

the NIH Pediatric & Wildtype GIST Clinic

## 4<sup>th</sup> GIST Clinic Lecture

# Results from the NIH Pediatric and wildtype GIST Clinic



## Characteristics of patients with Pediatric GIST

Younger patients with GIST tend to differ from adults

- female gender
- no mutations in *KIT* or *PDGFRA* (wildtype)
- **slower growth of tumors?**







# the NIH pediatric GIST clinic

## Objectives

To bring together healthcare providers who have the most experience treating and studying GIST, with every child and young adult with GIST

To obtain clinical history, response to prior treatments, histopathologic results, radiographic assessments and genetic/molecular analyses

Continue long-term follow-up for these patients

# the NIH pediatric GIST clinic

## Goal

To utilize the combined data from the clinic, with new research findings, to design innovative national treatment protocols

To collect tissue samples to perform clinical and laboratory studies to define new targets for potential treatment and to determine the biological differences between older and younger patients with GIST

# NIH GIST clinic Patients





# national pediatric GIST team

Alberto Pappo

Katherine Janeway

Michael LaQuaglia

George Demetri

Cristina Antonescu

Constantine Stratakis

Lee Helman

Su Young Kim

Phyllis Gay

Tricia McAleer

Pediatric Oncologist

Pediatric Oncologist

Pediatric Surgeon

Medical Oncologist

Pathologist

Endocrinologist

Pediatric Oncologist

Pediatric Oncologist

GSI

Life Raft Group

Texas Children's Hospital

Dana Farber Cancer Center

Memorial Sloan Kettering

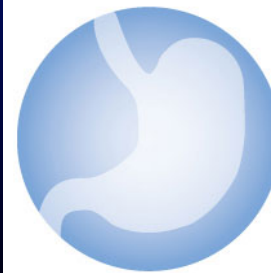
Dana Farber Cancer Center

Memorial Sloan Kettering

NICHHD

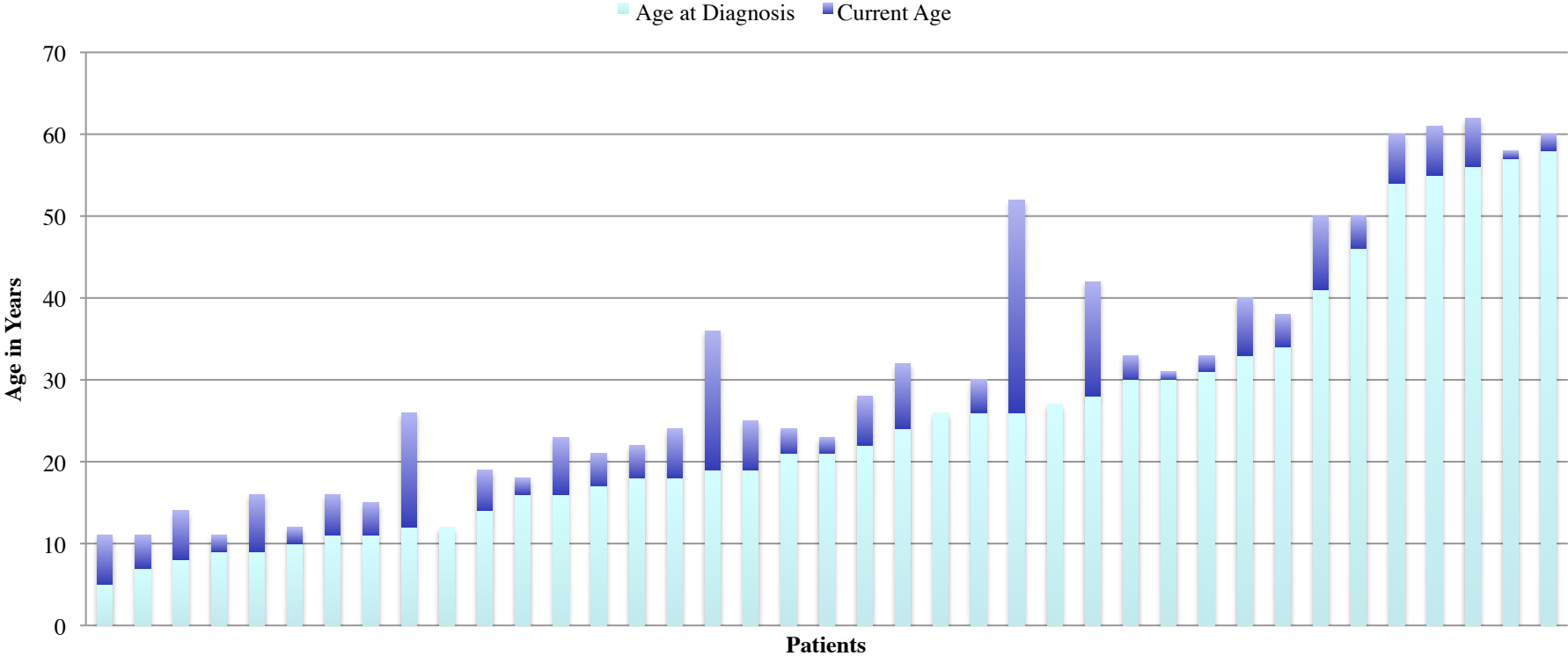
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**CPGR**  
Consortium for Pediatric  
& wildtype GIST Research

