Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Northwestern Medicine

Northwestern University Feinberg School of Medicine

An Overview of US-Based MPN Guidelines: A First Look

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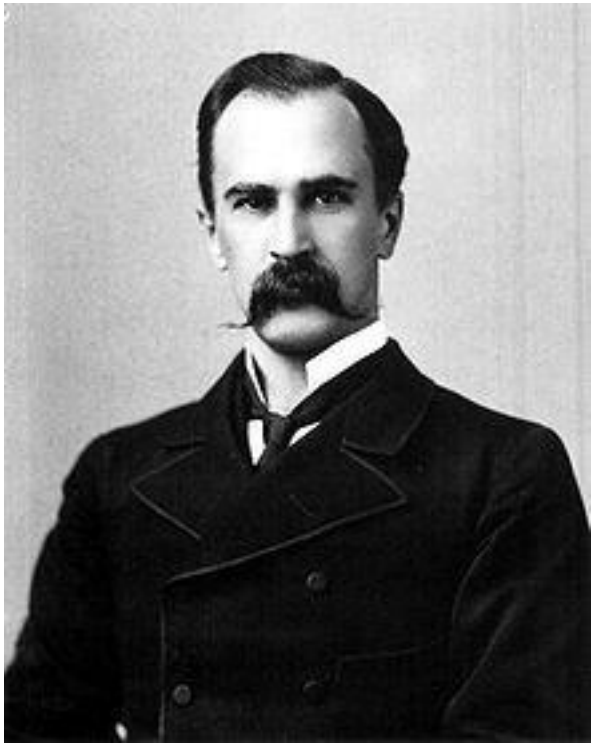
Northwestern University Feinberg School of Medicine



"Medicine is a science of uncertainty and an art of probability."

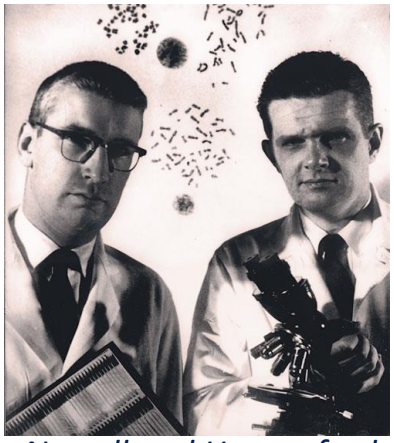
- William Osler

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

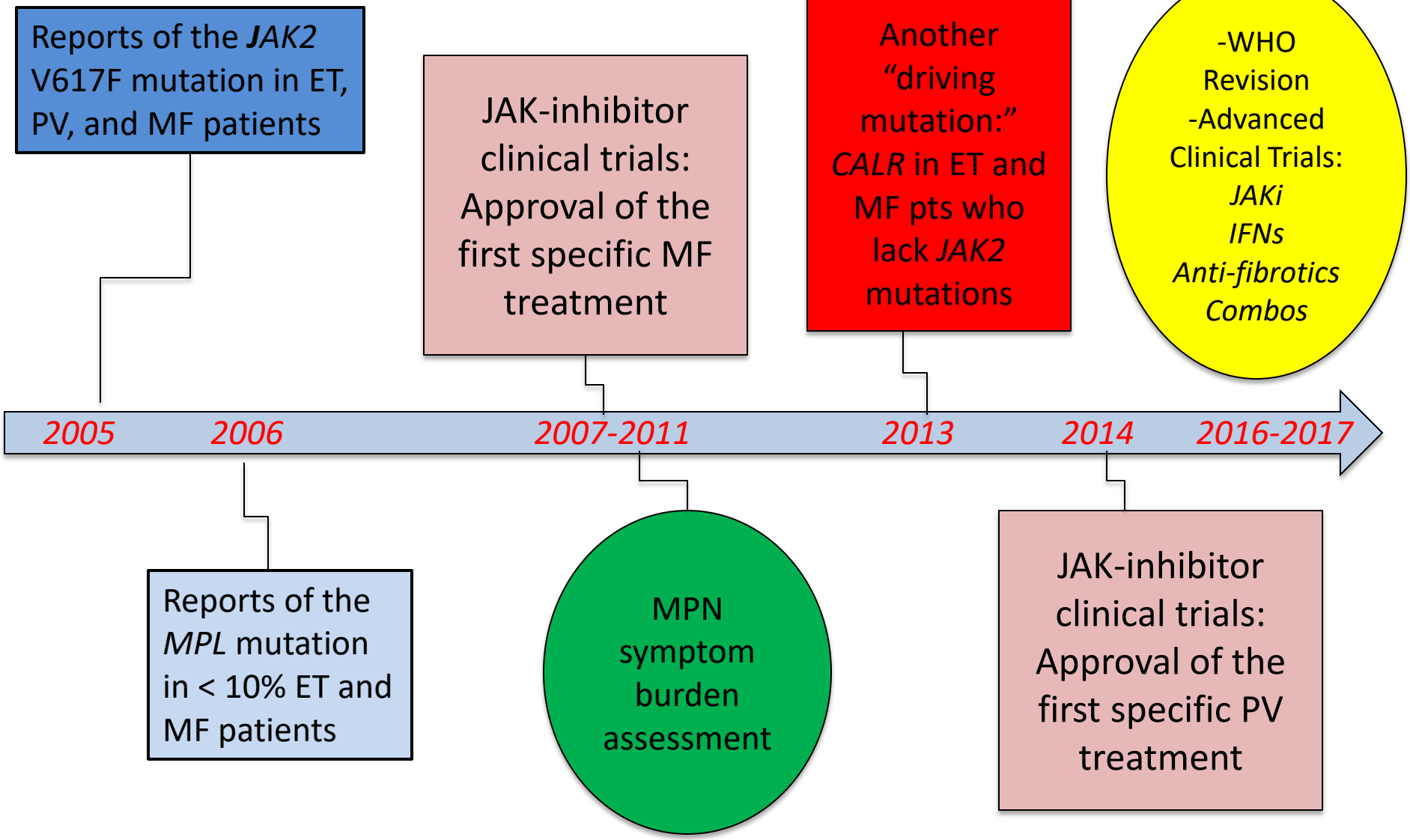
1879 — 1892-1903 — 1931 — 1951 — 1960 — 1967 — 1996

