Gender and MPNs

Developments and Considerations

Laura C. Michaelis, MD
Medical College of Wisconsin

2015 Joyce Niblack Memorial Conference on Myeloproliferative Neoplasms

Objectives

- Gender
  - Are there differences in these diseases between men and women?
- Select concerns facing female patients
  - Pregnancy
  - Thrombosis, Bleeding risks
- What's next?

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Incidence

- Is the occurrence of these diseases equally frequent in men and women?

Hematologic diseases

Disease	Male:Female Ratio
AML	1:1
ALL	1.3:1.0
HD	1.3:1.0
Multiple Myeloma	1.4:1
CLL	2:1
CML	3:2
ET	Female Predominance
PV	1.2:1.0
MF	1:1

N=11668 Insured individuals[1]	Polycythemia Vera	Essential Thrombocythemia	Myelofibrosis
Female	35%	67%	50%
Male	65%	33%	50%
Average Age	53 years	51 years	60 years

N=1425 MPN SAF[3]	Polycythemia Vera	Essential Thrombocythemia	Myelofibrosis
Female	46%	64%	47%
Male	54%	36%	53%
Average Age	62.8 years	60.7 years	63.5 years

N=272 Johns Hopkins[2]	Polycythemia Vera	Essential Thrombocythemia	Myelofibrosis
Female	64%	70%	36%
Male	36%	30%	64%
Average Age	50/56 years	50/48 years	59/61 years

[1]Mehta et al., Leuk Lymphoma 2014
[2]Stein et al., Haematologica 2010
[3]Emanuel et al., JCO 2012

Incidence of Disease by gender

- Polycythemia Vera
  - Historically studies have shown more frequent in men
  - Women are diagnosed at a younger age compared to men[1]
- Essential thrombocythemia
  - Historically, a female predominance has been cited
  - Large recent study showed incidence the same[2]
- Myelofibrosis
  - Likely a slight male predominance

[1]Stein et al., Haematologica Jul 2010
[2]Titmarsh et al., Am J Hem, March 2014

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Cancer and Gender

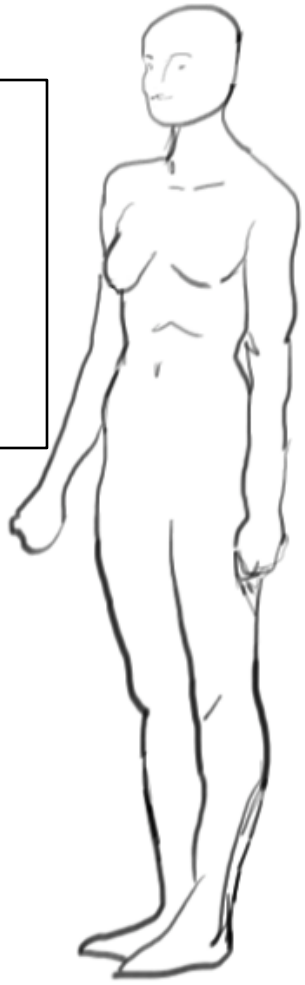
Why would a disease occur more frequently in one sex vs. the other?

- Biology?
- Diagnostic bias?
- Genetic predisposition?
- Exposure?

Why might the disease behave differently in one sex vs. the other?

- Modulated hormones?
- Gender-based lifestyle differences?
- Stem-cell biology?

Are there different consequences to the disease or treatment that depend on gender?



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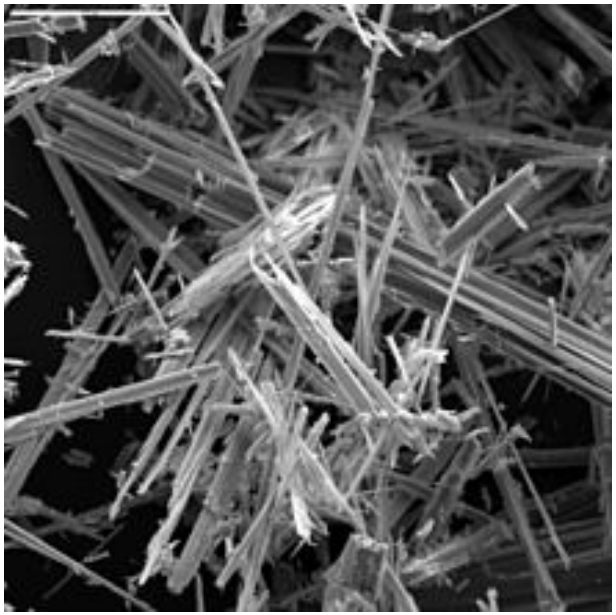

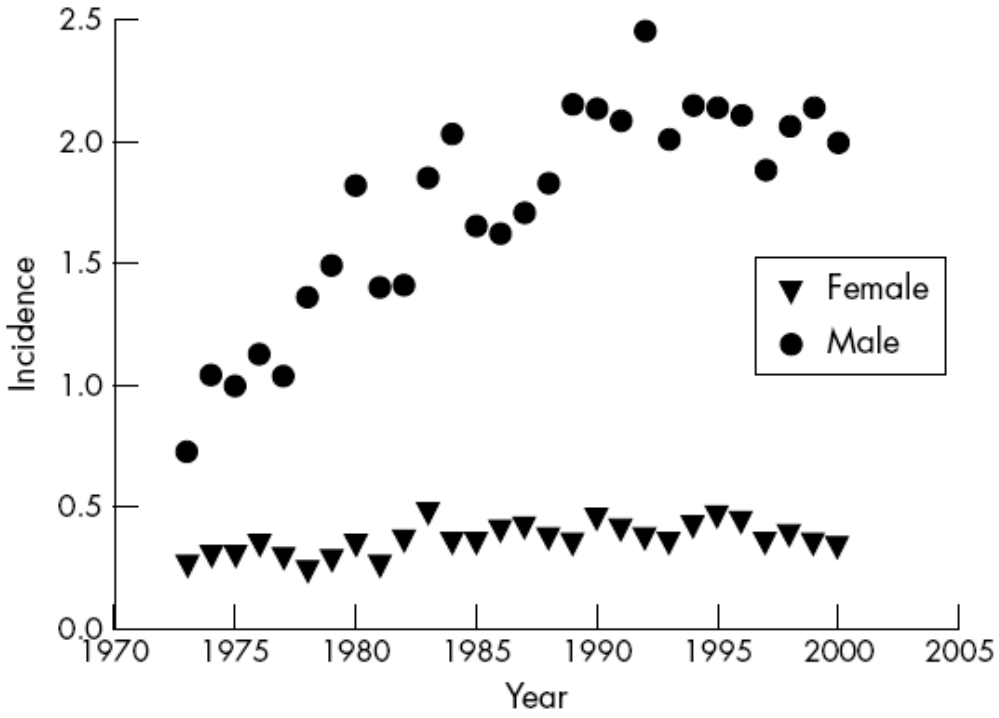

Figure 1 Age adjusted mesothelioma incidence (cases per 100 000) by gender.

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Cancer and Gender

Why would the disease occur more frequently in one sex vs. the other?

- Diagnostic bias?
- Exposure?
- Genetic predisposition?

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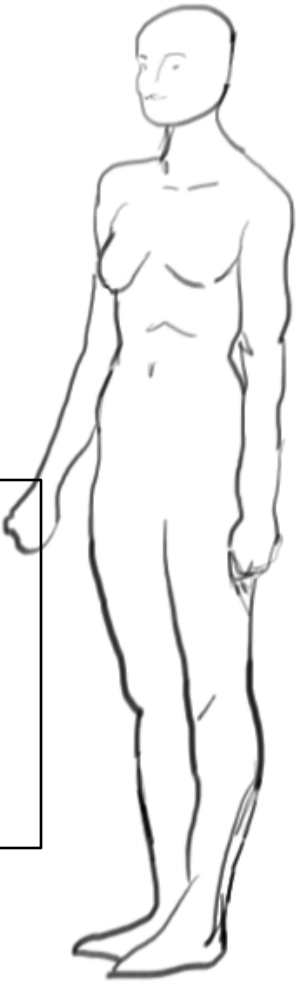

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Genetic Differences: PV

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Clinical Phenotypes in Polycythemia Vera

Jerry L. Spivak, M.D., Michael Considine, M.S., Donna M. Williams, Ph.D., Conover C. Talbot, Jr., B.A., Ophelia Rogers, A.A., Alison R. Moliterno, M.D., Chunfa Jie, Ph.D., and Michael F. Ochs, Ph.D.

