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Current Status of MPN Guidelines: Response and Treatment

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MPNs: A historical view—the pre-JAK2 era

G. Heuck describes MF "Two cases of leukemia with peculiar blood and bone marrow findings"

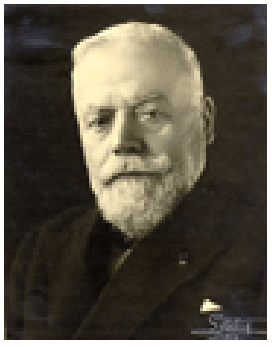
Epstein and Goedel describe ET, noting a pt with extreme increase in platelets and bleeding

The Ph Chromosome

Nowell and Hungerford

A change in cancer therapy

1879 | 1892-1903 | 1931 | 1951 | 1960 | 1967 | 1996

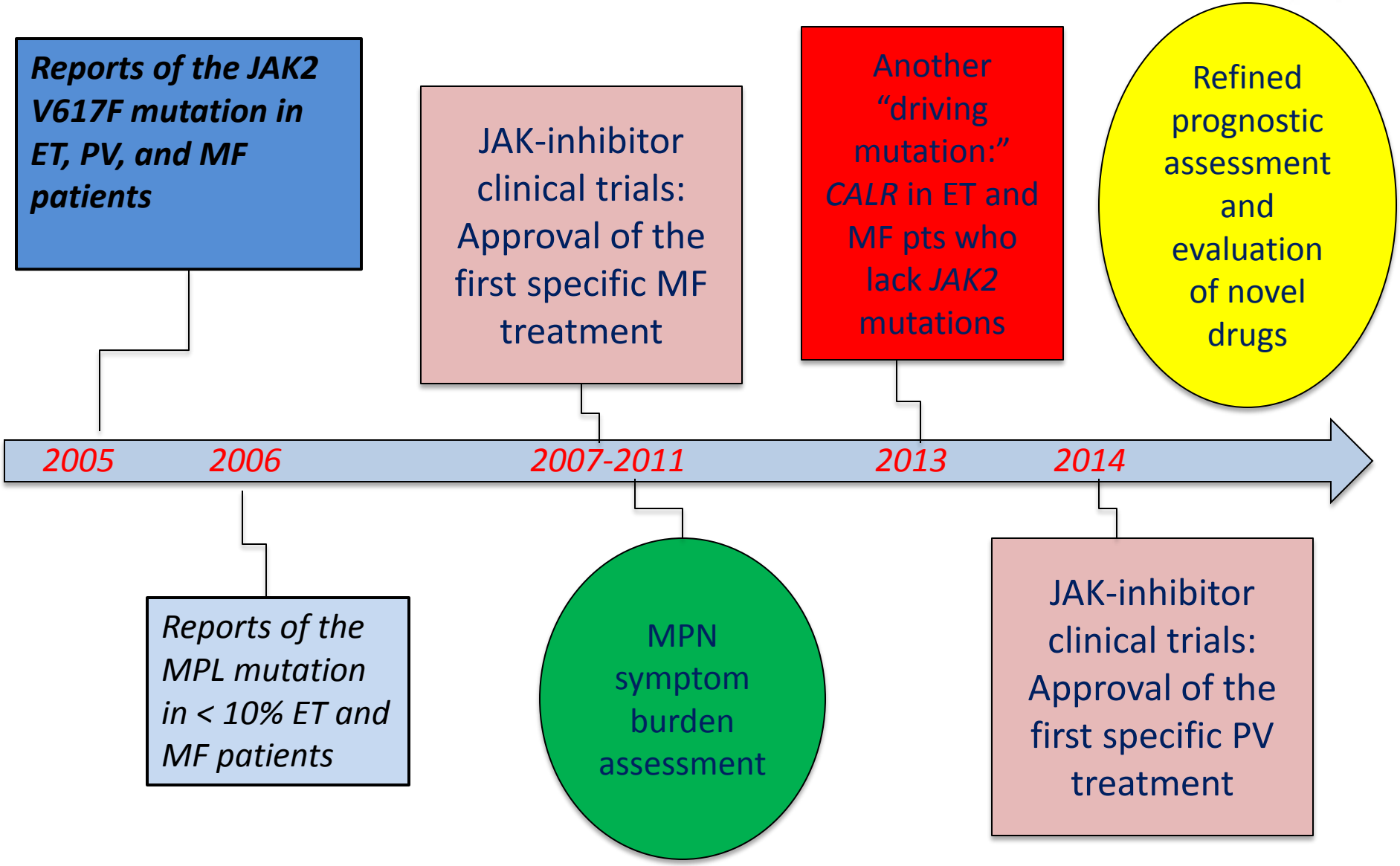


Vaquez and Osler describe PV

Dameshek coins the term, "MPD" and speculates on a shared pathogenesis

PVSG established: Conduct of pivotal clinical trials in PV

MPNs: The JAK2 discovery era



New mutations, evolving diagnostic criteria, new ways to assess symptoms, updated epidemiology, new prognostic assessments, new ***approved*** drugs, and many important clinical trials underway…..

Clinical Practice Guidelines

Created by expert panels that collect, organize, interpret and assess scientific evidence during a comprehensive review

Recommendations based on high and (low) quality evidence, and when lacking, based on expert/consensus opinion

Goals:

Optimizepatient care

Help physicians weigh options when evidence is limited, no consensus exists, or both (!)

