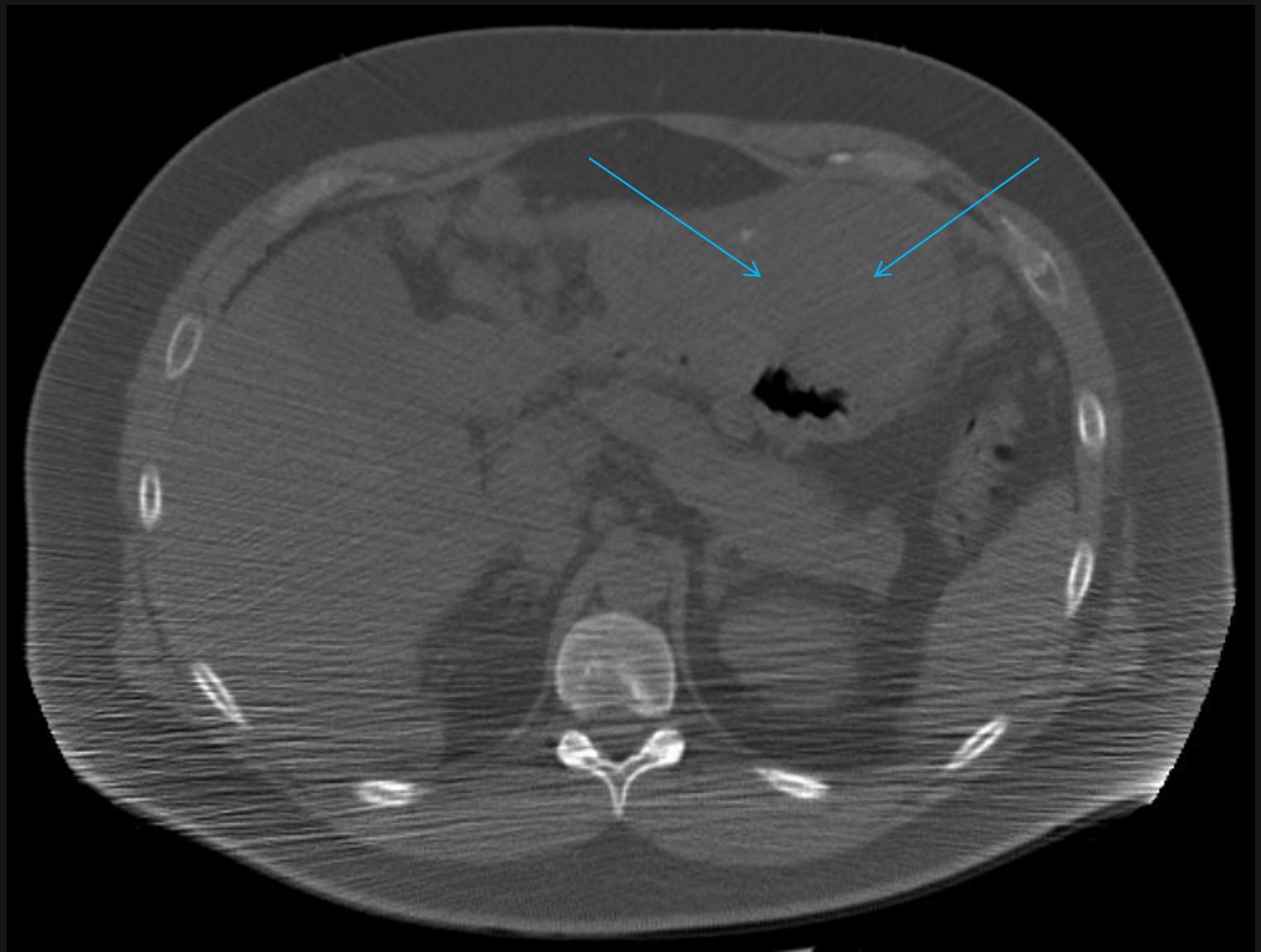
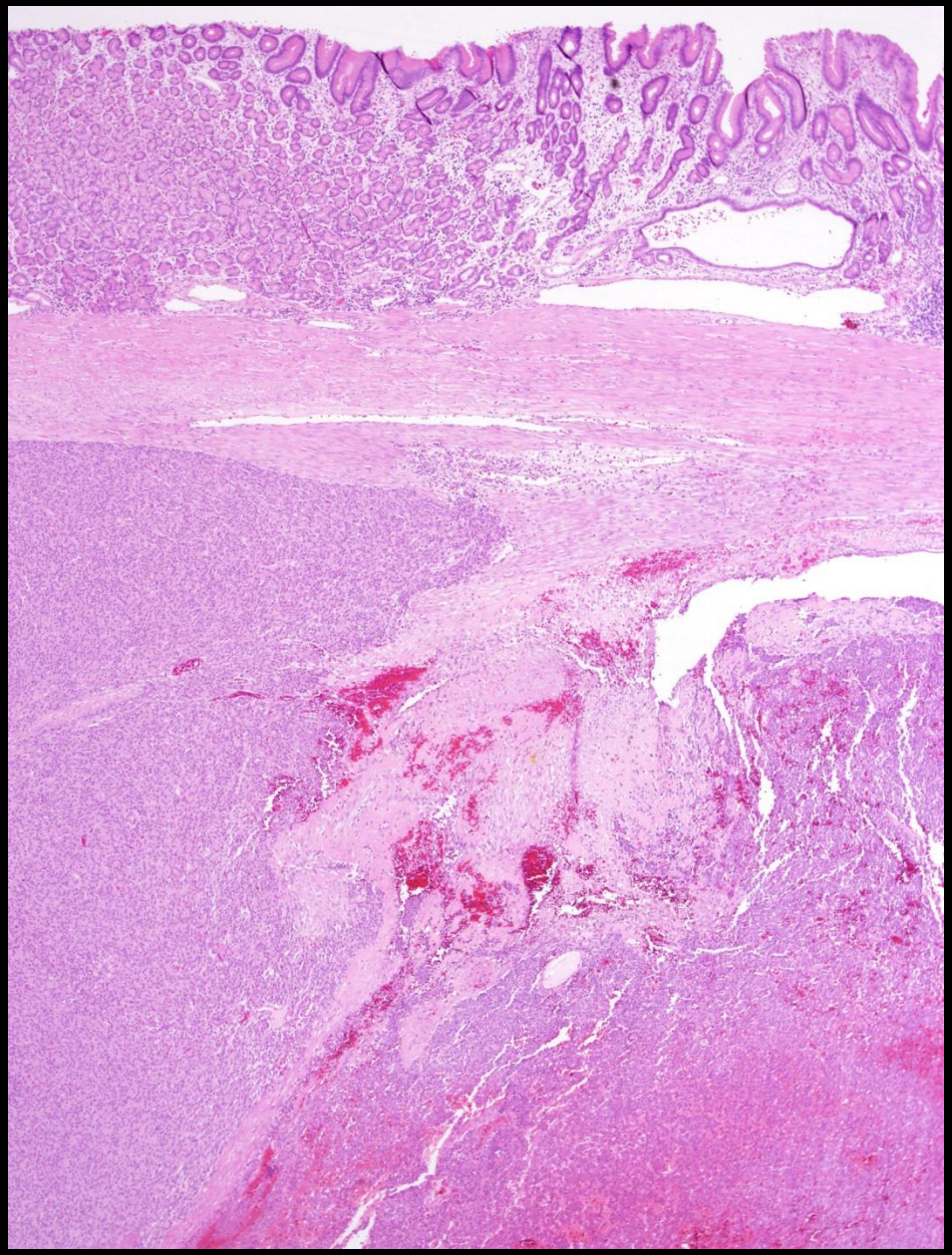
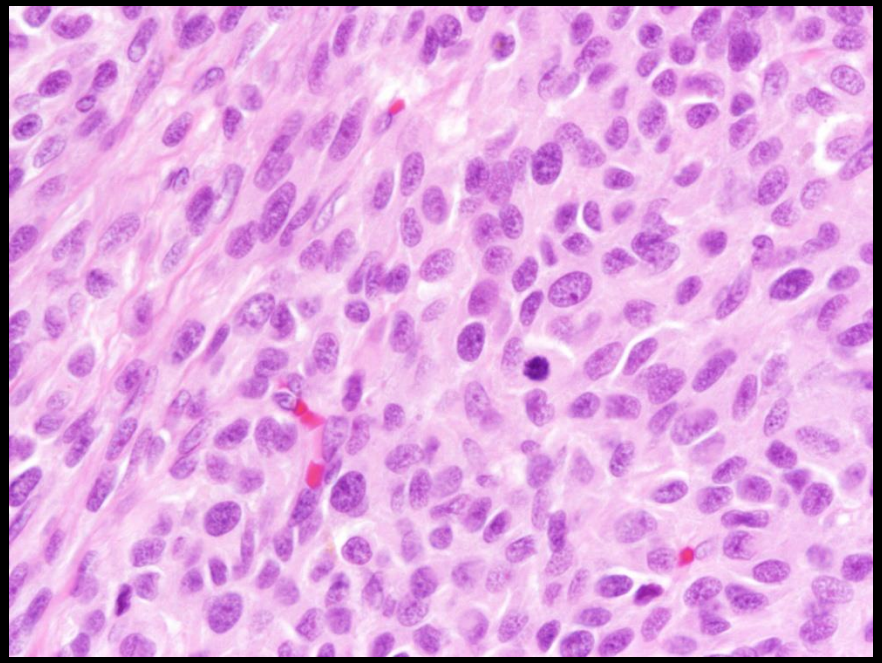