From the Division of Hematology, Department of Medicine (J.L.S., D.M.W., O.R., A.R.M.), Division of Biostatistics and Bioinformatics, Sidney Kimmel Comprehensive Cancer Center (M.C.), and the Basic Science Institute (C.C.T.), Johns Hopkins University School of Medicine, Baltimore; the Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago (C.J.); and the Department of Mathematics and Statistics, College of New Jersey, Ewing (M.F.O.). Address reprint requests to Dr. Spivak at the Division of Hematology, Johns Hopkins University School of Medicine, Traylor 924, 720 Rutland Ave., Baltimore, MD

ABSTRACT

BACKGROUND

Polycythemia vera is the ultimate phenotypic consequence of the V617F mutation in Janus kinase 2 (encoded by *JAK2*), but the extent to which this mutation influences the behavior of the involved CD34+ hematopoietic stem cells is unknown.

METHODS

We analyzed gene expression in CD34+ peripheral-blood cells from 19 patients with polycythemia vera, using oligonucleotide microarray technology after correcting for potential confounding by sex, since the phenotypic features of the disease differ between men and women.

RESULTS

Men with polycythemia vera had twice as many up-regulated or down-regulated

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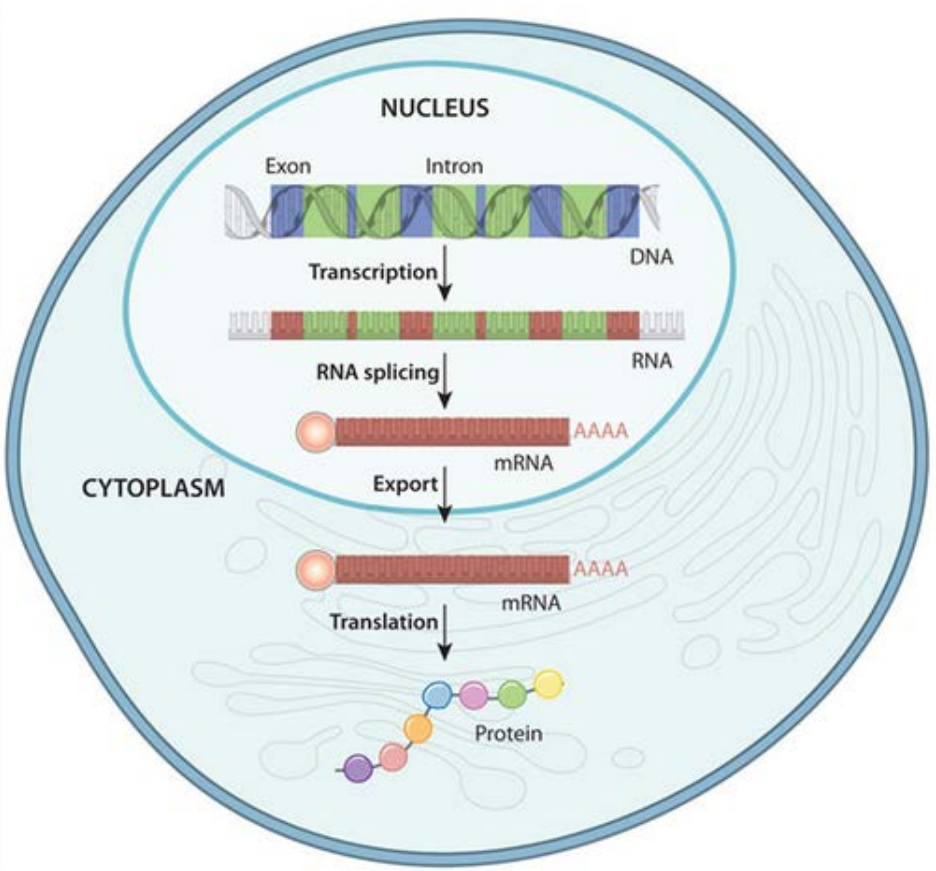


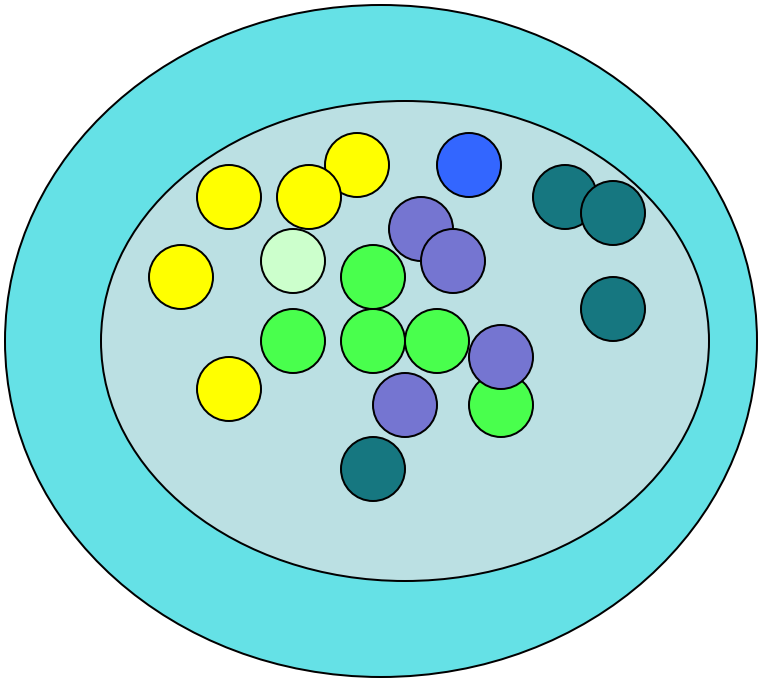
Comparison of DNA gene expression	
Control Men (n=3)	Men with MPD (n=8)
Control Women (n=3)	Women with MPD (n=11)

What is “gene expression?”

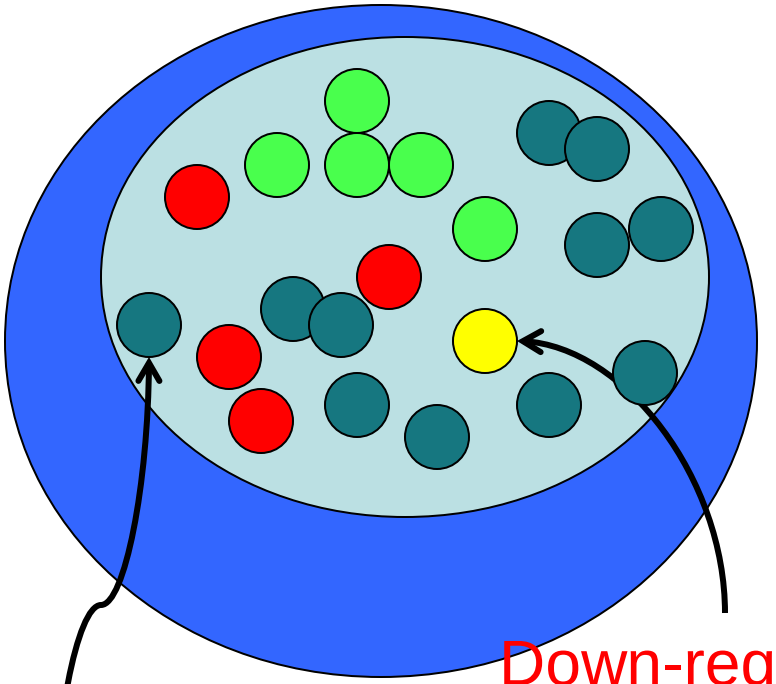
Play Form Often Kitchen Banana Blue-Eyes Extra Blood Clots Dog Loves Hates Very Cats Animals Platelets Salads Sunshine Adores Children Tumble Develop Over Make Fibrosis More Blood Clots Don’t Bleed Too Much Clean Obsessively Have

Grow Tall Often Earlobes Liver Blood Clots Toes Loves Grey Hair Very Webbed Long Toes Innovates Develop Tolerates Rain Depression Red Kalidoscopes Develop Blonde Blood Clots Significant Enjoy Eating Stay Quiet Fight Horror Movies Short Alcoholism