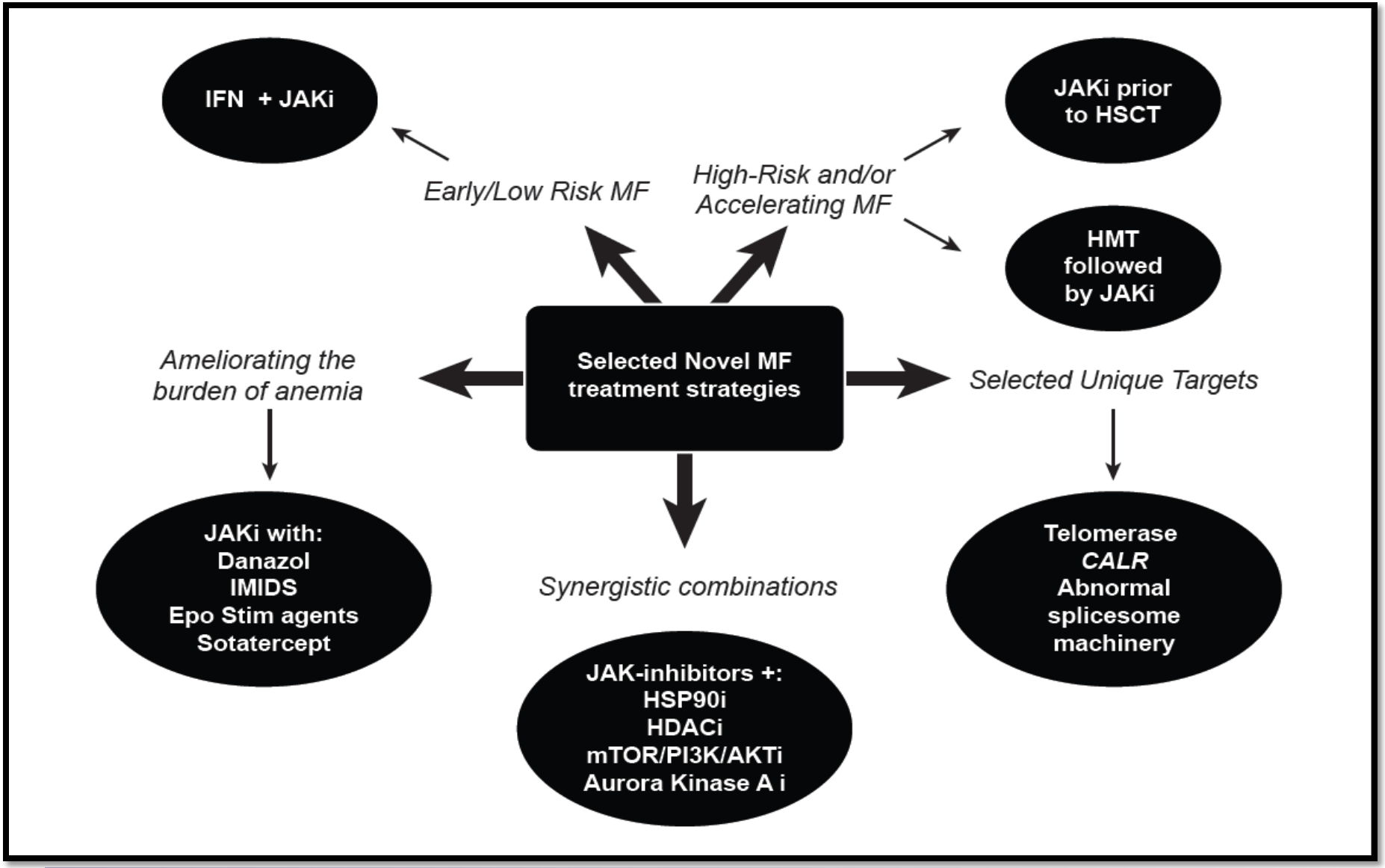
Highlight research priorities

Routinely updated to incorporate new information

Selected Existing MPN Guidelines and Consensus Statements

Source	Content
International Working Group for MPN Research and Treatment/ELN (IWG-MRT/ELN)	Response assessment in Myelofibrosis Response assessment in ET and PV
European Leukemia Net	Definition of Hydroxyurea Resistance or Intolerance
European Leukemia Net	Guidance regarding approach to diagnosis and treatment of ET, PV, and MF
Austrian/German Society of Hematology/Oncology	Management of Venous Blood Clotting Events: Primary and Secondary

Why are response criteria needed?
Many novel treatment strategies are emerging!



Stein et al Leukemia 2014

Response criteria help objectively assess the value of new drugs/clinical trials

1). Include response categories that suggest that the natural history of the disease is being modified

Response	Symptoms and Splenomegaly	Blood	Bone Marrow
Complete response	Resolution of MPN symptoms and splenomegaly	Normal blood counts Hgb > 10 g/dl Plts > 100,000 Neutrophils > 1000	-Restored productivity -Absence of scarring -Absence of immaturity

Partial response:
Remission in the blood and resolution of symptoms/splenomegaly, but not necessarily in the bone marrow
Remission in the marrow, but incomplete improvement in blood counts

