Waldenstrom's 101 & WM in the UK

WMFC
Waldenstrom`s Macroglobulinemia Foundation of Canada

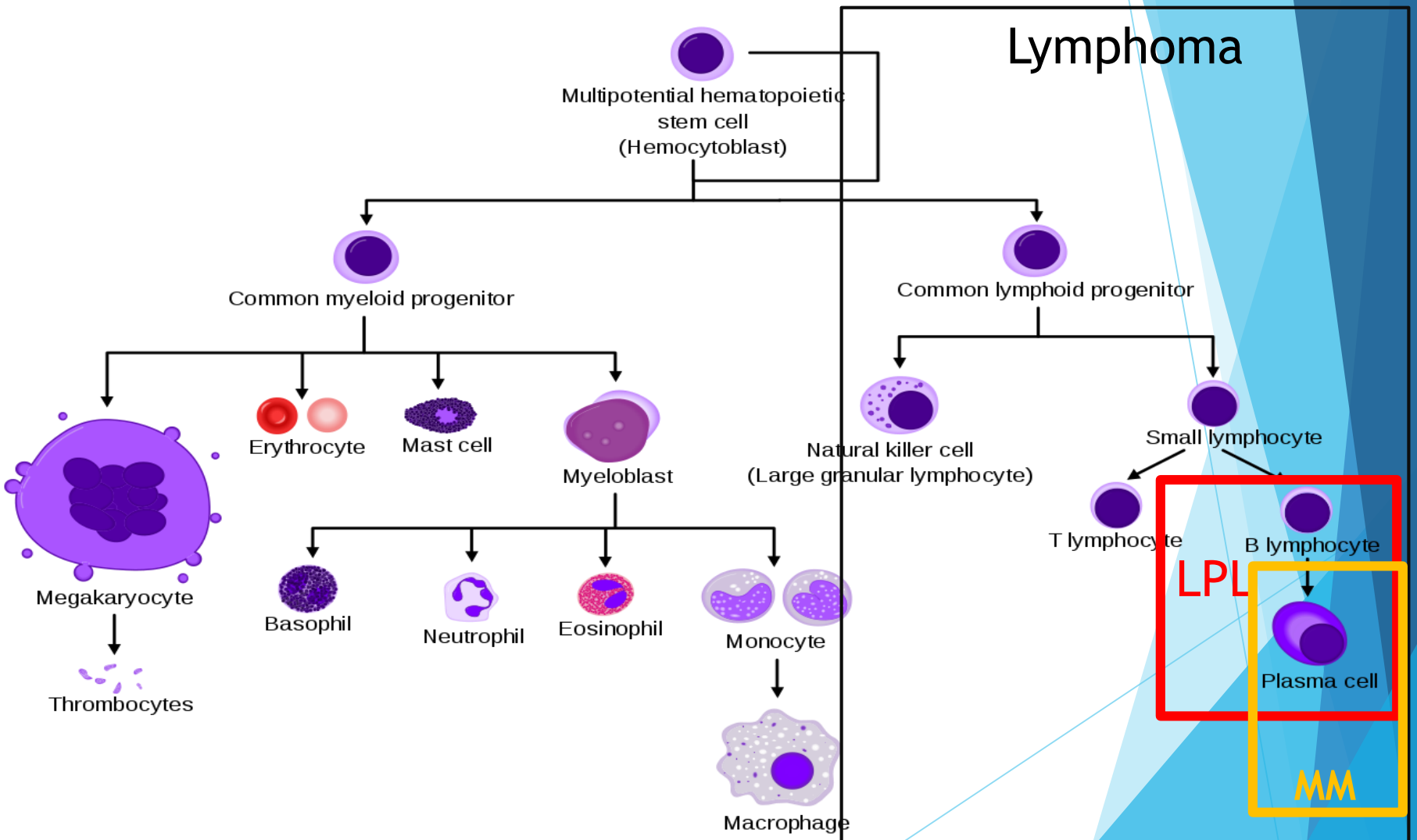
OCTOBER 27, 2018
EDUCATIONAL FORUM