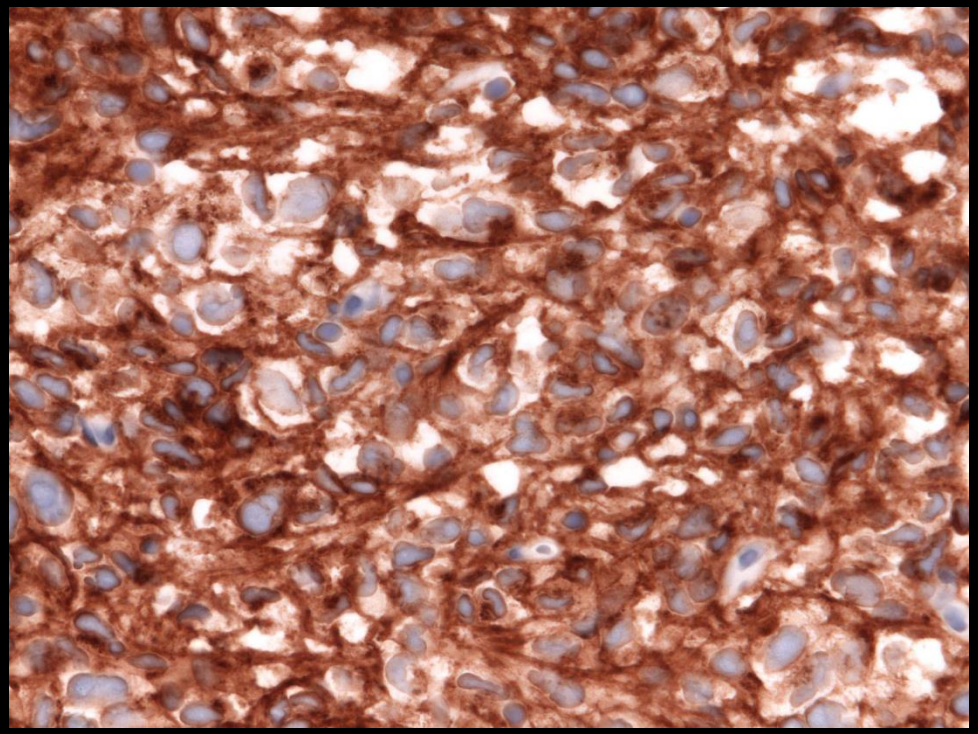
A 43 year old male presents with abdominal complaints. An axial CT reveals ….







