THE MOLECULAR BIOLOGY OF GIST

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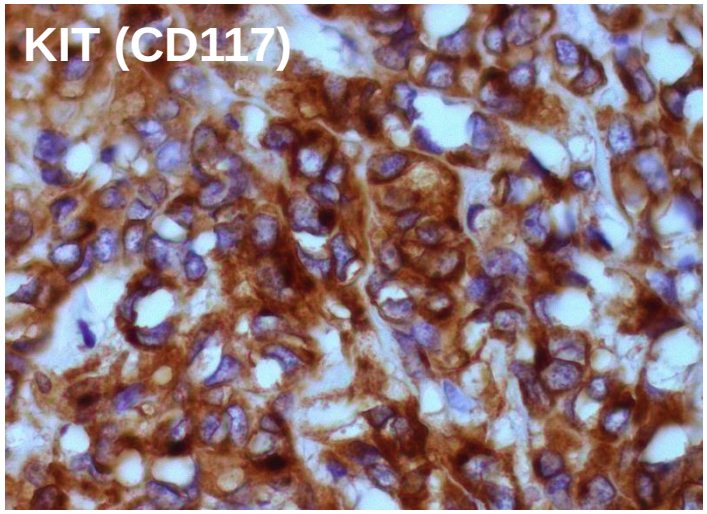
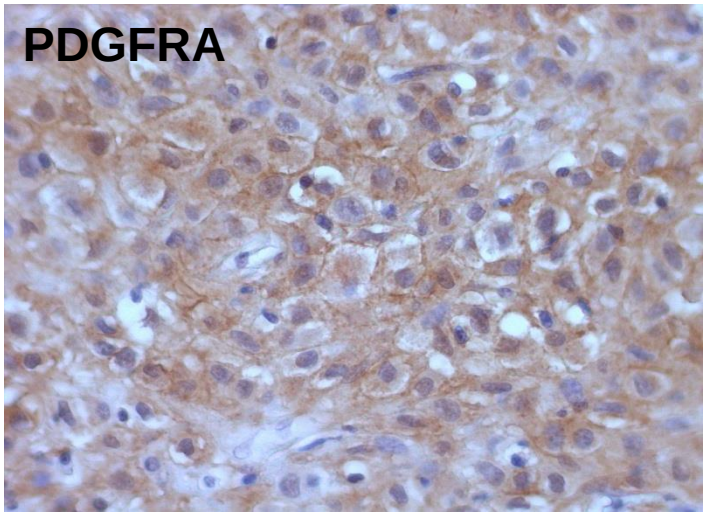
DISCLOSURE SLIDE