Dr Shirley D'Sa, UCLH Centre for WM and Related Conditions

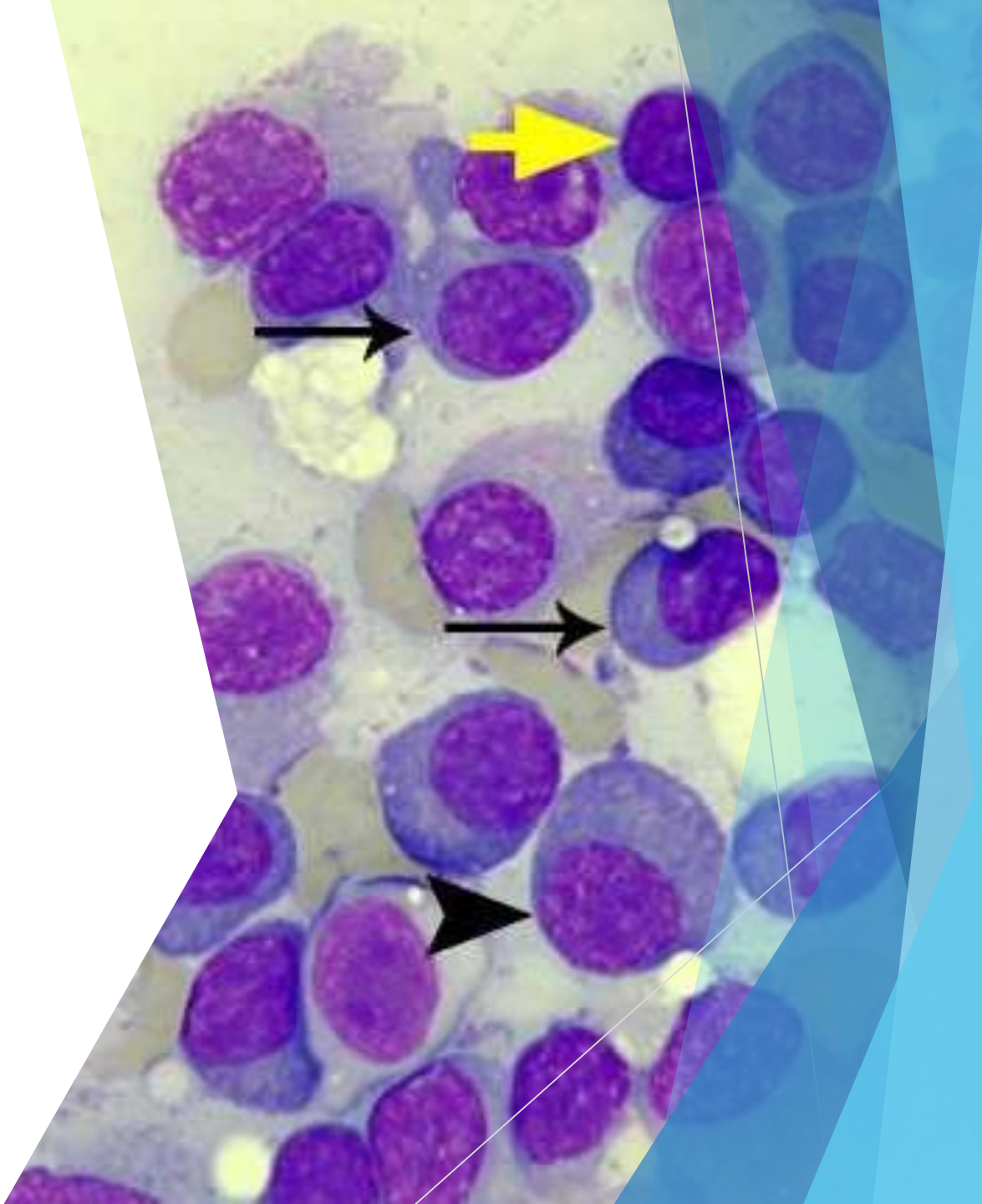
NHS
University College London Hospitals
NHS Foundation Trust

What is Waldenström's Macroglobulinaemia?