Tefferi et al, Blood 2013

Response criteria help objectively assess the value of new drugs/clinical trials

2). Objective evaluation of a drug's ability to improve the MF-symptom burden

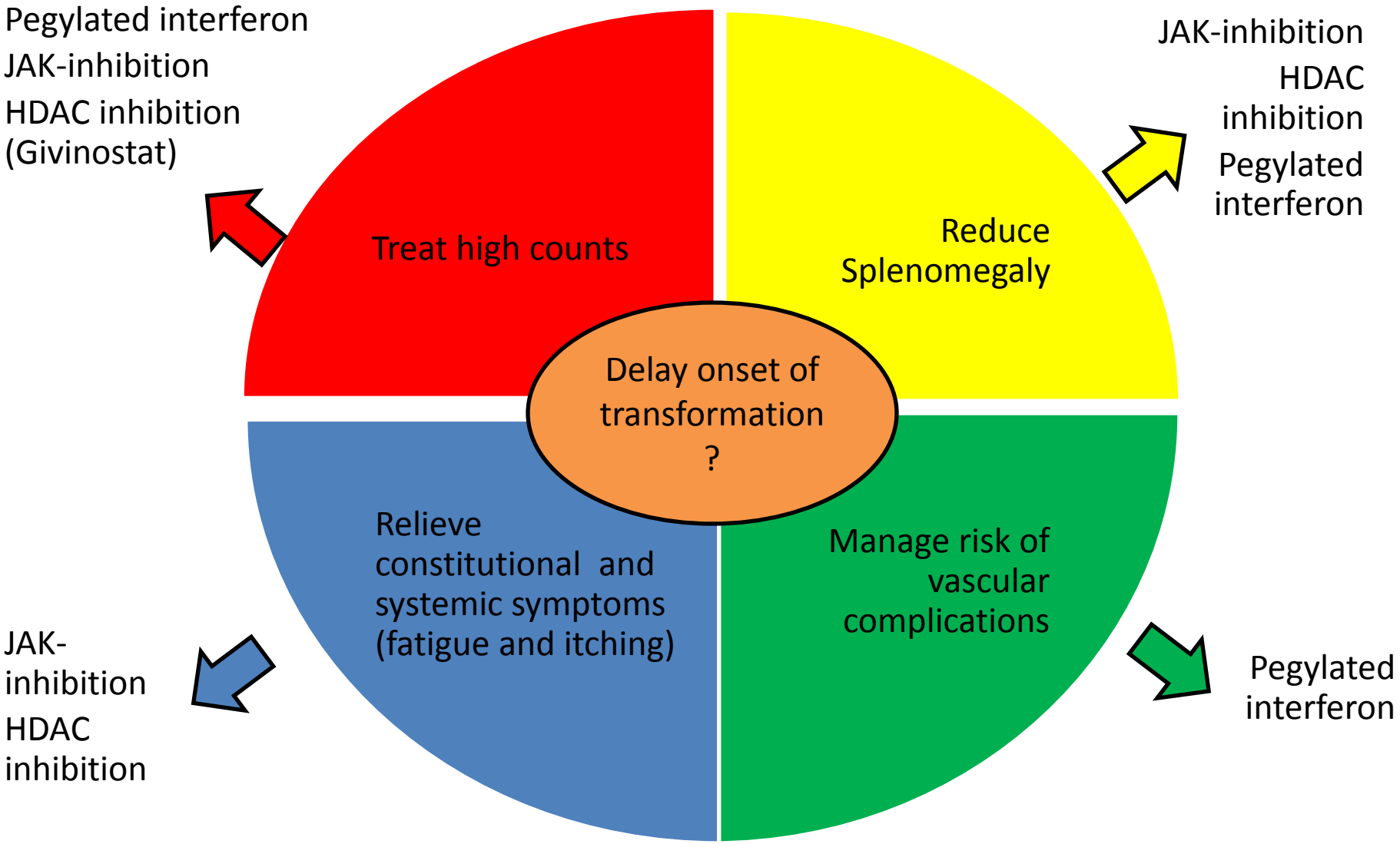
Response	MF-Symptoms	Splenomegaly	Anemia
Clinical Improvement	50% improvement in baseline symptom score, using valid instrument	--Modest spleen becomes non-palpable --50% reduction in marked splenomegaly Confirmed by imaging	2 gram increase in hemoglobin *Achieving transfusion-independence

Clinical improvement requires improvement in 1 aspect without worsening another

Transfusion-dependence: 6 units of blood in 12 weeks
Transfusion-independence: Hgb >8.5, and no transfusion in 12 weeks

Tefferi et al, Blood 2013

New treatments also emerging in ET and PV!



In Contemporary Management of Myeloproliferative Neoplasms, Editors B Stein and B McMahon, Jaypee Brothers 2014