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 (post 2005)



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

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

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:

Optimize patient care

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

Highlight research priorities

Routinely updated to incorporate new information

An overview of the process

1. Implicit plea to NCCN-our review article

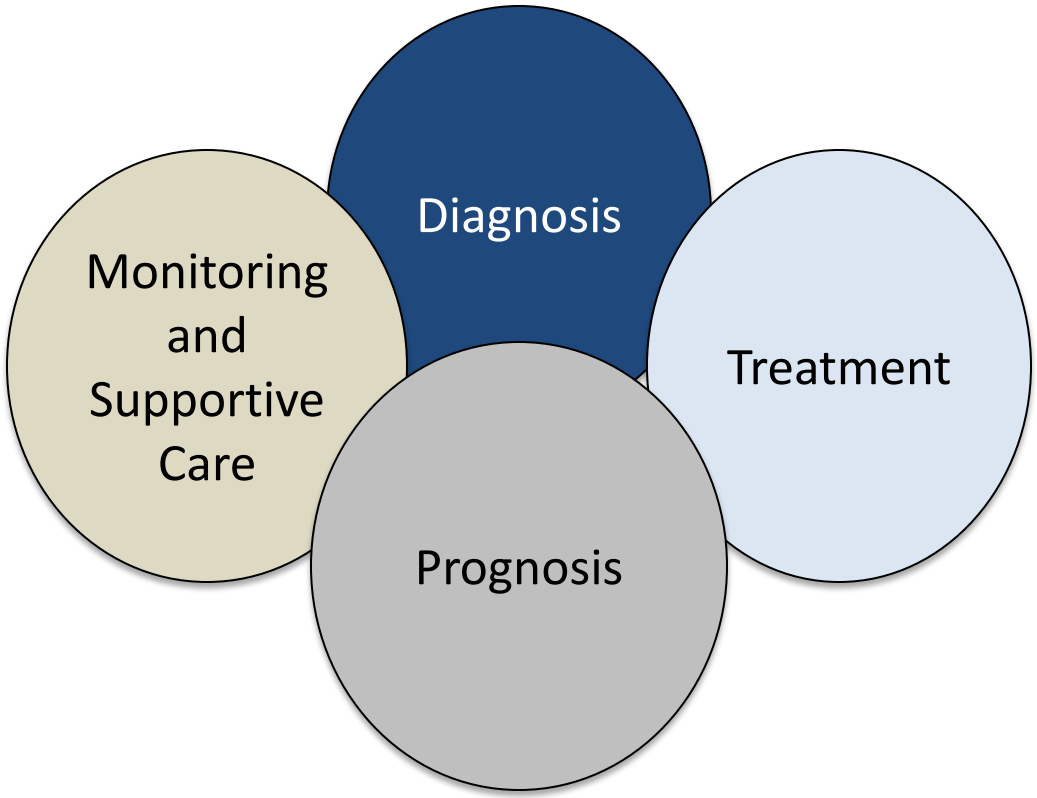
"Historical views, conventional approaches, and evolving management strategies for the MPN"

- Introduce important themes to an the NCCN audience
- Approach to diagnostic challenges
- Approach to prognostic assessment
- Introduction of symptom monitoring tools
- Overview of treatment options

