Waldenström's Macroglobulinemia (WM): Basic Training for WMers

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IWMF Education Forum Philadelphia 2019

SARAH CANNON
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Presbyterian/St. Luke's
Medical Center

HealthONE

Objectives

- Describe the roots underneath WM
- Review incidence, possible risk factors and clinical presentation of WM
- Explain diagnosis, symptoms, and treatment guidelines
- Talk about MYD88 and CXCR4 (genetics)
- Provide a refresher course for veteran WMers and prepare the new attendees to get the most out of the rest of the weekend here in the city of brotherly love

What is Waldenström's Macroglobulinemia?

- WM is a blood cancer, a type of non-hodgkin lymphoma
  - Occurs when blood cells called lymphocytes and plasma cells decide to break the rules that normally govern the behavior of cells and *both*:
    - reproduce out of control
    - don't die as normal cells do (More about this later, remember "bcl-2")
  - WM cells make excess "antibodies" (always IgM), heavy proteins which can perpetrate problems
  - Named after Jan Waldenström – Swedish oncologist (first identified in 1944)

What is Waldenström's Macroglobulinemia? (cont)

- Rare cancer affecting 3 in 1 million/year
- 1500 new diagnoses in the U.S. each year
- Median age at diagnosis is 64
- 60% of patients are male
- More common in Caucasians than other ethnic groups
- Familial disposition present ~20% cases

REAL/WHO definition

- Lymphoplasmacytic lymphoma (LPL)
  - IgM secretion AND
  - LPL cells in the bone marrow
- Symptomatic vs. asymptomatic (smoldering)
  - Symptomatic needs to be treated
  - Asymptomatic does not need to be treated
- MGUS with IgM protein is a precursor state sometimes associated with peripheral neuropathy

WM: lymphocytes & plasma cells are both present

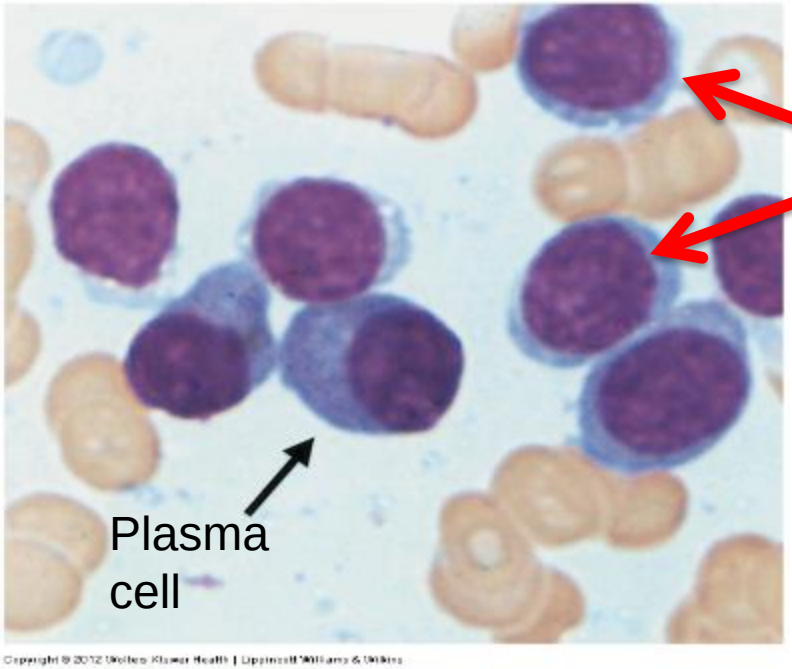
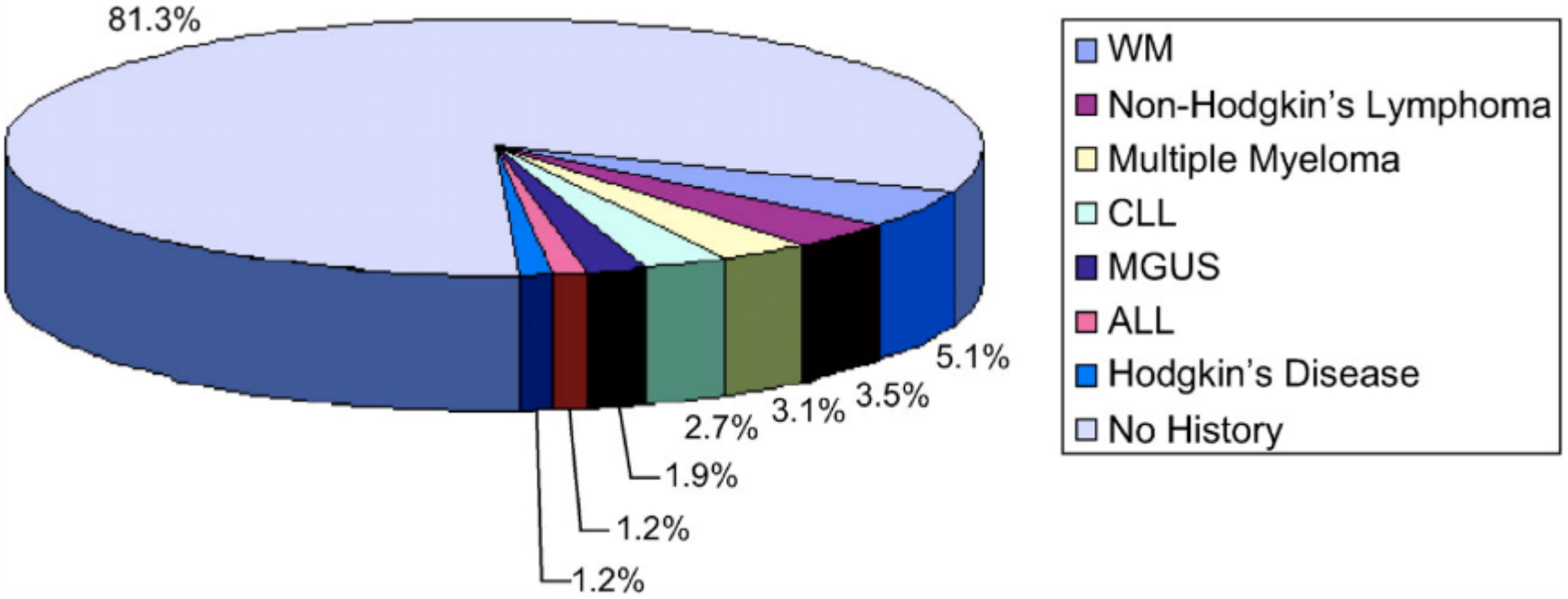


Figure 20.9 Waldenström. Bone marrow aspirate showing malignant cells with lymphoid and plasmacytoid morphology. (Reprinted with permission from Greer JP, et al. *Wintrobe's Clinical Hematology, 11th ed, Philadelphia, PA: Lippincott Williams &* Wilkins, 2004.)

What causes WM?

- Most cases are sporadic (occur by chance)
- I tell patients cause is usually “bad luck”
- Viet Nam veterans’ Agent Orange exposure
- About 20% are familial with at least 1 first degree relative with WM or another B cell disorder
- Main risk factor is the presence of IgM *MGUS*

Reported history of B-cell blood cancers among 1st degree relatives of 257 pt with WM



Treon S P et al. Ann Oncol 2006;17:488-494

A Word on Familial WM (comes up every year)

- Dr. Mary McMaster at the National Cancer Institute
- They have a unit interested in families-including WM
- What may run in family?
  - WM or IgM MGUS
  - Other B cell blood cancers
  - Autoimmune diseases (especially Sjogren's syndrome and thyroiditis)

We do not recommend routine screening of family members for WM (Dr. Kyle says "there is no risk") - concept of relative risk versus absolute risk-that is, if your chance of getting WM is 3 times higher, it is 9 in a million, not 3.

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LPL cells: in WM how do they misbehave?

- The actual lymphoma cells (LPL) can cause symptoms
- The plasma cells make an abnormal type of antibody or immunoglobulin protein called IgM that can cause symptoms
- Rarely- the LPL cells, which are usually slow growing, can mutate and become fast growing- this is called “transformation”- more on this later

The ”Bad clones” try an overrun the Normal Healthy Cells

- They are clones of each other and try to take over the bone marrow
- We can tolerate a few weeds normally

