

# Shining a light on MPN

Angela Fleischman MD PhD



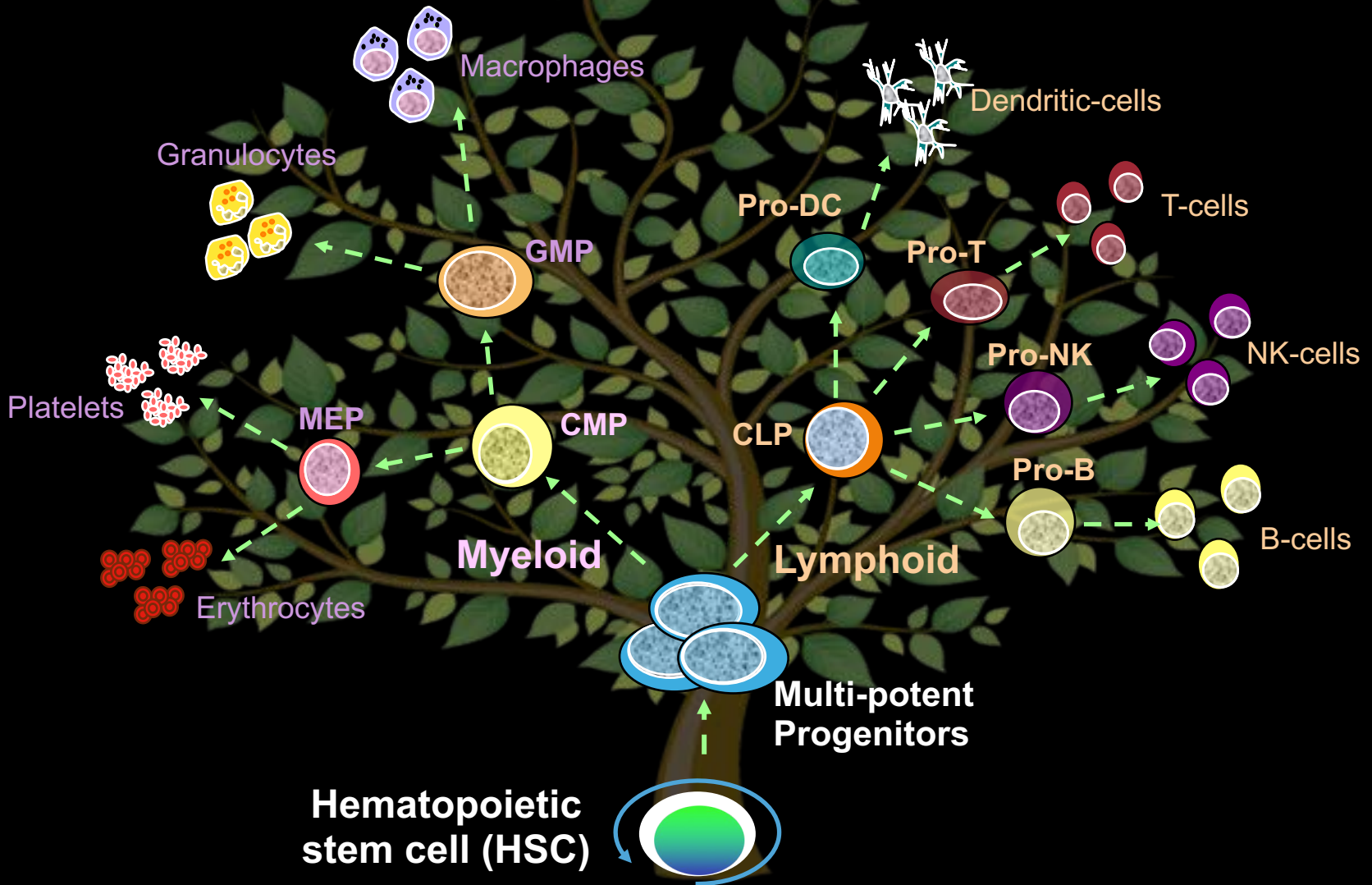
# Outline

MPN Biology

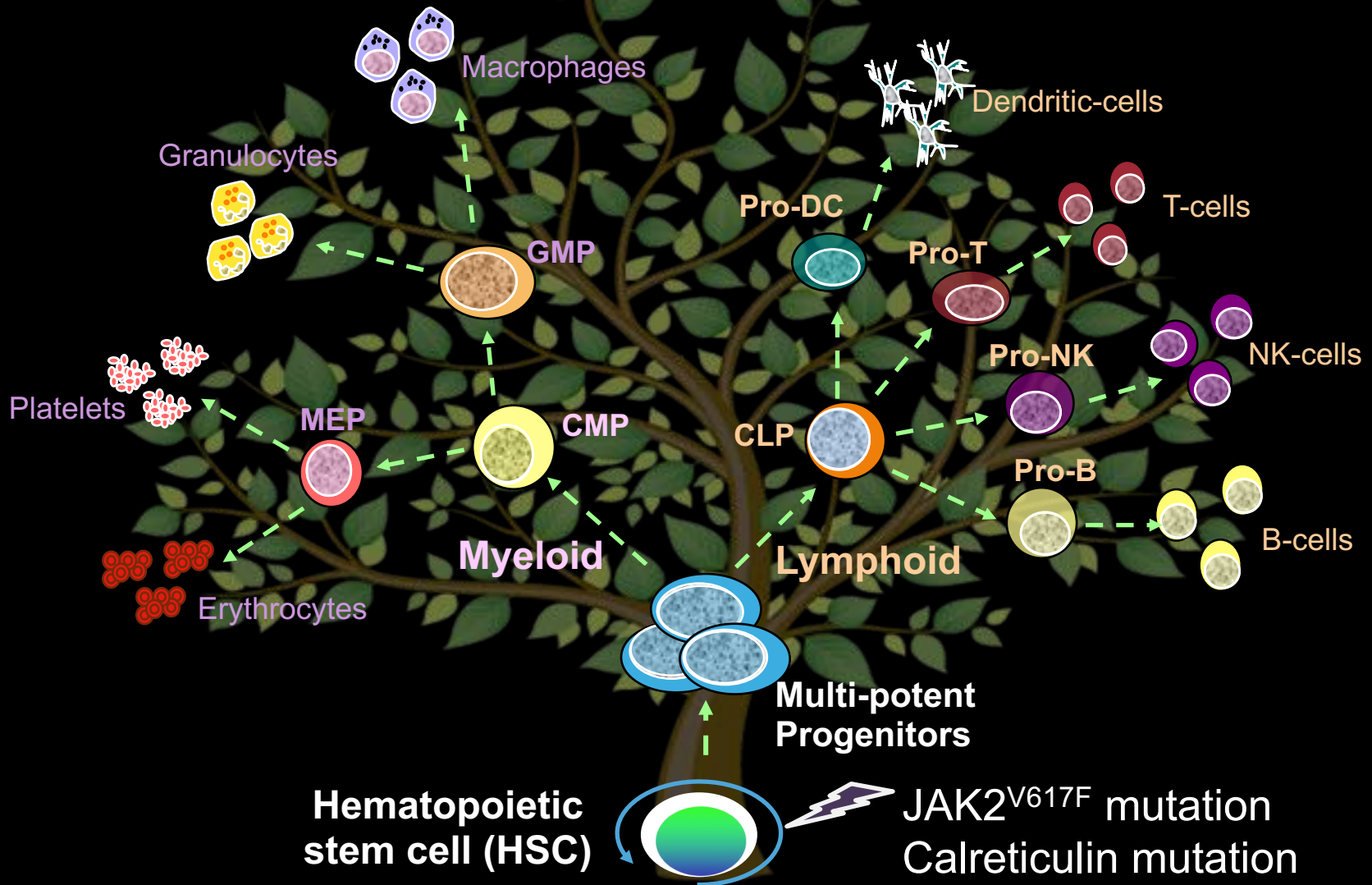
Symptoms and Quality of Life in MPN

Current treatments for MPN

# Normal Blood cell development

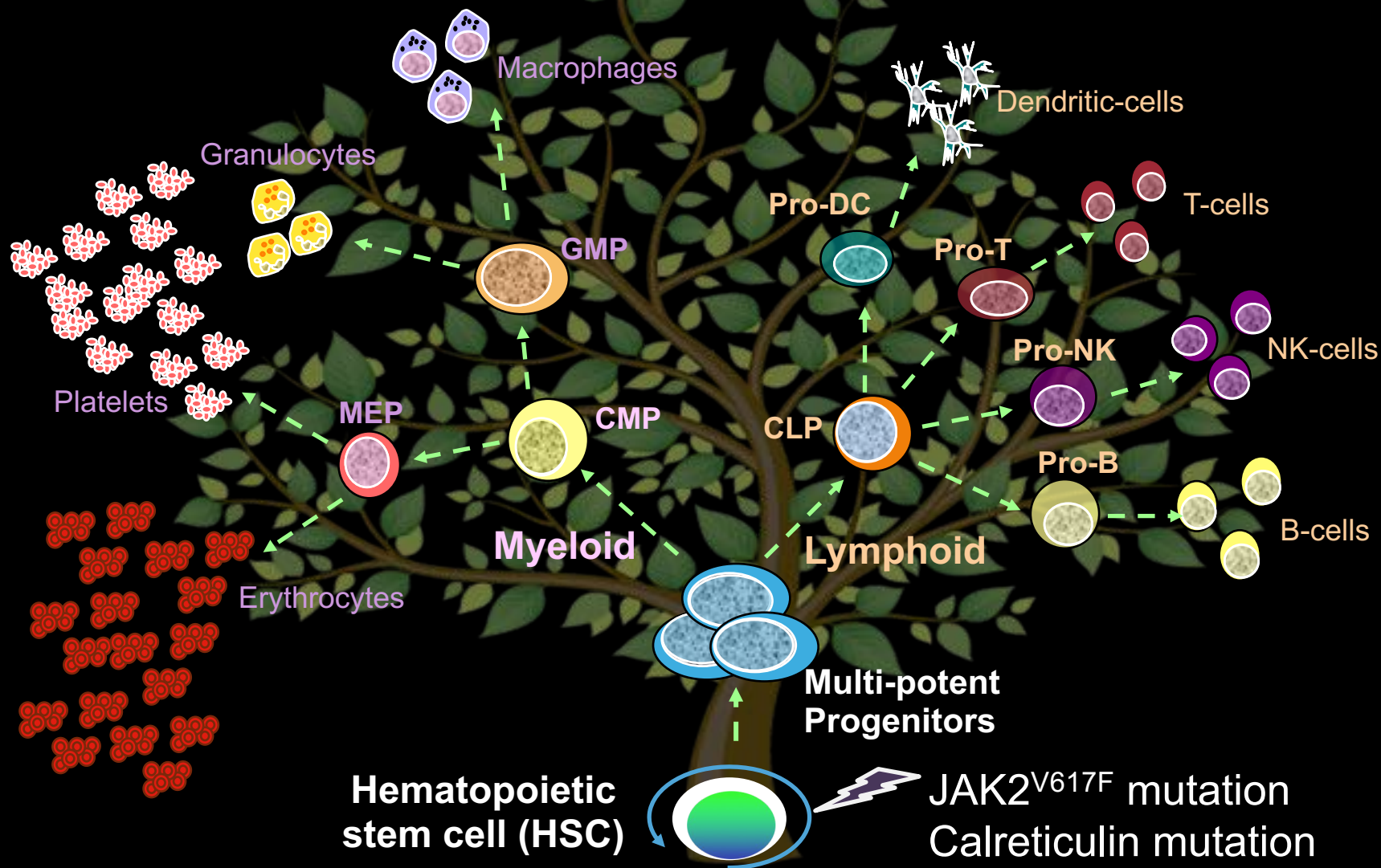


# MPN are disorders of blood stem cells



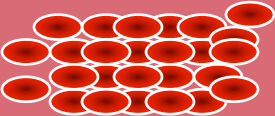


# Increased production of blood cells in MPN




# MPN subtypes

Polycythemia  
Vera  
(PV)



Red Cells

Essential  
Thrombocythemia  
(ET)



Platelets

Myelofibrosis  
(MF)

