MPN Horizons
Understanding the New Complexity of MPNs
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Know your ABCs:
multiple muddling myeloid mutations

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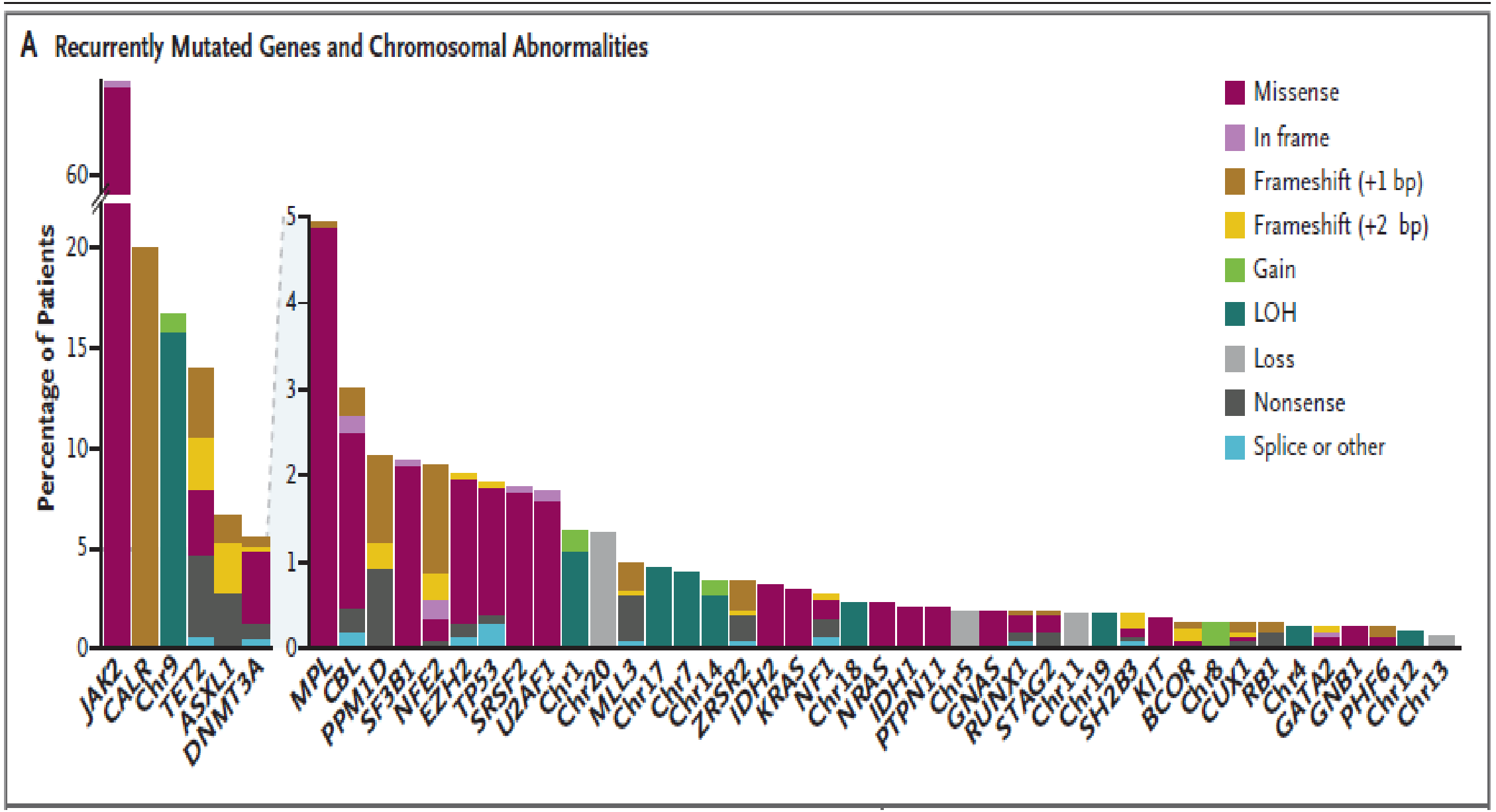
Outline

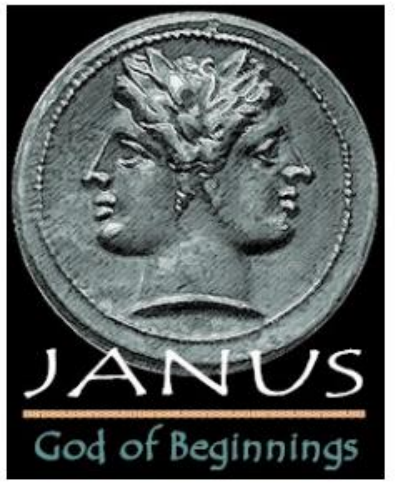
- What’s with the names?!
- Functional aspects of gene mutations
- Prognostic importance

