

Molecular Pathology of the Myeloproliferative Neoplasms

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Update on Molecular Pathology
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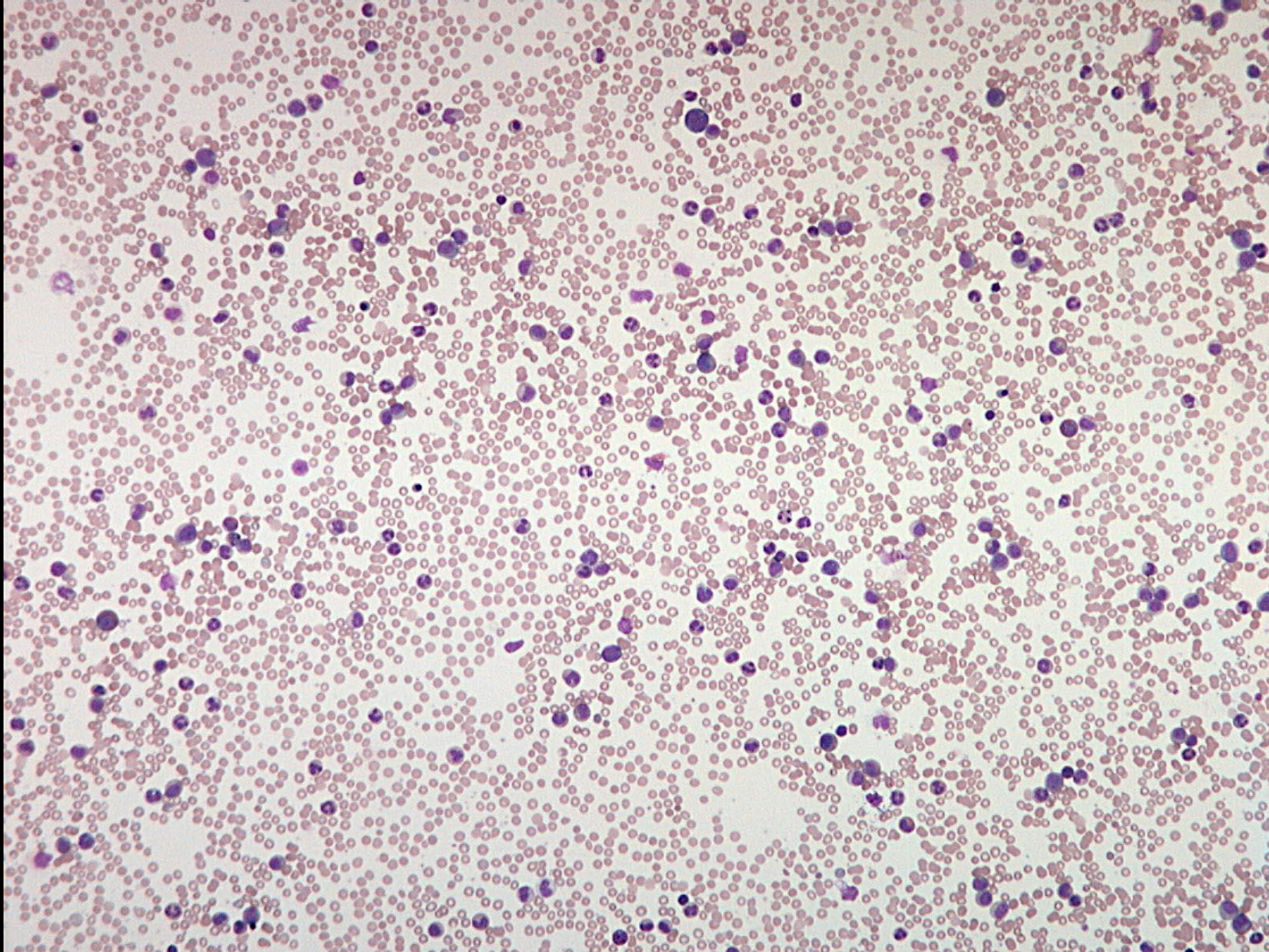
Myeloid
neoplasms

Myeloproliferative neoplasms

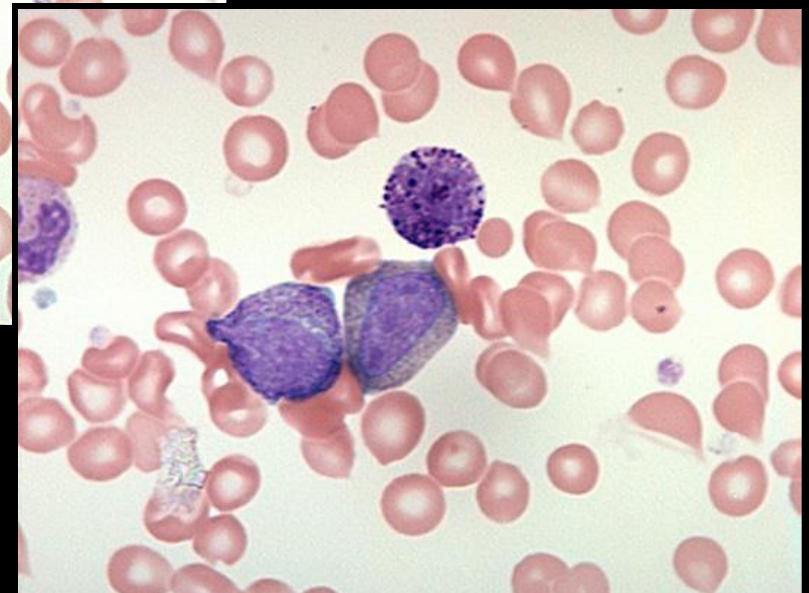
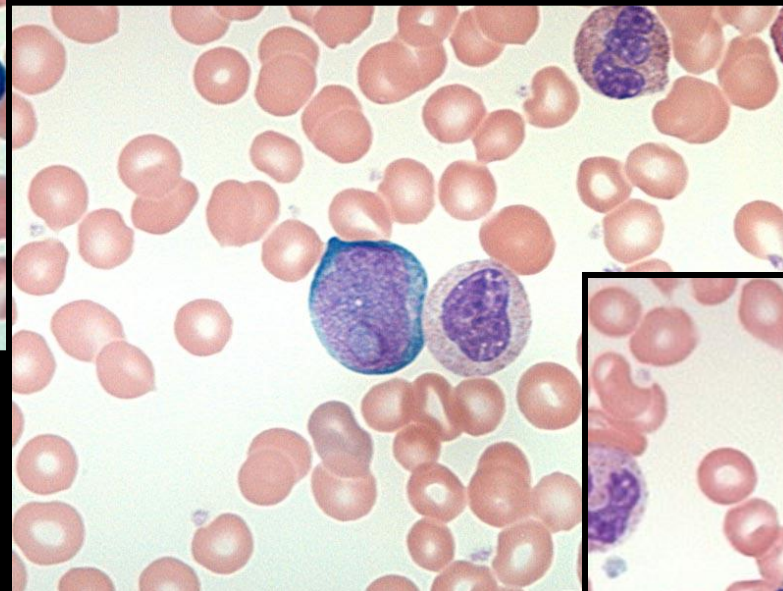
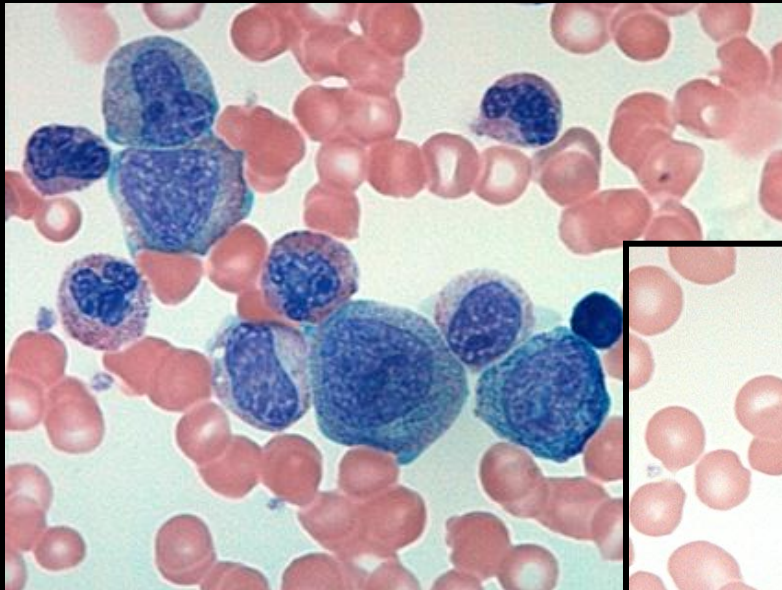