No conflict of interest to declear

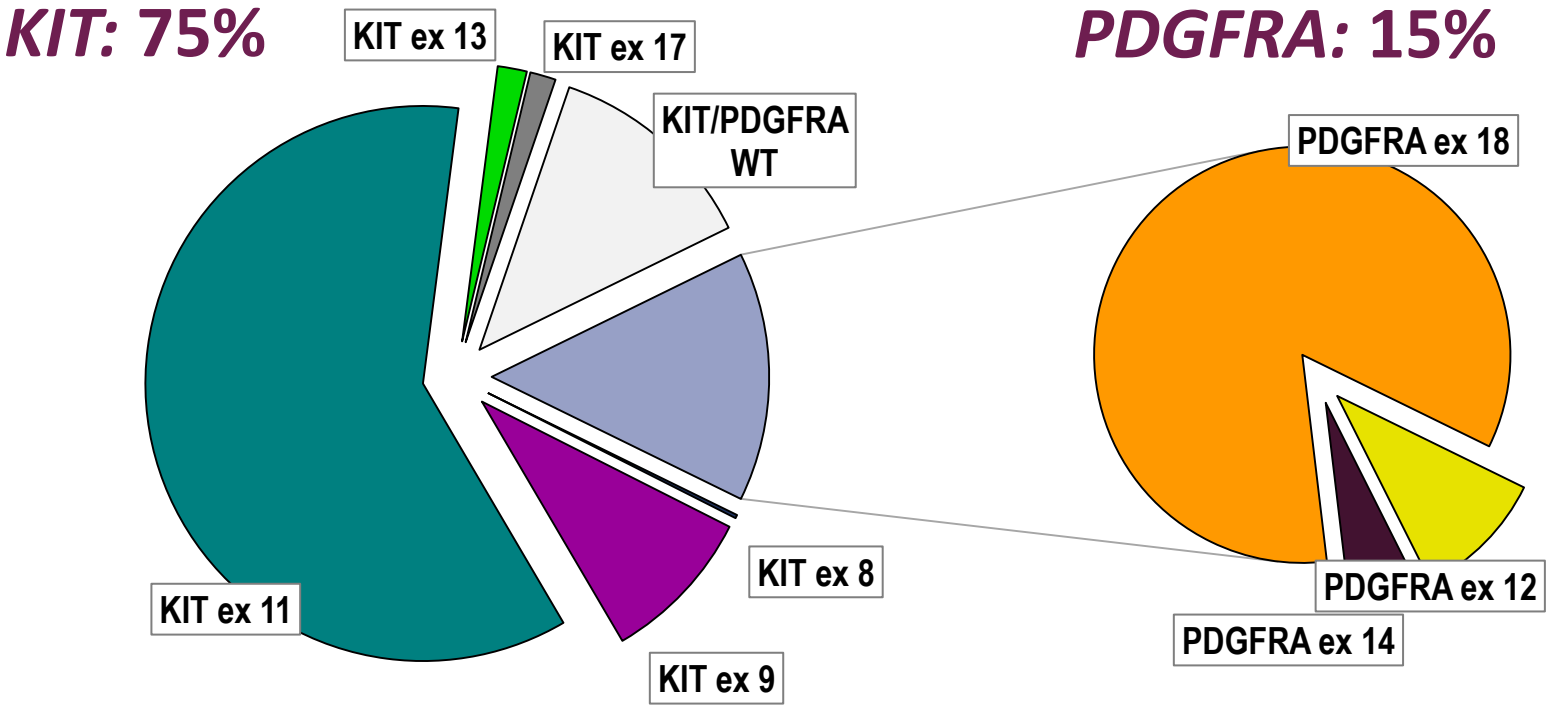
EXPRESSION OF KIT AND/OR PDGFRA IS CHARACTERISTIC FEATURE OF GIST





- diagnostic markers
- terapeutic targets

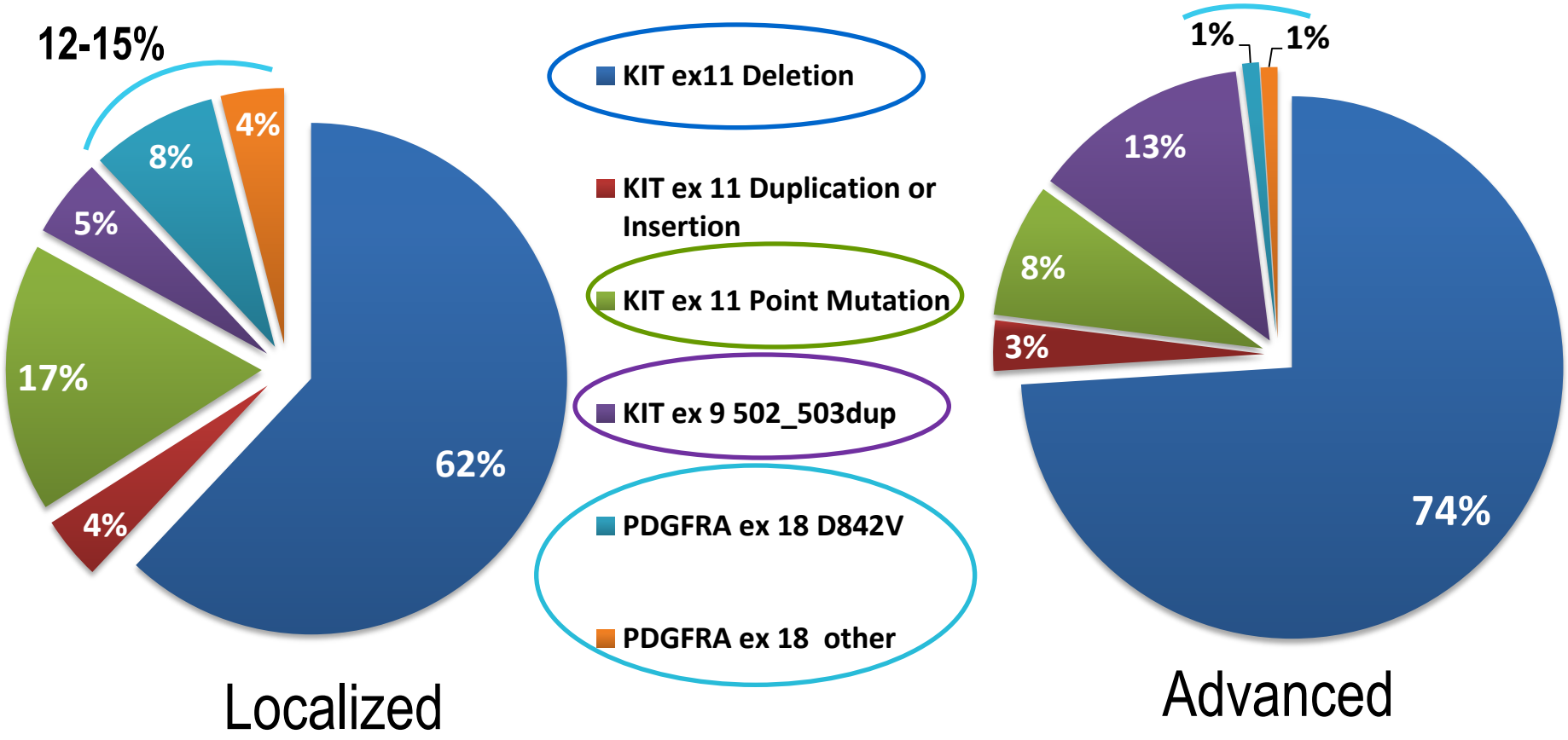
KIT AND *PDGFRA* MUTATIONS AS MAJOR DRIVERS IN GIST



85-90% of adult GISTs have gain-of-function mutations in either *KIT* or in *PDGFRA* genes

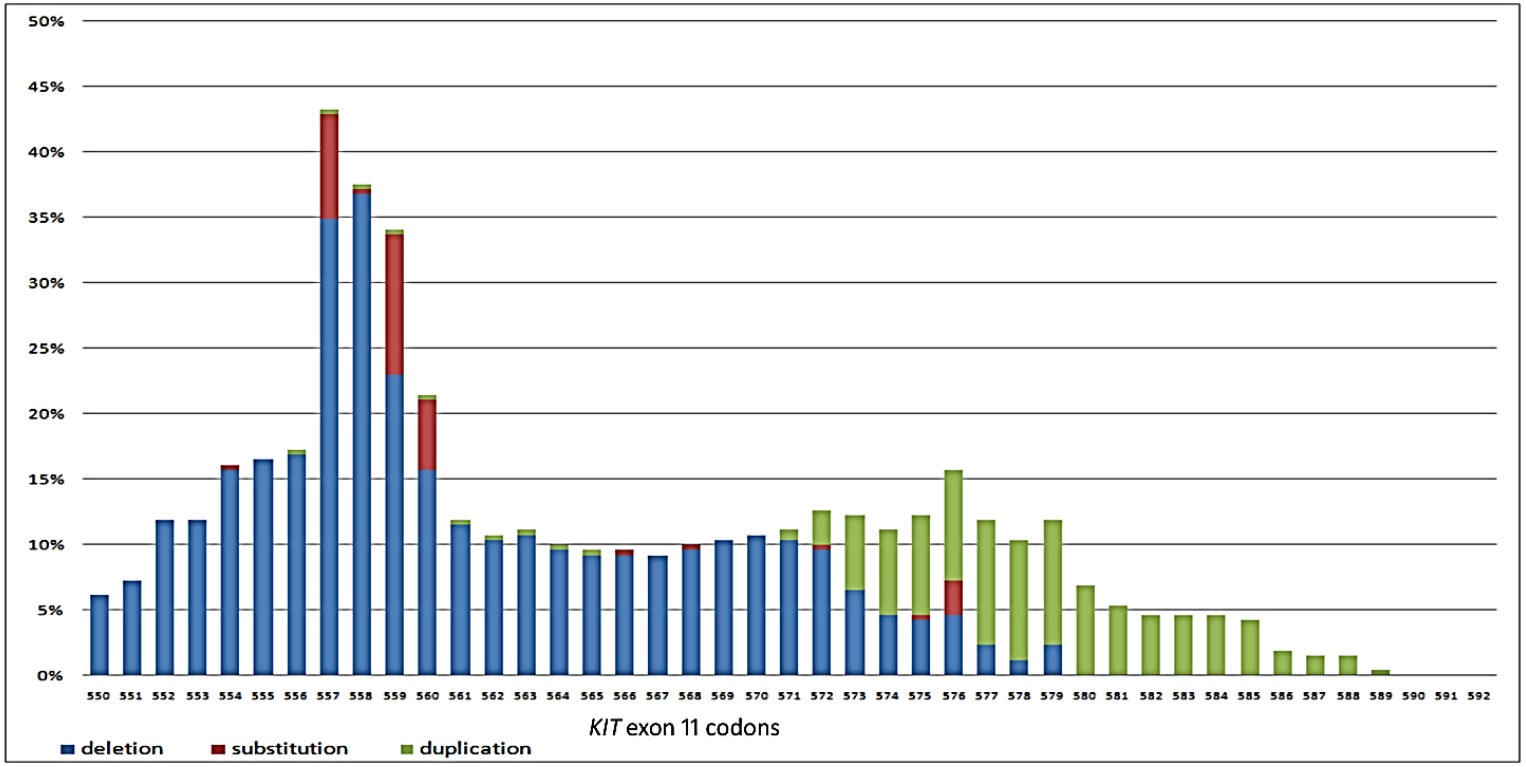
GIST Registry KU Leuven (n=1862)

MUTATION FREQUENCY IS DIFFERENT IN LOCALIZED THAN IN ADVANCED GIST



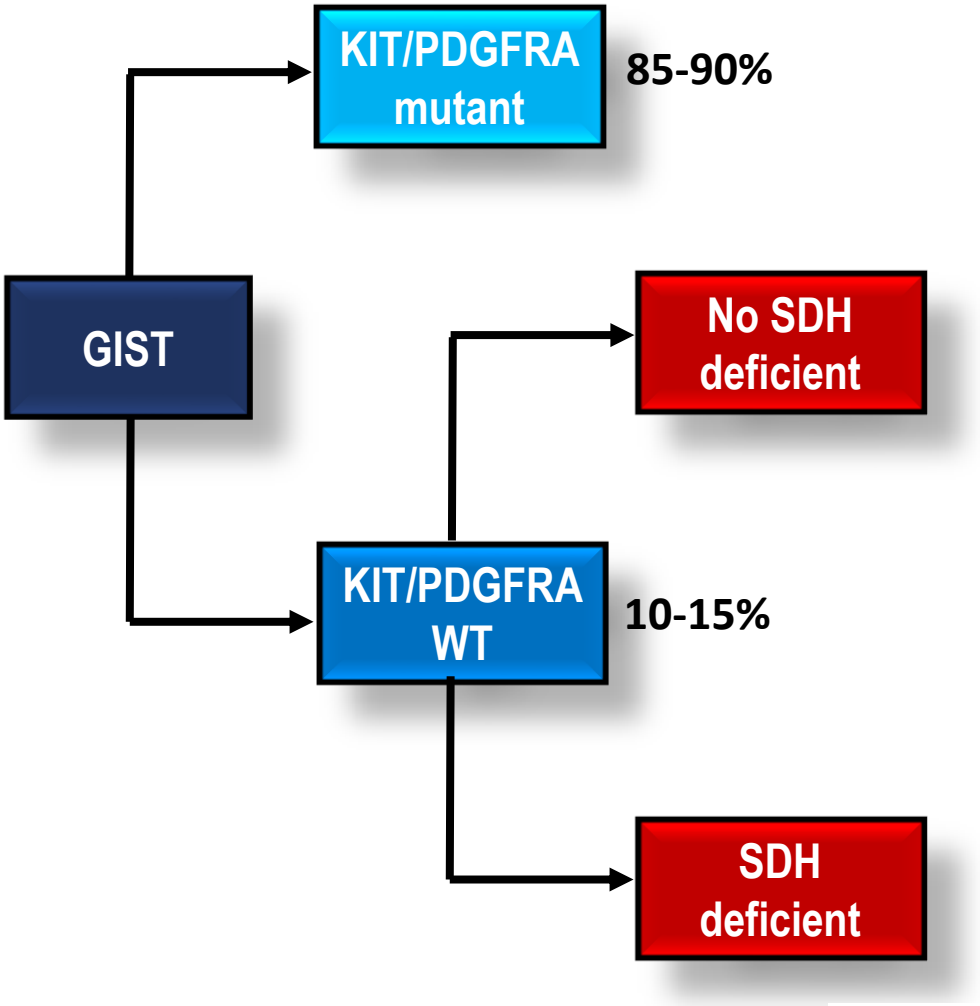
Wozniak et al. *Ann. Oncology*. 2012; 23:353
Emile et al. *Med Oncol.* 2012; 29:1765