Stein, B… (many other NCCN members)….Mesa, R et al JNCCN 2015

2. Explicit Plea to NCCN—our commentary

"Myeloproliferative Neoplasms are in need of US-Based Guidelines"

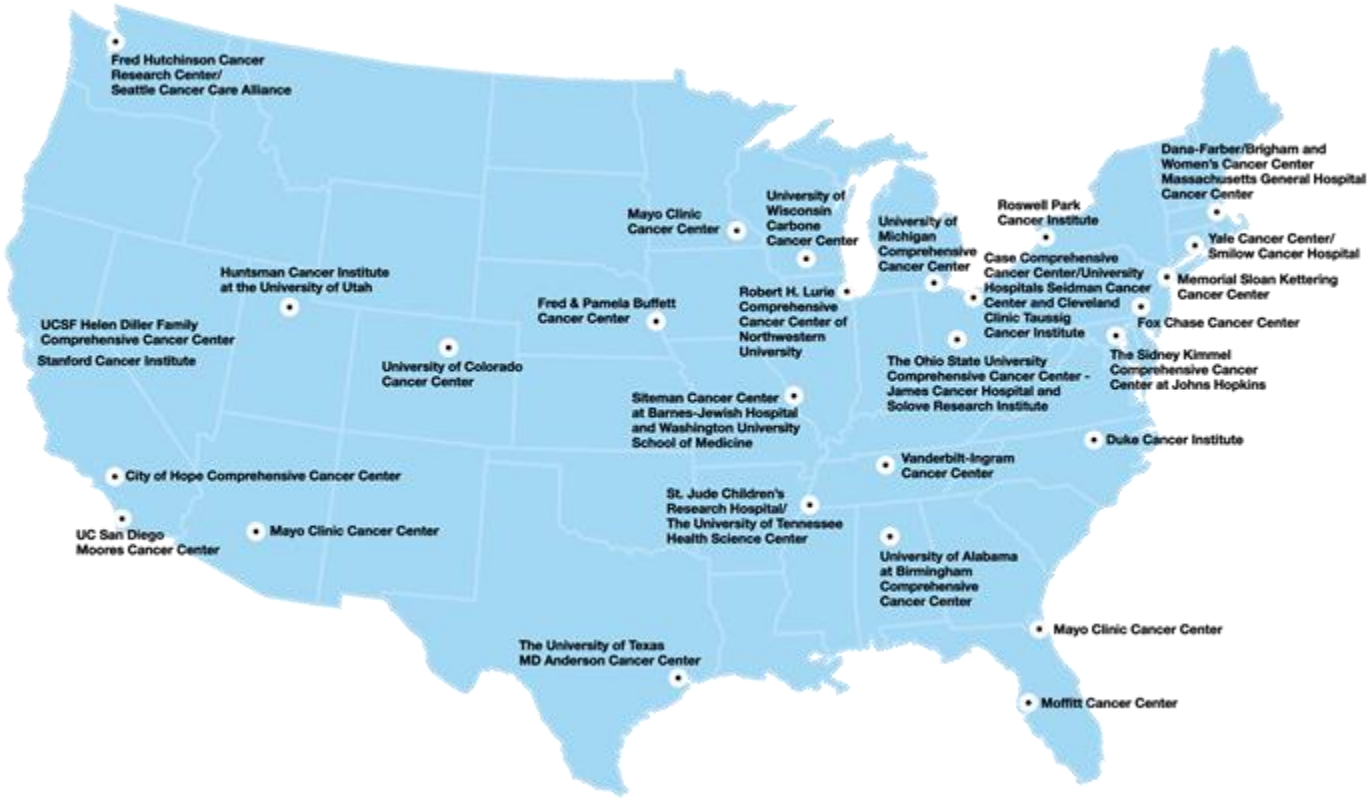


Brady L. Stein, Susan O'Brien, Peter Greenberg and Ruben A. Mesa

Published JNCCN 2015

3. Dr. Mesa invited to give a formal proposal to NCCN—they accepted!

4. MPN specialists from participating centers invited as panelists



Drafting the guidelines

Chair: Dr. Mesa; Co-chair: Dr. Jamieson; NCCN team and panelists

Themes: Symptoms and Risk Group

1. Symptom assessment (and reassessment!)

Emphasize use of **MPN-symptom assessment tool** at diagnosis, and throughout follow-up

Symptoms have a significant impact on decision-making in the algorithms!