A Good Place to Start…



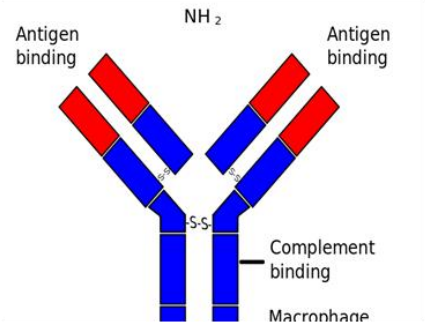
Under the Microscope… (bone marrow smear)

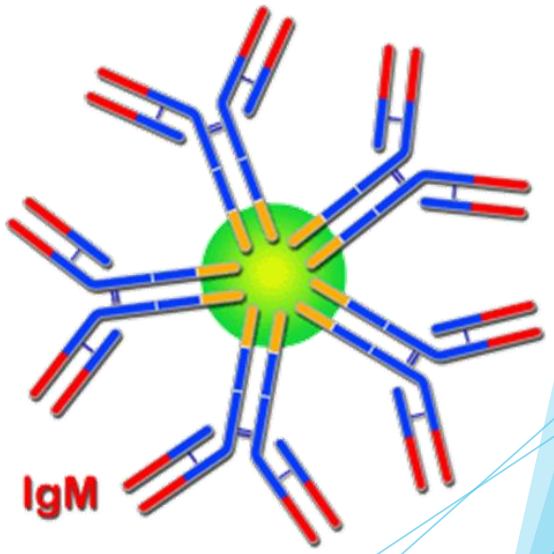


What do lymphocytes and plasma cells do?

- Produce different types of antibodies or immunoglobulin

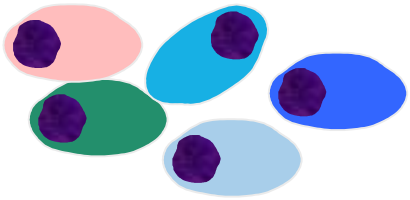
  (IgG, IgA, IgD, IgE, IgM)
- Response to infection and critical part of the immune system
- In WM are constantly being made **without** need
- Can be measured as the paraprotein if from a specific cancer cell



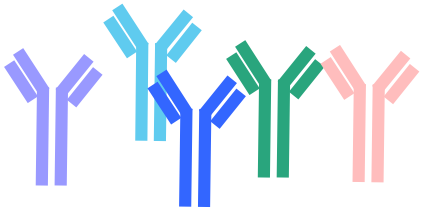


LARGE MOLECULES<--IgM circulates as pentamers= groups of 5

What is a paraprotein?

