Challenges (and opportunities) in approaching a Non KIT/PDGFRA mutated GIST

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&

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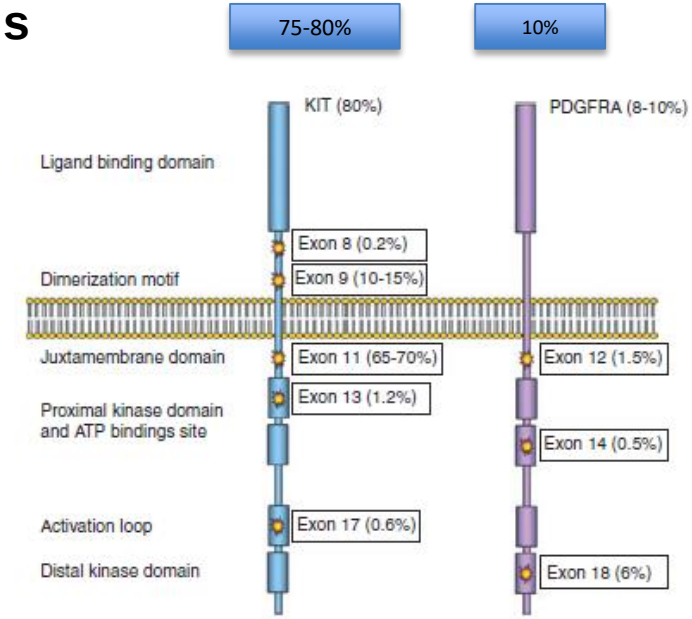
Gastrointestinal Stromal Tumours

- We have come a long way since
  - Seiichi Hirota 1998 Gain of function mutations of c-kit in GISTs
  - First GIST patient treated with Imatinib 2001 NEJM
  - Imatinib approved for metastatic/inoperable GIST
  - 2nd line Sunitinib (2006) and 3rd line Regorafenib (2012)

Most common genes involved in tumorogenesis

- KIT and PDGFRA—Chr 4
- Mutually exclusive
- 15% of GISTs
  - No activating mutations in KIT/PDGFRA
  - WILD Type term used to describe these
  - Non KIT Non PDGRFA mutant GISTs



WILD type GIST

- Perhaps we should back off from using the term WILD type
- May hinder or slow down the understanding of the biology
- Heterogeneity is acknowledged
- Define individual subtypes of WILD type GISTs
- This may help in understanding the biology, identifying oncogenic drivers and likely to lead to tailored treatments based on biology

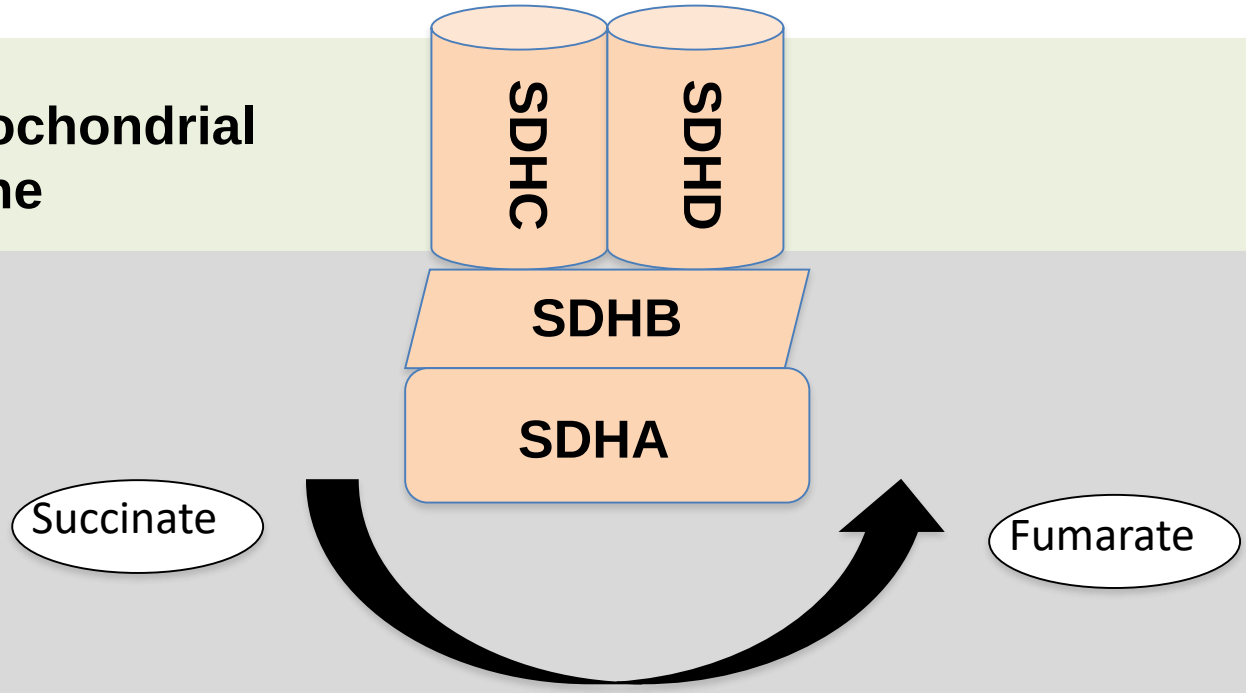
How far have we come since the identification of KIT/PDGFRA mutant GISTS ?

- New oncogenic drivers and pathways
  - BRAF mutant GISTs
  - NTRK fusion GISTs
  - FGFR pathway
  - Possibly others yet to be discovered
- Succinate dehydrogenase (SDH) deficient GISTs
- GISTs associated with NF1 syndrome
- Descriptive terms
  - Quadruple negative GISTs (KIT, PDGFRA, BRAF WT and SDH preserved)
  - Quintuple negative GISTs (KIT, PDGFRA, BRAF WT, SDH preserved, no NTRK fusion)

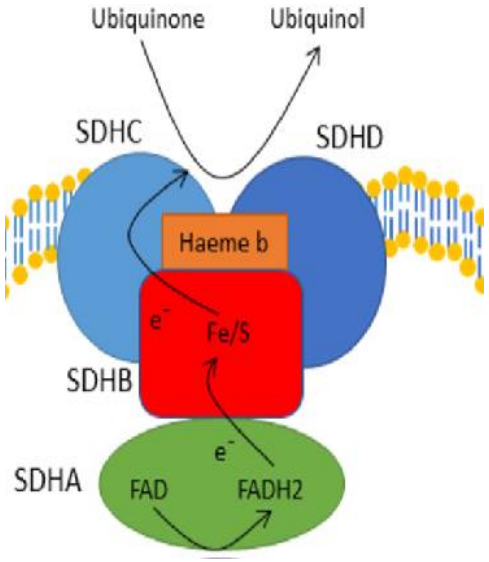
Classification of non *KIT* and non *PDGFRA* mutant GIST

- Step 1 is to determine if the GIST has a functioning SDH enzyme- ‘SDH deficient’ or ‘SDH preserved ‘

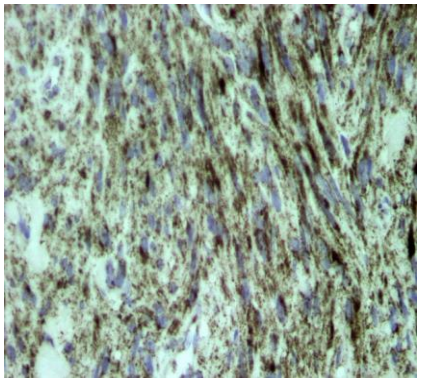
Succinate dehydrogenase



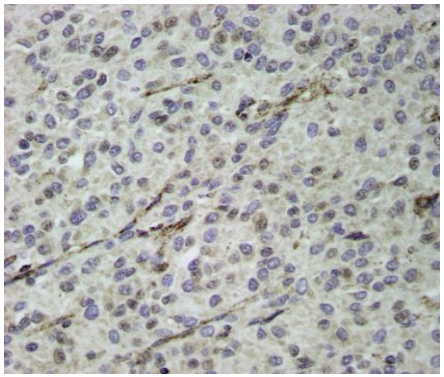
SDHB Immunohistochemistry



- **SDHB protein is at the core of the SDH complex**
- **A pathogenic variant in any of the four *SDHx* genes will affect expression of the SDHB protein**
- **Antibody directed against SDHB protein can be used to detect *SDHx* gene mutations**