2. Risk assessment

Treatment strategies can differ based on risk—this is especially the case when considering transplant

How we assess symptoms: TSS

1. Patient reported assessment

Absent to Worst Imaginable (0-10)

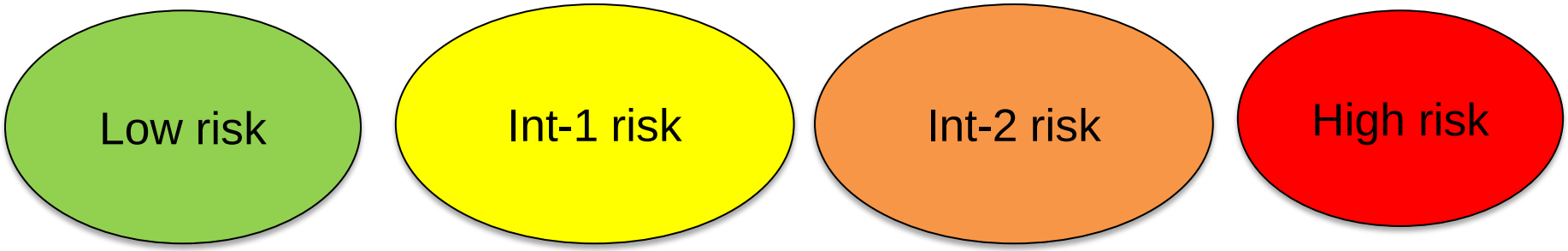
Fatigue (worst level last 24 hrs)
Filling up quickly when you eat (early satiety)
Abdominal discomfort
Inactivity
Problems w/ concentration compared to prior to my MPD
Numbness/Tingling Night sweats
Itching (pruritus)
Bone pain (diffuse not joint pain or arthritis)
Fever (>100 F)
Unintentional weight loss last 6 months

Emphasize need to combine subjective (symptoms) and objective (blood counts, spleen, etc) assessments

TSS=Total Symptom Score

How we assess risk: Myelofibrosis

"IPSS or Dynamic IPSS"		*Dynamic IPSS-plus
Age > 65 **Constitutional symptoms (fever, night sweats, weight loss)** **Anemia** **High white cell count** **≥1% circulating blasts**	+	**Transfusion-dependence** **Platelets < 100** **Abnormal chromosome testing**



We are moving towards use of molecular genetic markers to add precision

IPSS: newly diagnosed pts; dynamic can be assessed throughout disease

How we assess response

1). 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 > 100k 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, or remission in the marrow, but incomplete improvement in blood counts

***Guidelines emphasize that the response may not meet these thresholds, but still can be meaningful to our patients**

Tefferi et al, Blood 2013

How we assess response

2). Objective (and subjective) 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

***Guidelines emphasize that the response may not meet these thresholds, but still can be meaningful to our patients**

Tefferi et al, Blood 2013

Diagnosis/Workup

Guidelines include tables outlining WHO Diagnostic Criteria for ET, PV and MF, as well as post-ETMF, and post-PVMF

Suspicion for MPN: Key points

Key to establish the proper MPN diagnosis, giving overlapping symptoms and lab tests