- chronic eosinophilic leukemia/hypereosinophilic syndrome
- mast cell neoplasms
- chronic neutrophilic leukemia
- unclassifiable

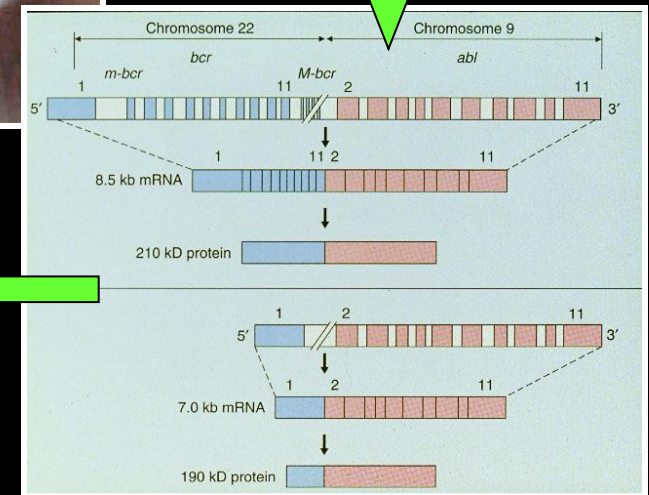
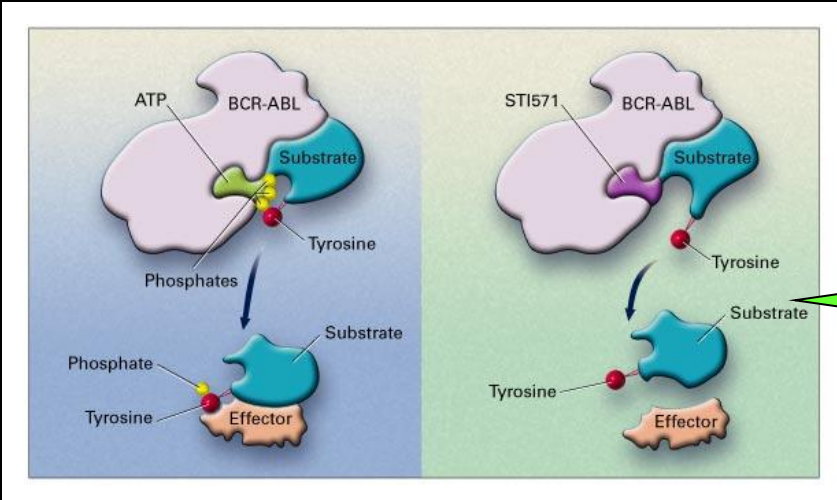
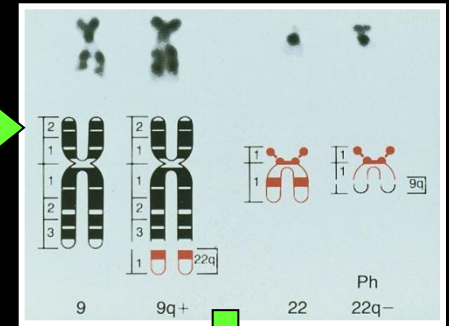
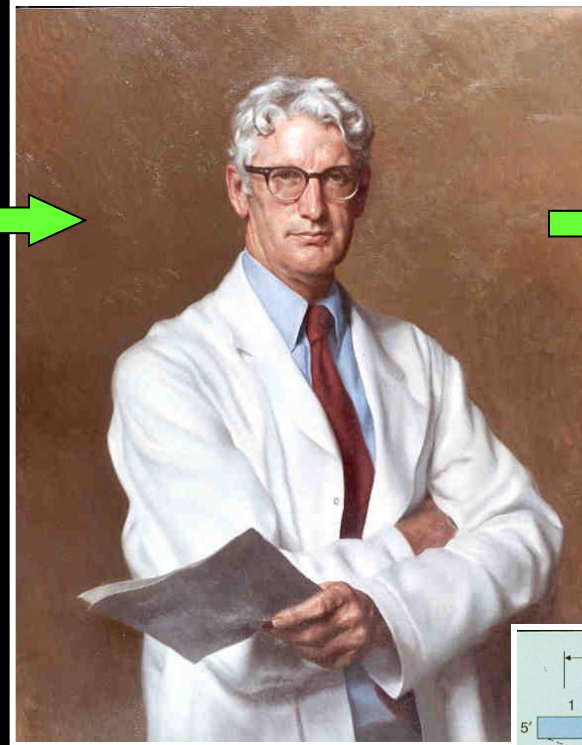
Chronic myelogenous leukemia