Diagnosis: Gastrointestinal Stromal Tumor



C-kit

Location: stomach

Size: 12 cm

Mitotic count: 10 mitoses / 50 high power fields

Risk Assessment: High risk of aggressive behavior

Definitions

Mutation

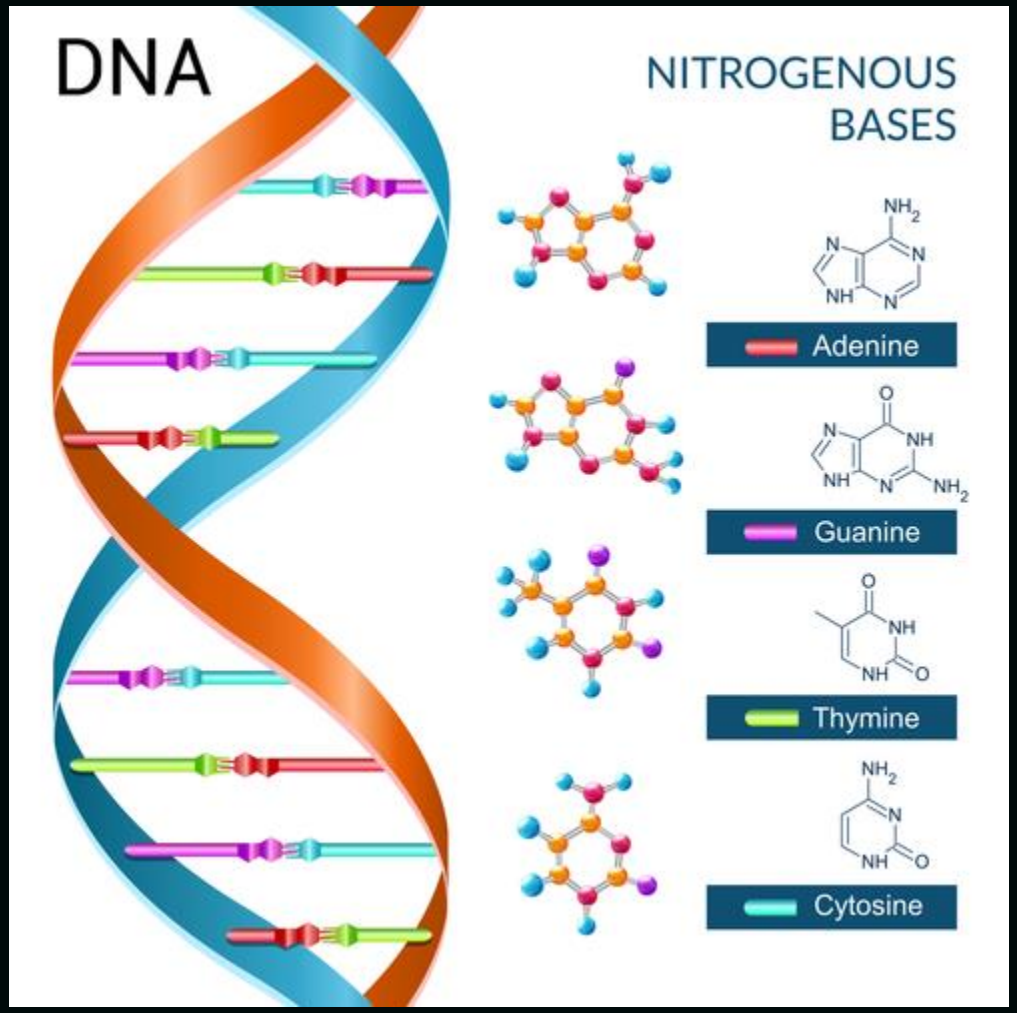
Any change in the DNA of a cell

Next Generation Sequencing

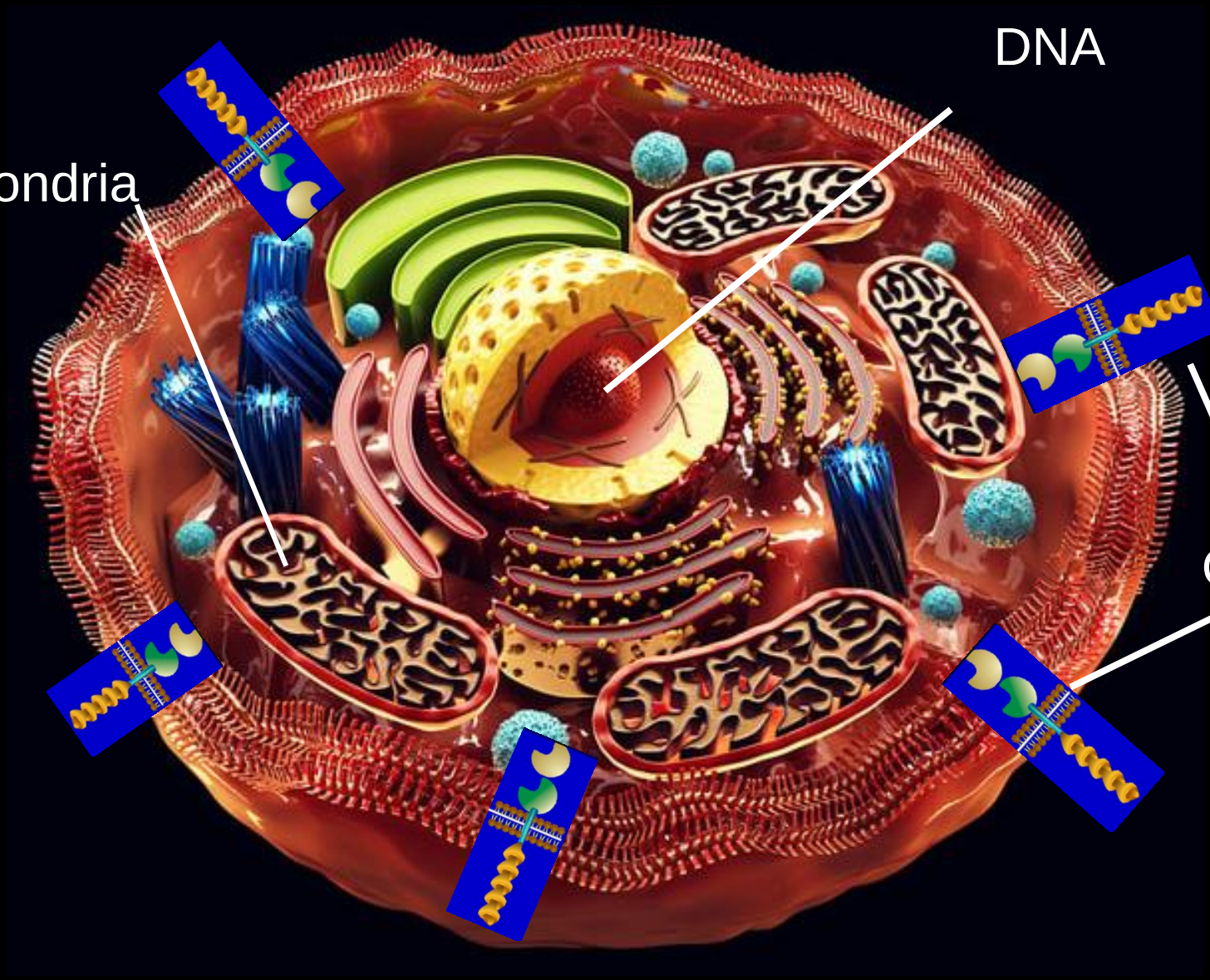
A technology that rapidly determines the sequence of molecules that compose DNA