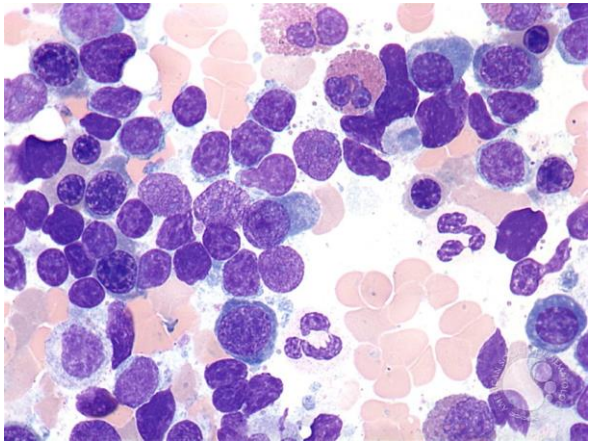


Healthy plasma cells

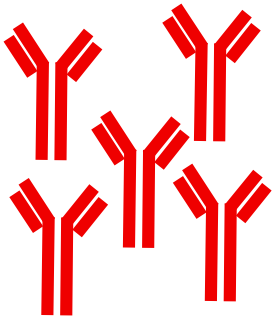


Various antibodies

Fight Infections



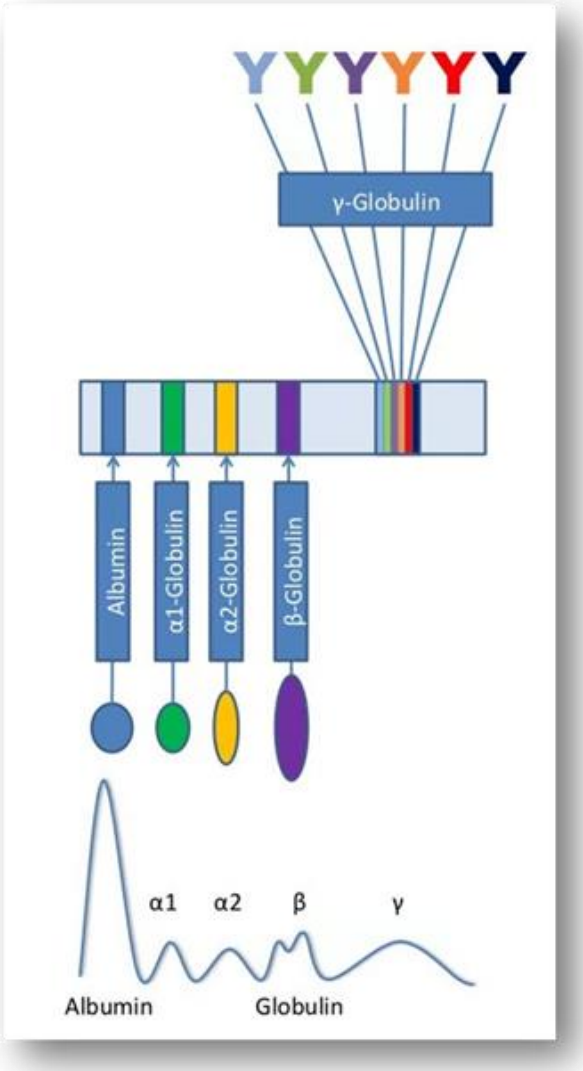
WM Plasma cells
(cancer cells)

