

Novel Molecular Markers in MPN: Use for diagnosis and prognosis



Heike L. Pahl
University Hospital Freiburg

Myeloproliferative Neoplasms (MPNs)

- **Polycythemia vera (PV)**
 - erythrocytosis
 - thrombocytosis
 - leukocytosis
- **Essential Thrombocythemia (ET)**
 - thrombocytosis
- **Primary Myelofibrosis (PMF)**
 - anemia
 - thrombocytopenia
 - leukopenia

Myeloproliferative Neoplasms (MPNs)

- clonal hematopoietic disorders
- cytokine independent colony growth
- thromboses
- propensity to develop acute leukemia
 - molecular causes complex (**JAK2^{V617F}**)
 - targeted therapies only palliative

MPN biomarkers

MPN biomarkers

classical

MPN biomarkers

classical

novel

MPN biomarkers

classical

JAK2 V617F

JAK2 exon 12

MPL W515X

KIT D816V, D816X

novel

MPN biomarkers

classical

JAK2 V617F
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KIT D816V, D816X

novel

TET2
LNK
CBL
ASXL-1
EZH-2
SOCS3
NF-1
IDH 1/2

MPN biomarkers - frequency

classical

PV

ET

PMF

JAK2 V617F

JAK2 exon 12

MPL W515X

KIT D816V, D816X

MPN biomarkers - frequency

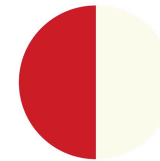
classical

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PMF

JAK2 V617F

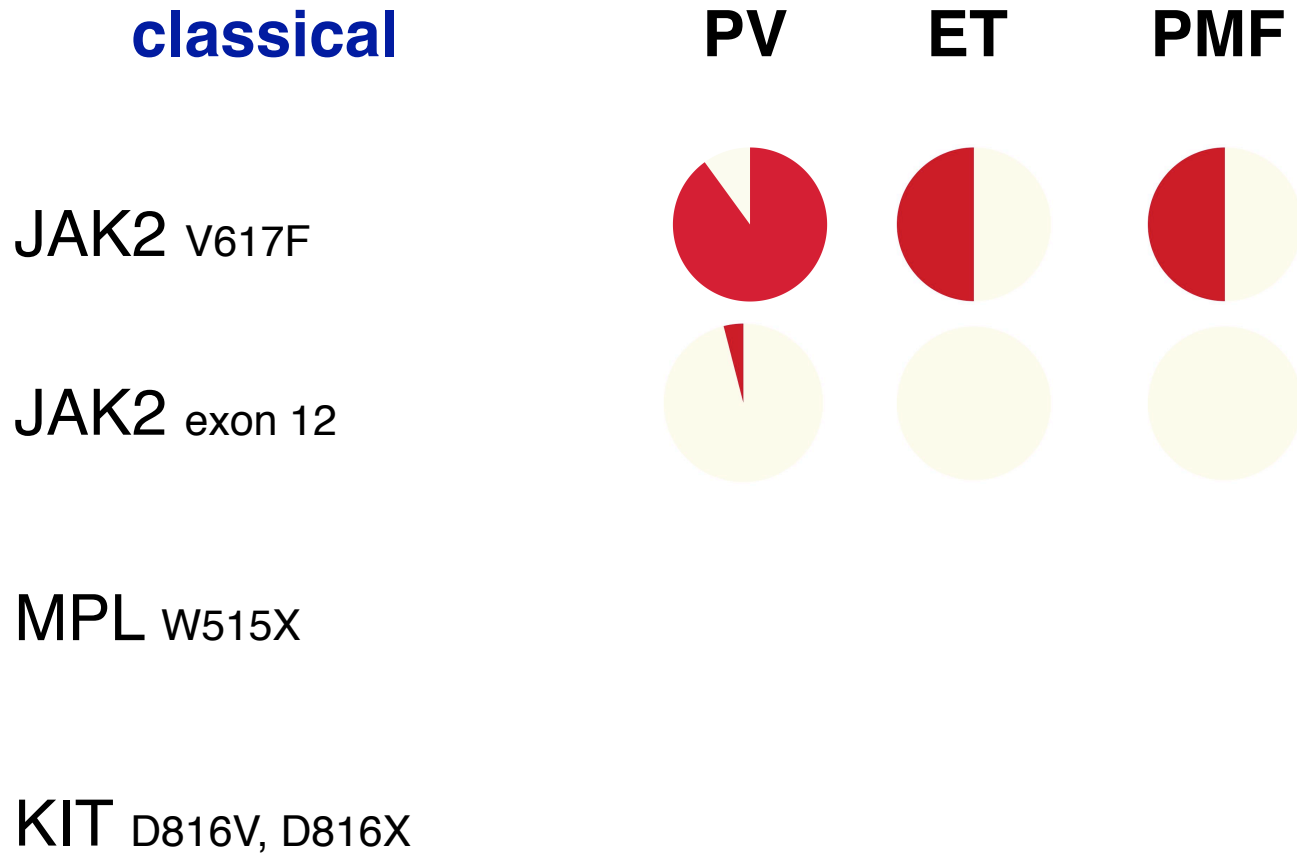


JAK2 exon 12

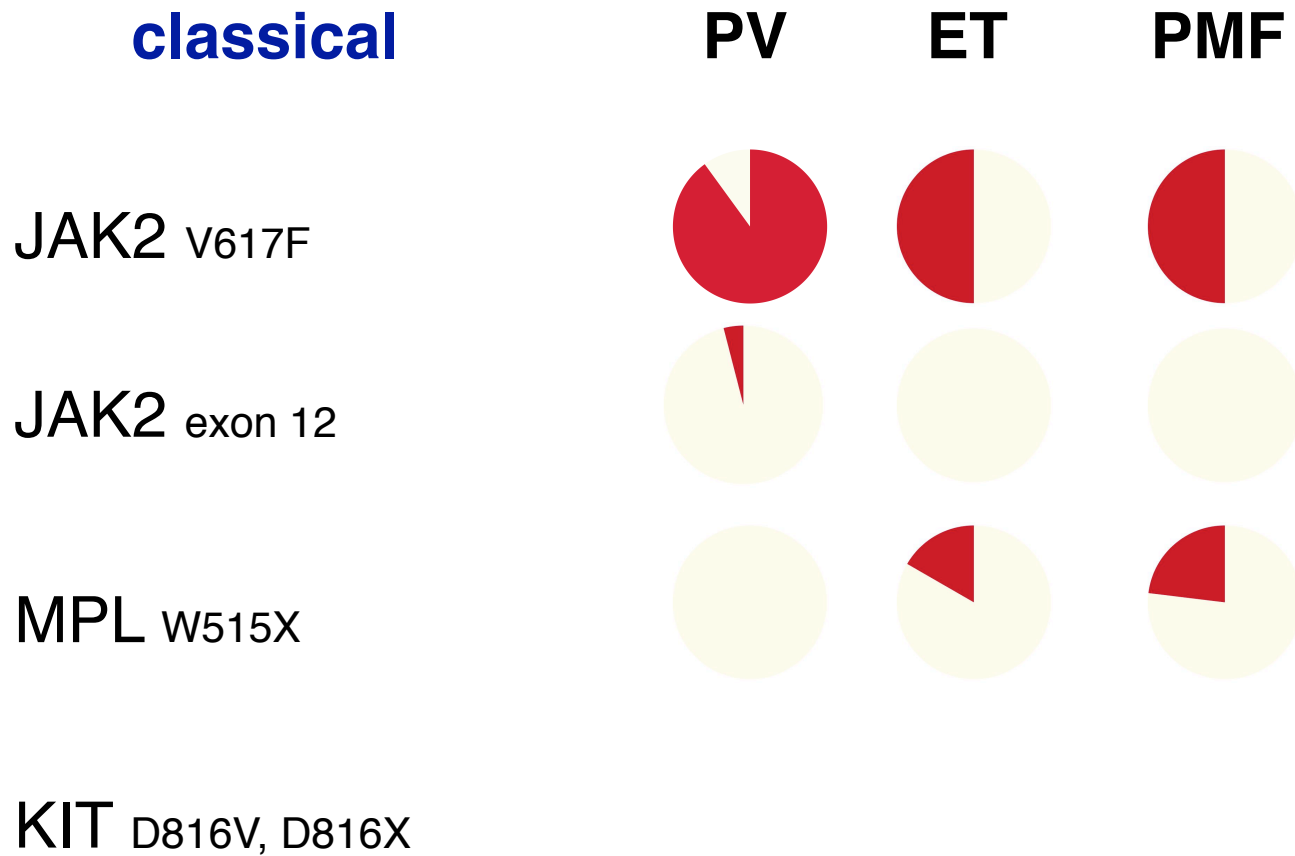
MPL W515X

KIT D816V, D816X

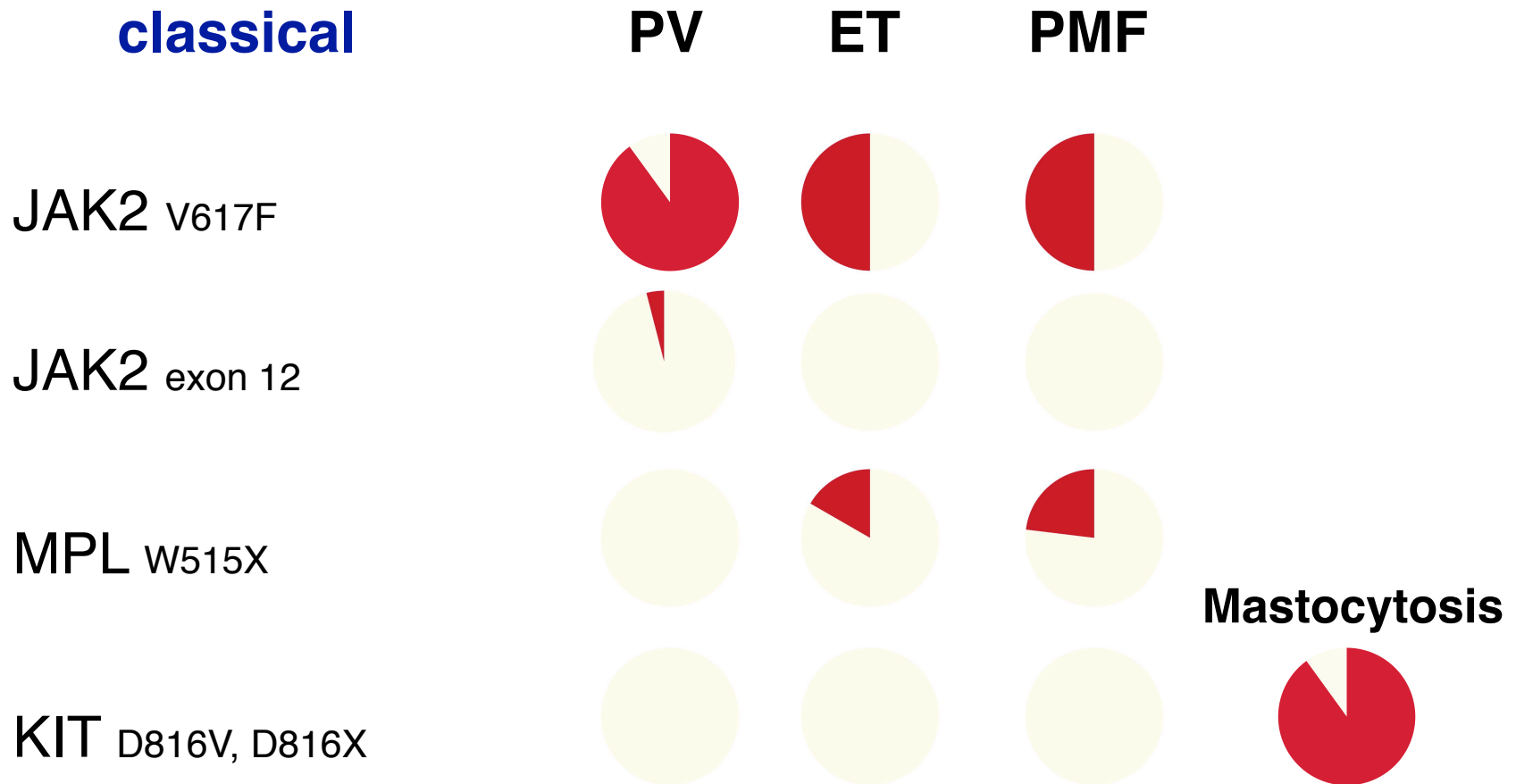
MPN biomarkers - frequency



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MPN biomarkers - frequency

novel

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CMML

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JAK2-wt
erythrocytosis

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MPN biomarkers - frequency

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erythrocytosis

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CMML

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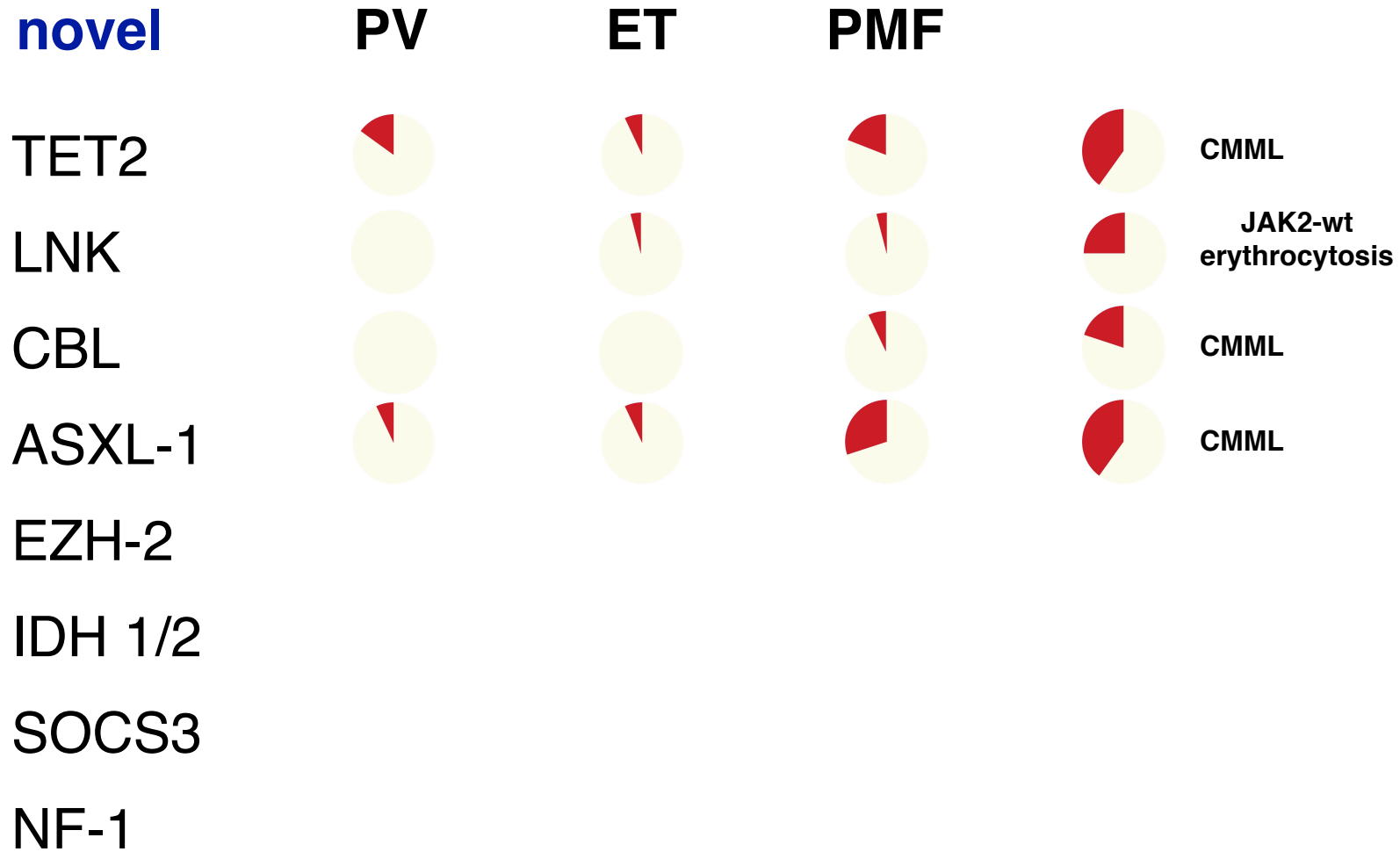
EZH-2