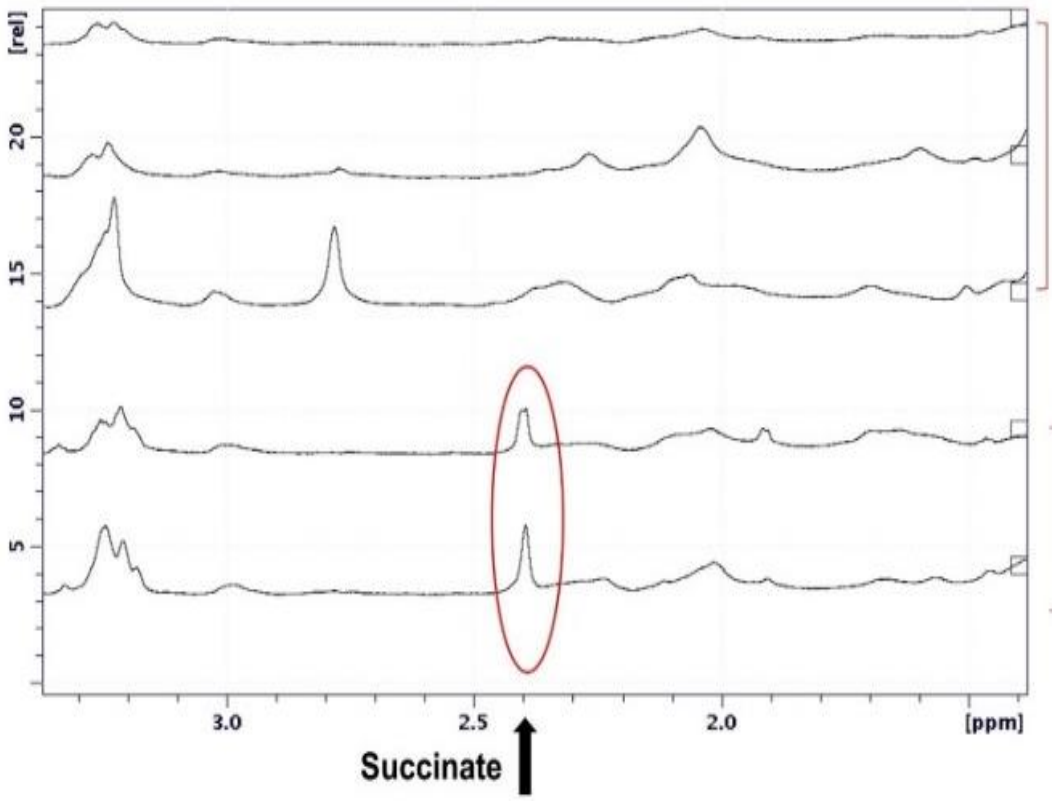
SDH proficient GIST



SDH deficient GIST

Testing for SDH status of GIST

Accumulation of the metabolite succinate in the excised tumour sample :



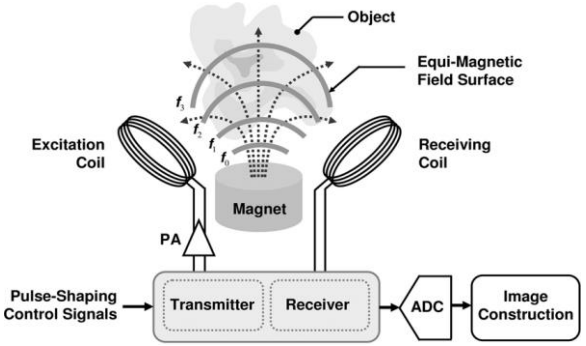
SDH preserved tumours

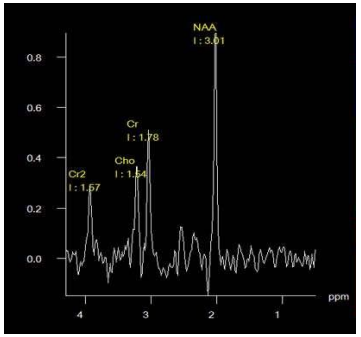
SDH deficient tumours

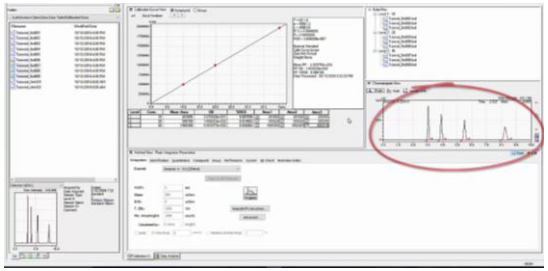
Detecting succinate in tumours using MRI spectroscopy

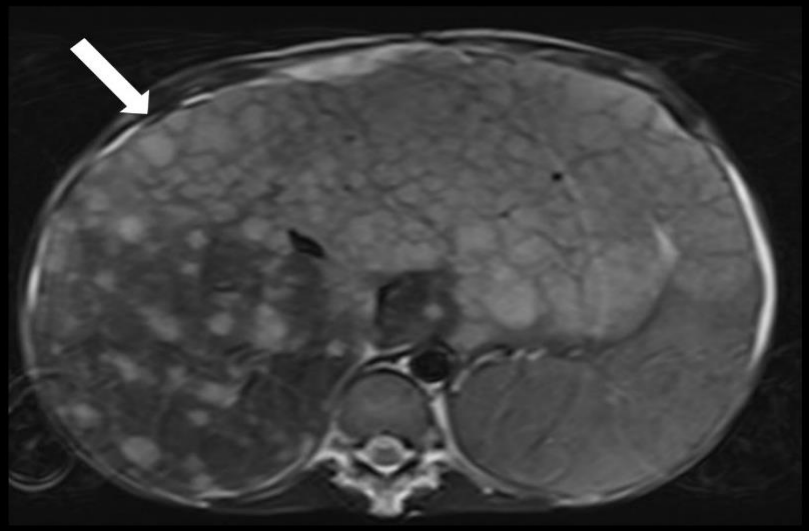
H^1-MRS

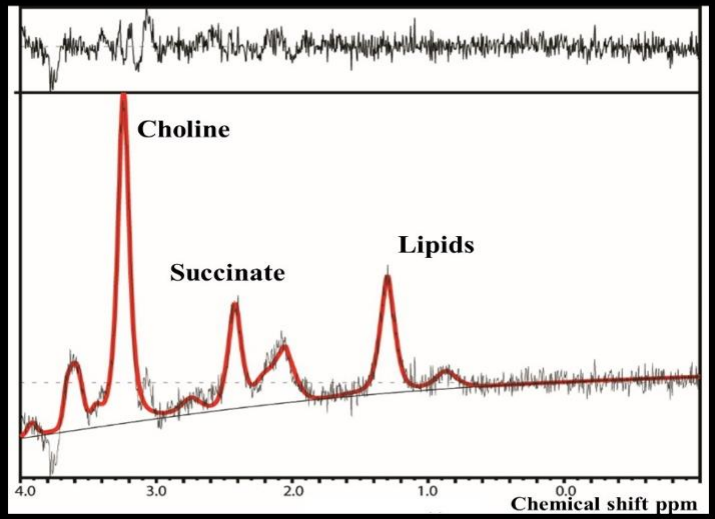
- **3T MRI scanner**
- **Non-contrast MRI**
- **Adjustment of magnetic field homogeneity pre-scan**
- **Spectra acquisition 15 mins**
- **Analysed using specific software and by an expert spectroscopist**