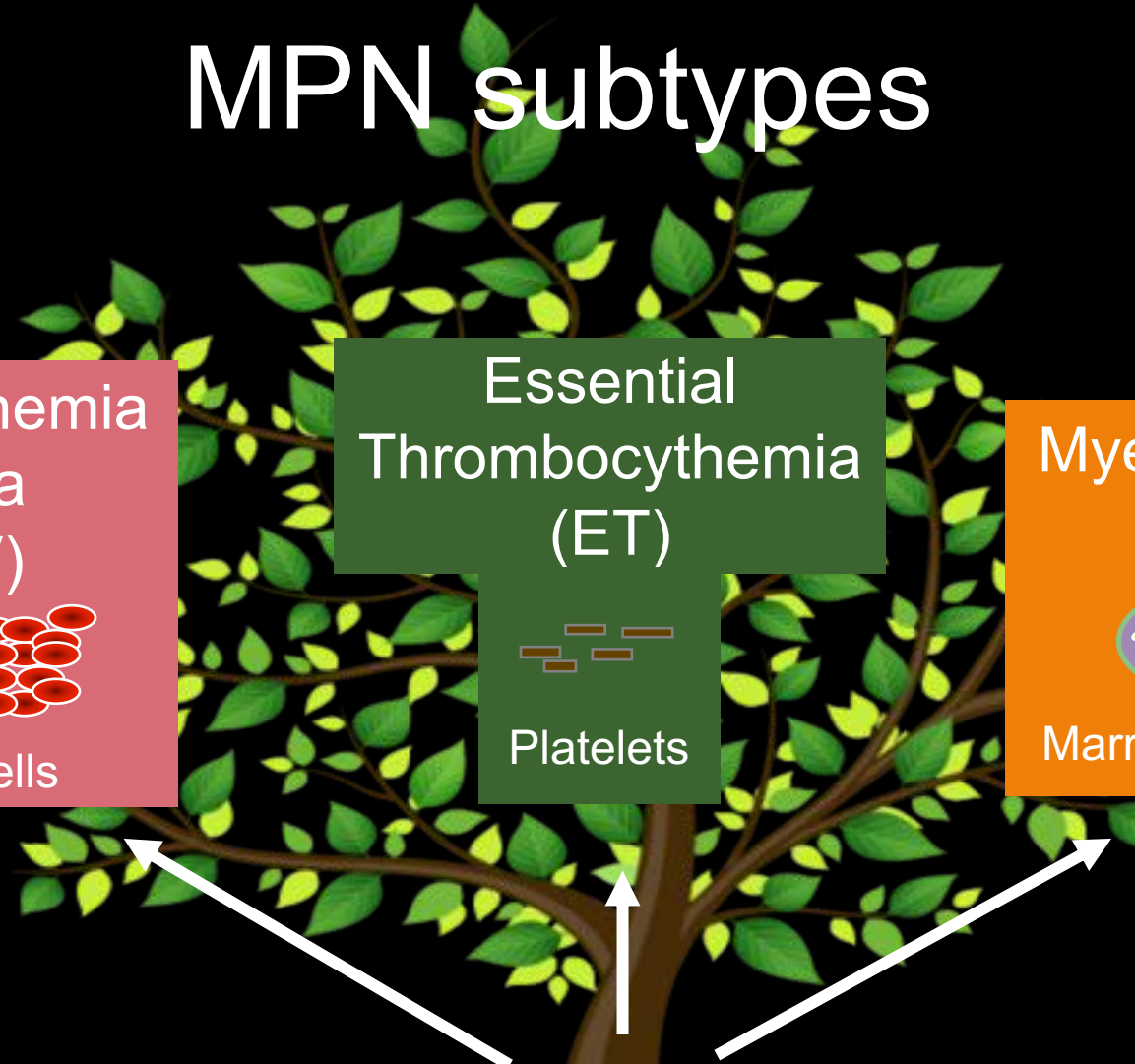


Marrow Fibrosis

Hematopoietic  
stem cell (HSC)

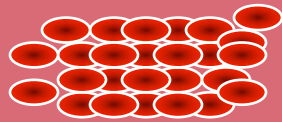


JAK2<sup>V617F</sup> mutation  
Calreticulin mutation



# Polycythemia Vera

Polycythemia  
Vera  
(PV)



Red Cells



Hematopoietic  
stem cell (HSC)



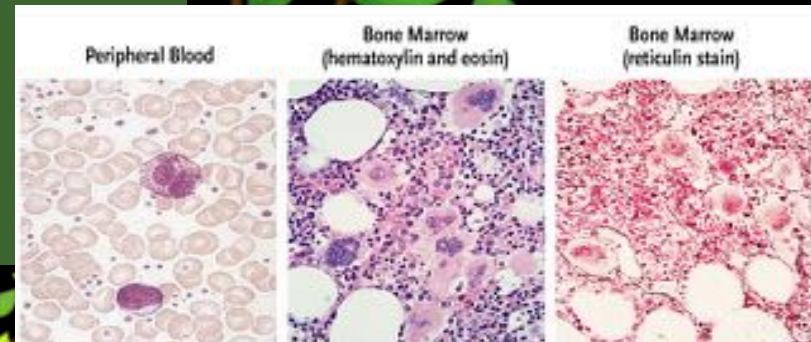
JAK2<sup>V617F</sup> mutation



# Essential Thrombocythemia

Essential  
Thrombocythemia  
(ET)

Platelets



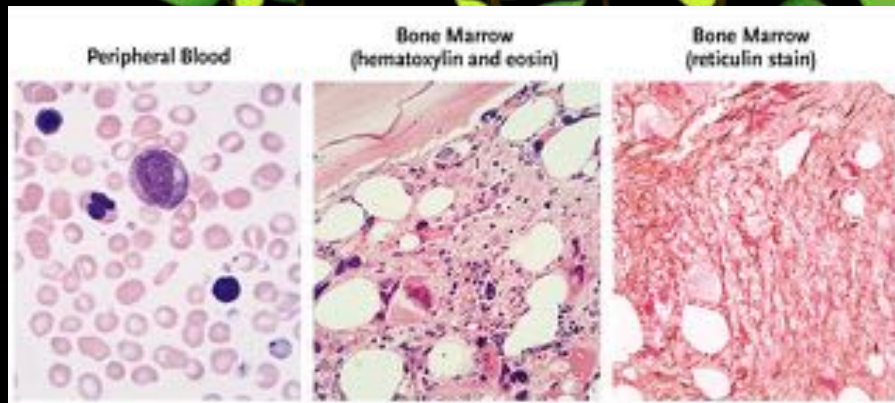
Hematopoietic  
stem cell (HSC)



JAK2<sup>V617F</sup> mutation  
Calreticulin mutation



# Myelofibrosis



Myelofibrosis  
(MF)



Marrow Fibrosis

Hematopoietic  
stem cell (HSC)



JAK2<sup>V617F</sup> mutation  
Calreticulin mutation

# Why is MPN called a “cancer”

After the identification of the JAK2 mutation  
the name was changed from

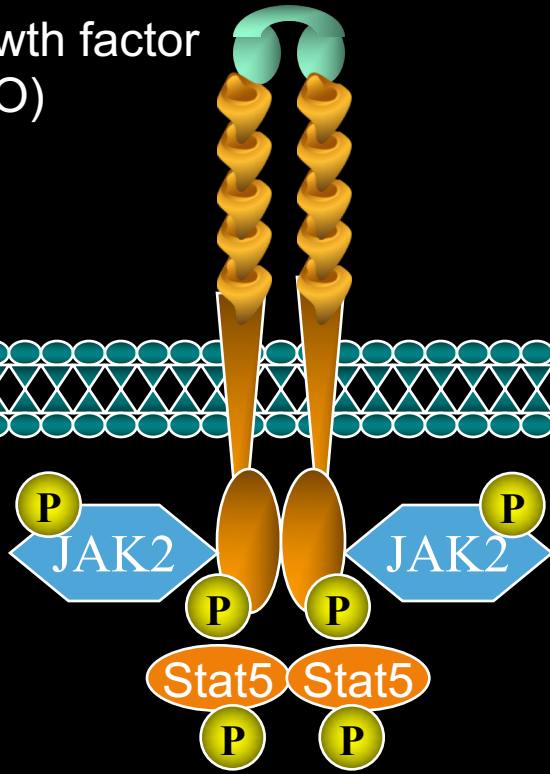
Myeloproliferative disorder to neoplasm

# Mutations in MPN

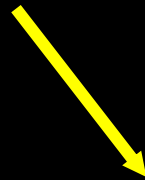
- Almost all MPN patients have a “driver mutation” which leads to turning on of growth signals in blood cell progenitors
- Driver mutations in MPN: JAK2, CALR, MPL

Growth factor  
(EPO)

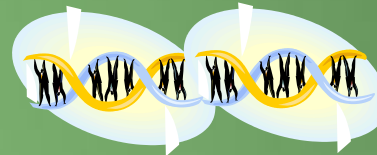
# JAK2's role in blood cell production



Growth factors are usually required for the signal to produce blood cells

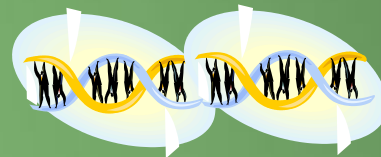
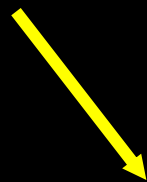
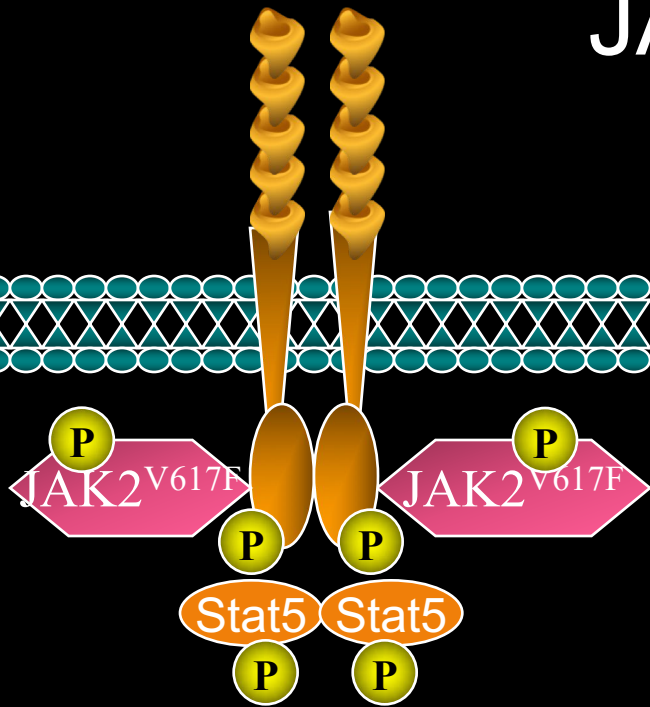