IDH 1/2

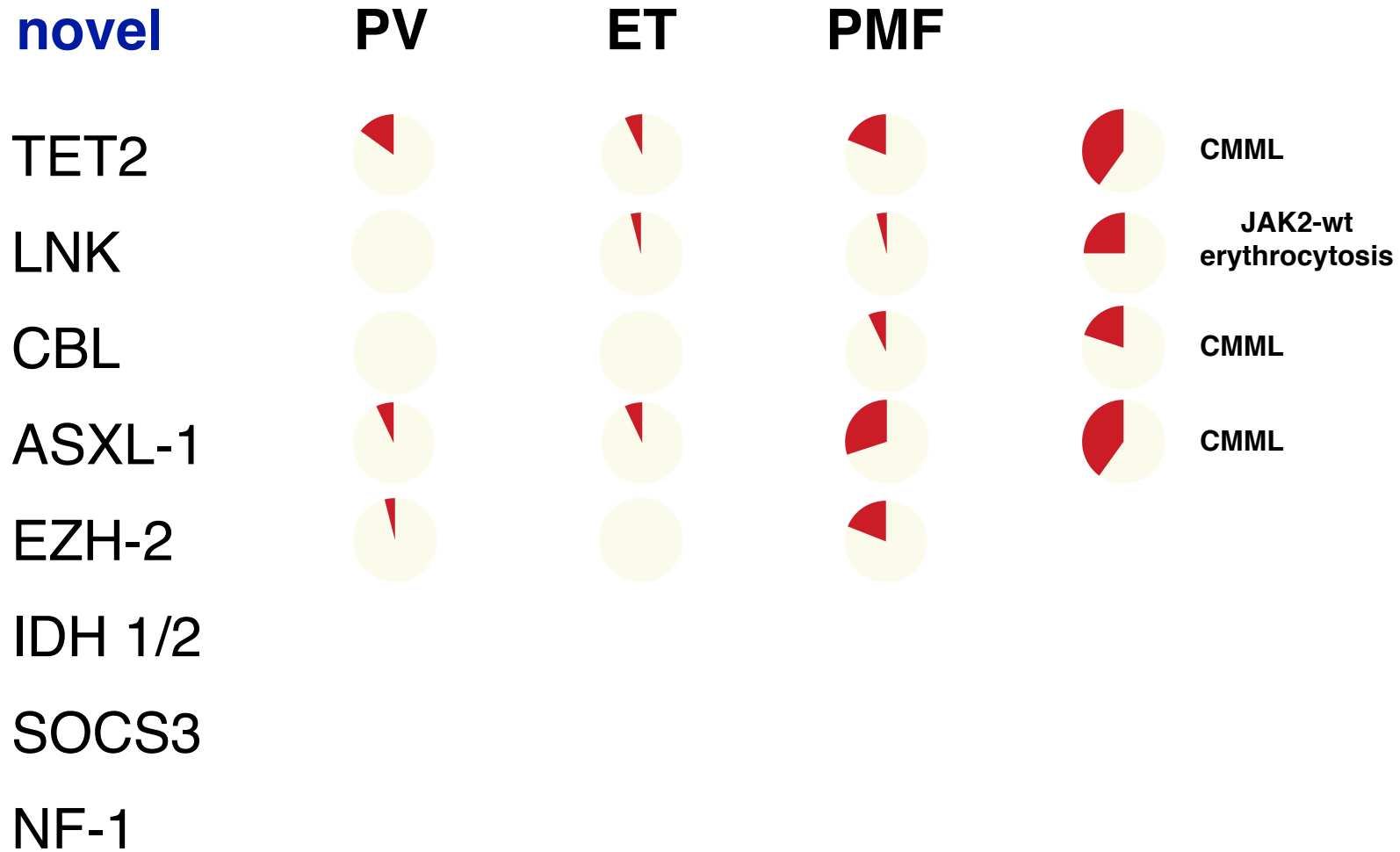
SOCS3

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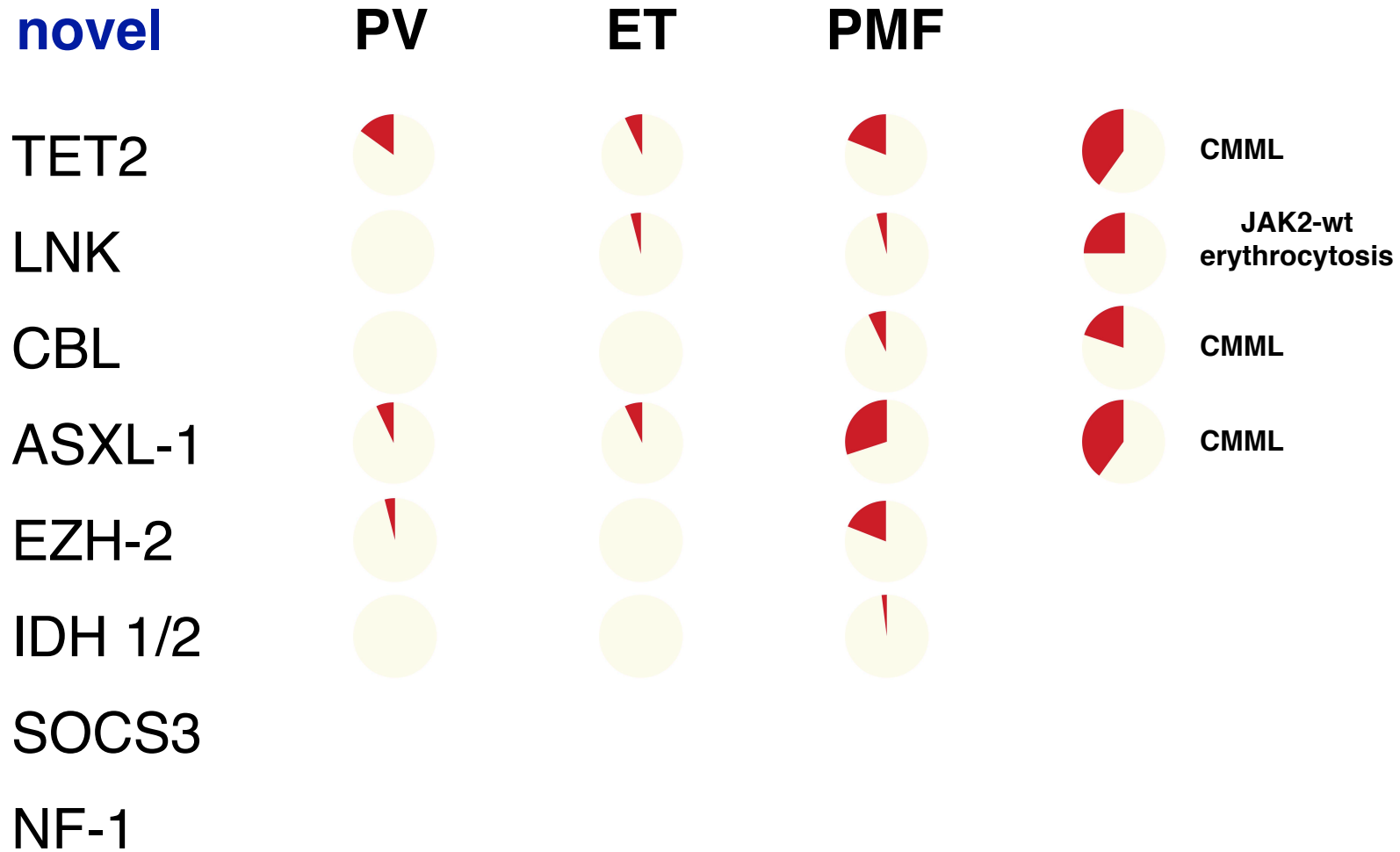
MPN biomarkers - frequency



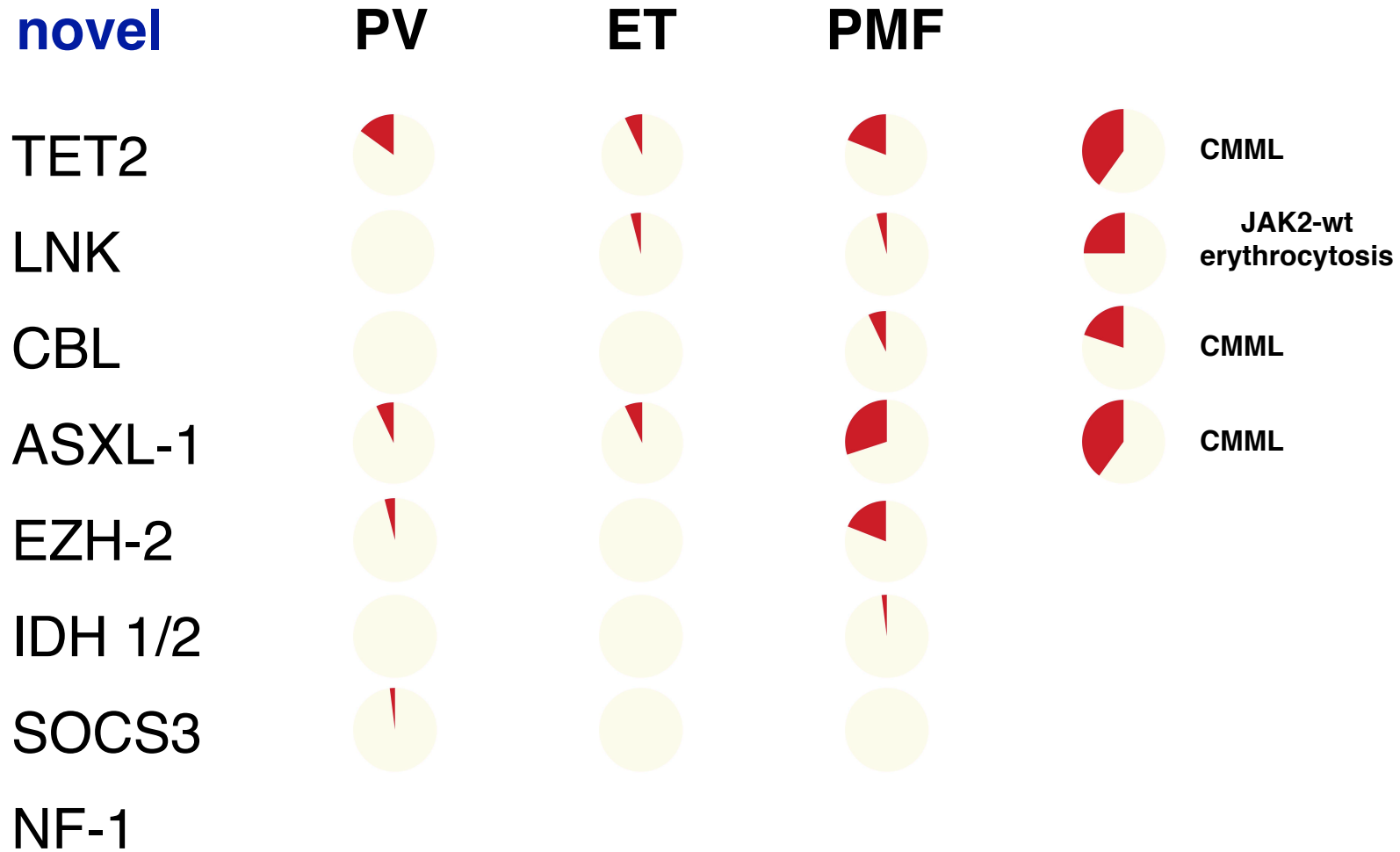
MPN biomarkers - frequency



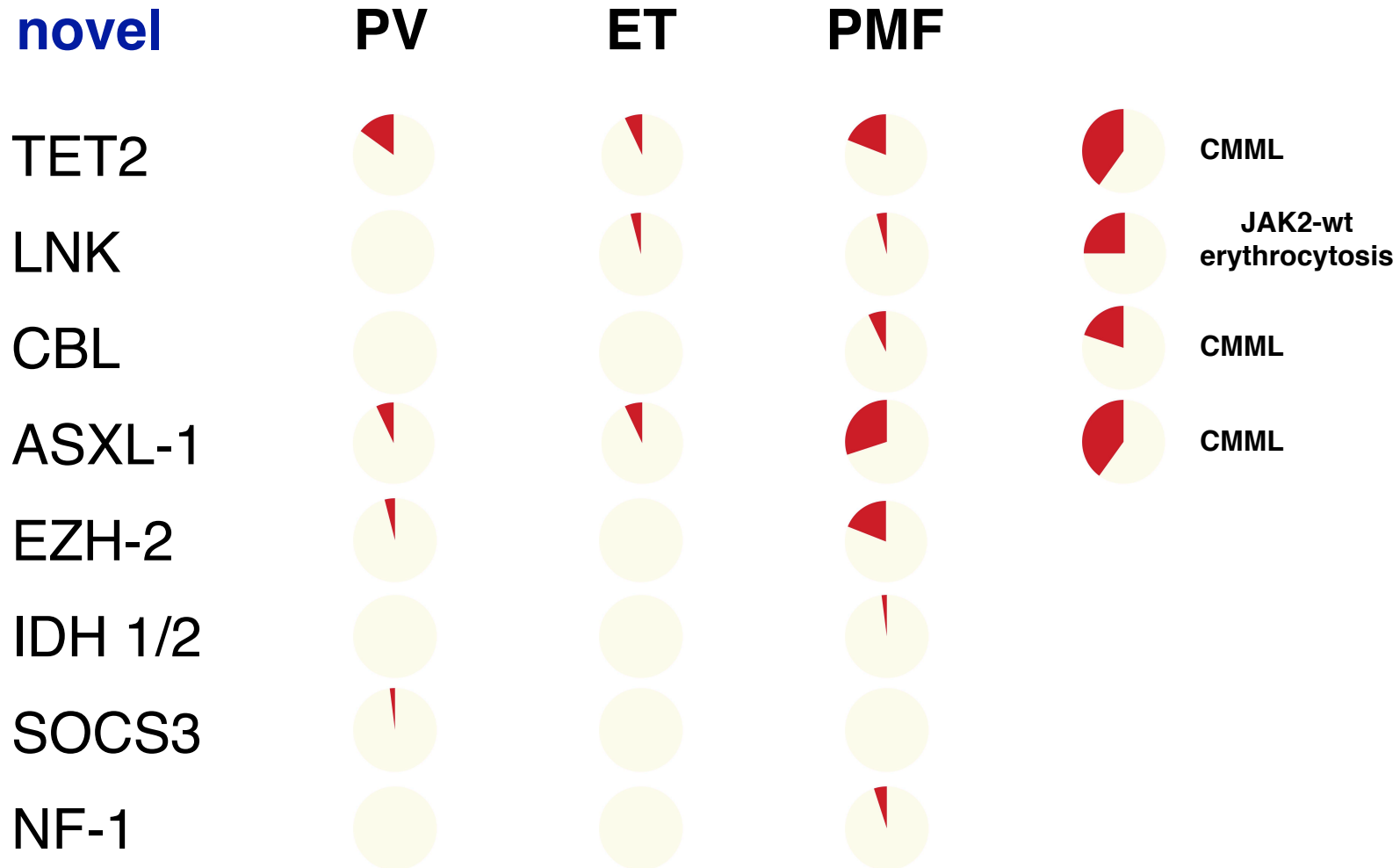
MPN biomarkers - frequency



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MPN biomarkers - frequency



MPN biomarkers

in clinical practice

Diagnosis
Follow up

Case 1

- 58 year old female
- CBC
 - Hct 48 % ↑
 - Hb 16.9 g/dl ↑
 - RBC 9.4 x 10⁹/l ↑
 - Plt 475 x 10⁹/l ↑
 - WBC 12.6 x 10⁹/l ↑
- no cause of 2ndary erythrocytosis
- BM consistent with PV
- Serum EPO: 4 U/l ↓

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JAK2 V617F

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if positive: Dx

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Molecular Markers ?