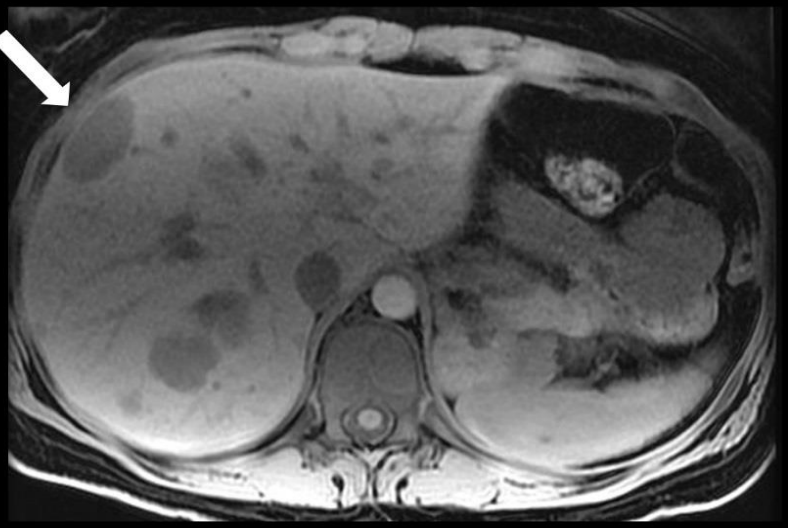


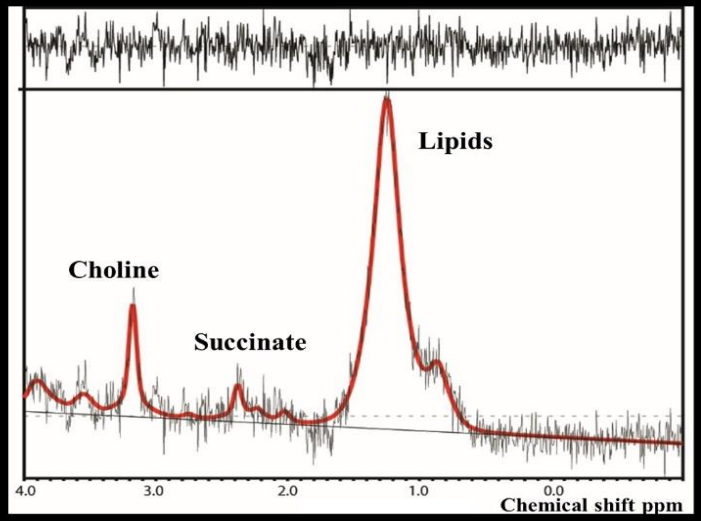






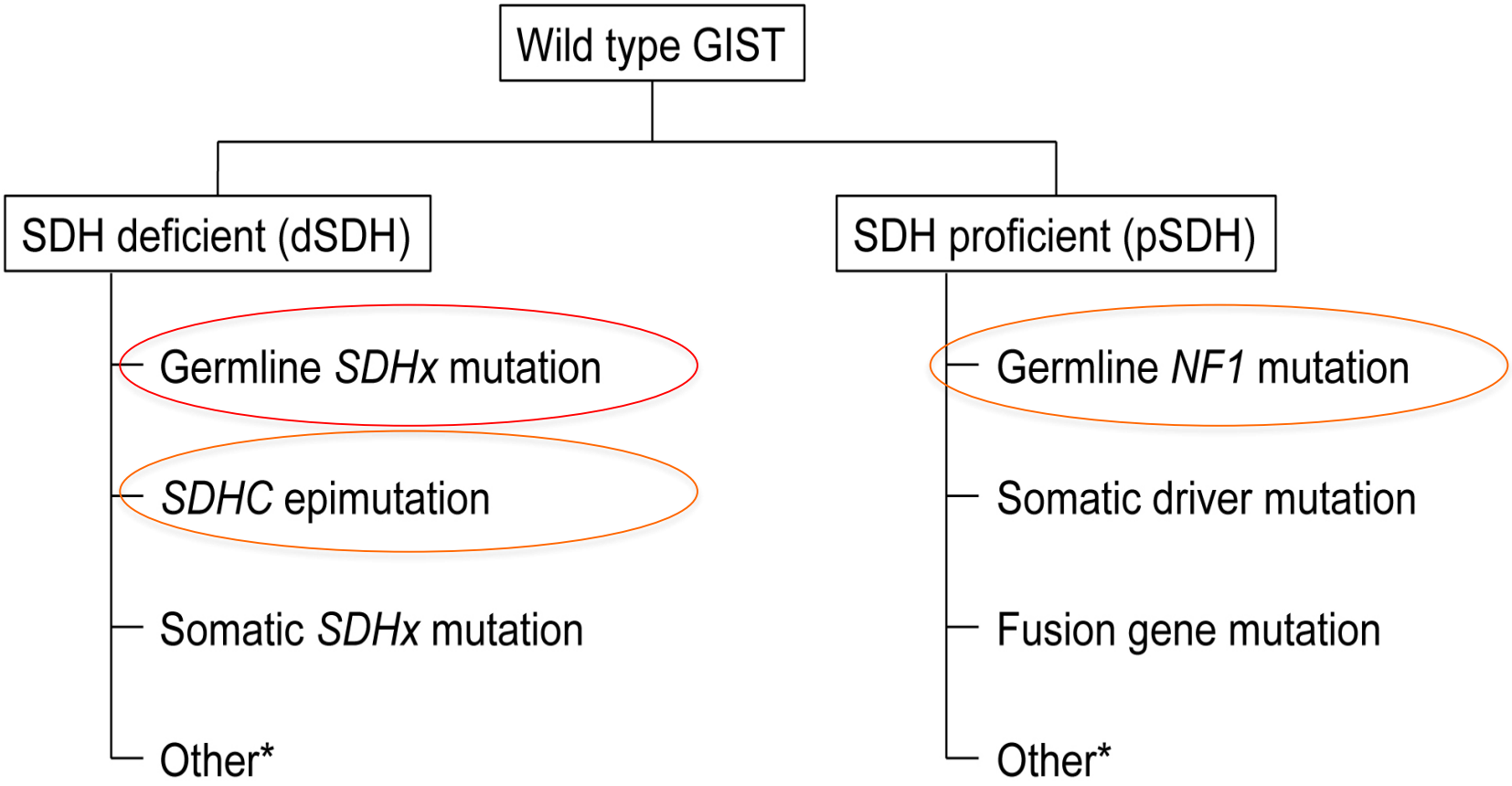






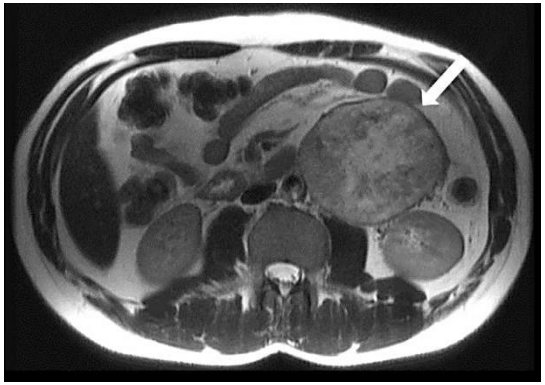
Casey RT, et al. JCO Precis Oncol. 2018 Mar 29;2:1-12. doi: 10.1200/PO.17.00191.