# Gastrointestinal Stromal Tumor (GIST)



**Children 26%**

**Teens 15%**

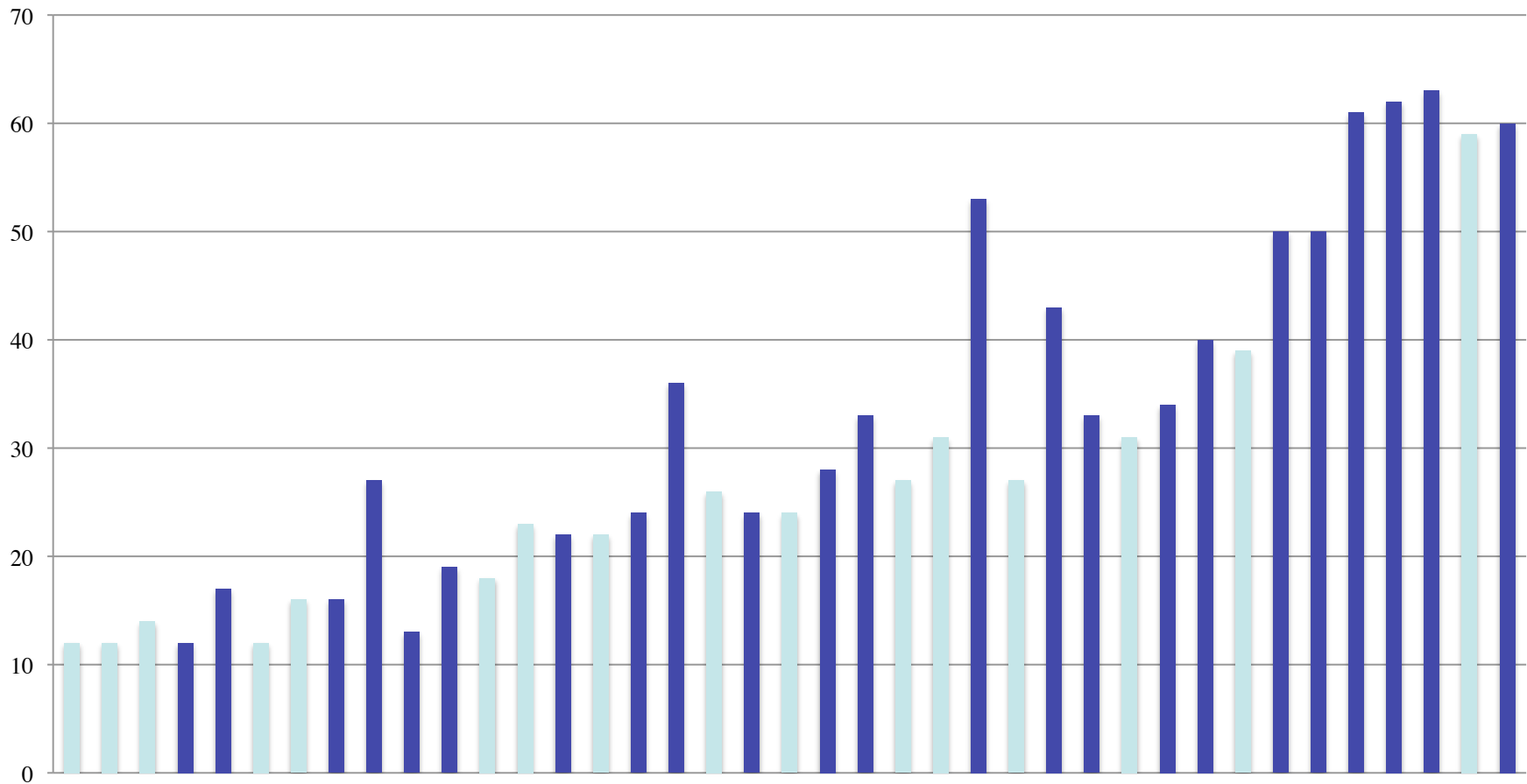
**Young Adults 41%**

**Adults 18%**

## Comparison of Adult KIT-mutated versus our patients

<b>Adult KIT-mutated</b>		<b>NIH Clinic</b>
56.0	age	<i>31.1</i>
46%	female gender	<b>79%</b>
uncommon	epithelioid histology	<b>70%</b>
90%	mutations	<i>0%</i>
50%	stomach primary	<b>79%</b>
rare	multifocal disease	<b>56%</b>

# Clinical Course



**Children 26%**

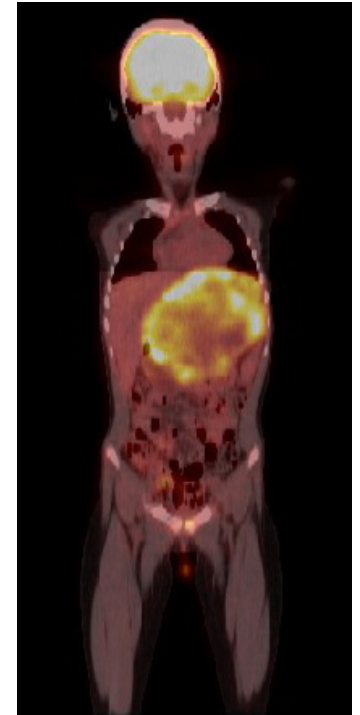
**Teens 15%**

**Young Adults 41%**

**Adults 18%**

## Clinical Course

	NED	SD	PD	Deceased	Total
Children	50%	30%	10%	10%	10
Adolescents	50%	37%		12%	8
Young Adults	42%	29%	29%		14
Adults	14%	57%	29%		7
Total	41%	36%	18%	5%	39



**It is still unclear if younger patients have less aggressive disease  
Will require more patients and a longer period of follow-up**

## Is There A Low-Risk (Benign) Form of GIST?

	FIRST NED	RECURRENCE	
average age	21.4 years ( 12 – 31 )	33.1 years ( 12 – 62 )	<b>p=0.02</b>