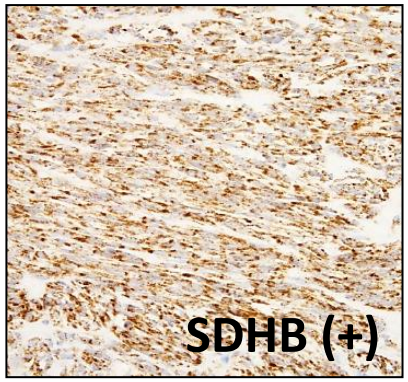
KIT EXON 11 CODONS AFFECTED BY DELETIONS, SUBSTITUTIONS AND DUPLICATIONS



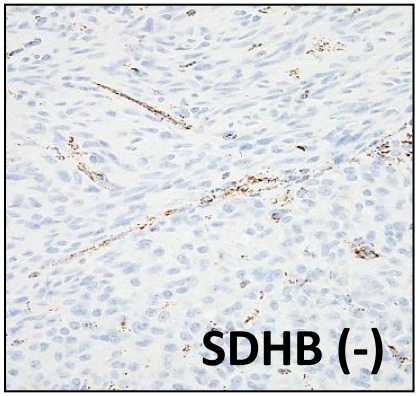
Wozniak et al. *Ann. Oncol*. 2012; 23:353

GIST IS MOLECULARLY HETEROGENOUS DISEASE





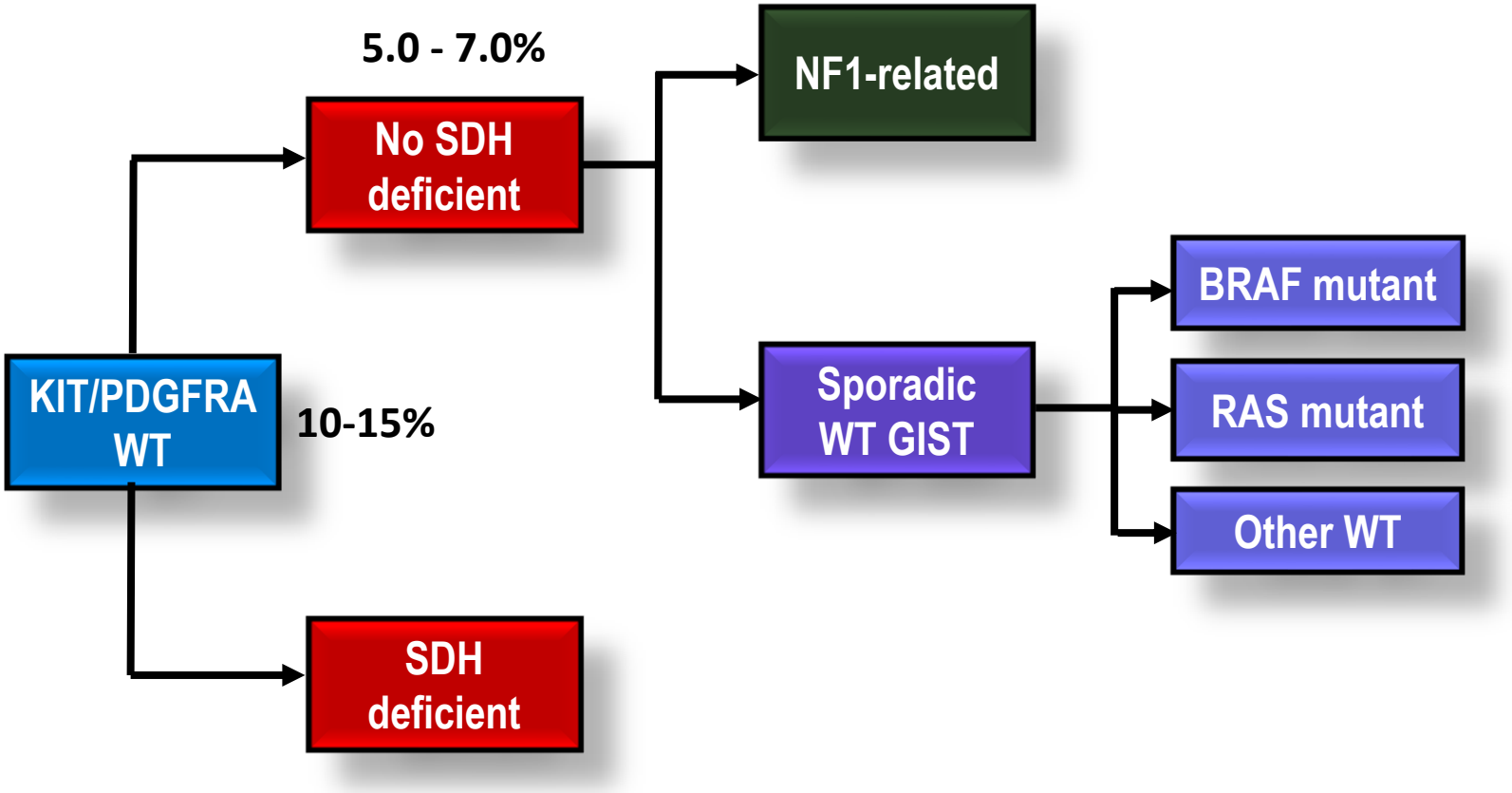
SDHB immunostaining



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

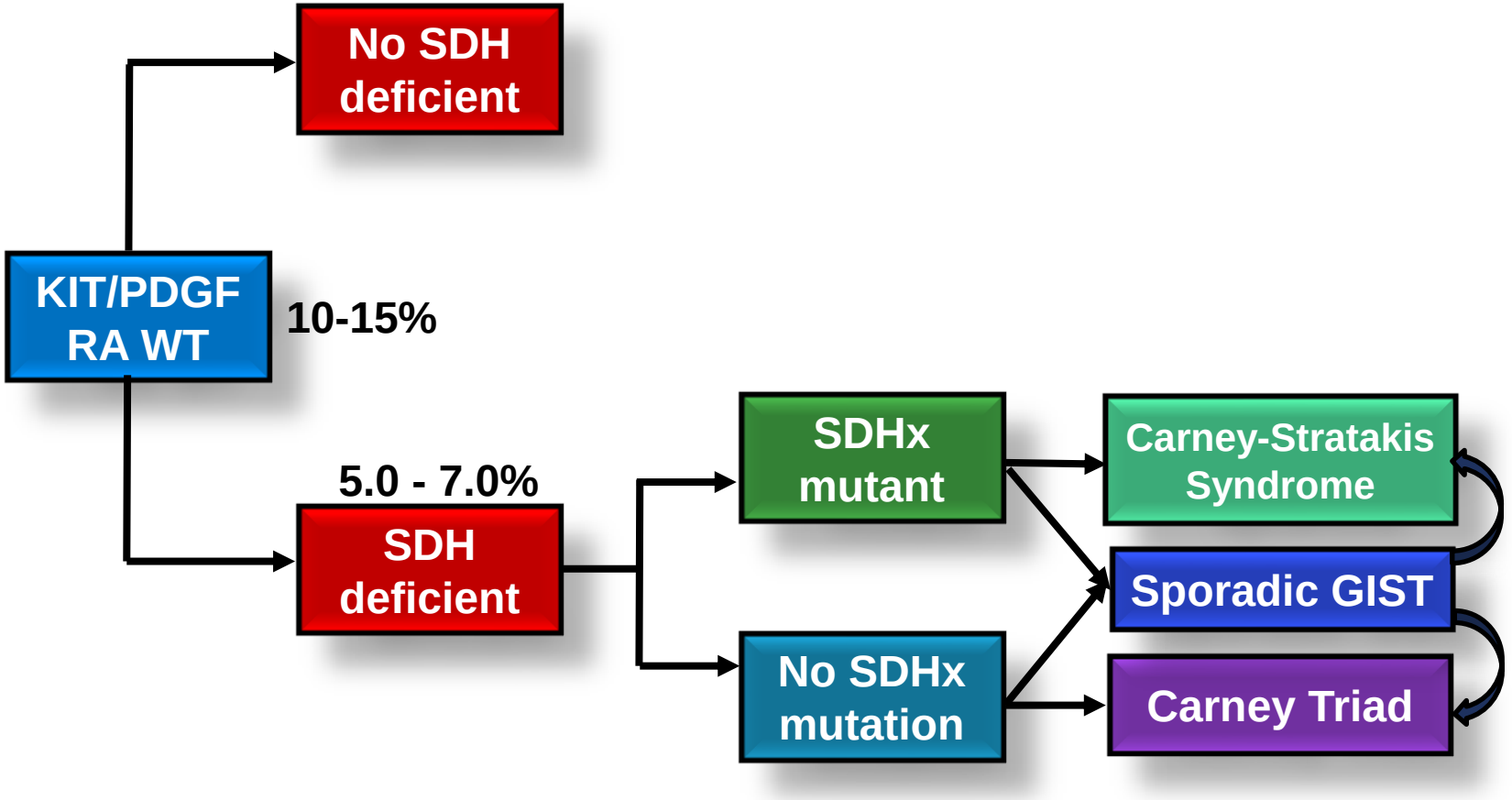
Boikos&Stratakis, *Endocrine* 2014; 47:401-408