Genetic Differences: PV



CD34+ PB
Healthy Male Controls



CD34+ PB
Males with PV

Up-regulated

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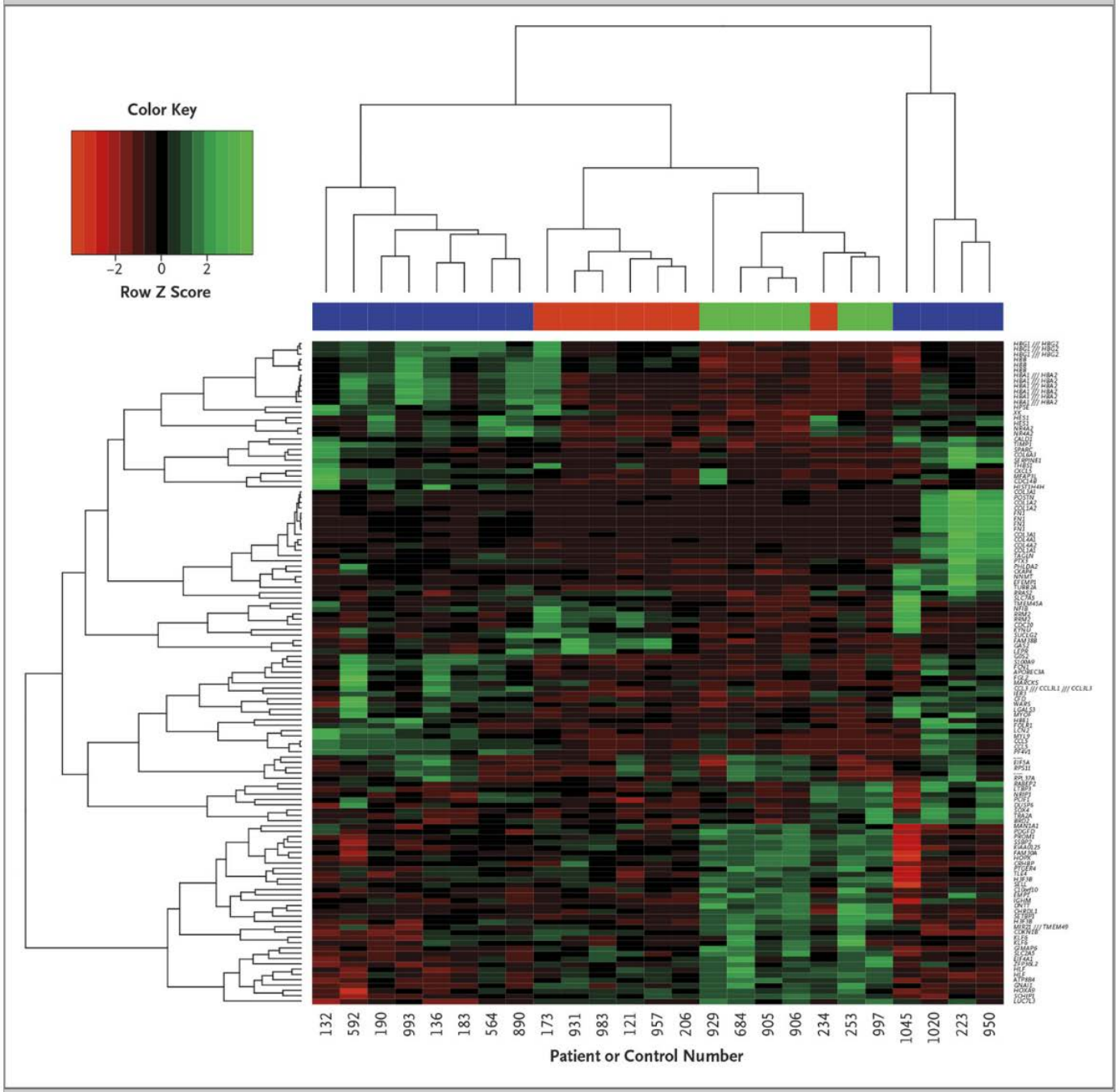
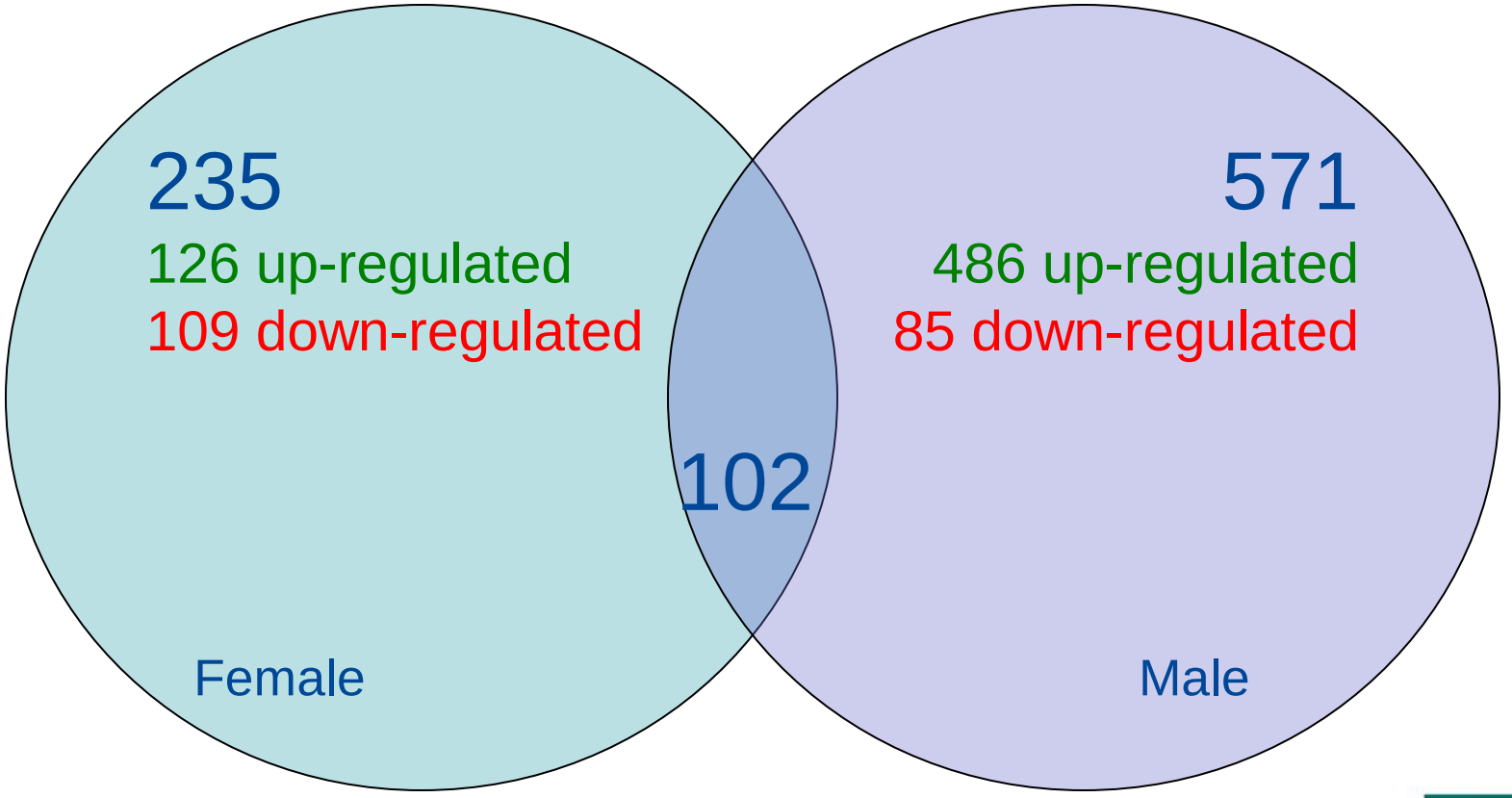


MEDICAL COLLEGE of WISCONSIN

Genetics of the PV clones



Spivak et al., NEJM 2015

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Table 2. Clinical Features Segregated with the Use of Unsupervised Hierarchical Clustering.

Characteristic	Patients with Aggressive Disease (N=7)	Patients with Indolent Disease (N=12)	P Value*
Sex — no.			
Male	4	4	
Female	3	8	
Median age (range) — yr	66 (48–74)	68 (46–82)	NS
Median disease duration (range) — yr	14 (7–24)	6 (1–25)	0.05†
Median *JAK2* V617F neutrophil allele burden (range) — %	100 (64–100)	85 (55–100)	NS
Median hemoglobin level (range) — g/dl	11.1 (8.3–12.9)	13.3 (10.7–15.9)	0.007†
Median white-cell count per mm^3 (range)	17,620 (10,020–171,190)	17,870 (4430–27,270)	NS
Median platelet count per mm^3 (range)	454,000 (171,000–1,017,000)	837,000 (151,000–1,480,000)	NS
Thrombosis — no. of patients	4	1	0.04‡
Palpable splenomegaly — no. of patients	7	6	0.03‡
Median spleen size (range) — cm below costal margin	20 (5–32)	2 (0–14)	0.005‡
Splenectomy — no. of patients	4	0	0.007‡
Chemotherapy — no. of patients	5	2	0.03‡
Transformation to acute leukemia — no. of patients	4	1	0.04‡
Surviving — no. of patients	1	11	0.001‡

* NS denotes not significant.
† The P value was calculated with the use of Student's t-test.
‡ The P value was calculated with the use of Fisher's exact probability test (two-sided).

Spivak et al., NEJM 2015

Cancer and Gender

Does the disease occur more frequently in one sex vs. the other?