Response criteria in ET and PV

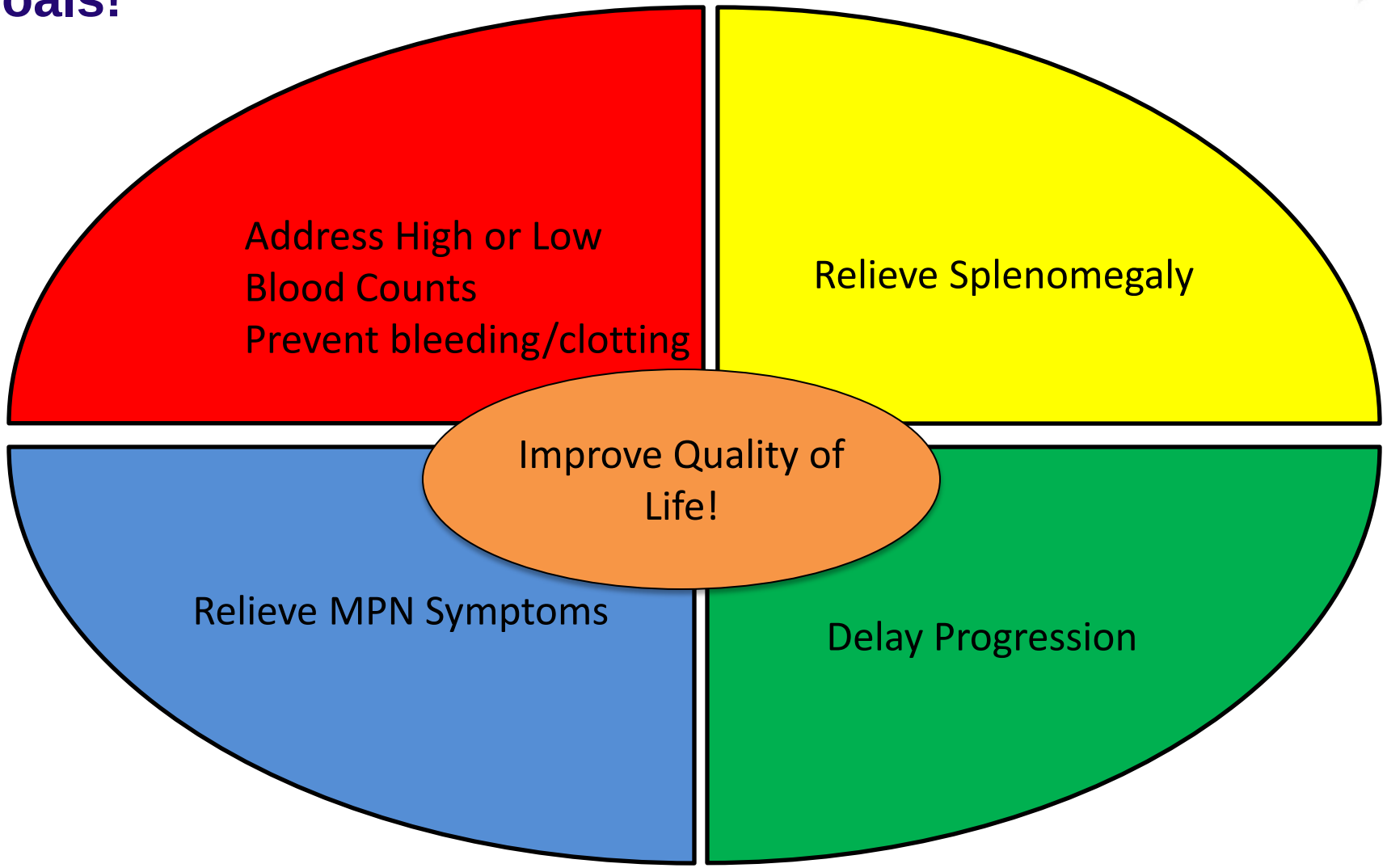
Aim: To provide response definitions in ET and PV that are clinically relevant, practical and reproducible

Complete Response	Symptoms and Splenomegaly	Blood counts	Vascular concerns	Bone Marrow
ET and PV	Durable (3 months) resolution of MPN-symptoms and splenomegaly	PV: Hct < 45% w/o phlebotomy ET and PV: Plts < 400,000 WBC < 10,000	No bleeding or clotting events	ET: Absence of scarring and normal megakaryocyte number (parent of plts) PV: Absence of scarring, improvement to normal degree of efficiency

Partial response: Improvement in symptoms, blood counts, and vascular concerns, but no remission in the bone marrow

Barosi, et al Blood 2014

Clinical trial goals can differ from an individual patient's goals!



Consensus Definition:
* “Hydroxyurea Resistance/Intolerance”

**Need for phlebotomy to keep Hct < 45%
**Plts > 400,000 and WBC > 10,000
**Failure to shrink the spleen or improve symptoms of splenomegaly
--Low white cell counts (neutrophils < 1000) --Low plts (< 100,000) --Anemia (< 10 g/dl)
Leg ulcers, GI symptoms, lung inflammation, fever

After at least 3 months, and at least 2 grams daily of Hydroxyurea

* At least one required

Barosi et al, Br J Haematology 2010

Critical Concepts and Management Recommendations: ELN/IWG-RT 2011

Diagnosis

Use of World Health Organization Criteria (2008)

Patient communication

Guidance on communication of expectations and natural history of the disease

Risk classification

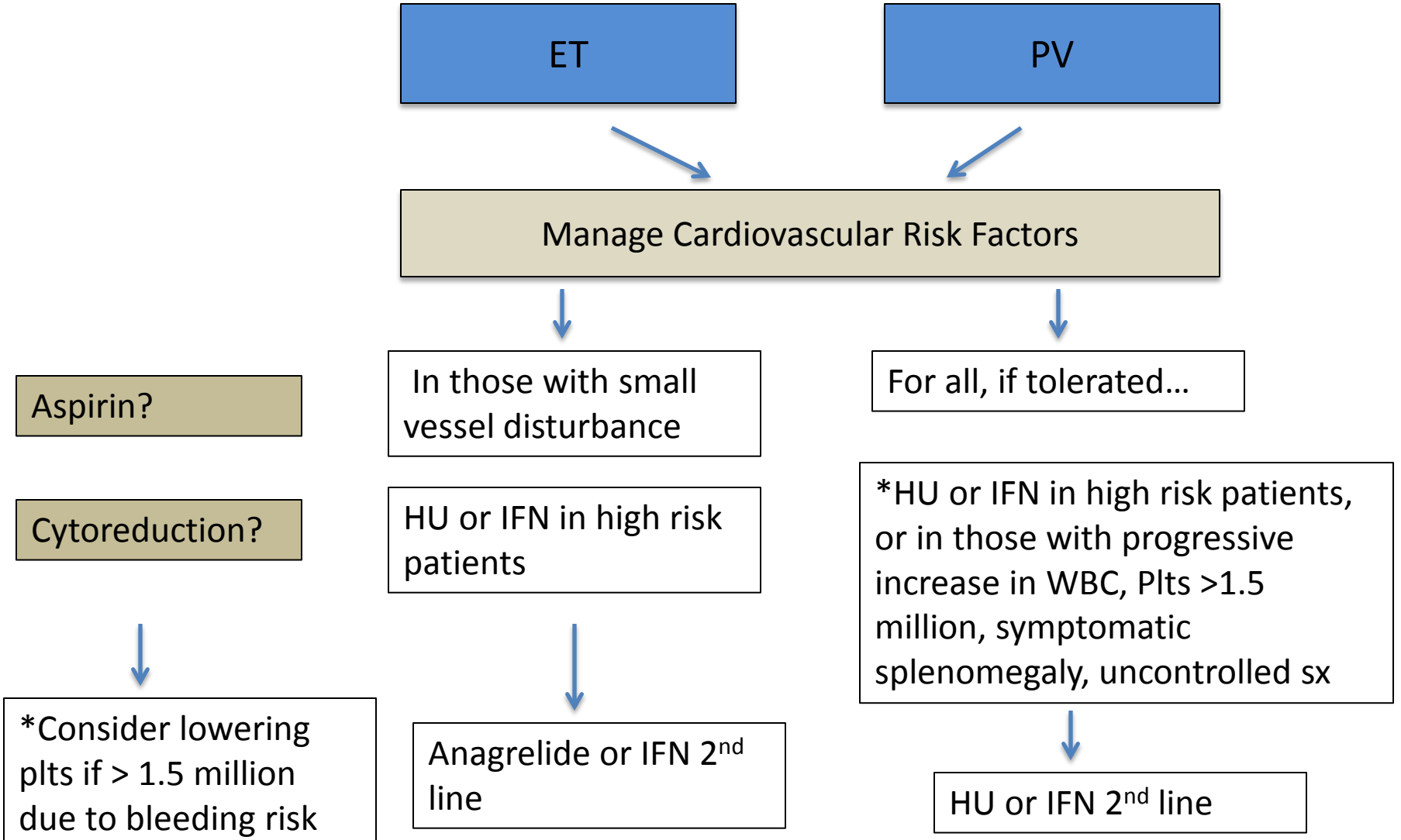
Age and prior history of thrombosis for ET/PV

