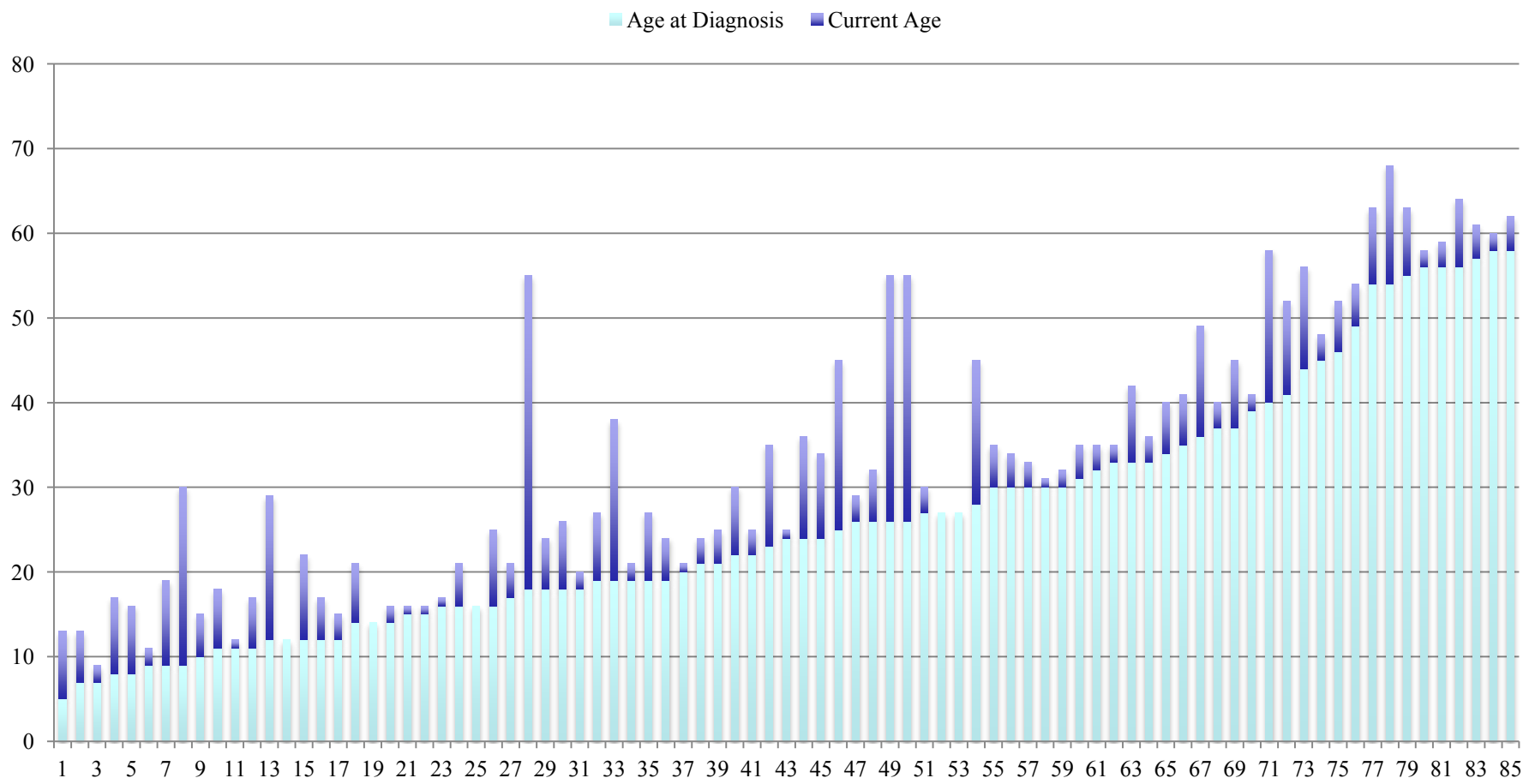


Pediatric and Wildtype Updates

Su Young Kim, MD PhD

**Bristol-Myers Squibb
Associate Medical Director
Discovery Medicine**

NIH Pediatric and Wildtype GIST Patients



Pediatric 36%

Adults 64%

GIST or not GIST

16 year old female

- Becomes very tired at the end of her varsity soccer games
- Sleeps in late
- Complains of vague stomach pains of three years duration
often this is associated with lots of homework