JAK2 V617F

↓ if positive: Dx

↓ if negative?

JAK2 Exon 12

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Case 1

What about the new MPN markers ?

Molecular Markers

- there is no data to support the use of novel MPN markers
 - for Dx in JAK2-positive cases
 - for decisions on therapy

JAK2 V617F

if positive: Dx

JAK2 Exon 12

if positive: Dx

Case 2

- 18 year old male
- 1yr history of erythrocytosis
 - headaches – improve with phlebotomy
- CBC (under therapy)
 - Hct 48.4 %
 - Hb 18.1 g/dl ↑
 - RBC 6.07 x 10⁹/l
 - Plt 248 x 10⁹/l
 - WBC 4.6 x 10⁹/l
- no cause of 2ndary erythrocytosis
- BM not evaluated
- Serum EPO: 9 U/l

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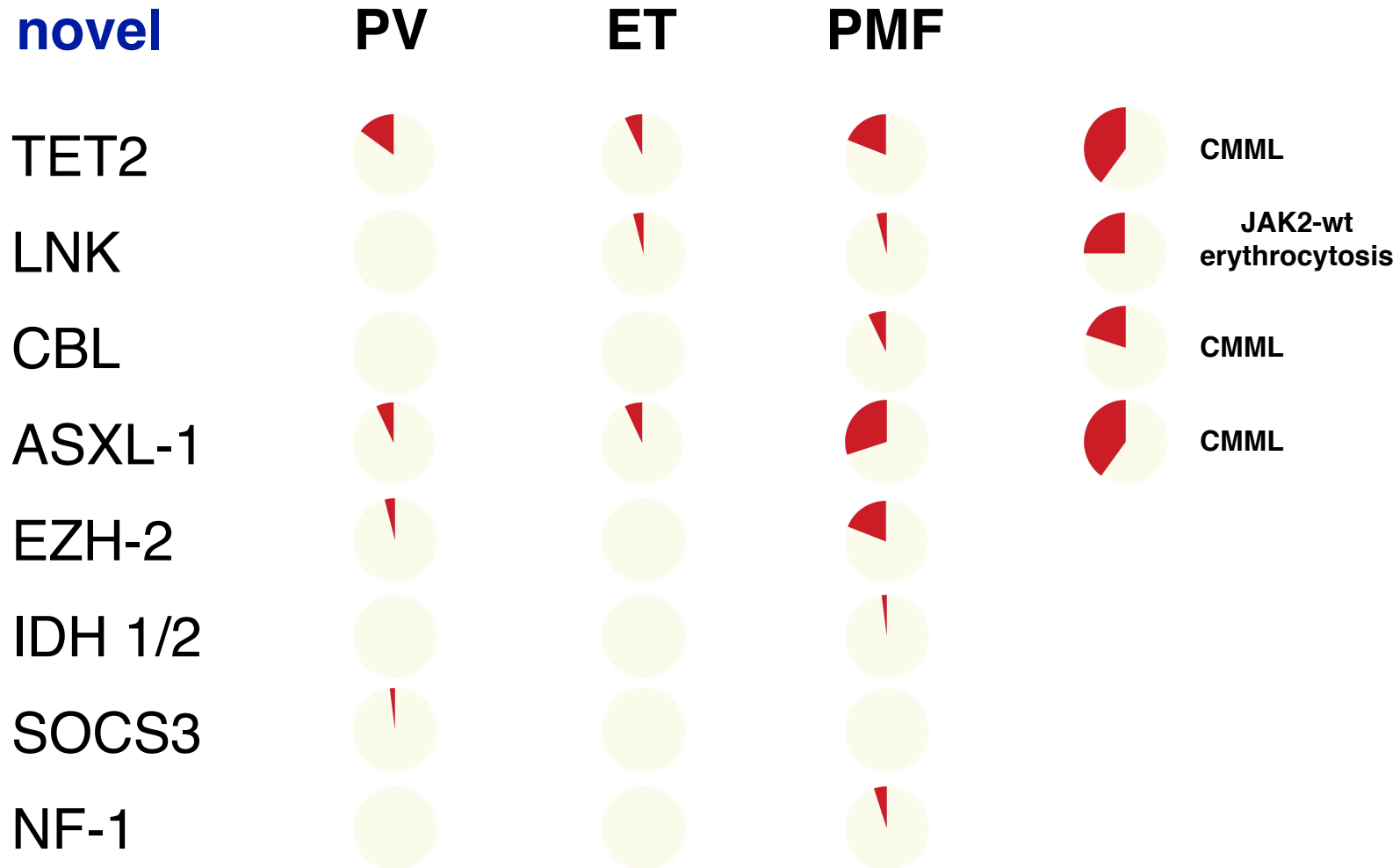
↓ negative

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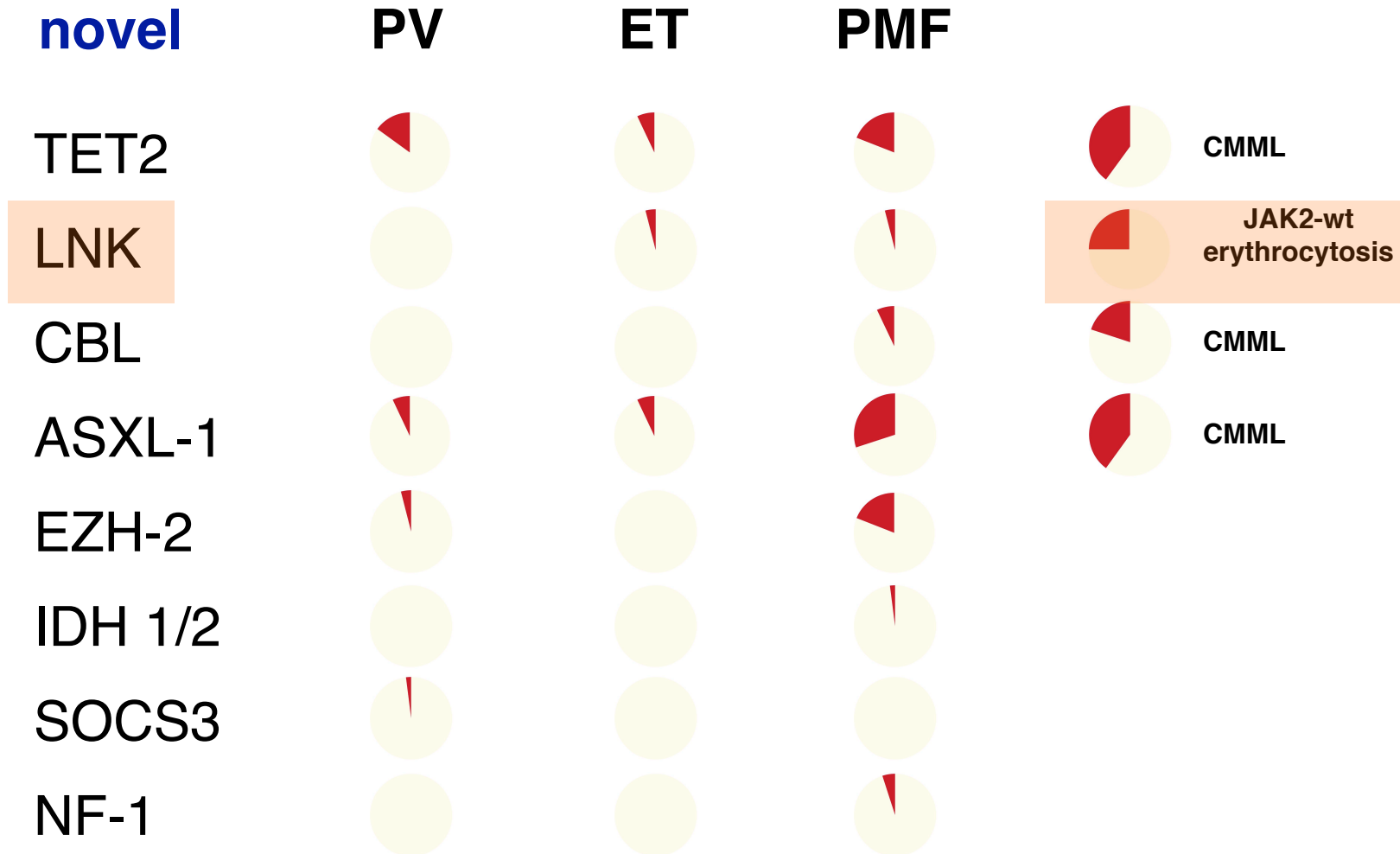
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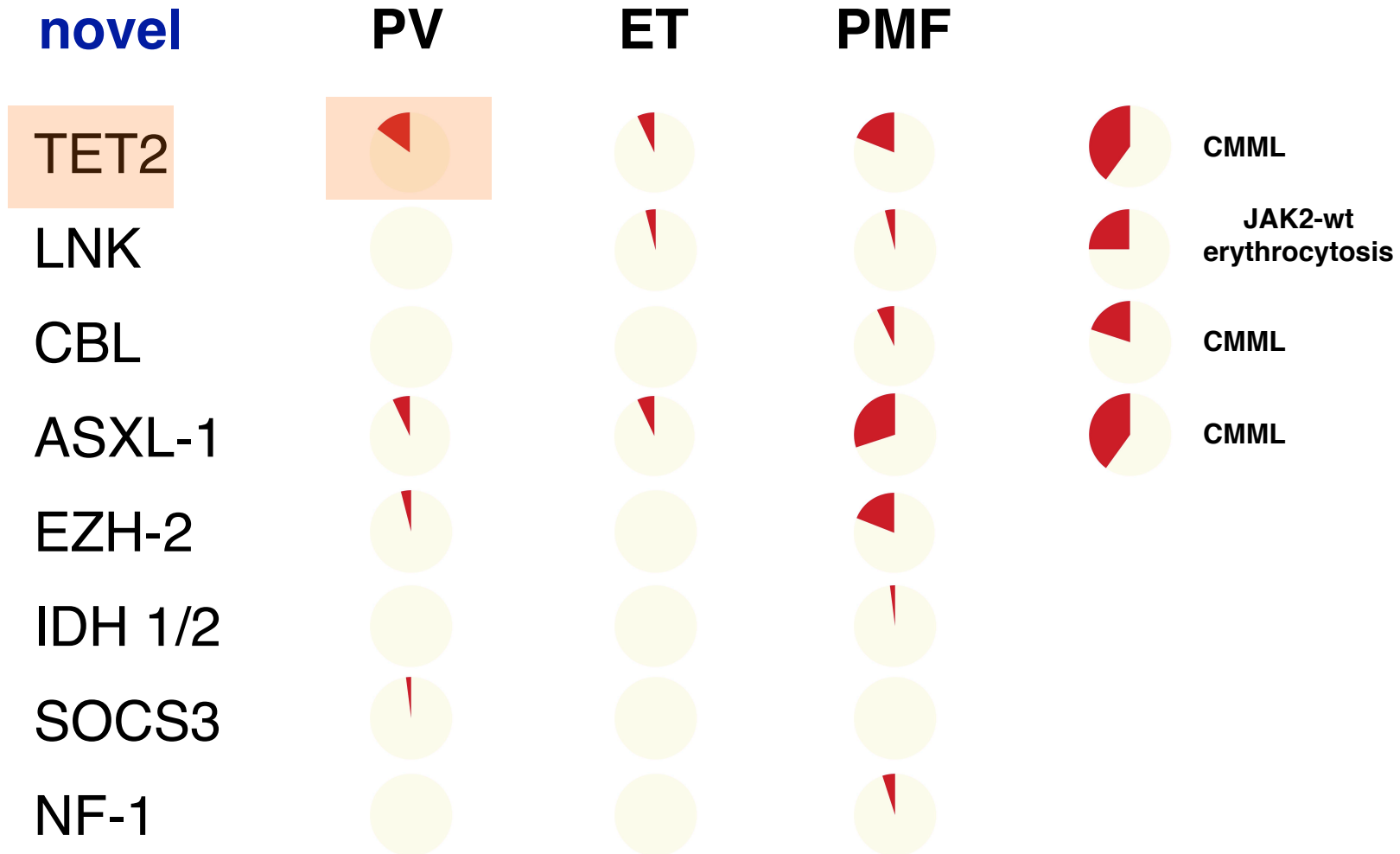
MPN biomarkers