Genetic Code

3 billion base pairs in each human cell
Organized into 23 pairs of chromosomes
15-70 trillion cells in human body
1 billion cells in a 1cm GIST



Human Cell

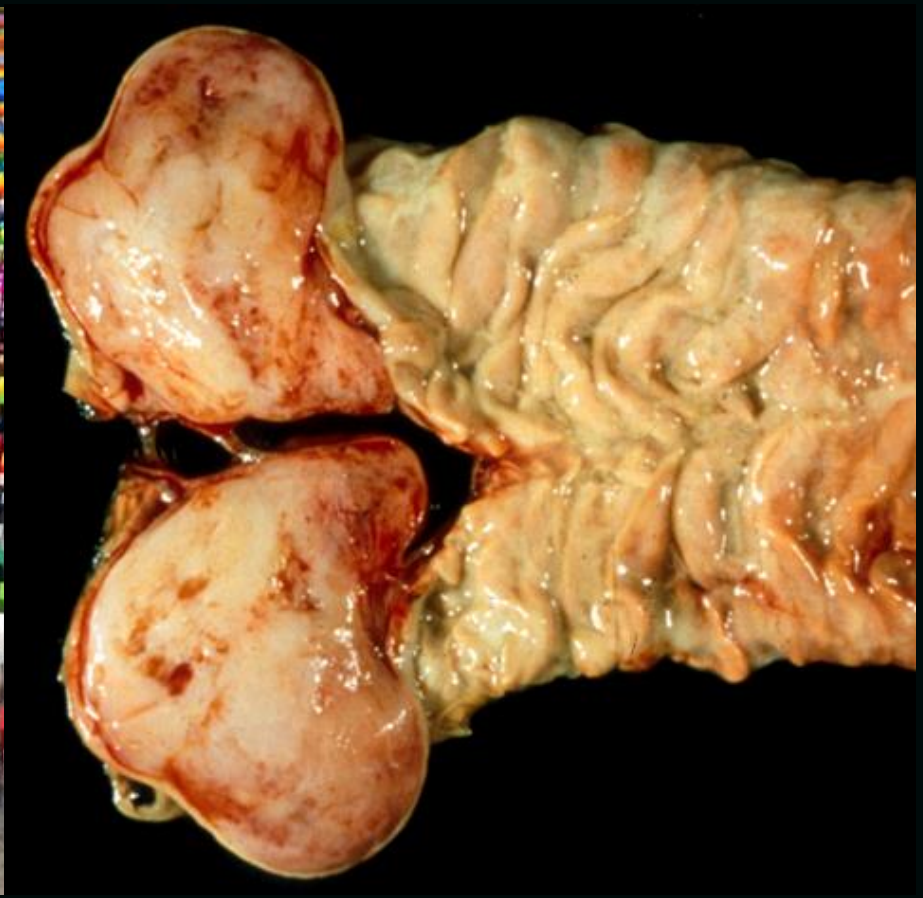


Mutations

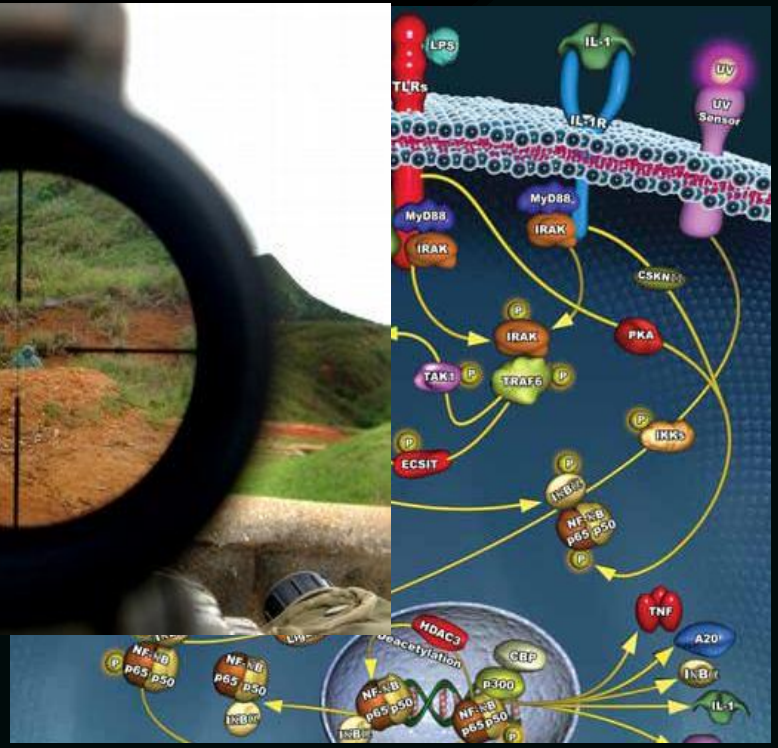
Deletion

Substitution

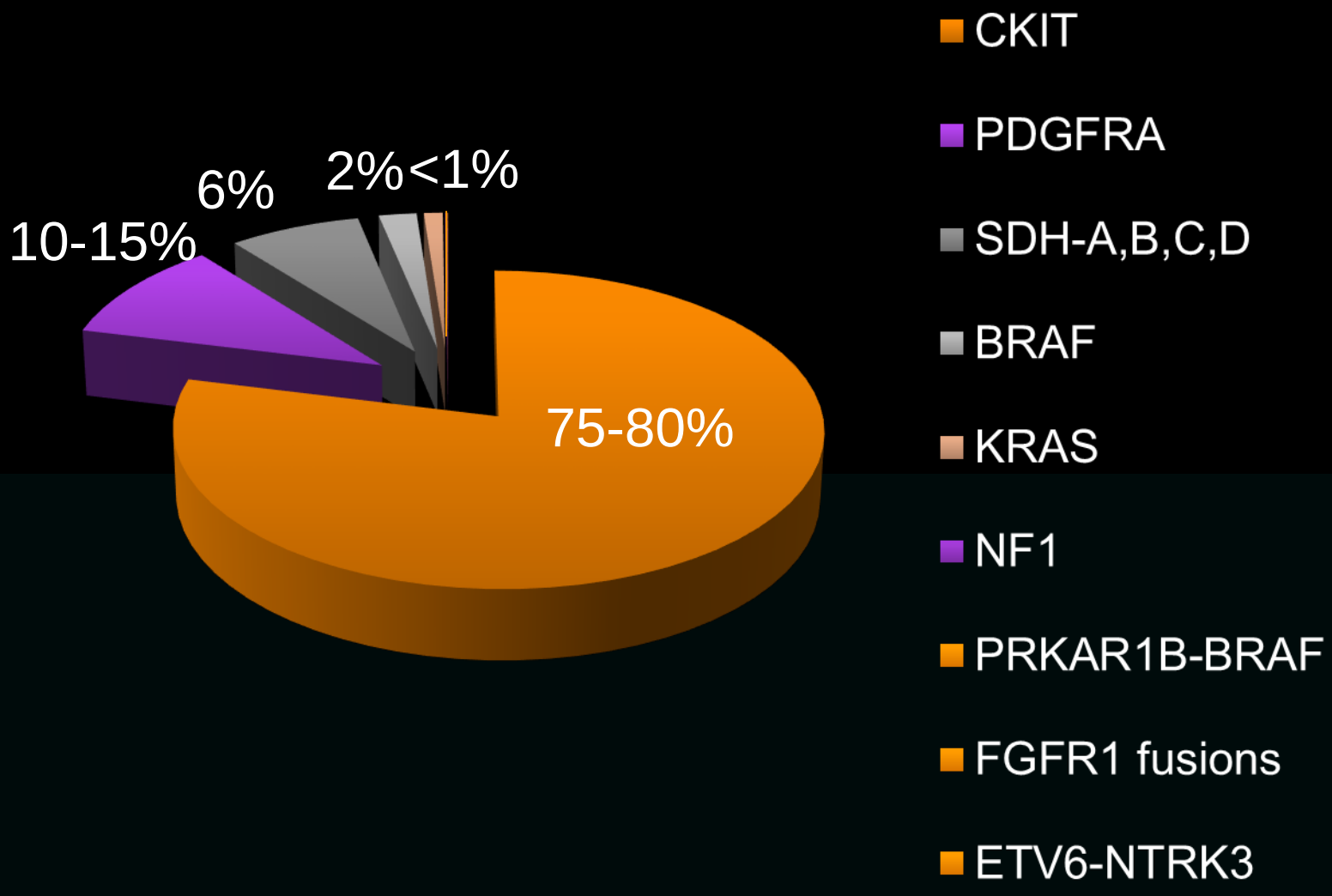
Mutations



Mutations


LPS
IL-1
TLRs
