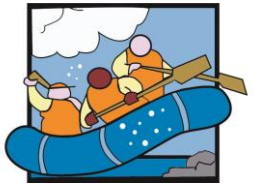
Origins of the NIH Pediatric GIST Clinic

ASCO 2006

the NIH Pediatric & Wildtype GIST Clinic

Established 2008

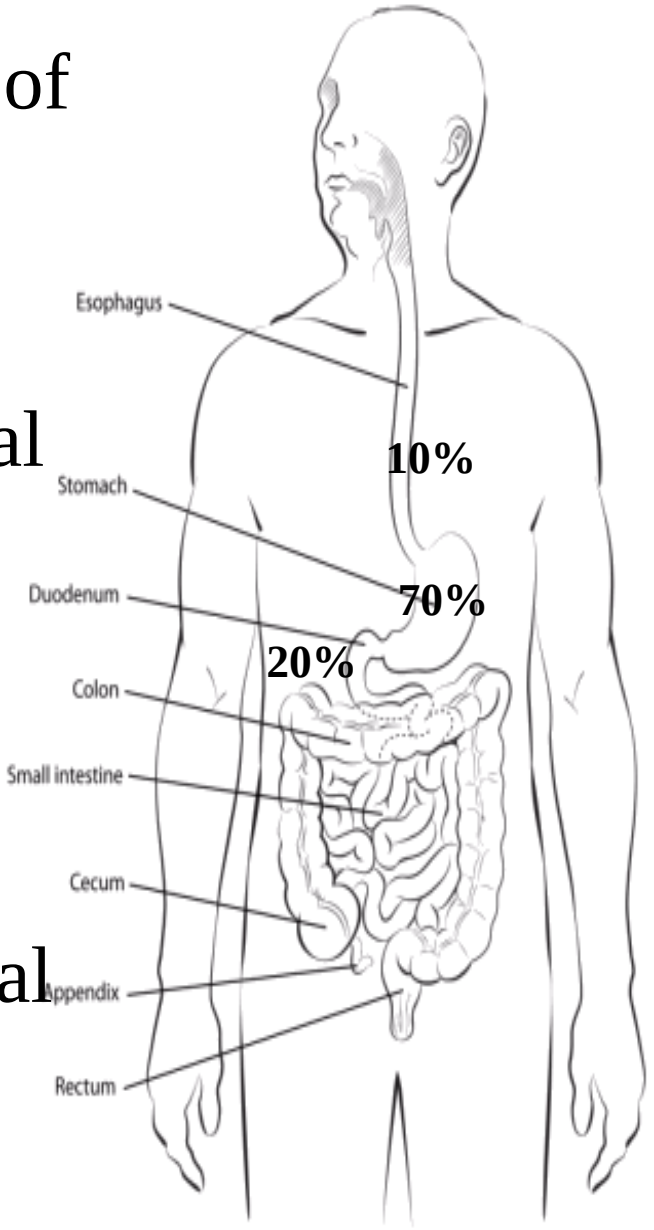


Outline

- **Background data-how targeted Rx directed at KIT/PDGFRA mutations with imatinib changed disease course in GIST**
- **Pediatric GIST-lack KIT/PDGFRA mutations**
- **Identification and management principles of SDH-deficient GIST**

Gastrointestinal Stromal Tumors: GIST

- Most common mesenchymal neoplasms of the gastrointestinal track; but fewer than 1% all GI tumors
- Originates in the Interstitial Cells of Cajal (smooth muscle pacemakers)
- Introduced as a diagnostic term in 1983
- Initially, management was mostly surgical