SDHB-IMMUNOPOSITIVE GIST



Martens et al. *Human Mol Genet* 2006; 15:1015
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014

SDHB-IMMUNONEGATIVE GIST



Janeway et al. *PNAS* 2011; 108:314-318
Pantaleo et al. *Eur J Hum Genet*. 2014; 22:32-39
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014

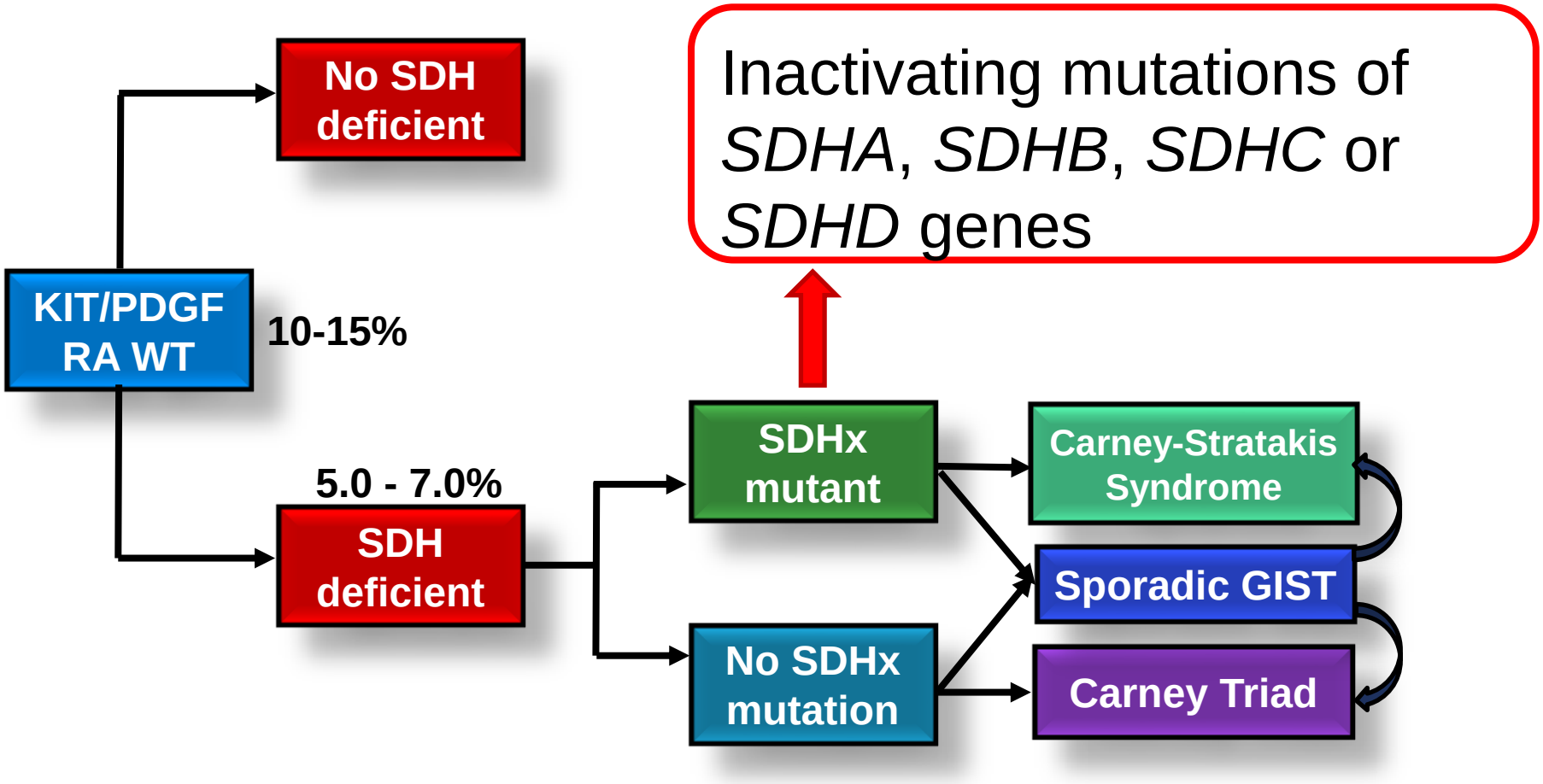
CARNEY-STRATAKIS SYNDROME (CARNEY DYAD)

- Hereditary condition, autosomal dominant inheritance pattern, incomplete penetrace
- Caused by germ-line inactivating mutations of *SDHB* (10%), *SDHC* (80%) or *SDHD* (10%) genes

  (the same mutations are found in paraganglioma hereditary syndrome)
- Multifocal, gastric GISTs, SDHB-immunonegative
- Imatinib treatment might be less effective than in sporadic *KIT*/*PDGFRA*-mutant GISTs

McWhinney et al. *NEJM* 2007; 357:1054-1056
Pasini et al. *Eur J Hum Genet*. 2008; 16:79-88
Janeway et al. *PNAS* 2011; 108:314-318

SDHB-IMMUNONEGATIVE GIST



Janeway et al. *PNAS* 2011; 108:314-318
Pantaleo et al. *Eur J Hum Genet*. 2014; 22:32-39
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014

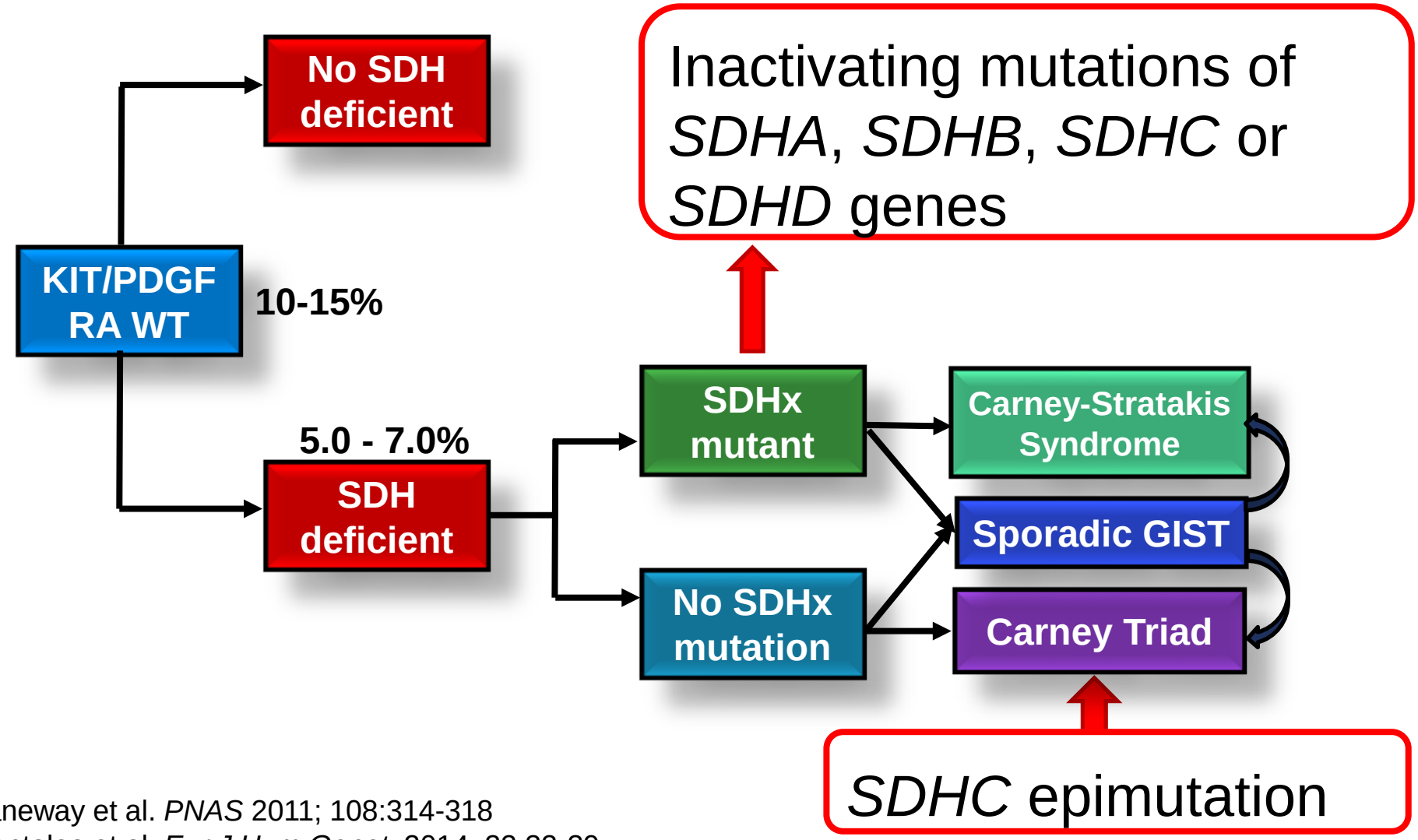
CARNEY TRIAD

- Non-familial association of different tumor types
  - Multifocal, gastric, epithelioid type of **GIST**, frequently CD117-immunonegative
  - **Pulmonary chondromas** (usually multiple)
  - **Paragangliomas**