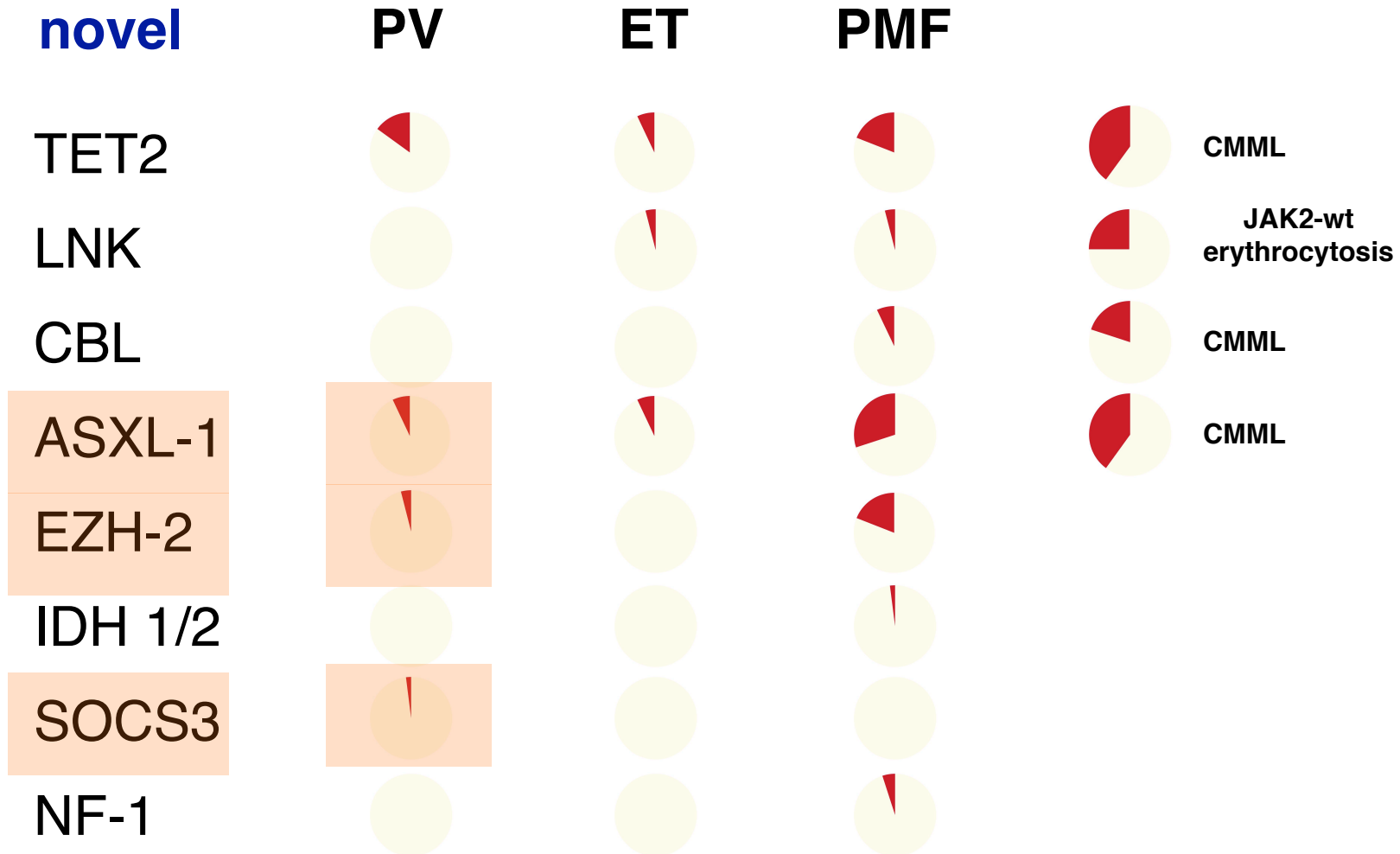
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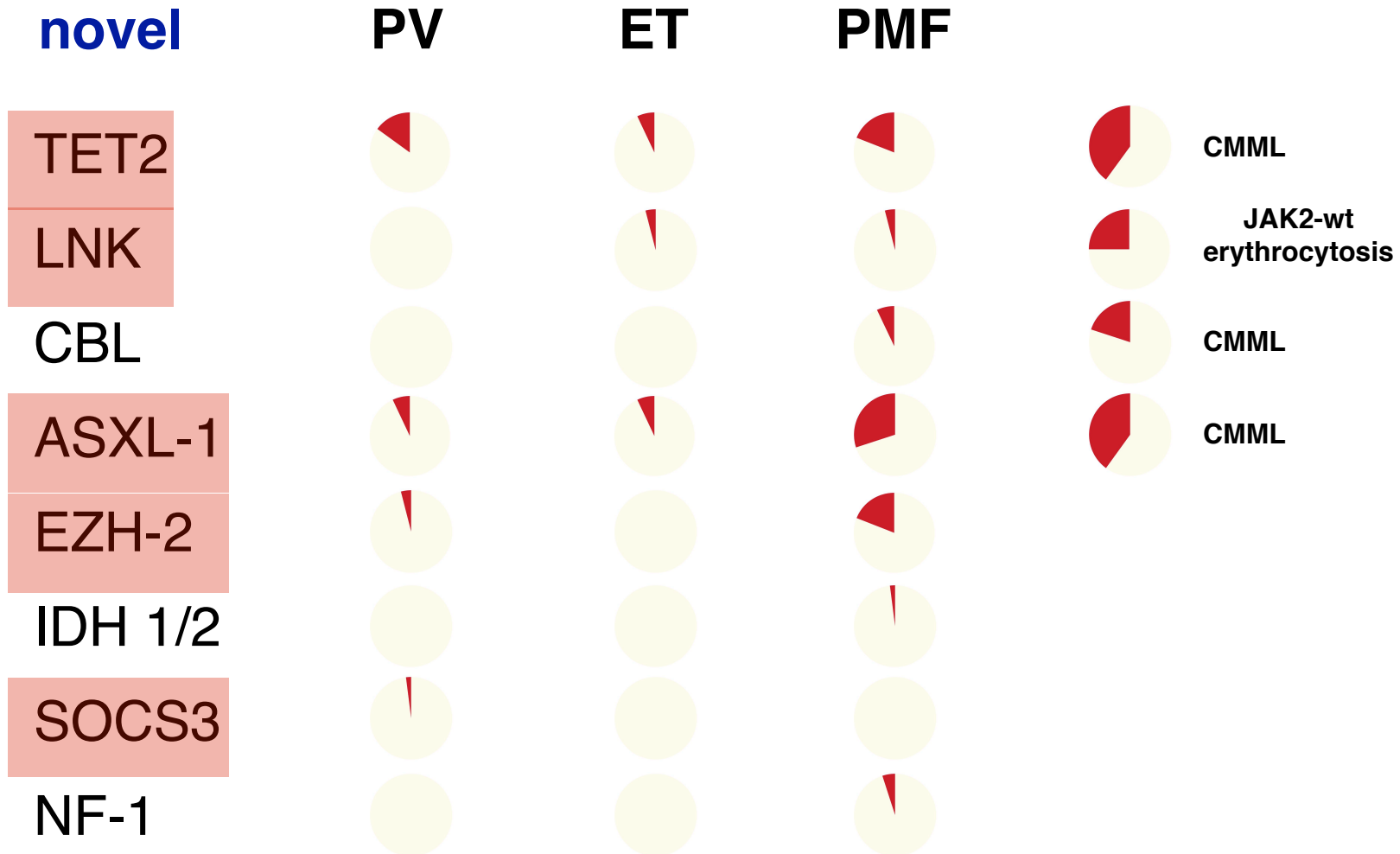
MPN biomarkers



MPN biomarkers



MPN biomarkers



The use of novel MPN markers for diagnosis

- challenging clinical cases of MPN
- JAK2 V617F and JAK2 Exon 12 – negative
 - not evaluated under IFN treatment

Case 3

- 40 year old male
- 1 yr history of thrombocytosis and leucocytosis
intermittent borderline erythrocytosis
 - microcirculatory symptoms
- CBC
 - Hct 47.8 % (51.8 %↑)
 - Hb 16.2 g/dl
 - RBC 6.41 x 10⁹/l ↑
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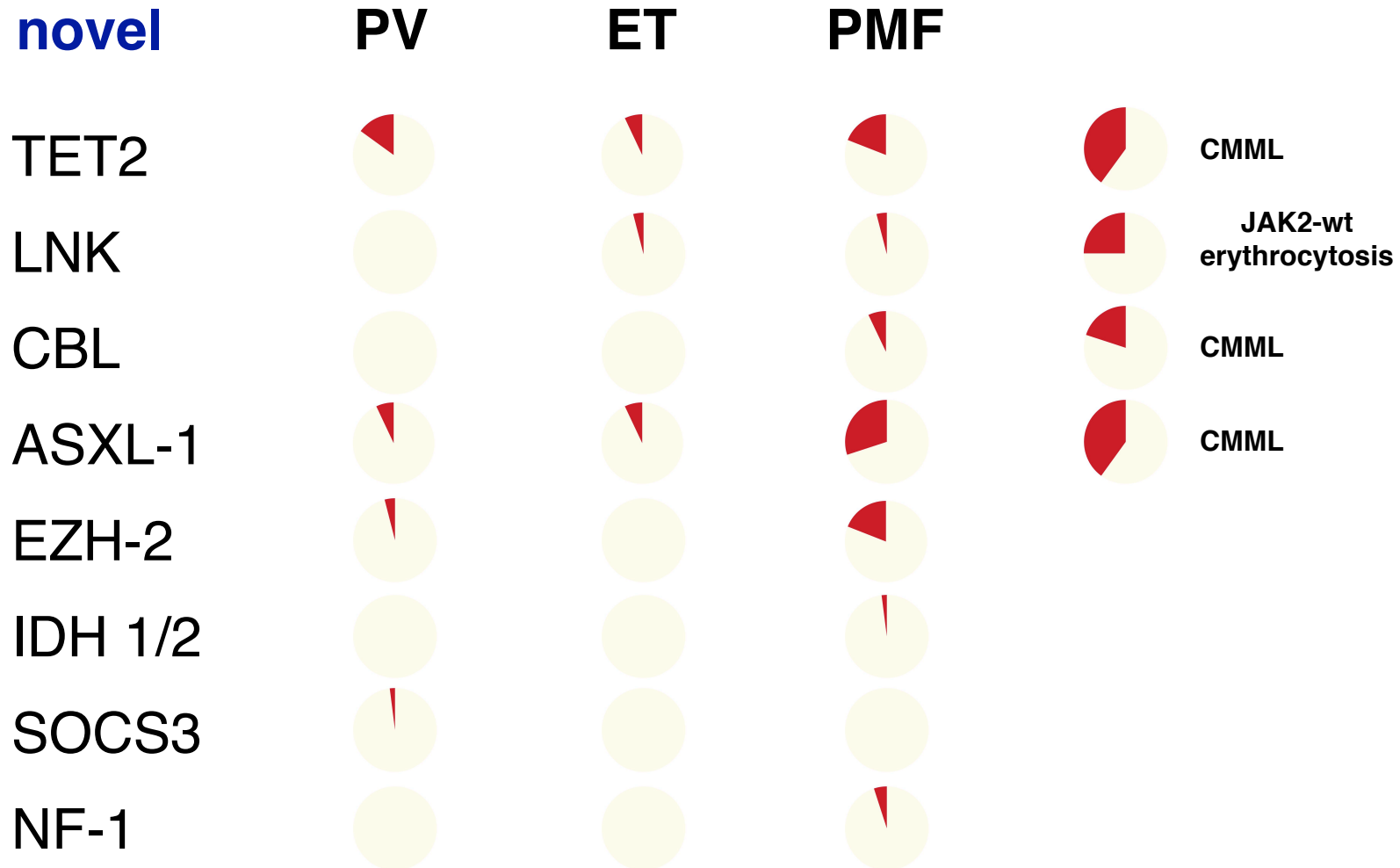
↓ negative

TET2

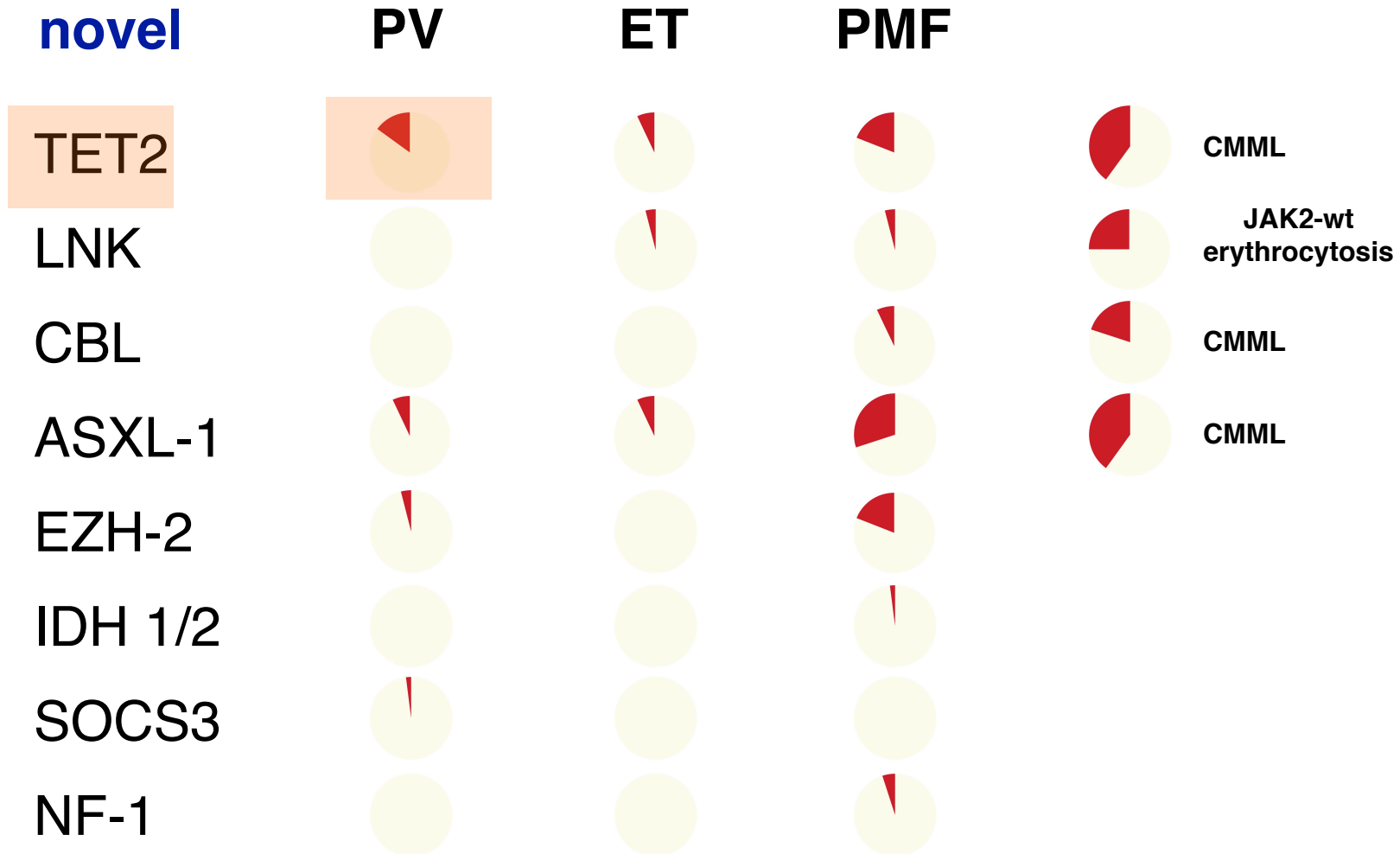
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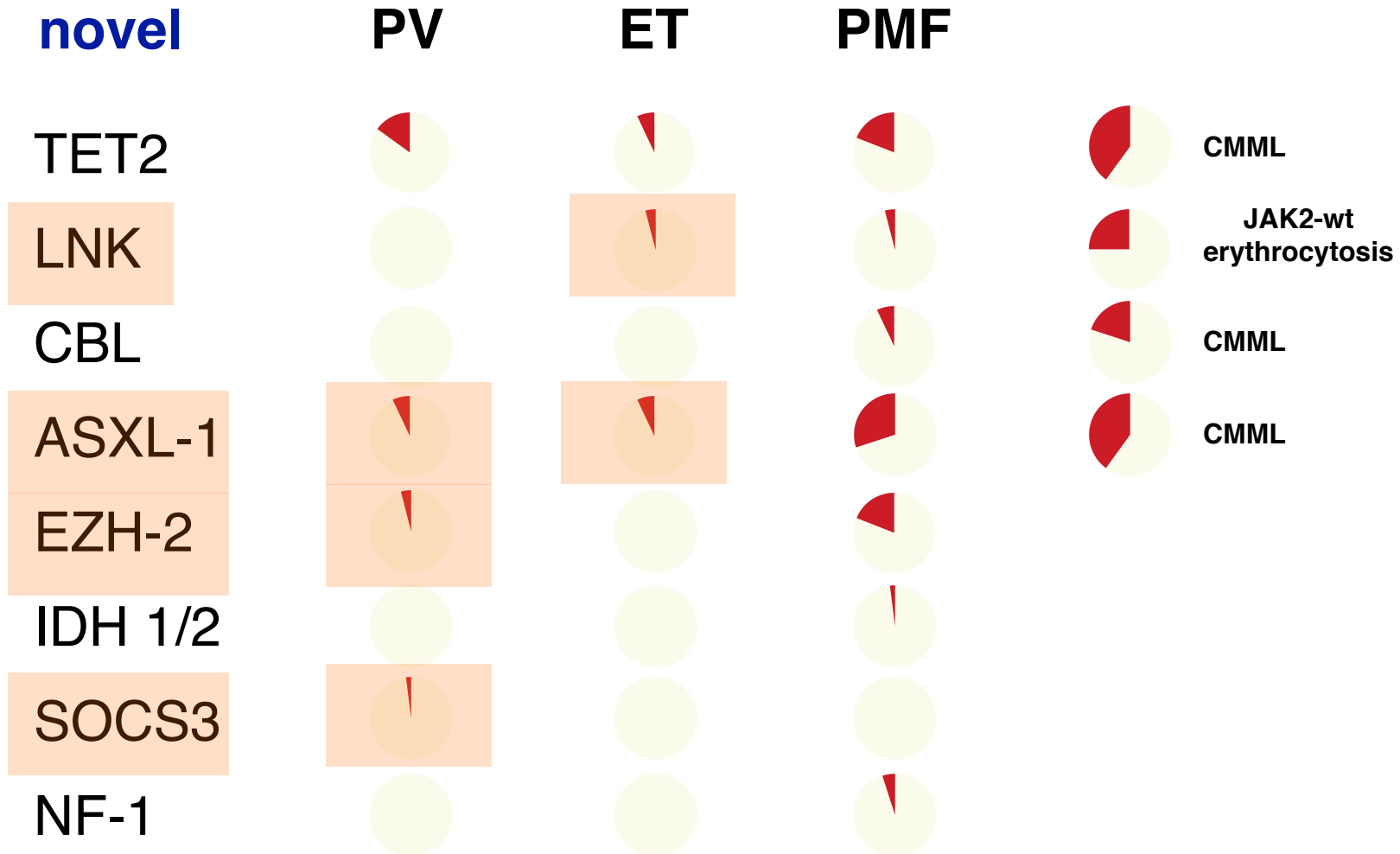
MPN biomarkers