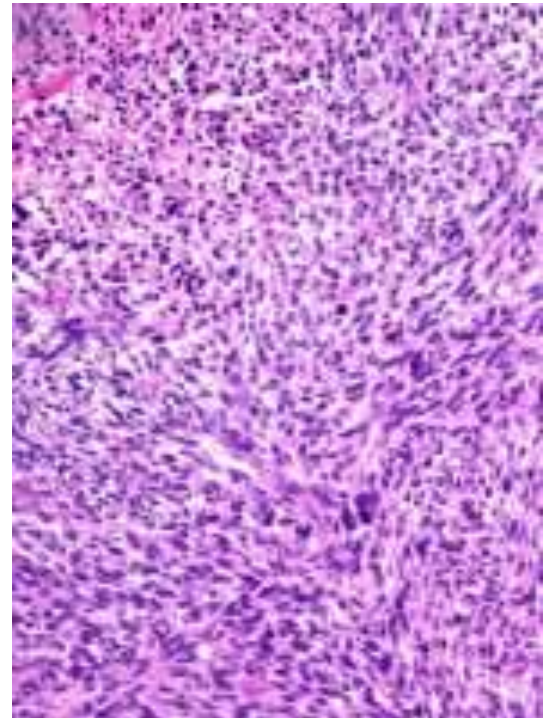
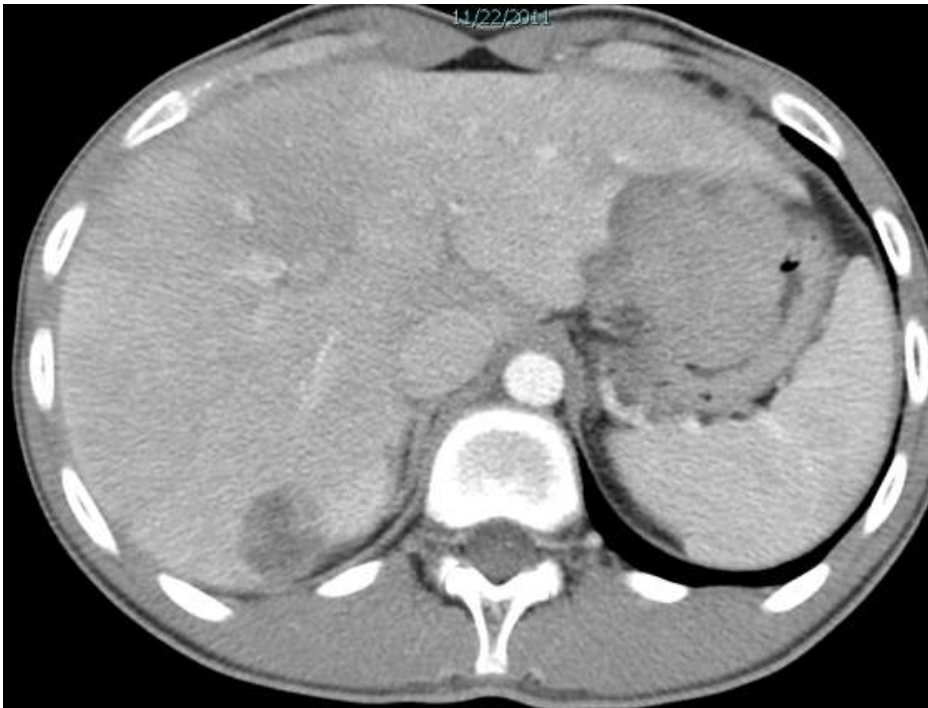
Typical Pediatric GIST Patient

16 year old female

- Becomes very tired at the end of her varsity soccer games
- Sleeps in late
- Complains of vague stomach pains of three years duration
often this is associated with lots of homework
- Then passes out or has black-colored stools
- CT shows a large bleeding mass in the bottom of the stomach and a smaller mass a few inches above that, there is a small nodule in the liver that is too small to be characterized

