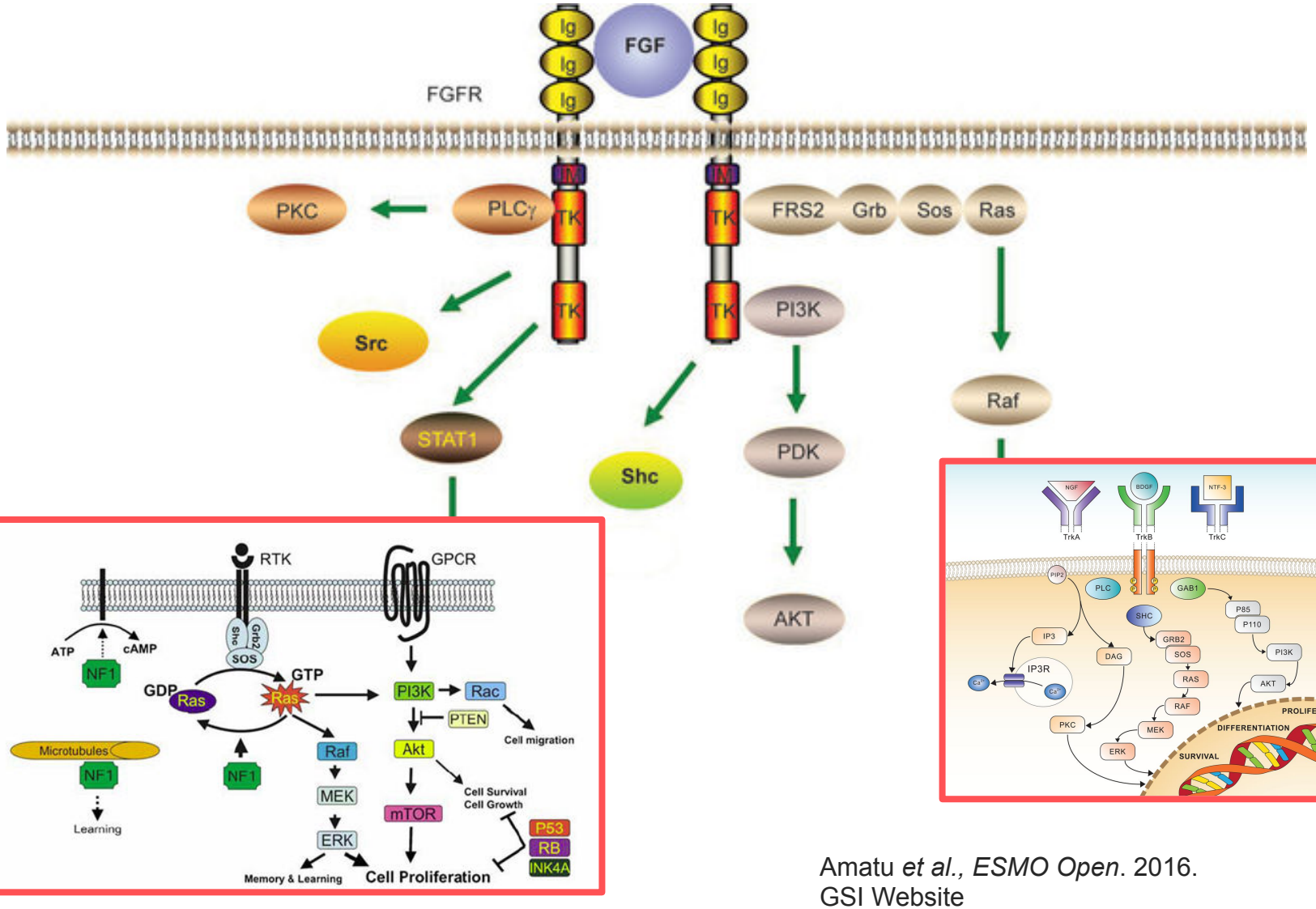
	Enrolled Patients with Confirmatory Response Data Available (n=50)
Objective Response Rate (ORR = PR+CR)	76% (95% CI: 62% – 87%)
Partial Response (PR)	64%
Complete Response (CR)	12%
Stable Disease	12%
Progressive Disease	12%



FGFR1 Gene Fusions Identified GIST



Fibroblast Growth Factor Receptor 1 (*FGFR1*)



Amatu *et al., ESMO Open*. 2016.
GSI Website

Lack Mutations in *KIT*, *PDGFRA*, RAS Pathway (*NF1*, *RAS*, *BRAF*) and *SDH* Subunits

Quadruple Wild-type (qWT) GIST

SDHB+
IGF1R-

Any age?
Equal sex?
Site?
Multifocality?

- **Genomics?**
- **Epidemiology?**
- **Disease Biology?**

Pantaleo *et al.*, *Cancer Medicine*. 2015.

Lack Mutations in *KIT*, *PDGFRA*, RAS Pathway (*NF1*, *RAS*, *BRAF*) and *SDH* Subunits

Quadruple Wild-type (qWT) GIST

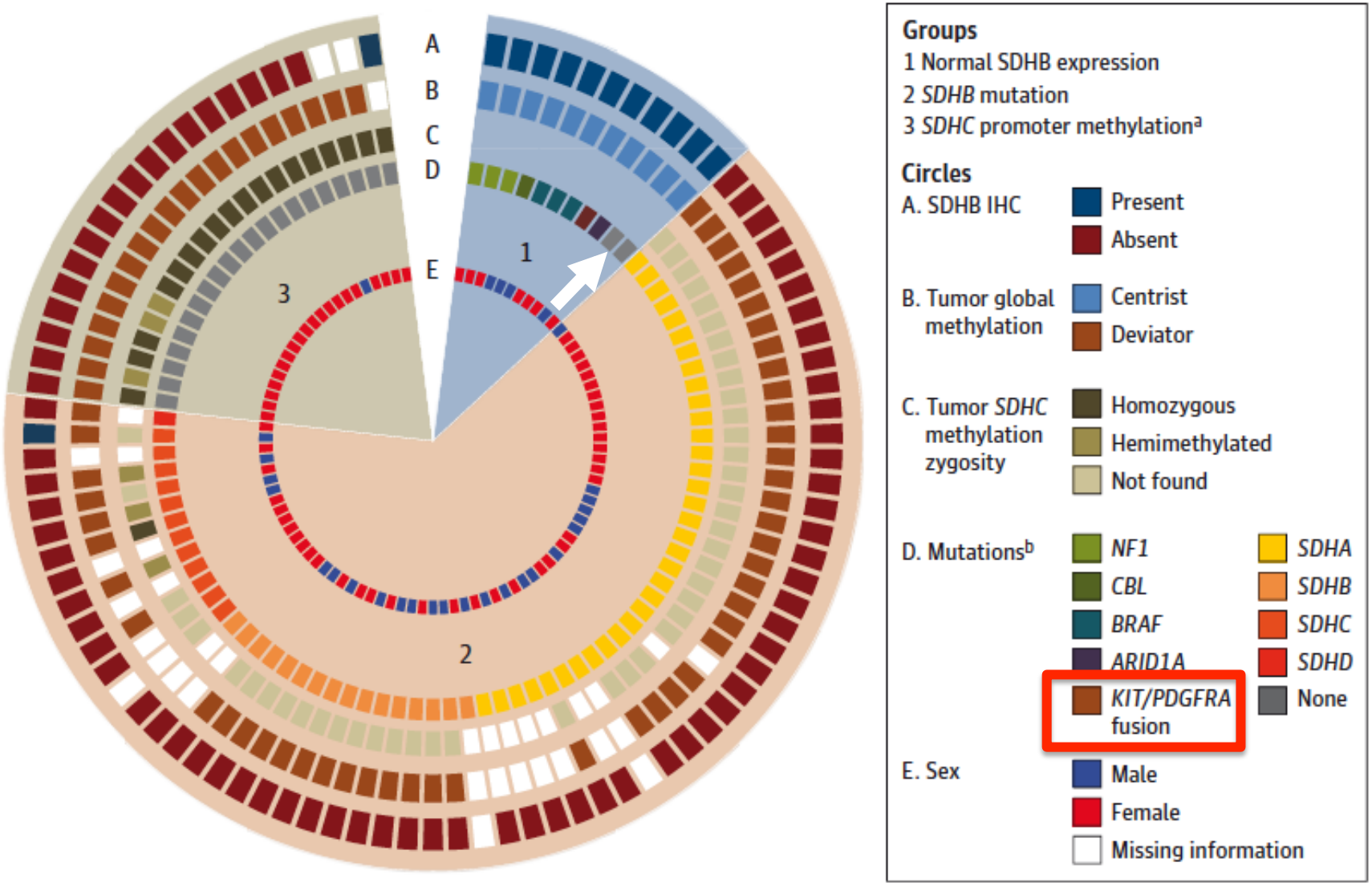
SDHB+
IGF1R-

Any age?
Equal sex?
Site?
Multifocality?