Production of blood cells



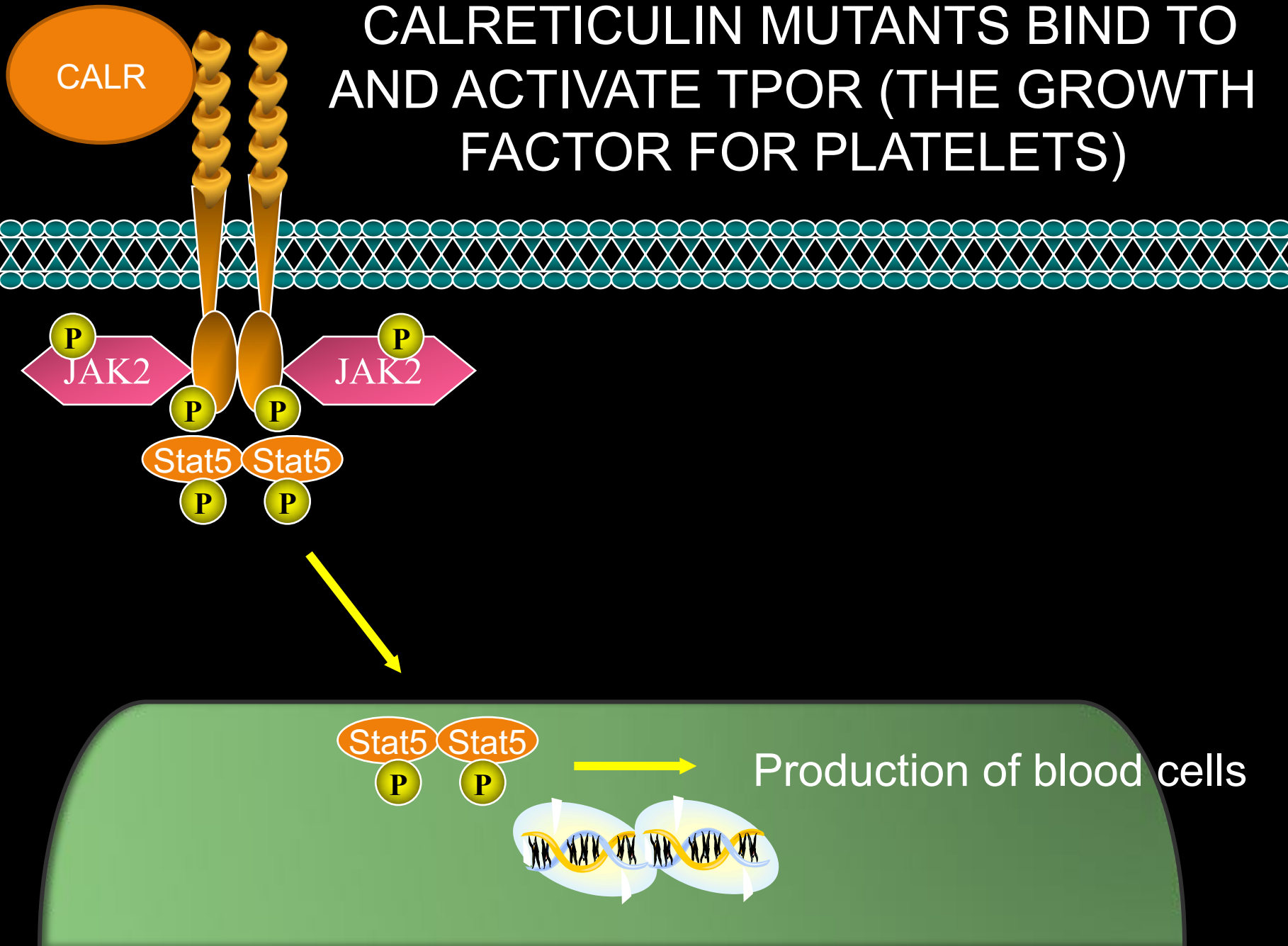


# JAK2<sup>V617F</sup> signals without growth factors

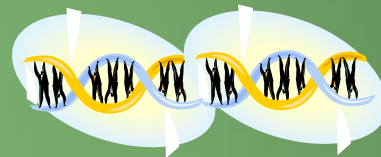
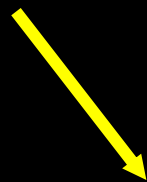
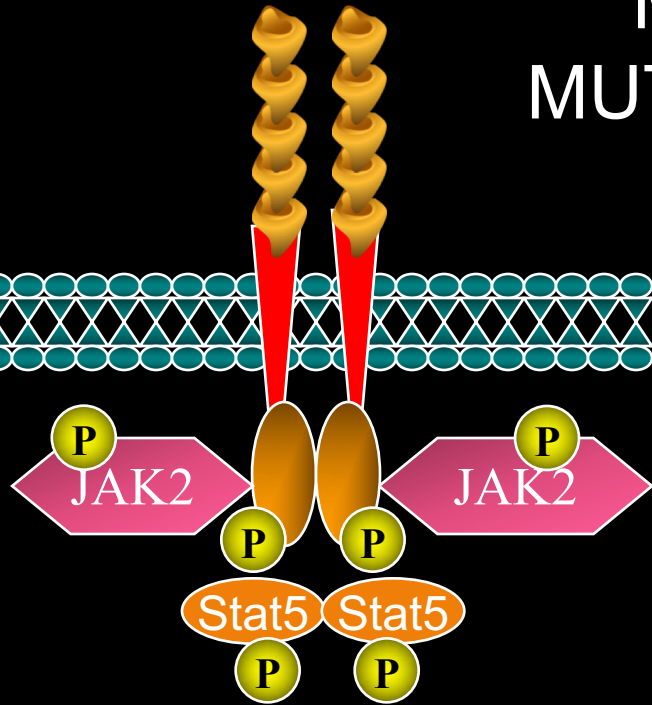