Chronic myelogenous leukemia



The Philadelphia story



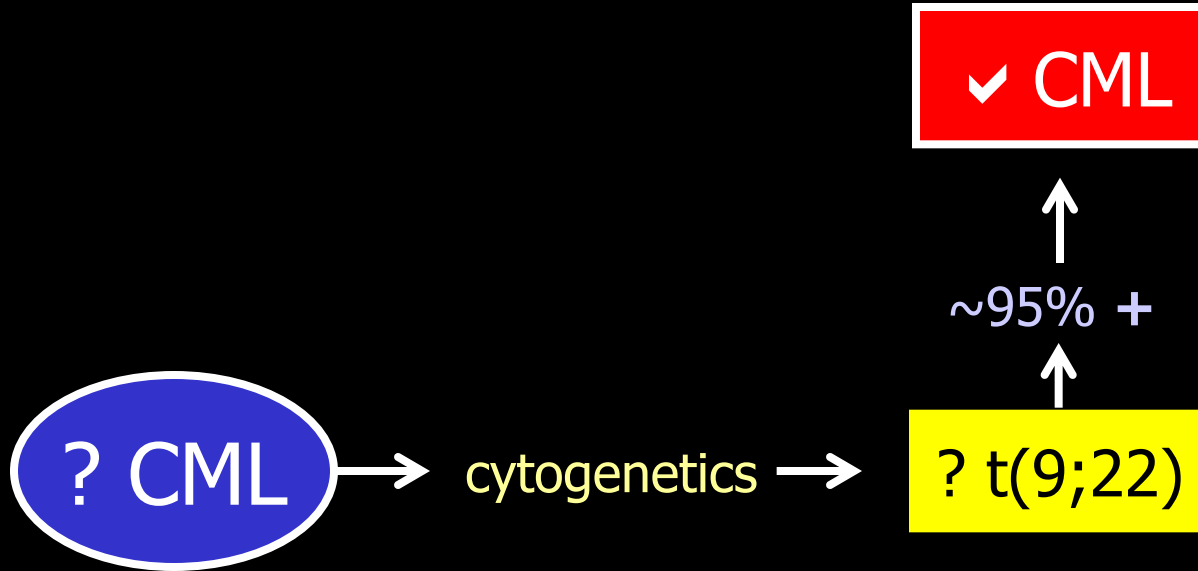
Molecular testing in CML

Diagnosis

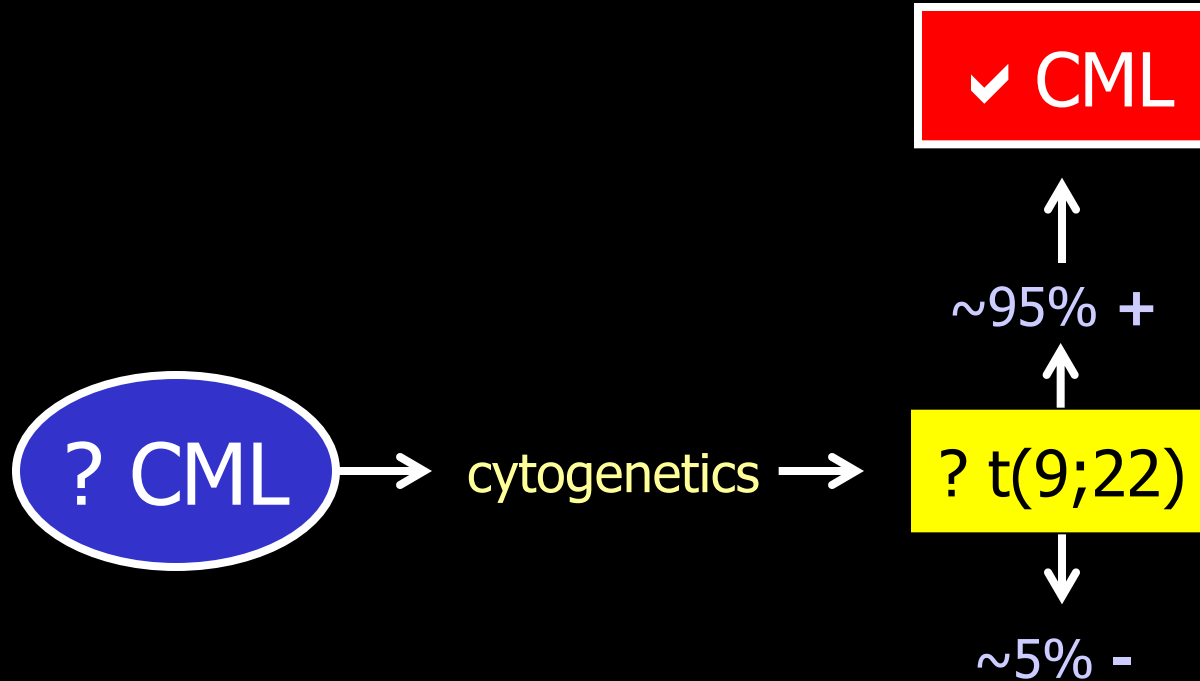