FGFR1 fusions
ETV6-NTRK3 fusions
ARID1B, ATR, LTK, SUFU, ZN217, PARK2 mutations
30s-50s
M≥F
Stomach > SB > Colon
Nodal and Distant Mets

Shi *et al.*, *JTM*. 2016.

NIH Wild-Type GIST Clinic: *KIT-PDGFRA* fusion



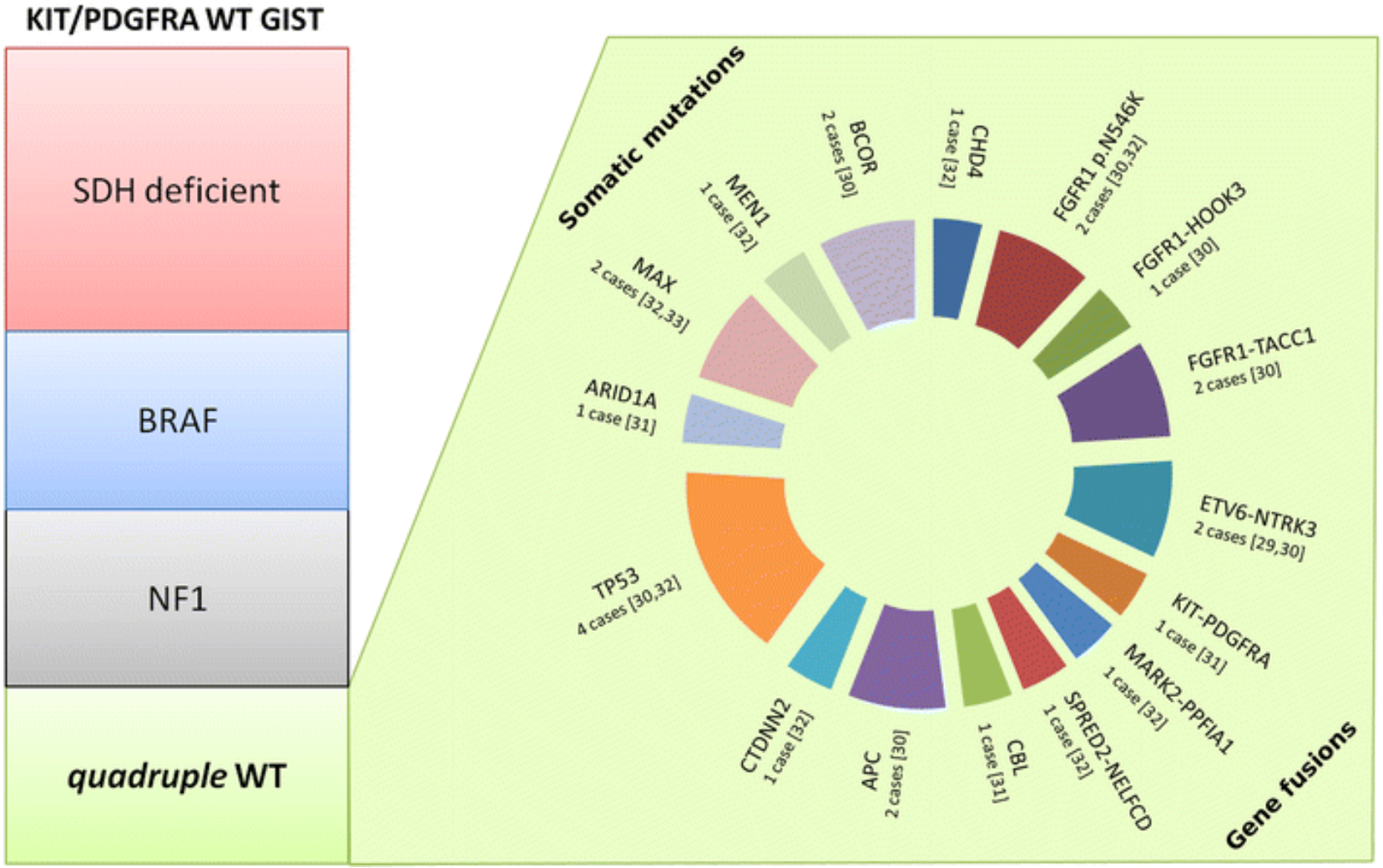
Boikos *et al.*, *JAMA Onc*. 2016.

9 Known Gene Fusions in GIST

Patient	Age (Years)	Sex	Primary Tumor Location	Tumor Stage	Gene Fusion
1	55	Male	Small bowel	T3N0M1	*ETV6-NTRK3*
2	54	Male	Colon	Unknown	*ETV6-NTRK3*
3	44	Male	Rectum	T2NxM0	*ETV6-NTRK3*
4	54	Male	Pelvis mass	Unknown	*FGFR1-TACC1*
5	54	Male	Stomach	T3N1M1	*FGFR1–TACC1*
6	38	Female	Small bowel	T3N1M1	*FGFR1–HOOK3*
7	Unknown	Female	Unknown	Unknown	*KIT-PDGFRA*
8	63	Female	Small bowel	T3N0M1	*MARK2-PPFIA1* *SPRED2-NELFCD*
9 *	30	Female	Small bowel	T4NxM0	*PRKAR1B-BRAF*
Summary	Average: 48 Median: 54	Male 56% Female 44%	44% small bowel, but spans stomach to rectum	22% nodal metastases 44% distant metastases	33% *ETV6-NTRK3* 33% *FGFR1* 33% *Others*

Shi *et al. J Translational Med*. December 2016.
Brenca *et al., J Pathology*. March 2016.
Boikos *et al., JAMA Onc*. July 2016.
Pantaleo *et al., Mol Cancer Res*. July 2017.
* UCSD Patient (unreported to date)

Progressive Fragmentation of “WT” GIST



Nannini *et al.*, *JTM. May* 2017.

Abandoning WT GIST

Journal of the National Comprehensive Cancer Network

The Call of "The Wild"-Type GIST: It's Time for Domestication

Maha Alkhuziem, MBBS, MAS; Adam M. Burgoyne, MD, PhD; Paul T. Fanta, MD; Chih-Min Tang, PhD; and Jason K. Sicklick, MD

Alkhuzeim et al., JNCCN. May 2017.

Table 1. Matching Genomic Alterations With Targeted Therapies in GIST: Theoretical Precision Actionabilities Meriting Investigations (cont.)