Production of blood cells

# CALRETICULIN MUTANTS BIND TO AND ACTIVATE TPOR (THE GROWTH FACTOR FOR PLATELETS)

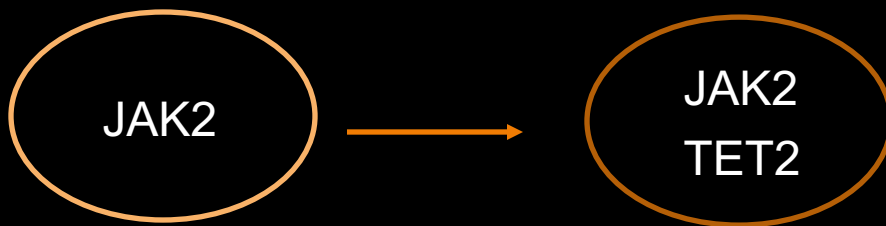


MPL is the TPOR, MPN MPL  
MUTATIONS LEAD TO ONGOING  
TPOR SIGNALING

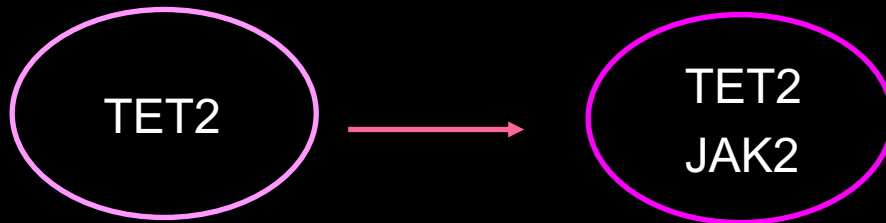


Production of blood cells

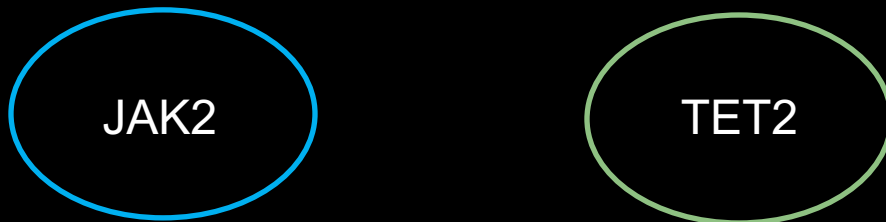
# MPN patients can have other mutations in addition to their driver mutation



JAK2 first, then another mutation in the same cell



Another mutation first, then JAK2 in the same cell



JAK2 and another mutation in different cells



Some of these other mutations  
carry with them a higher risk  
prognosis

- *ASXL1, SRSF2, U2AF1, EZH2,*  
and *IDH1/2*

# Is MPN “inherited”?

- MPN patients were not born with the JAK2 mutation, it was acquired sometime during their lifetime
- 15% of myMPN registry participants reported having a family member with MPN and 11% reported a family member with another blood cancer
- Family members of MPN patient have an increased risk of developing AML (RR 1.53), MDS (RR 6.87), and PV (RR 7.66) and ET (RR 6.3)
- Other cancers and autoimmune diseases also increased in MPN patients/families

# Therapeutic goals in MPN

- Reduce risk of blood clots
- Relieve symptoms

# Reduction of blood clotting risk

TREATMENT	WHO FOR
Reduce CV risk factors Aspirin Phlebotomy (goal hct<45%)	<b>All patients</b>
<b>Cytoreduction</b> (hydrea, anagrelide, IFN)	<b>High Risk Patients</b> age >60 prior blood clot plts>1500



# Management of MF

## Treatment for anemia

- Erythropoietin (growth factor)
- Corticosteroids
- Androgens (danazol) +/- Prednisone
- Thalidomide /lenalidomide+ Prednisone
- Transfusions

## Treatment for splenomegaly

- Hydroxyurea
- Splenectomy
- Ruxolitinib

# Ruxolitinib (JAKAFI)

JAK1/JAK2 inhibitor

FDA approved for:

Intermediate or high-risk Myelofibrosis (=80-90% of MF patients)

PV patients who are intolerant or resistant to hydrea

JAK2V617F NOT required

# Ruxolitinib (jakafi)

## WHAT IT DOES:

- Reduces spleen size
- Relieves symptoms

## WHAT IT DOESN'T DO:

- Improve anemia
- Significantly reduce the JAK2<sup>V617F</sup> allele burden

## WHAT IT MAY DO:

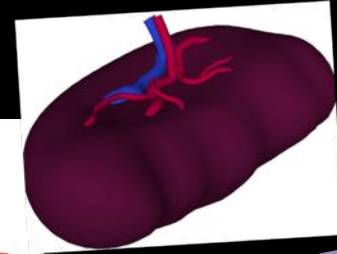
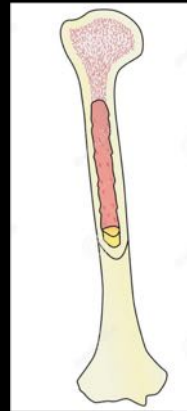
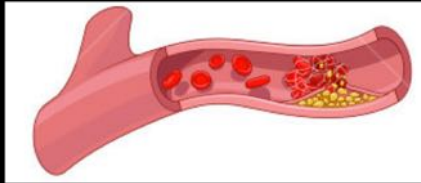
- Retard progression of fibrosis
- Extend lifespan

# Limitations of Ruxolitinib

- Not suitable for all patients
- Persistence of clone
  - Allele burden does not correlate with disease course
- Lack of improvement or worsening of cytopenias
  - Transient decrease in hemoglobin
  - Persistent drop in platelets
- Atypical infections
  - Herpetic infections
  - Mycobacterial
  - Hepatitis reactivation
- Does not decrease the risk of LT



# The Consequences of Inflammation in MPNs



## Inflammation

- Fatigue
- Weight loss
- Fevers
- Night sweats

## Thrombosis

- Visceral Clots = Abdominal Pain
- Pulmonary Clots = Cough
- Cerebral Vein Thrombosis = Headache

## Bone Marrow Fibrosis

- Bone Pain

## Extramedullary Hematopoiesis

Production of blood cells in organs where this should not happen

## Splenomegaly

- Abdominal Pain
- Early Satiety
- Nausea
- Constipation



# MPN10: allows visual assessment of symptoms

**MPN 10 KNOW YOUR SCORE** Name: \_\_\_\_\_ Date: \_\_\_\_\_

Fill out the form below to track the burden of your symptoms.

**Symptom: 1 to 10, 0 if absent and 10 being worst imaginable**

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours

Fatigue  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Circle the one number that describes how much difficulty you have had with each of the following symptoms during the past week

Filling up quickly when you eat (early satiety)  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Abdominal discomfort  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Inactivity  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Problems with concentration - compared to before my diagnosis  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Night sweats  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Itching (pruritus)  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Bone pain (diffuse, not joint pain or arthritis)  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Fever (>37.8°C or 100°F)  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (DAILY) (WORST IMAGINABLE)

Unintentional weight loss last 12 months  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

To help you get a clear overall picture of how you are feeling, you can add up all your scores to calculate your Total Symptom Score. Total: \_\_\_\_\_

You can also fill in this form and find more expert information about myeloproliferative neoplasms online at [www.spotlightonMPN.com](http://www.spotlightonMPN.com)

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**MPN 10 KNOW YOUR SCORE** Name: \_\_\_\_\_ Date: \_\_\_\_\_

Fill out the form below to track the burden of your symptoms.

