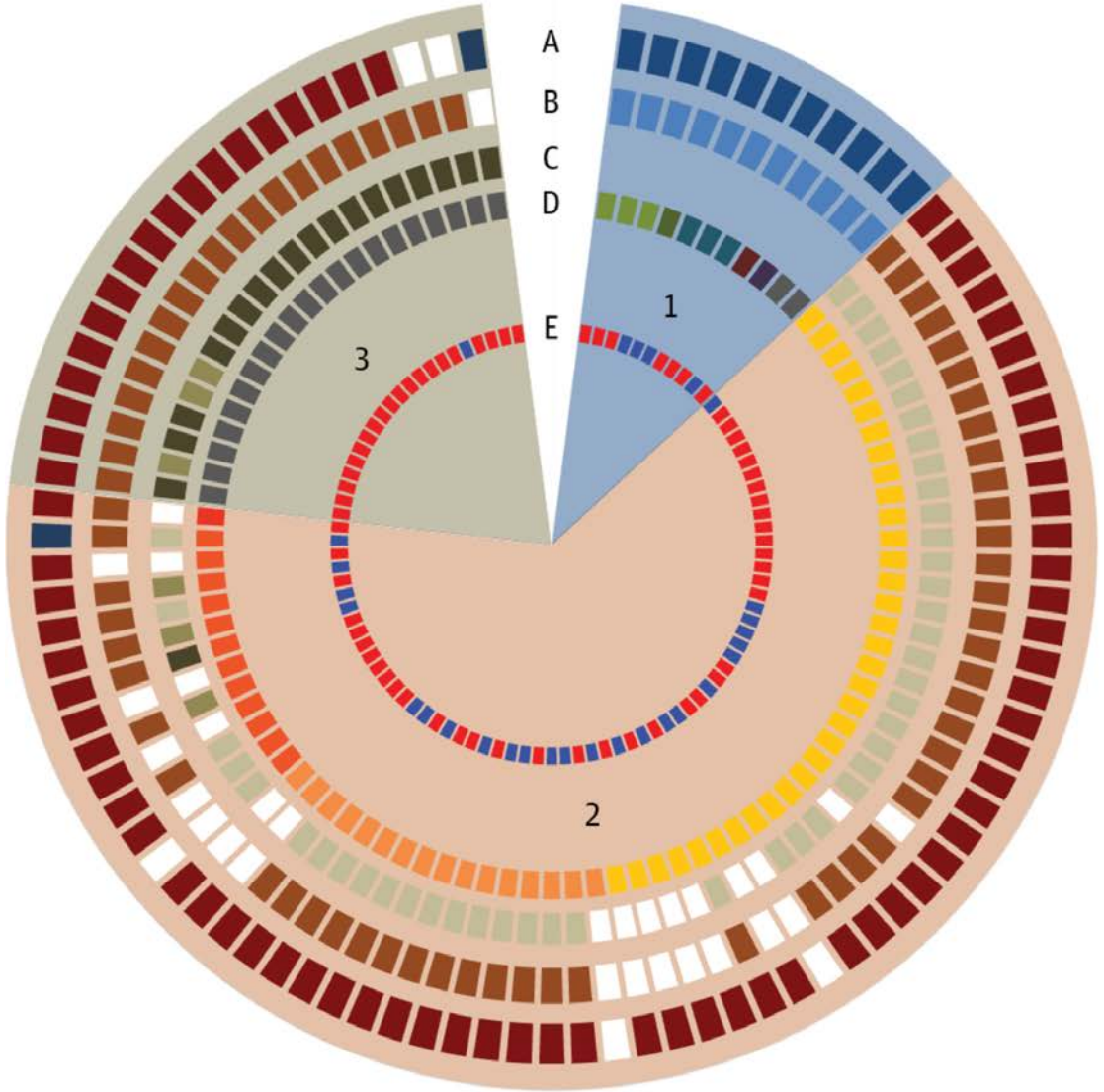
the NIH Pediatric & Wildtype GIST Clinic

Established 2008

Total of 95 GIST Pts Analyzed



Groups
1 Normal SDHB expression
2 *SDHB* mutation
3 *SDHC* promoter methylation[a]