remission or recurrence	37.6 months ( 13 – 55 )	22.5 months ( 3 – 57 )	<b>p=0.04</b>
tumor size	7.1 cm ( 4 – 9 )	7.0 cm ( 2 – 22 )	p=0.91
mitotic count	8.2 per 50 hpf ( 1 – 16 )	19.9 per 50 hpf ( 4 – 50 )	<b>p=0.01</b>

**Too much overlap to clearly define a low-risk cohort at this time**

## What is the Role of Surgery to Treat Recurrence?

9 patients remain in first remission	(27%)	9 - 55 months
24 patients have recurred	(73%)	3 - 57 months

13 have undergone a second surgery		
11 have recurred	(85%)	

2 underwent complete gastrectomy		
1 has recurred	(50%)	

**Surgery in itself is not curative in the vast majority of cases of recurrence in the setting of wildtype GIST**

**Avoid radical surgery**

## What is the Role of Tyrosine Kinase Inhibitors?

	CR	PR	SD	PD	side effects	N/A	adjuvant	recent	TOT
Imatinib	0	1	1	20	3	3	6	0	34
HD Imatinib	0	0	3	2	2	1	0	0	8
Sunitinib	1	0	4	10	3	3	2	1	24
Nilotinib	0	0	1	2	0	0	0	6	9
Sorafenib	0	0	0	0	3	1	0	0	4
Dasatinib	0	0	0	0	1	0	0	0	1
TOTALS	1	1	9	34	12	8	8	7	80
	(1%)	(1%)	(16%)	(60%)	(21%)				