Disease = weeds

Remission = healthy flowers

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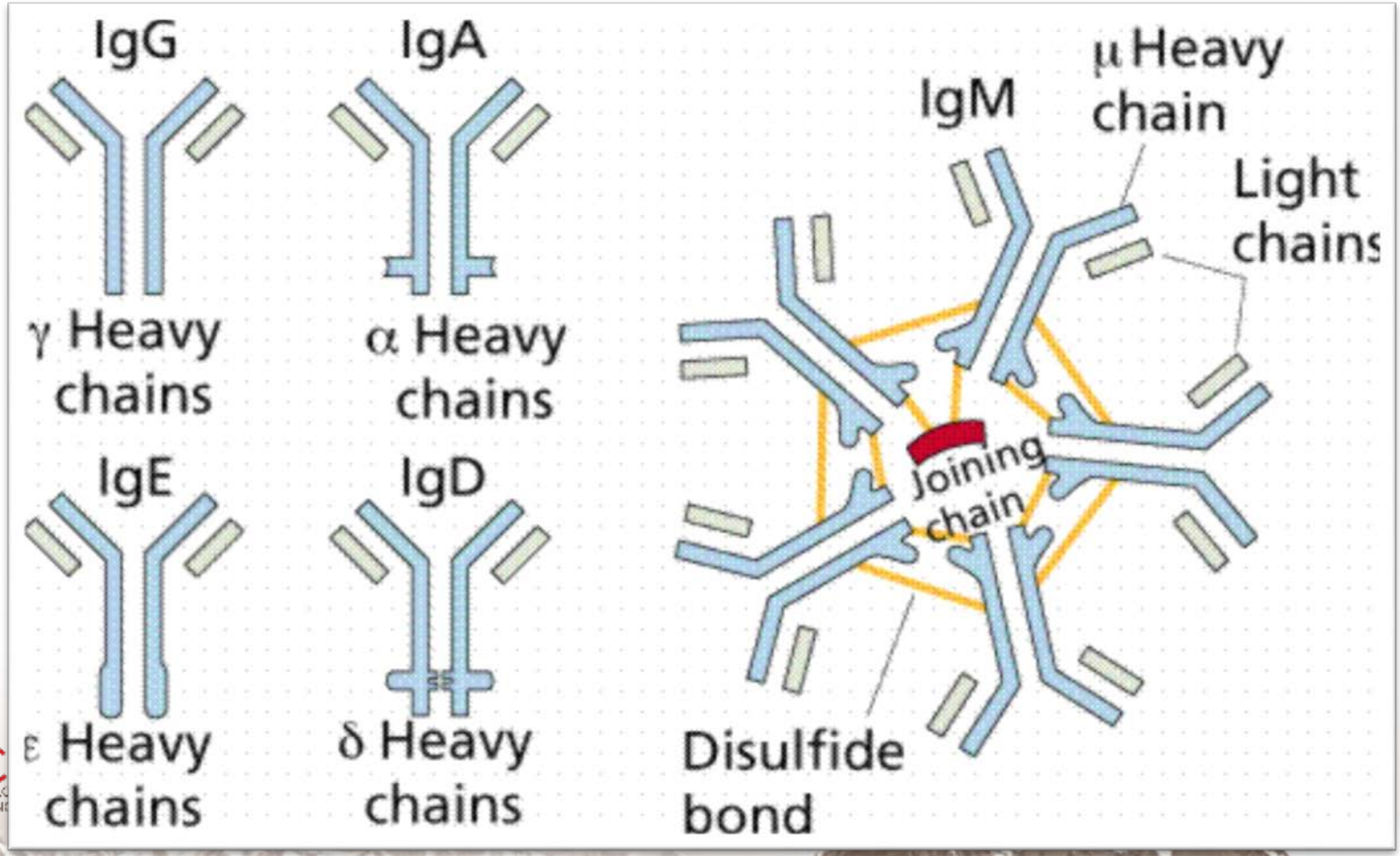
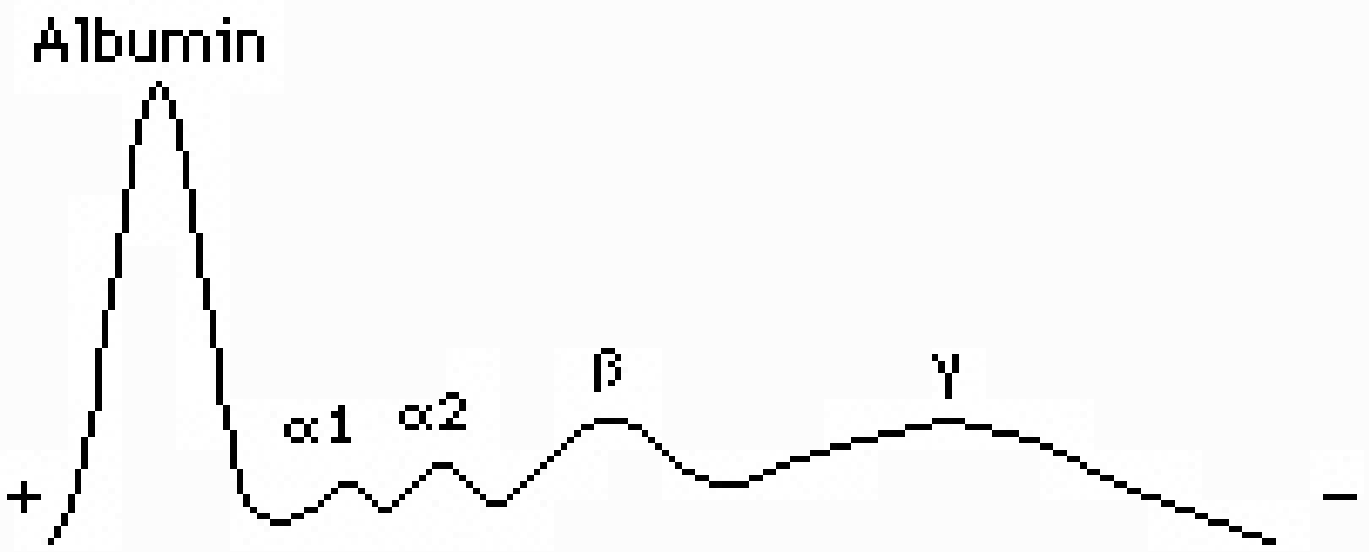
Immunoglobulin proteins (Ig's)/Antibodies are made up of heavy chains and light chains- *IgM is different than the rest*

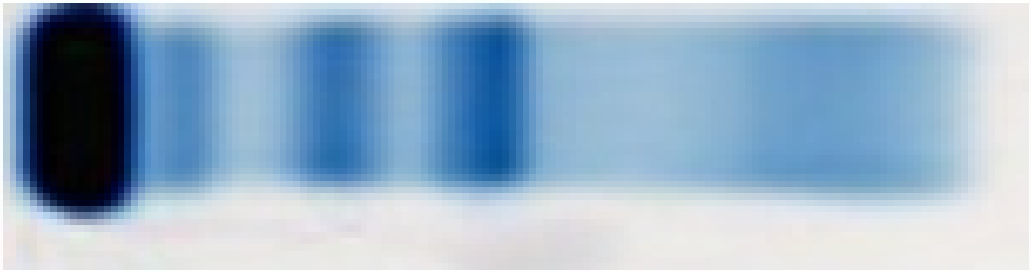


normally we have a nice mix of all different kinds of immunoglobulins- we call this” polyclonal”

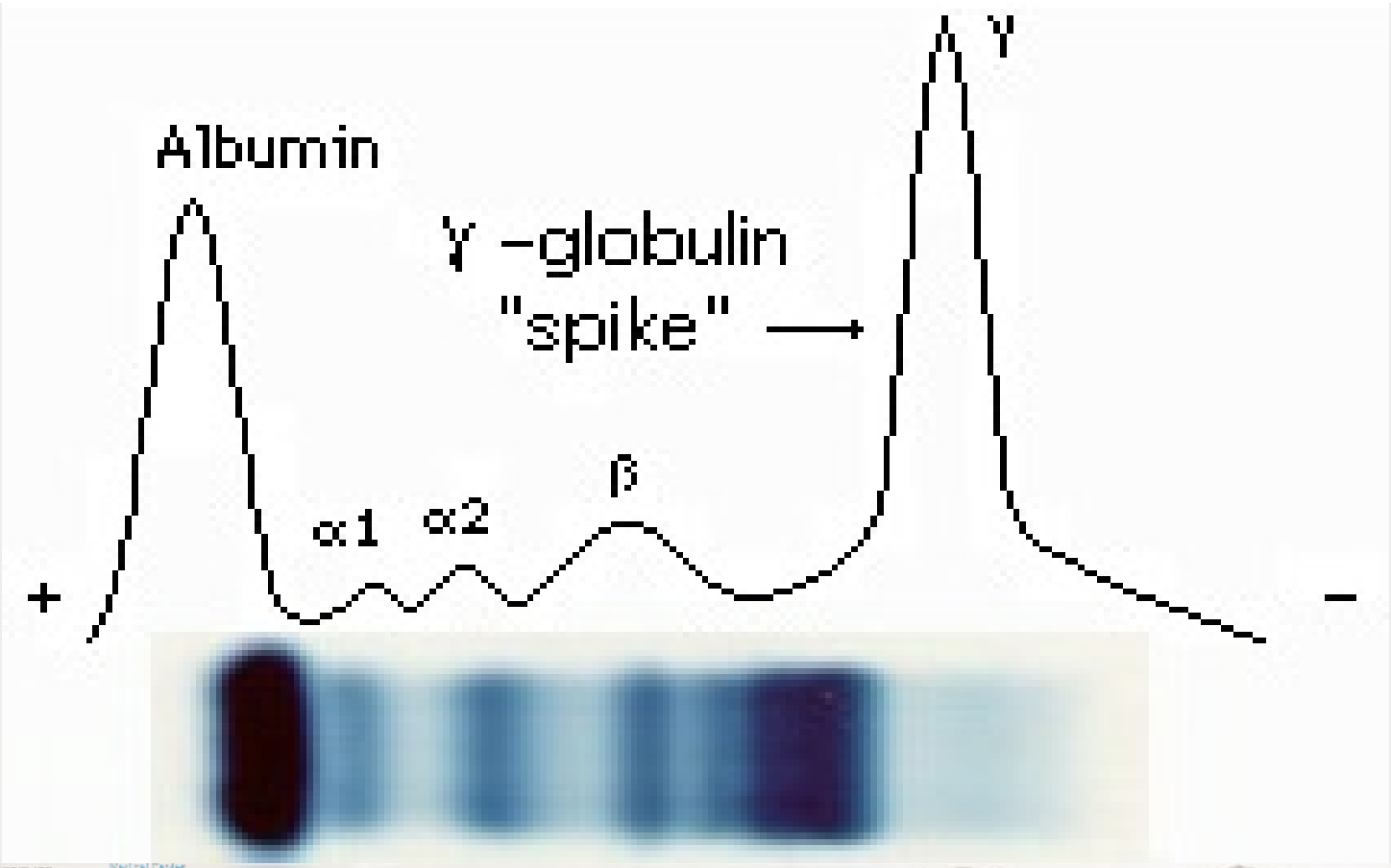
- In WM most of the IgM is completely identical, coming from clones of B cell/plasma cells
- We call this ”monoclonal”
- This can be detected on a blood test known as SPEP (serum protein electrophoresis), often ordered by a doctor who notices the protein levels are too high in the blood on routine testing
- The IgM level can be determined by two different blood tests: IgM or M spike