- Diagnostic bias?
- Exposure?
- Genetic predisposition?

Does the disease behave differently in one sex vs. the other?

- Different clinical consequences or complications?
- Different treatment strategies?

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Table 1. All-inclusive and gender-stratified outline of presenting features in 1545 patients with PV

	N evaluable	*All patients (N = 1545)*	*Females, N = 785 (51%)*	*Males, N = 760 (49%)*	P-values
Median age, years (range)	1545	61 (18–95)	62 (18–92)	59 (19–95)	<**0.01**
Ages below 40/50 years	1545	10/24%	10/23%	10/26%	0.58
Hemoglobin, median in g/dl (range)	1545	18.4 (15.1–26.5)	17.7 (15.1–24.5)	18.9 (17.1–26.5)	<**0.01**
Hematocrit (median and range)	1545	55 (36–78)	54 (36–76)	57 (42–78)	<**0.01**
Leukocyte count, median $\times 10^9$/l (range)	1545	10.4 (3–171.6)	10.3 (3–125.5)	10.5 (4.2–171.6)	0.85
Leukocytosis ($>10.5 \times 10^9$/l), *n* (%)	1545	751 (49%)	375 (48%)	376 (49.5%)	0.5
Platelet count, median $\times 10^9$/l (range)	1545	466 (7–2370)	509 (7–2370)	419 (37–1410)	<**0.01**
Thrombocytosis ($\geqslant 450 \times 10^9$/l), *n* (%)	1545	817 (53%)	472 (60%)	345 (45.4%)	<**0.01**
Extreme thrombocytosis ($\geqslant 1000 \times 10^9$/l), *n* (%)	1545	58 (4%)	46 (6%)	12 (1.6%)	<**0.01**
Palpable spleen, *n* (%)	1477	534 (36%)	241 (32%)	293 (40.3%)	<**0.01**
Pruritus, *n* (%)	1349	485 (36%)	240 (35.4%)	245 (36.6%)	0.64
Vasomotor symptoms, *n* (%)	1412	403 (28.5%)	213 (30%)	190 (27%)	0.26
Arterial thrombosis before/at diagnosis, *n* (%)	1545	246 (16%)	108 (14%)	138 (18%)	**0.02**
Venous thrombosis before/at diagnosis, *n* (%)	1545	114 (7.4%)	73 (9.3%)	41 (5.4%)	<**0.01**
Major hemorrhage before/at diagnosis, *n* (%)	572	24 (4.2%)	16 (5.5%)	8 (2.8%)	0.11
↑ Lactate dehydrogenase, *n* (%)	732	368 (50%)	203 (54%)	165 (47%)	0.07
Leukoerythroblastic smear, *n* (%)	1056	63 (6%)	28 (5%)	35 (7%)	0.26
Abnormal karyotype, *n* (%)	631	77 (12%)	29 (9%)	48 (15%)	0.02
JAK2 mutation, *n* (%)	1268	1239 (98%)	626 (98%)	613 (97.3%)	0.68
V617F/other *JAK2* mutation (%)	1268	95%/3%	95.6%/2.5%	95%/3%	0.68
Serum Epo ↓/normal/↑ (%)	1058	81%/17%/2%	83%/15%/2%	79%/19%/1%	0.17
EEC, *n* (%)	454	331 (73%)	182 (76%)	149 (69.3%)	0.10
Increased red cell mass, *n* (%)	306	277 (91%)	149 (87.7%)	128 (94%)	0.06
Hemoglobin >18.5 g/dl (>16.5 ♀) *n* (%)	1545	1122 (73%)	652 (83%)	470 (62%)	<**0.01**
History of tobacco use, *n* (%)	1301	206 (16%)	74 (11.3%)	132 (20.4%)	<**0.01**
History of diabetes, *n* (%)	1149	97 (8.4%)	41 (7%)	56 (11%)	0.11
History of hyperlipidemia, *n* (%)	1073	196 (18.3%)	98 (18%)	98 (18.5%)	0.85
History of hypertension, *n* (%)	1388	638 (46%)	339 (48%)	299 (43.7%)	0.09

Abbreviations: EEC, endogenous erythroid colony; Epo, erythropoietin; PV, polycythemia vera. Bold numeral indicate differences that were statistically relevant.

Tefferi, Leukemia 2013

Gender Differences: Clinical

Women with PV

- Diagnosed earlier than men
- Higher likelihood of splenomegaly
- Lower JAK2 allele burden
- More risk for a blood clot in the liver system
- “Occult” disease
- More likely to evolve from ET→PV than men

Women with ET

- Less likely than men to have CAL-R mutations
- More likely then men to have “Triple-Negative disease”

Stein et al., Thrombosis 2011

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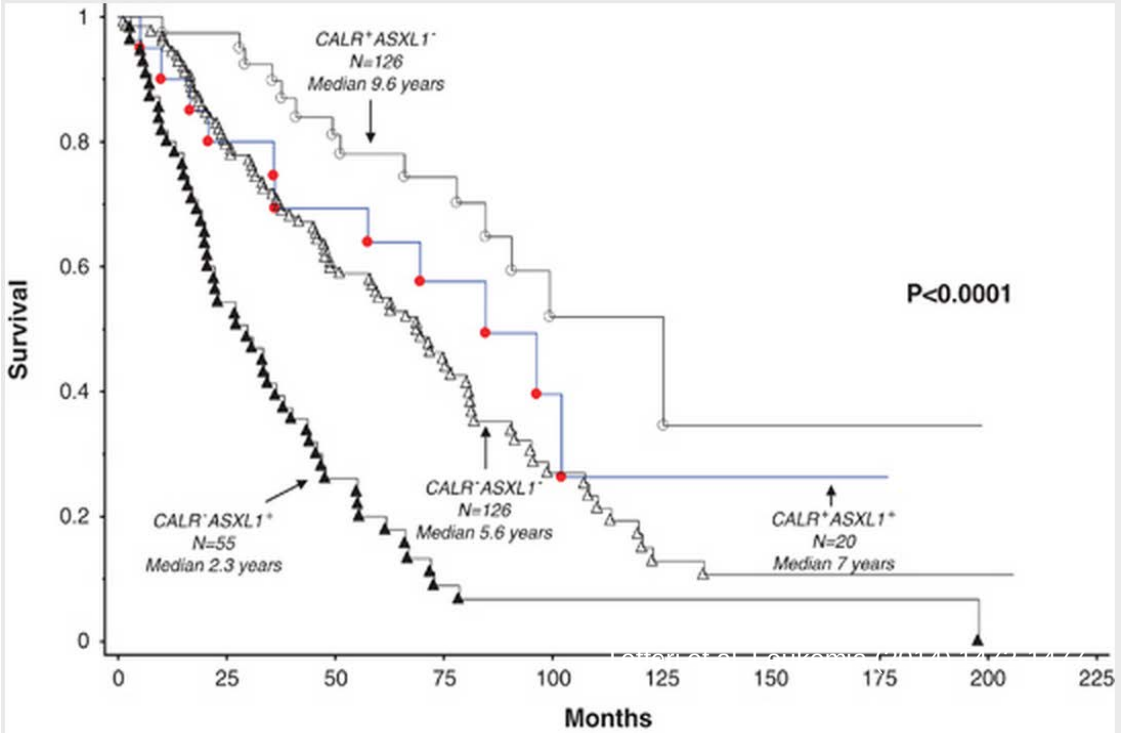
MF Risk Factors

- Monosomal karyotype
- inv (3)/i(17q) abnormalities
- Any two of the following: >9% circulating blasts, Leukocytes >40x10^9/L, unfavorable karyotype
- Absence of CALR, JAK2 and MPL mutation
- High-molecular risk category
  - *ASXL1, EZH2, SRSF2, IDH1/2*
  - *CALR-/ASX1+*