Prognostic scoring systems for MF (IPSS, DIPSS, DIPSS-plus)

Goals of therapy

Barbui, T et al: JCO 2011

Critical Concepts and Management Recommendations: ELN/IWG-RT 2011



HU=hydroxyurea; IFN=interferon

Barbui, T et al: JCO 2011

Critical Concepts and Management Recommendations: ELN/IWG-RT 2011

Treatment of Myelofibrosis: ***(Covered later today!)***

How to treat anemia

How to treat splenomegaly

When to consider surgery

How to address constitutional symptoms

Making decisions about transplantation

Treatment of special situations:

Pregnancy ***(Covered later today!)***

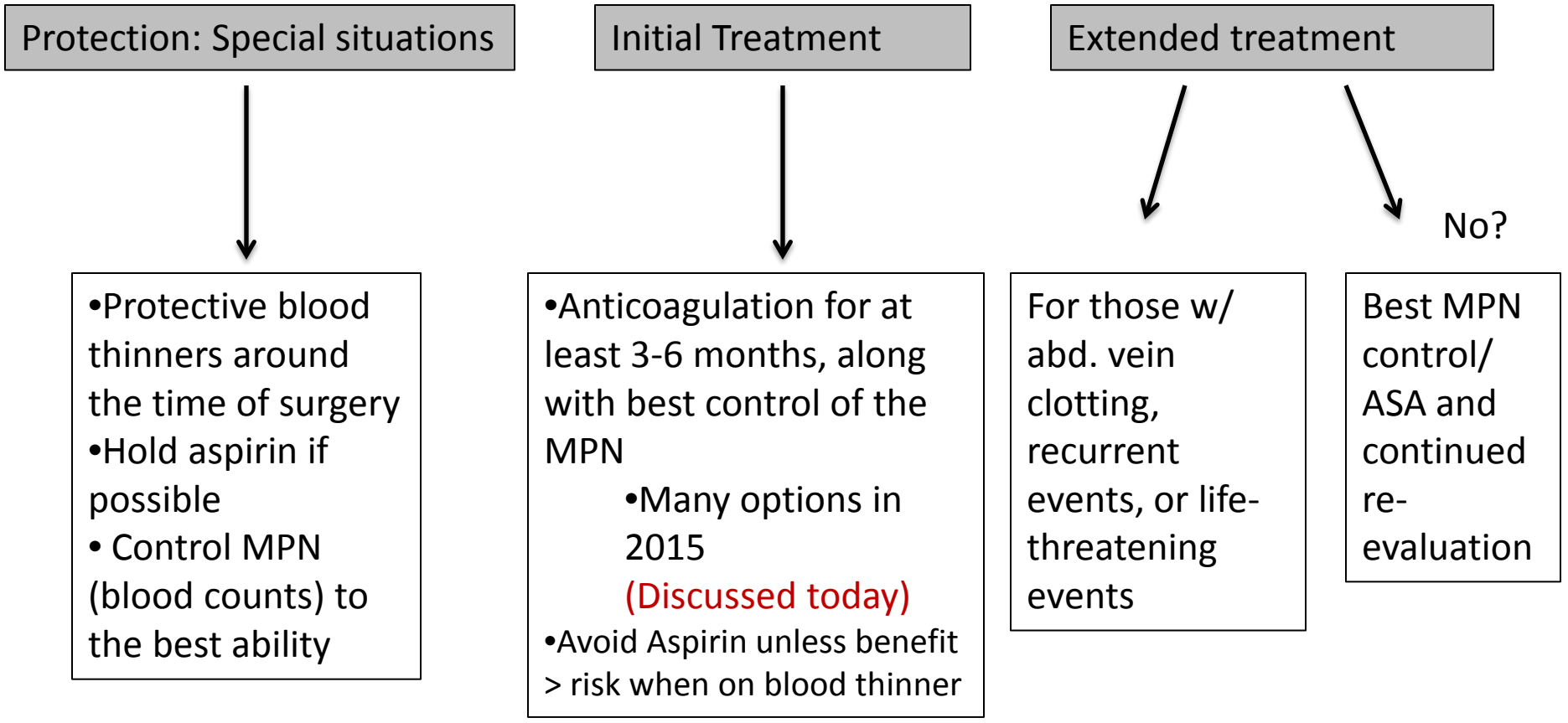
Blood clotting in unusual locations

Management of itching

Published prior to approval of JAK-inhibitors for MF and PV!