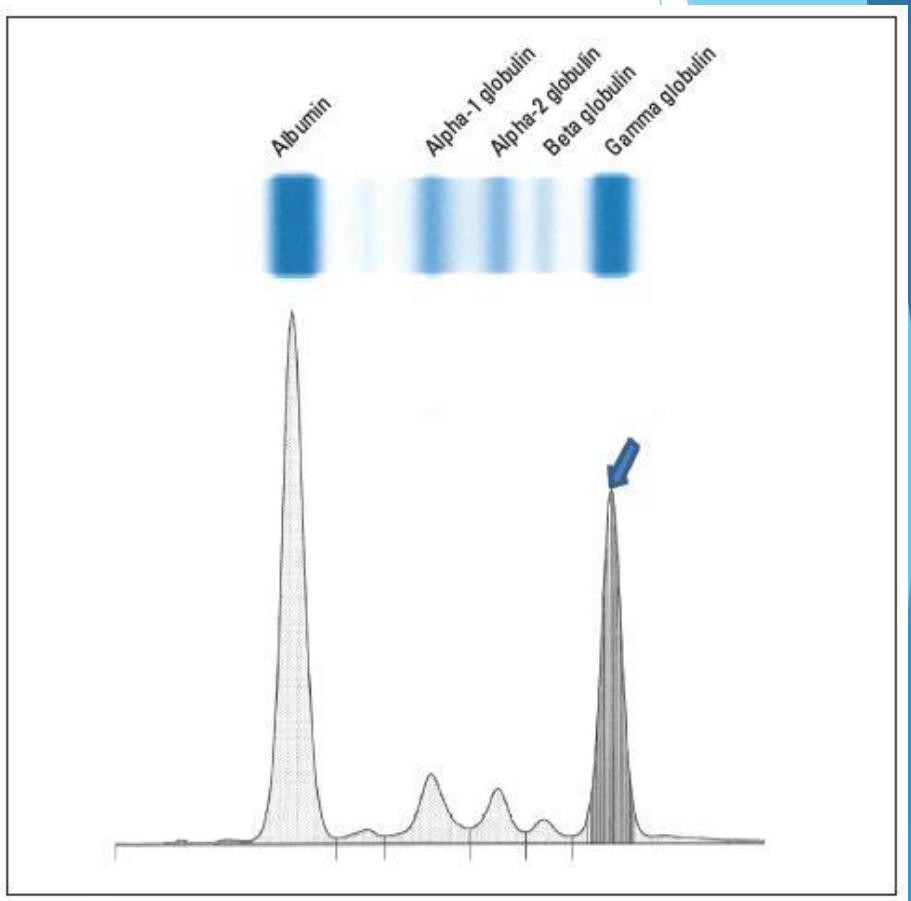


One variety (monoclonal) of antibody
= M-protein
= Paraprotein

Cause problems

Detecting a paraprotein: SPEP





Symptoms of WM

Major Components

Abnormal cell growth

Lymphoma

- Low red cells (anaemia)
- Low platelets (bleeding)
- Low neutrophils (Recurrent infections)
- Lymphadenopathy, splenomegaly, CNS
- Weight loss

Abnormal protein production

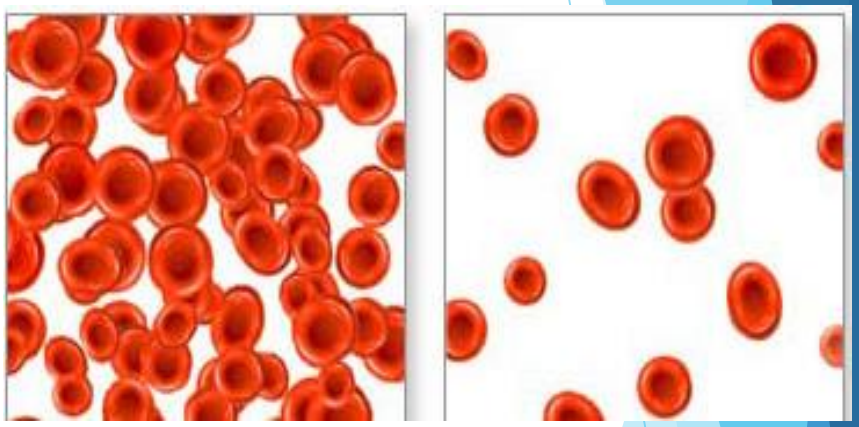
Paraproteinaemia

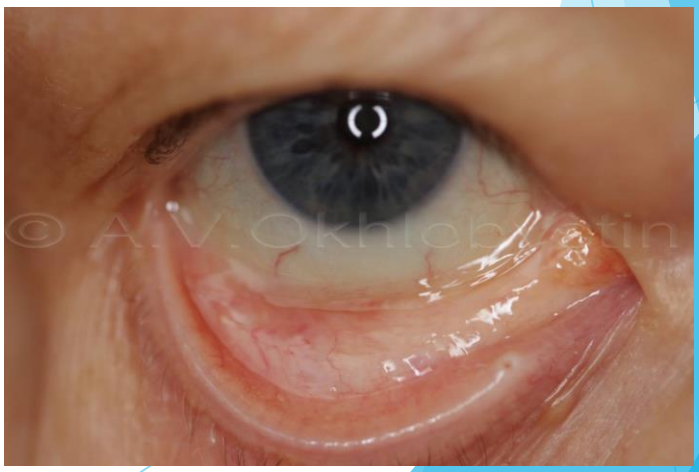
- Hyperviscosity
- Peripheral neuropathy
- Haemolysis (destruction of red cells)
- Amyloidosis
- Cryoglobulinaemia
- Clotting problems

Low Red Cells: Anaemia

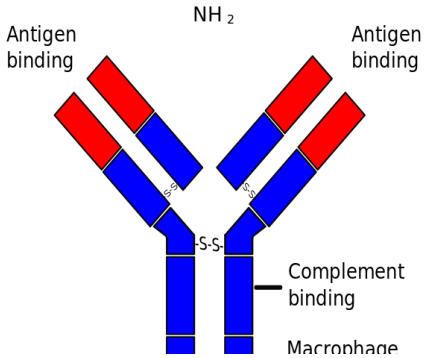
>>Reduced Oxygen to Tissues

- Fatigue
- Breathless
- Exercise tolerance
- Dizziness
- Palpitations
- Pounding in ears
- Looking pale