Typical Pediatric GIST Patient

Undergoes surgical resection to obtain tissue for diagnosis and to prevent further bleeding



Things You Need to Do

Get confirmation of the diagnosis

- Dana-Farber, MD Anderson, MSKCC, NIH, Oregon HSU

Organize a treatment team

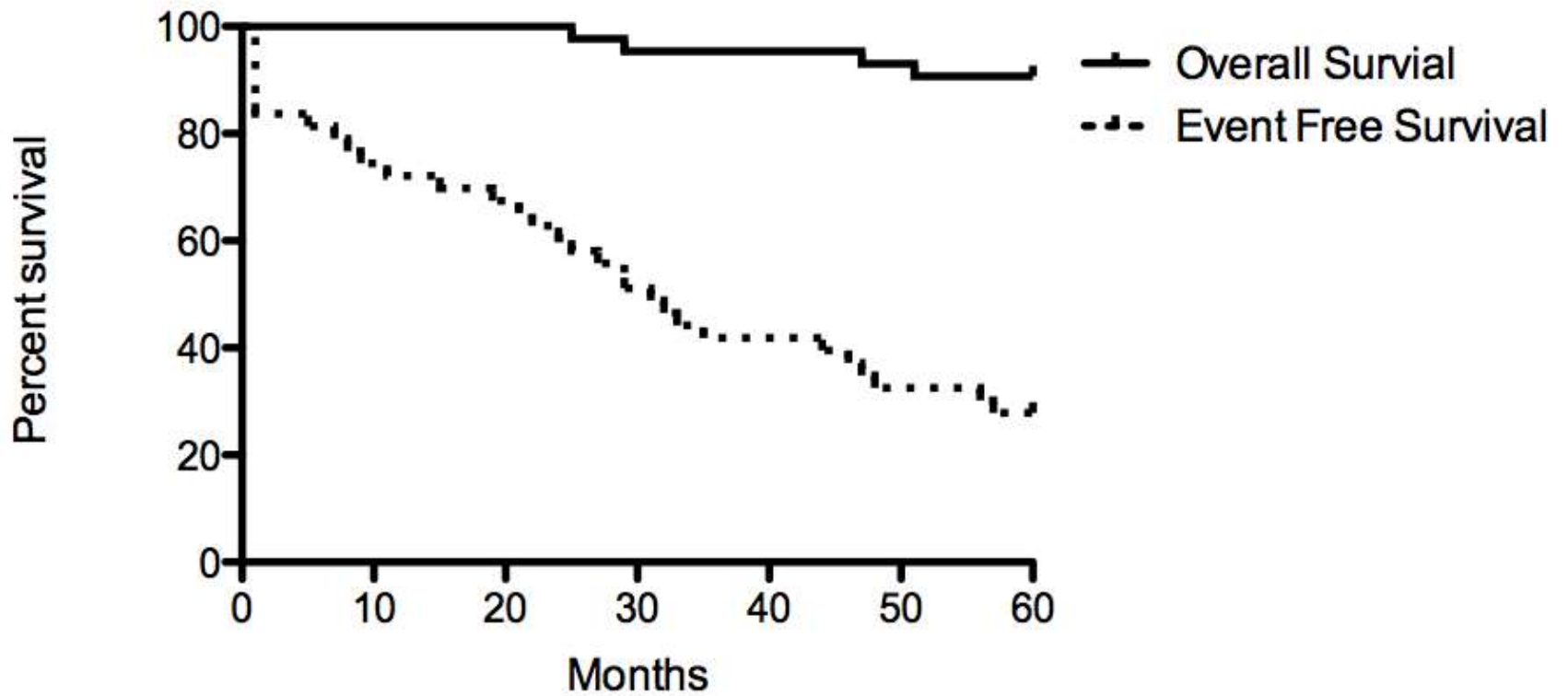
- primary team at home, center that sees more GIST patients
- all of the above, Fox Chase, Miami, St Jude, Huntsman Utah