Barbui, T et al: JCO 2011

Management of MPN-associated venous blood clotting complications



Consensus Statement from the German and Austrian Society of Hematology and Oncology: Annals of Hematology 2014

*(Selected) Practical Tips

S. Kreher, et al 2014

Selected Existing MPN Consensus/Guidelines

Source	Content
IWG-ELN	Response assessment in ET, PV, and MV *Designed for use in a clinical trial setting, not in clinical practice*
ELN	Definition of Hydroxyurea Resistance or Intolerance *Inadequate response may have a broader meaning in clinical practice*
ELN	Guidance regarding approach to diagnosis and treatment of ET, PV, and MF *Based on expert consensus, and published prior to JAK-inhibitor approval (2011 for MF, 2014 for PV)*
Austrian/German Hematology-Oncology Society	Management of Venous Blood Clotting *Practical, yet less of an evidence base here* *(not the fault of the society!)*

FYI: British Committee for Standards in Haematology also has guidelines for investigation and management of ET, PV, and MF, as well as guidance on MPN molecular markers

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Breast cancer

Lung cancer

Pancreatic cancer

Prostate Cancer

Practicing hematologists/oncologists could use practical, updated advice on approach to diagnosis, symptom and risk assessment, supportive care, and management strategies

PV practice patterns in the pre-JAK2 era

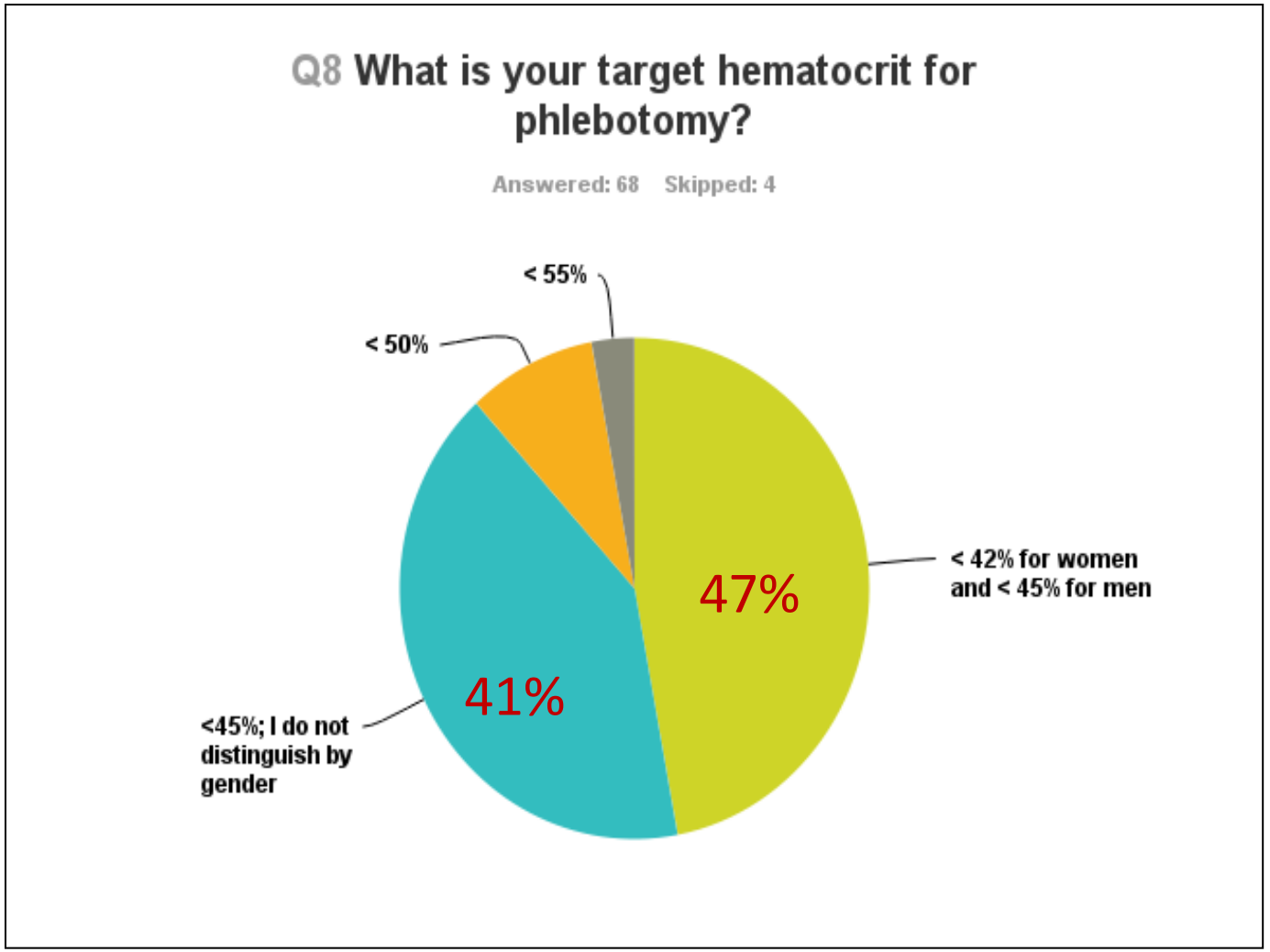
PV practice patterns, 2002

Survey of ~1000 American Society of Hematology members

- Red cell mass, Epo level and blood gas most commonly used for diagnosis
- Most respondents used a target Hct ≤ 44%, though 16% used a target of 50 or 55%.
- ~65% treated only when a plts > 1 million, while a ~20% used a lower threshold, or treated only those with symptoms (12%).
- Hydroxyurea (HU) was most commonly used to treat increased platelets and 55% and 15% percent of respondents avoided interferon (IFN), and aspirin (ASA), respectively as treatments