SPEP + M-protein (normal)
(serum protein electrophoresis + M)





SPEP + M-protein (abnormal) (serum protein electrophoresis + M)



Qigs – an important test for IgM (Quantitative Immunoglobulins)

- Measures the absolute number of IgM, IgG and IgA proteins
- In WM patients, IgM is HIGH and the other numbers are usually LOW
  - IgG (700-1600 MG/DL)
  - IgA (70-400 MG/DL)
  - IgM (40-230 MG/DL)
- Low numbers of IgA and IgG can lead to an increased risk of infection

WM occurs in phases: from MGUS to Smoldering to Symptomatic

- There are strict definitions
- We ONLY treat symptomatic WM

IgM Monoclonal Gammopathy of Undetermined Significance (MGUS)

Criteria

- Serum IgM monoclonal protein < 3.0 g/dL
- Bone marrow, lymphoplasmacytic infiltration <10%
- Absence of symptomatic anemia, lymphadenopathy, hepatosplenomegaly, or hyperviscosity
- Absence of constitutional symptoms

MAYO CLINIC Kyle et al., Sem. Oncol., 2003, 30:116

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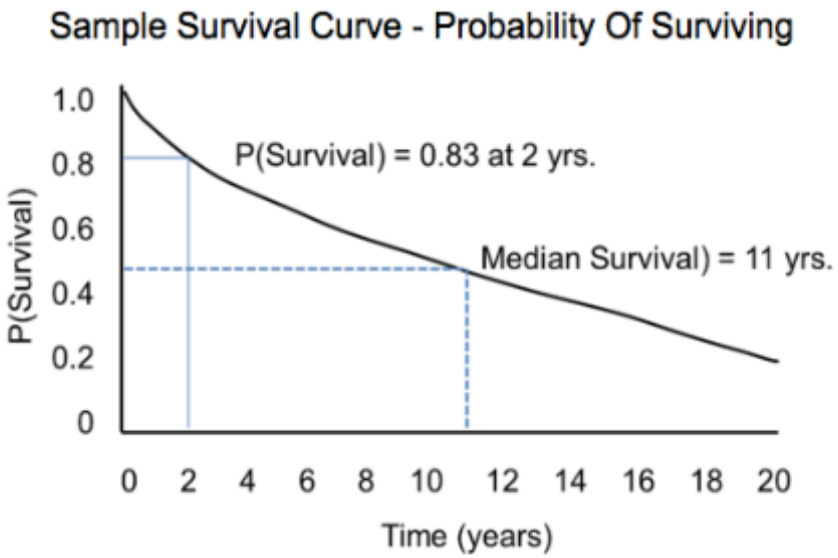
Chance of developing WM requiring treatment: 2%/year for first 10 years, then 1% thereafter

Oncospeak: Kaplan-Meier Curves: Doctors Always Show These



- Horizontal axis = time in years
- Vertical axis = probability of surviving or the proportion of people surviving
- At time zero everyone is alive
- The *probability* of survival is 83% at 2 yrs, 55% at 10 yrs, and the median survival is 11 yrs

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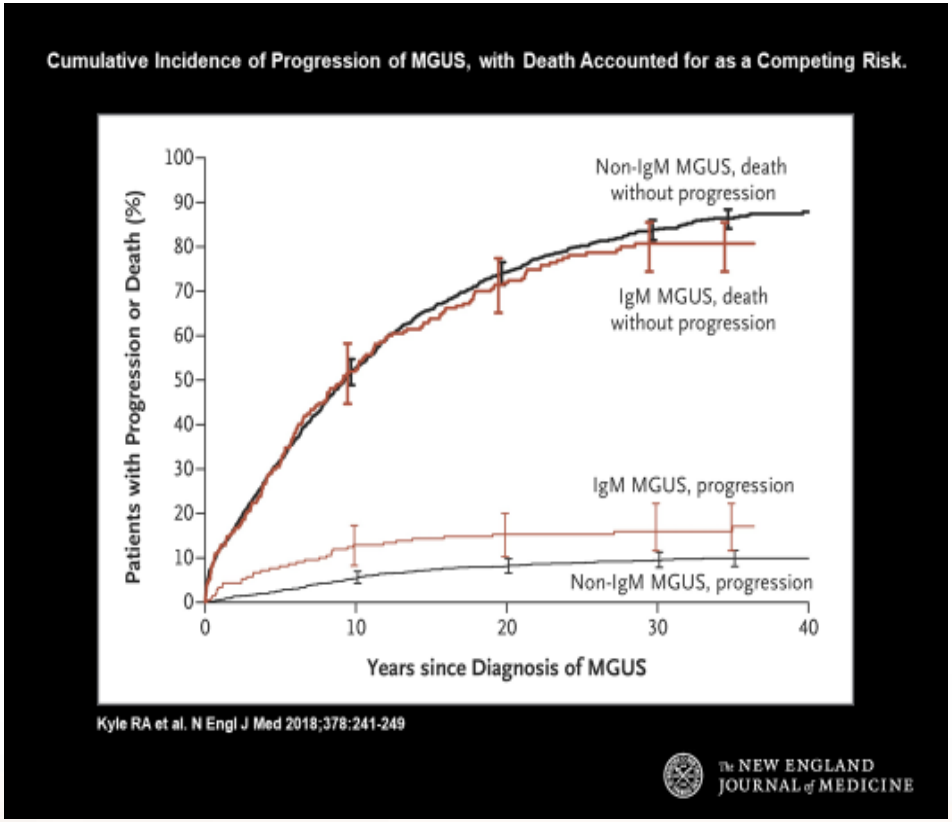
IgM MGUS- recent update by Dr. Kyle:

N Engl J Med 2018; 378:241-249 DOI: 10.1056/NEJMoa1709974

- Risk of progression 2% per year first 10 years, then 1% per year there after
- Increased risk with:
  - M spike > 1.5 g/dl
  - Abnormal free light chain ratio



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Smoldering Waldenström's Macroglobulinemia (SWM)

Criteria for Diagnosis

- Serum IgM monoclonal protein ≥ 3.0 g/dL and/or
- Bone marrow, lymphoplasmacytic infiltration ≥ 10%
- Absence of symptomatic anemia, lymphadenopathy, hepatosplenomegaly, or hyperviscosity
- Absence of constitutional symptoms

MAYO CLINIC

Kyle et al., Blood 119:4462, 2012

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Risk of worsening to point where symptoms are present and treatment is needed: ~12%/yr, but risk lessens after 5-6 years

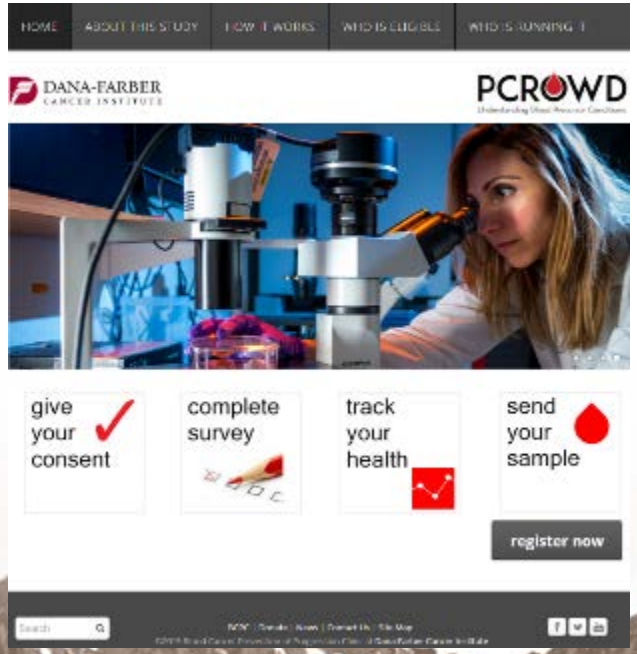
How does MGUS/Smoldering disease turn into symptomatic WM?

- Important research(Dr. Ghobrial and others) ongoing
- MYD88 mutation increases risk (virtually all have the mutation)
- Many more patients need to be studied
- Researchers want samples from patients
  - Example: PCROWD for Dr. Ghobrial in Boston

How can you help?