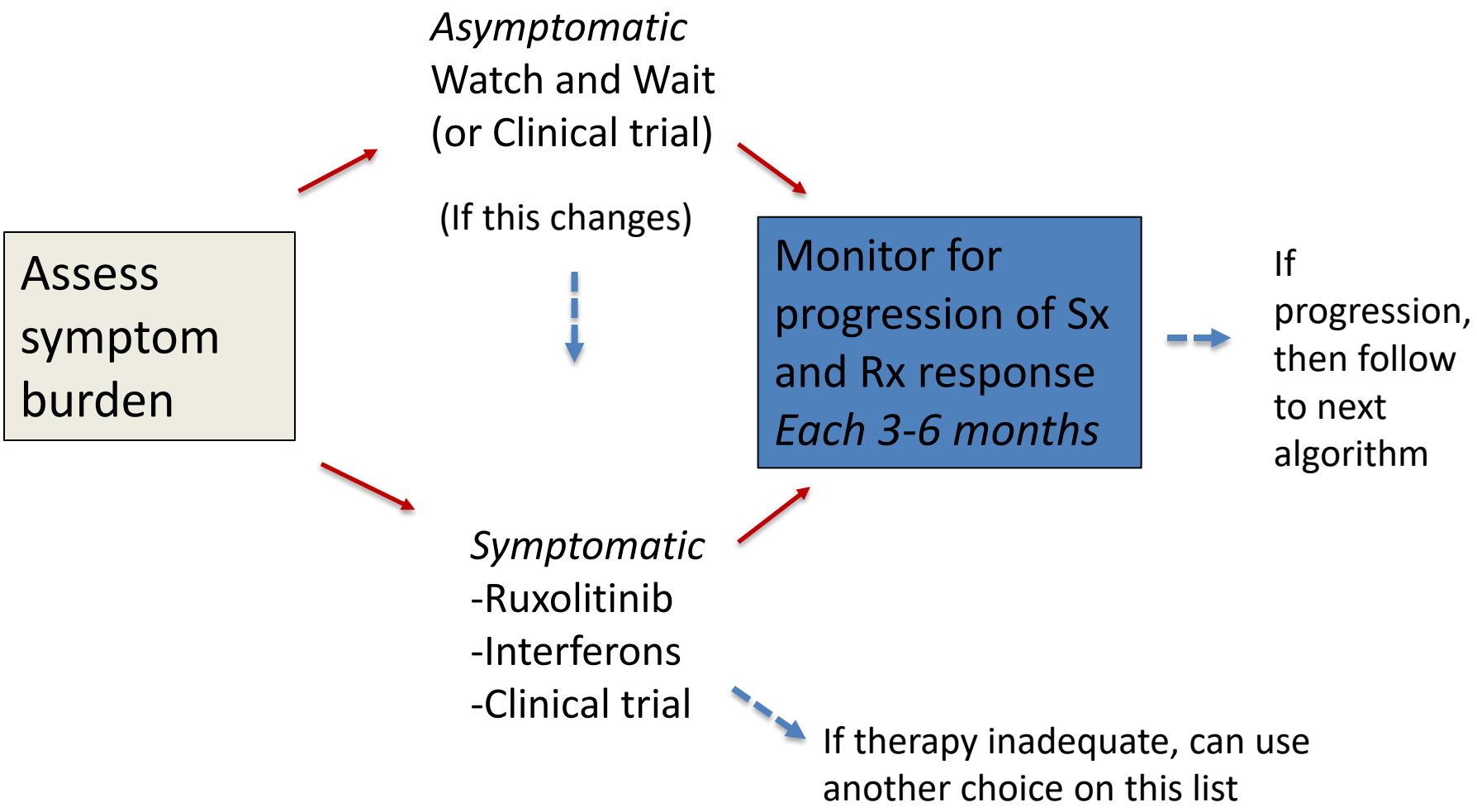
- History taking: Assess MPN symptoms and clotting and/or bleeding history
- Physical Examination: Measure spleen (by palpation)
- Blood counts and chemistry testing
- Molecular testing (*JAK2*, *MPL*, *CALR*)
- *Bone marrow testing
- Other tests, based on need:
  Bleeding evaluation?

***Diagnosis is based on World Health Organization 2016 revision**

Treatment Algorithms

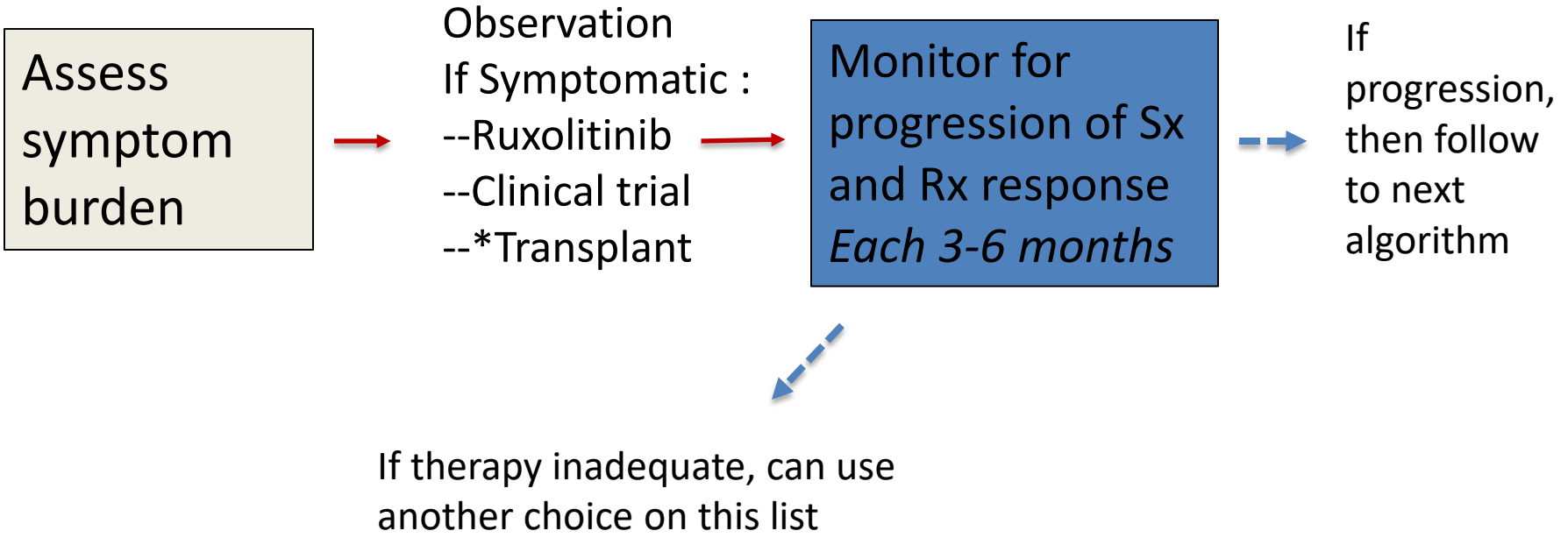
Low risk MF
Int-1 MF
Int-2/High Risk MF
Anemia algorithm
Higher risk situations