Recurrent mutations in MPN



Origins of the names

- JAK= Janus kinase
- CALR = calreticulin
- MPL= myeloproliferative leukemia
- ASXL= “additional Sex-Combs like”
- EZH= “enhancer of zeste homolog”
- SRSF= “serine and arginine rich splicing factor”
- TET= “ten to eleven” – chromosome translocation
- VAV= sixth letter in the Hebrew alphabet



Functional aspects

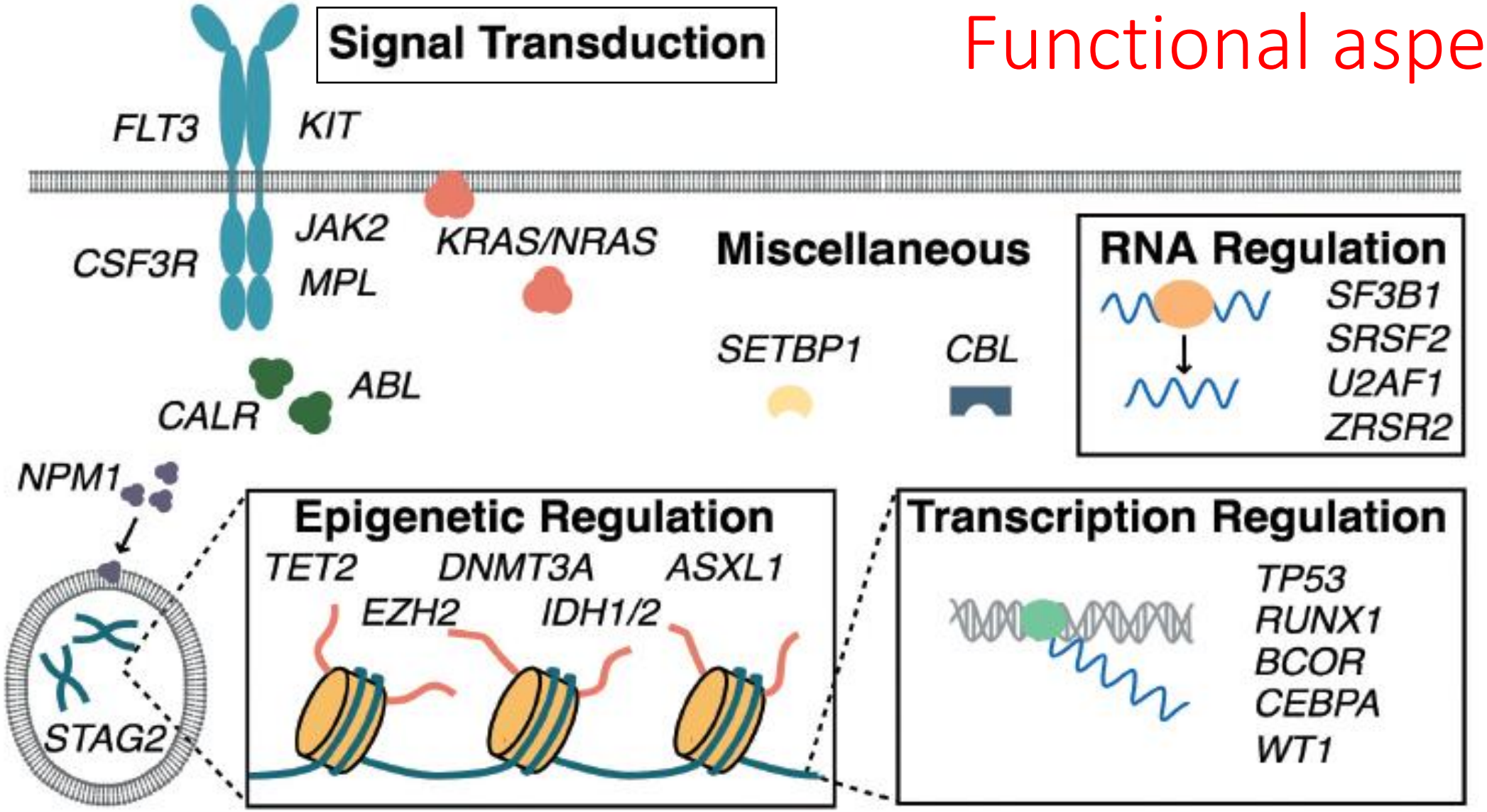
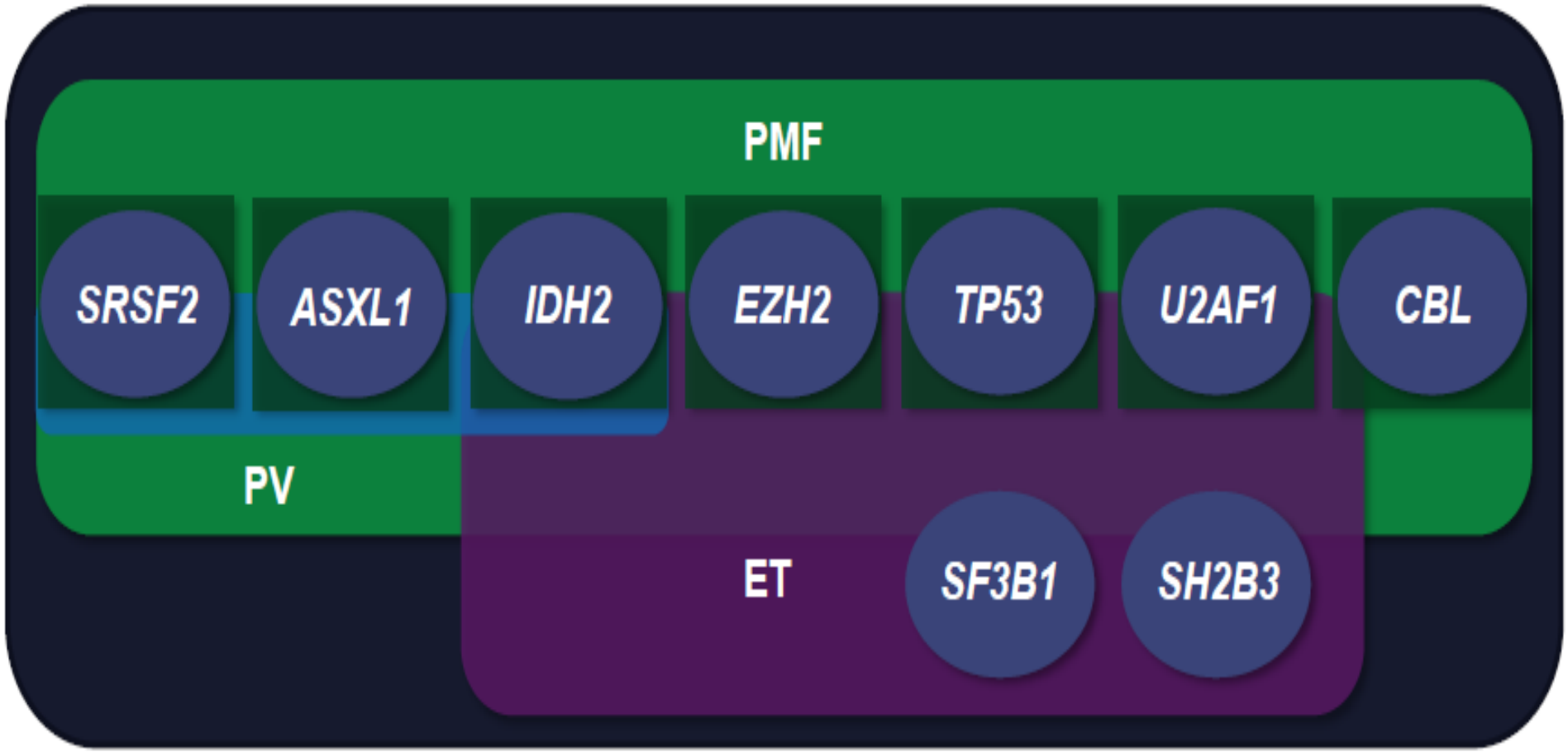