UV
UV Sensor
IL-1R
MyD88
IRAK
MyD88
IRAK
CSKN
IRAK
PKA
TAK1
TRAF6
IKKs
ECSIT
NF-κB p65 p50
TNF
HDAC3
Deacetylation
CBP
P300
A20
IL-1

Mutations in GIST

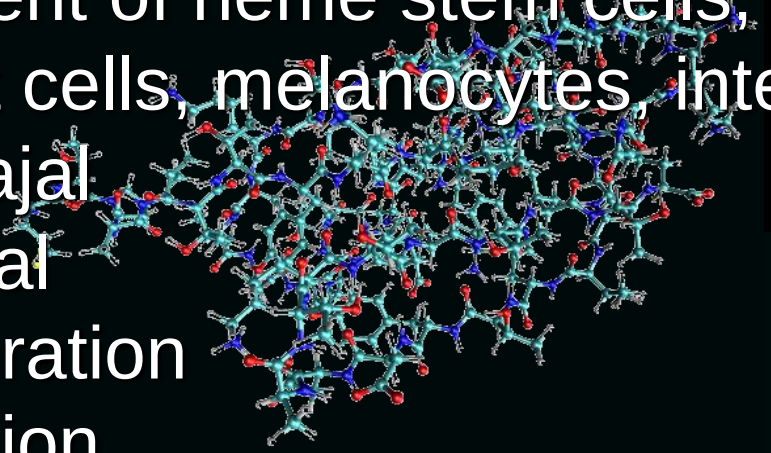


C-KIT

Protein – cell surface receptor - tyrosine kinase

Chromosome 4

Development of heme stem cells, germ cells, mast cells, melanocytes, interstitial cells of Cajal