Low risk MF



Sx: Symptoms; Rx: Treatment

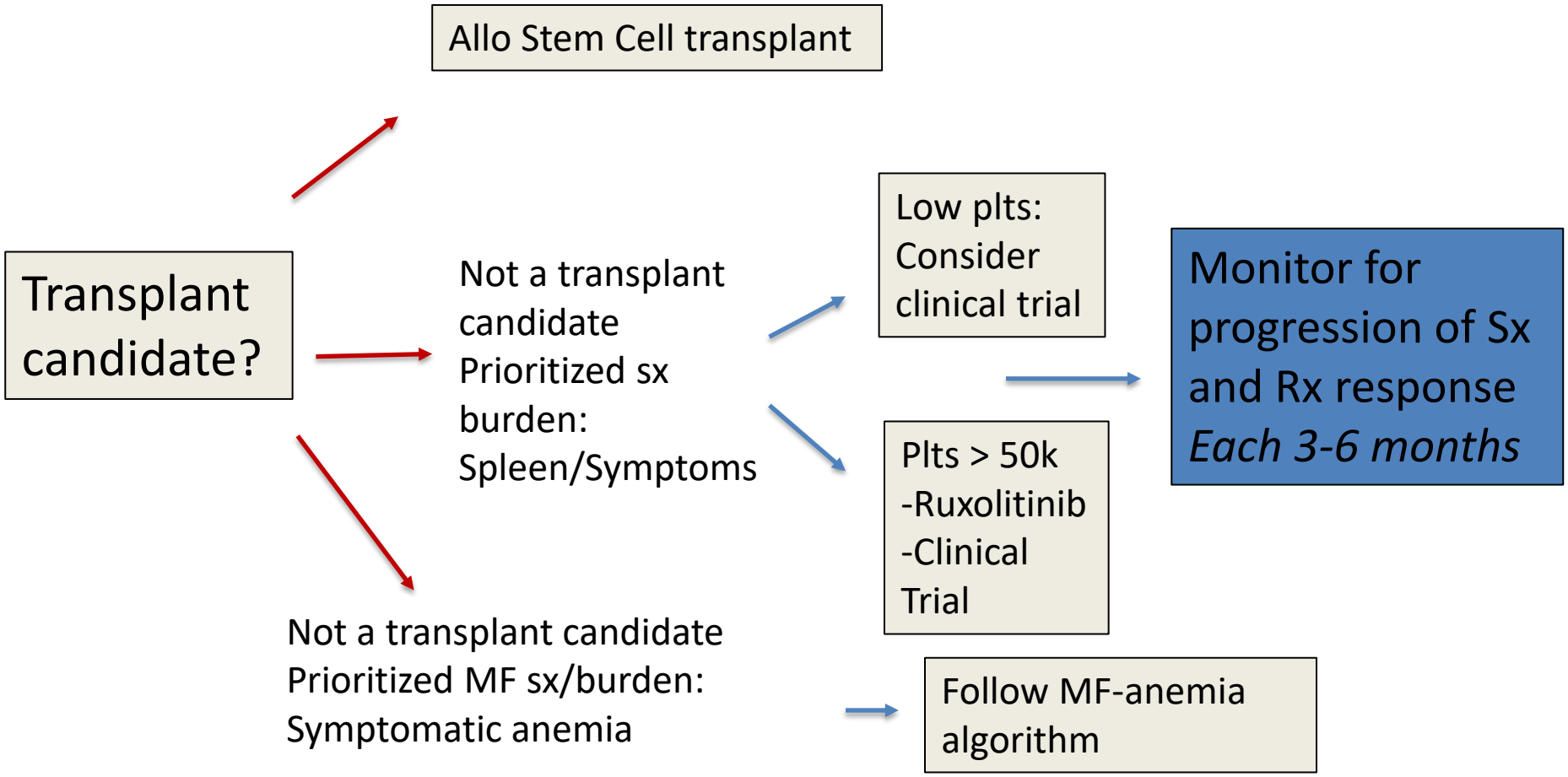
Intermediate-1 risk MF



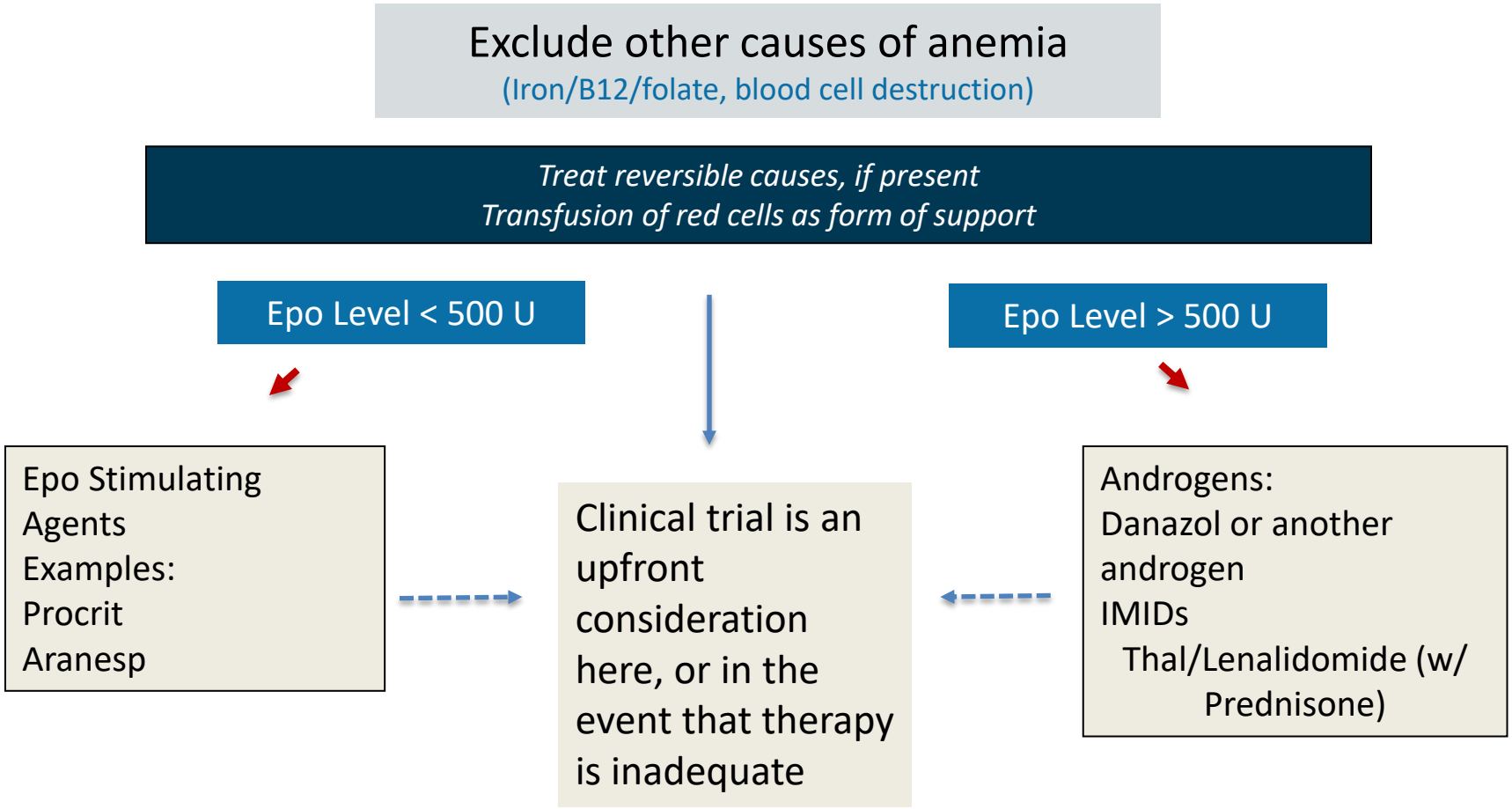
*If there was a risky genetic marker, for example

Sx: Symptoms; Rx: Treatment

Intermediate-2/High risk MF



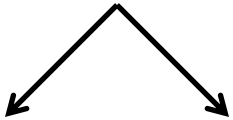
Management of MF-anemia



Accelerated or Blast Phase Disease

MPN-Accelerated Phase
Blasts 10-19% in peripheral blood or bone marrow

MPN-Blast Phase
Blasts 20% in peripheral blood or bone marrow



Transplant Candidate?
Hypomethylating Agent or chemotherapy with hope to induce remission or control disease prior

-Clinical trial
-Hypomethylating Agent (an example here is Vidaza or Dacogen)
-Low intensity induction chemotherapy (per NCCN AML guidelines)

If on ruxolitinib, may be continued for control of splenomegaly/symptoms

Other helpful information

Special considerations regarding use of Ruxolitinib

Special considerations for use of Ruxolitinib

Monitoring recommendations

- Symptom assessment at baseline and during follow-up
- Blood count monitoring recommendations
- Caution about premature discontinuation/rebound

Dosing recommendations

- Initial, based on platelet count
- Modifications based on insufficient response
- Modifications based on low platelets/white cells

Side effects to watch for:

Infection, Skin Cancer, Weight gain, cholesterol changes

NCCN Evidence Blocks

- Evidence blocks will be added soon to the NCCN guidelines
- These blocks are a graphic representation of the panel's scores of efficacy, safety, quality of evidence, consistency of evidence, and affordability of each regimen recommended in the algorithms
- The aim of evidence blocks within the guidelines is to assist clinicians when discussing and selecting treatment options with patients.