Monitoring

Resistance

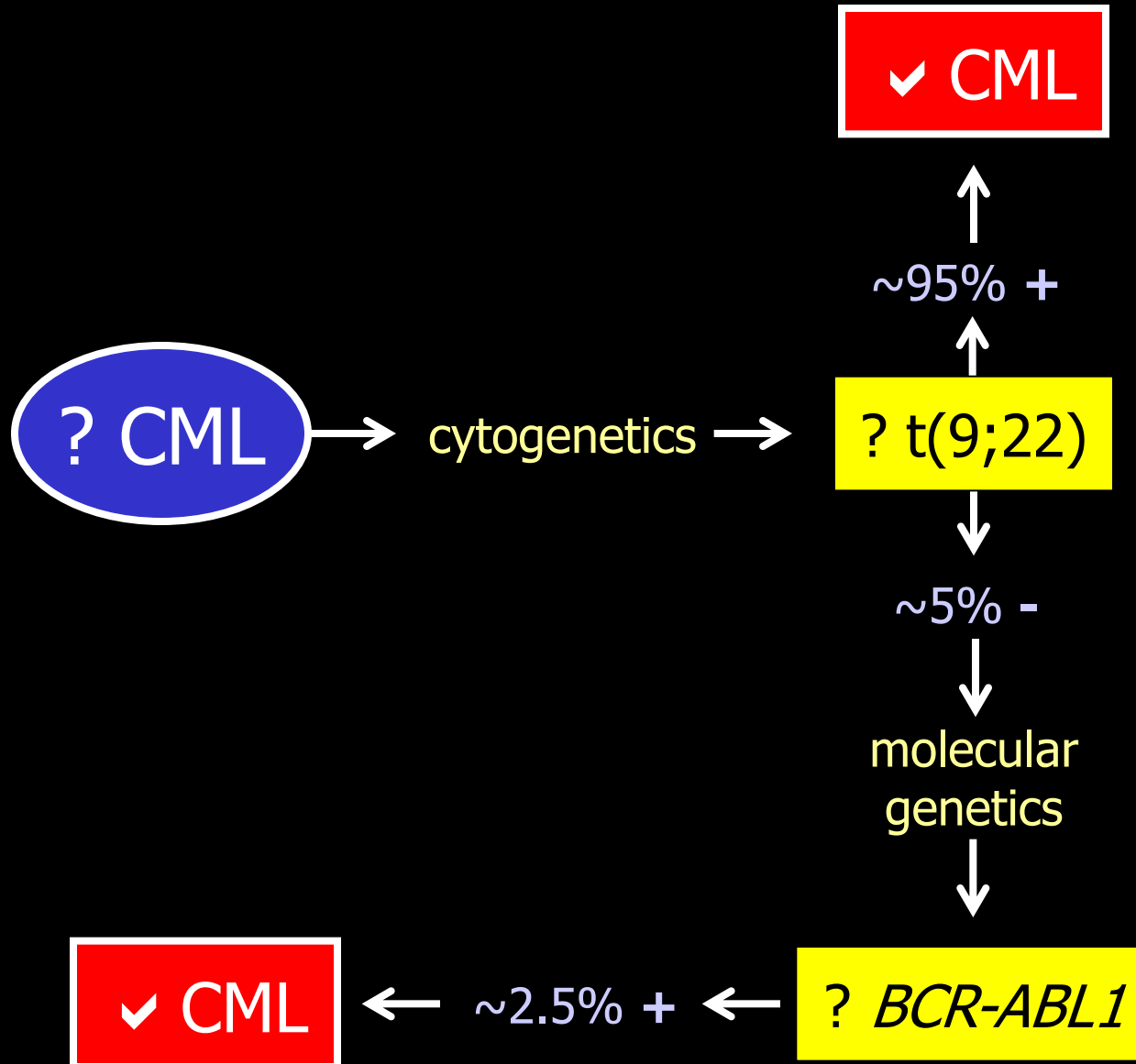
CML diagnosis: t(9;22) and BCR-ABL1



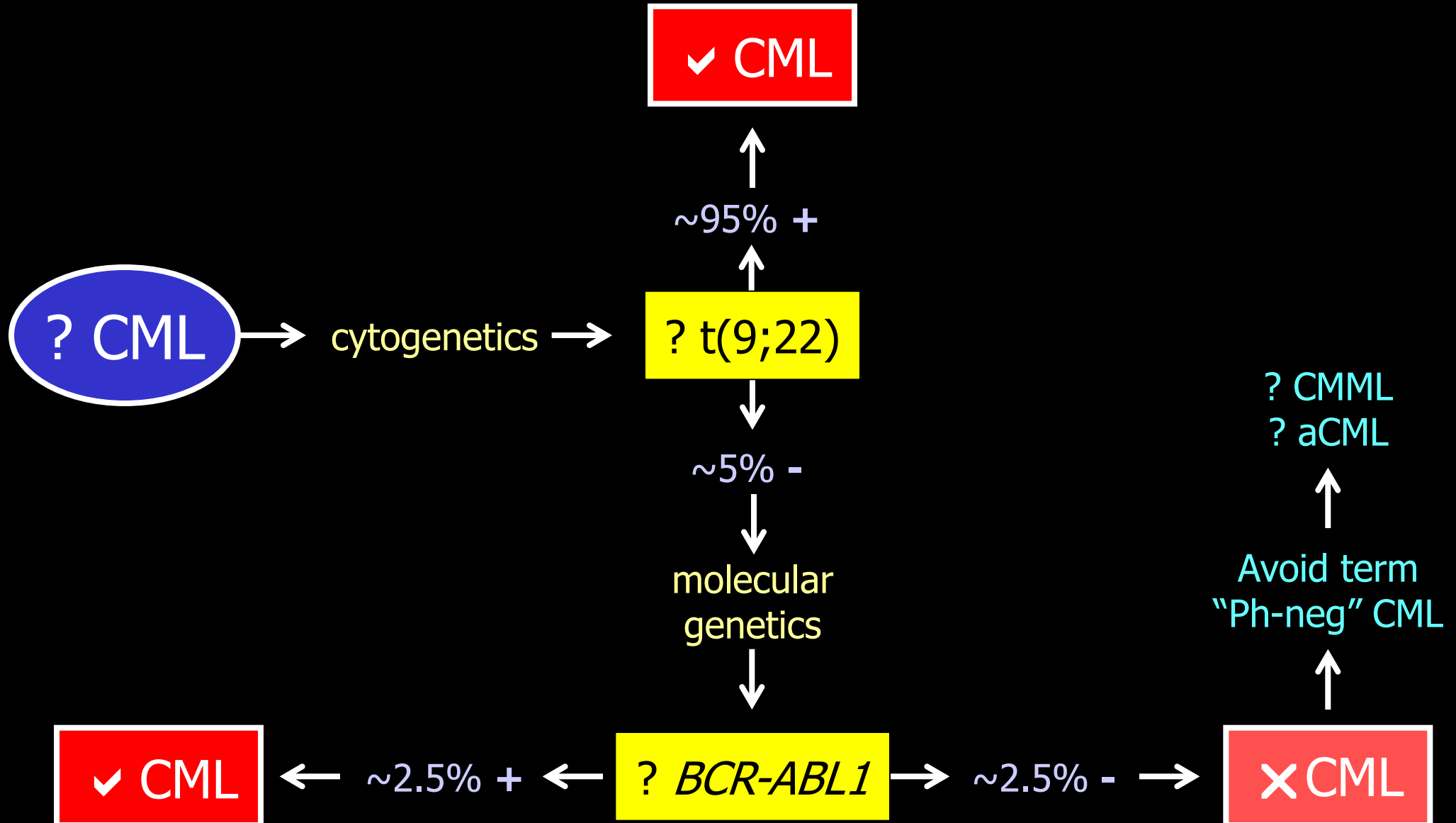