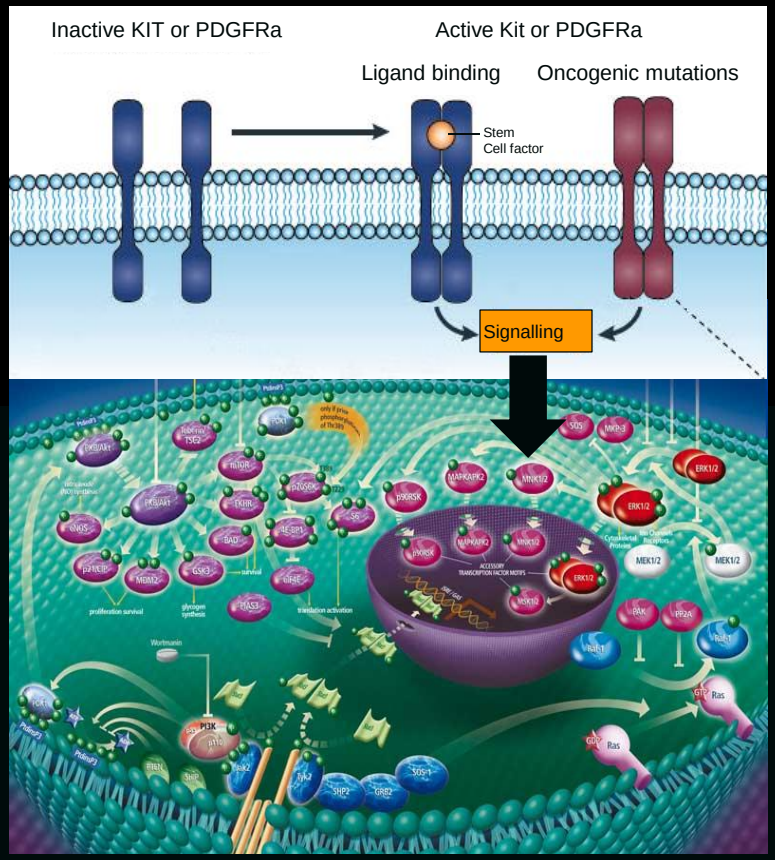
Cell survival

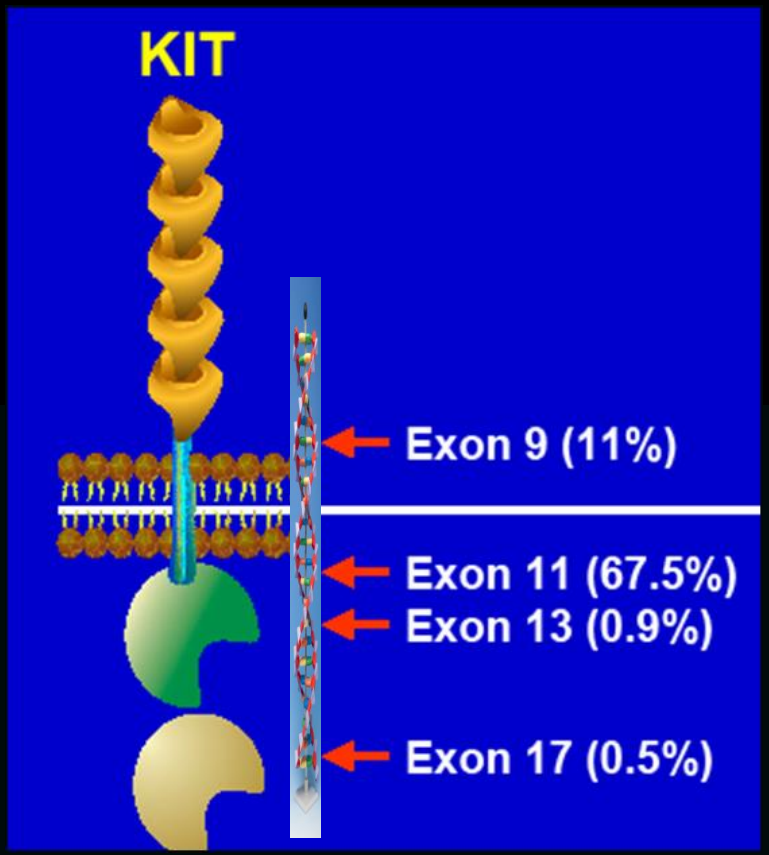
Cell proliferation

Cell adhesion

Cell differentiation and maturation

Gastrointestinal Stromal Tumors





Gastrointestinal Stromal Tumors

Kit mutations - worse prognosis than PDGFRa mutations

- deletions in exon 11 most aggressive
- exon 9 mutations associated with intestinal location and more aggressive course

PDGFRa exon 14 and 18 mutations - gastric origin, epithelioid morphology and favorable outcome