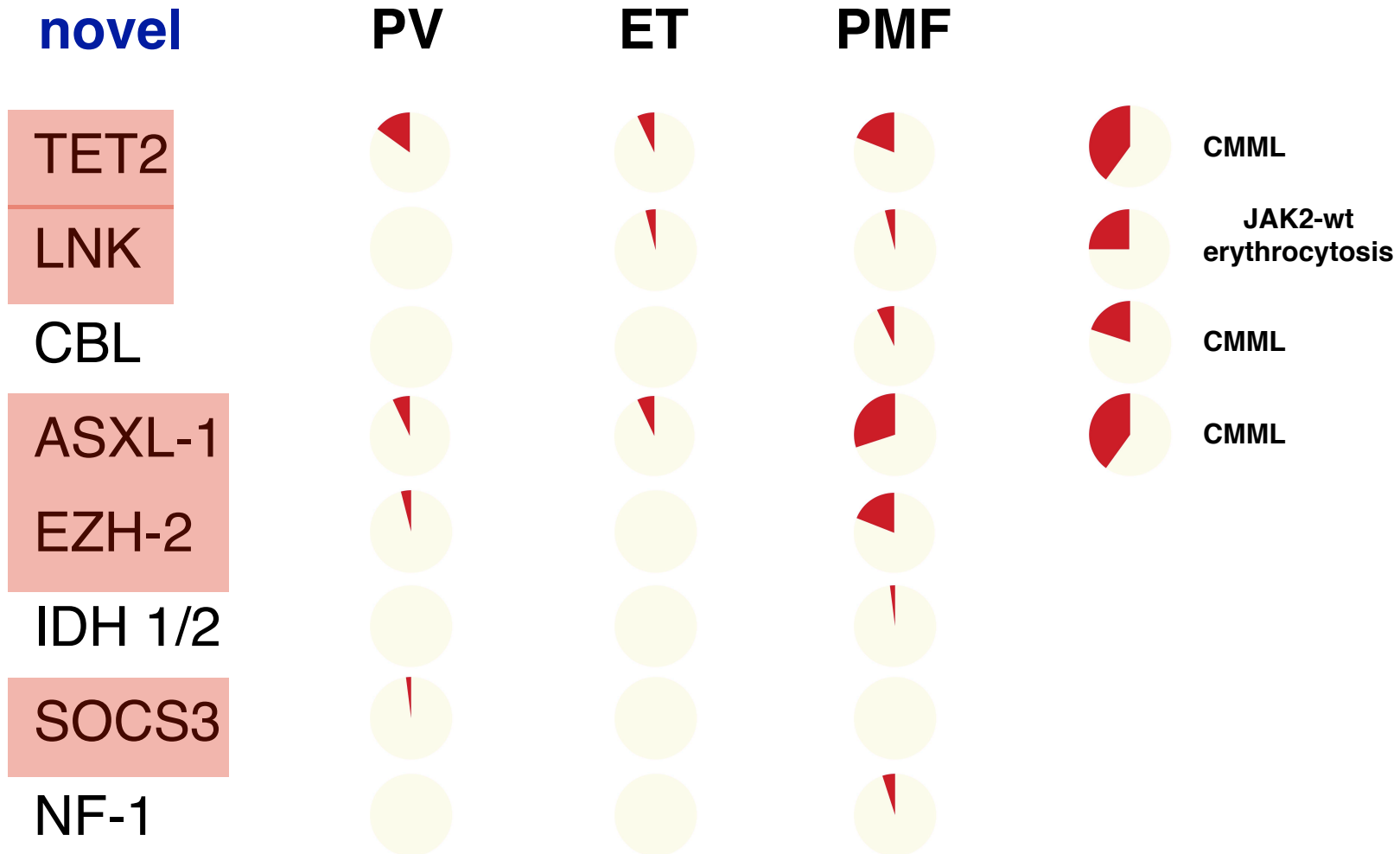
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19 “MPN markers”

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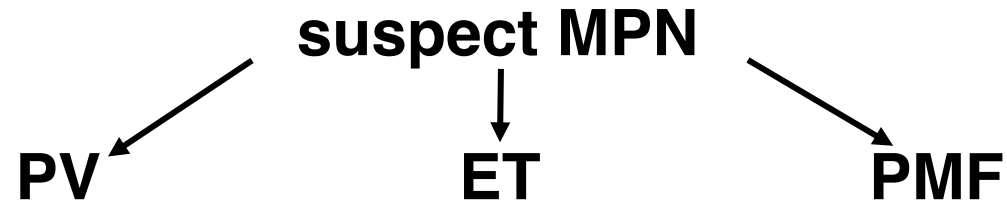
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The use of novel MPN markers for diagnosis

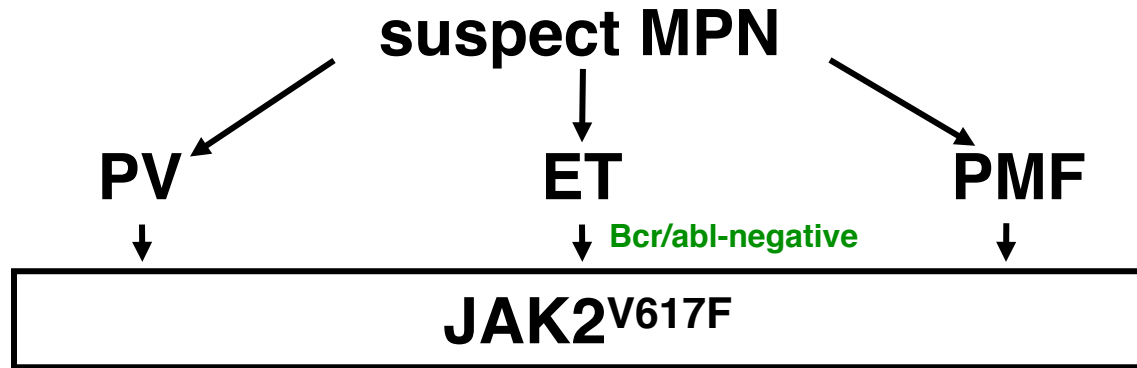
- challenging clinical cases of MPN
- JAK2 V617F and JAK2 Exon 12 – negative
 - not evaluated under IFN treatment
- secondary causes of erythrocytosis and thrombocytosis ruled out
 - a molecular marker is no substitute for a good clinical work up
 - new markers should compliment,
not replace old pathophysiological truths