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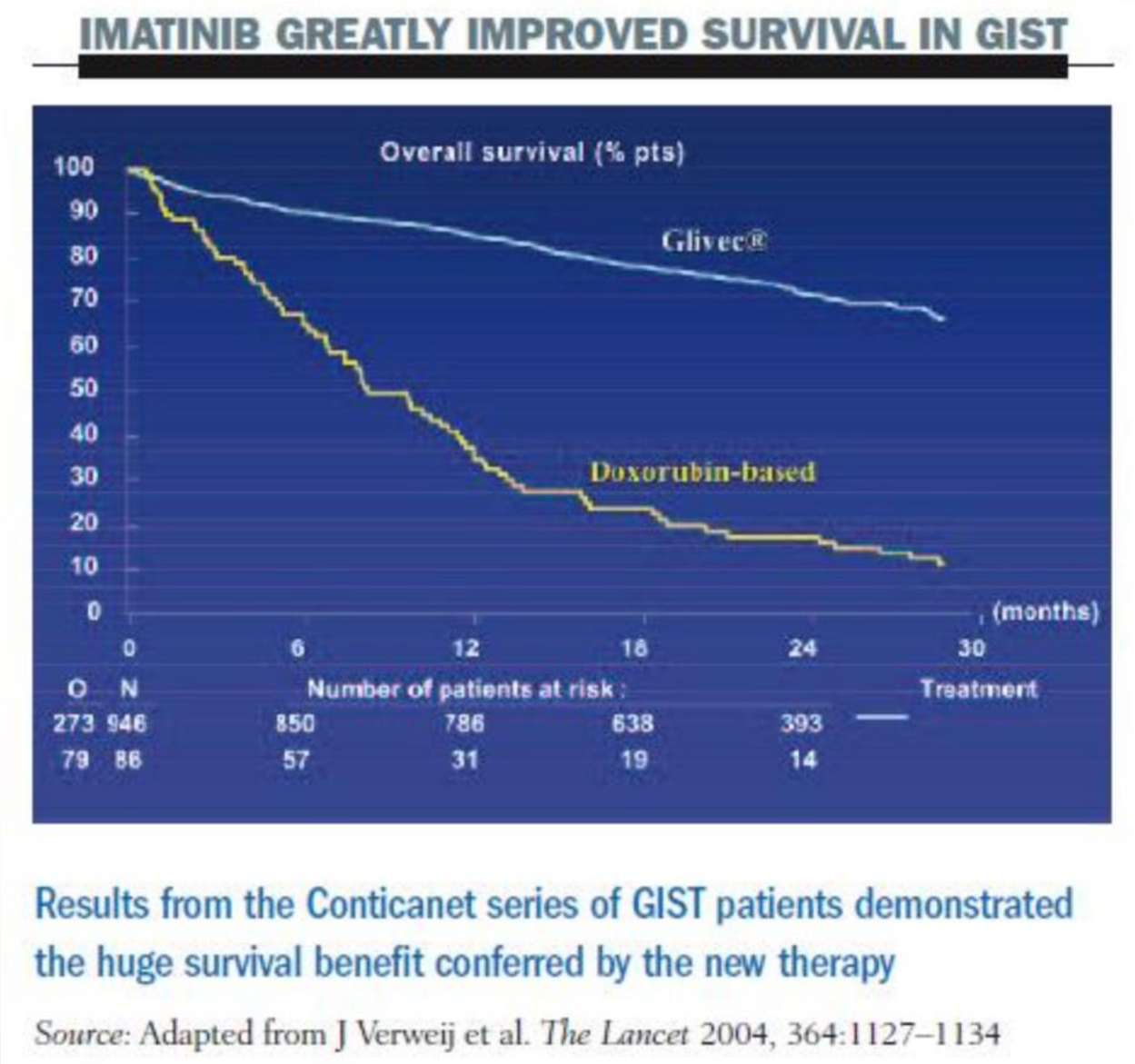
- **Response to chemotherapy < 5%**
- **ICC were found to express high levels of cKIT**
- **GISTs were found to have cKIT and PDGFRA activating mutations**
- **Imatinib (tyrosine kinase inhibitor first approved for CML, that also inhibits cKIT and PDGFRA) approved for unresectable and metastatic GIST in 2002**
- **2 Year survival has increased from 20% to 75-80%**
- **Well described criteria for use in high risk resected tumors has decreased risk of recurrence**