Gene	Pathways/Signaling	Matching FDA-Approved, On-Label Agents With Targets in GIST	Matching FDA-Approved, Off-Label Agents With Targets in GIST	Clinical Trials Enrolling Patients With GIST
KRAS	MAPK		MEK inhibitors: cobimetinib, trametinib	
LTK	Transcriptional regulation Insulin receptor signaling		TKI: crizotinib	
NF1	MAPK		MEK inhibitors: cobimetinib, trametinib	
NRAS	MAPK		MEK inhibitors: cobimetinib, trametinib	
PARK2	E3 ubiquitin ligase Cyclin-CDK complexes		CDK4/6 inhibitor: palbociclib	Phase II (CDK4/6 inhibitor): palbociclib
PDGFRA	MAPK PI3K/AKT/mTOR JAK/STAT	Imatinib (first line) Sunitinib (second line) Regorafenib (third line)	TKI: ponatinib	Phase I (PDGFRA/TKI inhibitors): BLU-285, DCC-2618 Phase II (PDGFRA/TKI inhibitors): dovitinib, famitinib, olaratumab, onalespib, motesanib Phase III (PDGFRA inhibitor): crenolanib
SDHA	Epigenetic methylation HIF1-alpha expression		Hypomethylating agents: 5-azacytidine, decitabine	Phase I (glutaminase inhibitor): CB-839
SDHB	Epigenetic methylation HIF1-alpha expression		Hypomethylating agents: 5-azacytidine, decitabine	Phase I (glutaminase inhibitor): CB-839
SDHC	Epigenetic methylation HIF1-alpha expression		Hypomethylating agents: 5-azacytidine, decitabine	Phase I (glutaminase inhibitor): CB-839
SDHD	Epigenetic methylation HIF1-alpha expression		Hypomethylating agents: 5-azacytidine, decitabine	Phase I (glutaminase inhibitor): CB-839
SUFU	Hedgehog pathway		GLI inhibitor: arsenic trioxide	
ZNF217	Transcriptional regulation			

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Table 1. Matching Genomic Alterations With Targeted Therapies in GIST: Theoretical Precision Actionabilities Meriting Investigations

Gene	Pathways/Signaling	Matching FDA-Approved, On-Label Agents With Targets in GIST	Matching FDA-Approved, Off-Label Agents With Targets in GIST	Clinical Trials Enrolling Patients With GIST
ARID1A	Chromatin remodeling PI3K/AKT/mTOR		mTOR inhibitors: everolimus, temsirolimus	Phase I (PI3K inhibitors): alpelisib, buparlisib, TGR-1202
ARID1B	Chromatin remodeling PI3K/AKT/mTOR		mTOR inhibitors: everolimus, temsirolimus	Phase I (PI3K inhibitors): alpelisib, buparlisib, TGR-1202
ATR	DNA repair		DNA damaging agents: cisplatin, gemcitabine, topotecan PARP inhibitors: olaparib, rucaparib Radiotherapy	
BRAF	MAPK	Regorafenib (third line)	BRAF V600E inhibitors: dabrafenib, vemurafenib MEK inhibitors: cobimetinib, trametinib	Phase II (BRAF V600E inhibitor): dabrafenib Phase II (MEK inhibitors): binimetinib, trametinib
ETV6-NTRK3	MAPK PI3K/AKT/mTOR JAK/STAT		TKI: crizotinib	Phase I (TRK inhibitor): larotrectinib Phase II (TRK inhibitor): entrectinib
FGFR1	FGF	Regorafenib (third line)	FGFR inhibitors: lenvatinib, pazopanib, ponatinib	Phase I (FGFR inhibitors): BGJ398, dovitinib Phase II (FGFR inhibitor): semaxanib
HRAS	MAPK		MEK inhibitors: cobimetinib, trametinib	
KIT	MAPK PI3K/AKT/mTOR JAK/STAT	Imatinib (first line) Sunitinib (second line) Regorafenib (third line)	TKIs: dasatinib, nilotinib, ponatinib	Phase I (TKIs): DCC-2618, OSI-930, PLX9486 Phase II (TKIs): BBI503, cabozantinib, dasatinib, famitinib, ganetespib, nilotinib, pexidartinib, sorafenib, sunitinib Phase III (TKI): masitinib

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Summary #1

- "Quadruple Wild-Type: or "Unclassified" GIST occur in younger patients, occur in similar locations as non-qWT GIST, frequently metastasize to lymph nodes, and most are not truly "WT."
- Potentially deleterious gene fusions occur in adults with GIST and these are potentially targetable with drugs.
  - KIT inhibitors (*KIT-PDGFRA* fusion)
  - NTRK3 inhibitors (*ETV6-NTRK3* fusion)
  - FGFR1 inhibitors (*FGFR1-TACC1/HOOK3* fusions)
  - BRAF inhibitors (*BRAF-PRKAR1B* fusion)
- Other driver genes at play:
  - *ARID1A/D, ATR, LTK, MAX, PARK2, SUFU, ZNF217*

Shi *et al. J Translational Med*. December 2016.
Boikos *et al., JAMA Onc*. July 2016.
Pantaleo *et al., Mol Cancer Res*. July 2017.
Alkhuzeim et al., JNCCN. May 2017.

Is Location is a Biomarker for Gene Mutations?

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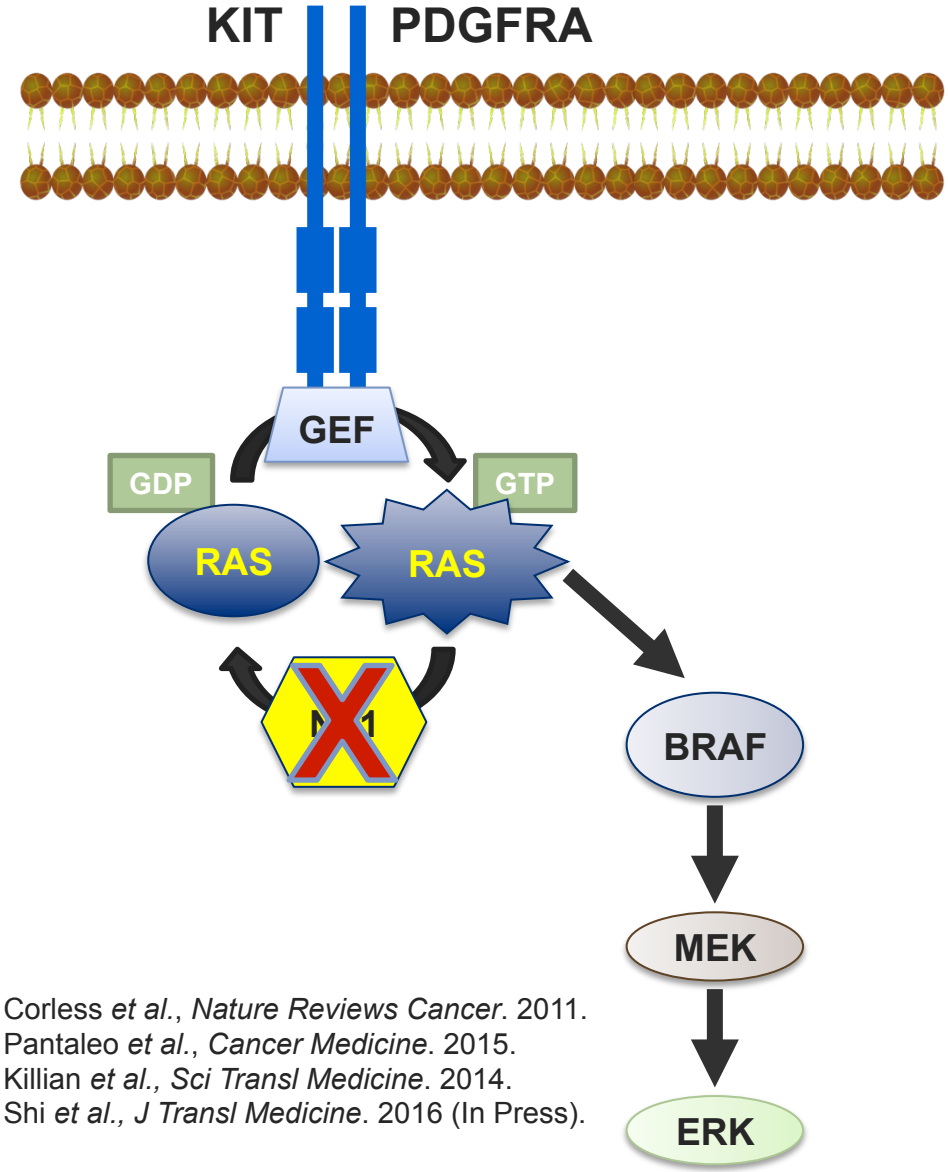
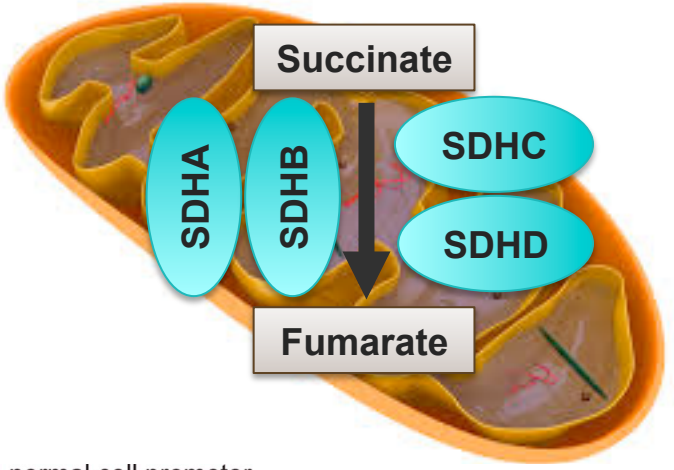
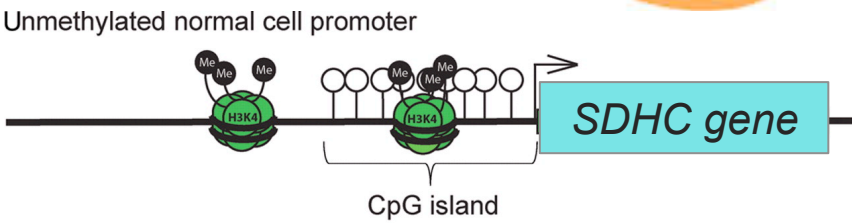
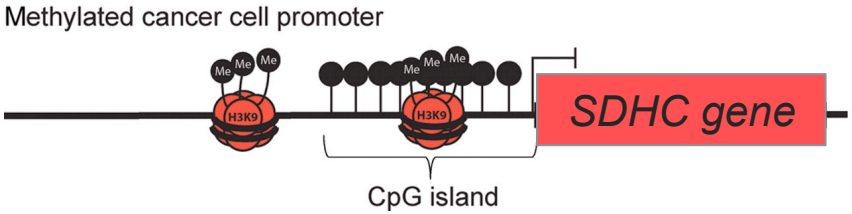
Known Driver Genes in GIST