**Symptom: 1 to 10, 0 if absent and 10 being worst imaginable**

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours

Fatigue  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Circle the one number that describes how much difficulty you have had with each of the following symptoms during the past week

Filling up quickly when you eat (early satiety)  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Abdominal discomfort  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Inactivity  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

Problems with concentration - compared to before my diagnosis  
0 1 2 3 4 5 6 7 8 9 10  
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Night sweats  
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0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (DAILY) (WORST IMAGINABLE)

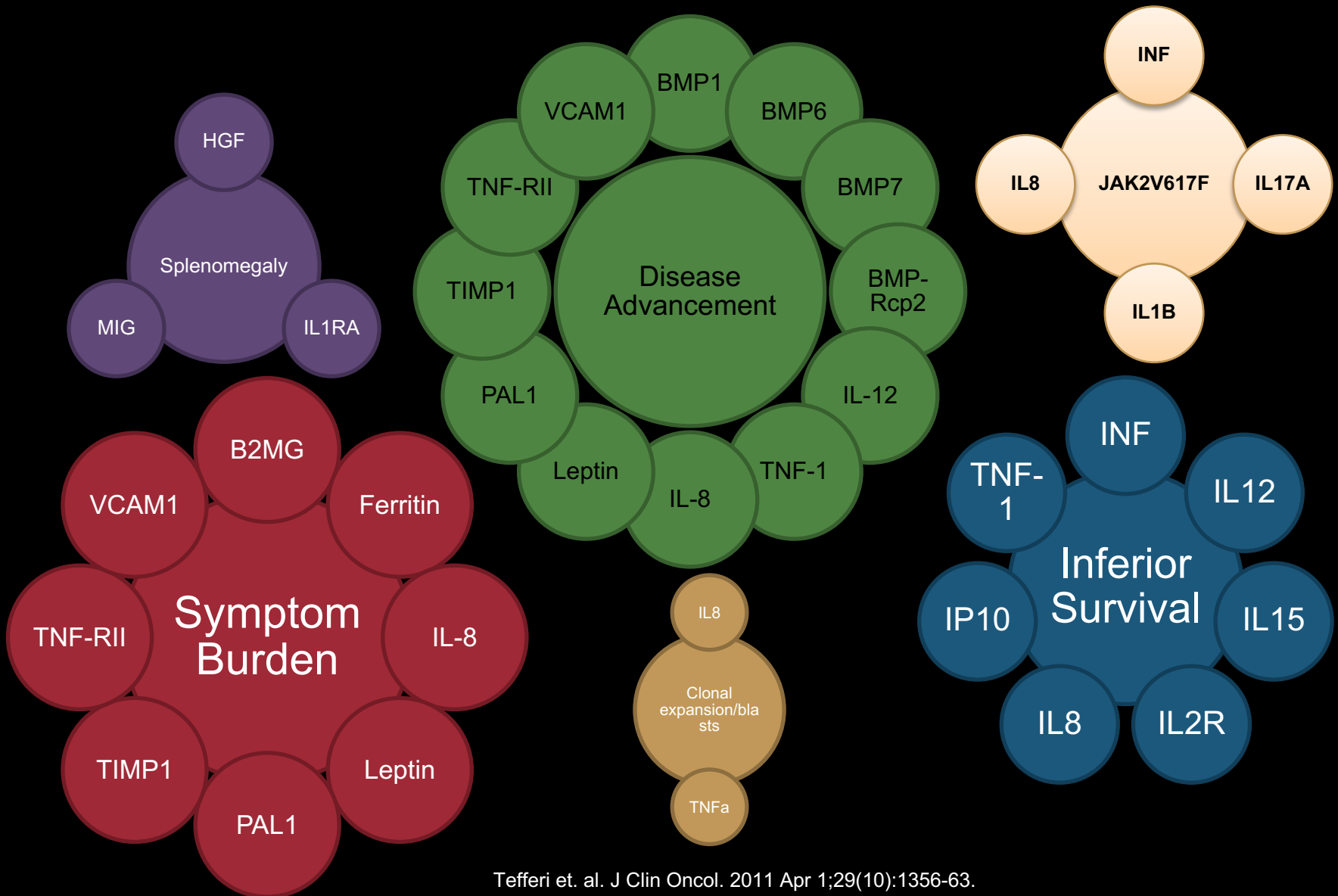
Unintentional weight loss last 6 months  
0 1 2 3 4 5 6 7 8 9 10  
(ABSENT) (WORST IMAGINABLE)

To help you get a clear overall picture of how you are feeling, you can add up all your scores to calculate your Total Symptom Score. Total: \_\_\_\_\_

You can also fill in this form and find more expert information about myeloproliferative neoplasms online at [www.spotlightonMPN.com](http://www.spotlightonMPN.com)

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# Inflammatory Cytokines and Chemokines in the MPNs



# What are methods to control inflammation?

- Prescription Medications
- Over the counter medications and supplements
- Stress reduction/mindfulness
- Exercise
- Diet

Can we utilize non-pharmacologic interventions in such a way as to equip patients to self-manage their inflammation and symptoms?

# Diets and Inflammation

## *Dietary Interventions in Other Pro-inflammatory Diseases*

- Diets emphasizing anti-inflammatory properties have demonstrated good efficacy when utilized in nutritional intervention for high-inflammation disease states such inflammatory bowel disease.
  - In an intervention among patients with IBD (N=40)
    - 60% had “good” or “very good” response in IBD severity after four weeks of dietary compliance
- *To date, no dietary interventions have been evaluated in MPN patients.*



# Mediterranean diets and Inflammation

## *Effective in Non-MPN Disease*

- Mediterranean diet adherence associated with **reduced all cause mortality**
  - Men: HR 0.79 (95% CI, 0.76-0.83)
  - Women: HR 0.80 (95% CI, 0.75-0.85)
- Individuals in with the highest tertile of dietary compliance with the Mediterranean diet had (N=3,042):
  - Inflammatory markers:
    - 20% lower **CRP** (p = 0.015)
    - 17% lower **IL-6 levels** (p = 0.025).
  - Coagulation markers
    - 15% lower **homocysteine levels** (p =0.031)
    - 14% lower **white blood cell counts** (p = 0.001)
    - 6% lower **fibrinogen levels** (p =0.025).



Estruch et al, NEJM 2013

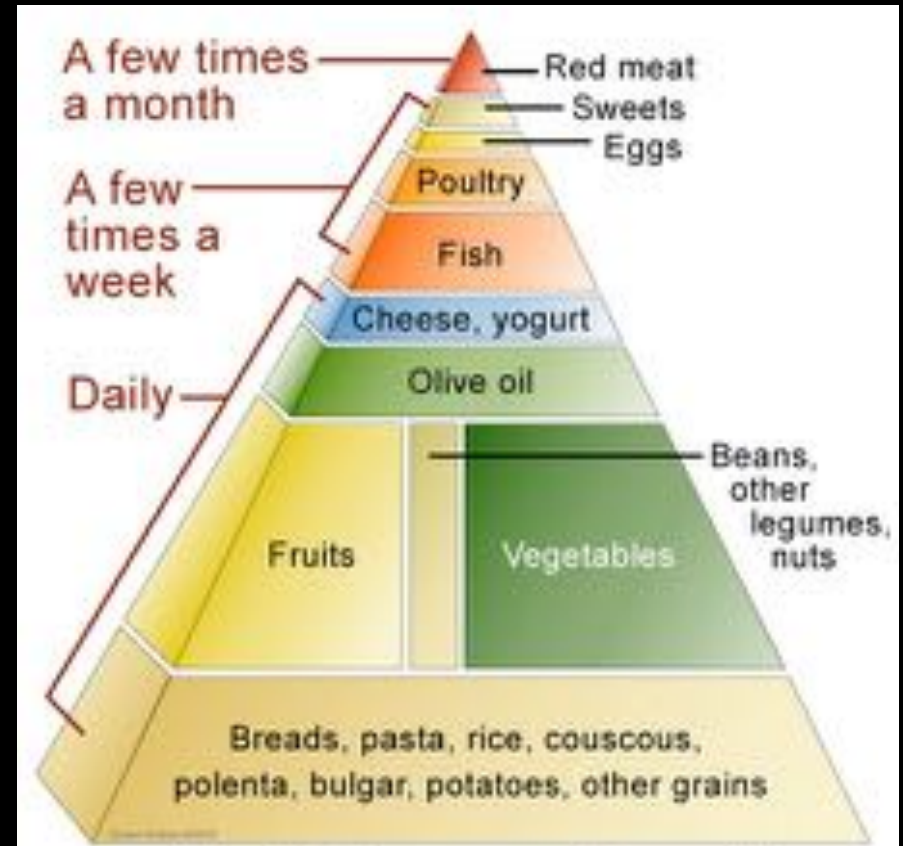
Mitrou et. al. Arch Intern Med. 2007;167(22):2461-2468.