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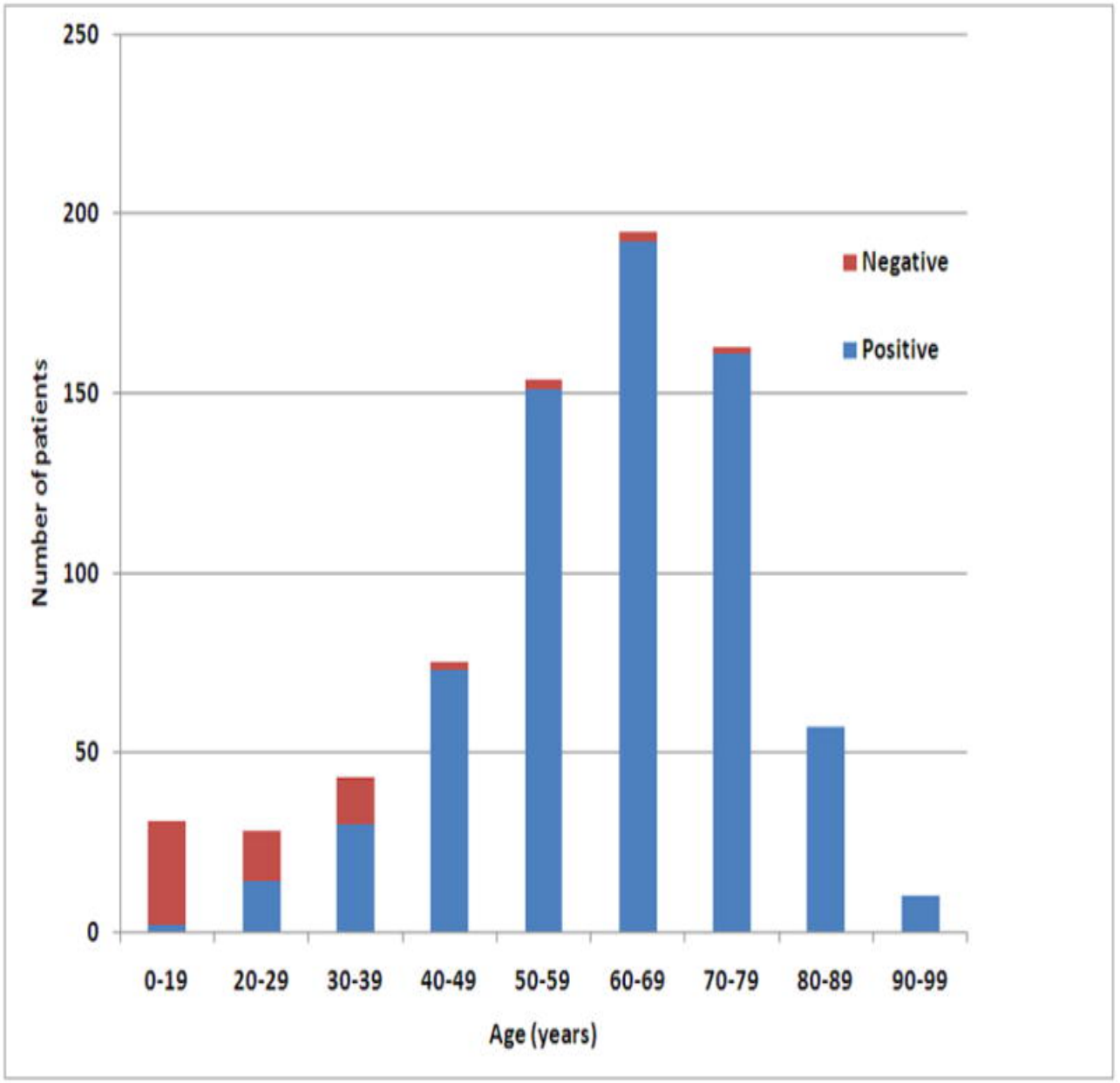
Frequency of SDHB-negative and SDHB-positive gastric GISTs as a function of age