Plan for the future

- junior/senior prom, homecoming, college applications/interviews
- goal of the treatment team is to allow you to do everything that you want to do

Survival

5 year Overall Survival / Event Free Survival

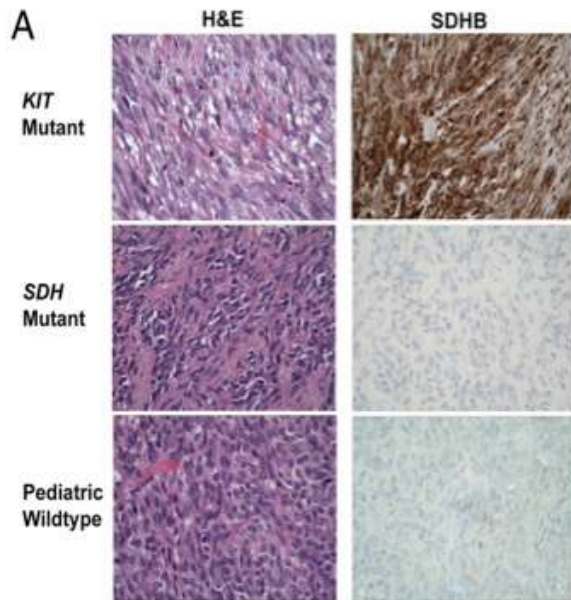


Clinical Characteristics

Characteristic	adults (literature)	adult wildtype (n = 45)	pediatric (n = 24)
female	46 %	78 %	83 %
stomach	50 %	73 %	96 %
multi-focal	rare	38 %	50 %
epithelioid	rare	62 %	78 %
wildtype	10 %	by definition	96 %

Clinical Characteristics

Characteristic	adults (literature)	adult wildtype (n = 45)	pediatric (n = 24)
female	46 %	78 %	83 %
stomach	50 %	73 %	96 %
multi-focal	rare	38 %	50 %
epithelioid	rare	62 %	78 %
wildtype	10 %	by definition	96 %
SDHB-negative	5%	70%	96%