C-Kit and PDGFRa Negative GIST

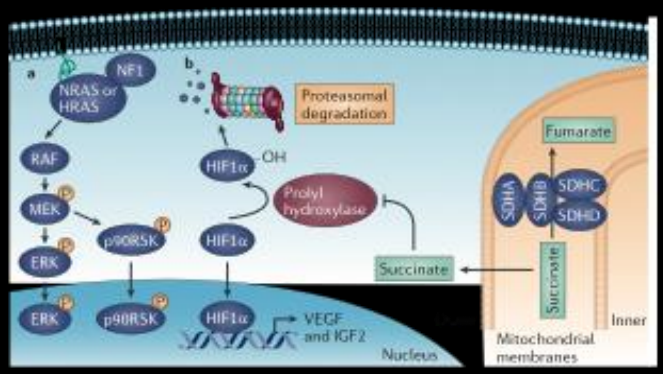
Account for 12% of GIST

epithelioid/stomach

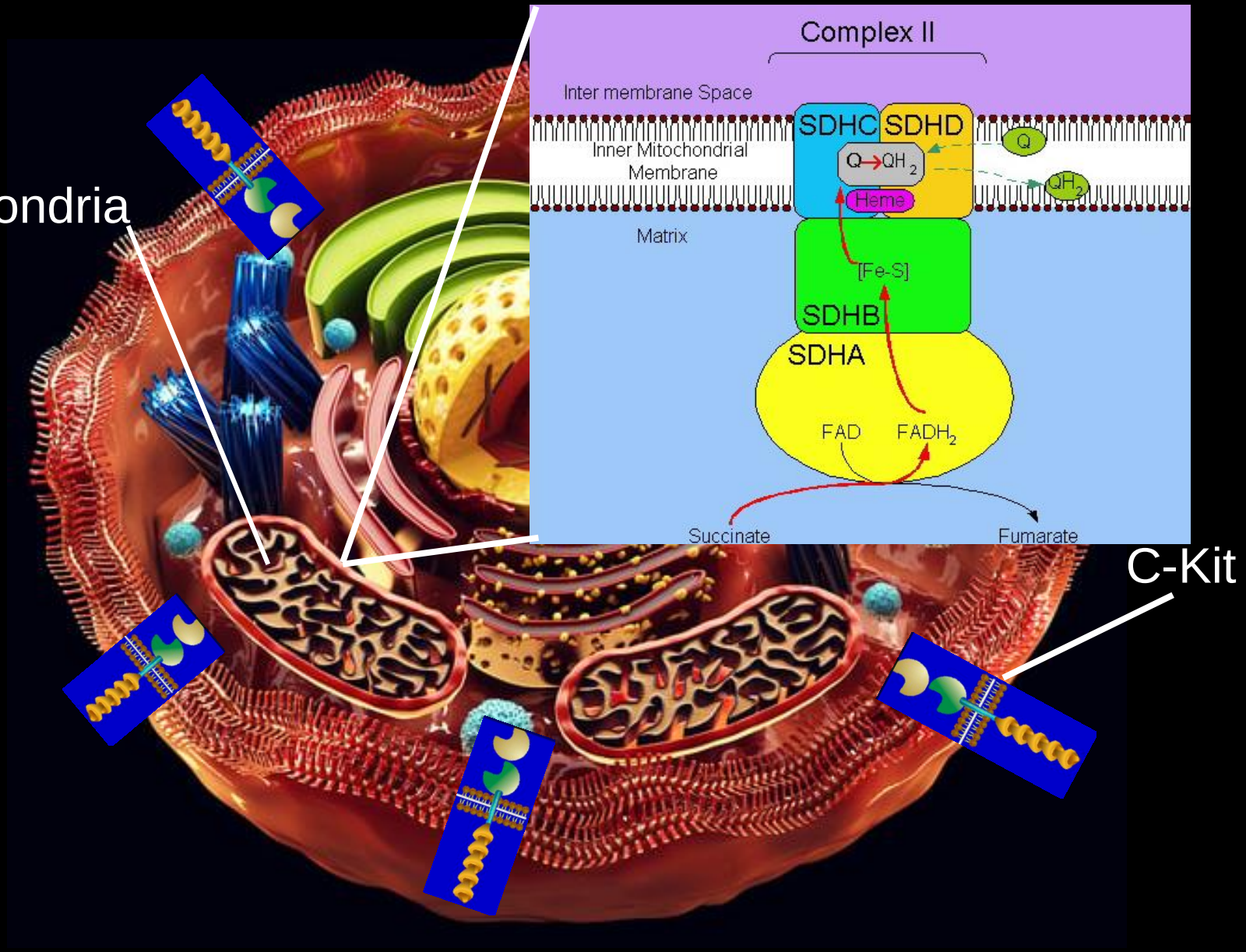
BRAF
NRAS
KRAS
ETV6-NTRK3
FGFR1 fusions

NF1

loss of function mutation
– succinate dehydrogenase &
IGFR amplification



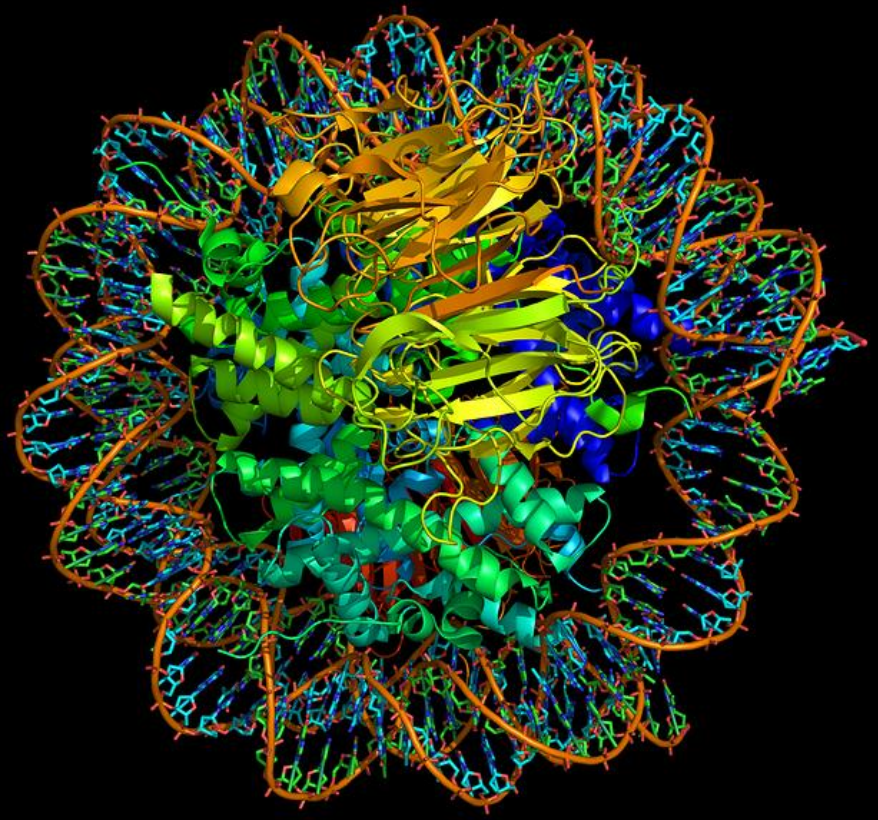
Human Cell


Mitochondria
Complex II
Inter membrane Space
SDHC
SDHD
Q
Q→QH2
Inner Mitochondrial Membrane
QH2
Heme
Matrix
[Fe-S]
SDHB
SDHA
FAD
FADH2
Succinate
Fumarate
C-Kit