  Only 20% all three components
  - Less frequently: pheochromocytomas, adrenal adenomas, esophageal leiomyoma
- Female predilection, young age at diagnosis
- Lymph node involvement
- Caused by primary/de novo **SDHC epimutation**
  - GIST by IHC: SDHB (-), SDHA (+)
- Imatinib less effective than for KIT/PDGRA-mutant GIST

Kim et al. Science Transl Med. 2014, 268ra177
Zhang et al. Am J Surg Pathol. 2010; 34:53-64
Matyakhina et al. J Clin Endocrinol Matab. 2007; 92:2938-43

SDHB-IMMUNONEGATIVE GIST



Janeway et al. *PNAS* 2011; 108:314-318
Pantaleo et al. *Eur J Hum Genet*. 2014; 22:32-39
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014

NON-SYNDROMIC SDH-DEFICIENT GIST

- Typically occur in children and young adults (85%), female predominance
- Multinodular or multiple, exclusively gastric tumors, common lymphovascular invasion, may remain clinicall stable after metastatic spread
- 50% have *SDH* gene mutation, often germ-line
  - Most commonly *SDHA* (30%)
    - SDHA-immunonegative, occur at an older age
- Hypermethylation of the SDHC promoter is an alternative mechanism
- Less sensitive to tyrosine kinase inhibition
- Overexpress IGF1R – possible target for the therapy

Janeway et al *PNAS* 2011; 108:314-318
Nannini et al. *J Med Genet*. 2013; 50:653-661.

WT GIST COUNSELING AND MUTATIONAL TESTING

- Patients may require referral for genetic counselling:
  - Patients with stigmata of NF-1 syndrome
  - Patients with paragangliomas
  - Patients without evidence of the Carney triad
- Underscores the need to perform mutation testing in GIST tumors

IS THE MUTATION SUBTYPE REVELANT IN GIST?

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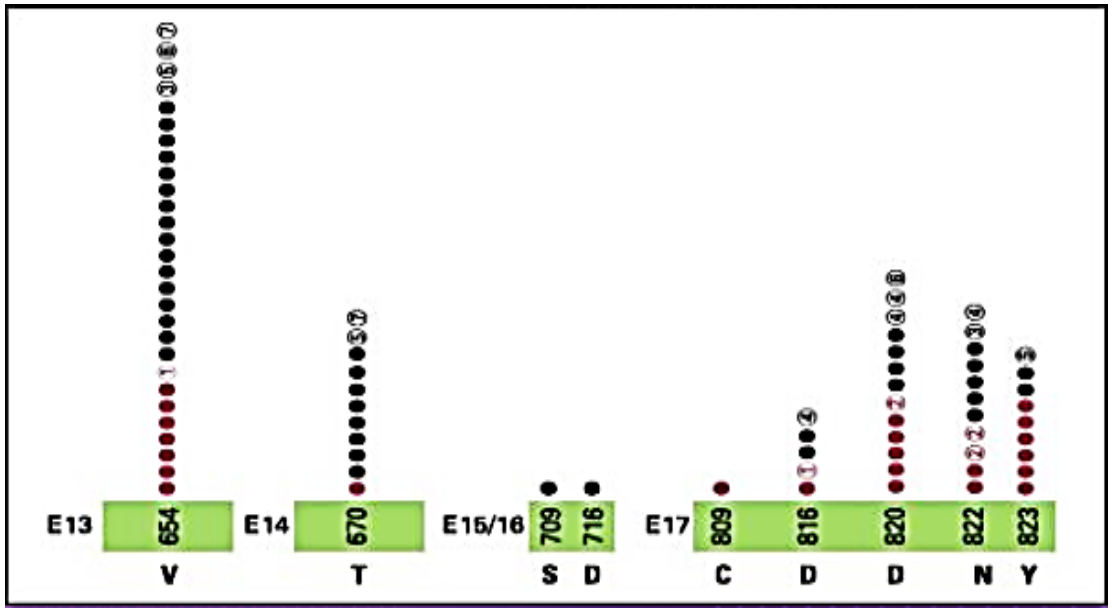
PREDICTION

of response to treatment with **imatinib**

- *KIT* exon 11 best response
- *KIT* exon 9 intermediate response
- GIST-*WT* less responsive
- *PDGFRA-D842V* exon 18 primarily resistant

SECONDARY REFRACTORY *KIT* MUTATIONS AS MECHANISM OF RESISTANCE

Distribution of Resistant Mutation



ATP binding domain

Activation loop domain

Frequency of Resistant Mutation

1º Mutation	2º Mutation
Exon 11	63%
Exon 9	17%
WT	0%

Inter- and intra-lesional heterogeneity

Debiec-Rychter et al. *Gastroenterology* 2005;128:270-9
Heinrich, et al. *J Clin Oncol*. 2008;26:5352-9
Liegl et al. *J Pathol*. 2008; 216:64-74

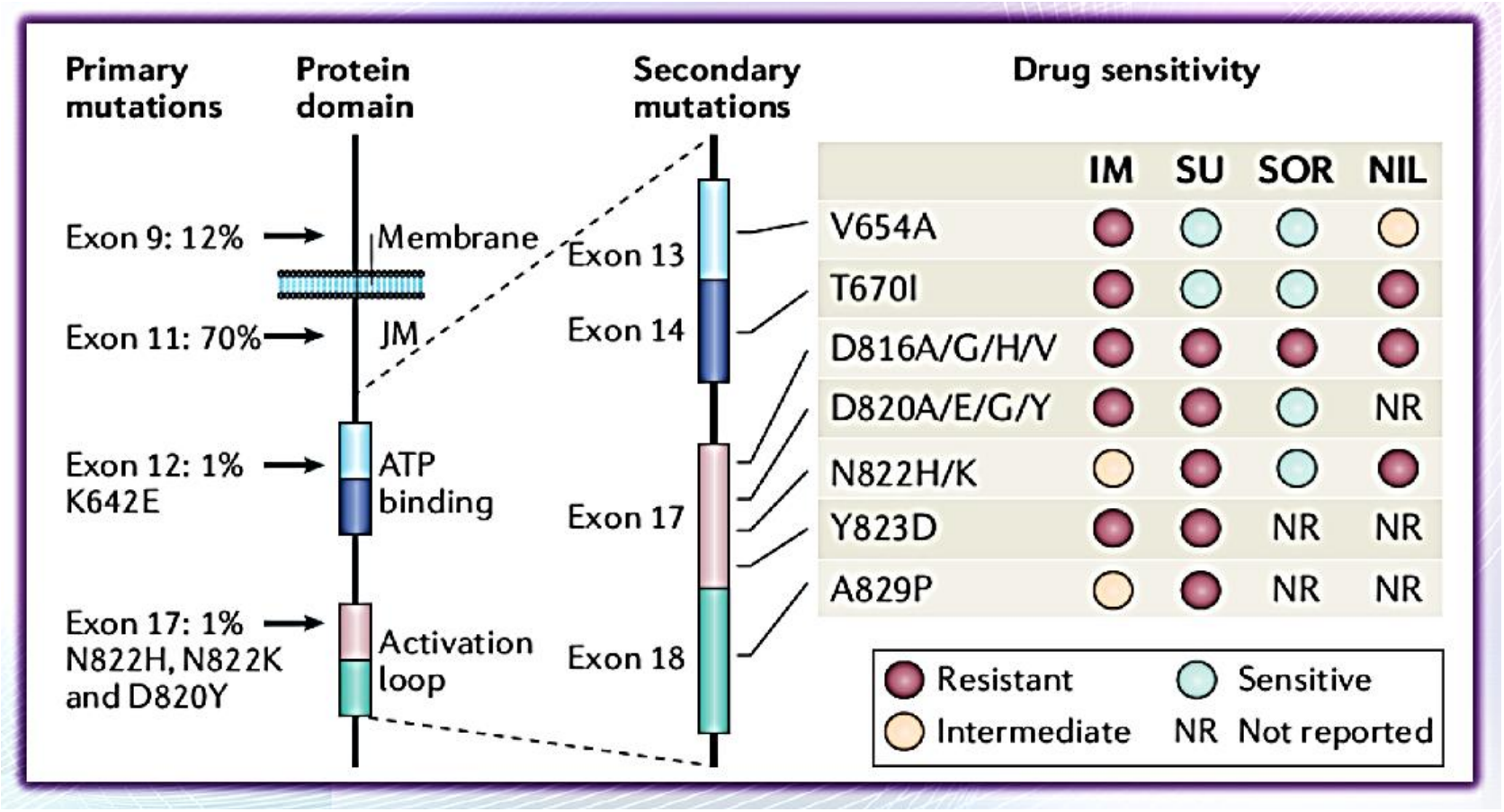
IS THE MUTATION SUBTYPE REVELANT IN GIST?