Novel Markers for MPN Diagnosis

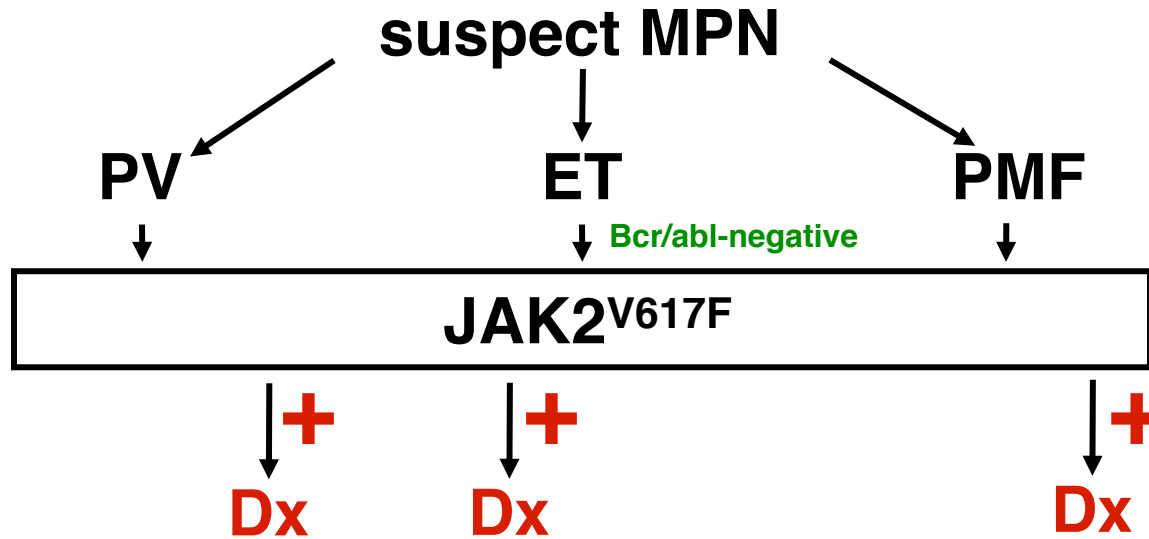
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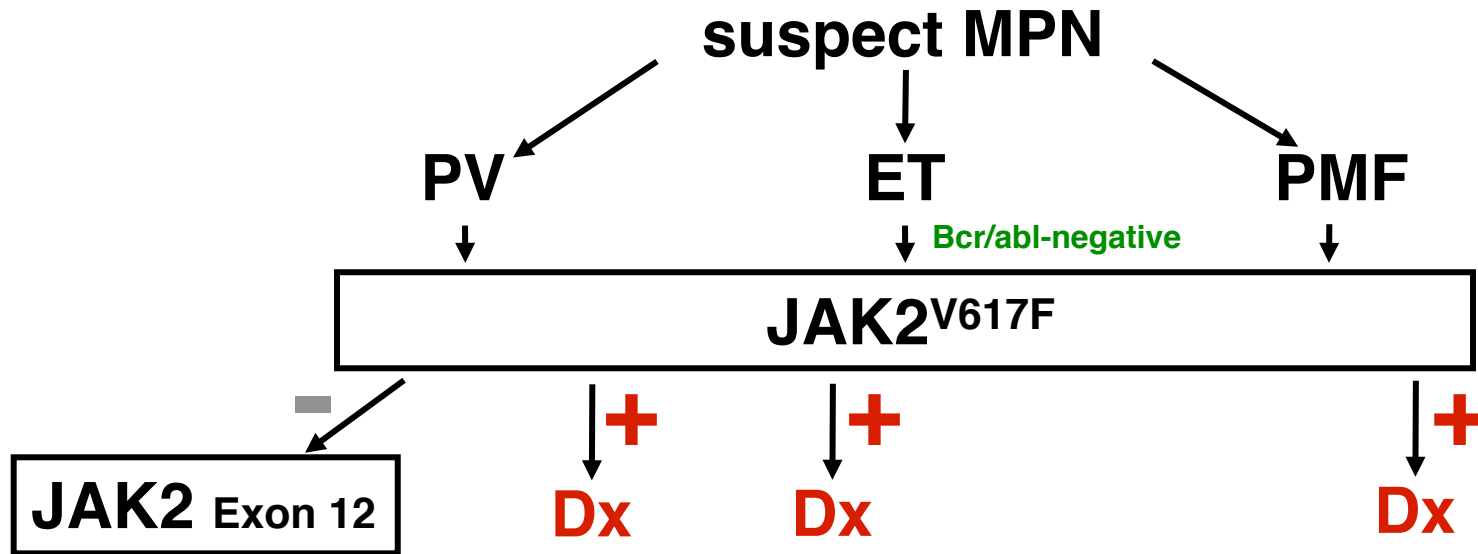
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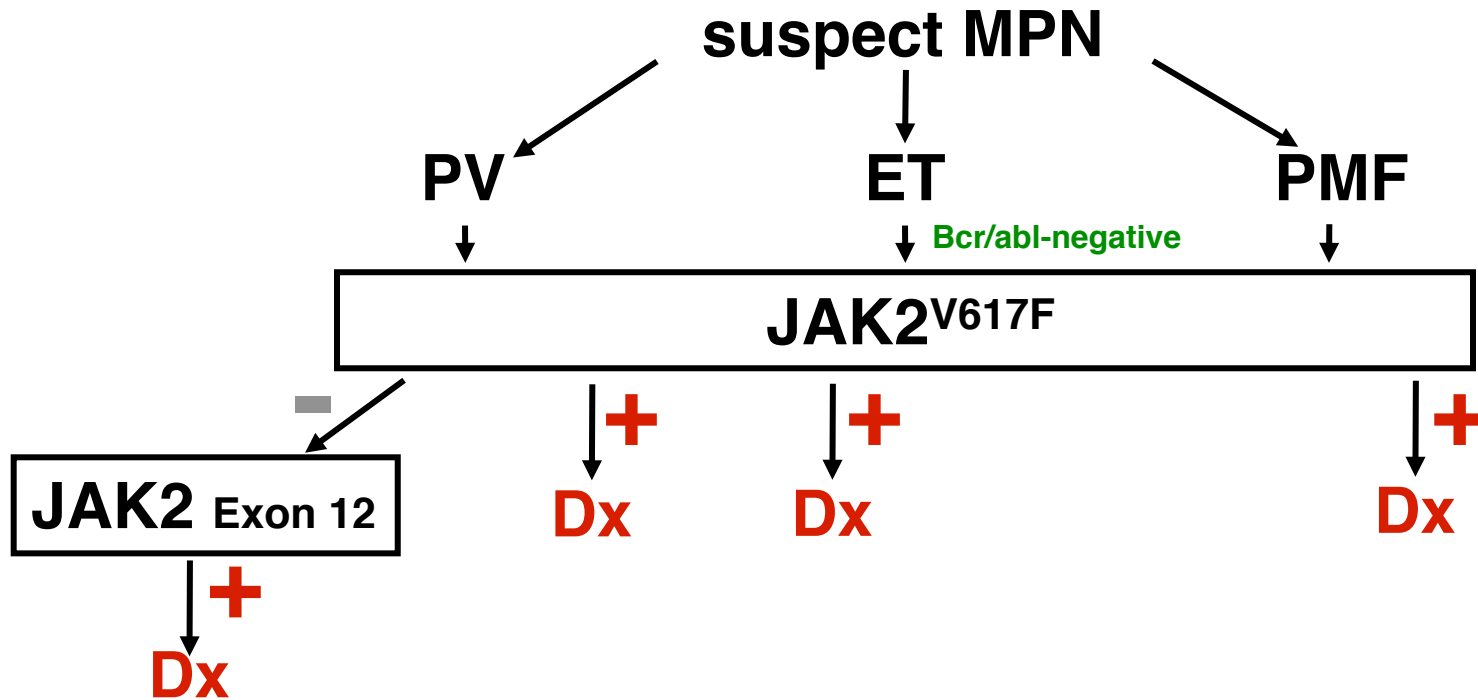
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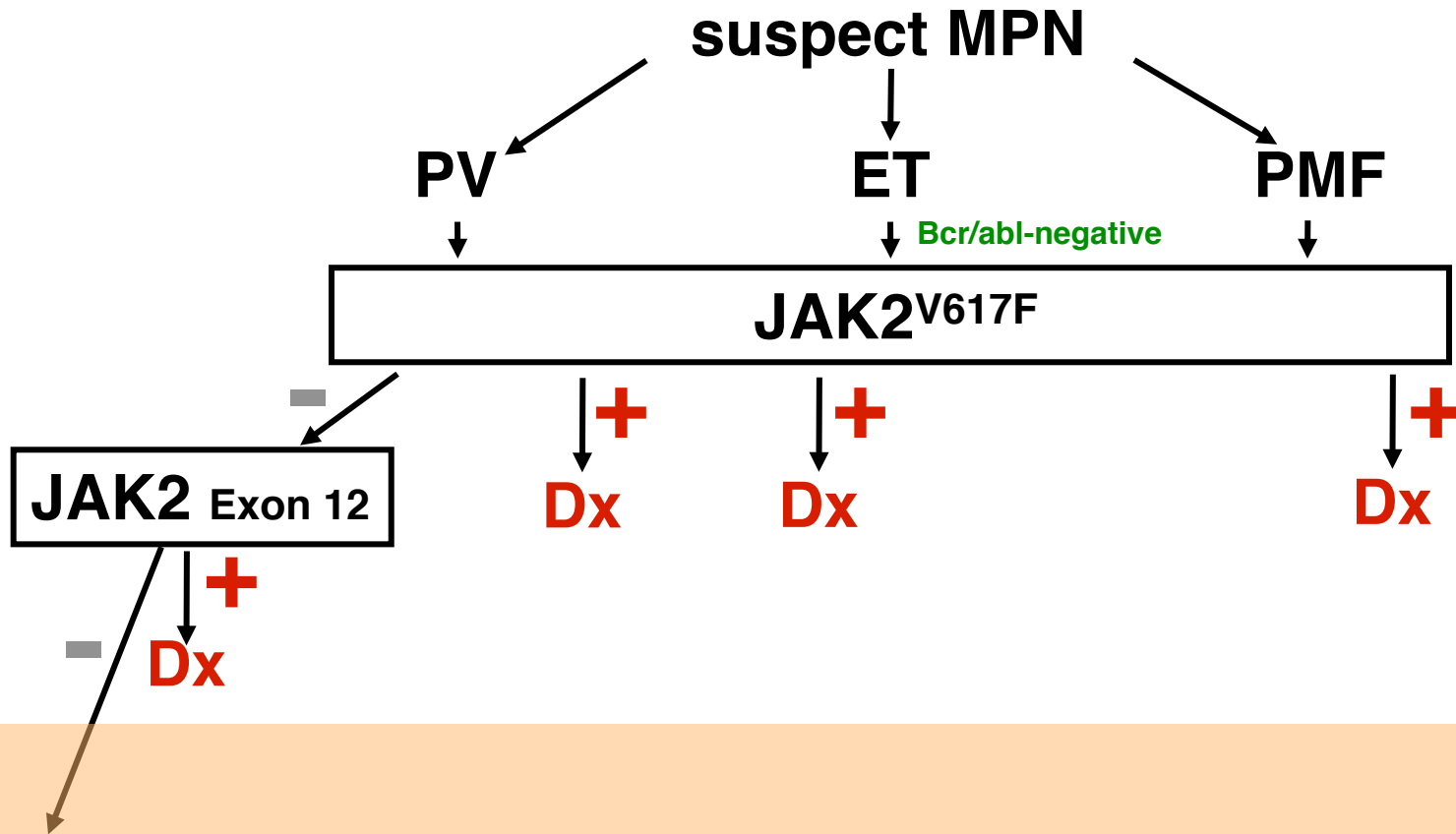
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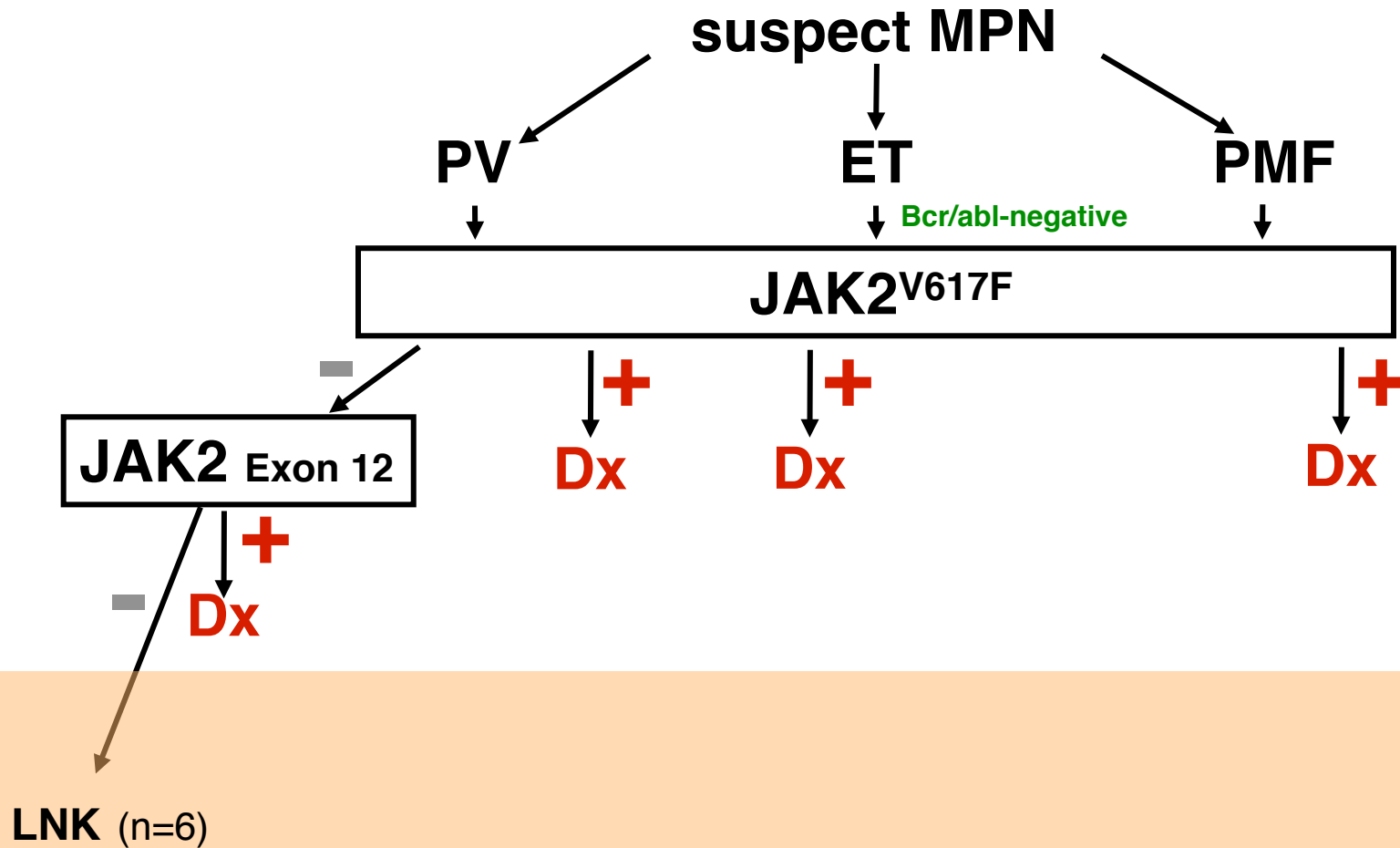
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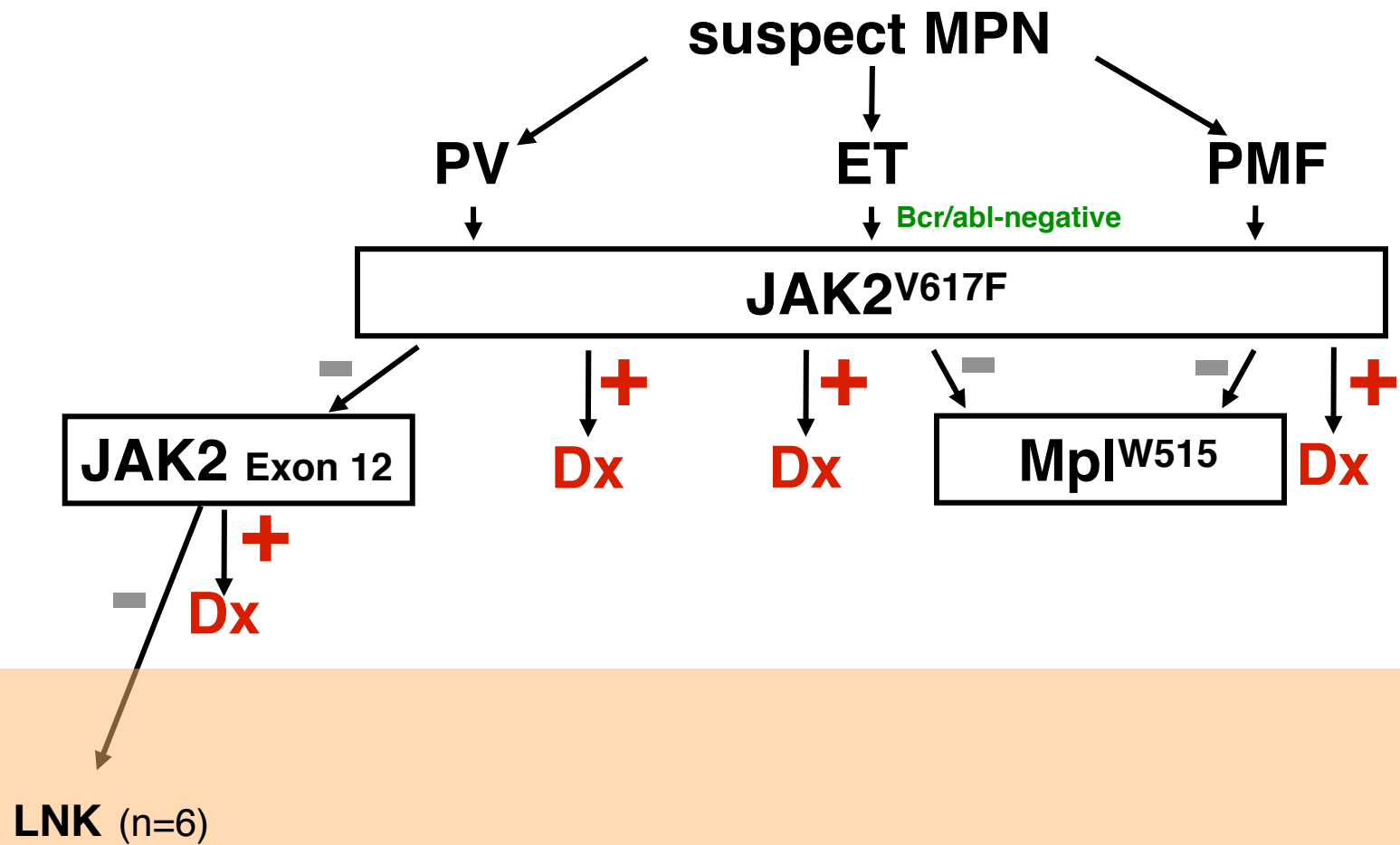