Classification of non *KIT* and non *PDGFRA* mutant GIST

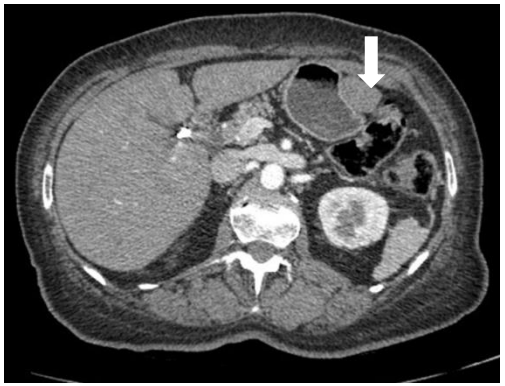


Succinate dehydrogenase gene mutations

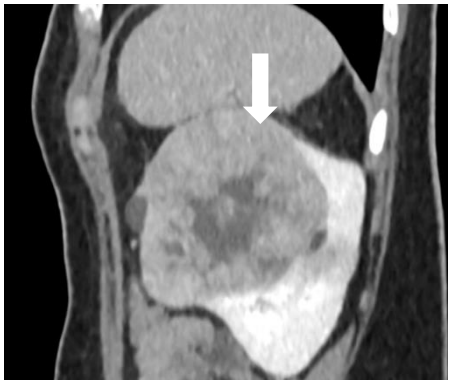
- Germline mutations in *SDHA*/*SDHB*/*SDHC*/*SDHD*
- Account for 30% of all hereditary cases of PPGL
- Increased risk of malignancy
- Lifetime risk of multi-focal and synchronous tumours
- Predispose to PPGL, GIST, RCC and pituitary tumours



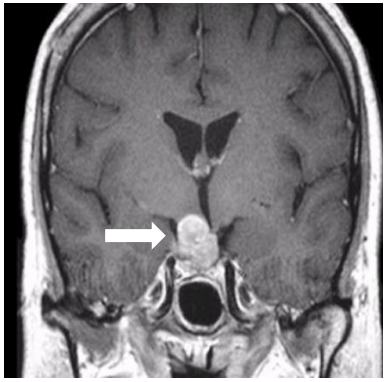
PPGL



GIST



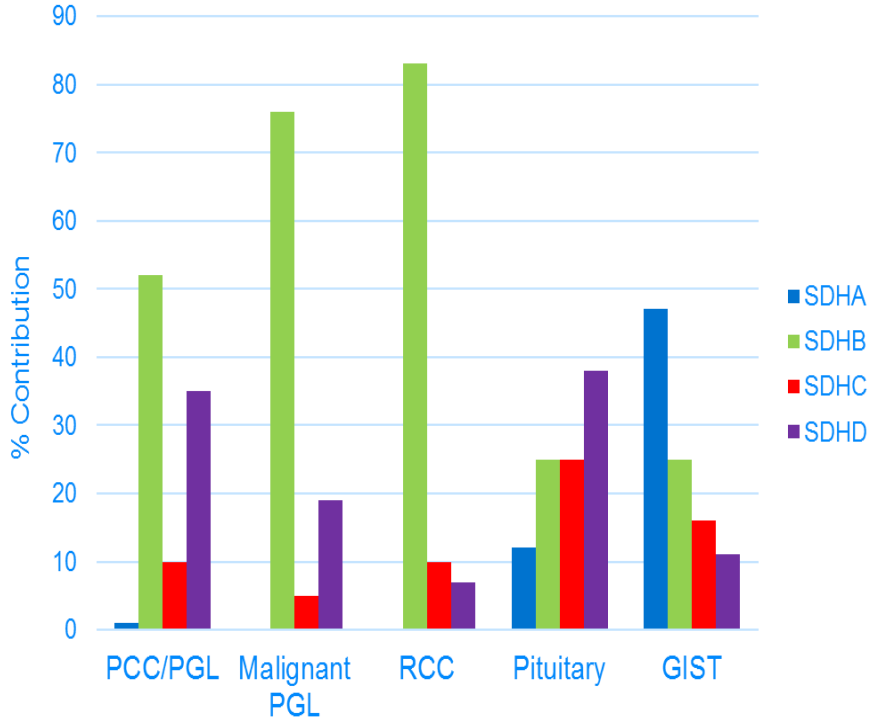
RCC



Pituitary adenoma

MacFarlane J,et al. A review of the tumour spectrum of germline succinate dehydrogenase gene mutations: Beyond phaeochromocytoma and paraganglioma. Clin Endocrinol (Oxf). 2020 Jul 19. doi: 10.1111/cen.14289

Genotype-Phenotype correlations



Toward an improved definition of the genetic and tumor spectrum associated with *SDH* germ-line mutations

Lucie Evenepoel, MS[1–3], Thomas G. Papathomas, MD[2], Niels Krol, BS[2], Esther Korpershoek, PhD[2], Ronald R. de Krijger, MD, PhD[2,4], Alexandre Persu, MD[1] and Winand N.M. Dinjens, PhD[2]

TABLE 1 Phenotype described in association with specific *SDHx* gene subunits

SDHx subunit gene	PC	HNPGL	Thoracic PGL	Malignant PGL	Abdominal/pelvic PGL	wtGIST	RCC	PA
SDHA	+	+	+	+	+	+++	+	+
SDHB	+	++	++	+++	+++	++	+++	+
SDHC	+	++	+	+	++	++	+	+
SDHD	++	+++	+	+	+	+	+	+

Abbreviations: HNPGL, Head and neck paraganglioma; PA, pituitary adenoma; PC, phaeochromcocytoma; PC, phaeochromocytoma; PGL, paraganglioma; RCC, renal cell carcinoma; wtGIST, wild-type gastrointestinal stromal tumour.

*This table is based on reported frequencies of tumours in association with the specific SDH subunit mutations.

MacFarlane J, et al. A review of the tumour spectrum of germline succinate dehydrogenase gene mutations: Beyond phaeochromocytoma and paraganglioma. Clin Endocrinol (Oxf). 2020 Jul 19. doi: 10.1111/cen.14289

Penetrance of tumours in *SDHx* mutation carriers

Kaplan Meier analysis, Andrews et al. 2018:

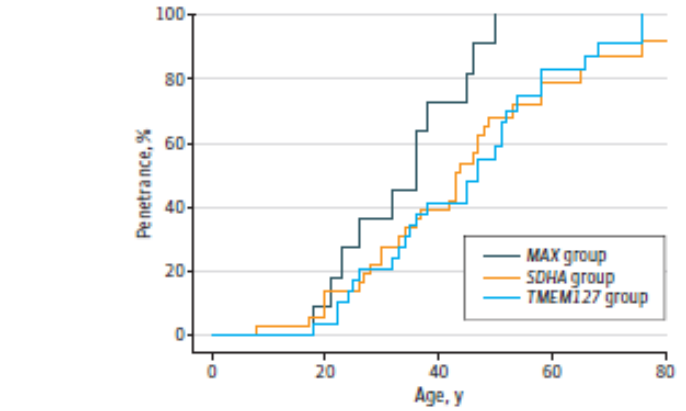
Penetrance by age 60:	PPGL/HNPGL
SDHB – non-probands	23%
SDHC – non-probands	25%
SDHD – non-probands	50%

Bayesian analysis, Benn et al. 2018:

Lifetime penetrance:	PPGL/HNPGL
SDHA	1.7%
SDHB	22%

Kaplan Meier analysis, Bausch et al. 2017:

Figure 1. Age-Related Penetrance of Any Pheochromocytoma and Paraganglioma



Kaplan-Meier analysis includes all 57 symptomatic probands (index patients) and 20 relatives (n = 77) with germline mutations of the *SDHA* (succinate dehydrogenase subunit A) (n = 37), *MAX* (Myc-associated factor X) (n = 11), and *TMEM127* (transmembrane protein 127) (n = 29) genes from this study.

- Benn DE, Zhu Y, Andrews KA et al. **Bayesian approach to determining penetrance of pathogenic SDH variants.** J Med Genet. 2018 Sep 10. pii: jmedgenet-2018-105427.
- Bausch B, et al. **Clinical Characterization of the Pheochromocytoma and Paraganglioma Susceptibility Genes SDHA, TMEM127, MAX, and SDHAF2 for Gene-Informed Prevention.** JAMA Oncol..

Asymptomatic Paediatric *SDHx* carriers

SDHx subunit gene	Penetrance at age 5 y		Penetrance at age 10 y		Penetrance at age 16 y		Penetrance at age 18 y	
	PPGL	HNPGL	PPGL	HNPGL	PPGL	HNPGL	PPGL	HNPGL
SDHB n = 598	0.17% [95% CI 0.0-0.51]	0%	1.7% [95% CI 0.67-2.8]	0%	7.6% [95% CI 5.4-9.8]	0.38% [95% CI 0.0-0.90]	10.2% [95% CI 7.6-12.7	0.58% [95% CI 0.0-1.2]
SDHD n = 137	0%	0%	0.28% [95% CI 0.0-0.82]	0%	3.1% [95% CI 0.062-6.0]	1.6% [95% CI 0.0-3.7]	7.0% [95% CI 2.5-11.3]	3.2% [95% CI 0.063-6.1]
SDHB[a] n = 371	0%	0%	0.28% [95% CI 0.0-0.82]	0%	1.2% [95% CI 0.023-2.4]	0%	2.2% [95% CI 0.56-3.7]	0.32% [95% CI 0.0-0.94]
SDHD[a] n = 67	0%	0%	0%	0%	0%	0%	6.4% [95% CI 0.13-12.3]	1.7% [95% CI 0.0-4.9]

NB. No confidence intervals are given before the first noncensored event (if no children in the cohort have experienced tumours by the age specified).