Tefferi AJH Vol 89, Sept 2014 917-924

Tefferi et al. Leukemia 20141472-1477

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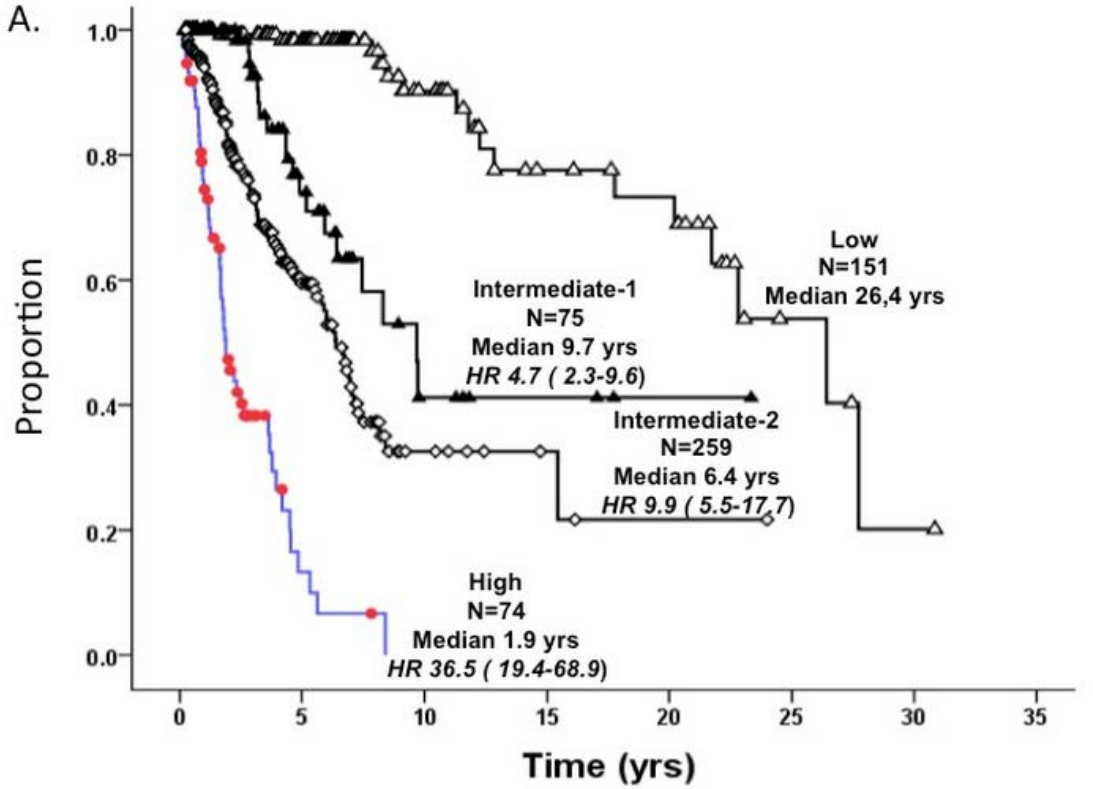
MF:MIPSS



Age > 60	1.5	“Triple Neg” for JAK2, MPL, CALR	1.5
Symptoms	0.5	JAK2 + or MPL +	0.5
Hgn <10g/dL	0.5	ASKL1	0.5
Platelets <200	1.0	SRSF2	0.5

Vannuchi et al. ASH 2014 Abstract 405

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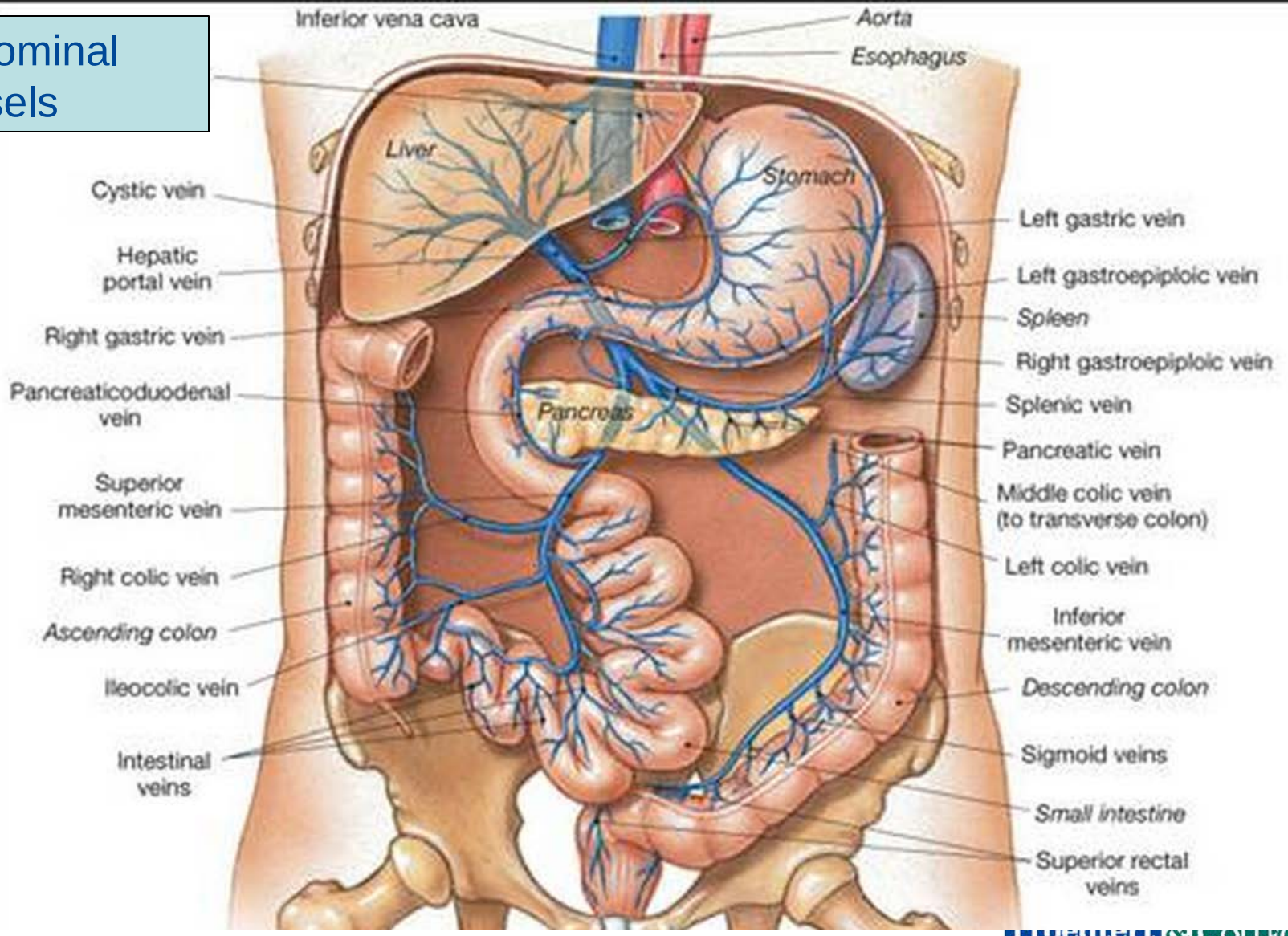
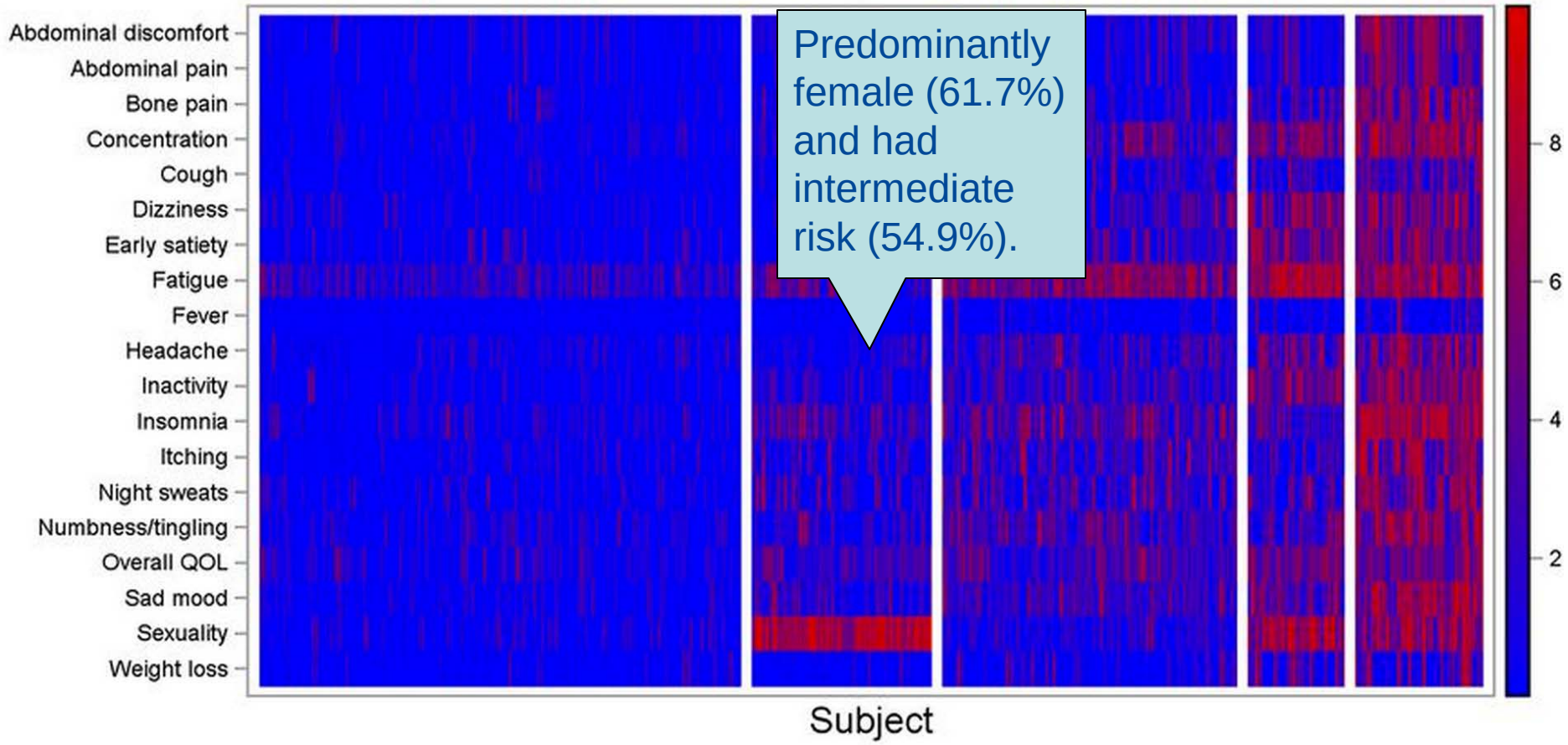
Gender and Blood Clots