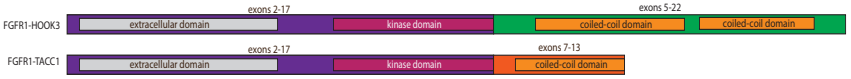








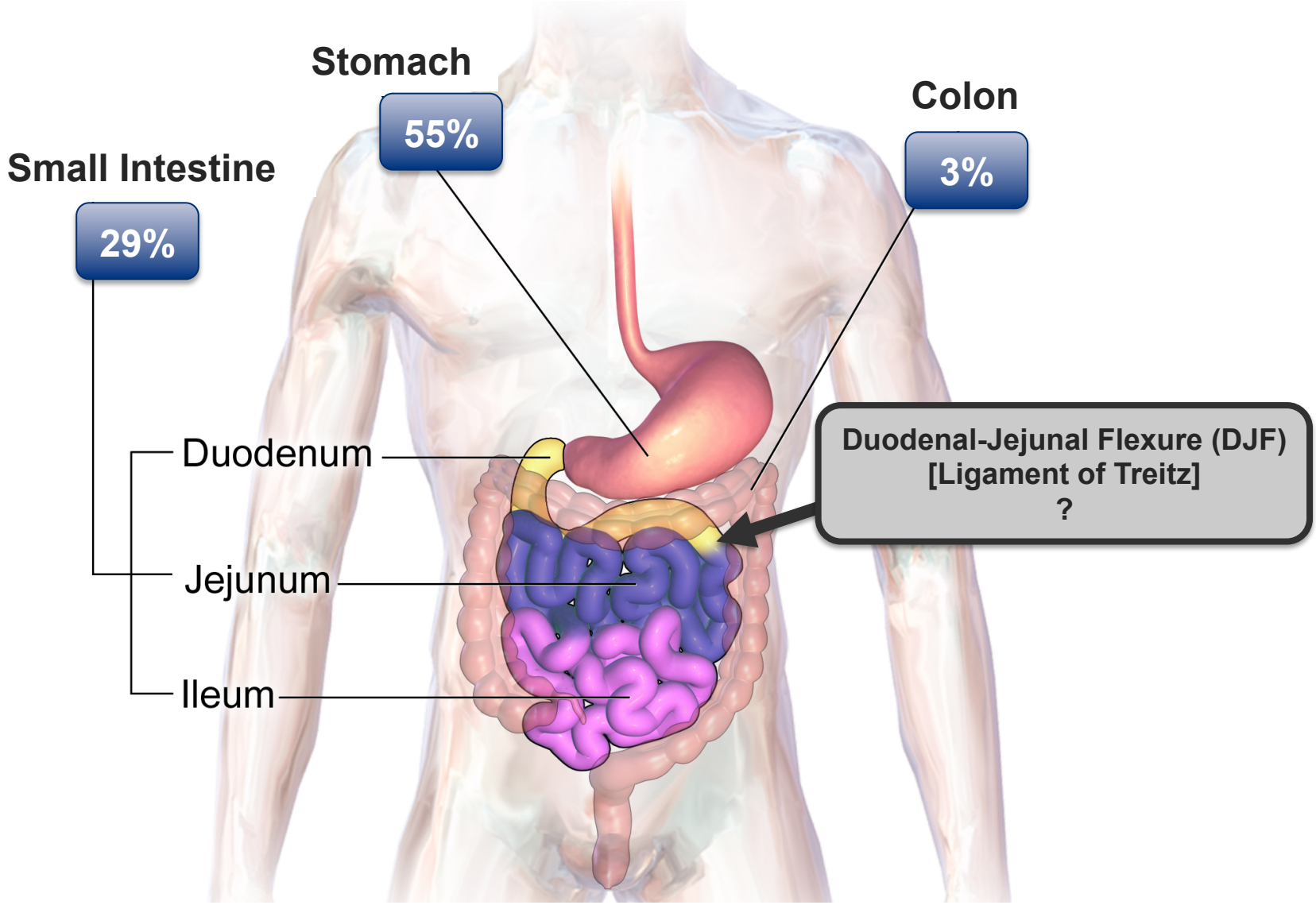
FGFR1-HOOK3 or –TACC1 fusions



ETV6-NTRK3 fusion

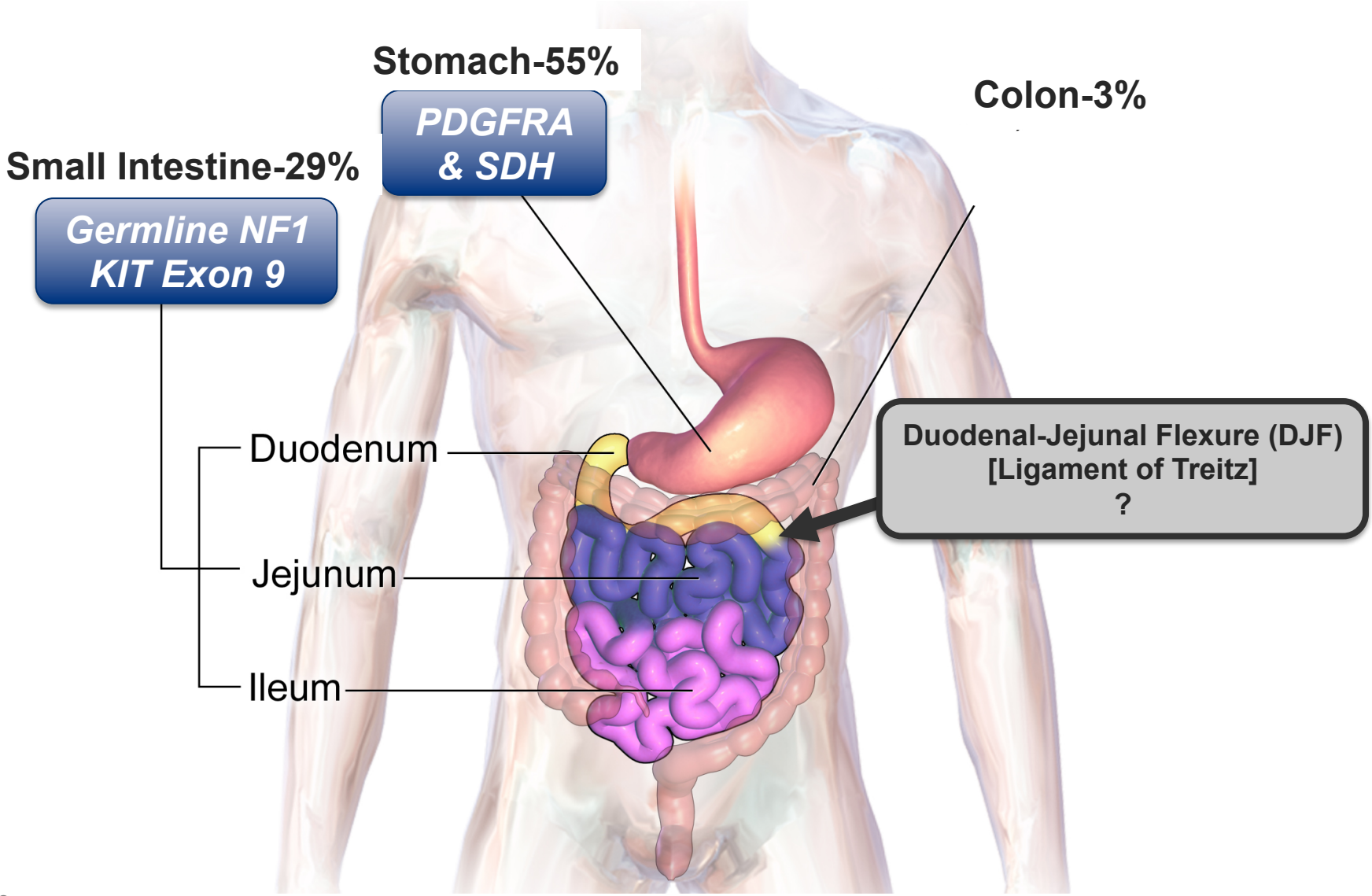
Corless *et al.*, *Nature Reviews Cancer*. 2011.
Pantaleo *et al.*, *Cancer Medicine*. 2015.
Killian *et al., Sci Transl Medicine*. 2014.
Shi *et al., J Transl Medicine*. 2016 (In Press).

Anatomic Localization of GIST



Ma *et al.*, *CEBP*. 2015.

Genes and Localization of GIST



Ma *et al.*, *CEBP*. 2015.

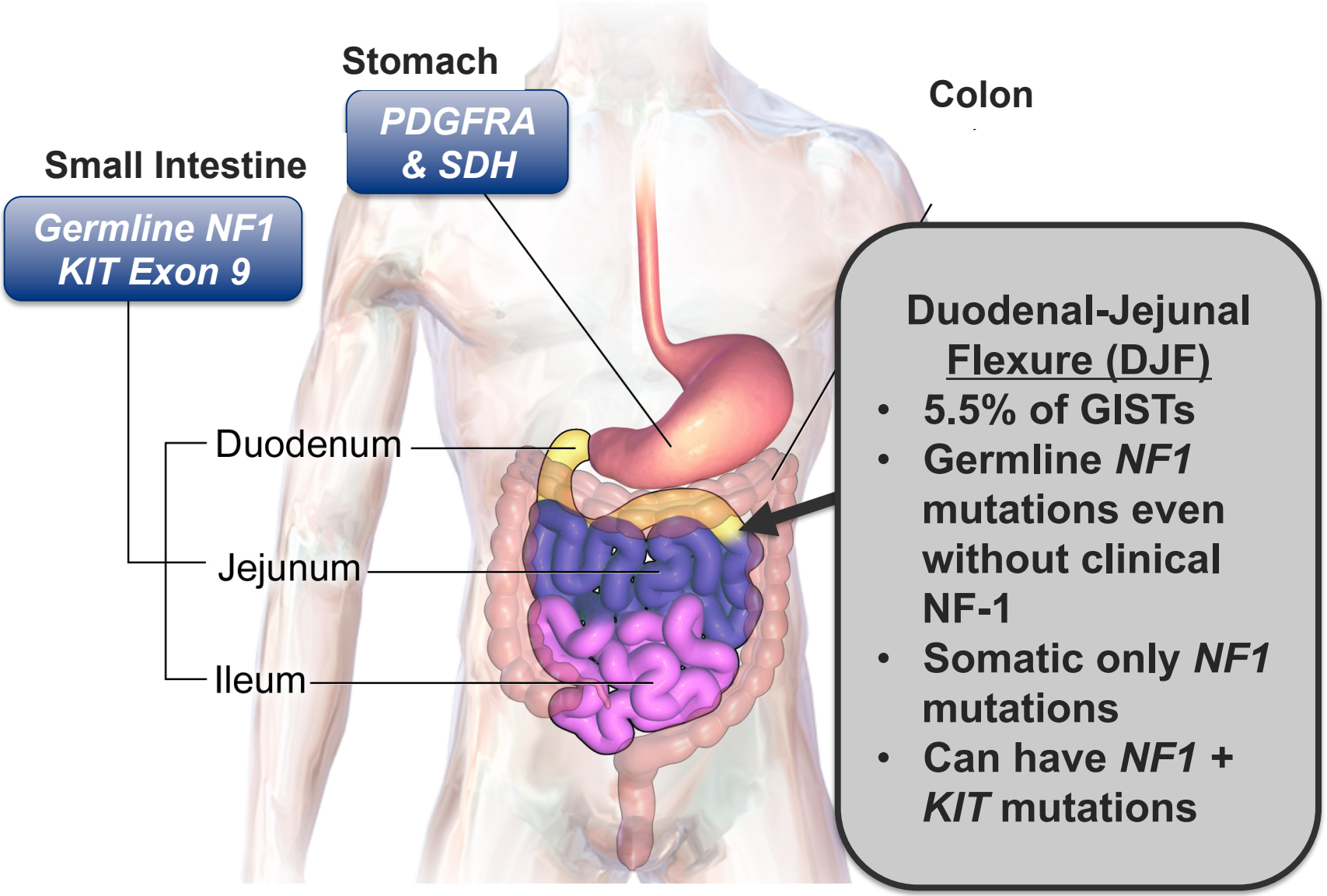
Background: *NF1* Mutant GIST

1. Often multifocal small intestine GISTs associated with Neurofibromatosis type 1 (NF-1)
2. NF-1 associated with 1.5% of GISTs
3. Somatic *NF1* mutant small bowel GIST was recently reported in the absence of a germline *NF1* mutation (Belinsky *et al.*, *BMC Cancer*, 2015).
4. *NF1* gene mutations associated with NF-1 were recently reported (Gasparotto *et al.*, *Clin Cancer Research*, 2016):
   - Frequent in GISTs lacking *KIT/PDGFRA/BRAF* mutations or *SDH* inactivation
   - Especially if multifocal or with a multinodular growth pattern and a non-gastric location.