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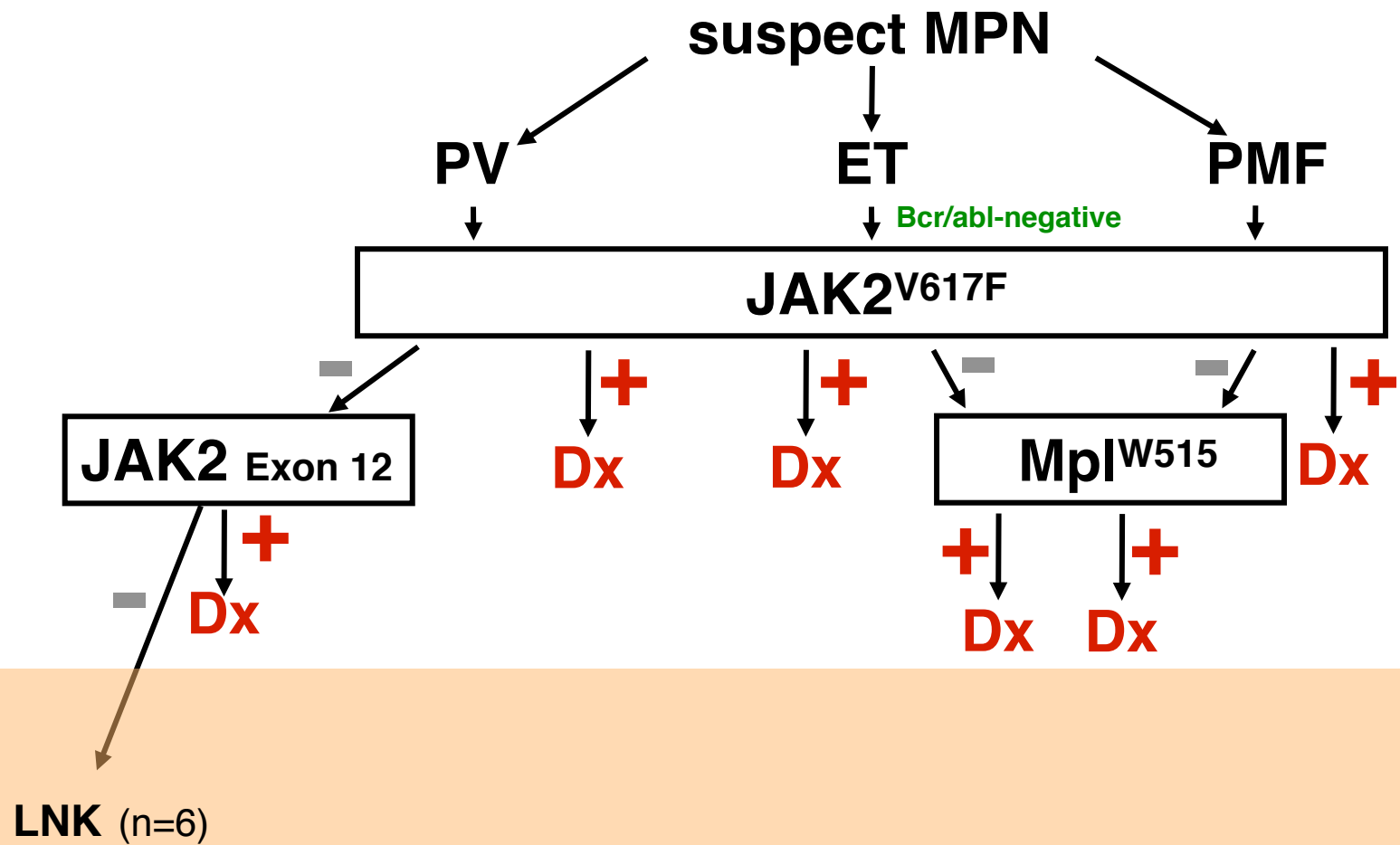
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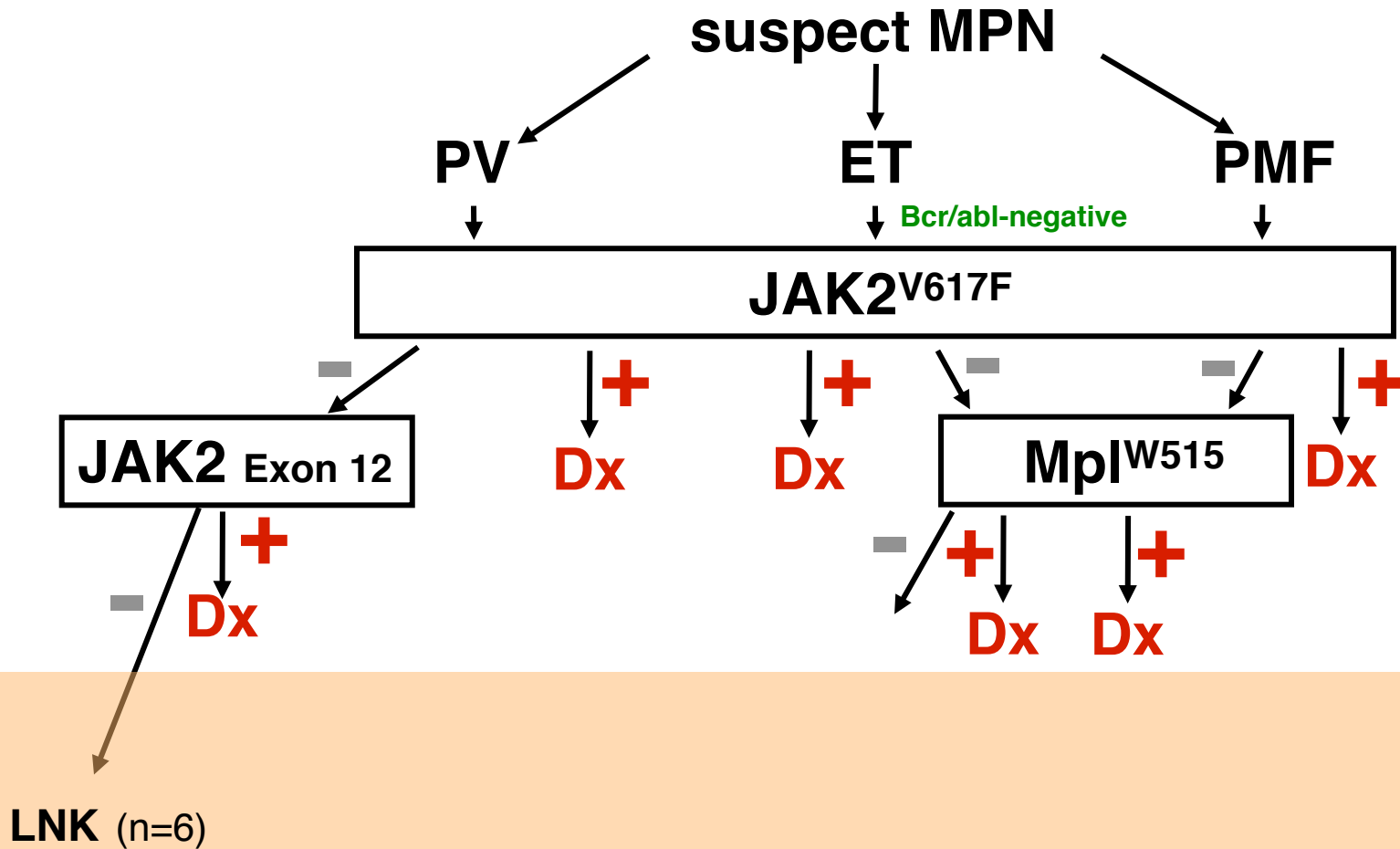
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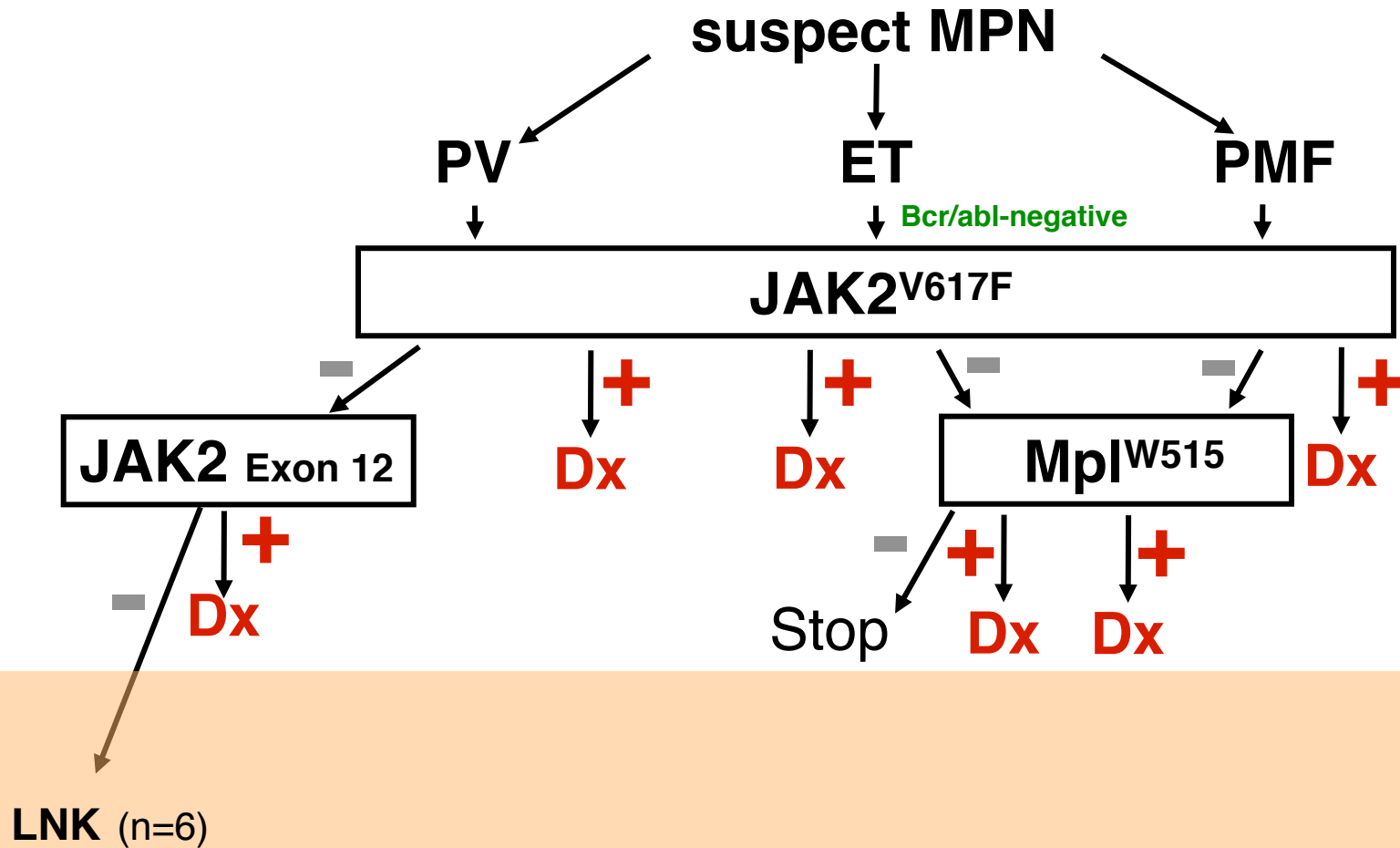
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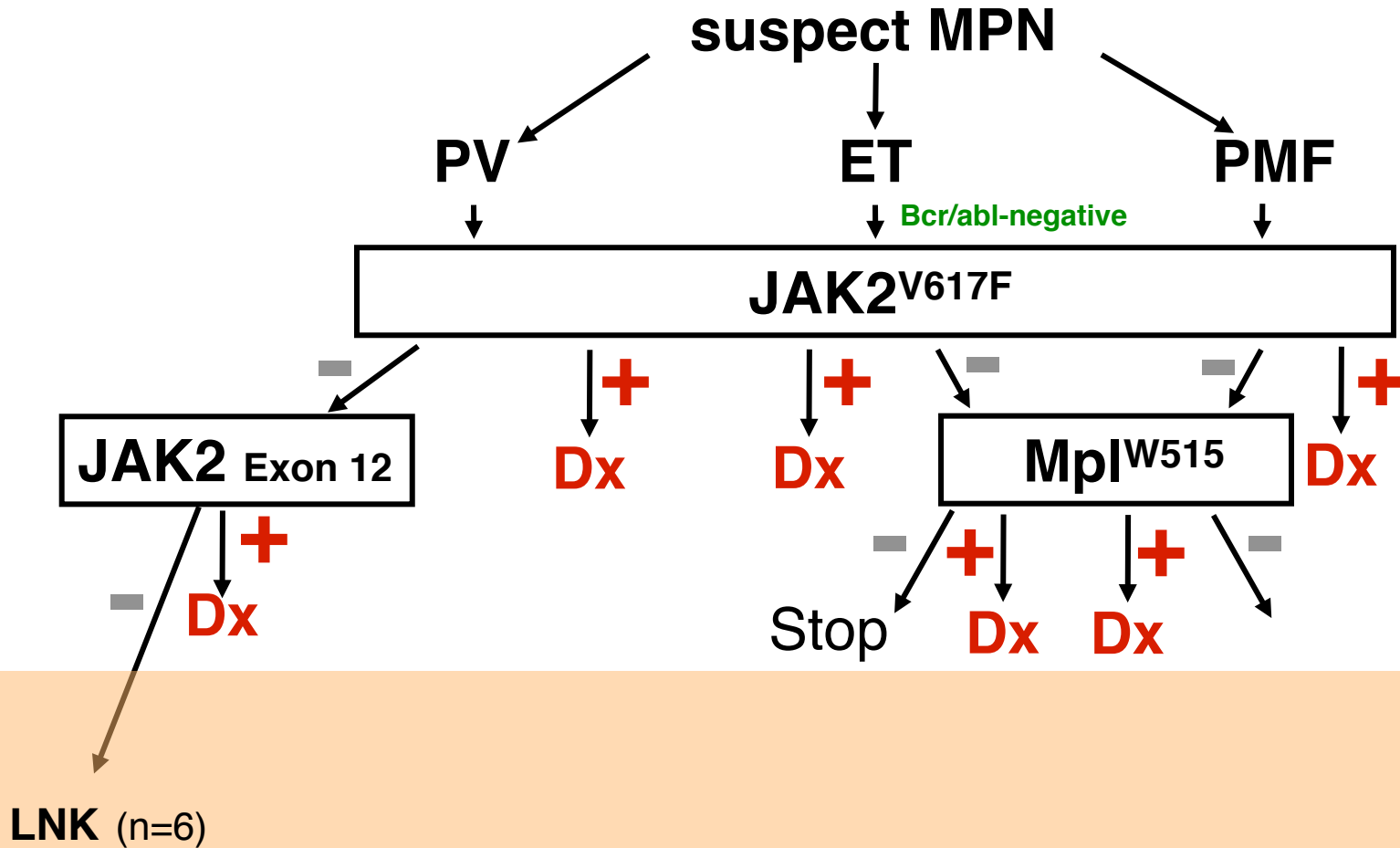
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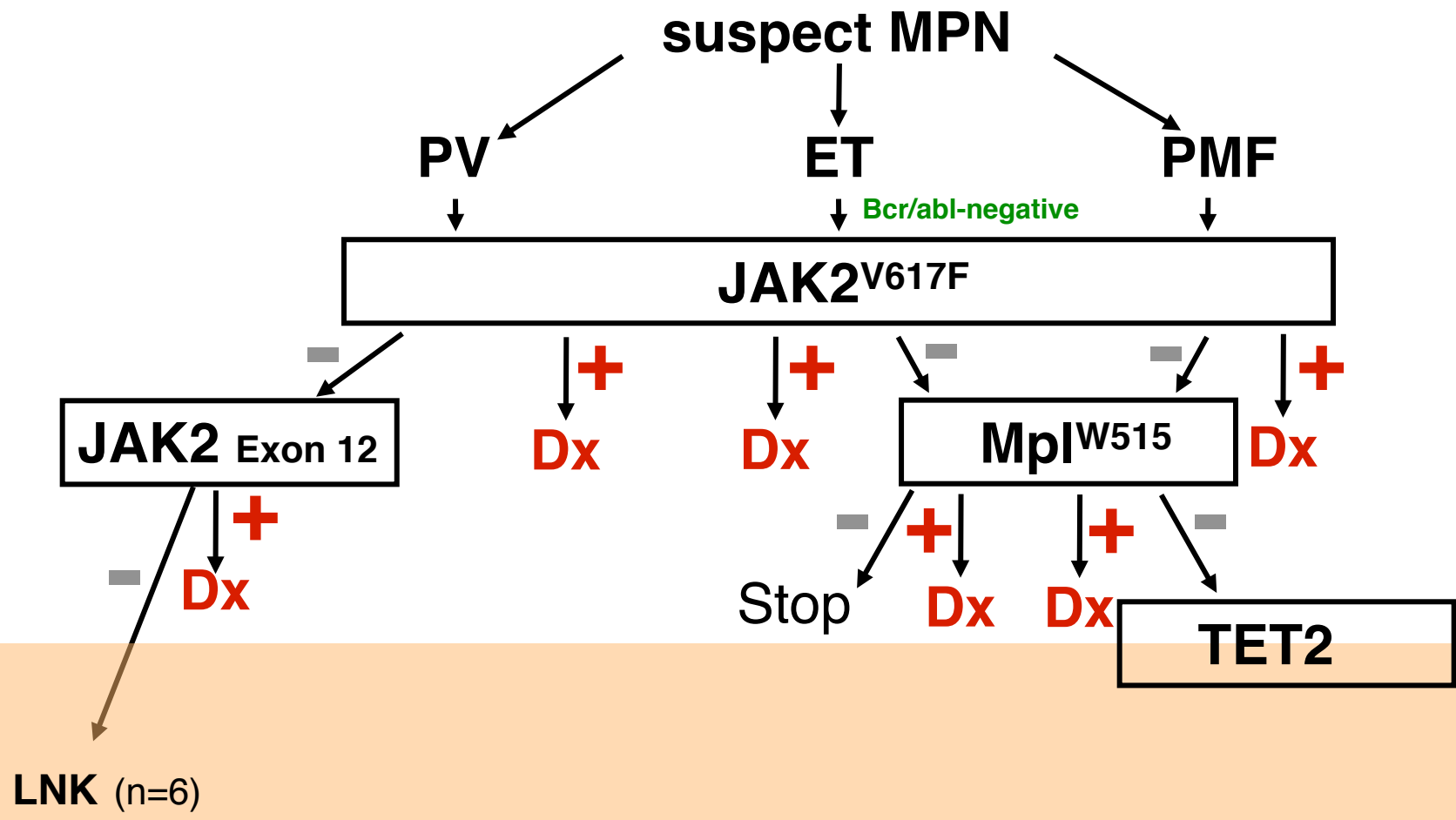
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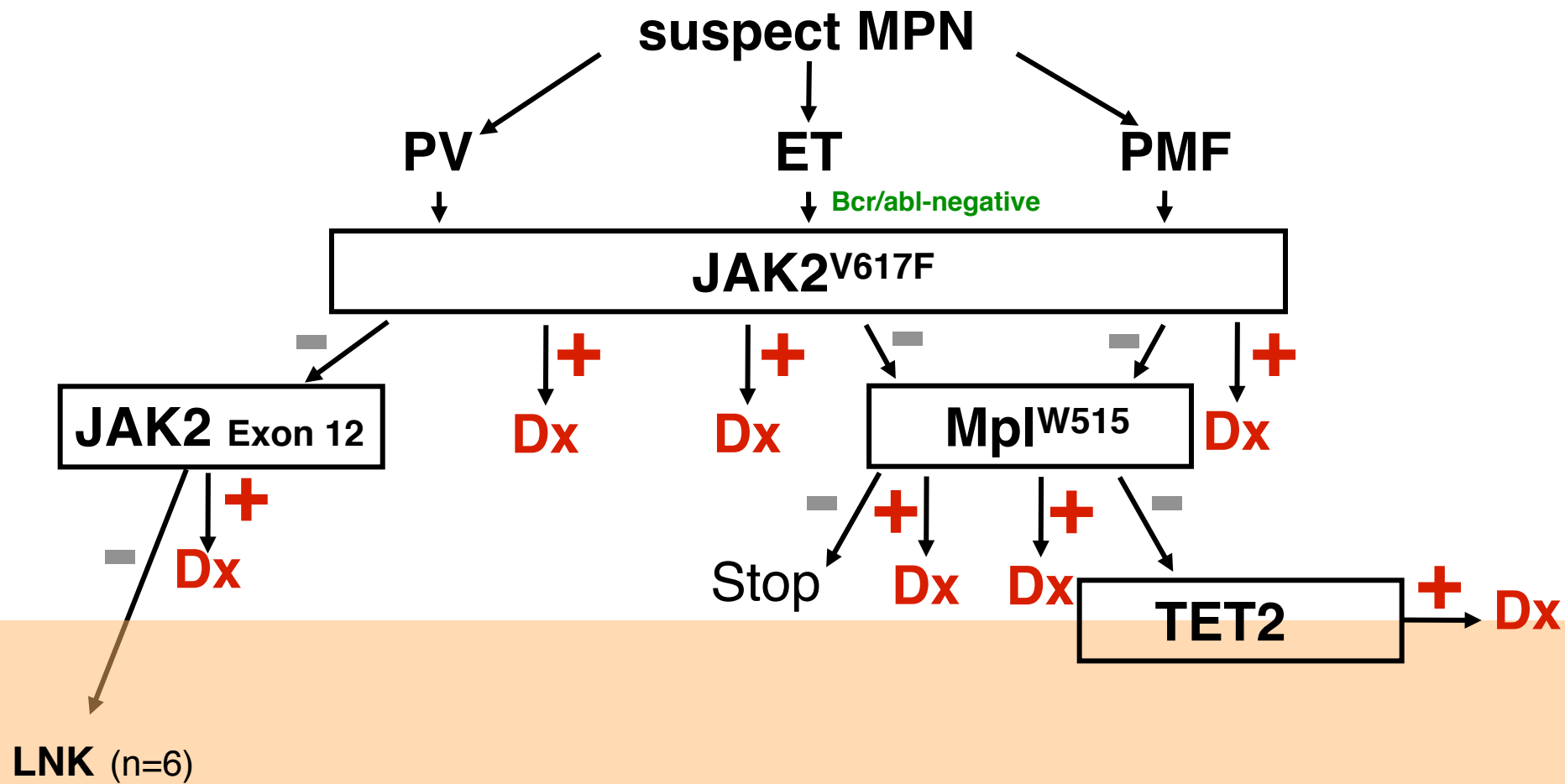
Novel Markers for MPN Diagnosis