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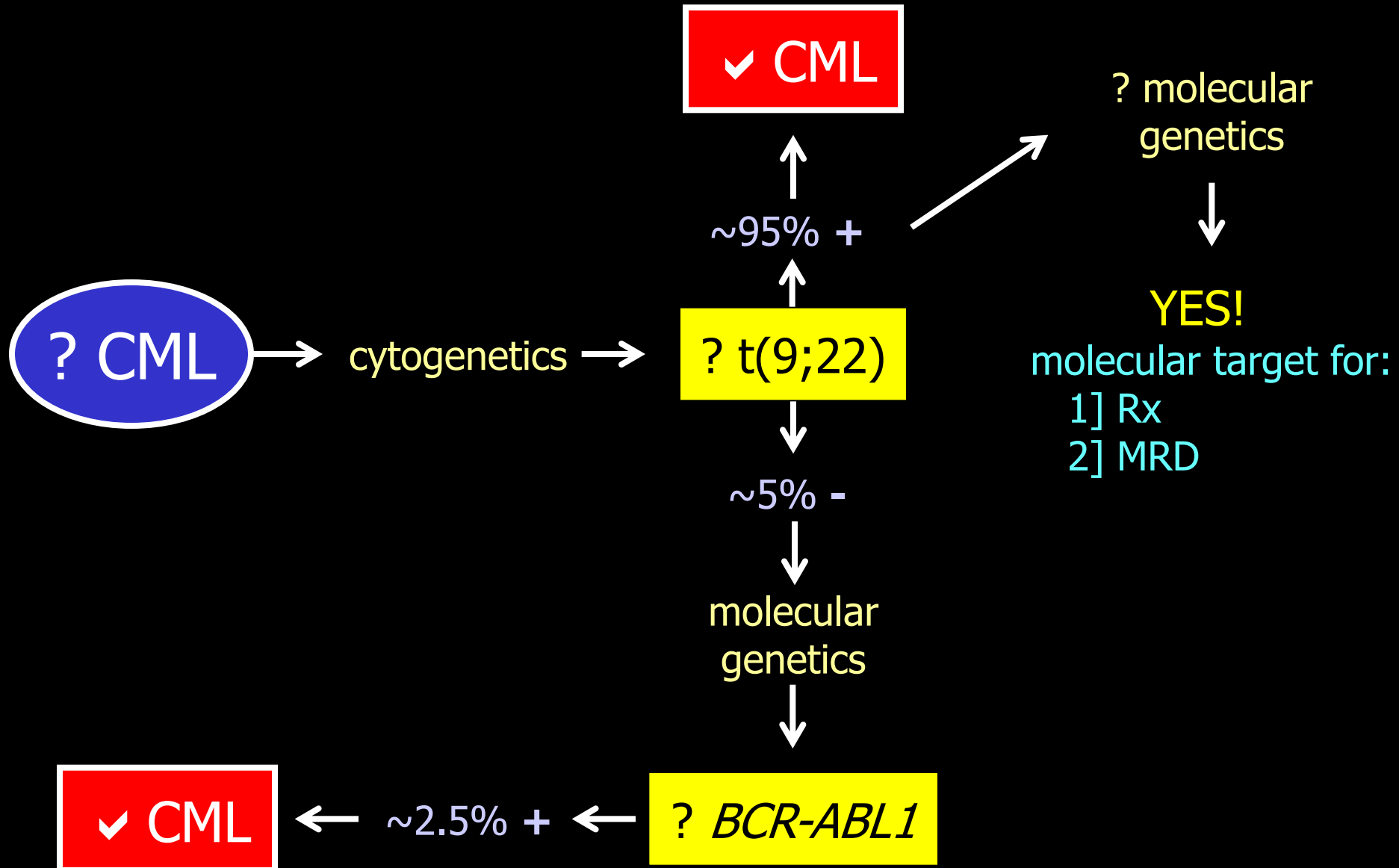
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