PREDICTION

of response to treatment with **Sunitinib**

- *KIT* exon 9 and GIST-*WT* best response
- *KIT* exon 11 intermediate response
- Secondary *KIT* exon 17 mutations as mechanism of resistance

SECONDARY RESPONSE IN ADVANCED DISEASE WITH *KIT* MUTATIONS



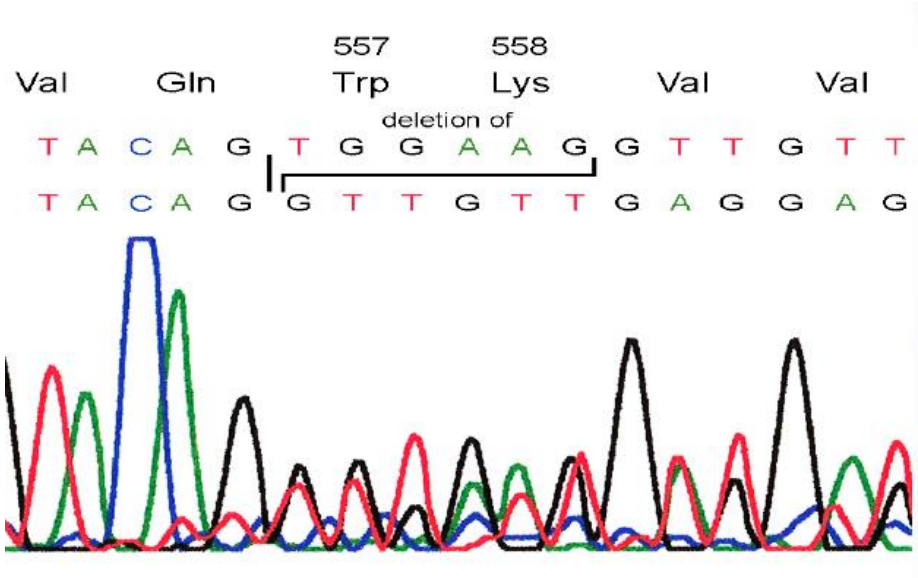
Corless CL, et al. *Nat Rev Cancer* 2011;11:865-78

IS THE MUTATION SUBTYPE REVELANT IN GIST?

PROGNOSIS

More aggressive subtypes

- **Codons 557-558 deletion in the *KIT* exon 11 (~20% of GIST)**



GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

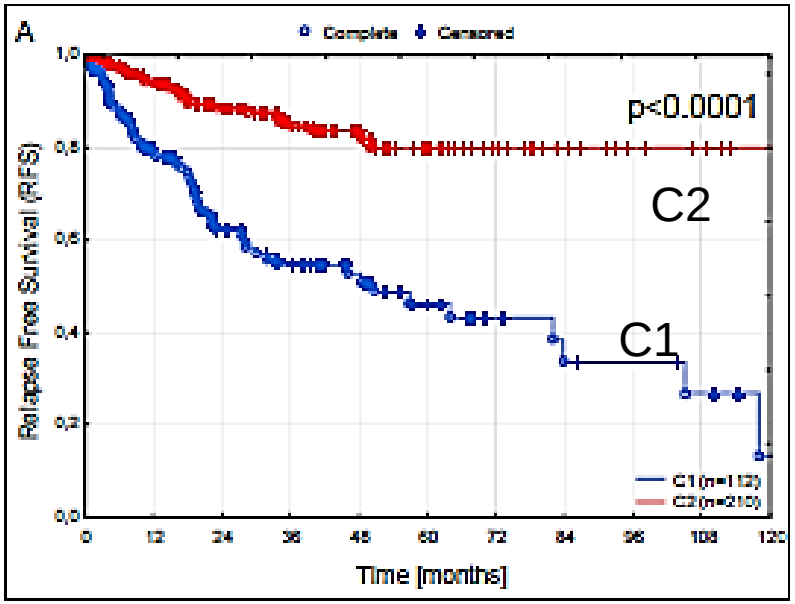
Wardelman at al. *Int J Cancer*, 2005
Martin at al. *J Clin Oncol.* 2008

IS THE MUTATION SUBTYPE REVELANT IN GIST?

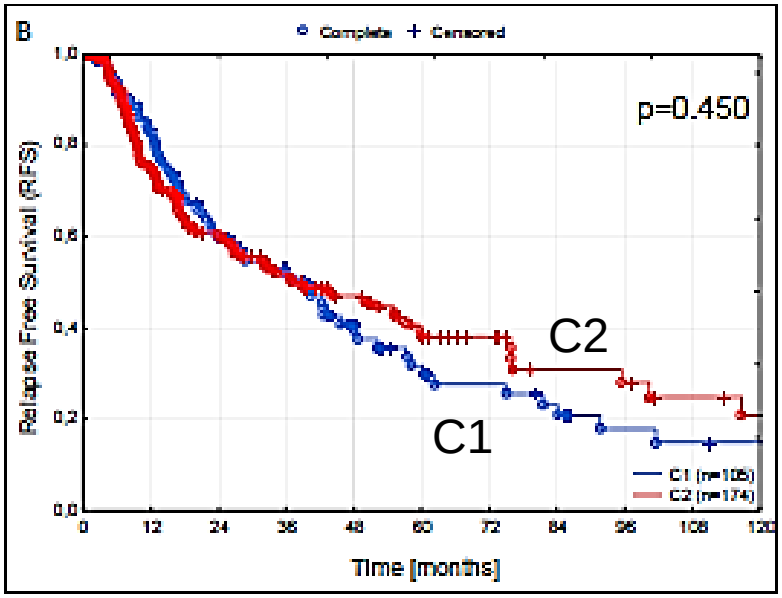
PROGNOSIS

- Codons 557-558 deletion in the *KIT* exon 11 is an independent prognostic factor in gastric GIST

Gastric



Non-gastric



Relapse free survival (RFS)

C1 - exon 11 *KIT* deletions inv. 557-558, **C2** - other *KIT* ex. 11 mutations

RENCE 2016

Wozniak et al. *Clin Cancer Res* 2014; 20:6105-16

IS THE MUTATION SUBTYPE REVELANT IN GIST?