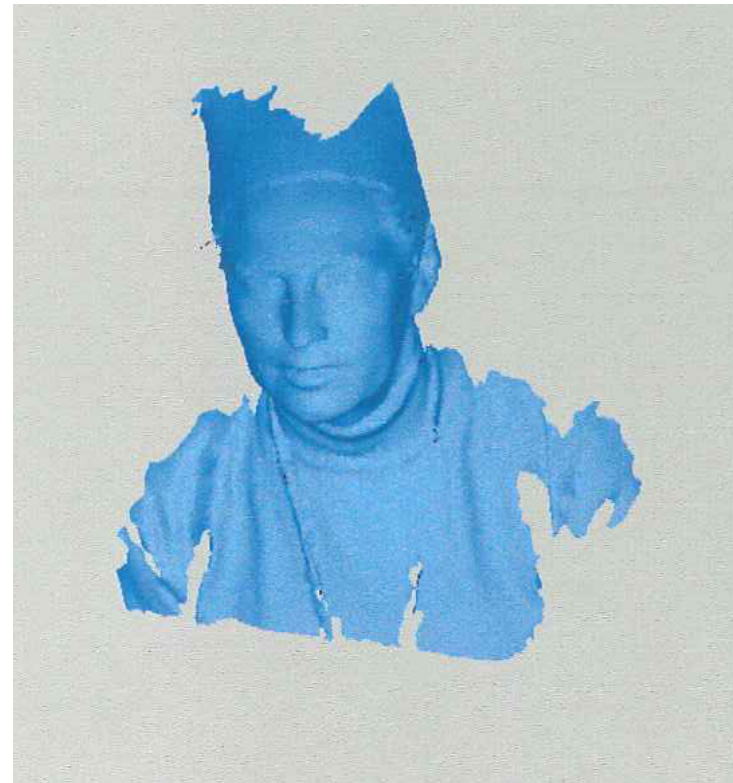
**The response rate to TKI therapy is much lower than for adults with KIT/PDGFRα mutated GIST**