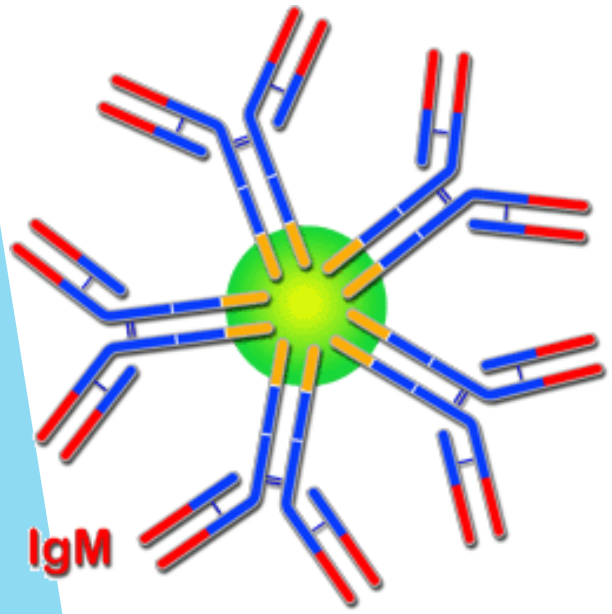


Paraprotein-related symptoms



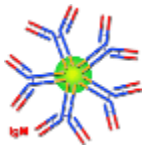
Each paraprotein has unique:

- Physical properties
- Binding properties



- Hyperviscosity
- Cryoglobulinaemia
- Auto-antibodies
- Amyloid
- Bleeding Problems

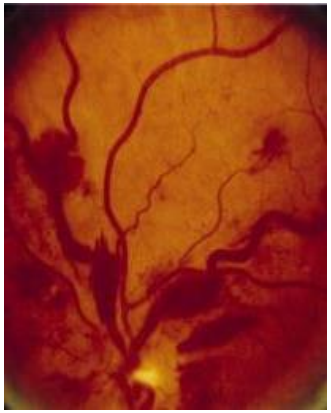
Dimpopoulos Blood 1994



Hyperviscosity syndrome (HVS)

Normal

HVS



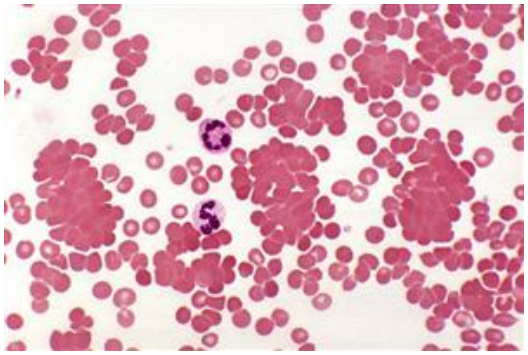
Symptoms:

- Fatigue
- Headaches
- Blurred Vision
- Bleeding gums & nose
- Confusion

- 15 %-40 % patients
- Likely if plasma viscosity >5 mPa (normal range 1.4-1.8 mPa)
- Increased risk
  - IgM > 50 g/L
  - Vascular Risks