Circles
A. SDHB IHC
- Present
- Absent

B. Tumor global methylation
- Centrist
- Deviator

C. Tumor *SDHC* methylation zygosity
- Homozygous
- Hemimethylated
- Not found

D. Mutations[b]
- *NF1*
- *CBL*
- *BRAF*
- *ARID1A*
- *KIT/PDGFRA* fusion
- *SDHA*
- *SDHB*
- *SDHC*
- *SDHD*
- None

E. Sex
- Male
- Female
- Missing information

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

JAMA Oncol. Published online March 24, 2016. doi:10.1001/jamaoncol.2016.0256

Table. Patient Demographics and Tumor Characteristics

Characteristic	Group 1: SDH-Competent GIST (n = 11)	Group 2: *SDHX*-Mutant GIST (n = 63)	Group 3: *SDHC*-Epimutant GIST (n = 21)	All Patients (n = 95)
Age, median (range), y[a]	46 (30-78)	23 (7-58)	15 (8-50)	23 (7-78)
Female sex, No. (%)[b]	7 (64)	39 (62)	20 (95)	66 (70)
Tumor size at resection, median (range), cm	8.9 (4.7-13.5)	5.6 (1.5-21)	4.7 (2-16)	5.6 (1.5-21)
Focality, proportion (%)[c,d]				
Unifocal	9/10 (90)	33/55 (60)	5/18 (28)	47/83 (57)
Multifocal	1/10 (10)	22/55 (40)	13/18 (72)	36/83 (43)
Primary location, No. (%)[e]				
Gastric	1 (9)	63 (100)	21 (100)	85 (89)
Small bowel	9 (82)	0	0	9 (9)
Abdominal	1 (9)	0	0	1 (1)
Histologic subtype, proportion (%)[d,f]				
Epithelioid	1/11 (9)	22/59 (37)	9/20 (45)	32/90 (36)
Spindle	9/11 (82)	9/59 (15)	2/20 (10)	20/90 (22)
Mixed	1/11 (9)	28/59 (47)	9/20 (45)	38/90 (42)
Metastasis at presentation, proportion (%)[d]				
Liver	0/10	12/58 (21)	7/19 (37)	19/87 (22)
Peritoneum	1/10 (10)	6/58 (10)	1/19 (5)	8/87 (9)
Lymph nodes	0/4	15/23 (65)	3/8 (38)	18/35 (51)
No liver or peritoneal metastases at presentation, proportion (%)[d]	9/10 (90)	41/58 (71)	12/19 (63)	62/87 (71)

Abbreviations: GIST, gastrointestinal stromal tumor; SDH, succinate dehydrogenase.

[a] There was a significant difference in age between the 3 groups ($P < .001$). Pairwise comparisons were significantly different: group 1 vs 2, $P < .001$; group 1 vs 3, $P < .001$; group 2 vs 3, $P = .002$.

[b] There was a significant difference in distribution of sex by group ($P = .02$); in pairwise comparisons, there was no difference between groups 1 and 2 ($P = .91$), but the distribution of sex differed significantly between group 1 and group 3 ($P = .02$) and between group 2 and group 3 ($P = .004$).

[c] There was a significant difference between focality of presentation for SDH-competent and SDH-deficient GIST ($P = .02$).

[d] The number of cases is less than the number of patients because of incomplete information.

[e] There was a significant difference in the distribution of primary location of tumors. All group 2 and 3 patients had gastric tumors while 1 of 11 group 1 patients had a gastric tumor ($P < .001$).

[f] There was a significant difference in histologic subtype among the groups. Group 1 vs 2: $P < .001$, group 1 vs 3: $P < .001$, group 2 vs 3: $P = .76$.