Succinate Dehydrogenase is

part of the Kreb's cycle

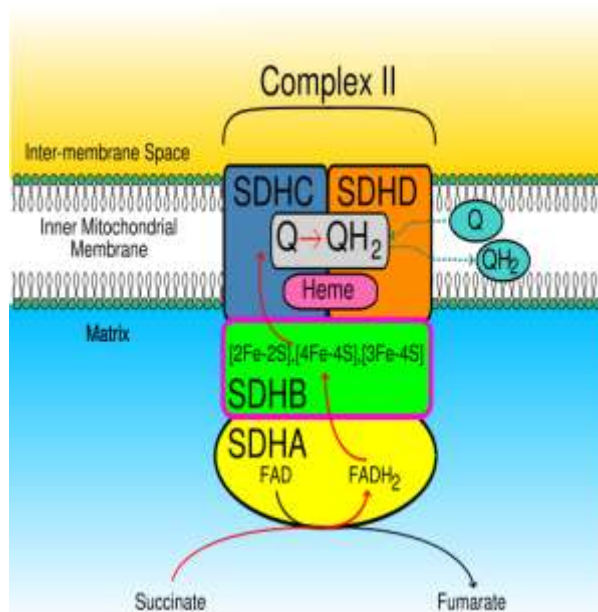
part of the electron transport chain

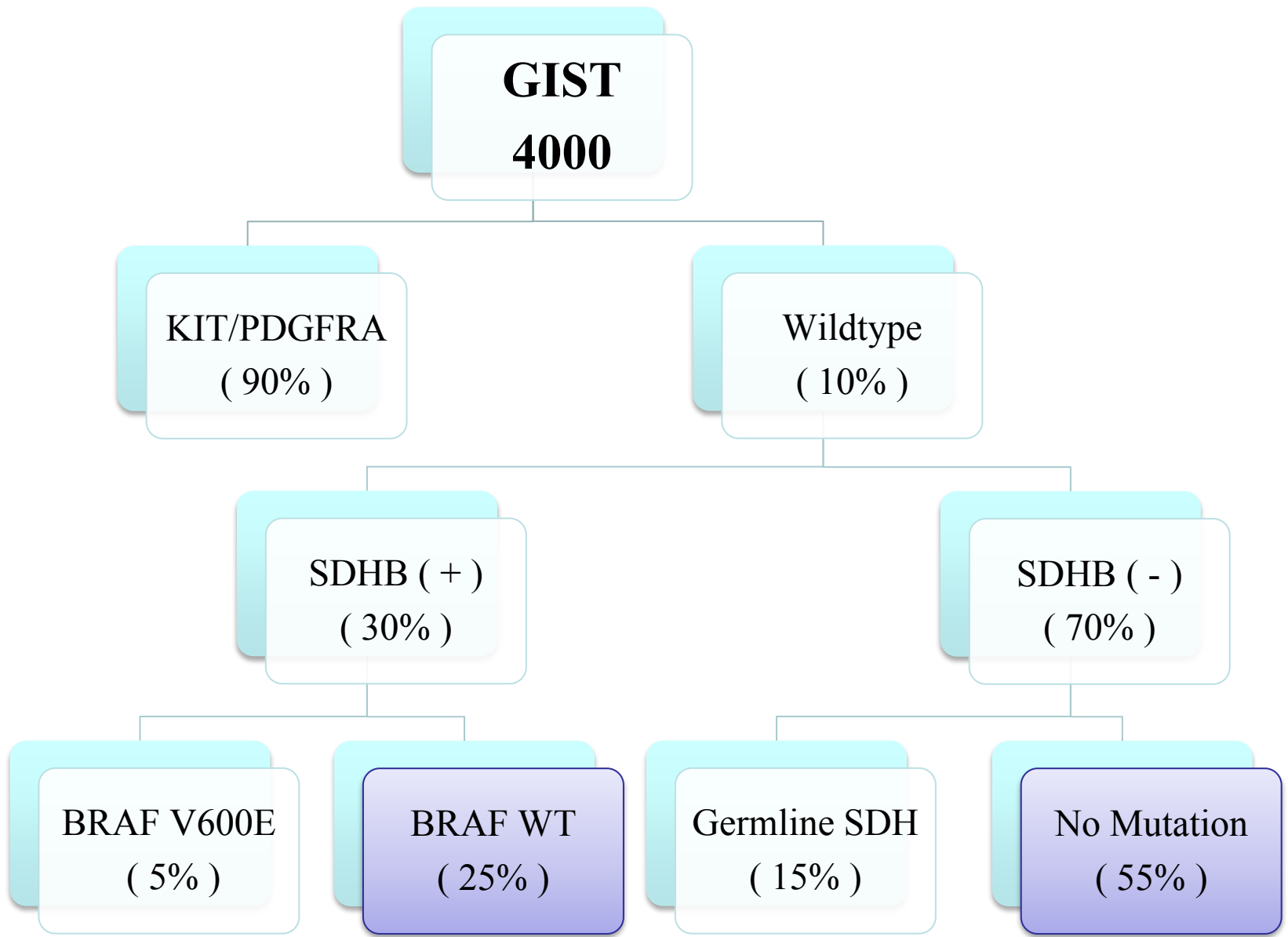
A, B catalytic units

C, D membrane anchor proteins

AF1, AF2

assembly complex





30% of adults and no peditrics

Most adults and almost all peditrics

SDHB-positive versus SDHB-negative

	SDHB (+)	SDHB (-)
Age at diagnosis	39.7	24.2
Stomach primary	25%	100%
Overall survival	75%	96%
Response to TKI	50%	3%

Hypothesis For SDHB(+) BRAF(wt) Patients

30 yo female or male with a single GIST lesion in the small intestine

These tumors are driven by:

- . activating mutations in other exons of KIT/PDGFR
- . activating mutations in a gene very closely related to KIT and PDGFR (either known or unknown)
- . a non-TK, non-SDH dependent pathway