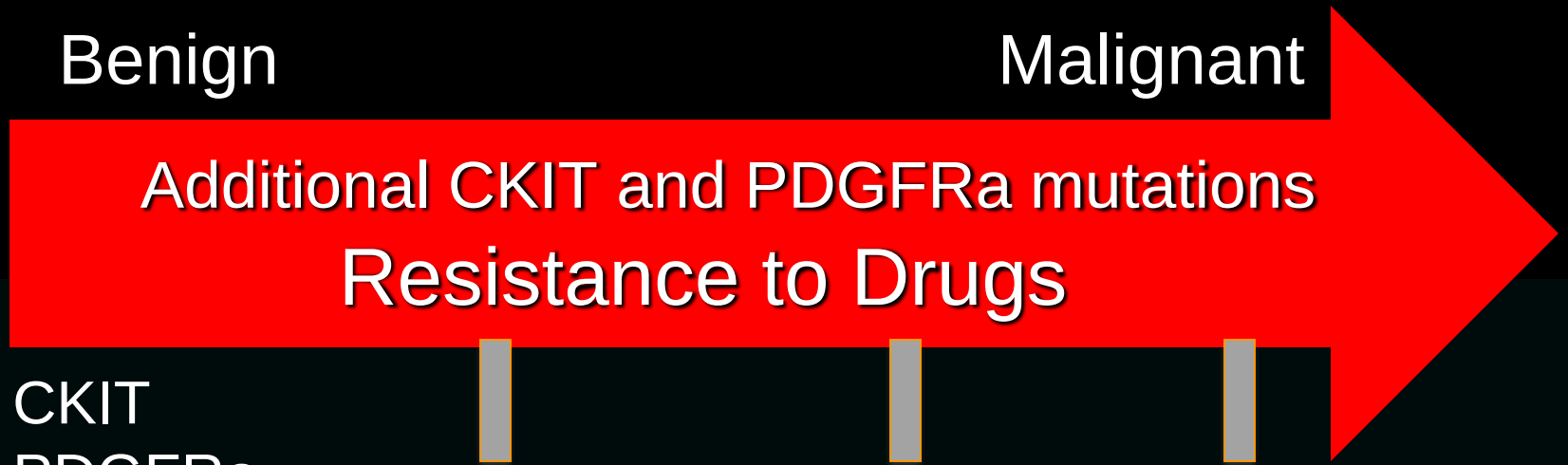
Succinate Dehydrogenase Deficient GIST

- Most frequent wild type *KIT/PDGFRA*- GIST
- Mutation results in buildup of succinate
- Leads to aberrant DNA methylation and dysfunction
- Component of Carney Stratakis syndrome (gastric GIST and paraganglioma) and Carney triad (gastric GIST,paraganglioma, pulmonary chondroma)
- Affects young females (<20yrs), multiple, plexiform architecture, high rate of metastases, long survival
- Not responsive to tyrosine kinase inhibitors

Succinate Dehydrogenase Deficient GIST - Epimutant



Progression of Molecular Aberrations in GIST

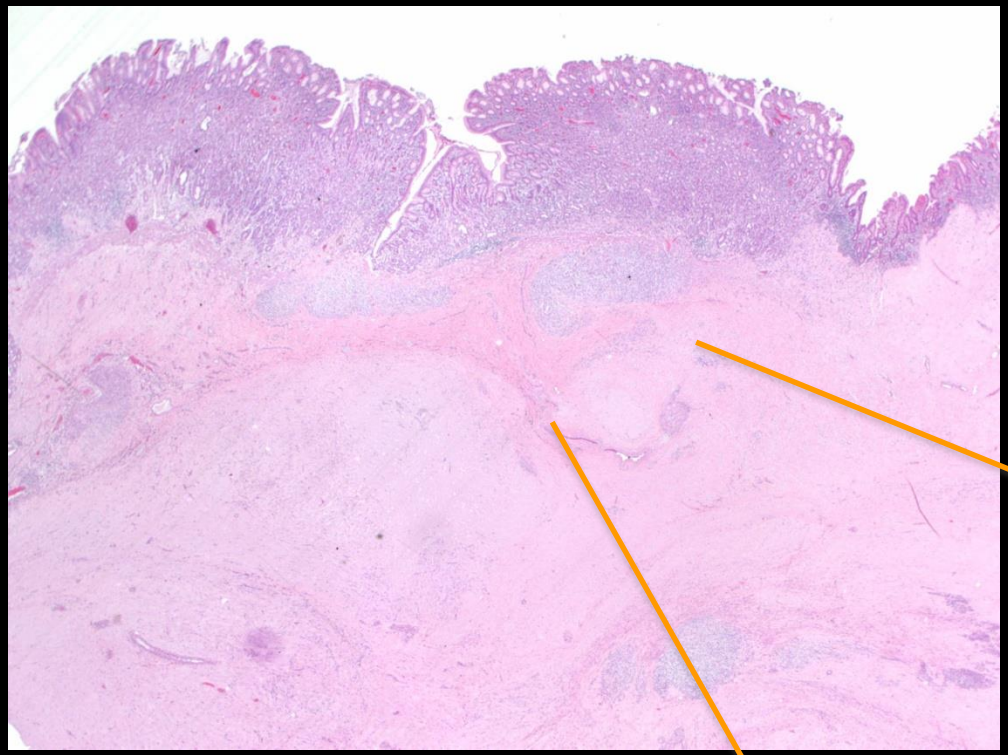


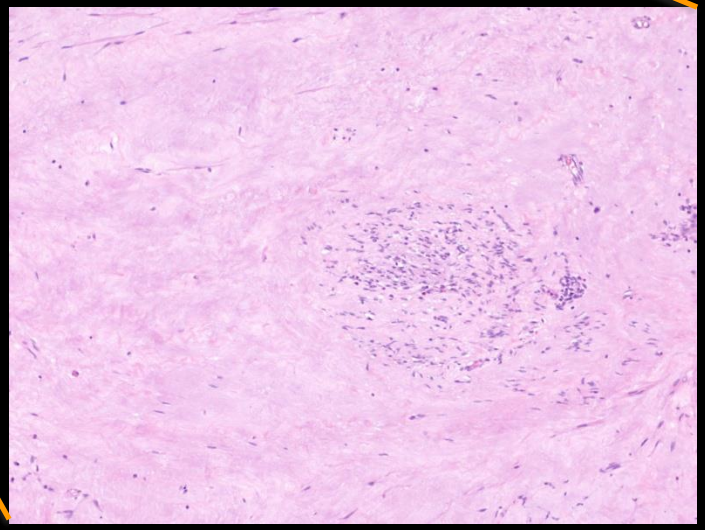
Mutational Analysis in Gastrointestinal Stromal Tumor

All tumors that are intermediate or high risk should be tested

Mutation identification provides information

- prognosis
- responsiveness to tyrosine kinase inhibitors
- genetic transformation over time
- tumors associated with syndromes
- targets for therapy





GIST – Treatment Effect