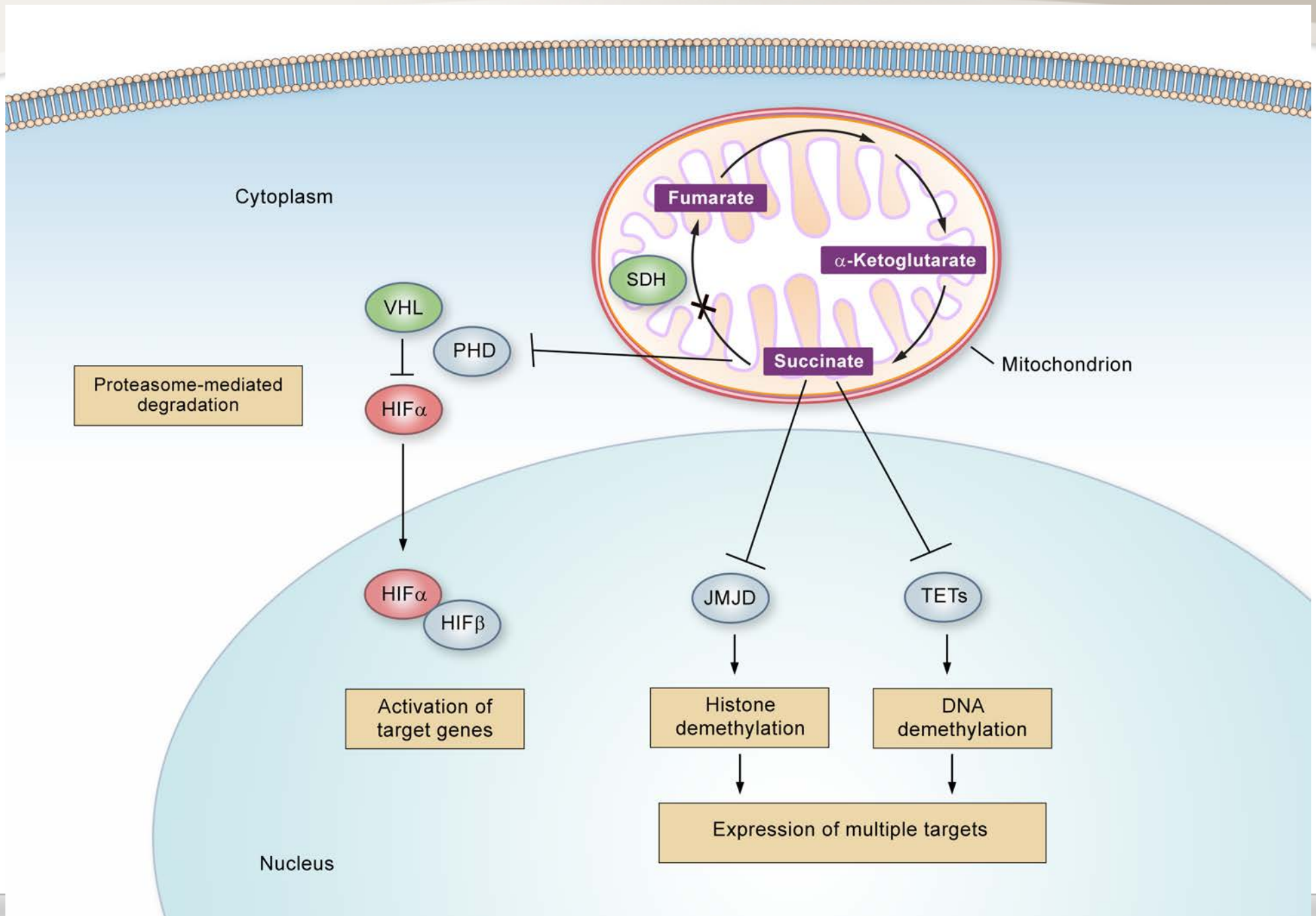
Table Title:

Patient Demographics and Tumor Characteristics

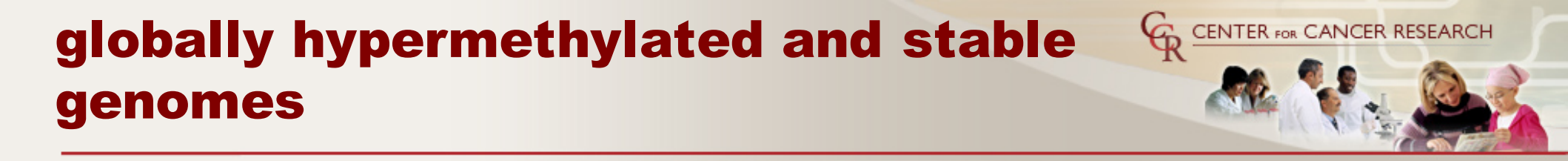
Consequences of dSDH

- **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 Deficiency Leads to Blockade of αKG Catalyzed Reactions