Streiff et al, Blood 2002

PV practice patterns in the post-JAK2 era



Survey of practice patterns in the diagnosis and treatment of PV in 2014

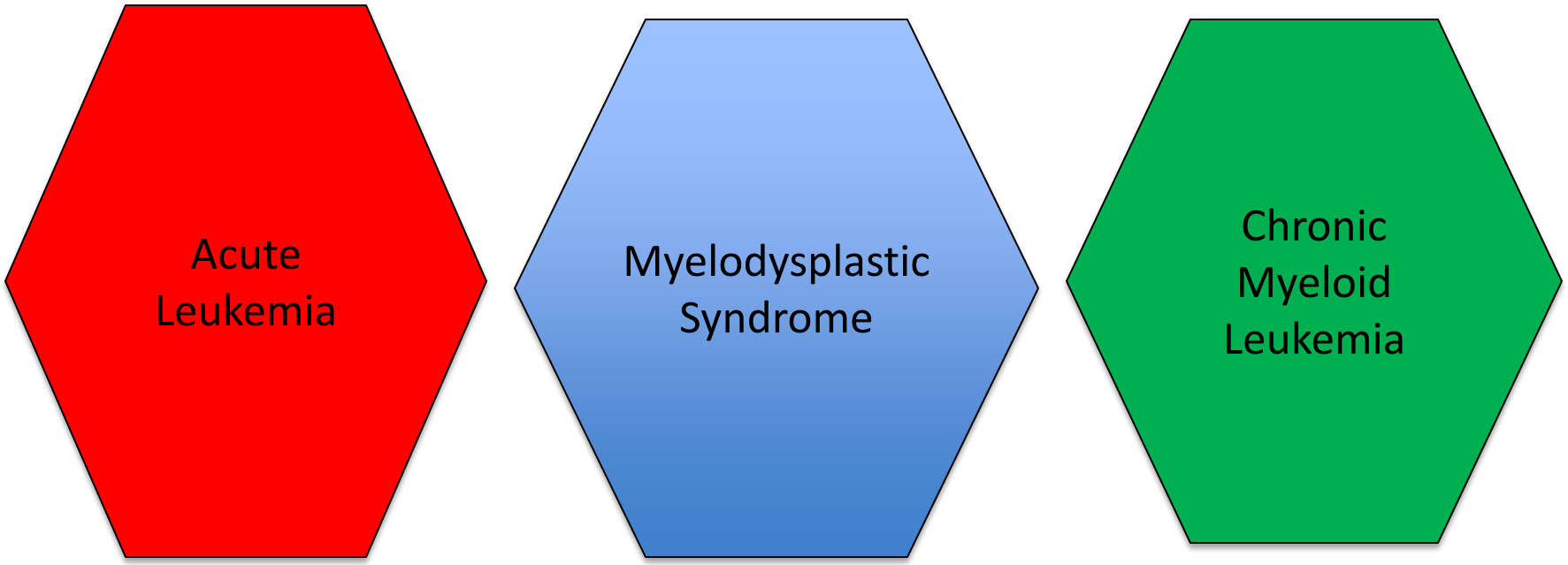
Stein, BL et al, American Society of Hematology 2014, poster presentation

Consensus is needed!

Query	Respondents answer
Indications for cytoreduction:	--Blood clotting: 75% --Small vessel disturbance: 73% --Age > 60 years: 59%
Agent of choice:	Hydroxyurea, 89%
Age restriction for cytoreduction: Concerns regarding younger age?	*50% prescribed regardless of age 34% avoided in those < 40 yrs 16 yrs vs. < 15 yrs experience (67% vs. 31% regardless of age)
Do you universally prescribe aspirin?	79% universally prescribed, but more likely in those with <15 yrs experience vs. > 16 years experience (91% vs. 69%)

Stein, BL et al, American Society of Hematology 2014, poster presentation

US Guidelines: Myeloid Neoplasms



Represented by the National Comprehensive Cancer Network:

--Diagnosis/Workup

--Supportive Care

--Treatment

Comprehensive, contemporary US-based MPN Guidelines….