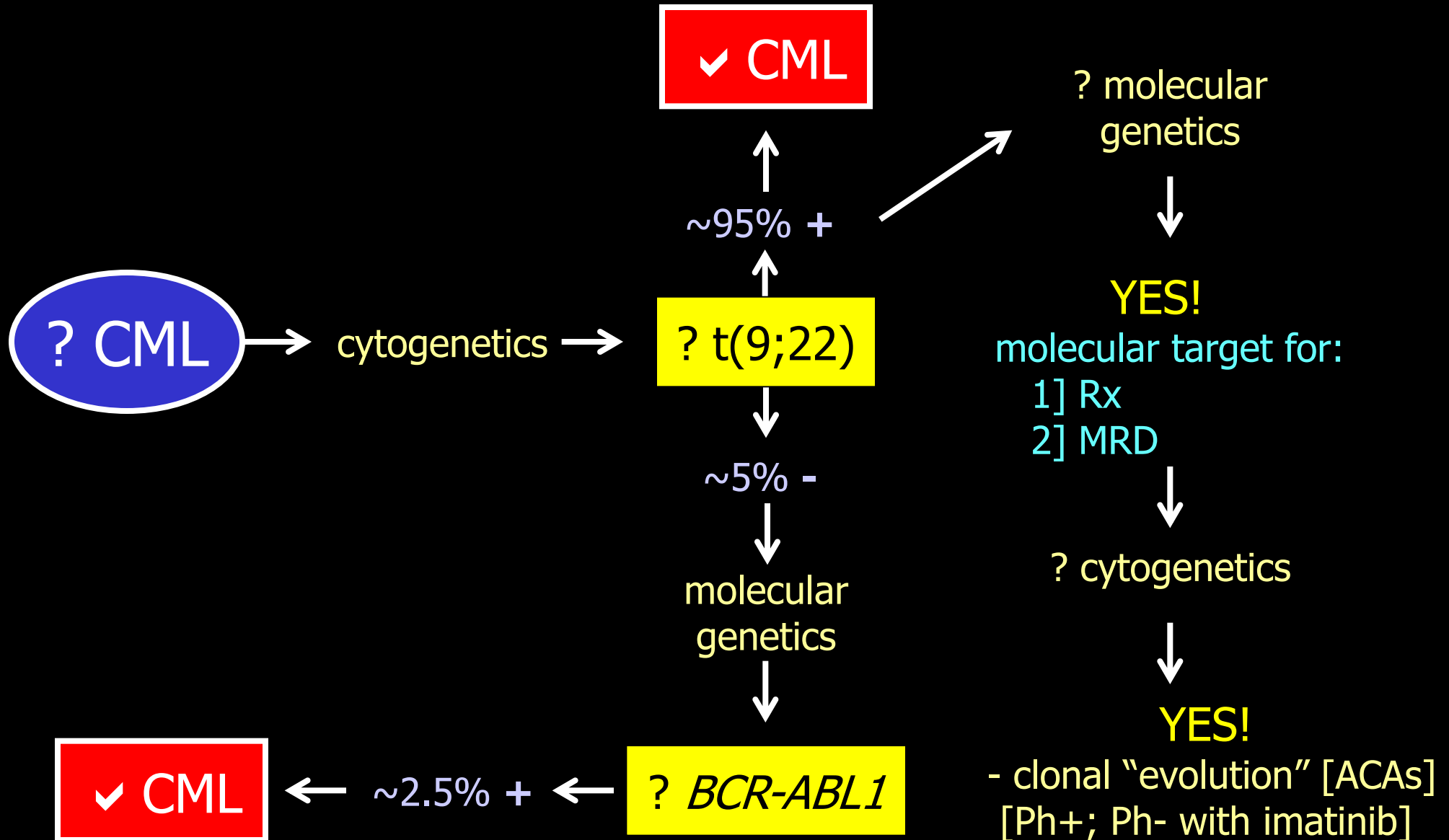
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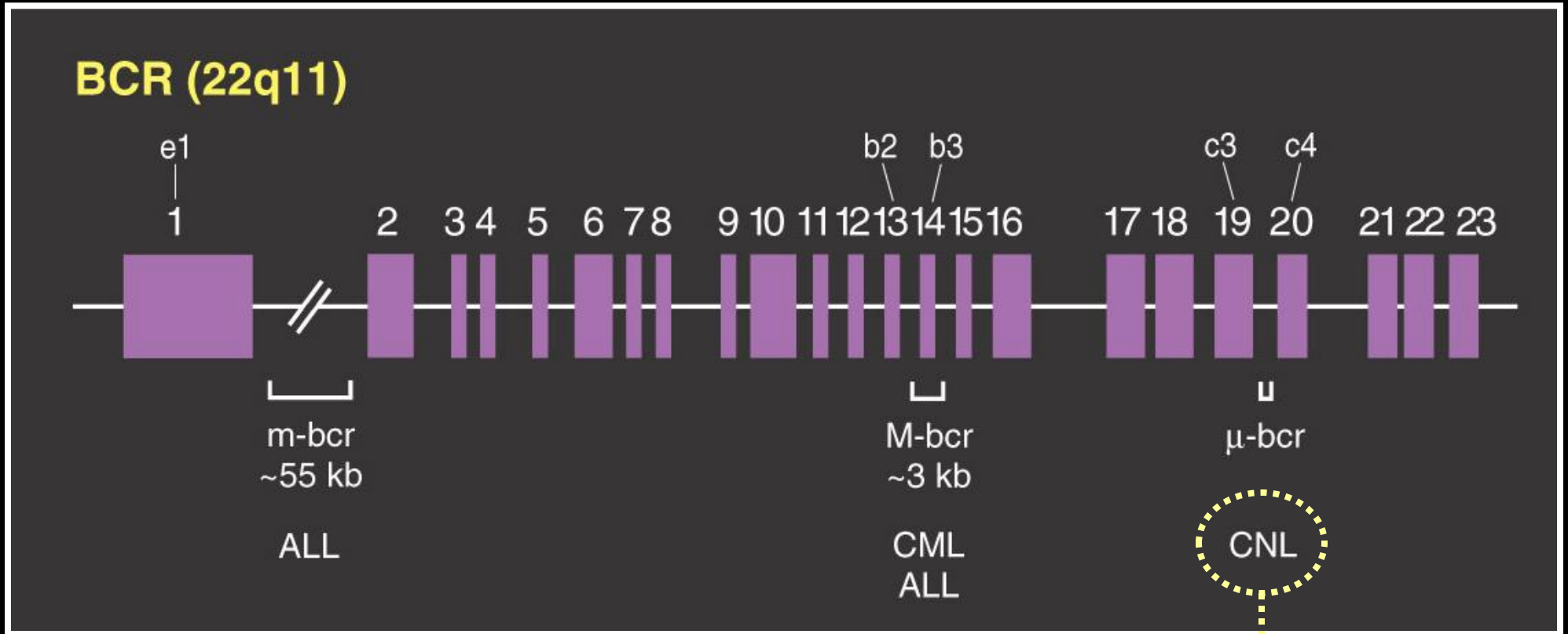
CML diagnosis: t(9;22) and BCR-ABL1