HNPGL, head and neck paraganglioma; PPGL, phaeochromocytoma and paraganglioma.

[a]Nonproband gene carriers only (probands excluded from analysis).

Wong MY1, et al. **Clinical Practice Guidance: Surveillance for phaeochromocytoma and paraganglioma in paediatric succinate dehydrogenase gene mutation carriers**. Clin Endocrinol (Oxf). 2018 Dec 27. doi: 10.1111/cen.13926

Adult asymptomatic *SDHx* carriers

Gene	Recommended surveillance
SDHB	• Annual clinical review and biochemistry • Abdominal imaging at baseline and if normal every 12-24 months • MRI/CT of neck, thorax at baseline and if normal every 3 years
SDHD	• Screening should only be offered to patients who have a paternally inherited SDHD variant * • Annual clinical review and biochemistry • Abdominal imaging and MRI/CT of neck, thorax at baseline and if normal every 3 years
SDHC	• Annual clinical review and biochemistry • Abdominal imaging and MRI/CT of neck, thorax at baseline and if normal every 3 years
SDHA	• Annual clinical review and biochemistry • Abdominal imaging and MRI/CT of neck, thorax at baseline and if normal every 3-5years

- **CLINICAL GUIDELINE FOR PHAEOCHROMOCYTOMA AND PARAGANGLIOMA CUHFT**

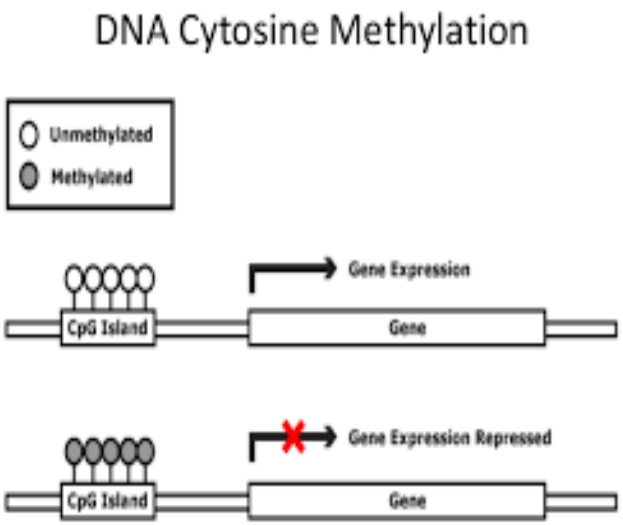
Suggested surveillance for asymptomatic paediatric *SDHx* carriers:

SDHB	**Age**
Genetic testing	5 years
Clinical evaluation	5 years
Biochemical testing	5 years
Imaging (MRI or if not tolerated US) Repeat every 2-3 years	10 years

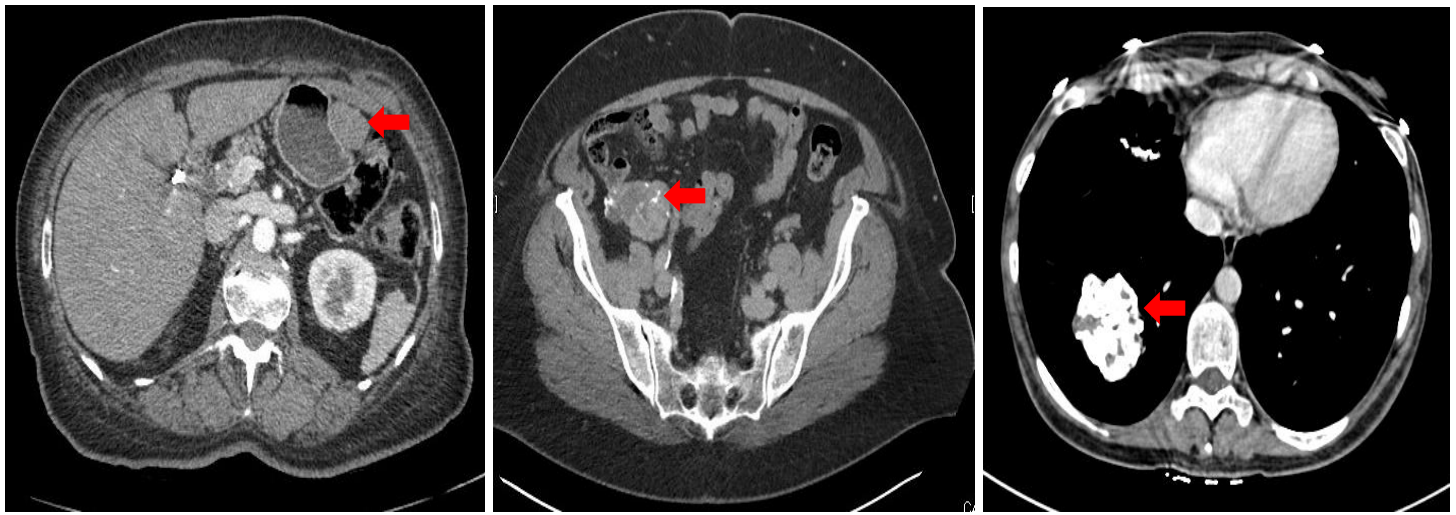
SDHA, SDHC, SDHD	**Age**
Genetic testing	10 years
Clinical evaluation	10 years
Biochemical testing	10 years
Imaging (MRI or if not tolerated US) Repeat every 3-5 years*	15 years

Wong MY1, et al. **Clinical Practice Guidance: Surveillance for phaeochromocytoma and paraganglioma in paediatric succinate dehydrogenase gene mutation carriers**. Clin Endocrinol (Oxf). 2018 Dec 27. doi: 10.1111/cen.13926

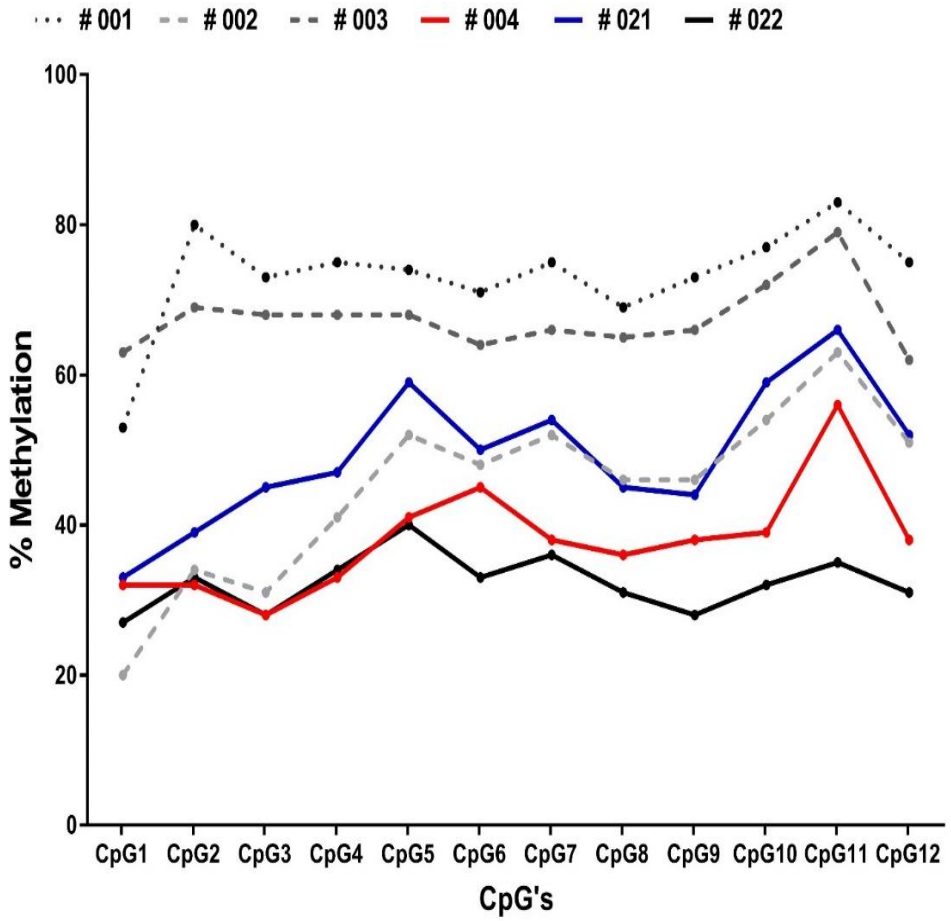
Epi-mutation in *SDHC*



"Carney's Triad"