Miettinen et. al
Am J Surg Pathol.
2011

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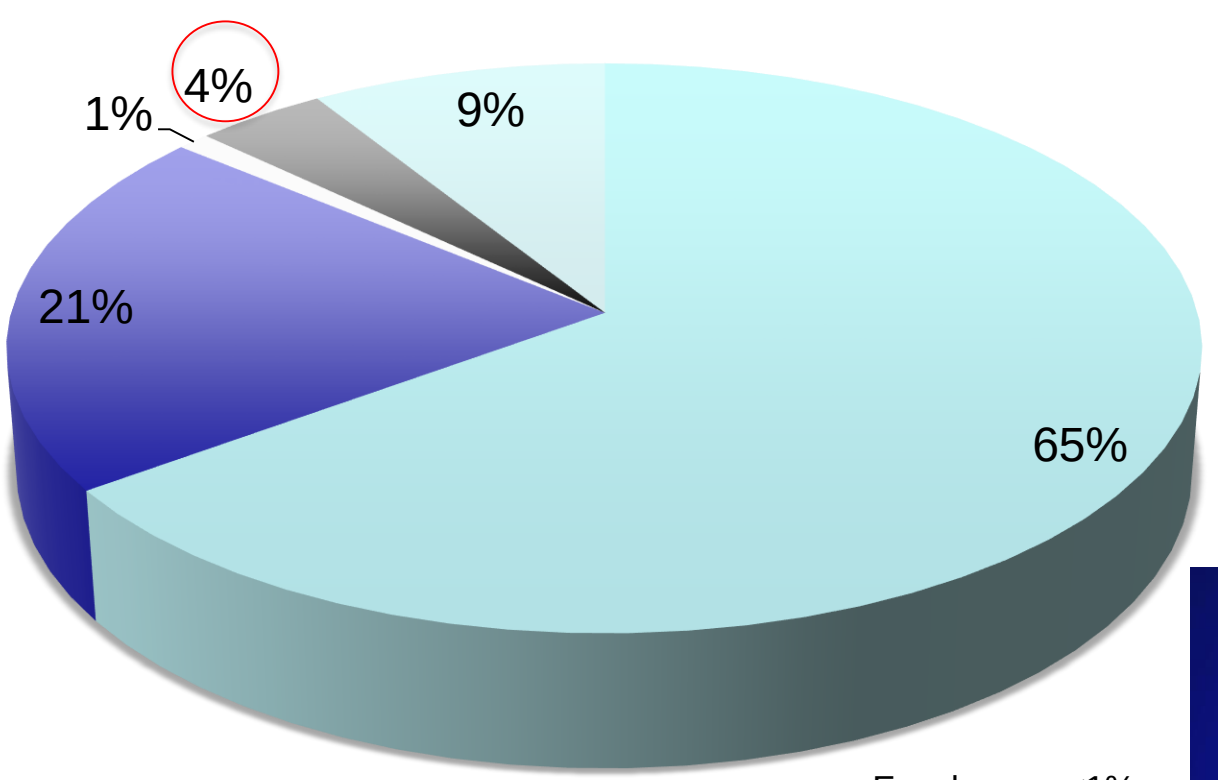
GIST Molecular Subtypes



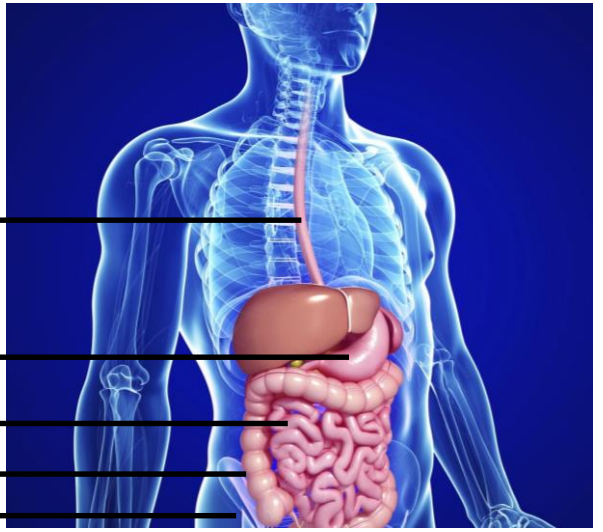
KIT

PDGFRA

BRAF

SDH-deficient

SDH+ Unknown



Esophagus <1%

Stomach 56%

Small intestine 32%

Colon/rectum <6%

Other <6 %

Rossi et al., Am J Pathol 2015
Søreide et al., Cancer Epidemiology 2016
Miettinen et al., Am J Surg Pathology

The NIH pediatric and wildtype GIST clinic

- **Bi-annual/annual clinic at NIH established June, 2008**
  - **Collaborative effort between clinicians, researchers, support groups and patients**
  - **Objective: further the investigation of the clinical features and oncogenic mechanisms underlying wild-type GIST**

Proc Natl Acad Sci U S A. 2011 Jan 4;108(1):314-8. doi: 10.1073/pnas.1009199108. Epub 2010 Dec 20.

Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations.

Janeway KA[1], Kim SY, Lodish M, Nosé V, Rustin P, Gaal J, Dahia PL, Liegl B, Ball ER, Raygada M, Lai AH, Kelly L, Hornick JL; NIH Pediatric and Wild-Type GIST Clinic, O'Sullivan M, de Krijger RR, Dinjens WN, Demetri GD, Antonescu CR, Fletcher JA, Helman L, Stratakis CA.