Clinical implications

**neo-adjuvant TKI therapy with Imatinib/Sunitinib
surgery if response, then indefinite oral therapy**

SDHB(-) Patients

This is a homogenous group of patients who have very similar clinical histories

Age at diagnosis 24.4 years (median 21, range 7-58)

15% harbor germline SDH mutations (B, C, D)

25% harbor a germline SDH mutation in (A)

30% do not have detectable mutations

Hypothesis For SDHB(-) Patients

These tumors are driven by loss of SDH activity and accumulation of succinate

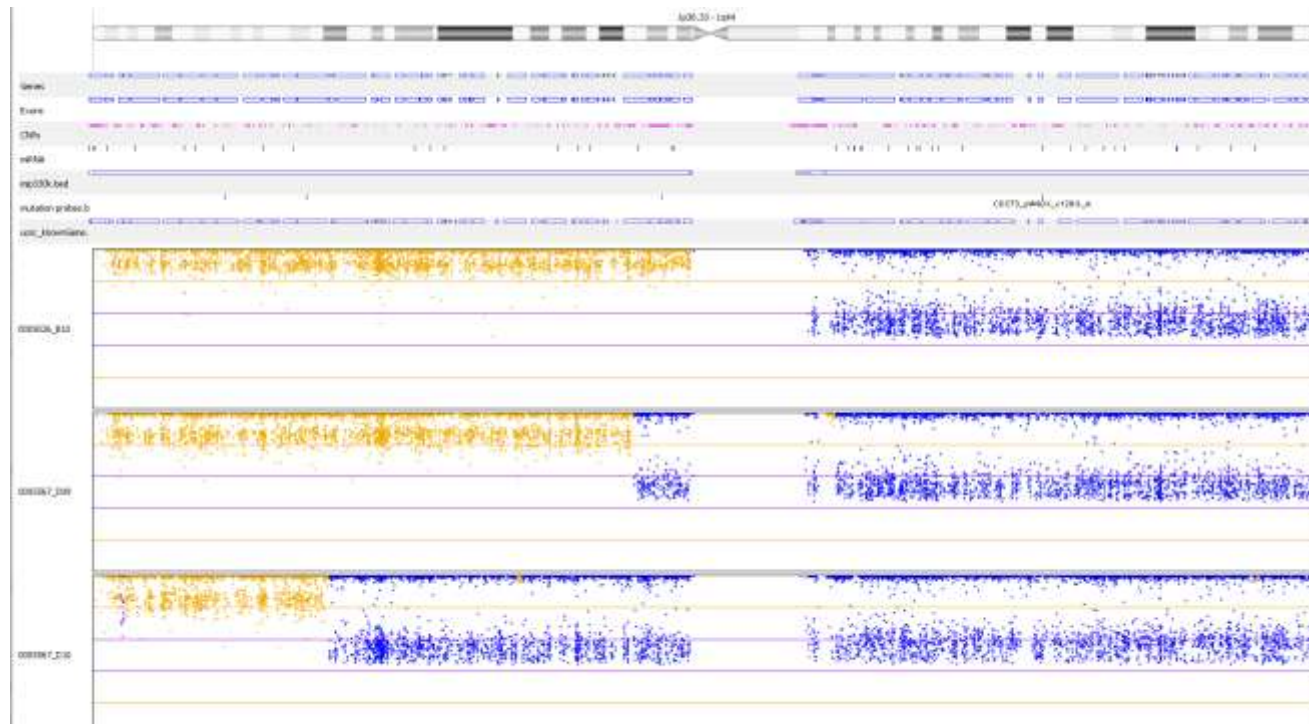
Patients will have a germline mutation in SDH and a somatic loss of the remaining allele