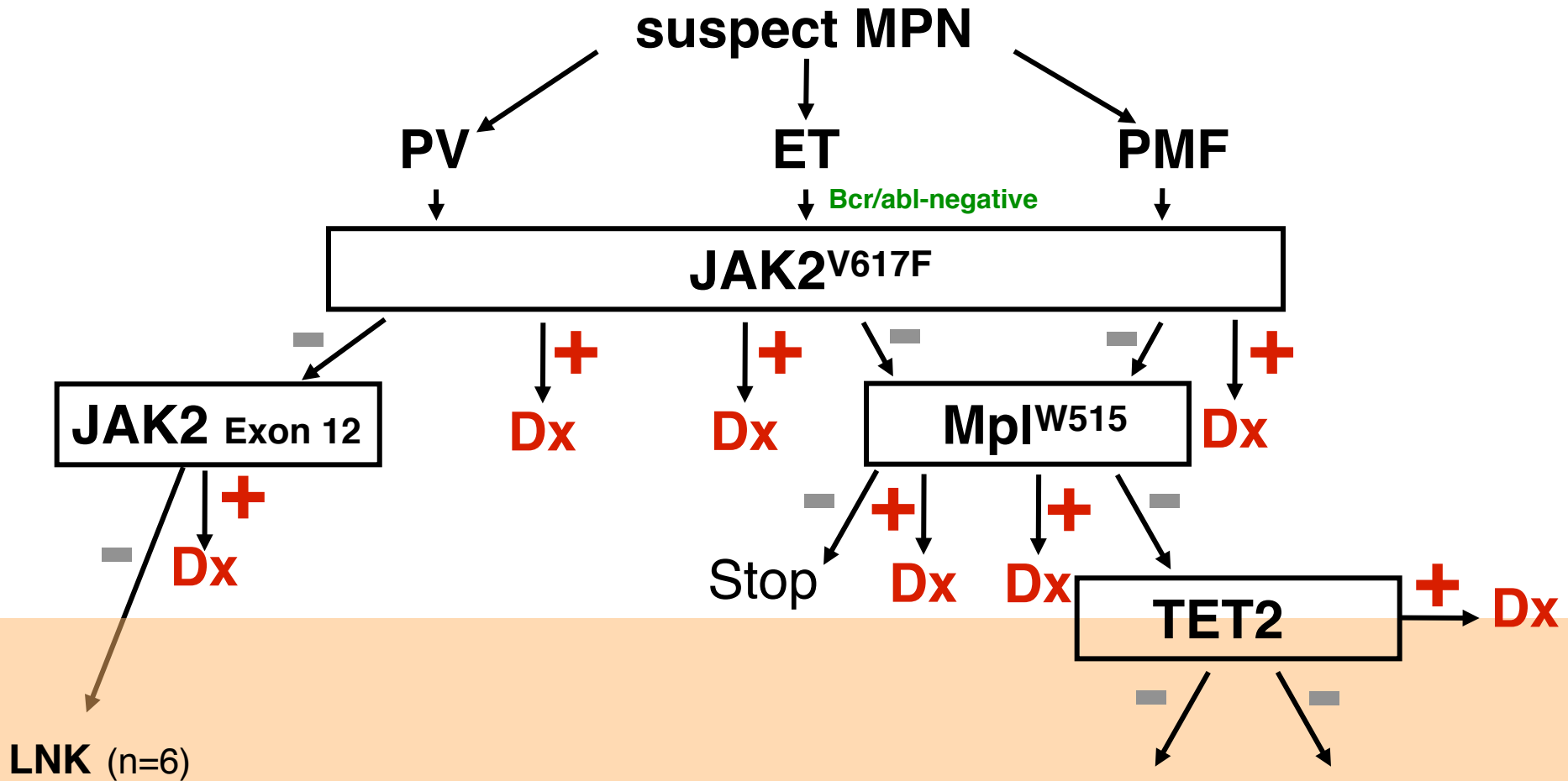
Novel Markers for MPN Diagnosis



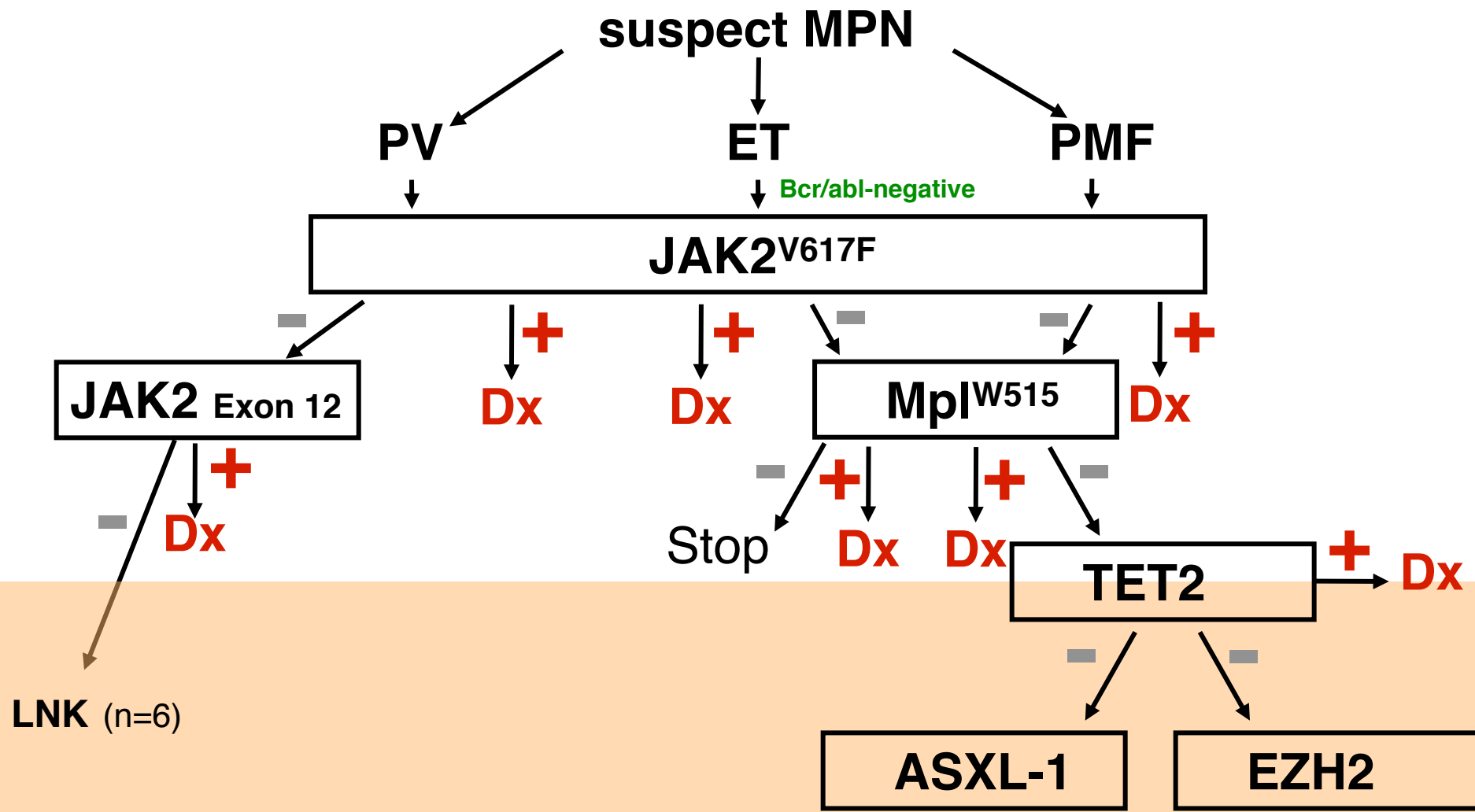
Novel Markers for MPN Diagnosis



Novel Markers for MPN Diagnosis



Novel Markers for MPN Diagnosis



The use of MPN markers for follow up

- JAK2 V617F decreases with IFN treatment
 - treatment discontinuation based on JAK2 V617F - negativity has not been studied in a large cohort of patients
- there are no reports on the response of **novel** MPN markers to therapy in large series of patients
 - currently no indication for follow up measurements

Molecular Markers in MPN used wisely

- For diagnosis
 - one marker is sufficient
 - PV
 - expand clinical workup before using novel markers (>98% positive: JAK2 V617F and Exon12 mutations)
 - ET
 - “marker negative” ET is a well worked up patient
 - PMF
 - diagnosis may be facilitated by novel markers
 - availability
 - costs / insurance

Molecular Markers in MPN used wisely

- For follow up
 - only during IFN treatment
 - implication for discontinuation of therapy unclear

Molecular Markers in MPN used wisely

- For clinical trials
 - large clinical trials using novel molecular markers are needed
 - to establish
 - prognostic consequences
 - differences in response to therapy
 - results from these trials will change recommendations for routine use
 - the previous slides will change by 2013