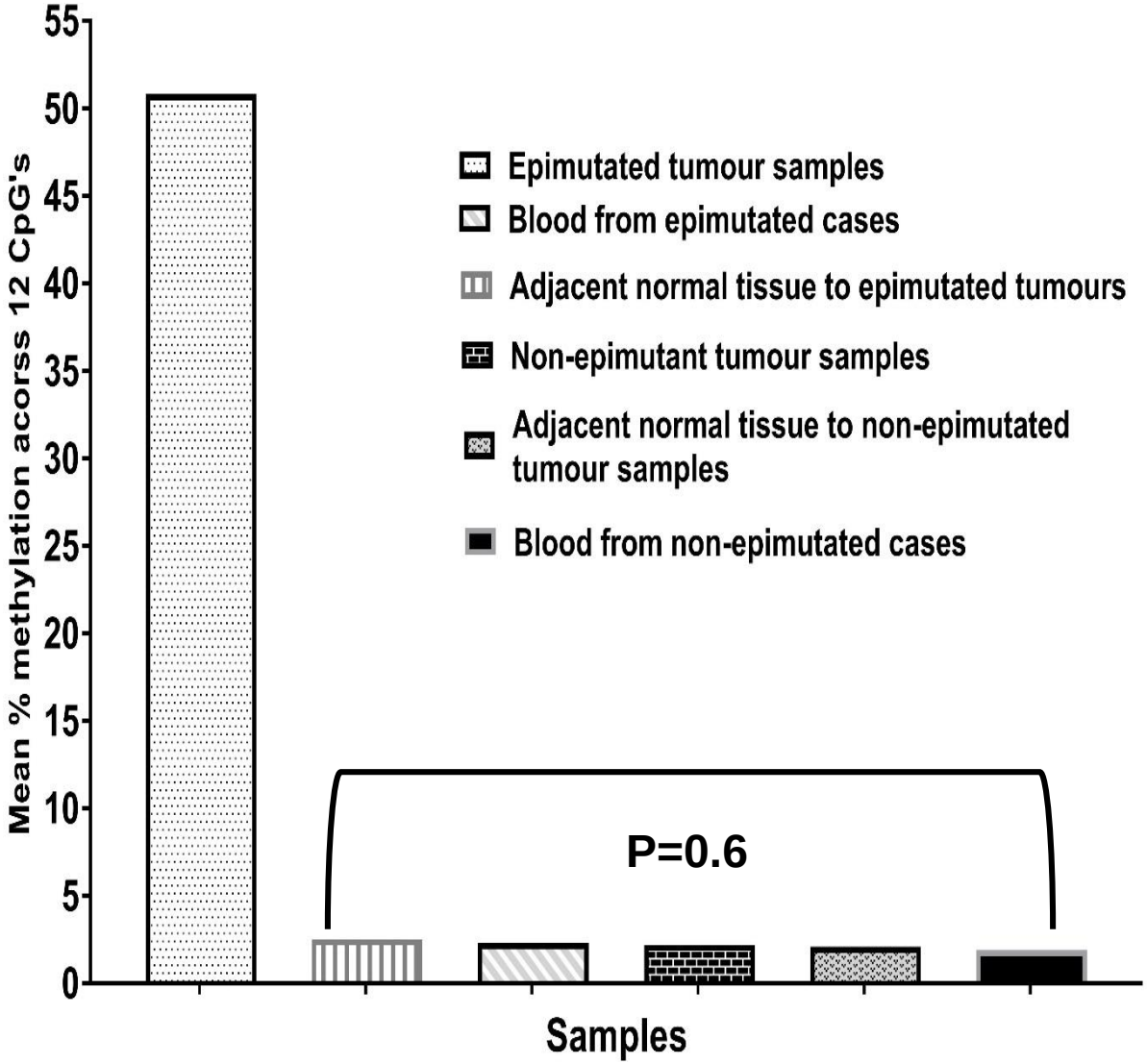
Epimutant cases



- Comparing epimutated cases with non-epimutated cases an association was made with :
- wtGIST (P=0.005)
- Female sex (P=0.02)
- Metastatic disease (P=0.03)
- Younger age at diagnosis
- Multiple primary tumours (P=0.03)

Casey RT, et al. Sci Rep 2019. SDHC epi-mutation testing in gastrointestinal stromal tumours and related tumours in clinical practice

Epimutation somatic v's constitutional?



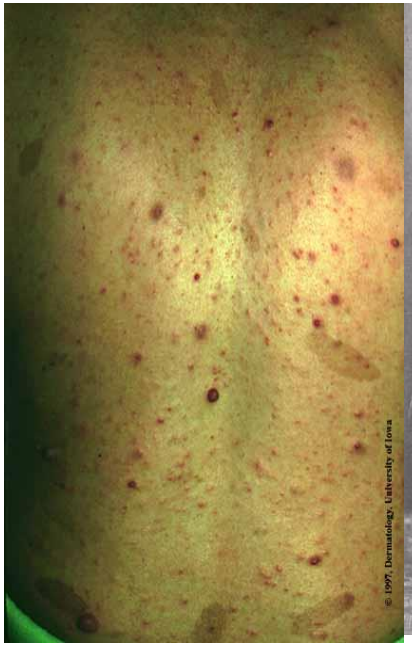
Casey RT, et al. Sci Rep 2019. SDHC epi-mutation testing in gastrointestinal stromal tumours and related tumours in clinical practice

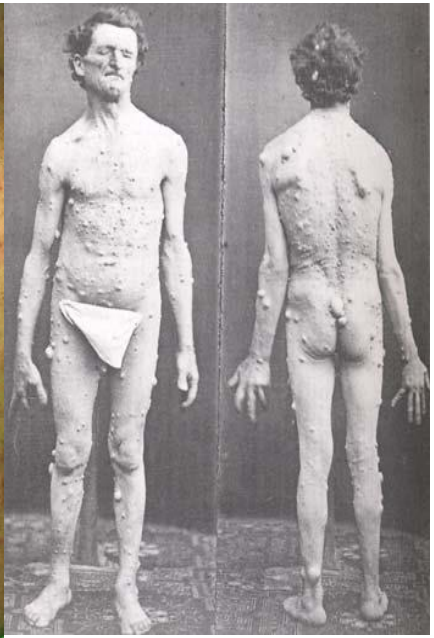
Screening for patients with an *SDHC* epimutation

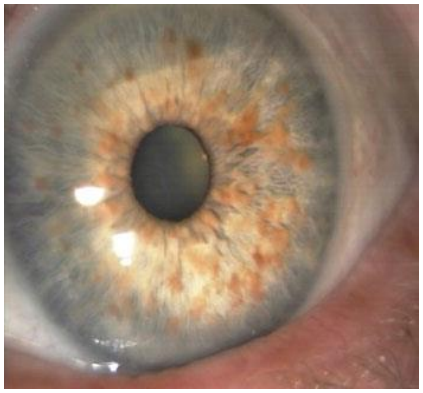
- **Screening protocol needed is not clear**
- **We advise screening for PPGL should follow similar guidance as for SDHA germline mutations for the patient**
- **No family screening recommended**

Neurofibromatosis Type 1

- Autosomal dominant *NF1* gene
- CAL, cutaneous neurofibromas, Lisch nodules, axillary freckling, optic tumours, nerve sheath tumours, neuroendocrine tumours
- Lifetime risk of phaeochromocytoma ~2%







GIST in NF1

- A retrospective register based study looking for a diagnosis of GIST identified 1410 diagnoses in NF1 patients between 1987-2013

- Tumours are most commonly in the small bowel and can be multiple

Ylä-Outinen H, et al. Mol Genet Genomic Med. 2019 Sep;7(9):e927. doi: 10.1002/mgg3.927.