PCROWD
Understanding Blood Precursor Conditions

- ✓ **Step 1:** Become a Participant
- ✓ **Step 2:** Send in your Samples
- ✓ **Step 3:** Send in your clinical information
- ✓ **Step 4:** Complete the survey
- ✓ **Step 5:** Spread the word



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Contact information

PCROWD
Understanding Blood Precursor Conditions

- Contact: Adriana Perilla-Glen
- Visit: www.dana-farber.org/cpop

and http://pcrowd.dana-farber.org/

- E-mail: precursor@partners.org
- Call: 617.582.8664
- Fax: 617.394.2603

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How do WM patients present to their doctors?

- They have symptoms or signs which make the doctor suspect it (we'll review these)

Or

- It is found incidentally by suspect routine blood testing, often indicating either anemia or an overall increased level of protein in the blood

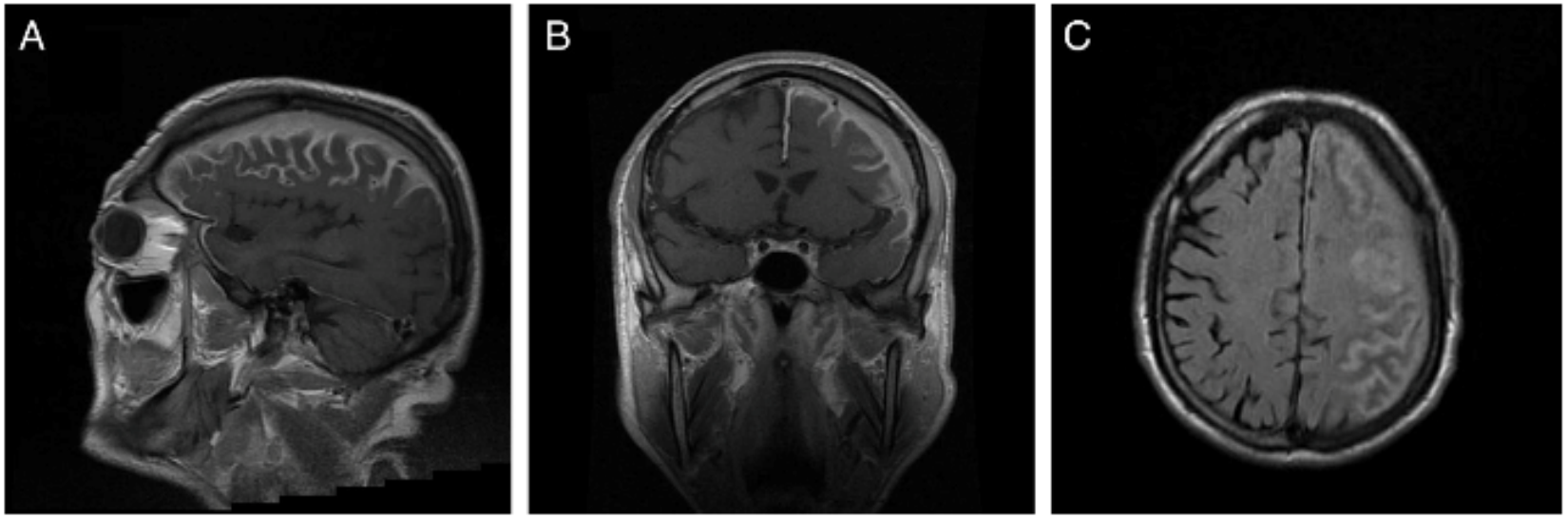
Presenting Symptoms of WM

- Weakness and fatigue
- Bleeding manifestations
- Hyperviscosity symptoms
- Weight loss
- Neurologic symptoms
- Visual disturbances
- Raynaud's phenomenon
- Symptoms of amyloidosis

WM can sometimes affect the central nervous system- “Bing-Neel Syndrome”

- Rare
- Can occur at any time point
- Symptoms variable
- Can occur even when the WM does not otherwise appear to be worsening or even it is improving on treatment
- To diagnose: start with contrast MRI, then biopsy best or special testing of spinal fluid (MYD88 testing, flow cytometry)

Bing Neel Syndrome



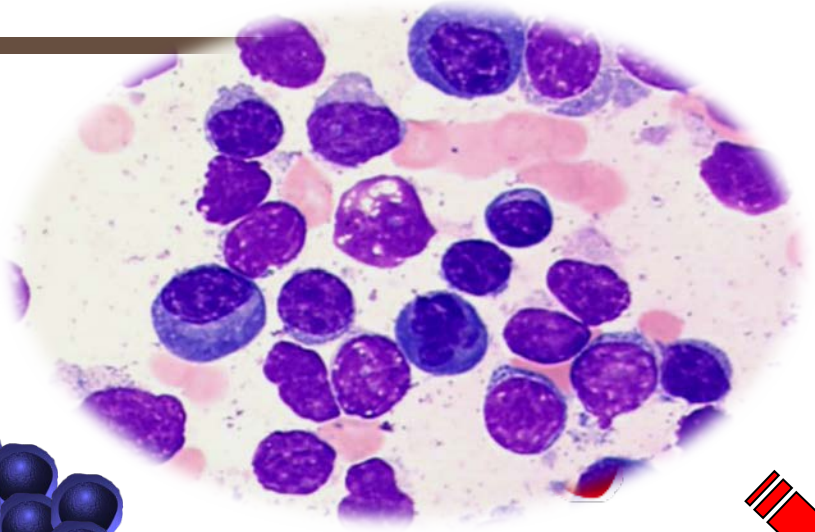
Important: WM is different in everybody

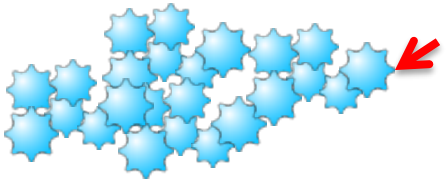
- Your course will be just that, unique to you
  - Symptoms
  - How you respond to treatment
  - Which treatment(s) may be right for you

- There is great information for WM patients from IWMF and forums such as this one, but remember, one's person's experience may not be yours

LPL Cells and/or the IgM can produce symptoms

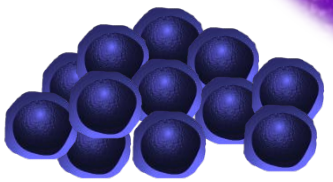
↓HCT, ↓PLT, ↓WBC





IgMs

Hyperviscosity Syndrome: Epistaxis, HA, Impaired vision
>4.0 CP



Adenopathy, splenomegaly
≤20%

Fatigue, Sweats

IgM Neuropathy (22%)
Cryoglobulinemia (10%)
Cold Agglutinemia (5%)

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Treon and Merlini, Williams Hematology 2011

Some of you have IgM Neuropathy

- And often have IgM MGUS (low IgM levels)
- There are different kinds of IgM neuropathy
  - With or without anti MAG (myelin assoc. glycoprotein)
  - DADS- distal acquired demyelinating symmetric
  - With ganglioside antibodies (GM1)
- Above diagnoses overlap symptomatically
- The clinical course is variable
- Can be debilitating
- Treatment is variably effective

What tests do we perform in a patient suspected of having WM?

- Blood work
- Urine test (looking for amyloid* or other rare kidney issues)
- Bone marrow biopsy with MYD88 testing
- Sometimes CT or CTPET scans

- Most important: talk to the patient!

*amyloidosis is beyond the scope of this talk but there are two great issues of the TORCH by Drs.Gertz & Merlini about this

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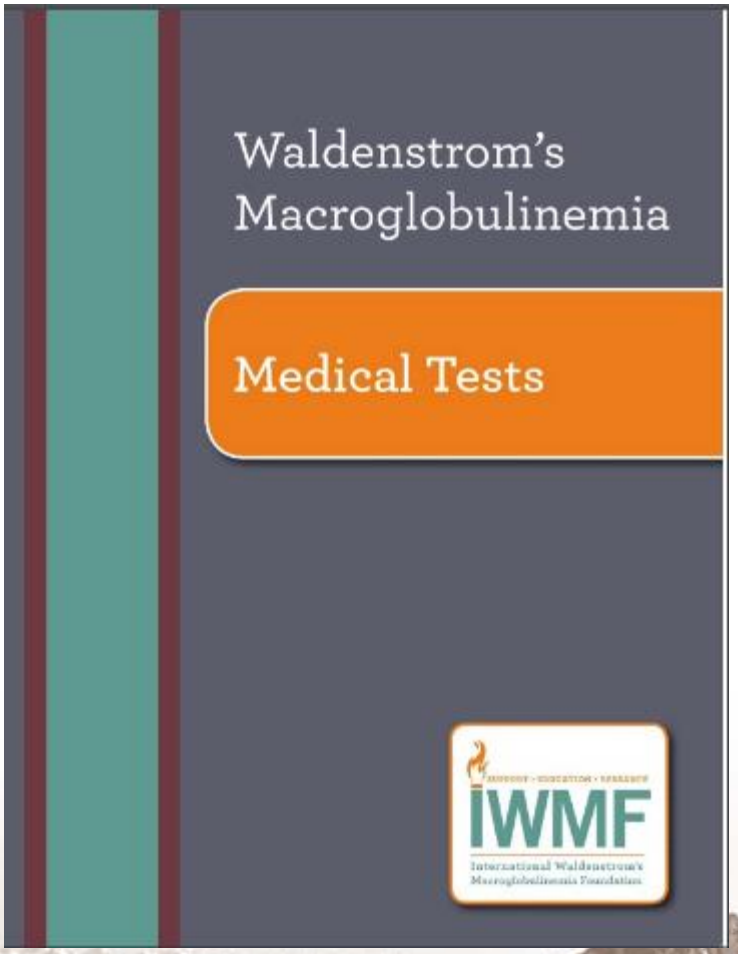
Other important tests