New Key Findings

1. In three series, GISTs more frequently than 1.5% possess *NF1* genomic alterations
   - 6.1% (MSKCC, 7/115)
   - 9.7% (UCSD, 6/62)
   - 9.7% (FMI, 18/186)

New Key Findings



Ma *et al.*, *CEBP*. 2015.

Methods

Primary Study Population

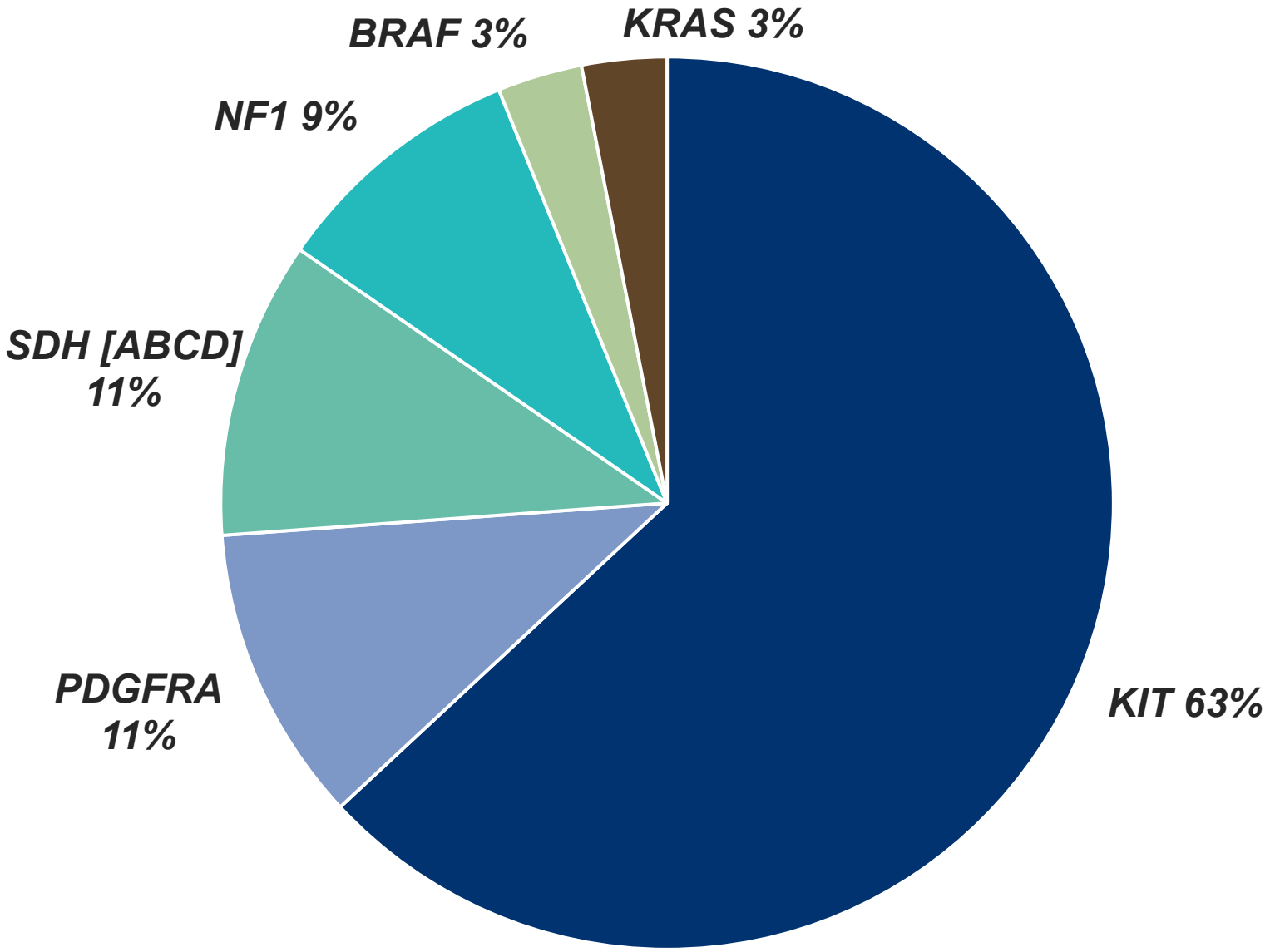
- Retrospective study of 165 GIST patients with from January 1, 2000 to April 30, 2017 at the UC San Diego Moores Cancer Center
- Data collected included age, sex, race, ethnicity, primary GIST site, tumor size, and mitotic index.

Next Generation Sequencing

- 62 patients underwent NGS of cancer-related genes beginning in 2014:
  - Foundation Medicine (315 genes)
  - UC San Diego Heath System Clinical Genomics Laboratory (397 genes)

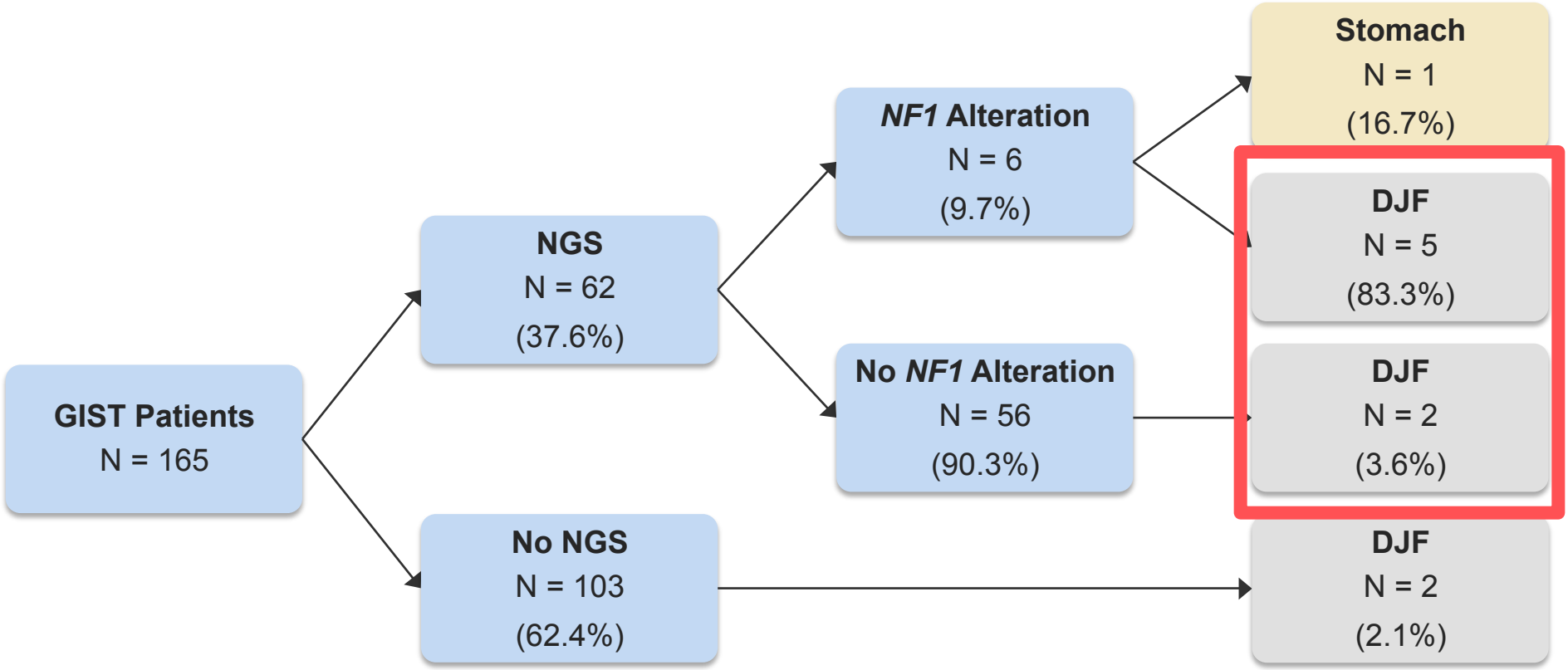
Burgoyne *et al.*, *JCO Precision Oncology*. 2017.