or

Patients will have two somatic alterations in both alleles of a SDH gene

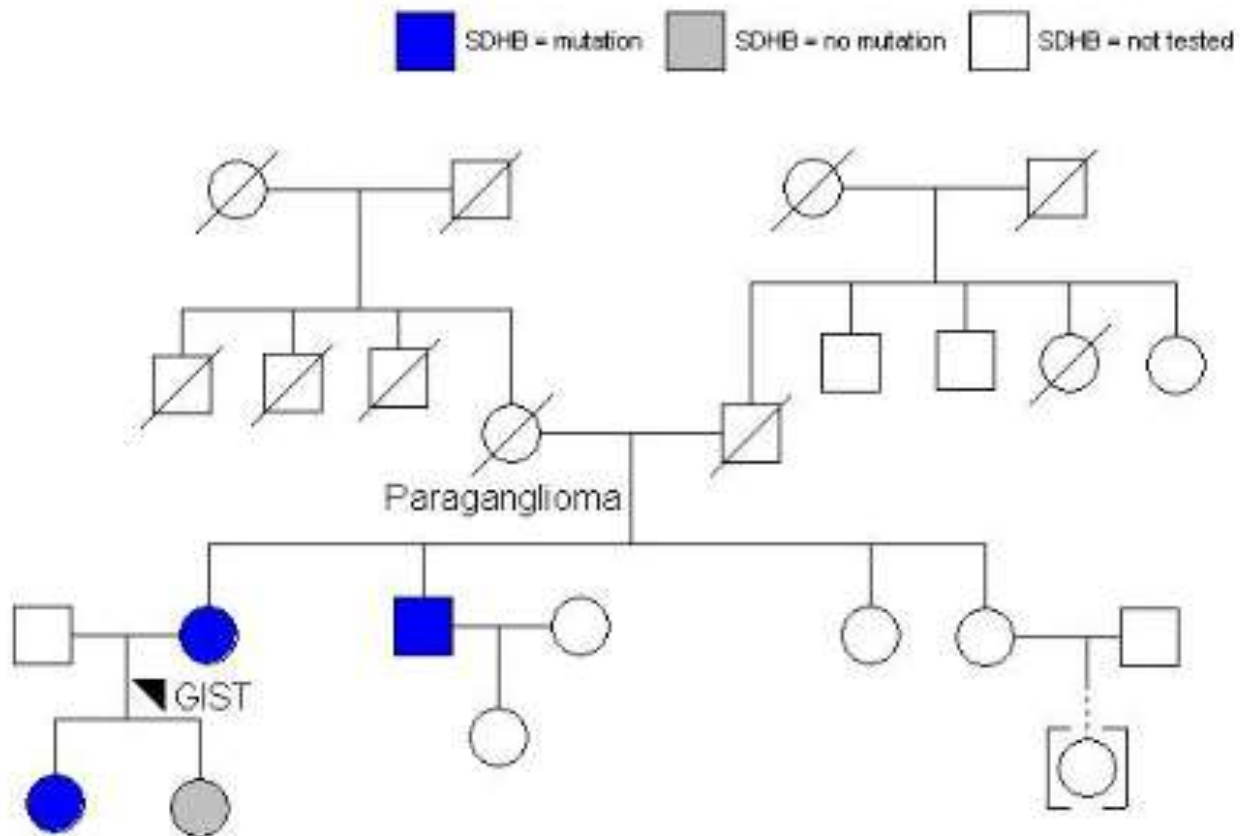
Patients with SDHB germline mutations show chromosomal loss at the SDHB locus