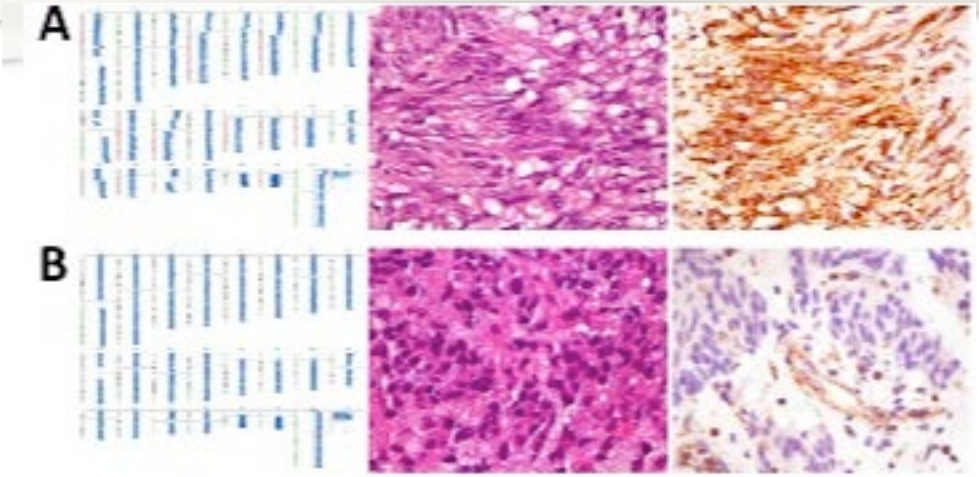


globally hypermethylated and stable genomes



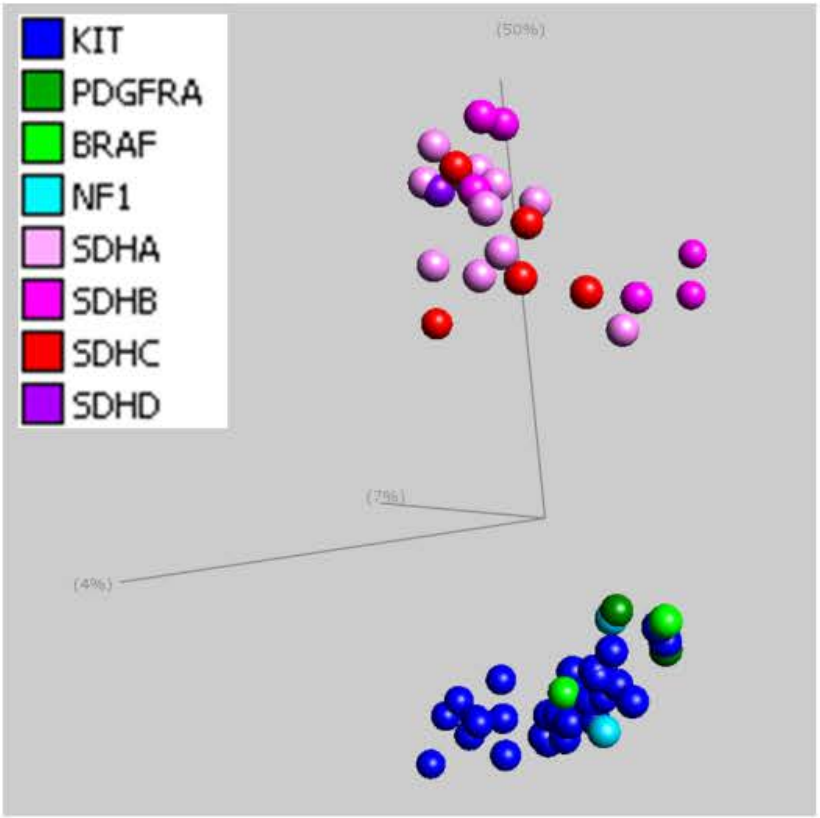
KIT Mutant GIST

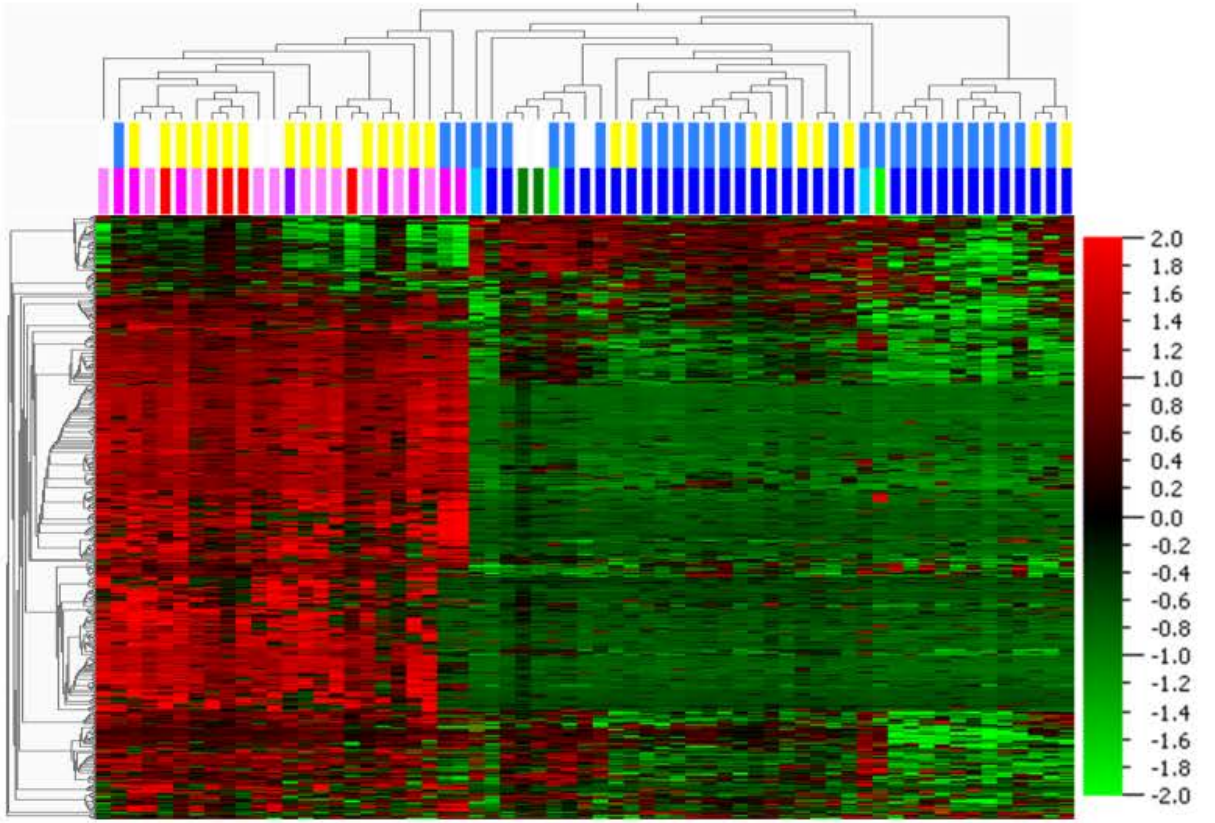
SDH Mutant GIST



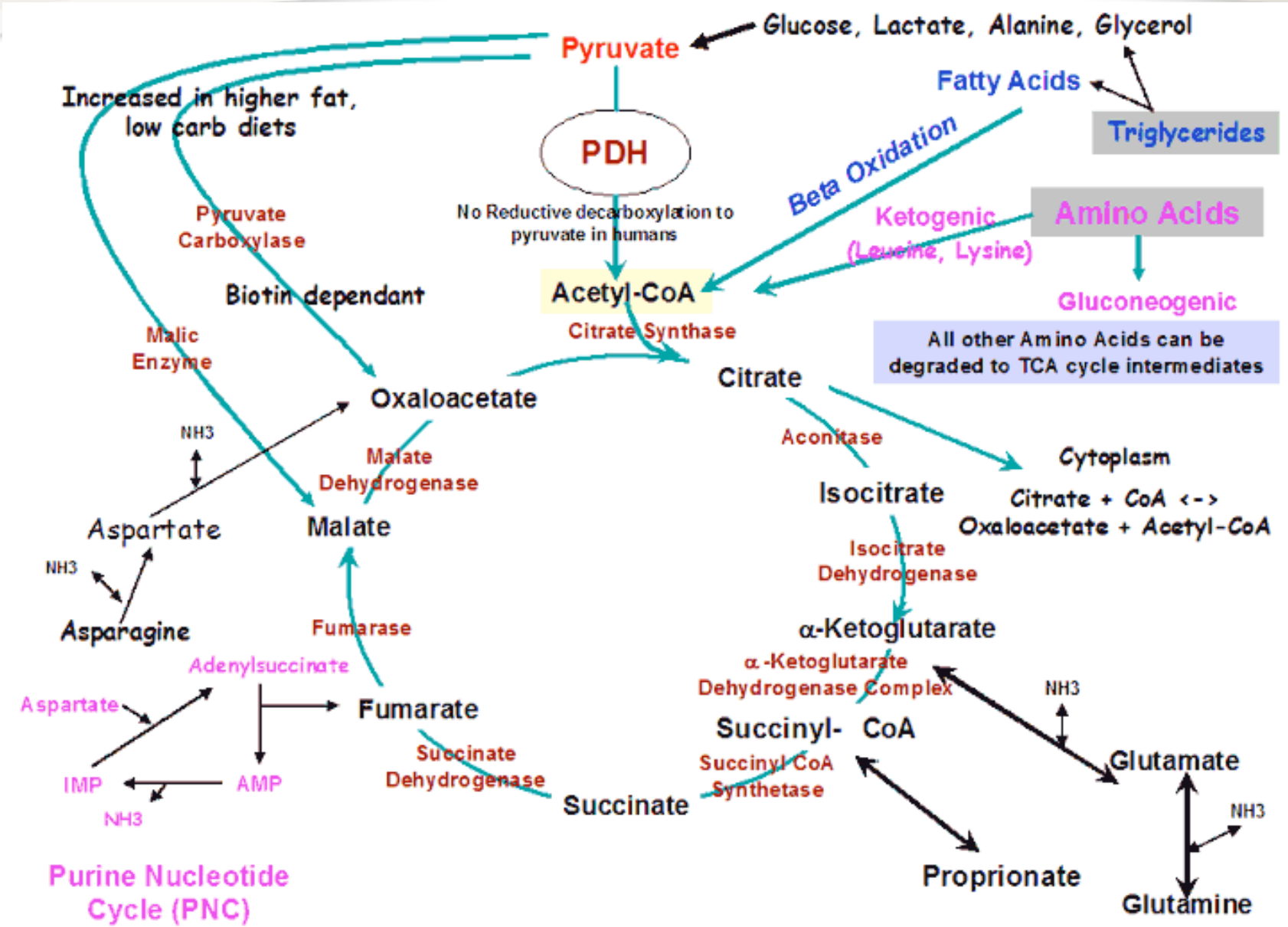
CGH H&E SDH IHC

Killian K et al.
Cancer Discovery 2013





Krebs Cycle


Glucose, Lactate, Alanine, Glycerol
Pyruvate
Fatty Acids
Triglycerides
Increased in higher fat, low carb diets
PDH
No Reductive decarboxylation to pyruvate in humans
Beta Oxidation
Pyruvate Carboxylase