Succinate Dehydrogenase Mutation Underlies Global Epigenomic Divergence in Gastrointestinal Stromal Tumor

J. Keith Killian[1], Su Young Kim[1], Markku Miettinen[1], Carly Smith[1], Maria Merino[1], Maria Tsokos[1], Martha Quezado[1], William I. Smith Jr[2], Mona S. Jahromi[4], Paraskevi Xekouki[3], Eva Szarek[3], Robert L. Walker[1], Jerzy Lasota[1], Mark Raffeld[1], Brandy Klotzle[5], Zengfeng Wang[1], Laura Jones[1], Yuelin Zhu[1], Yonghong Wang[1], Joshua J. Waterfall[1], Maureen J. O'Sullivan[7], Marina Bibikova[5], Karel Pacak[3], Constantine Stratakis[3], Katherine A. Janeway[6], Joshua D. Schiffman[4], Jian-Bing Fan[5], Lee Helman[1], and Paul S. Meltzer[1]

Cancer Discovery 2013

Molecular Subtypes of *KIT/PDGFRA* Wild-Type Gastrointestinal Stromal Tumors
A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic

Sosipatros A. Boikos, MD; Alberto S. Pappo, MD; J. Keith Killian, MD, PhD; Michael P. LaQuaglia, MD; Chris B. Weldon, MD; Suzanne George, MD; Jonathan C. Trent, MD, PhD; Margaret von Mehren, MD; Jennifer A. Wright, MD; Josh D. Schiffman, MD; Margarita Raygada, PhD; Karel Pacak, MD, PhD; Paul S. Meltzer, MD, PhD; Markku M. Miettinen, MD; Constantine Stratakis, MD, DSci; Katherine A. Janeway, MD; Lee J. Helman, MD

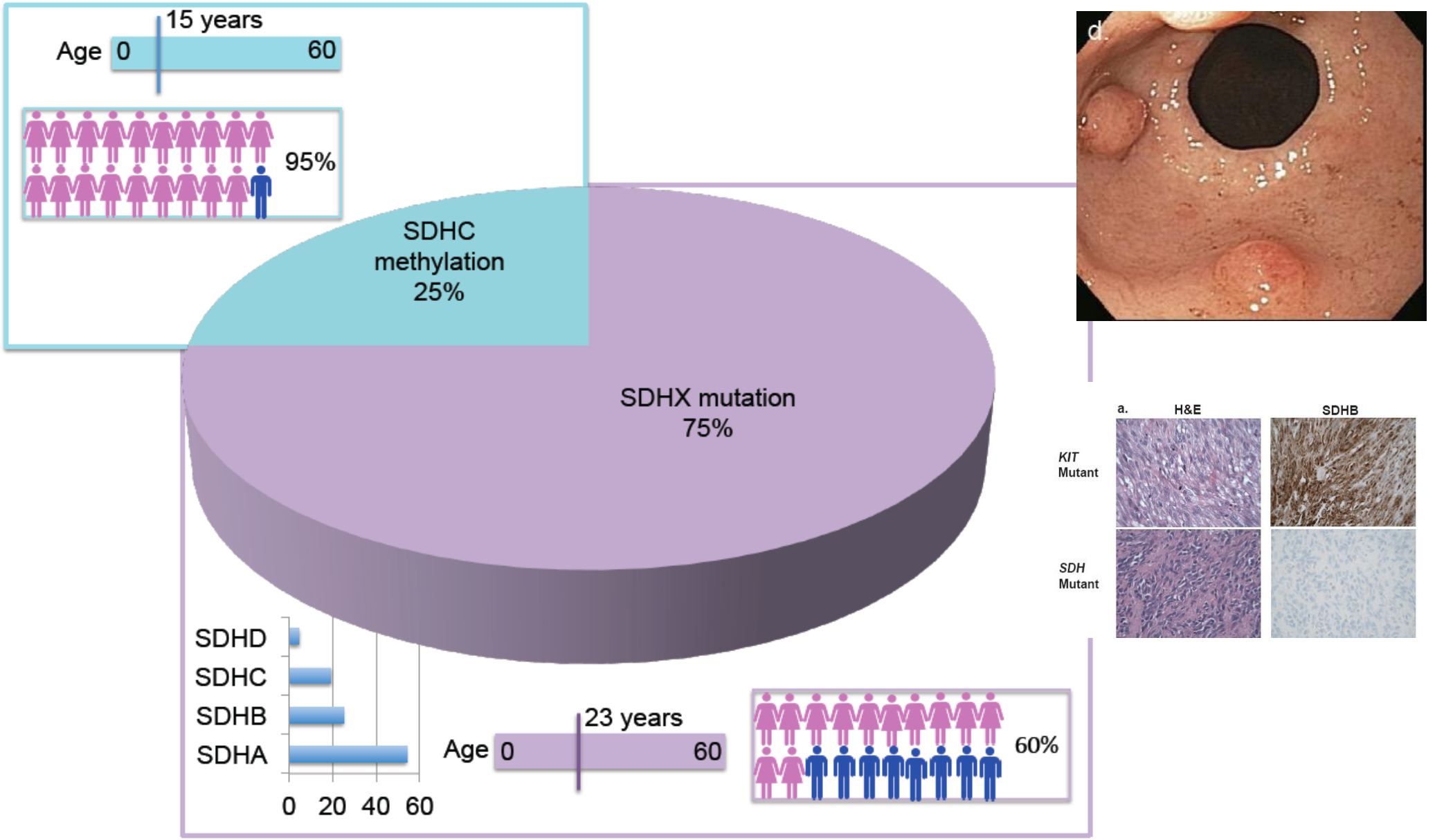
JAMA Oncology 2016

J Clin Oncol. 2017 Feb 10;35(5):523-528. doi: 10.1200/JCO.2016.68.6733. Epub 2016 Dec 28.