## Keloid Formation



## Facial Phenotypes

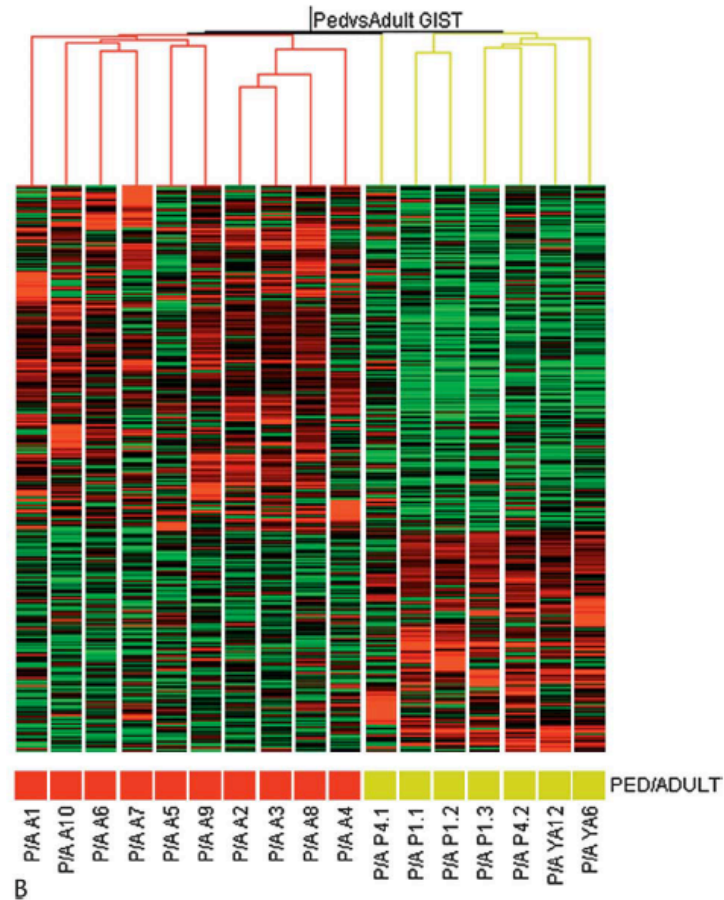


3DMD – facial videography – overlays expected following 4<sup>th</sup> clinic

Dr. Demetrio Domingo, DDS MS

Dental Clinic Director

## Pediatric versus Adult GIST Microarray



B

Prakash 2005 *J Pediatr Hematol Oncol* 27:179

Gene Fold Change

NLGN4 16.71

ASRGL1 14.89

**IGF1R 14.22**

FOXD1 13.13

FZD2 12.22

ANK3 10.56

GPRC5B 6.22

PHKA1 3.76

CDKN2A 2.50

MITF 2.24

GLIPR1 - 6.00

**PDGFRA - 9.39**

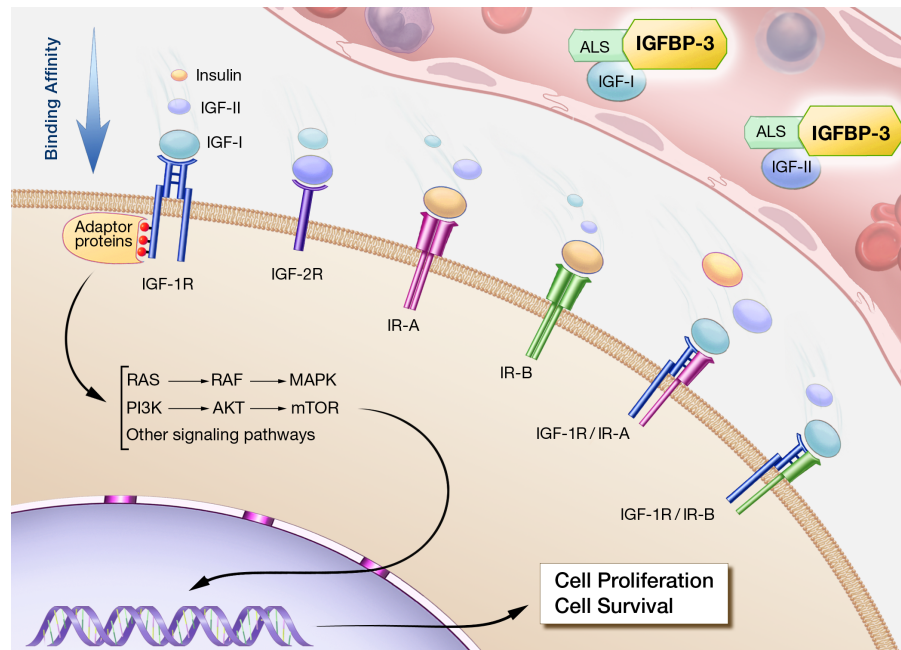
ABCC9 - 12.54

GPR88 - 16.32

RAB38 - 22.28

DPT - 36.19

# SARC 015 : A Phase II Trial of R1507 for Wildtype GIST



Principal Investigators

Margaret von Mehren  
Fox Chase Cancer Center

Katherine Janeway  
Children's Hospital Boston

Sarcoma Alliance for  
Research through Collaboration

## Inclusion Criteria

age >2 years  
wildtype KIT and PDGFRA  
advanced, measurable disease

## Treatment Regimen

R1507 IV 16 mg/kg q3weeks  
CT and PET at baseline  
CT q 3-4 cycles

## BRAF Mutations

benign melanotic nevi have BRAF mutations  
- 95% of mutations are BRAF V600E

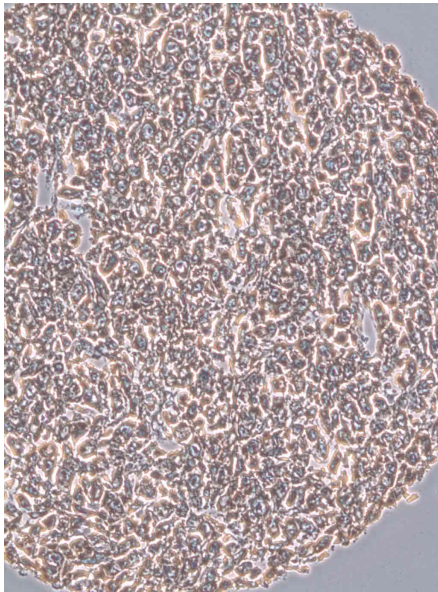
(Poynter et al. 2006 Melanoma Research 16:267)

a small number of GISTs have BRAF mutations  
(Agaram et al. 2008 Genes, Chromosomes & Cancer 47:853)