- Cryoglobulins
- Cold agglutinins
- some tests to look for a rare complication known as amyloid
- Special tests if there is too much bleeding (rare- a hemophiliac like condition known as von Willebrand's)
- Neuropathy tests- anti MAG or GM1

An Important Resource for Understanding Blood Tests in WM



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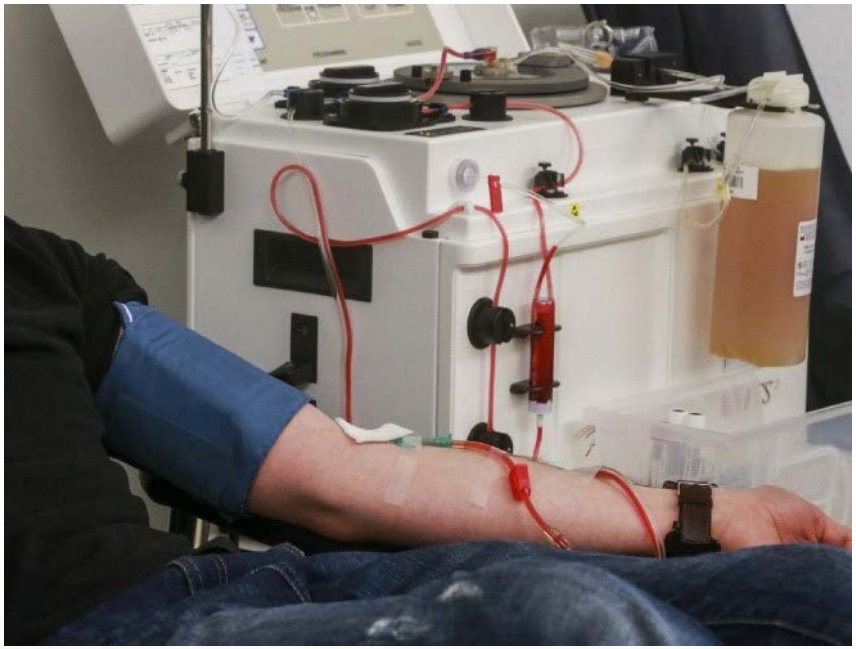
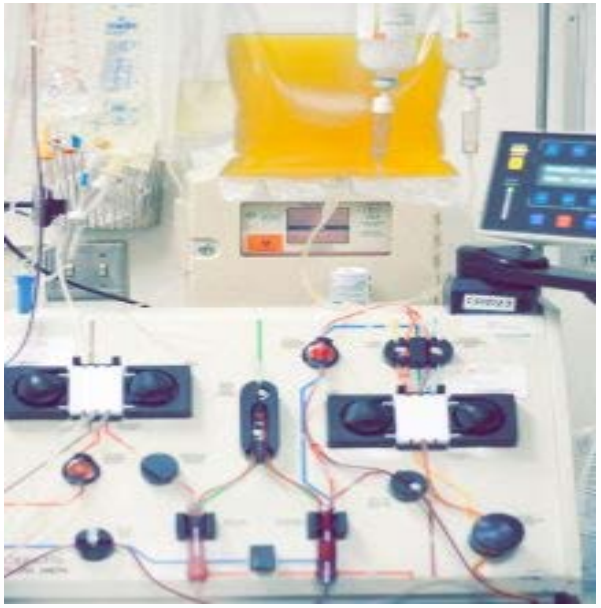
Serum Viscosity

- Measures the resistance of fluid to flow
  - Water flows readily, less viscous = “thin”
  - Oil flows less readily, more viscous = “thick”

- IgM proteins make the blood more viscous
  - Can be mild and not cause symptoms
  - Or can thicken the blood causing headaches, nosebleeds, vision changes, or serious medical problems
  - May need plasmapheresis to remove IgM and then treat underlying production

Plasmapheresis





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Required to Properly diagnose WM

- A bone marrow biopsy MUST be done and show a type of non-hodgkin lymphoma called LPL
- There MUST be monoclonal IgM in the blood

- Now in newly diagnosed patients testing for a mutation in the LPL cells called MYD88

Typical BM Biopsy Report in a patient with WM

BONE MARROW BIOPSY:

Variably cellular, overall mildly to moderately hypocellular marrow (60-70% fat).

Approximately 30-40% of the cellularity and 10-20% of intertrabecular space is comprised of a predominantly nodular and interstitial population of small to intermediate sized lymphocytes, plasma cells, and lymphoplasmacytoid forms.

Mast cells are seen in association with the lymphoid aggregates.

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Courtesy Dr. Steve Treon

Prognosis
Pay very little attention to what you read

- There are clinical lab features that can help with prognosis but I do not find them helpful
- In the future we'll probably determine this by sophisticated DNA testing of the WM cells

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Prognosis in WM

- ISSWM
- 587 patients at first therapy

Risk	Low	Intermediate	High	
Age > 65 years	-	X	> 2 factors	
		or		
Hb ≤ 11.5 g/dL Platelet ≤ 100 x10^9/L B2M > 3 mg/L IgM > 7 g/dL	≤ 1 factor	2 factors		
N (%)	158 (27%)	223 (38%)	206 (35%)	
Survival at 5 years	87%	68%	36%	P<0.001

Hb : hemoglobin; B2M : beta2-microglobulin; N : number of patients; % : percentage

Morel et al, Blood 2009

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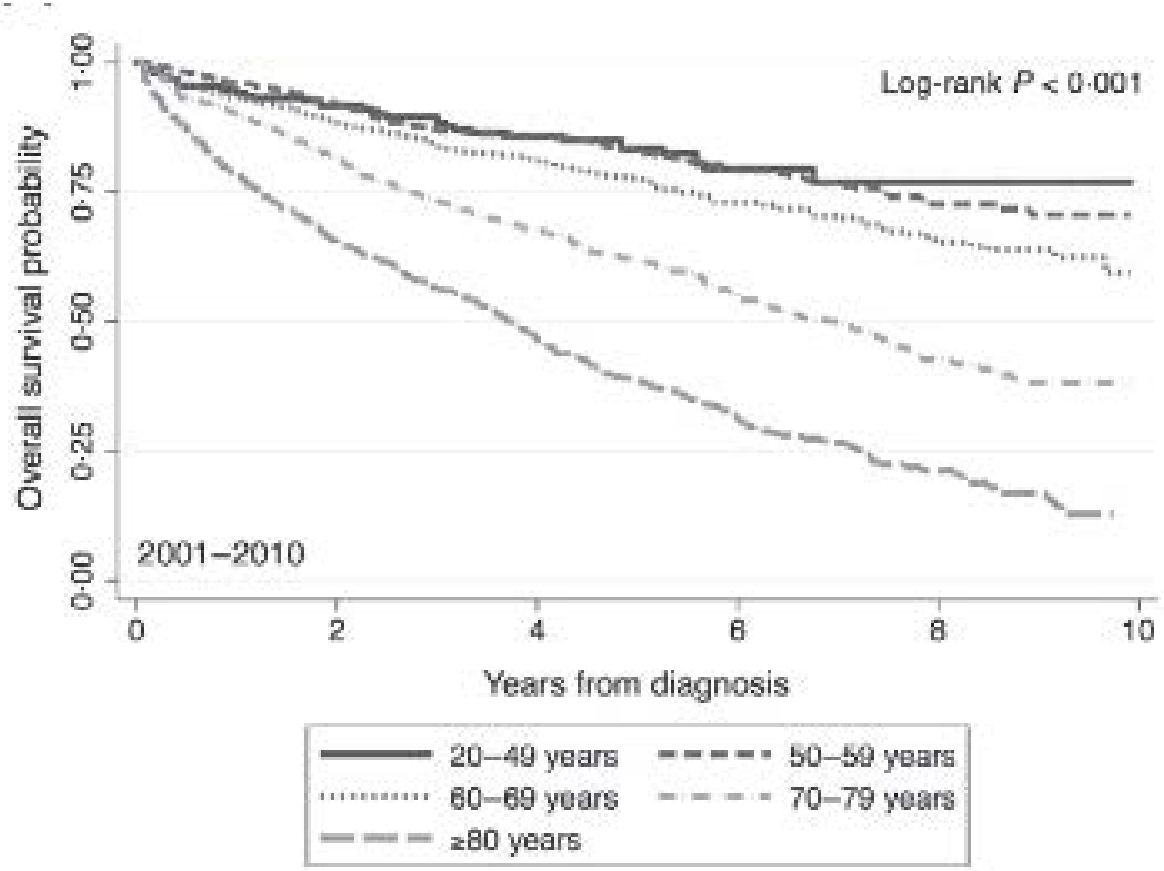
Survival: it is long. Data can be challenging. Here is for patients diagnosed between 2001-2010 (as of 2014)



Castillo et al BJH 2014

Treatment- doc's perspective

- Important to define the goals of treatment
- Is my patient young/vigorous or old/frail?
- Am I interested in just making my patient feel better (symptoms, fix anemia) or do I believe that the deepest, best remission possible is important?
- Is my patient interested in fixed duration therapy (months, maybe a few years if maintenance) or continuous therapy (take treatment until side effects or relapse dictate otherwise)?
- Does mutational status (MYD88, CXCR4 make a difference?
- Do we need rapid control of disease and symptoms?
- Is there underlying neuropathy before treatment?