Surgical Management of Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Pediat and Wildtype GIST Clinic.

Weldon CB[1], Madenci AL[1], Boikos SA[1], Janeway KA[1], George S[1], von Mehren M[1], Pappo AS[1], Schiffman JD[1], Wright J[1], Trent JC[1], Pacak K[1], Stratakis CA[1], Helman LJ[1], La Quaglia MP[1].

SDH Deficient GIST

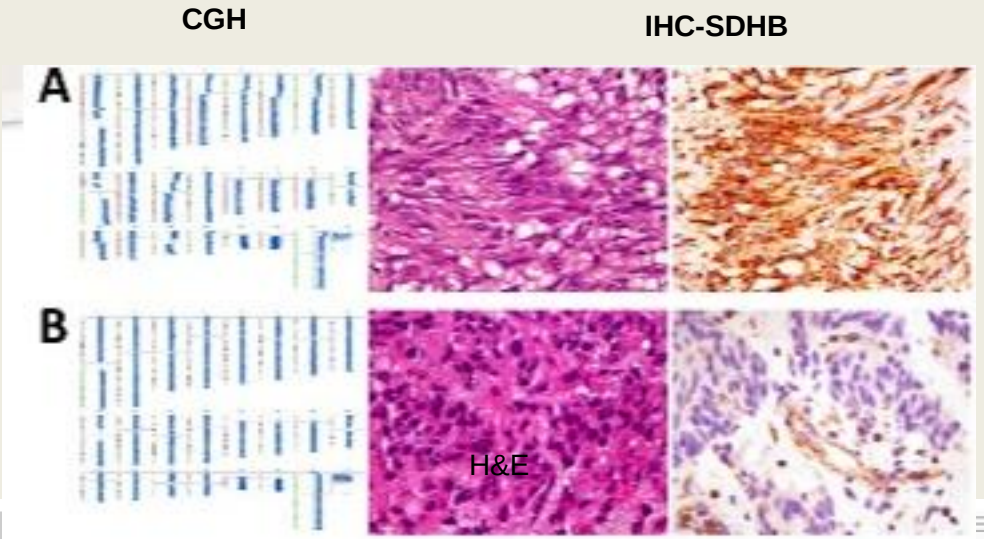


Janeway K, Inherited and Syndromic GIST. In: Gastrointestinal Stromal Tumors: Bench to Bedside (Scoggins CR, Raut CP, Mullen JT eds.)
Based on Boikos S., JAMA Oncology 2016

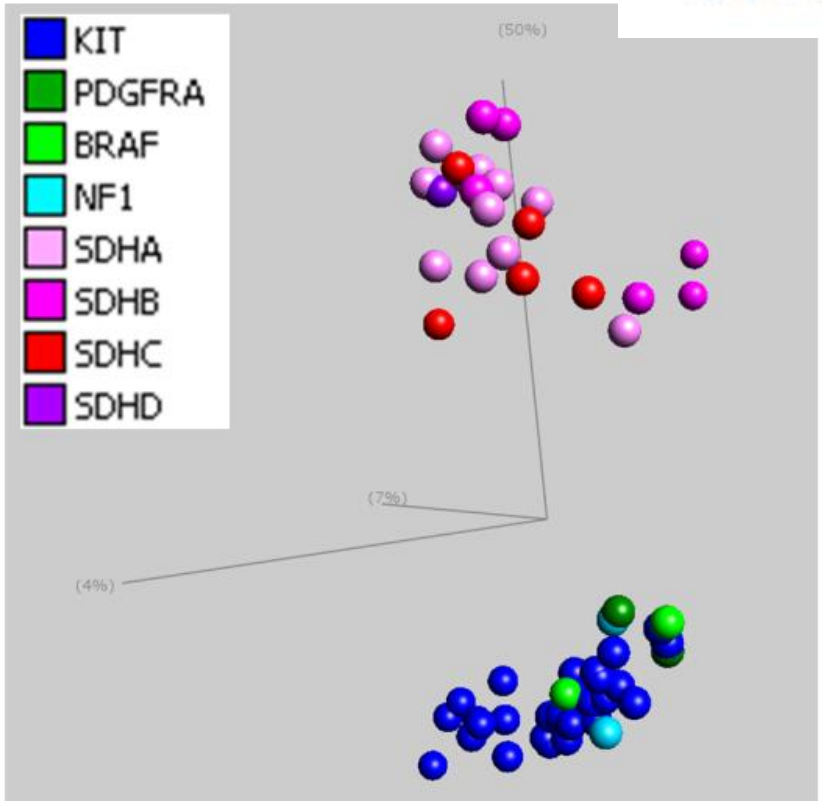
globally hypermethylated and stable genomes