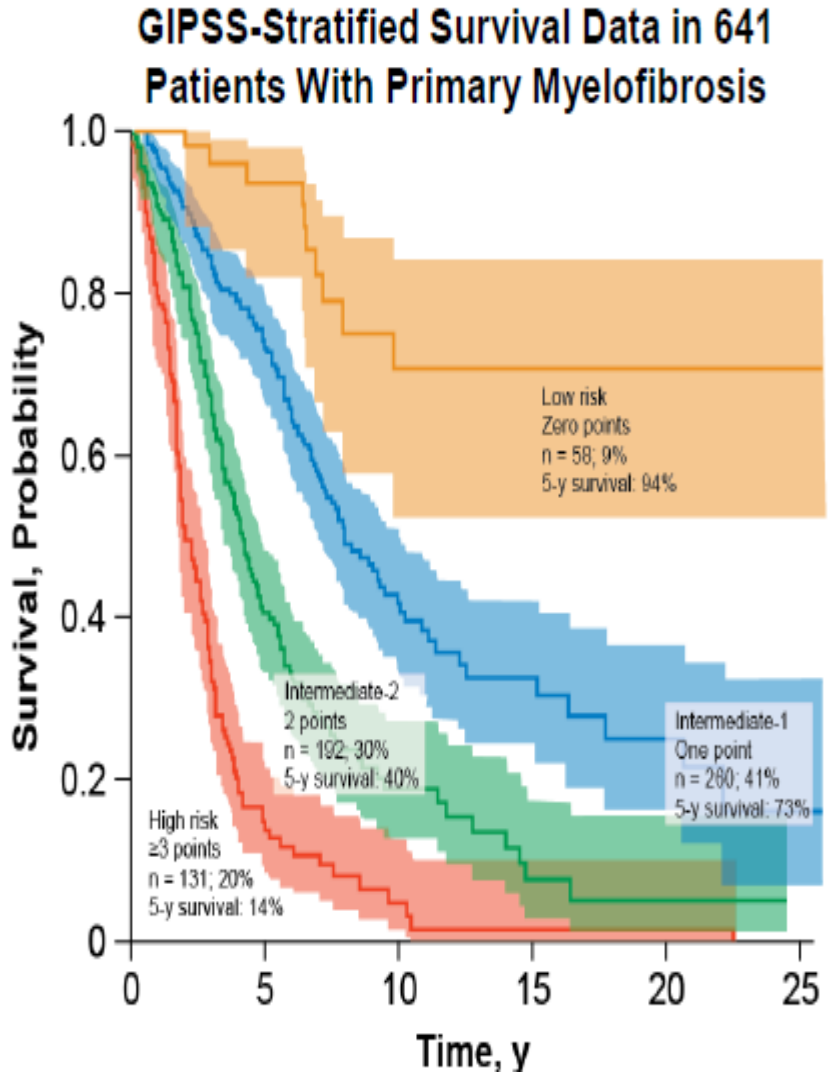
Figure 1. Genes Recurrently Mutated in Myeloid Malignancies Categorized by Oncogenic Mechanism—Mutations in genes involved with signal transduction, regulation of transcription, and epigenetic modification have diagnostic, prognostic, and therapeutic consequences.

“Non-Driver” Mutations

Prognostically important genes,
other than *JAK2/CALR/MPL*, in ET, PV, and MF



GIPSS:
Genetically Inspired Prognostic Scoring System[1]



- **Karyotype**
  - Very high risk = 2 points
  - Unfavorable = 1 point
- **Driver mutations**
  - Type 1–like *CALR* absent = 1 point
- **High-risk mutations**
  - *ASXL1* mutation = 1 point
  - *SRSF2* mutation = 1 point
  - *U2AF1* Q157 mutation = 1 point

Table 1 Comparison of genetic-based risk models in myelofibrosis

Clinical or genetic variable	MIPSS70	MIPSS70+V2.0	GIPPS
Anemia	X	X[a]	
Leukocytosis	X		
Thrombocytopenia	X		
Blasts	X	X	
Constitutional symptoms	X	X	
Bone marrow fibrosis	X		
High-risk karyotype		X	X
Absence of good-risk CALR type 1 mutation	X	X	X
Presence of high-risk ASXL1 mutation	X	X	X
Presence of high-risk SRSF2 mutation	X	X	X
Presence of high-risk EZH2 mutation	X	X	
Presence of high-risk IDH1/IDH2 mutation	X	X	
Presence of U2AF1 mutation		X	X

[a]Defines sex-specific hemoglobin thresholds (severe: women < 8 g/dL and men < 9 g/dL, moderate: women 8–9.9 g/dL and men 9–10.9 g/dL)

What to do with the information?

- No “mutation-directed therapy” currently
- “Bad” mutations may drive decision to transplant
- HOPEFULLY THIS WILL CHANGE!
  - RAS inhibitors
  - p53 pathway inhibitors
  - Specific JAKm inhibitors
  - CALR directed immunotherapy