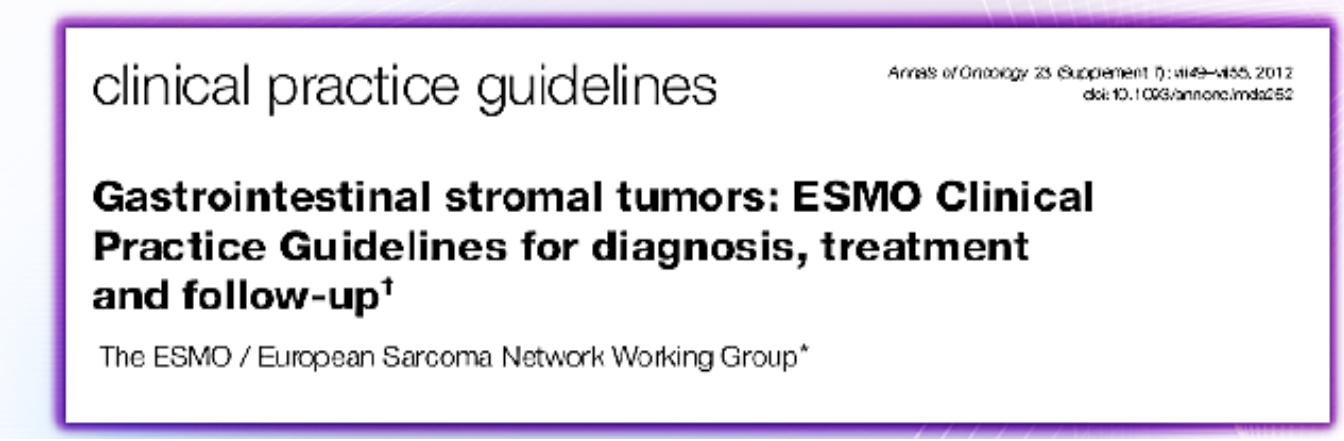
PROGNOSIS

More aggressive subtypes

- Codons 557-558 deletion in the *KIT* exon 11 in gastric GISTs

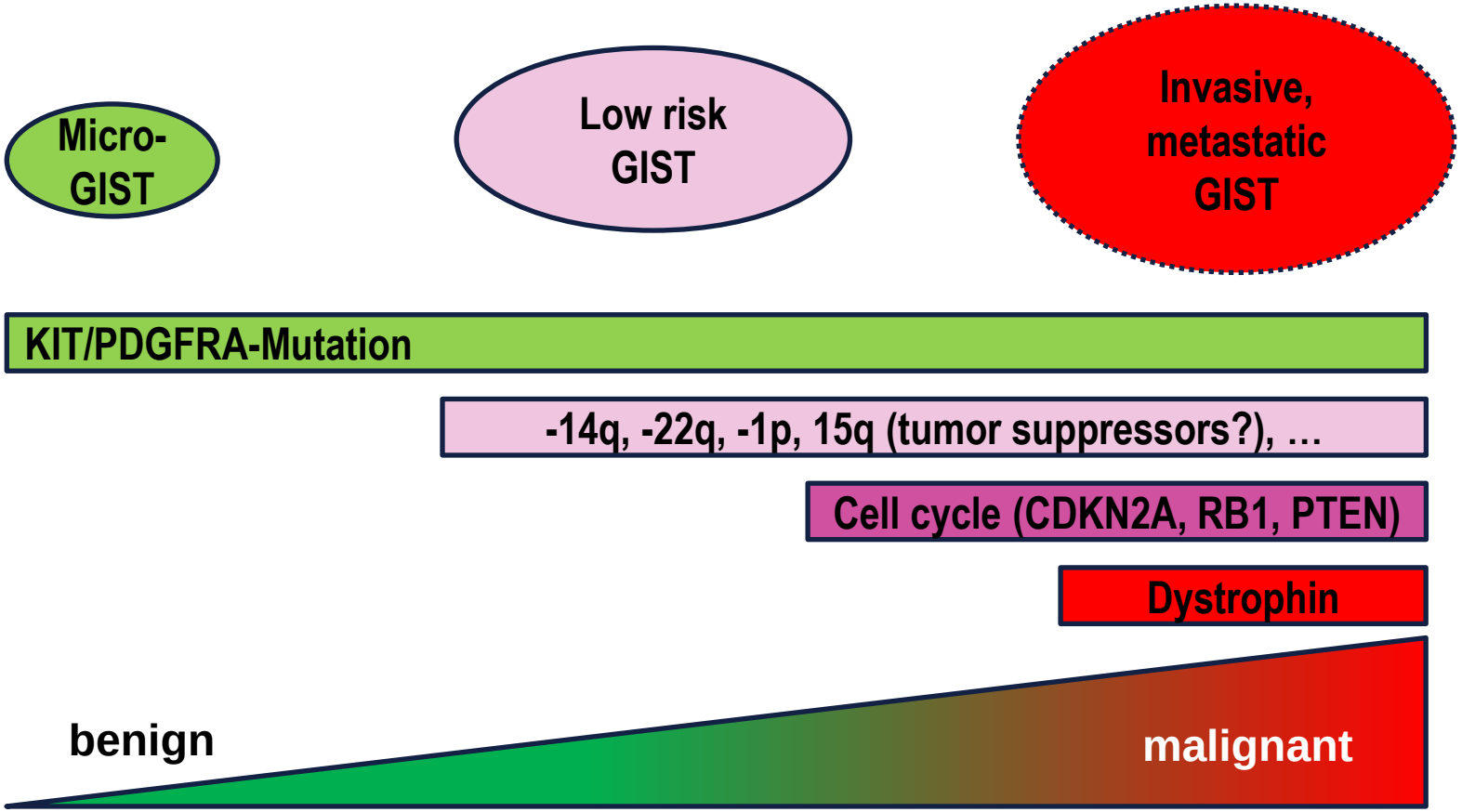
Less aggressive subtypes

- ***PDGFRA* mutations are associated with good prognosis**
  - **83% follow a benign course**
- **NF1- GISTs show commonly a benign nature**
- ***SDHx* mutations may be associated with indolent behaviour in metastatic disease**
  - **Long interval from primary tumor to metastases**
  - **Survival 10-18 years with peritoneal or liver metastasis**



- Mutational analysis has predictive value for sensitivity to molecular-targeted therapy and prognostic value, so that *its inclusion in the diagnostic work-up of all GIST should be considered standard practice*
- Centralization of mutational analysis in a laboratory may be useful