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Consensus panel recommendations for initiation of therapy in WM.

- A high IgM level is not by itself an indication to initiate therapy.
- Hematocrit <30; Platelet count <100,000.
- Alleviate symptoms attributable to WM.
- Symptomatic Hyperviscosity (>4.0 CP).
- Moderate-Severe Neuropathies.
- Symptomatic cryoglobulinemia, cold agglutinin disease.

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Semin Oncol 30: 116, 2003

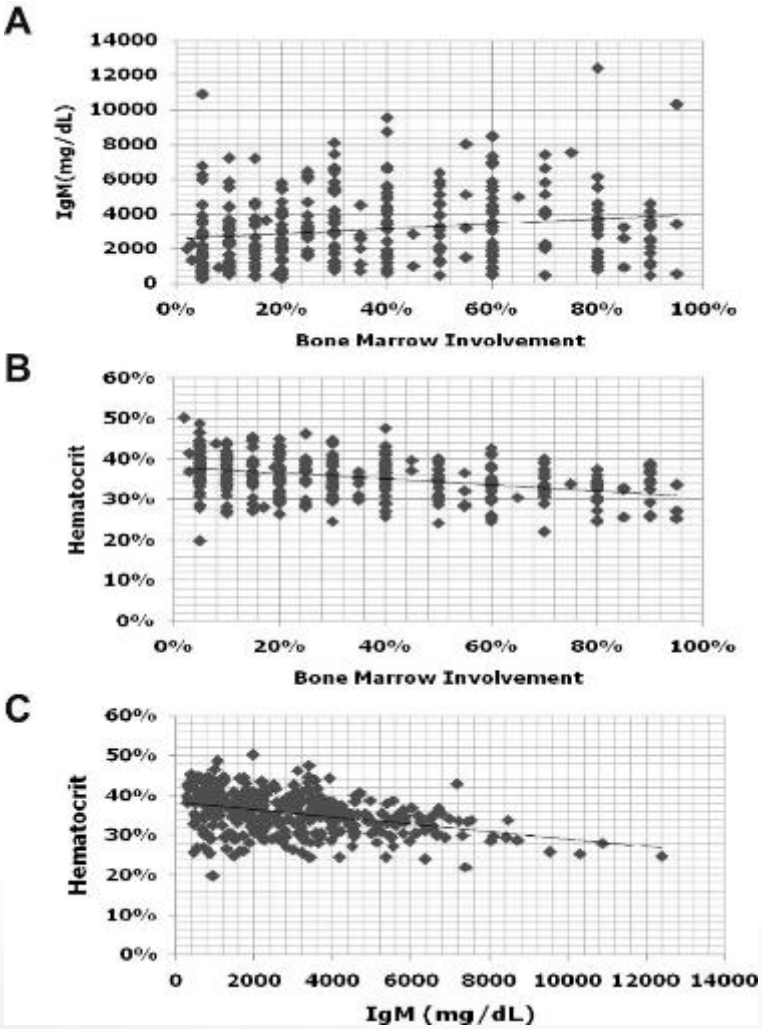
Very important

- The level of IgM and/or the percentage of LPL (WM) cells in the bone marrow varies tremendously between WM patients
- Some patients with very low IgM levels have lots of symptoms while others with very high levels may not have symptoms at all!

What on earth does this mean?
This demonstrates how the level of IgM, degree of anemia, and # of LPL cells in the marrow vary TREMENDOUSLY between patients

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Don't worry! I'll walk you through this



Treon, S. P. Blood 2009;114:2375-2385

We need to learn about mutations in 2019

- We are talking about genetic mutations (changes in the DNA) inside the blood cells that are acquired- you were not born with them nor can you pass them on (SOMATIC)
- The 2 big ones in WM are MYD88 and CXCR4
- We are learning that these mutations influence how the WM might behave clinically as well as respond to certain treatments
- MYD88 is almost always one specific mutation (L265P)and is present in over 90% of WM patients- testing common
- CXCR4- many different mutations present in about 40% of WM patients- tested less often- CXCR4 testing is more challenging technically and not all docs order it

This was a major breakthrough in WM- finding a genetic mutation picked up by chance during life which has major role in the development of WM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

There are many more types of CXCR4 mutations compared to MYD88

Over 30 types of CXCR4 C-terminal somatic mutations in WM

N=	MYD88 Status	CXCR4 Mutation	Nucleotide change	Amino acid change
1	L265P	Nonsense	r.997 A>T[1]	K333X[1]
3	L265P	Nonsense	r.1000C>T	[illegible]
7	L265P	Nonsense	r.1013C>A	S338X
15	L265P	Nonsense	r.1013C>G[2]	S338X[2]
1	WT	Frameshift	r.931_933insT	[illegible]
3	L265P	Frameshift	r.952_954insA	T318fs
2	L265P	Frameshift	r.951_953delACCTC	T318fs
1	L265P	Frameshift	r.954_956insC	S319fs
1	L265P	Frameshift	r.958_960delTG	V320fs
1	L265P	Frameshift	r.963_965insC	R322fs
1	L265P	Frameshift	r.969_971insG	S324fs
1	L265P	Frameshift	r.978_980insT	K327fs
1	L265P	Frameshift	r.984_986insT	L329fs
1	L265P	Frameshift	r.993_995insA	G332fs
1	L265P	Frameshift	r.1005_1007insT	G336fs
2	L265P	Frameshift	r.1013_1015delATCT	S338fs
1	L265P	Frameshift	r.1013_1015delATCTGTTTCCACTGAGT	S338fs
3	L265P	Frameshift	r.1012_1014insT	S338fs
1	L265P	Frameshift	r.1015_1017delCT	S339fs
1	L265P	Frameshift	r.1020_1022delT	S341fs
1	L265P	Frameshift	r.1024_1026delCT	S342fs
1	L265P	Frameshift	r.1030_1041CTGAGTCTTC>GT	S344fs
1	L265P	Frameshift	r.1033_1035delAG	E345fs

@50%

Sanger Sequencing of CD19-sorted BM cells Treon et al, Blood 2014

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More oncospeak- you'll need to know this for the rest of the Ed Forum

- RR- response rate (% of patients who had at least a 50% reduction in measurable WM)
- PFS- progression free survival- how long patients went before a relapse or dying
- OS- overall survival- just what it says
- Wild type (WT)- UNMUTATED gene, applied to MYD88/CXCR4. This is the opposite of MUTATED (MUT)
- Mutated CXCR4 a.k.a. "WHIM"
- Mutated MYD88 a.k.a. "L265P
- Mutations in CXCR4 can be "nonsense" or "frameshift" types

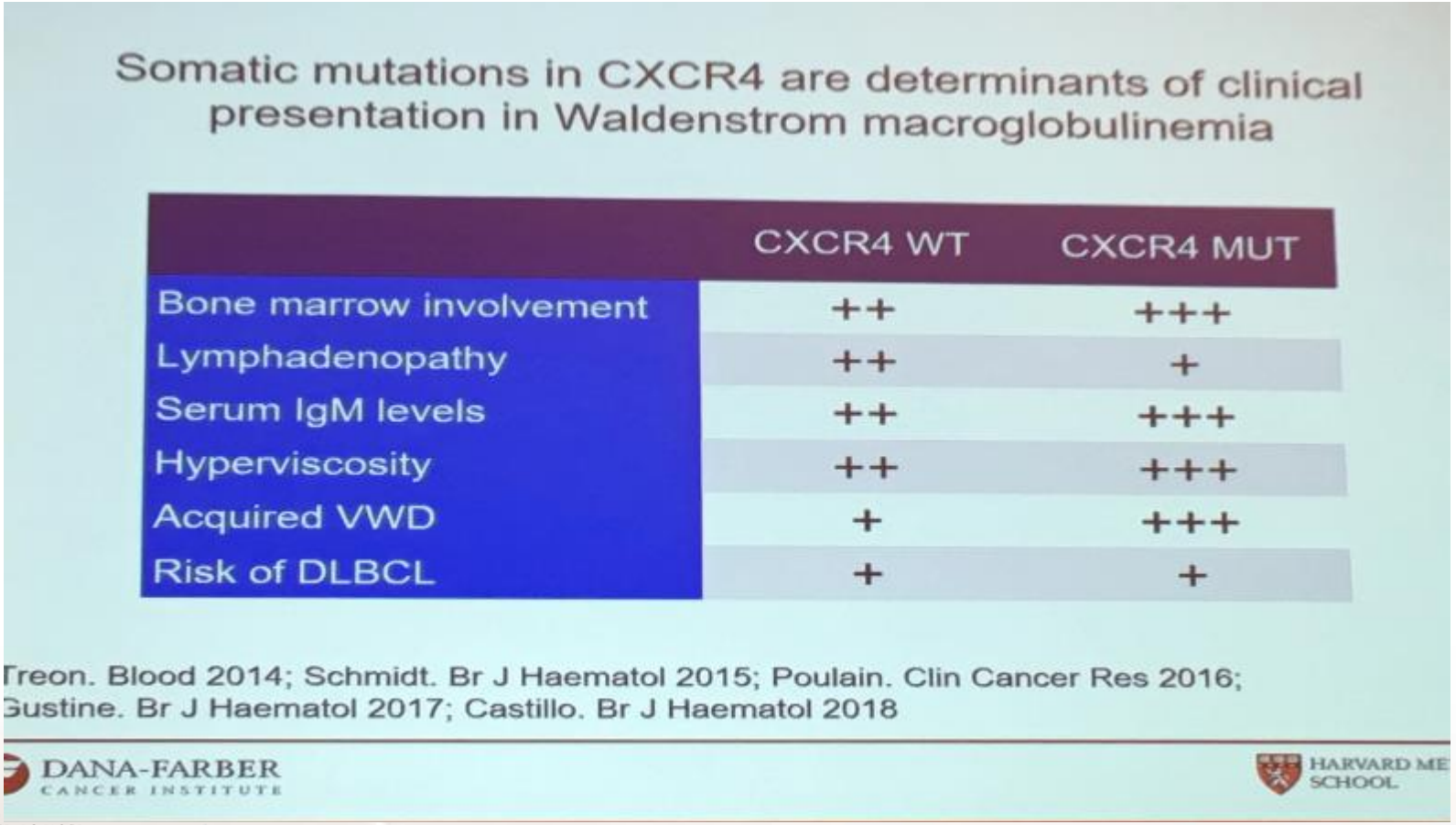
How does MYD88/CXCR4 testing help distinguish between different diseases?