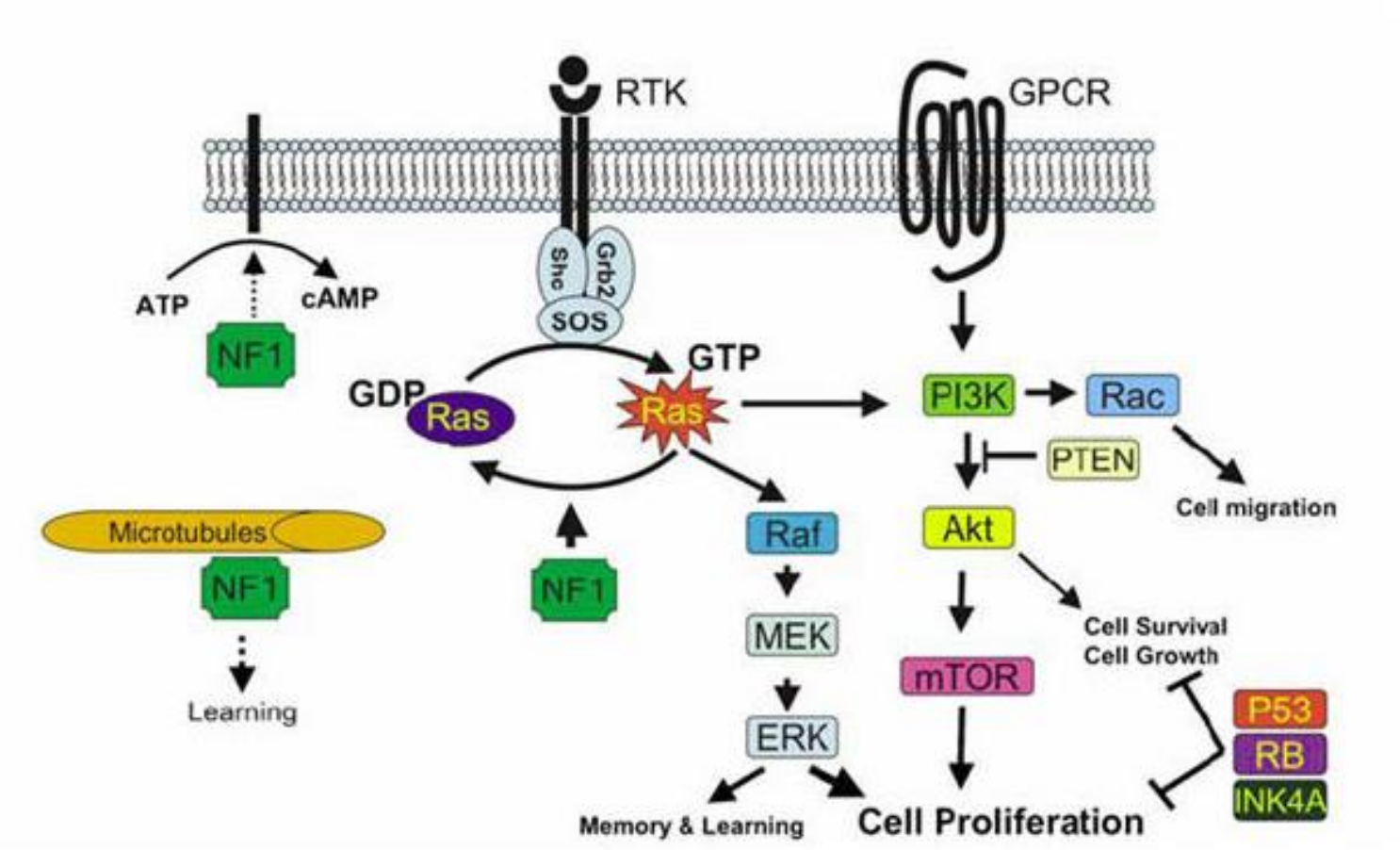
What is the standard of care for Non KIT/PDGFRA GISTs ?

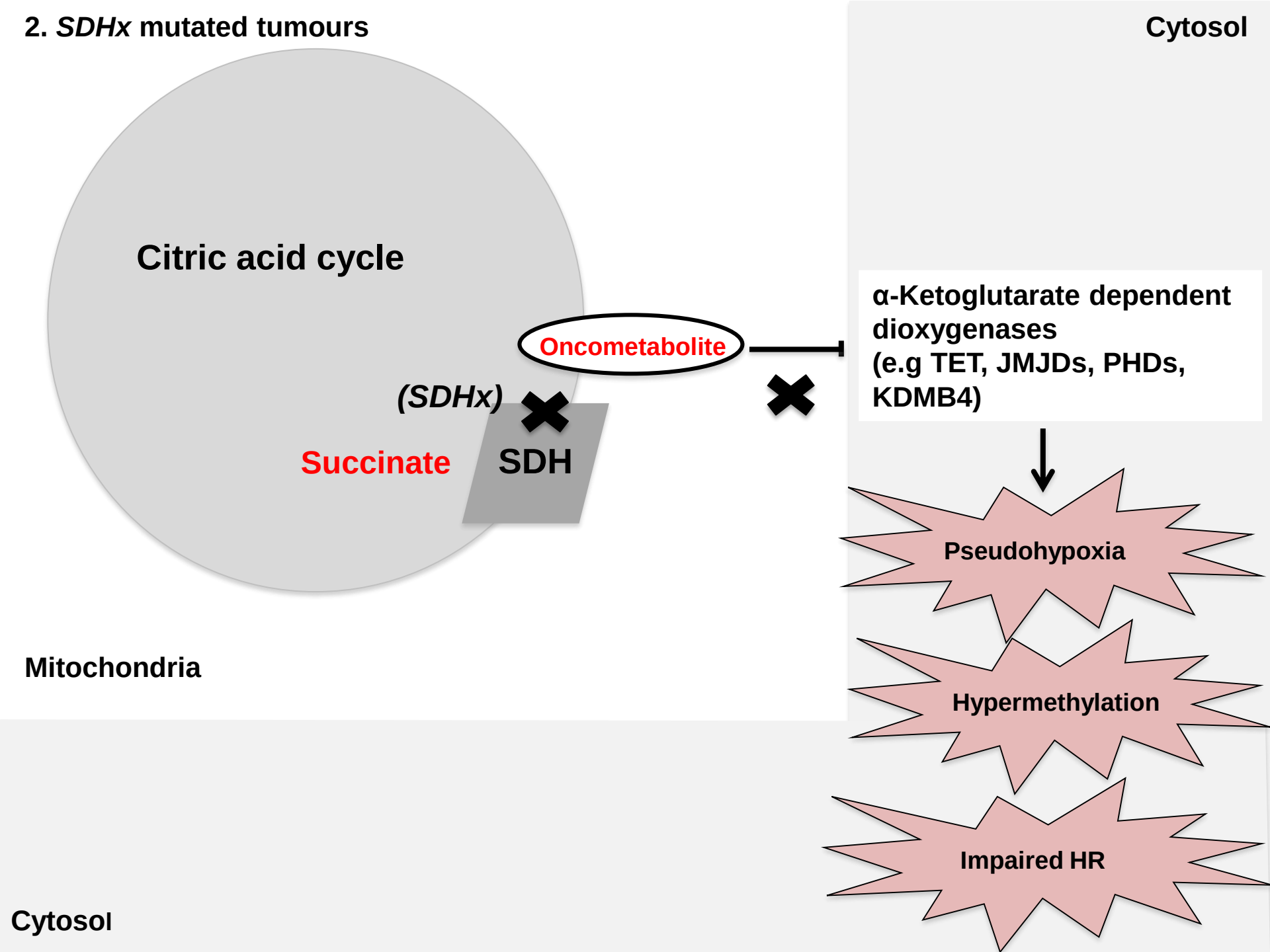
- Oncogenic driver identified
  - Eg BRAF mutant—BRAF kinase inhibitors
  - NTRK fusion GIST—NTRK inhibitors (agnostic license)
- What about the three TKIs we have right now?
  - Imatinib—no benefit—anecdotal cases of ‘response’—could be just the natural history of GIST
  - Sunitinib—some activity in SDH def GISTs
  - Regorafenib– some activity in SDH def GISTs & NF1 GISTs
  - Concern re long term side effects of multi targeted TKIs in younger patients

Back to the drawing board!!!