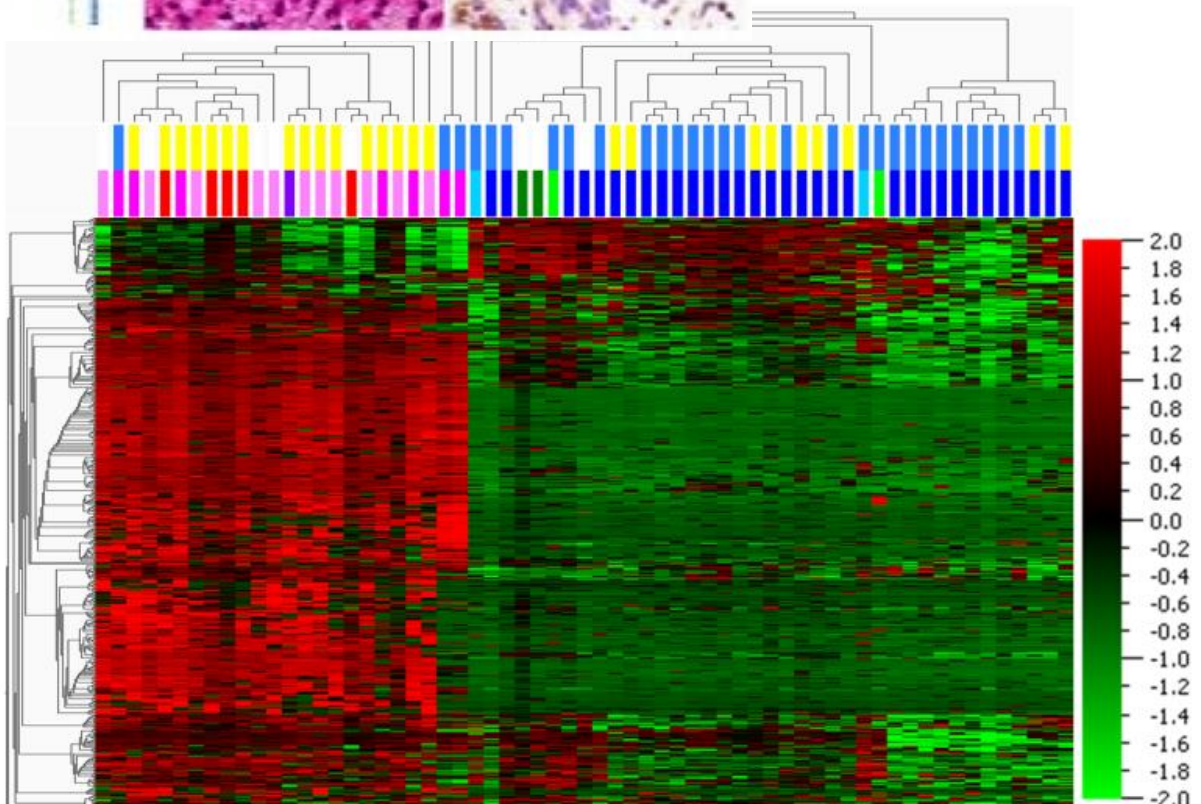
KIT Mutant GIST

SDH Mutant GIST



Killian K et al.
Cancer Discovery 2013





Consequences of dSDH

- **Increased succinate/αKG ratios due to dSDH inhibits αKG dependent dioxygenase catalyzed reactions:**
  - TET2 ⟶| global DNA hypermethylation
  - PHD ⟶| pseudo hypoxic state due to accumulation of HIF-1α thru blockade of HIF prolyl hydroxylation
  - Histone demethylase JMJD3 ⟶| histone methylation