Next steps

Annual review/update of MF guidelines, to incorporate changes in clinical practice

1st draft of ET and PV guidelines underway

First conference call to review draft 1 in late January

Emphasis on:

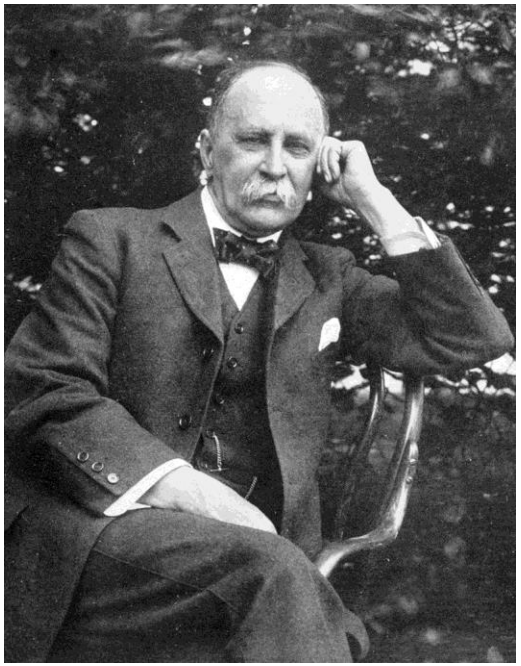
Diagnosis

Prognostic assessment

Treatment based on risk and symptoms

Special situations: Thrombosis, Surgery, Pregnancy

Thank you—to our patients



"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all"

--William Osler

Acknowledgements

Ruben Mesa

My Northwestern Colleagues

MPN Research Foundation

MPN Advocacy International

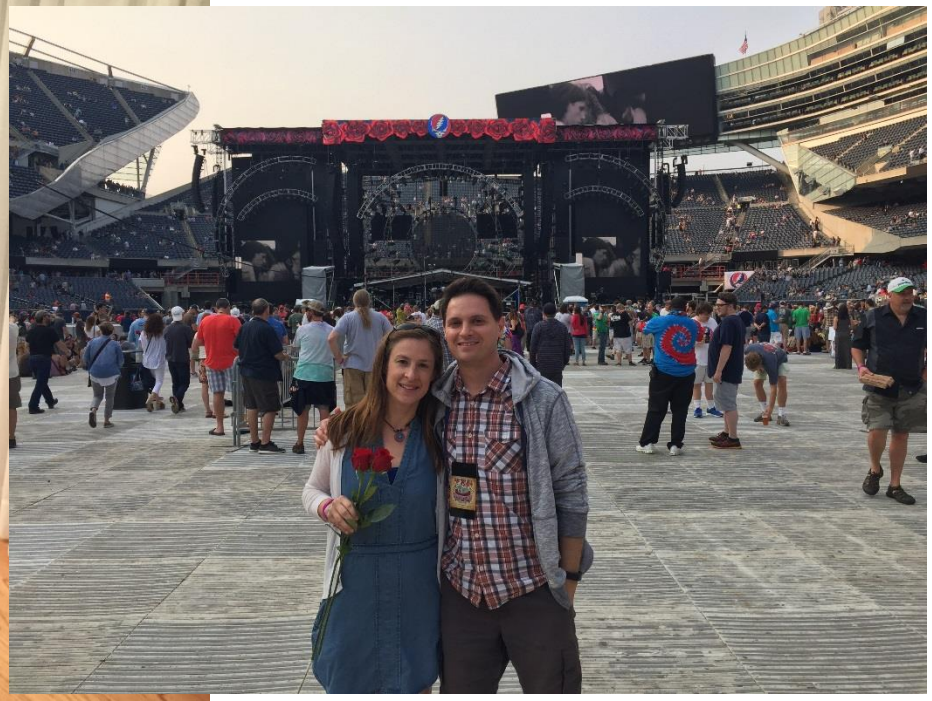
Jim and Antje Hjerpe/MPN-NET

My patients…..

My family!

Outside of work….

Before the playoffs



The Grateful Dead 50 yr anniversary concert

Thank you for your attention!

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