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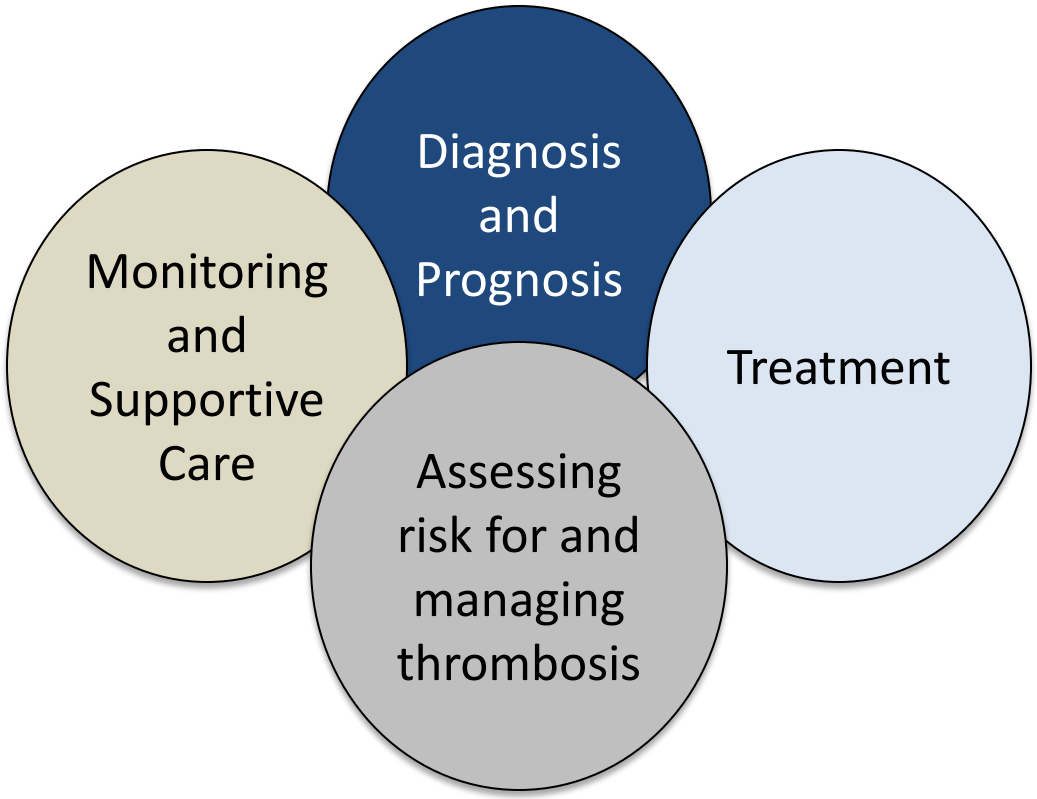
Commentary for the Journal of the National Comprehensive Cancer Network

"Myeloproliferative Neoplasms are in need of United States-Based Guidelines"



Brady L. Stein, Susan O'Brien, Peter Greenberg and Ruben A. Mesa

Commentary accepted, JNCCN 2015

Collaborators from NCCN member institutions

"Historical views, conventional approaches, and evolving management strategies for the MPN"

- *Impact of mutations (JAK2 V617F, CALR, MPL)*
- *Appropriate settings for testing*
- *MPN "mimicry"*

  "Occult MPN"—

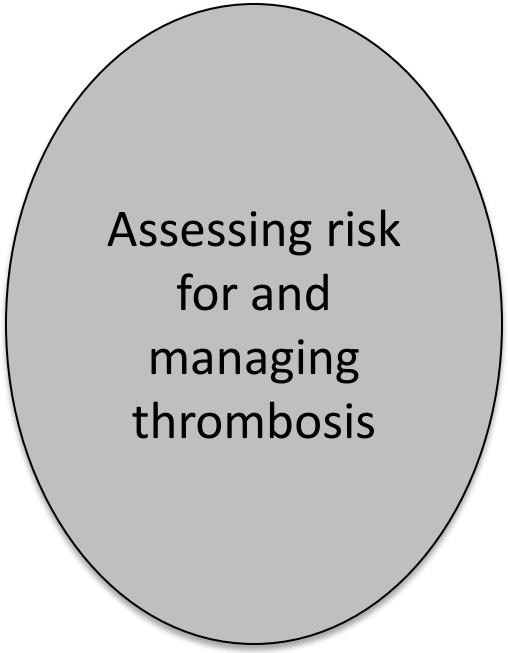
  (presentation with abdominal vein thrombosis)

  Distinguishing ET from PV and early MF

This is a review, not a guideline!

Accepted for publication, JNCCN 2015

"Historical views, conventional approaches, and evolving management strategies for the MPN"



Risk assessment for thrombosis

Age, blood clotting history

Mutational status, CV risk factors

? WBC count, allele burden, and other?

Prevention and treatment

Options, efficacy and safety of agents to lower counts (HU)

Interferon

Phlebotomy, blood thinning (duration?), anti-platelet agents

Special situations: Pregnancy, Surgery

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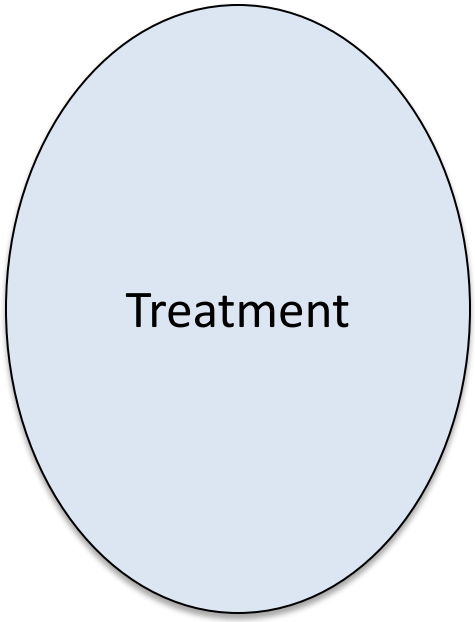

Use of JAK-inhibitors in MF and PV

Ruxolitinib in MF and PV

Novel JAK-inhibitors in clinical trials (momelotinib, pacritinib)

Positive effects, Side effects

The role and timing of stem cell transplant

Pre-transplant therapy, donor options, use of prognostic scoring systems (IPSS, etc)

This is a review, not a guideline!

Accepted for publication, JNCCN 2015

"Historical views, conventional approaches, and evolving management strategies for the MPN"

Supportive Care

Symptom management

Addressing low blood counts

Treating anemia, iron overload

Massive splenomegaly (surgery vs radiation)

****Other MPN's need guidance as well!***

Mastocytosis, Hypereosinophilia, Chronic Neutrophilic Leukemia

This is a review, not a guideline!

*In commentary

Accepted for publication, JNCCN 2015

Comprehensive, contemporary US-based MPN Guidelines….

Hopefully we fill this slide in years to come!

Acknowledgements

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MPN Research Foundation

MPN Advocacy International

Jim and Antje Hjerpe/MPN-NET

My patients…..

Thank you for your attention!

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