Frequency of *MYD88* and *CXCR4* Mutations in Patients With B-Cell Malignancies

	Total Patients, n	*MYD88*^{L265P}	*CXCR4*^{WHIM}
Healthy donors	32	0%	0%
IgM MGUS	12	50%	17%
Non-IgM MGUS	7	0%	0%
Untreated WM	102	95%	43%
Treated WM	62	92%	34%
MZL	20	10%	5%
CLL	32	3%	0%
MM	14	0%	0%

Xu L et al. *Br J Hematol*. 2016;172:735-744.
Abbreviations: CLL, chronic lymphocytic leukemia; IgM, immunoglobulin M; MGUS; monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MZL, mantle zone lymphom
WM, Waldenström macroglobulinemia

CXCR4- impact of mutations on disease behavior



Different genetic types of WM

What the DNA is

How it looks in the actual patient

Genotypic-Phenotypic Association in WM[a]

Clinical Characteristics	*MYD88*^{L265P} *CXCR4*^{WT}	*MYD88*^{L265P} *CXCR4*$^{WHIM/FS}$	*MYD88*^{L265P} *CXCR4*$^{WHIM/NS}$	*MYD88*^{WT} *CXCR4*^{WT}
IgM	↑↑	↑↑	↑↑↑↑	↑
BM infiltration	↑↑↑	↑↑	↑↑↑↑	↑
Sensitivity to BTK inhibitors	↑↑↑	↑↑	↑	↓
Incidence, %	~60	27-40[b]	27-40[b]	< 10
	MUT/WT	MUT/MUT	MUT/MUT	WT/WT

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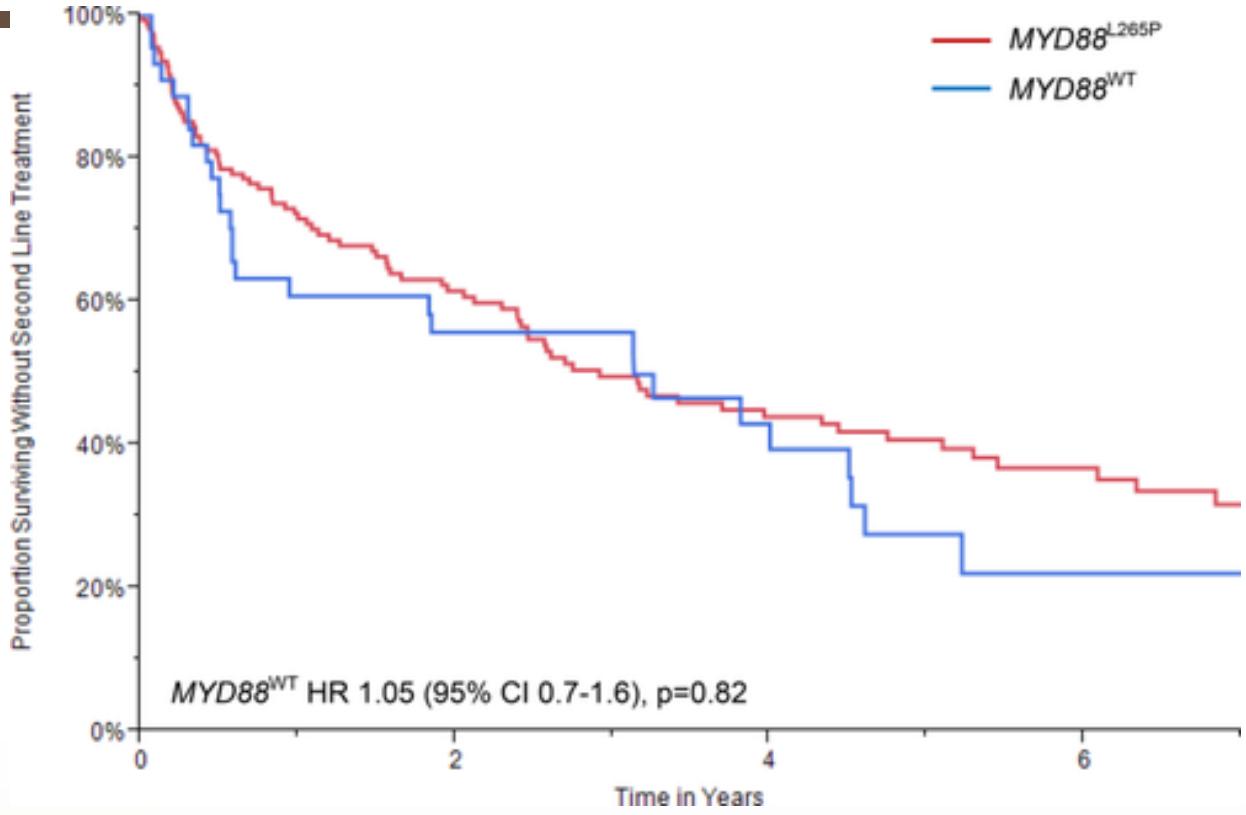
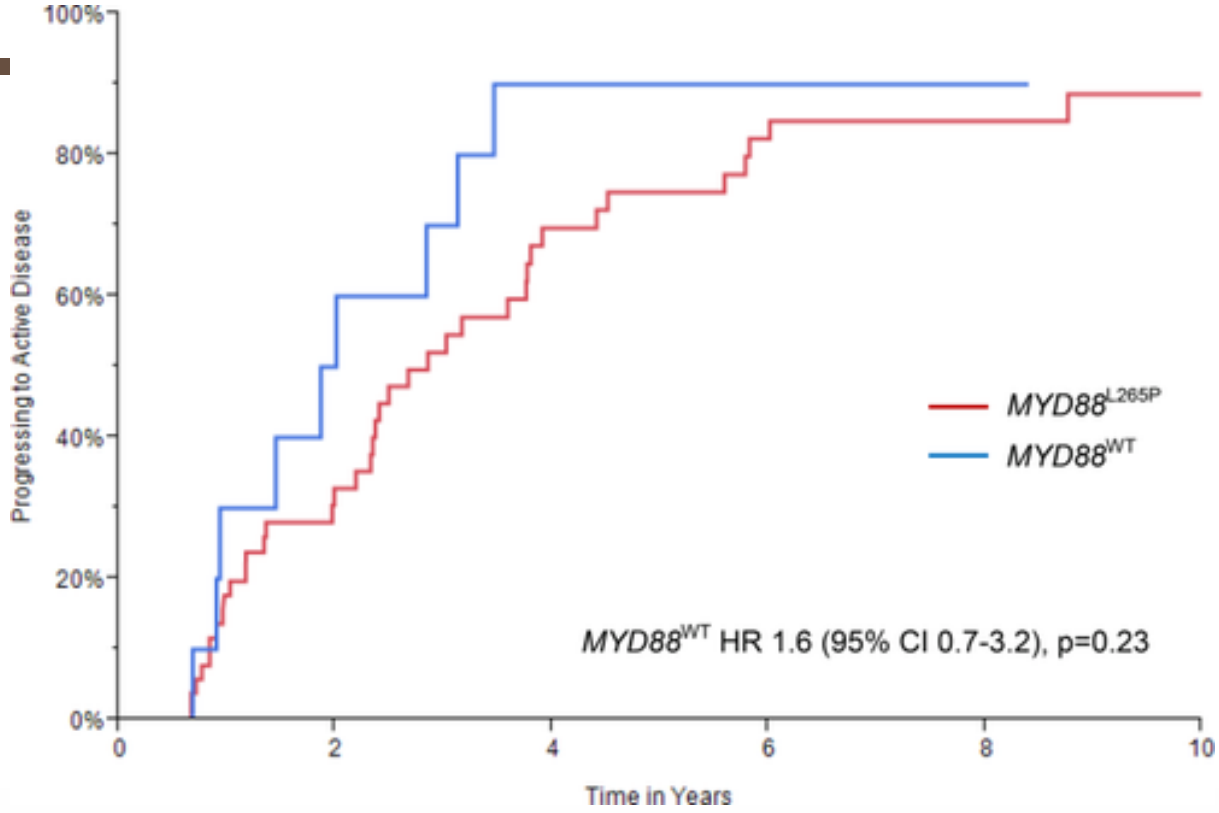
MYD88 mutation status does not impact time to next treatment (TTNT) in Waldenström macroglobulinemia