Chrysohoou et. al. *J Am Coll Cardiol.* Jul 7 2004;44(1):152-158.

# USDA vs Mediterranean Dietary Recommendations



USDA Pyramid

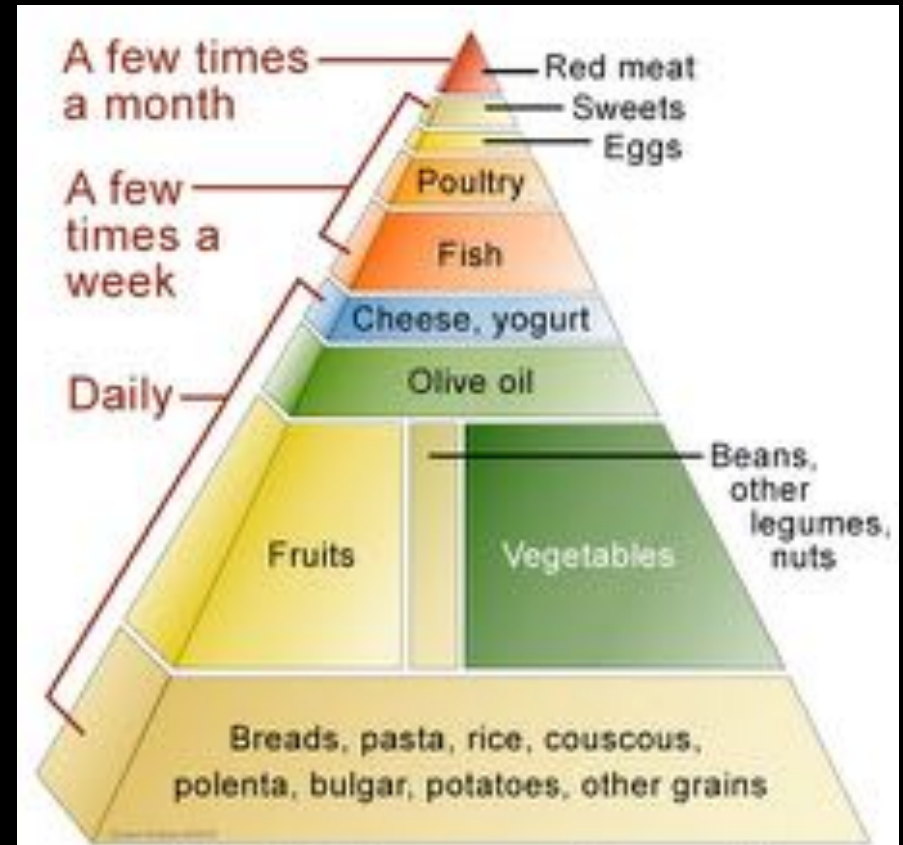


Mediterranean Diet Pyramid



# Mediterranean Diet

- High consumption of fruits, vegetables, bread, and other cereals, potatoes, beans, nuts and seeds. Focus is on whole grains
- Olive oil is an important monounsaturated fat source
- Dairy products, fish and poultry are consumed in low to moderate amounts
- Little red meat
- Eggs 0-4 times/week
- Wine in low to moderate amounts



Mediterranean Diet Pyramid

# The NUTRIENT Trial

(NUTRitional Intervention among myEloproliferative Neoplasms Trial)

*Completed March 2017*

**Stage Ia:**

**Online MPN Nutritional Questionnaire (N=1,300)**

- Nutritional Habits
- Supplement Intake
- Dietary Needs
- Symptom Assessment

*Open Now*

**Stage II:**

**12 week Trial Assessing Feasibility and Adherence of Mediterranean Diet (N=30)**

- Dietician counseling and online diet curriculum
- Blood markers of inflammation at week 0, 6, 12
- Q2week Mediterranean diet adherence and 24hr diet recall (ASA24)
- Q2week MPN-SAF
- Q2week feasibility questionnaire

**Stage III:**

**Large Randomized Trial Testing Efficacy of Diet Reduce Symptom Burden and Inflammatory Cytokines**

*Completed April 22-23<sup>rd</sup>, 2017*

**Stage Ib:**

**Determine MPN Dietary Needs and Preferences (N=30)**

- Focus groups
- Metabolic/Nutritional Assessment
- MPN-SAF Symptom Assessment
- Cytokine Analysis
- Body Fat Composition