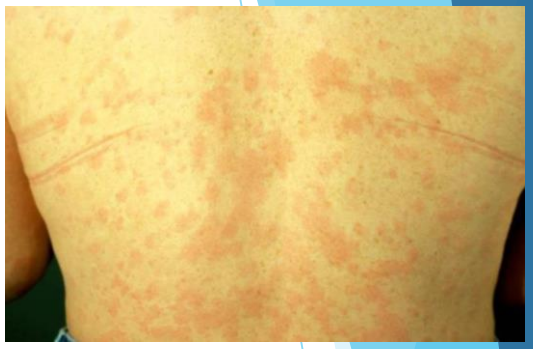
Ghobrial haematology 2012

Autoantibody activity= activity against self

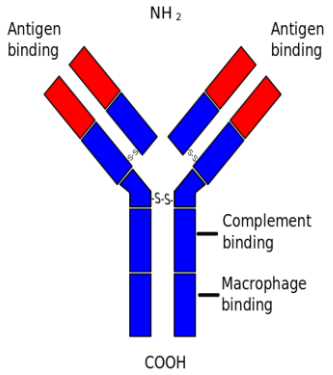


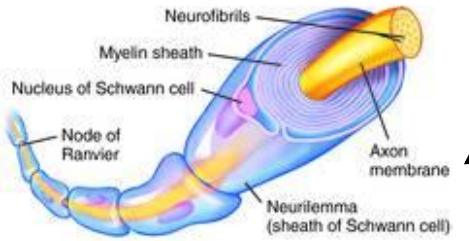
Cold Agglutinin Disease

Red Blood Cell

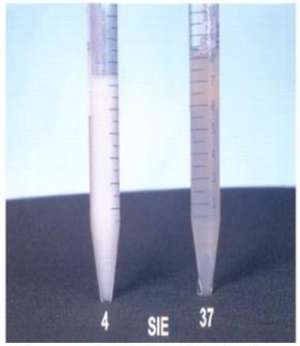


Schnitzler syndrome

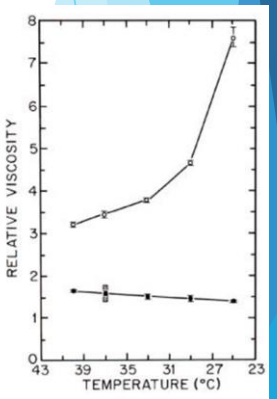




Myelin (MAG) Neuropathy



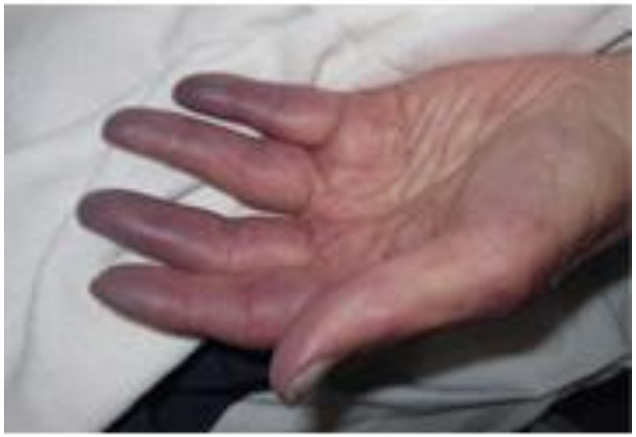
Serum at 4° C and 37° C .



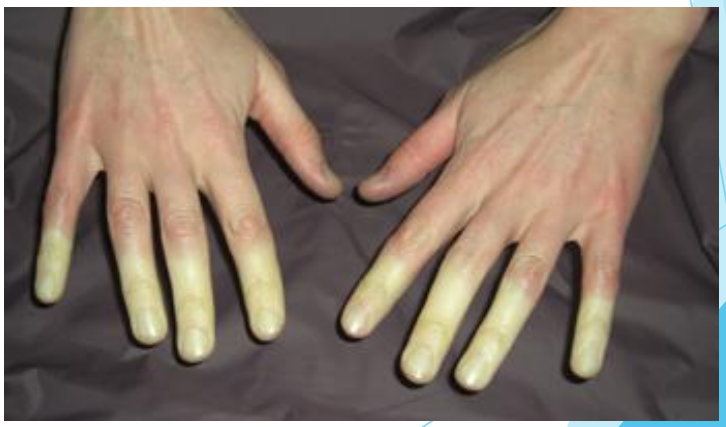
Cryoglobulins (type II)

Cold activity

- Cold agglutinin disease (CAgD)
  - ‘Cold’ haemolysis- red cell breakdown (anaemia and dark urine)
- Cryoglobulinaemia
  - Potential damage to kidneys, joints, skin, circulation, nerves



Acrocyanosis



Raynaud’s syndrome

Neuropathy: nerve damage

Peripheral

24 % patients

- Symptoms
  - Tingling or numbness
  - Abnormal sensation
  - Weakness arms & legs
  - Loss of reflexes
  - Fatigue