American Journal of Hematology, Volume: 93, Issue: 2, Pages: 187-194, First published: 28 October 2017, DOI: (10.1002/ajh.24955)

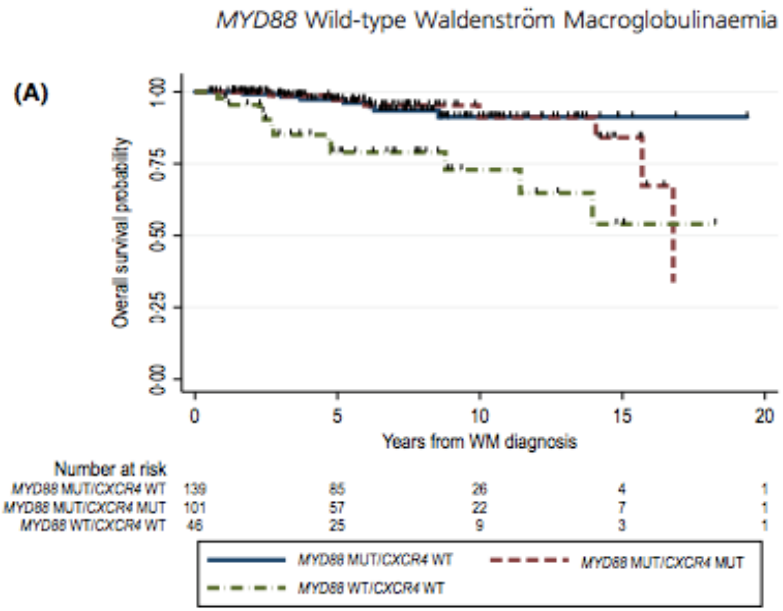
MYD88 mutation status does predict progression into active disease in smoldering Waldenström macroglobulinemia



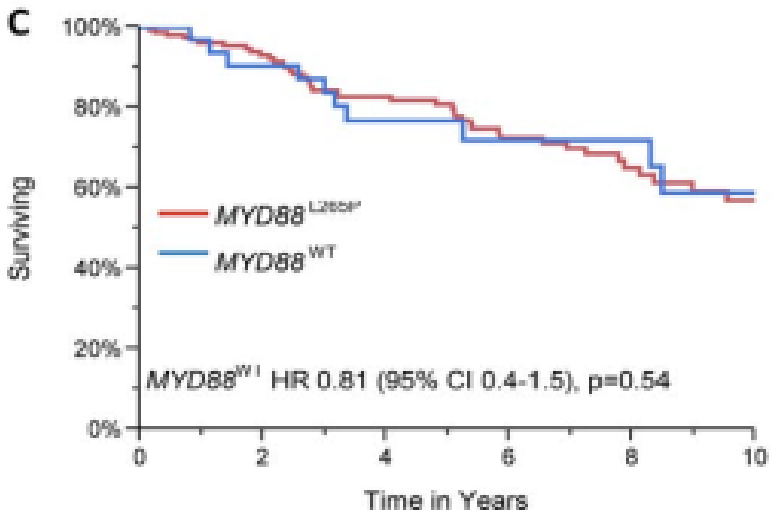
American Journal of Hematology, Volume: 93, Issue: 2, Pages: 187-194, First published: 28 October 2017, DOI: (10.1002/ajh.24955)

OS by MYD88 mutational status: Mayo vs. DFCI analysis

DFCI BJH 2018



Mayo AJH 2018



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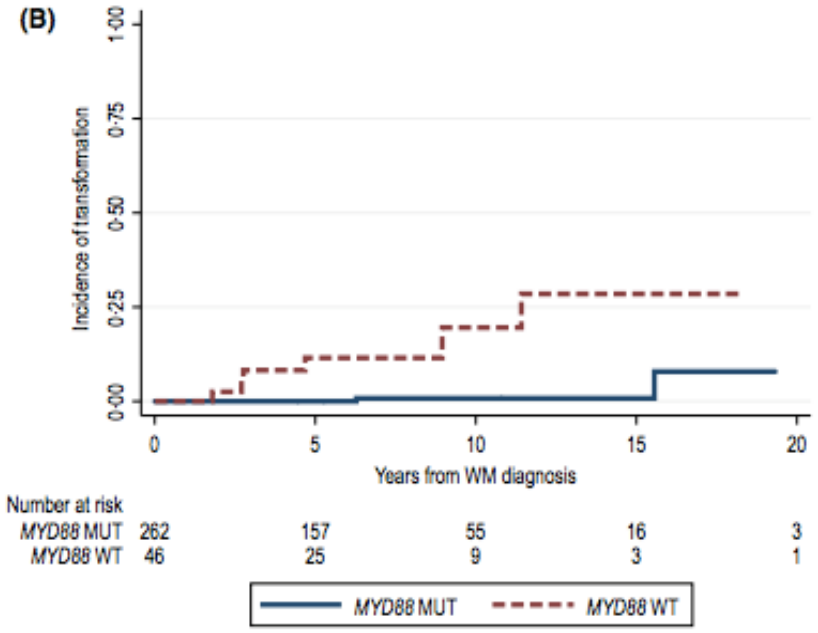
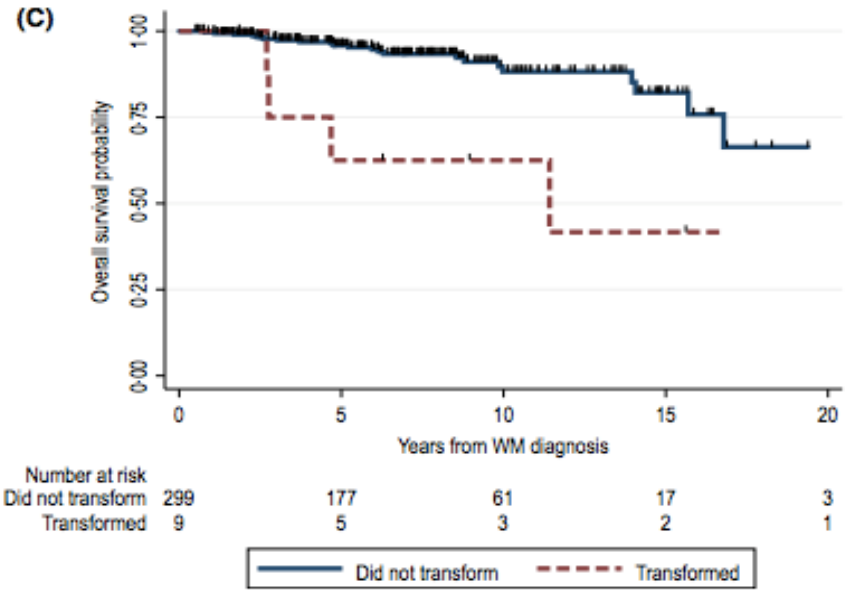
Transformation is a serious event for WM patients and is higher in MYD88 WT





Treon et al BJH 2018

What about the 10% of WM patients who do NOT have the MYD88 mutation?

***MYD88* wild-type Waldenstrom Macroglobulinaemia: differential diagnosis, risk of histological transformation, and overall survival**

- Be sure these patients not have IgM Myeloma- perhaps 30% do
- The MM patients often have chromosome 14 mutations, lytic bone lesions and no CXCR4 mutations

Treon et al BJH 2018

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Dr. Waldenström: I get to show this first but you'll see it many more times

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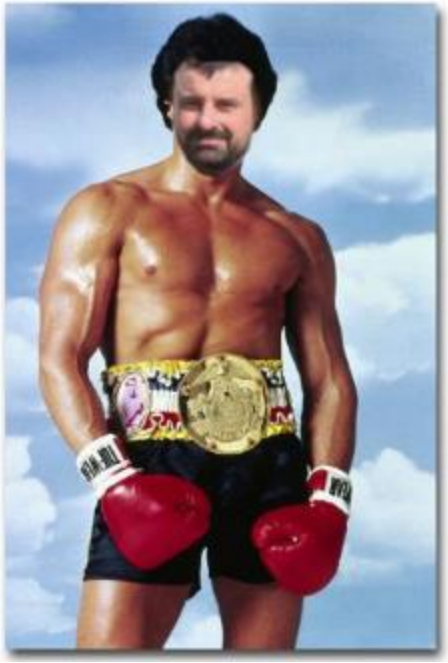
Another Giant in WM- I have cited his work many times and want to give proper acknowledgment. Everyone knows the city of brotherly love is celebrated around the globe for ROCKY

Another Giant in WM- I have cited his work many times and want to give proper acknowledgment. Everyone knows the city of brotherly love is celebrated around the globe for ROCKY



Dr. Steve Treon

With apologies, and credit to C. Patterson

OK let’s take some questions

And thank you!

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