# The NUTRIENT Trial

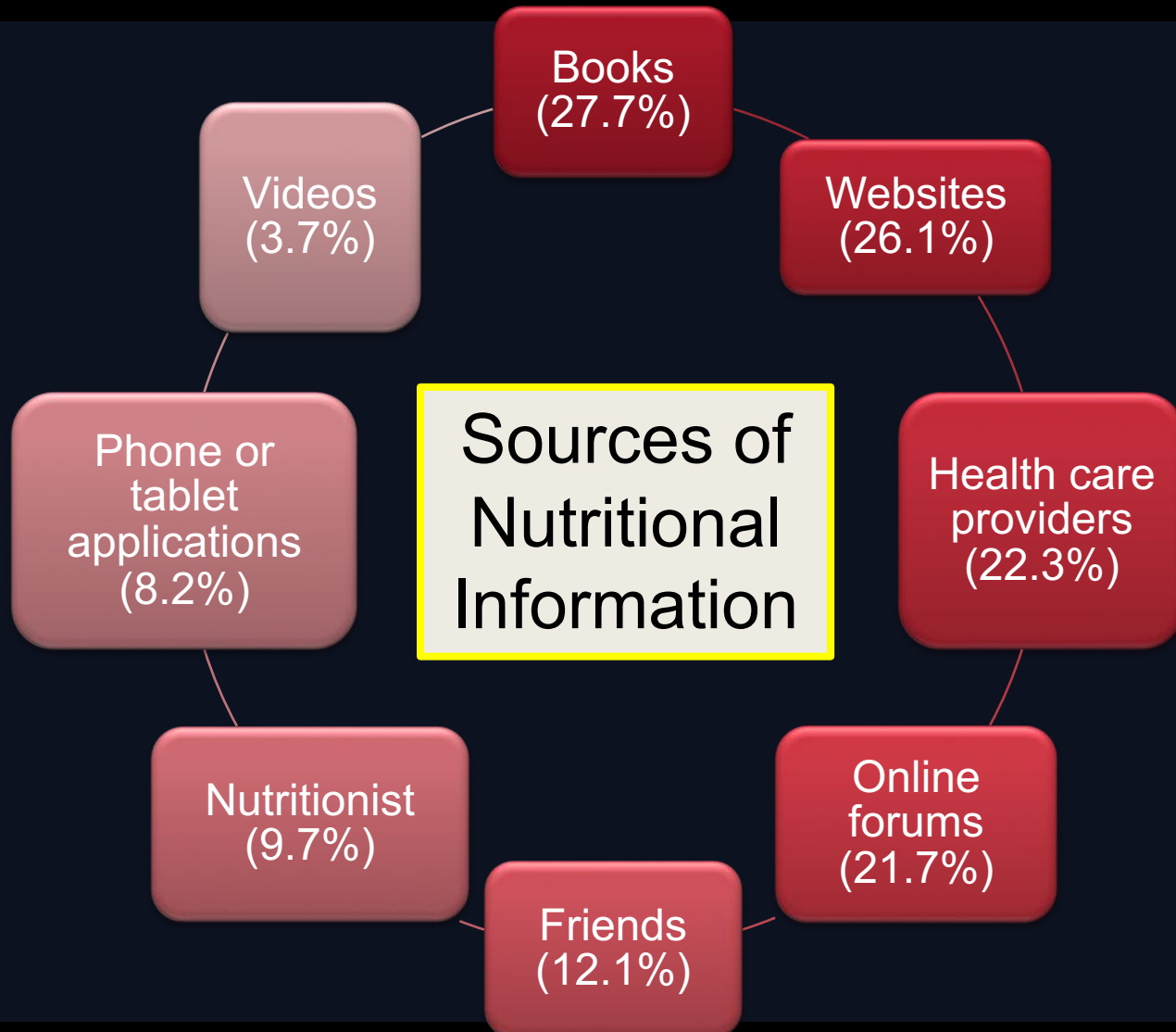
## *Nutritional Survey: Part IA*

An internet-based survey hosted by the Mayo Clinic Survey Research Center and promoted on multiple MPN-based forums, Facebook pages and websites during February of 2017.

- N=1329
- Respondents represented MPN patients from 40 countries
- 55-item questionnaire regarding nutritional and supplement use habits, needs and preferences

# The NUTRIENT Trial

## *Sources of Nutritional Information*



# The NUTRIENT Trial

*MPN patients are interested in diet interventions*

34.0% of patients endorsed **using diet** to help control their **symptoms** or **MPN disease**.

96.2% of MPN patients endorsed being **willing** restrict their diet if it helped to control symptom burden

98% of patients were **willing** to restrict their diet if they could help their MPN to stabilize or reduce the risk of their MPN getting **worse**.



# Food restrictions in MPN patients

Food allergies and/or Intolerances	Frequency among all respondents
Milk	8.3%
Wheat	6.9%
Fruit	4.1%
Shellfish	2.8%
Soy	2.3%
Peanuts	1.7%
Egg	1.4%
Tree Nuts	1.4%
Fish	1.3%
<b>Dietary Restrictions</b>	
Low salt	6.6%
Gluten-free	6.5%
Mediterranean diet	6.0%
Vegetarian	5.7%
Low fat	5.3%
Anti-inflammatory	5.1%
Lactose intolerant	3.9%



# The NUTRIENT Trial

## *Nutritional Survey Diet Correlates*

Correlative	Mean symptom burden (MPN-10)		P-value
<b>Diet</b>	<b>Not Following Diet</b>	<b>Following Diet</b>	<b>Pr &gt; t </b>
Diabetic diet	3.33	4.67	<0.0001
Lactose Intolerant	3.35	3.87	0.0433
<b>Food Intake (Dichotomous)</b>	<b>Never</b>	<b>At Least Once Per Week</b>	<b>Pr &gt; t </b>
Alcohol	3.62	3.11	<0.0001
Fast Food	3.24	3.59	0.0015
Fried Foods	3.22	3.46	0.0198
Rice	3.57	3.30	0.0452
Soda	3.22	3.72	<0.0001
<b>Food Intake (Continuous)</b>		<b>Pearson</b>	<b>P-value</b>
Alcohol	-	-0.139	<0.0001
Baked Goods	-	-0.070	0.0212
Dairy other than Cheese (milk, cream)	-	-0.069	0.0240
Fast Food	-	0.104	0.0007
Fried Foods	-	0.086	0.0051
Pasta	-	-0.072	0.0183
Pre-made Snack Foods	-	0.067	0.0296
Soda	-	0.121	<0.0001
Refined Sugars	-	0.075	0.0139
Tacos	-	0.068	0.0277

Foods associated with worsened symptom score in **red**, foods associated with improved score in **green**

# The NUTRIENT Trial

## *Nutritional Survey Supplement Use Frequency*

- 72% of MPN respondents reported use of over the counter supplements.
- Supplement use was significantly more common among females (74%) than among males (66%,  $p=0.01$ ).
- Supplement users were significantly more likely to be:
  - older (mean age 59 vs 56 years old,  $P<0.001$ )
  - lower self-reported body mass index (mean 25.7 vs 26.6,  $P=0.02$ )
  - higher frequency of engaging in at least 30 minutes of physical activity (mean of 4 days vs 3 days per week,  $P=0.04$ ).

# The NUTRIENT Trial

*Correlates of specific supplements and symptoms*

Supplement	Frequency of Use	MPN-10 Symptom Score		
		Taking Supplement	Not taking supplement	P-value
<b>Amino Acids</b>	3.70%	2.8	3.39	0.02
<b>N-Acetylcysteine</b>	0.90%	2.37	3.38	0.02
<b>Bach flowers</b>	0.90%	5.22	3.35	0.008

Supplements associated with worsened symptom score in **red**, supplements associated with improved score in **green**

# Inflammation as a Treatment Target in MPNs

*Supplements with Effectiveness in MPN Mouse Models*

## N-Acetylcysteine

- Restored blood parameters

- Decreased spleen size

- Reduction in JAK2V617F mutant cells in spleen and bone marrow



- Reduced DNA oxidative damage and double strand DNA breaks

# The NUTRIENT Trial

## *Part 1B: Nutrition and Supplement Use Focus Groups*

- MPN participants recruited from the “We are MPN” participant conference in Irvine, California in April 2017.
  - N=13, 77% female, 45% from the Irvine, California area

Patients frequently have **food restrictions or intolerances that are related to their MPN disease course and symptoms**

Patients are **enthusiastic** regarding participation and execution of a dietary intervention

Patients desired the ability to **connect with each other and with researchers**

Patients express concern over the **lack of resources** regarding diet

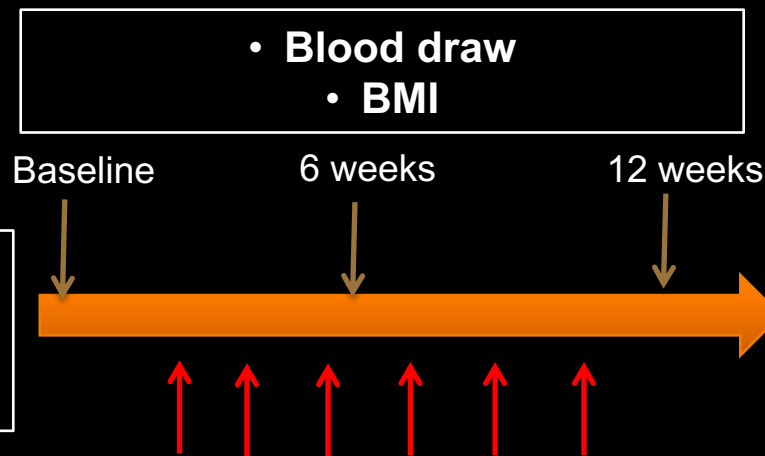
Patients desire a **tailored dietary intervention** which addresses their needs and preferences

# The NUTRIENT Trial

## Part II: Feasibility and Adherence to a Diet Intervention

Enrollment  
N=30

Meeting with  
a nutritionist  
for diet  
education



- Blood draw
- BMI

**Primary Endpoint:**  
combined >70% Dietary  
Adherence and >5/10  
patient-reported  
feasibility

**Secondary endpoint:**  
BMI  
percentage body fat  
nutritional markers  
inflammatory markers  
plasma cytokines  
JAK2 allele burden

- Adherence to  
Mediterranean diet
- Feasibility questionnaire
- MPN-10



# Questions?

Contact Info:

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