ACCUMULATION OF ADDITIONAL GENETIC EVENTS IS NECESSARY TO TRANSFORM „MICRO-GIST" INTO MALIGNANT TUMORS

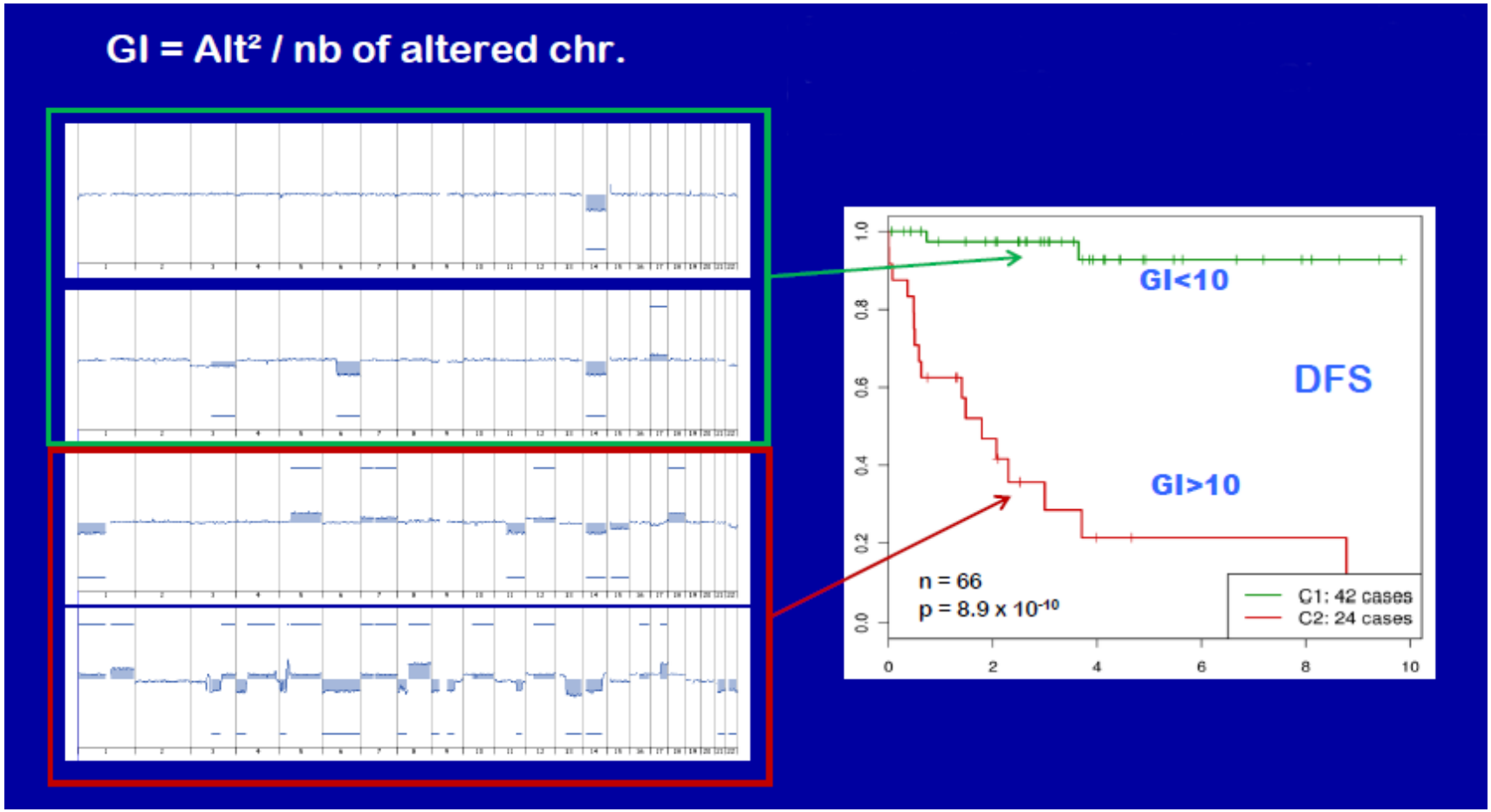


Ylipää et al. *Cancer* 2011; 117:380-9

Lagarde et al. *Clin Cancer Res*. 2012; 18:826-38

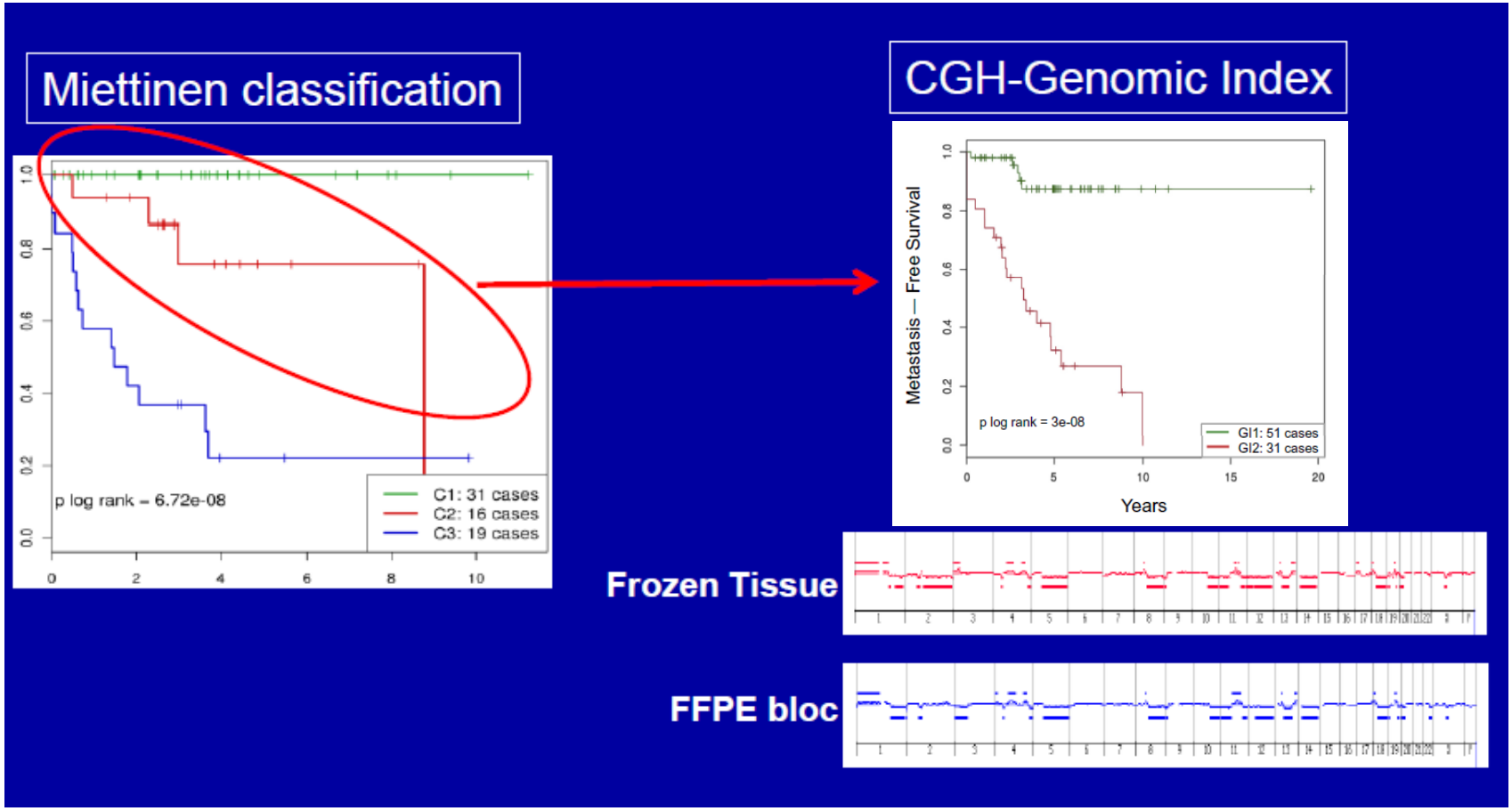
Wang et al. *Nat Genet*. 2014; 46:601-6

aCGH: GENOMIC INDEX (GI) IS A PROGNOSTIC FACTOR IN GIST



Lagarde et al. *Clin Cancer Res*. 2012; 18:826-38.

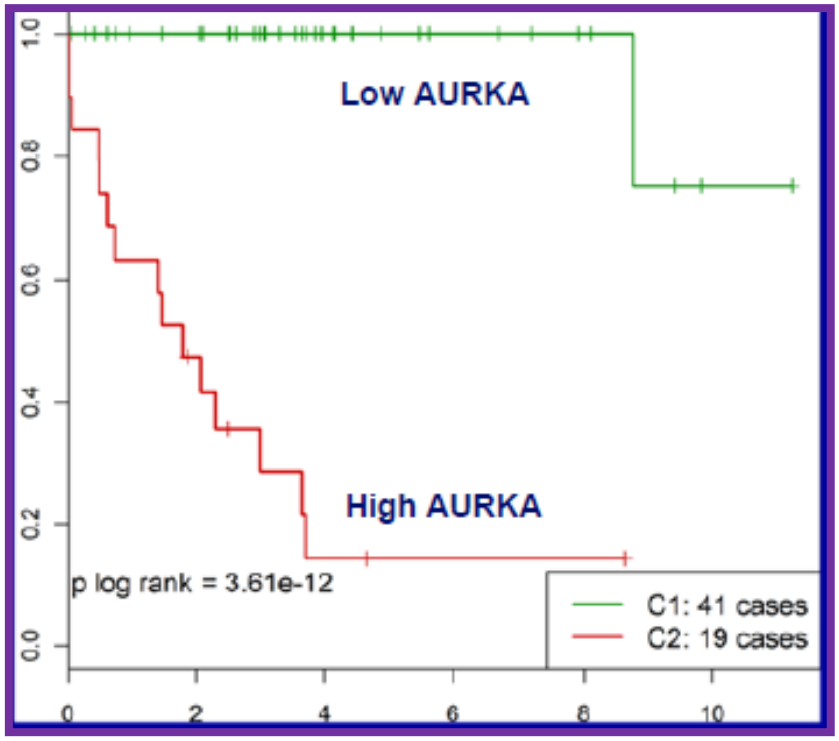
RISK ASSASMENT ACCORDING TO GI OUTPERFORMS THE AFIP CLASSIFICATION

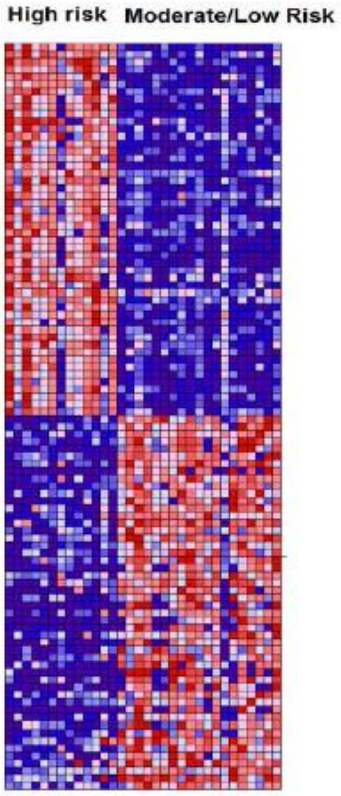


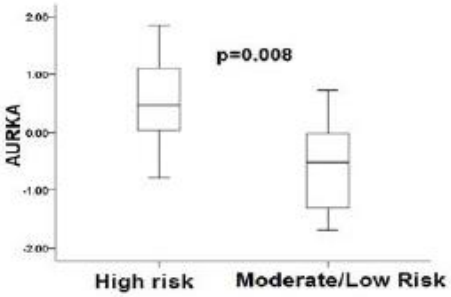
Evaluation of GI can be performed on paraffin embedded material

Lartigue et al. *Eur J Cancer* 2015; 1:75-83

GENE EXPRESSION PROFILING IN LOW-RISK VS. HIGH-RISK GISTS IDENTIFIES PROGNOSTIC BIOMARKERS







AURKA is an independent prognostic factor in GIST

Yamagushi et al. J Clin Oncol. 2008; 26:4100-8
Lagarde et al. *Clin Cancer Res*. 2012; 18:826-38
Yen et al. *Ann Surg Oncol*. 2012; 19:3491-99

SUMMARY

- The molecular background and underlying pathogenesis of GIST is heterogenous
- Mutational analysis has predictive value for sensitivity to molecular-targeted therapy and *its inclusion in the diagnostic work-up of all GIST should be considered standard practice*
- Novel molecular biomarkers have a prognostic value that might add to the better medical management of the disease


KU LEUVEN
Thank You
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