- Both genders get blood clots
- In one study, women were
  - less likely to have high cholesterol
  - less likely to smoke
  - but more likely to get blood clots (odds 1.9:1)
- Men – more likely to have heart attacks or blood clots in the legs
- Women – more likely to have blood clots in the large blood vessels of the abdominal cavity
  - “Budd-Chiari Syndrome”
  - Portal Hypertension

Abdominal vessels



Symptom differences? ET



Geyer et al., Blood 2014

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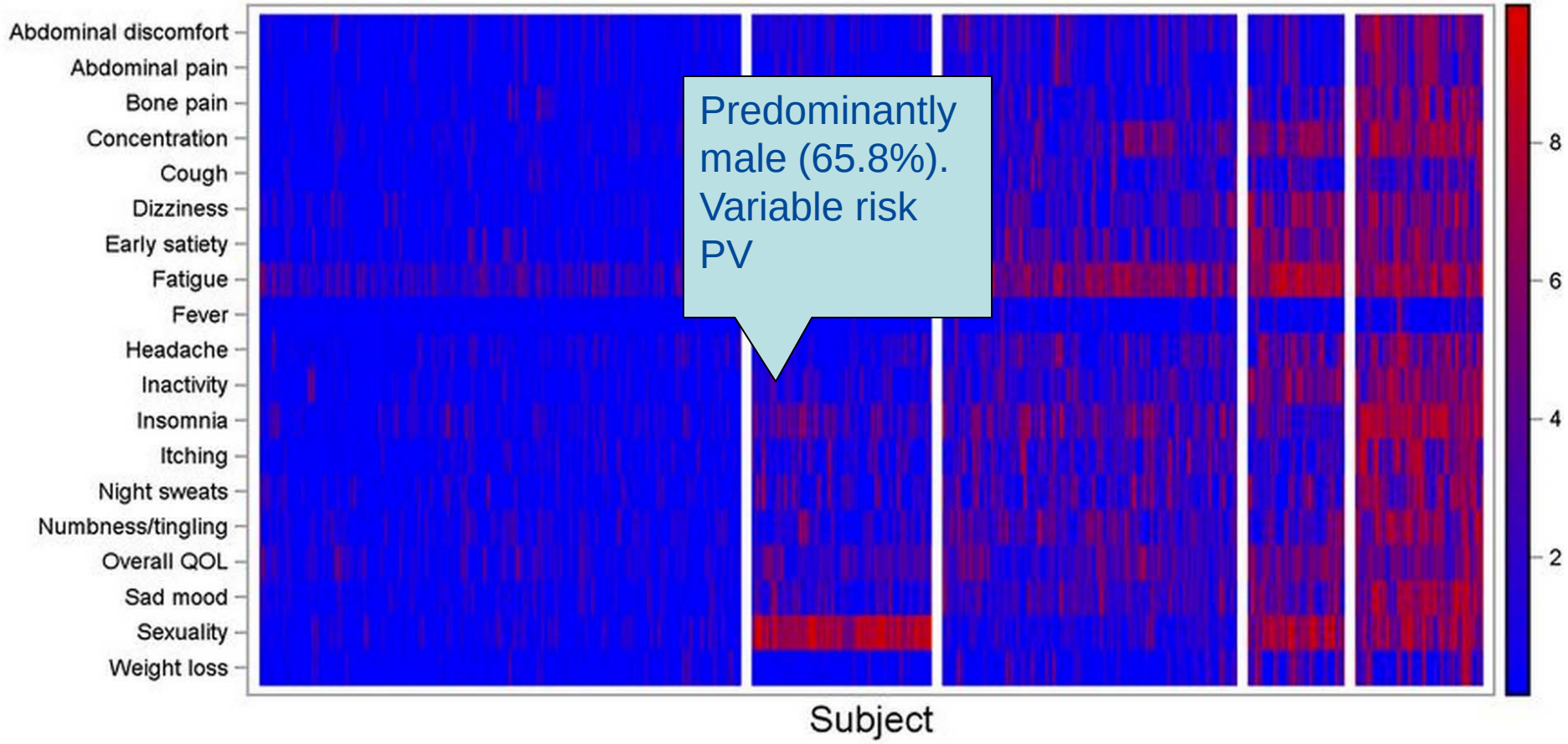
Symptom differences? PV



Geyer et al., Blood 2014

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Symptom Differences

- Females
  - Lower rates of thrombocytopenia
  - Higher rates of fatigue
  - Higher rates of microvascular symptoms
    - Migraines
    - Erythromelalgia

Objectives

- Gender differences
  - Risks of acquiring disease
  - Risks for symptoms
  - Risks for complications
- What are special concerns facing female patients
  - Fertility
  - Bleeding, Clotting risks
- Newest research on this issue

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Challenges: Fertility

- Contraception
  - Combination hormones >progesterone only OCPs
  - General population have a 3–6-fold increased risk of venous thrombosis with OCPs
- One retrospective study of >300 ET patients. Subset on OCPs
  - ET + OCPs = 23% VTE
  - ET no OCPs = 7% VTE
- Recommendation: Avoid combination OCPs, Discuss carefully the use of hormones of any kind

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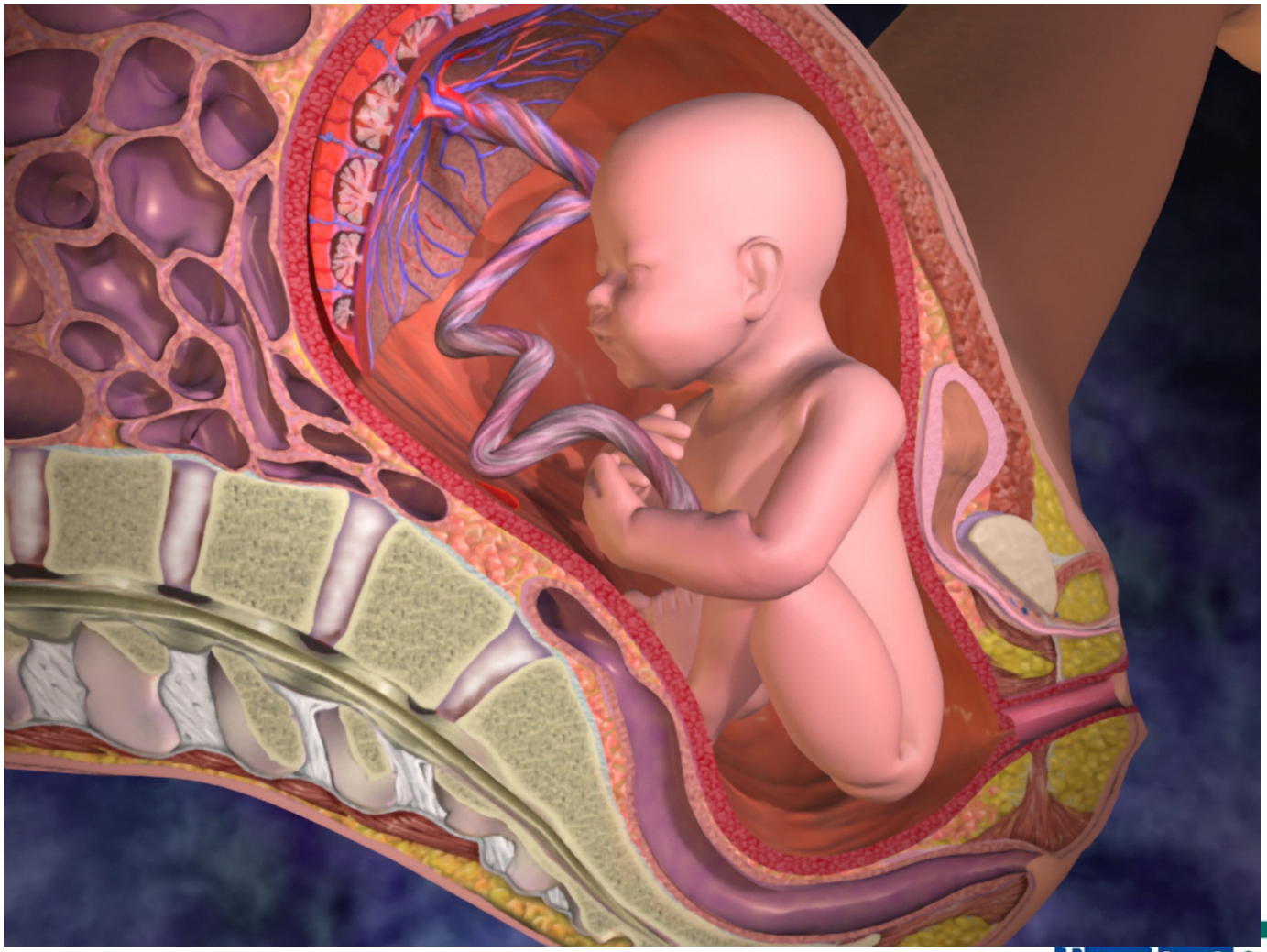
Challenges: Pregnancy