Ketogenic (Leucine, Lysine)
Amino Acids
Biotin dependant
Acetyl-CoA
Gluconeogenic
Malic Enzyme
Citrate Synthase
All other Amino Acids can be degraded to TCA cycle intermediates
Oxaloacetate
Citrate
NH3
Aconitase
Malate Dehydrogenase
Cytoplasm
Isocitrate
Citrate + CoA <-> Oxaloacetate + Acetyl-CoA
Aspartate
Malate
Isocitrate Dehydrogenase
NH3
Asparagine
α-Ketoglutarate
Fumarase
Adenylsuccinate
α-Ketoglutarate Dehydrogenase Complex
NH3
Aspartate
Fumarate
Succinyl- CoA
Glutamate
Succinate Dehydrogenase
Succinyl CoA Synthetase
IMP
AMP
NH3
NH3
Succinate
Proprionate
Glutamine
Purine Nucleotide Cycle (PNC)

Future Directions

- **Continue to accrue patients with dSDH GIST**
  - Study genotype/phenotype correlations
- **Accrue more patients with NF-1 GIST**
  - Determine role of Mek inhibitors in treatment
- **Based on increased succinate/αKG ratios ⟶ global DNA hypermethylation + PHD inhibition ⟶ "pseudo-hypoxic" state:**
  - Test more potent VEGF inhibitors (completed testing Vandetanib)-unfortunately no activity
  - Test more potent DNMT inhibitors, e.g., SGI-110 (guadecitabine)