Driver Mutations in 62 UCSD GIST



Burgoyne *et al.*, *JCO Precision Oncology*. 2017.

NF1 Genomic Alterations are Frequent at DJF



Burgoyne *et al.*, *JCO Precision Oncology*. 2017.

9 DJF GIST Patient Demographics

Characteristic	Number	%
Age, years		
Median (range)	55 (36-80)	
Average	55.9 ± 15	
Sex		
Male	4	44.4%
Female	5	55.6%
Race		
Caucasian	7	77.8%
African American	1	11.1%
Asian/Pacific Islander	1	11.1%
Ethnicity		
Non-Hispanic white	5	55.6%
Hispanic/Latino	4	44.4%

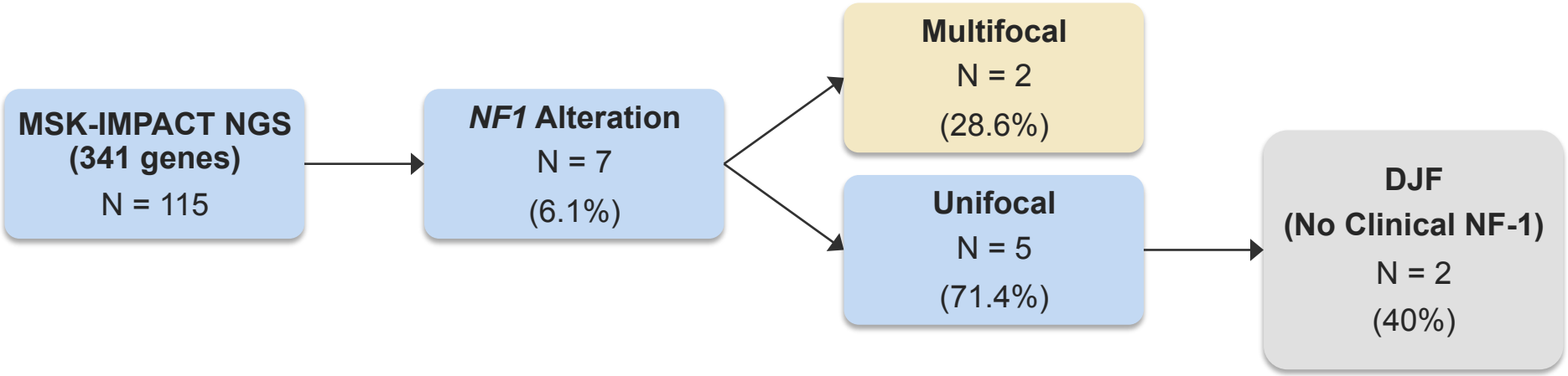
Burgoyne *et al.*, *JCO Precision Oncology*. 2017.

DJF GIST Clinicopathologic Features

Characteristic	Number	%
Stage		
Localized	6	66.7%
Regional	0	0.0%
Distant	1	11.1%
Unknown	2	22.2%
Tumor Size, cm		
Median (range)	9 (1.5 - 15)	
Average	8.0 ± 5.0	
Mitotic Index		
Low	4	44.4%
High	3	33.3%
Unknown	2	22.2%
Cell Morphology		
Spindle	5	55.6%
Epithelioid	0	0.0%
Mixed	3	33.3%
Unknown	1	11.1%

Burgoyne *et al.*, *JCO Precision Oncology*. 2017.

MSKCC Validation Cohort



Burgoyne *et al.*, *JCO Precision Oncology*. 2017.

3	11	2	1	4	5	10	7	6	CASE	
15	8	1.5	13	5.3	3	1	2.5	2.1	**Size (cm)**	**Tumor**
									MI (per 5 mm^2)	
									***NF1* (somatic)**	**Reported GIST Drivers**
			SNP						***NF1* (germline)**	
									***KIT* (somatic)**	
									***BRAF* (somatic)**	
									***ARID1A* (somatic)**	
CDC73	*EP300*	*NOTCH2*		*MAML2*					**Notch Pathway**	**Others**
ASXL1 *MEN1*	*ERBB4* *RB1* *TSC2*				*BCOR*				**Others**	

Mitotic Index
- High
- Low
- Unknown

Genomic Alteration
- Nonsense
- Frameshift
- Missense
- In frame indel
- Deletion
- Splicing

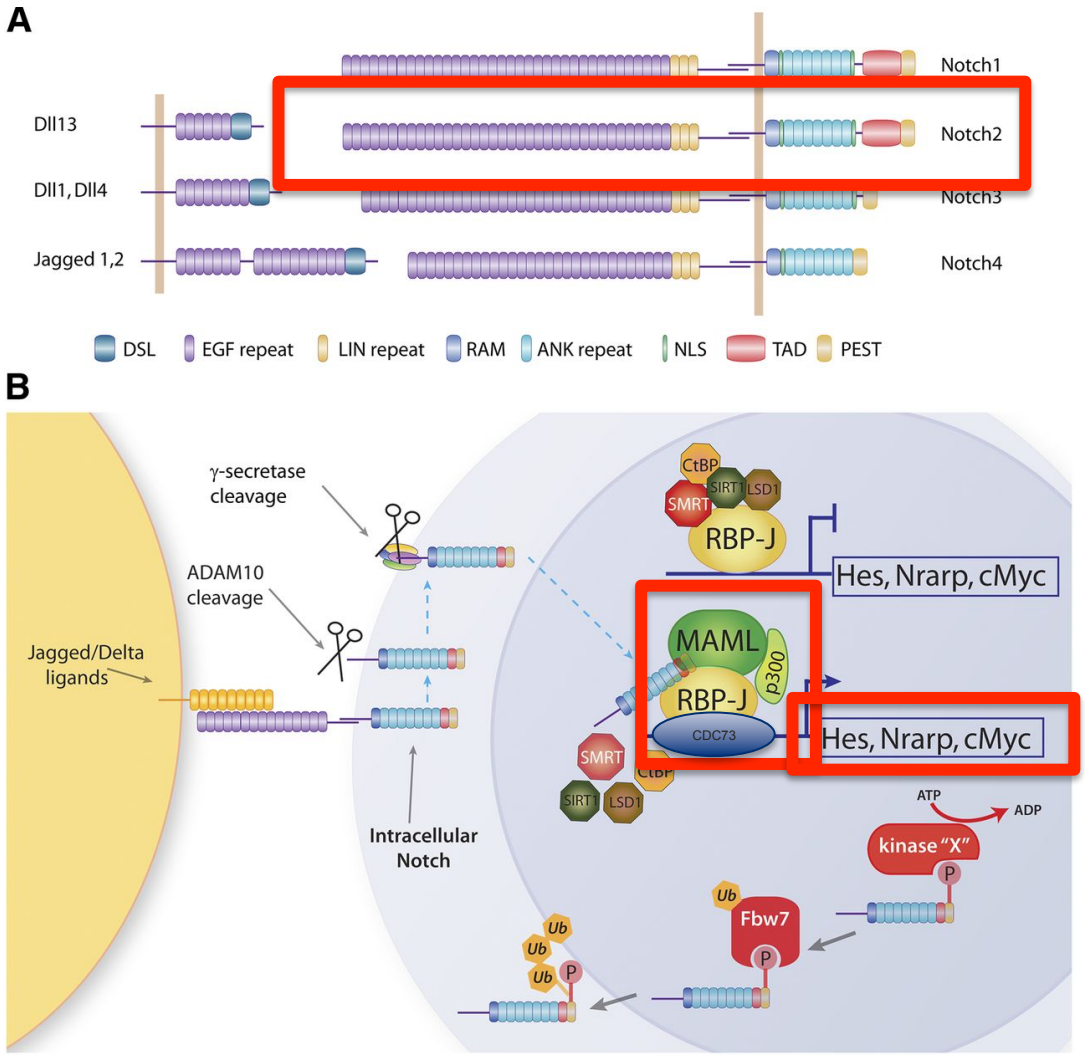
Burgoyne *et al.*, *JCO Precision Oncology*. 2017.