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Challenges: Pregnancy

- Pregnancy outcomes impacted by MPNs
  - Live birth rate 50-70%
  - First trimester loss 10-20%
  - Late pregnancy loss 10%
  - Increased rates of placental abruption, intrauterine growth restriction
- Can we change those outcomes?

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Preconception Counseling

- Risk Assessment
  - Prior VTE or arterial clot
  - Prior hemorrhage
  - Prior pregnancy complication
  - Diabetes or Hypertension requiring treatment
  - Platelet count of >1500 X 10^9 before or during pregnancy

Preconception Counseling

- Multidisciplinary approach
- Discussion of teratogenic drugs
- Therapeutic options
  - Aspirin
  - LMWH
  - Cytoreductive therapy
- Delivery and post-partum plan
- Breastfeeding information

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Pregnancy: Low-Risk Patients

- Generally
  - Continue low-dose aspirin
  - Monitor platelet or Hct
    - Keep HCT under 45%
    - Consider venesection if necessary
  - Increased plasma volume of pregnancy means no set targets

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Pregnancy: High-risk patients

- Remove possible teratogeneic drugs
  - Taper off hydrea or anagrilide 3-6 months prior to conception
  - Hydrea likely contraindicated, men and women
  - Anagrilide crosses the placenta
- Cytoreduction
  - Interferon-alpha -- Case reports indicating likely safe
- Prevent Clotting
  - LMWH
  - Prophylactic or, in some cases, therapeutic doses

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Challenges: Clotting

- Be aware of additive risks
  - Hospitalization, surgery, immobility, smoking, obesity
- Surgical risk
  - Ask about anticoagulation post-operatively
  - Discuss all surgeries with your hematologist
- Duration of anticoagulation
  - Depends on clot, other factors influencing risk

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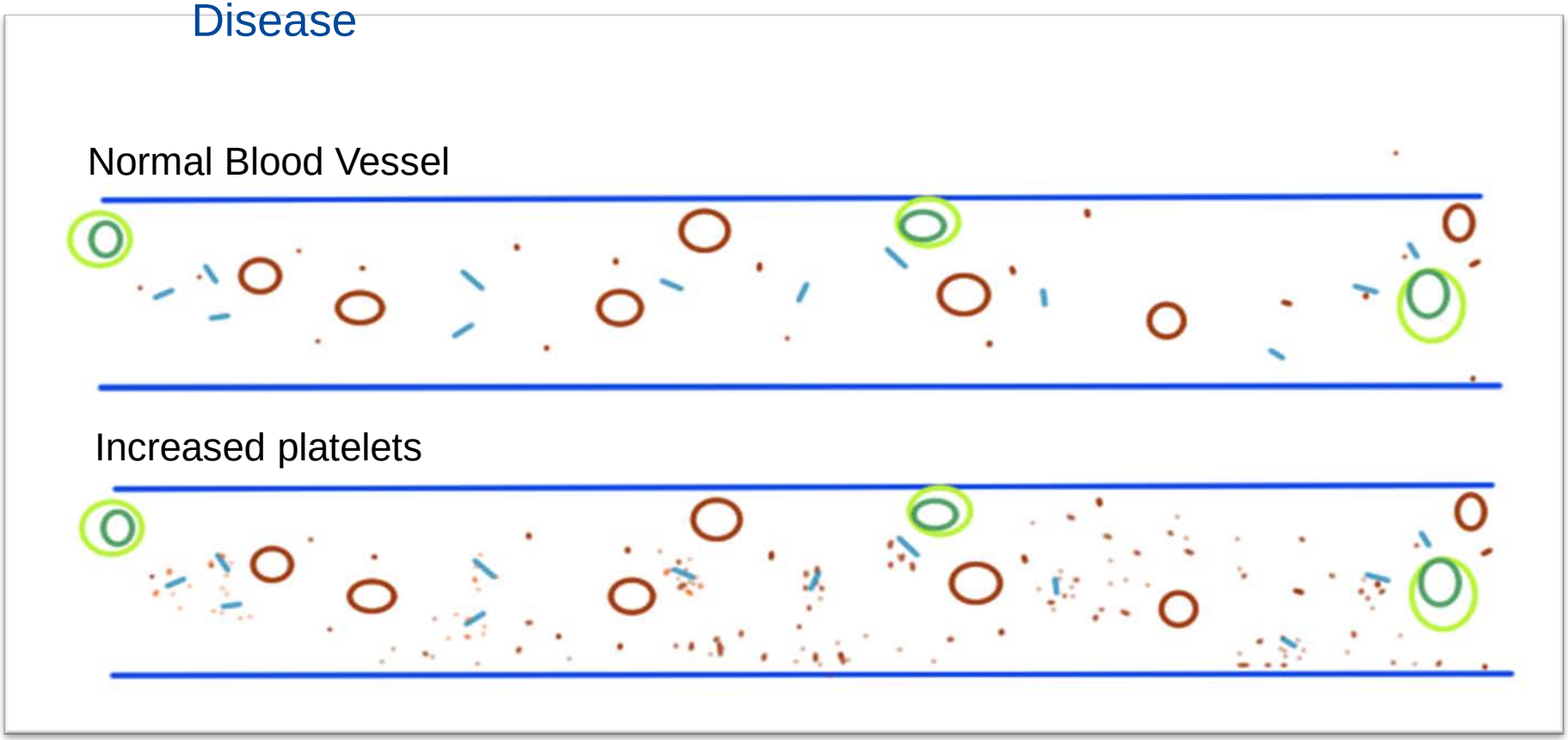
Challenges: Bleeding

- More common when platelets are elevated
  - 1,000-1,500 X 10^9 -- Often related to acquired Von Willebrands Disease



Objectives

- Gender differences
  - Risks of acquiring disease
  - Risks for symptoms
  - Risks for complications
- Select concerns facing female patients
  - Contraception
  - Pregnancy
  - Clotting
  - Bleeding risks