↓ SDHB



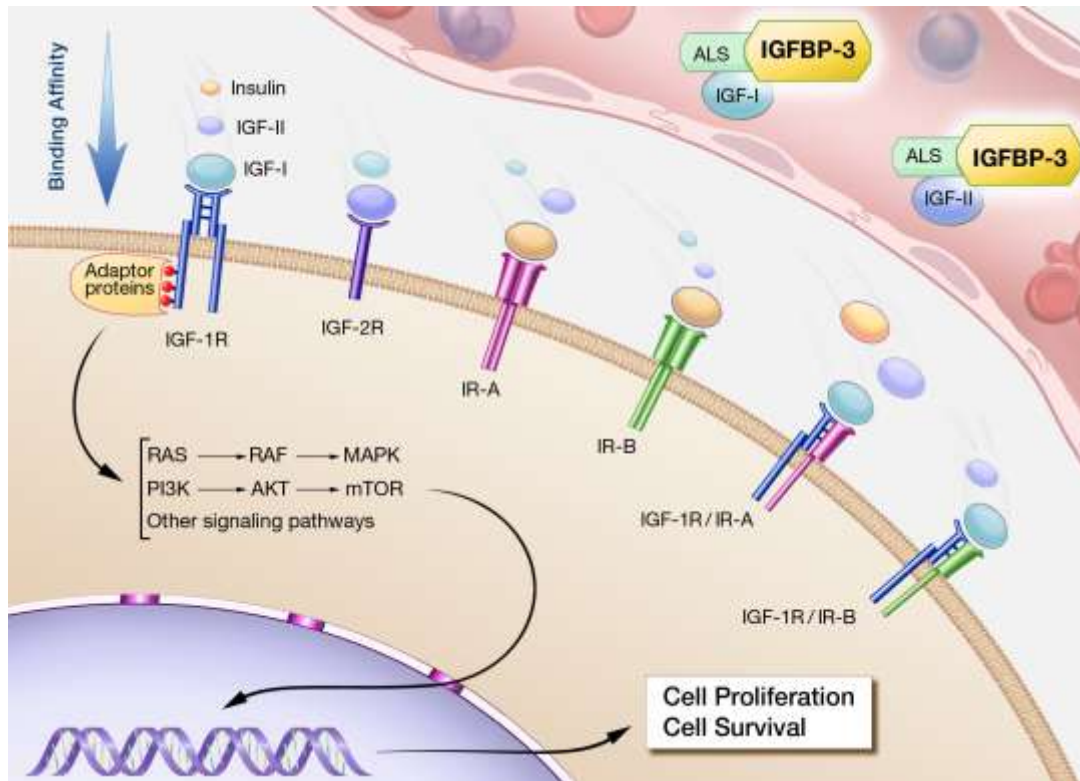
Joshua Schiffman (Huntsman Cancer Center, University of Utah)

Other Family Members with SDH mutations



Radiographic and biochemical monitoring protocols

The Role of IGF-1R in WT GIST



89% (71/80)

SDHB(-) are IGF1R(+)

1% (9/625)

SDHB(+) are IGF1R(+)

Lasota, Wang, Kim, Helman, Miettinen
2012. Am J Surg Pathol

the NIH pediatric GIST team

Art Therapist

Megan Robb

Clinical Nurses

Joan Sheeren, Patty McGinley

Complementary Medicine

Scott Miller

Coordinator

Sherri DePollar

Dermatologist

Heidi Kong

Geneticists

Constantine Stratakis, Margarita Raygada, Maya Lodish

Medical Oncologists

Shivanni Kumar

Nutritionist

Jennifer Graf

Pediatric Oncologists

Lee Helman, Su Young Kim

Radiologist

Baris Turkbey, Peter Choyke

Research Nurses

Christine Graham, Donna Bernstein, Lauren Long, Robyn Bent

Pain Specialist

Ann Berger, Dan Handel

Pathologist

Maria Tsokos

Psychosocial Specialist

Lori Wiener

Rehabilitation Medicine

Donna Gregory

Social Worker

Barbara Santangini

Videography

Demetrio Domingo

the NIH Pediatric & Wildtype GIST Clinic



Children's Hospital Boston
The first place for children

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
*Making Cancer History**

NATIONAL
CANCER
INSTITUTE



DANA-FARBER
CANCER INSTITUTE



Eunice Kennedy Shriver
NICHHD
National Institute of Child Health
& Human Development



FOX CHASE
CANCER CENTER


St. Jude Children's
Research Hospital
ALERT • DARING • DETERMINED
Finding cures. Saving children.

 **National Human**
Genome Research
Institute


HUNTSMAN
CANCER INSTITUTE
UNIVERSITY OF UTAH


Peter Mac
EXCELLENCE INNOVATION COMPASSION


National Institute of Dental
and Craniofacial Research



Thanks

**To the physicians who volunteer
To the NIH GIST healthcare team
To LRG and GIST Support International
To the patients and their families**

**Becky Bensenhaver
Phyllis Gay
Julie Royster
those from GSI here today**