CML diagnosis: t(9;22) and BCR-ABL1



What's going on at the DNA level ...



not really!

Molecular testing in CML

Diagnosis

Monitoring

Resistance

CML monitoring

Two major forms of therapy ...

TKI

SCT

CML monitoring: definitions of response

complete hematologic

cytogenetic # Ph+

molecular

responses

diagnosis

complete hematologic remission

complete cytogenetic remission

major molecular response

"complete molecular remission"
undetectable transcript

imatinib
responses

@ 5 years

~98%

~85%

~75%

~10%

... yet overall survival ~95%

no
no
no

g



Molecular testing in CML

Diagnosis

Monitoring

Resistance

Resistance to imatinib (and other TKIs ...)

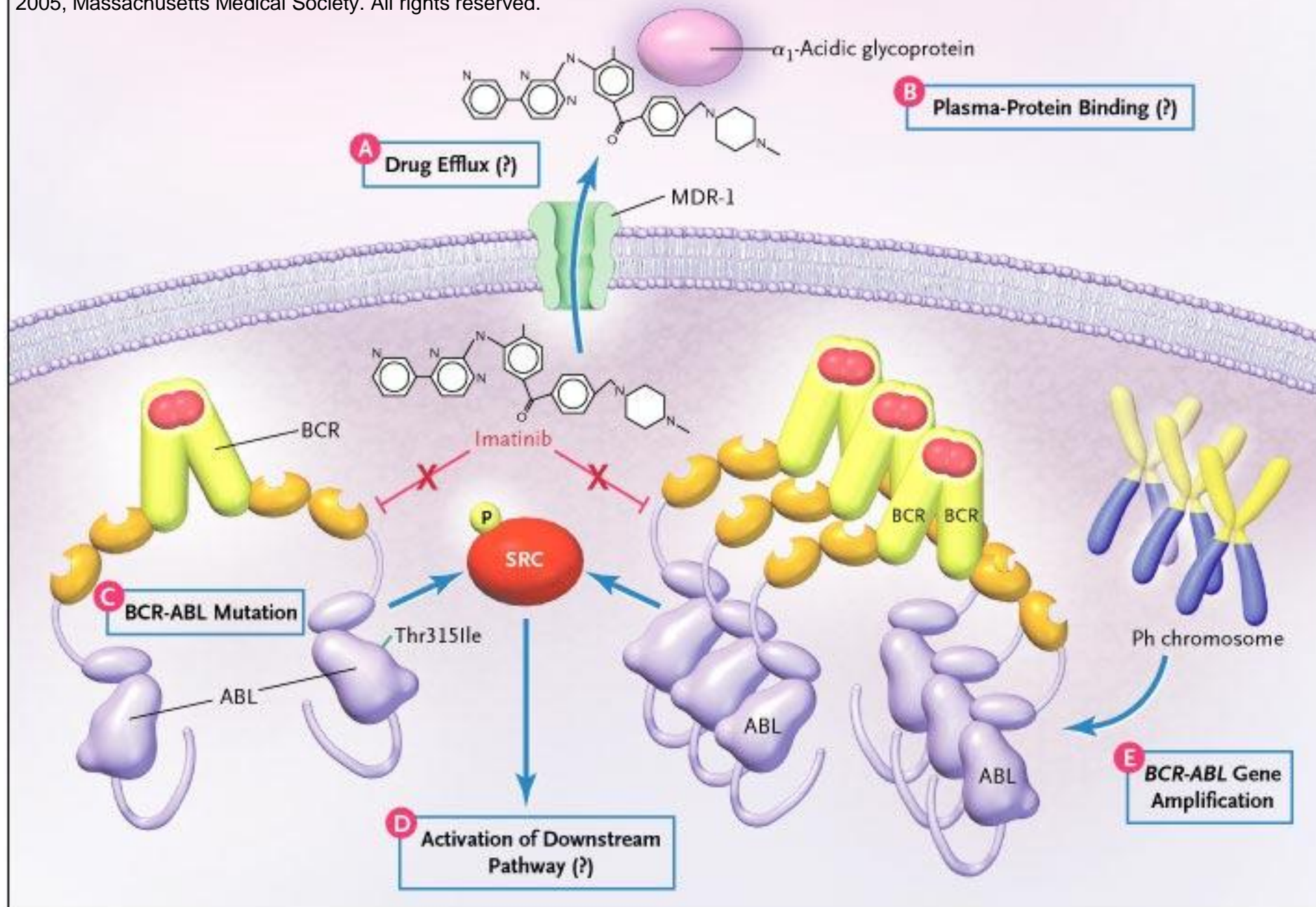
primary

secondary

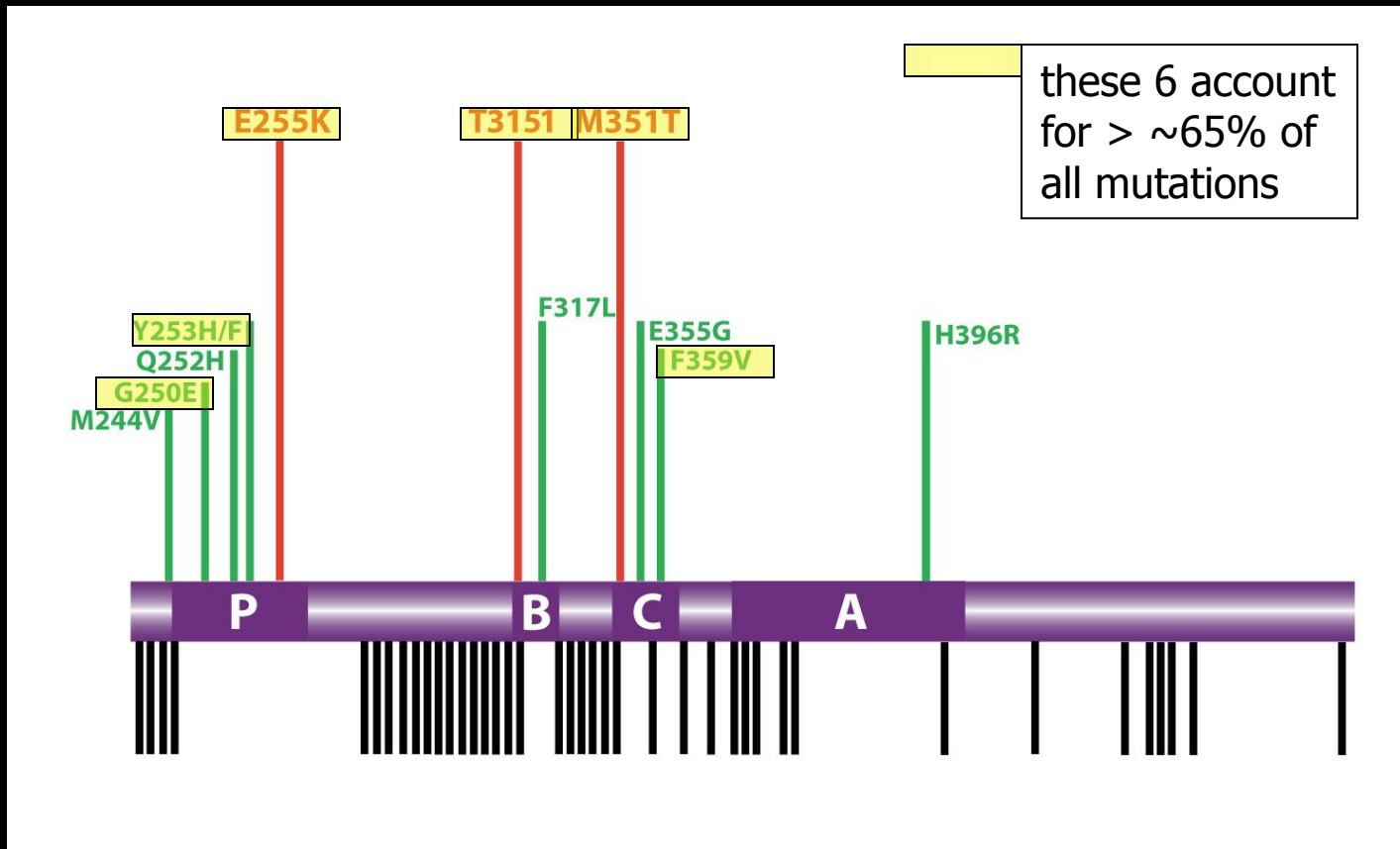
Mechanisms of resistance to imatinib

BCR-ABL1
dependent

BCR-ABL1
independent



Kinase domain mutations



> 100 different mutations

green 2-10% of patients

red >10% of patients

P = P loop

- ATP-binding site
- ? worst mutations

B = Binding domain

- where imatinib binds

C = Catalytic domain

A = Activation loop

- conformation altered
- affects imatinib binding
- closed: inactive
- open: active

Kinase domain mutations

- most common cause of resistance
- not induced by Rx
- ? BCR-ABL1 induced
- not all are created equally

Indication for mutation testing

treatment failure/
suboptimal response

loss of response

anyone in AP or BC

Genetic testing in CML: summary

Diagnosis

Monitoring

Resistance



Molecular and other testing in non-CML MPNs

pre-2005 ...

	karyotype	genes	PRV1	EEC	↓ mpl megas	↓GATA1 megas	↑ circ CD34+
PV	9p+, +8+9	?	+	+	+	?	-
ET	?	?	+ [50%]	+ [50%]	+/-	?	-
PMF	del(13q14)	?	-	-	+/-	+	+
PPMF	1q+	?	?	?	?	?	?

Molecular and other testing in non-CML MPNs

post-2005 ...

	karyotype	genes	PRV1	EEC	↓ mpl megas	↓GATA1 megas	↑ circ CD34+
PV	JAK2 V617F mutation (etc)						
ET							
PMF							
PPMF							

JAK2 is out of the box ...