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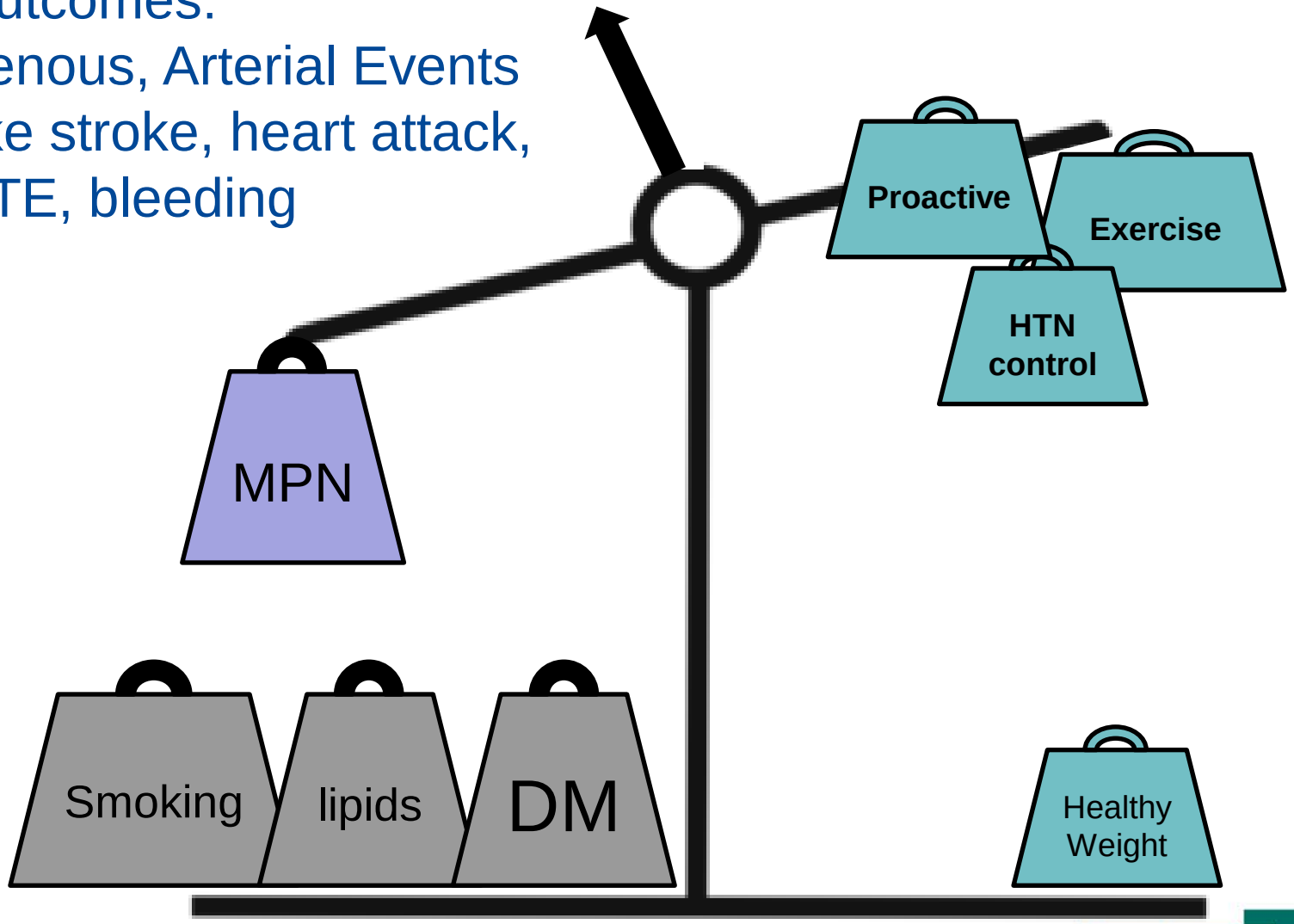
Outcomes:
Venous, Arterial Events like stroke, heart attack, VTE, bleeding



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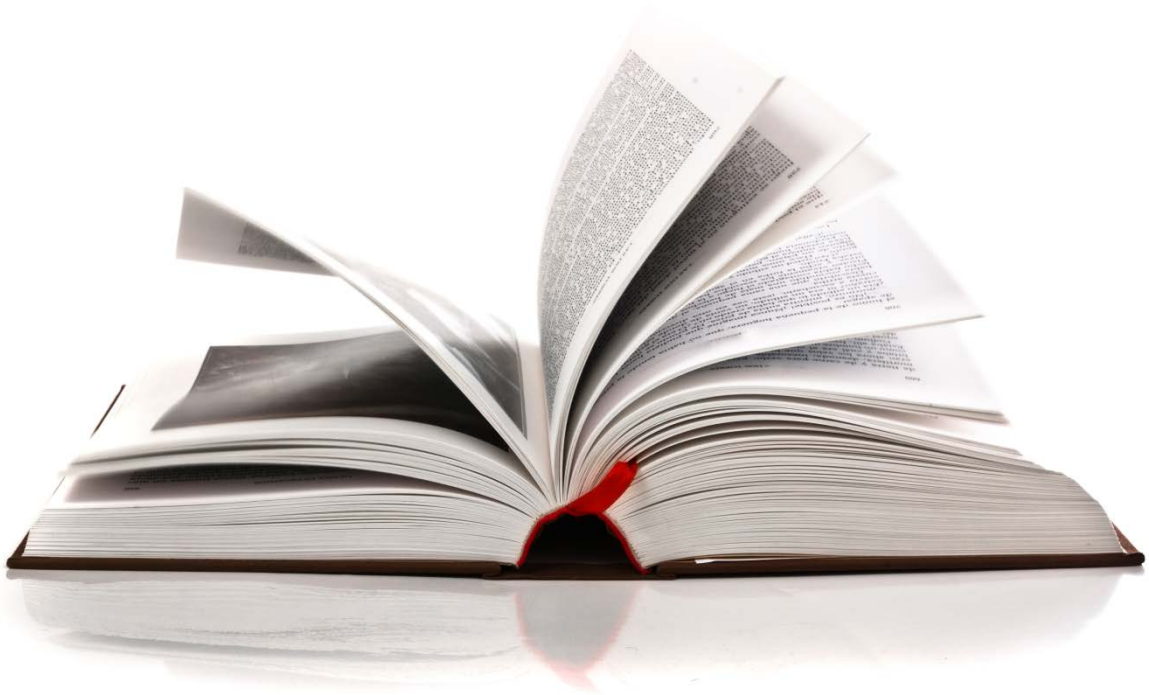
What's next?



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What if?

- We could link genetic characteristics (clone DNA, gender, somatic DNA) to future disease behavior?
- We could deliver *just enough* treatment to mitigate those risks?

We understood these diseases well enough to eradicate them?

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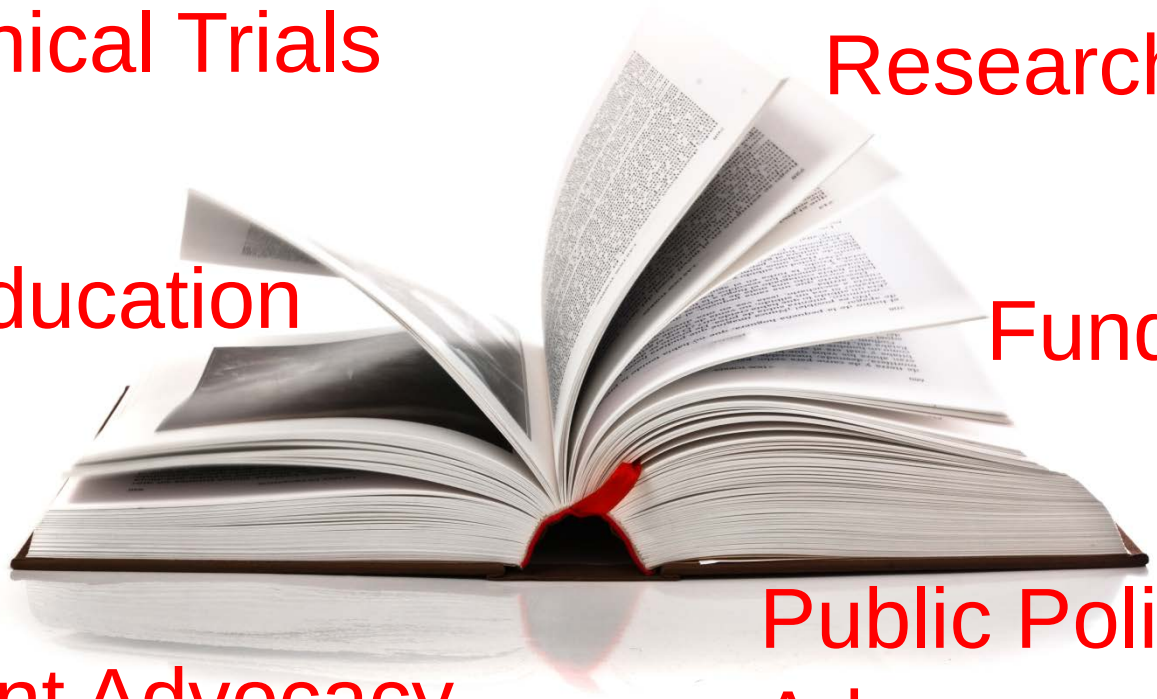
What's next?

Translational Research

Clinical Trials



Peer Education

Fund Raising

Public Policy Advocacy

Patient Advocacy

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“The kind of hope I often think about…I understand, above all, as a state of mind… it is a dimension of the soul…”
“Hope is not the same thing as optimism… but the certainty that something makes sense, regardless of how it turns out…”
Vaclav Havel

Thanks

- To all of you for your continued engagement in this journey of research and development

- Ruben Mesa, John Camoriano and conference organizers for the kind invitation to join you this year

- My colleagues, mentors, advisors and friends
  - Ruben Mesa
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  - P. Hari
  - Serge Verstovsek
  - Brady Stein
  - Mary Horowitz
  - Linda Brubaker
  - Jason Gotlib
  - Ehab Atallah