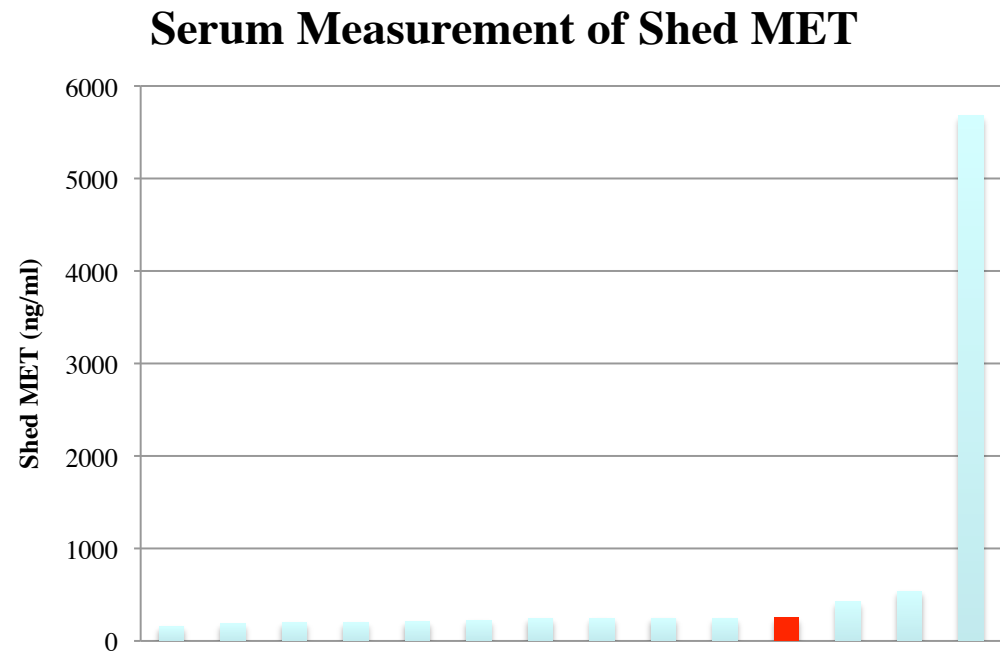


# MET Expression

**MET is a cell surface tyrosine kinase receptor**



Lillian Guenther and Natasha Fewks  
Pediatric Oncology Branch



## Moving from Natural History to Treatment

Gene	Primary Test	Secondary Test	Therapy
<b>B-RAF</b>	2 / 39	0 / 1	BRAF TKI
<b>MET</b>	3 / 12	pending	MET TKI
<b>EGFR</b>	12 / 16	pending	EGFR antibody
<b>NY-ESO</b>	0 / 17	will not pursue	modified T-cell
<b>SDH</b>	7 / 38	0 / 2	Topotecan / Avastin
<b>IGF-1R</b>	measurable disease		IGF-1R antibody

# 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®*

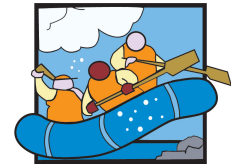
NATIONAL  
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INSTITUTE



DANA-FARBER  
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*Eunice Kennedy Shriver*  
NICHD  
National Institute of Child Health  
& Human Development



FOX CHASE  
CANCER CENTER

St. Jude Children's  
Research Hospital  
ALSAC • Danny Thomas, Founder  
*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



# 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

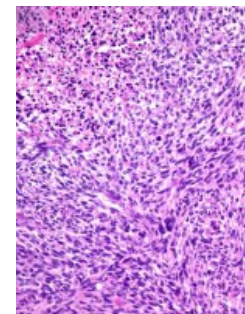
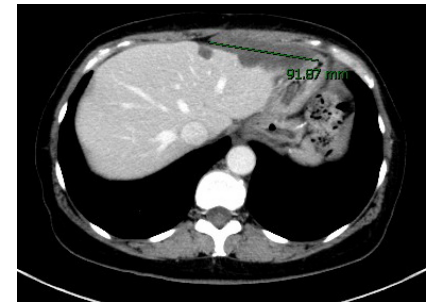
# the NIH Pediatric & Wildtype GIST Clinic

## **Vision of the Future**

Utilize the NIH Pediatric GIST website as a portal for:

HIPPA regulation secure storage of medical information  
- medical records, radiographic images, pathology slides

Weekly Tumor Board to discuss new or problematic cases  
- patient, physician, CPGR participants, specialists





**Thanks**

- To the patients and families**
- To members of the support groups**
- To physicians who volunteer**
- To the NIH GIST healthcare team**



**Joanna Meadors**

**Kaylee Nuckolls**

**Shannon Larabie**

**Laurie Griffin**