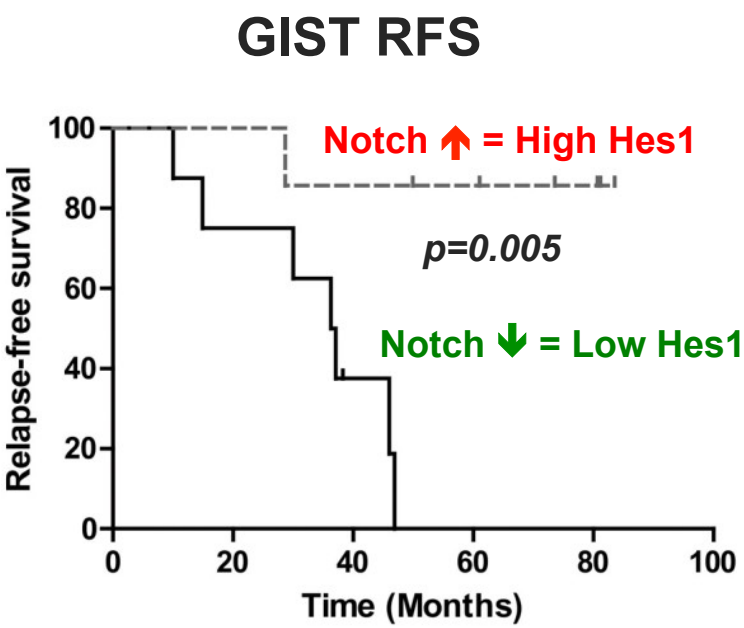
Summary #2

- Duodenal-Jejunal Flexure (DJF) or Ligament of Treitz GISTs frequently possess *NF1* alterations (somatic and/or germline), which occur even in the absence of clinical NF-1
- This represents a previously unappreciated presentation of clinical NF-1.

Solitary GIST arising at the DJF may be a biomarker for clinically occult NF-1, even if single gene testing reveals a *KIT* mutation.

NF1 and *Notch* Genomic Alterations





Lobry *et al.*, *Blood*. 2014.

Dumont *et al.*, *Carcinogenesis*. 2012.

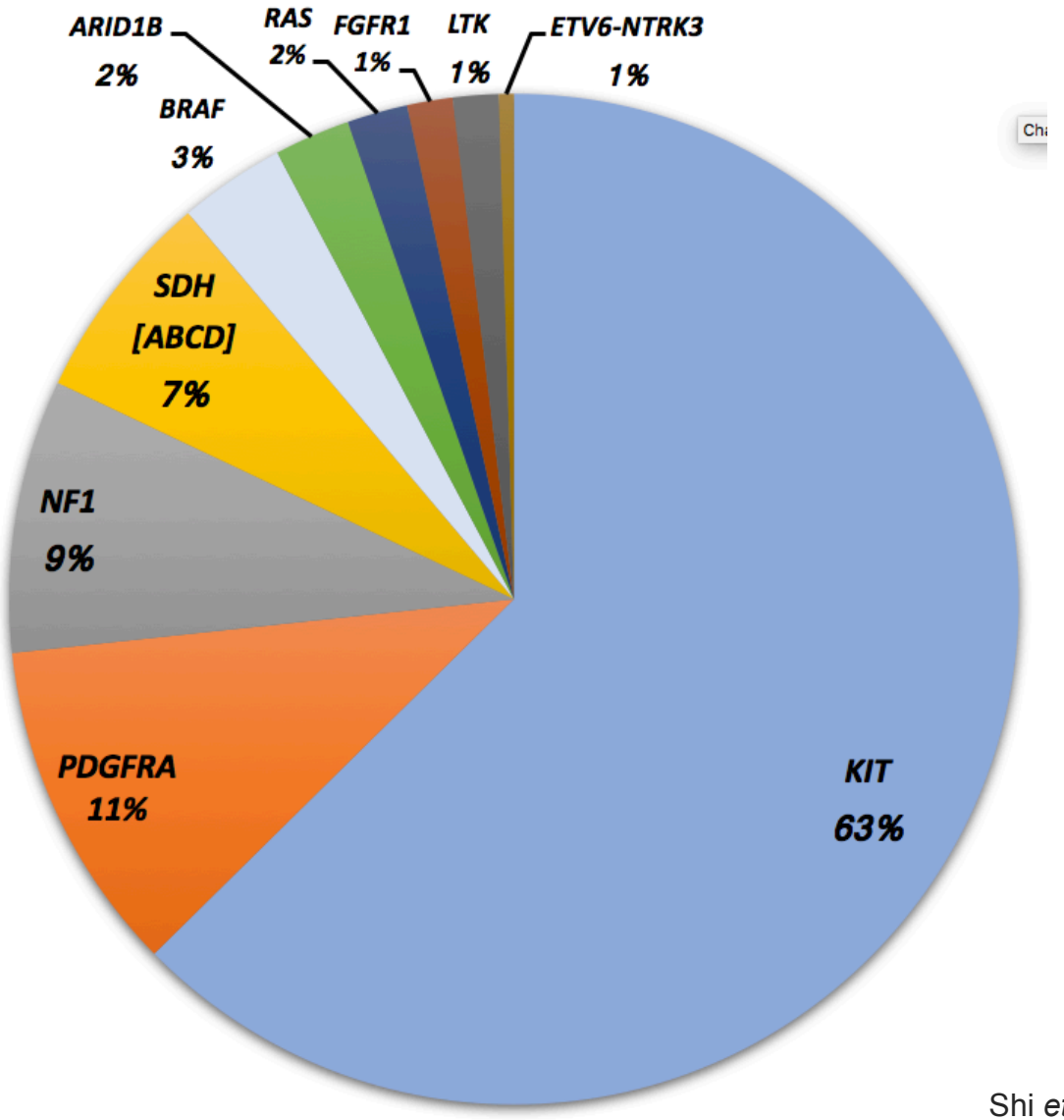
Clinical Implications

Any DJF GIST may be considered for *NF1* gene analysis, and any positive result has the following clinical implications:

1. Additional cancer screening according to expert guidelines.
2. Familial genetic counseling and screening.
3. Personalizing systemic therapy as *NF1* mutant GISTs tend to be imatinib-resistant.

Burgoyne *et al.*, *JCO Precision Oncology*. 2017.

Slicing the Pie…It's Time for Personalization



Shi *et al.*, *JTM*. 2016.

Funding

UC San Diego

NIH

The Society for Surgery of the Alimentary Tract SSAT

PEDAL THeCAUSE™ A WORLD WITHOUT CANCER.

The Kristen Ann Carr Fund

SDH-RA SDH-Deficient GIST Research Advocates

Lighting the Path Forward for Gastrointestinal Stromal Tumor (GIST) Cancer Research UC San Diego Health

Hope for a Cure Foundation Support and Hope in the Quest for a Cure

gsi GIST Support International

The Life Raft GROUP

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UC San Diego Moores Cancer Center

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Billy Wang

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OHSU
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Chris Corless

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Tamas Ordog
Sabriya Syed

Columbia
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Andrea Califano

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