SDH mutations

- We have found mutations in all 4 SDH genes (A,B,C,D)-most of these (80%) are germline
- We have also found silencing of SDHC by "epimutation"-hypermethylation of the SDHC promoter
- Why does this matter? SDH mutations and epimutations lead to both Carney Triad and Carney-Stratakis syndrome -most critical issue is paragangliomas (PG).
- These distinctions are important for genetic counseling and screening for PG

What We Have Learned

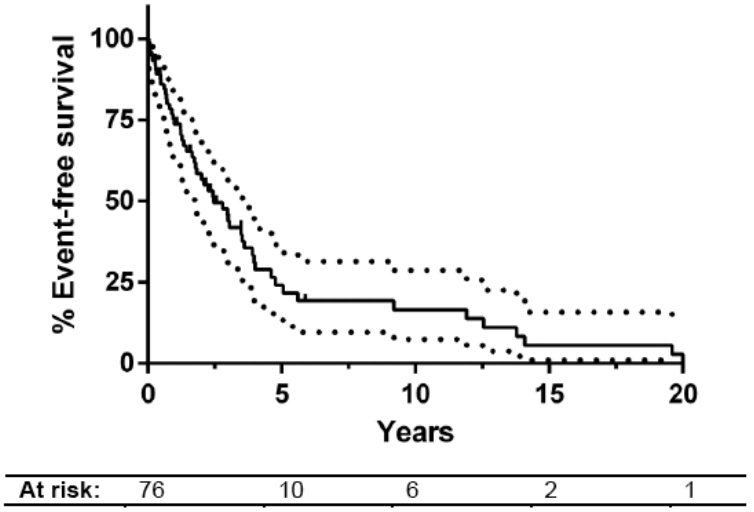
- **Best screen is SDHB IHC**
- **dSDH GISTs overwhelmingly gastric in location and most are multifocal and/or metastatic at presentation**
  - Implications for management
  - Only 1 small bowel dSDH GIST
- **None respond to imatinib; definite responses to sunitinib and regorafanib**
  - Likely due to effects on VEGF
- **Most SDH mutations are germline**
  - Implications for genetic counseling

Surgical Approach

- **Potential benefits of surgery must be tempered by the long-term morbidity of extensive resections in a disease that may persist for decades even when there is recurrence or disease is advanced**

- **76 patients at the NIH GIST clinic SDH deficient GIST**
  - Pathology reviewed at NIH
  - Surgical reports reviewed by 2 surgeons
  - Resection classified R0, R1, R2

- **Median EFS 2.5 years**
- **Overall survival 90%**



- **Among patients with non-metastatic disease, R0 resection was not significantly associated with improved EFS**

- **We recommend gastric wedge resection with regional lymph node examination rather than radical approaches like gastrectomy**

Weldon, CW et al; JCO 2017

Cancer Risk

- **SDH-deficinet GIST**
  - 80% germline
  - Risk of: paraganglioma / pheochromocytoma / RCC
  - Referral to cancer risk program
- **NF-1 associated GIST**

Clin Cancer Res. 2017 Jan 1;23(1):273-282. doi: 10.1158/1078-0432.CCR-16-0152. Epub 2016 Jul 7.

Quadruple-Negative GIST Is a Sentinel for Unrecognized Neurofibromatosis Type 1 Syndrome.

Gasparotto D[1], Rossi S[2], Polano M[1], Tamborini E[3], Lorenzetto E[1], Sbaraglia M[2], Mondello A[1], Massani M[4], Lamon S[5], Bracci R[6], Mandolesi A[6], Frate E[7], Stanzial F[8], Agaj J[9], Mazzoleni G[10], Pilotti S[3], Gronchi A[11], Dei Tos AP[2], Maestro R[12].

Future Directions

- **Continue to accrue patients with dSDH GIST**
  - Study genotype/phenotype correlations
  - **Need cell lines and/or models!**
    - **Dr. Sicklick at this meeting describing cell lines**
  - We are still learning (SmBowel dSDH GIST just discovered)
- **Based on increased succinate/αKG ratios⟶global DNA hypermethylation + PHD inhibition "pseudo-hypoxic" state**
- **Test more potent DNMT inhibitors, e.g., SGI-110 (guadecitabine) study opened at NCI**
  - Combinations (maybe with anti-angiogenic drugs)
- **Understand disease over time**
- **Develop prognostic marker (cfDNA-hypermethylation)**


"At the GIST Clinic at the POB, everbody can share
stories with people who are dealing with what you are
An awesome experience and I am learning so much."
Jennifer and Alyssa, GIST patient