Molecular biology

1. *NF1* mutated tumours




2. SDHx mutated tumours
Cytosol
Citric acid cycle
Oncometabolite
(SDHx)
Succinate
SDH
α-Ketoglutarate dependent dioxygenases (e.g TET, JMJDs, PHDs, KDMB4)
Pseudohypoxia
Hypermethylation
Impaired HR
Mitochondria
Cytosol

Personalised medicine

Symptoms

Quality of life

Disease biology and location

Personal wishes

Side effects of treatment

Drug efficacy

Evidence based medicine

Institutional and national protocols

So what can we do?

- Clinical trials
  - Biology based
  - Multi centre, multi national
  - Patient driven

- Learn from other cancers—Local interventions
  - Surgical debulking
  - Radiofrequency Ablation (RFA)
  - Embolization
  - Selective Internal Radiotherapy
  - External beam radiotherapy

Clinical Trials

- Guadecitabine NIH study
- SDH-deficient GIST, PHEO/PGL, and HLRCC-associated renal cell carcinoma.
- Patients >12 years of age received guadecitabine subcutaneously at 45mg/m^2/day for 5 consecutive days on a 28-day cycle
- Activity via imaging response was assessed utilizing RECISTv1.1
- No patients had a complete or partial response
- In this single site, open label, phase II study in patients with SDH-deficient GIST, PHEO/PGL, and HLRCC-associated renal cell cancer guadecitabine was tolerated by the majority of patients.
- Clinical trial information: NCT03165721

A phase II trial of the DNA methyl transferase inhibitor, SGI-110 (Guadecitabine), in children and adults with SDH-deficient GIST, pheochromocytoma, and paraganglioma, and HLRCC-associated kidney cancer.

Mary Frances Wedekind, Jaydira Del Rivero, Fernanda Irene Arnaldez, Ramaprasad Srinivasan, Melissa Spencer, Seth M. Steinberg, Cody J. Peer, William Douglas Figg, Jonathan Keith Killian, Paul S. Meltzer, W. Marston Linehan, Brigitte C. Widemann, John Glod

Pediatric Oncology Branch, NCI, NIH, Bethesda, MD; Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; National Institutes of Health, Bethesda, MD; National Cancer Institute at the National Institutes of Health, Bethesda, MD; NCI, Bethesda, MD; Biostatistics and Data Management Section, National Cancer Institute, NIH, Bethesda, MD; National Cancer Institute, Bethesda, MD; Clinical Pharmacology Program, National Institutes of Health, Bethesda, MD; Foundation Medicine, Cambridge, MA; Center of Cancer Research, Bethesda, MD; Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Why did we not see a 'signal' in this cohort of patients????!!!

NF1 GISTs

- Selumetinib in NF1 GISTs—NIH study

- Mitogen Activated Protein Kinase Kinase (MEK1/2) Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in People With Neurofibromatosis Type 1 (NF1) Mutated Gastrointestinal Stromal Tumors (GIST)
- clinicaltrials.gov:NCT03109301
- Closed due to poor (NO) accrual

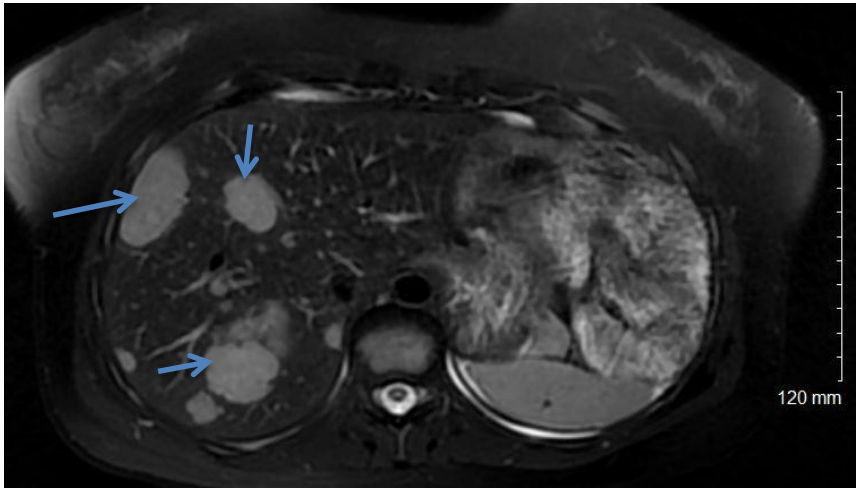
- Worth pursuing as part of multinational effort
- Dual inhibition RAF/MEK ??

TEMOGIST Study

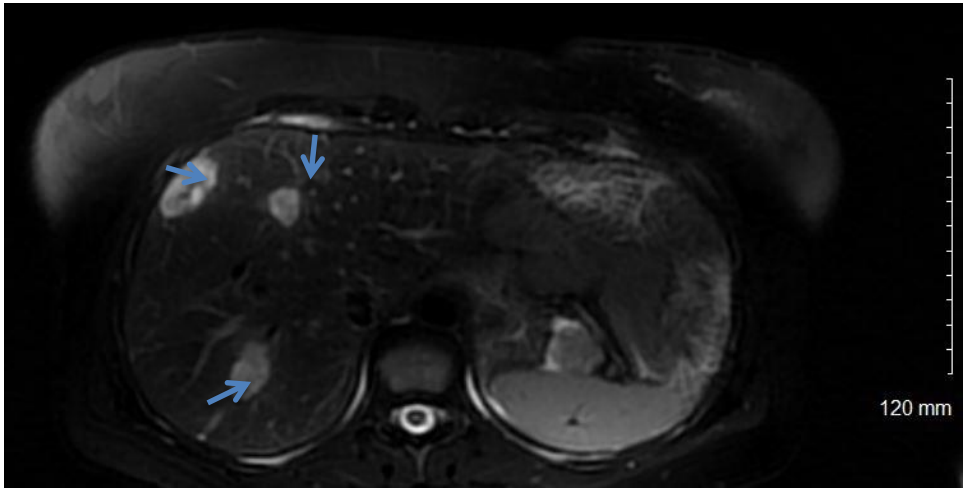
- Temozolomide (TMZ) In Advanced Succinate Dehydrogenase (SDH)-Mutant/Deficient Gastrointestinal Stromal Tumor (GIST)
- TMZ 85 mg/m2 mg orally once for 21 days followed by 7 days without treatment in 28 day cycles.
- Treatment will continue for 6 months (with option to continue if benefiting treatment) or until disease progression or unacceptable toxicity
- Primary Outcome Measures :
  - Overall Response Rate [Time Frame: 6 months]To determine overall response rate at 6 months for TMZ therapy in patients with SDH-mutant/deficient GIST
- Secondary Outcome Measures □ : 1.Progression-free survival [Time Frame: 4 years]
  - 2.Overall survival [Time Frame: 4 years]
  - 3.Adverse events related to TMZ [Time Frame: 6 months]
- Ongoing
- Anecdotal reports of some efficacy (off label use in Europe/USA)

SIRT in SDH deficient GISTs

Baseline pre SIRT Sept 2019
Liver MRI



9 months post SIRT
Liver MRI



Summary

- Heterogeneity is the hallmark of ‘wild-type’ GIST
- Specialist multi-disciplinary team is key to the management
- Balancing the potential benefits of treatment versus effects on quality of life for each individual is critical
- Collaboration and clinical research at a national and international level will enable ongoing developments in this field
- Keeping patients and patient advocates at the centre should be the driver for successful progress

Thank you

Questions???

GIST Paediatric Adolescent Wild-type Syndromic