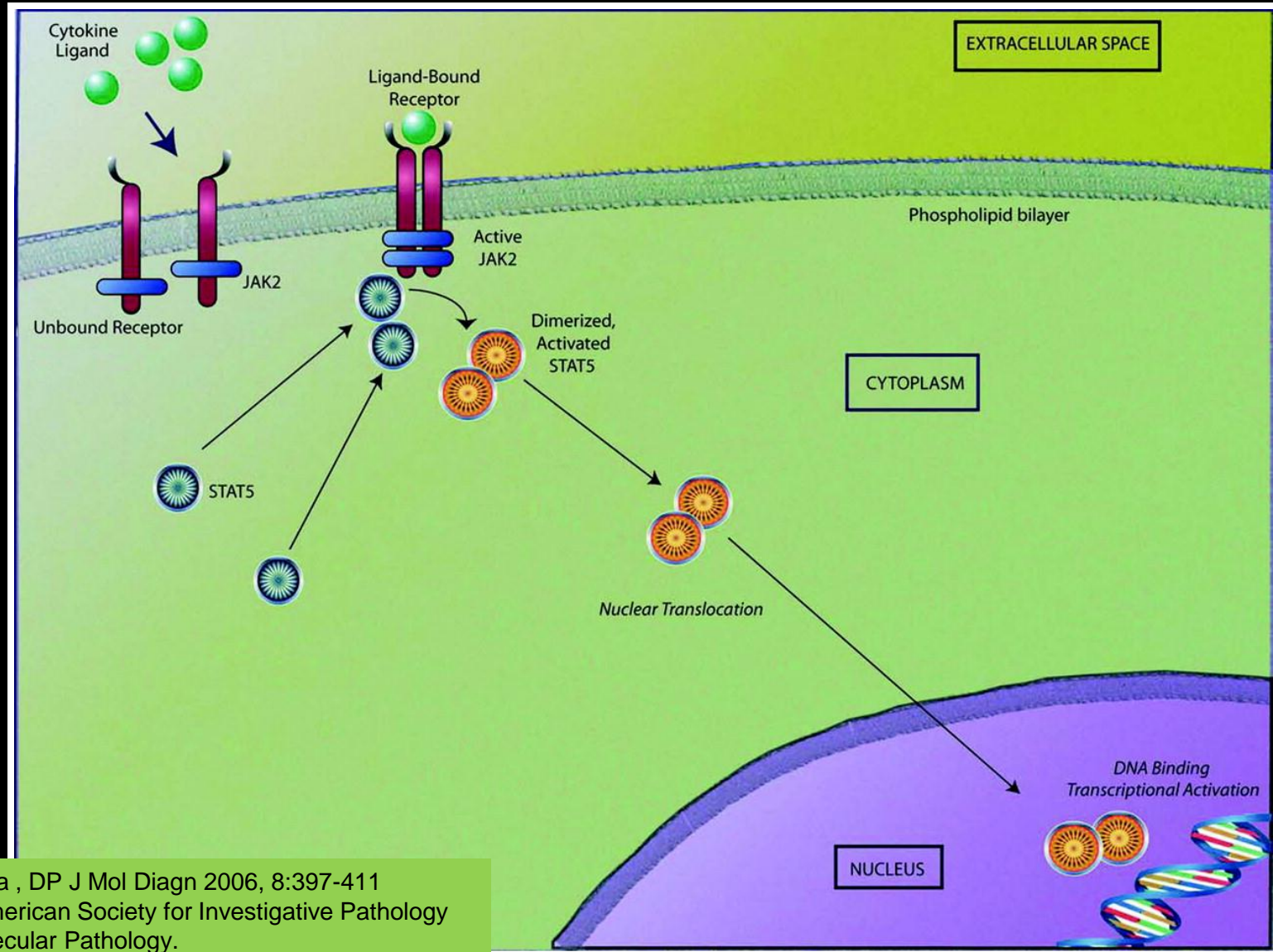


- **J**ust **A**nother **K**inase
 - one of many cloned at the time (1989)
- **J**anus **K**inase
 - two-headed Roman god of gates and passages

- non-receptor tyrosine kinase (TK)
- has 2 TK domains (**hence the name**)
 - most TKs have only 1
- 4 members of JAK family
 - JAK1, JAK2, JAK3 and TYK2

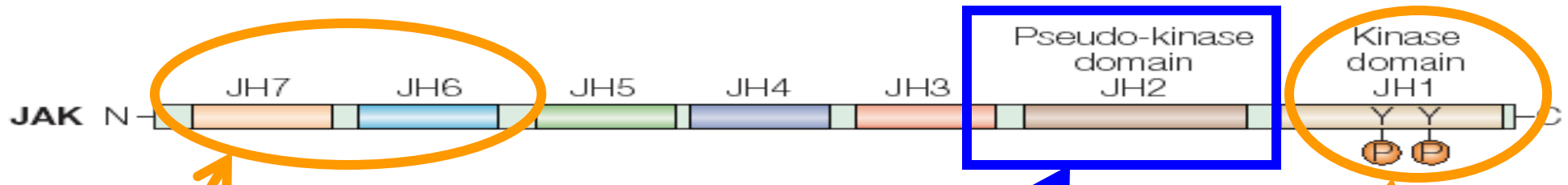


JAK-STAT pathway



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JAK2 structure, function, mutation



mediates binding
to receptor

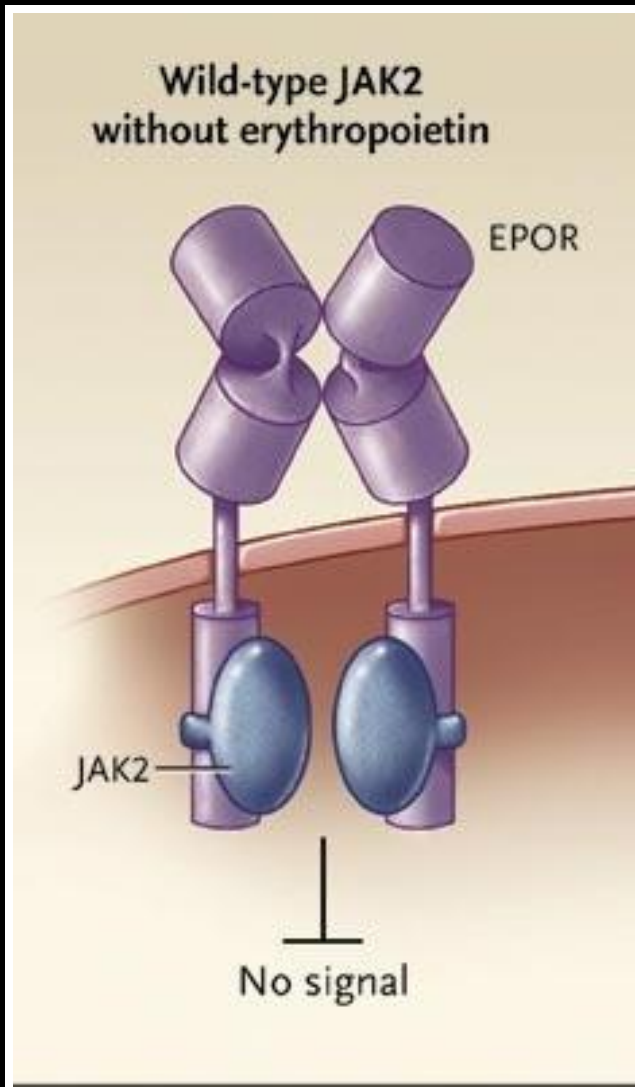
autoinhibitory
activity

phosphorylated
after ligand
binding

~50% ET
~50% PMF
~95% PV

V617F
Mutation

JAK2: wild-type and mutant



Eosinophilic neoplasms and mastocytosis

Systemic mastocytosis

- ~95% *KIT* mutation
- D816V
- imatinib resistant

Any questions ...