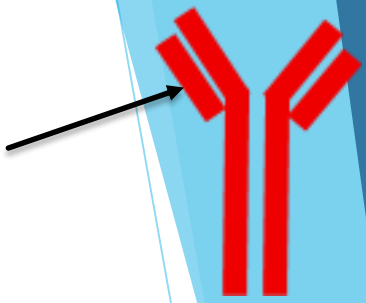
Autonomic

- Symptoms
  - Constipation or diarrhoea
  - Dizziness on standing
  - Bladder problems

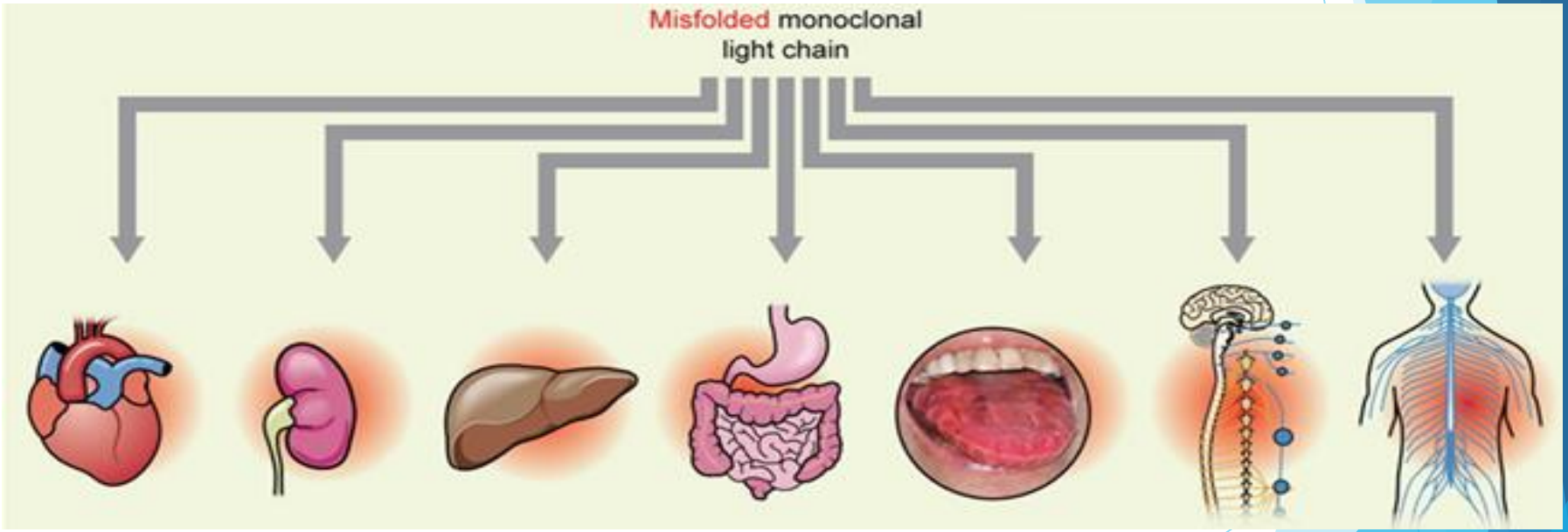
Causes

Anti-myelin associated Glycoprotein Ab (MAG)
Amyloidosis
Cryoglobulinaemia

AL Amyloid- deposition of misfolded light chains (kappa or lambda)



>>results in progressive tissue damage



Heart 74 %

kidney 74 %
Nephrotic

Liver 74 %

gut 74 %

Soft tissues 17 %

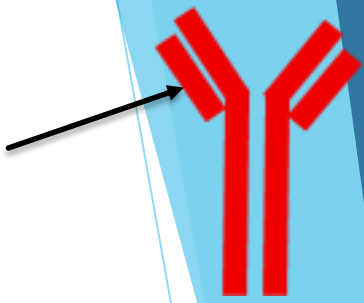
ANS 14 %

PNS 15 %

< 5 % WM patients affected

Modified from Merlini G, Blood 2012;119:4343-4345

AL Amyloid- deposition of misfolded light chains (kappa or lambda)

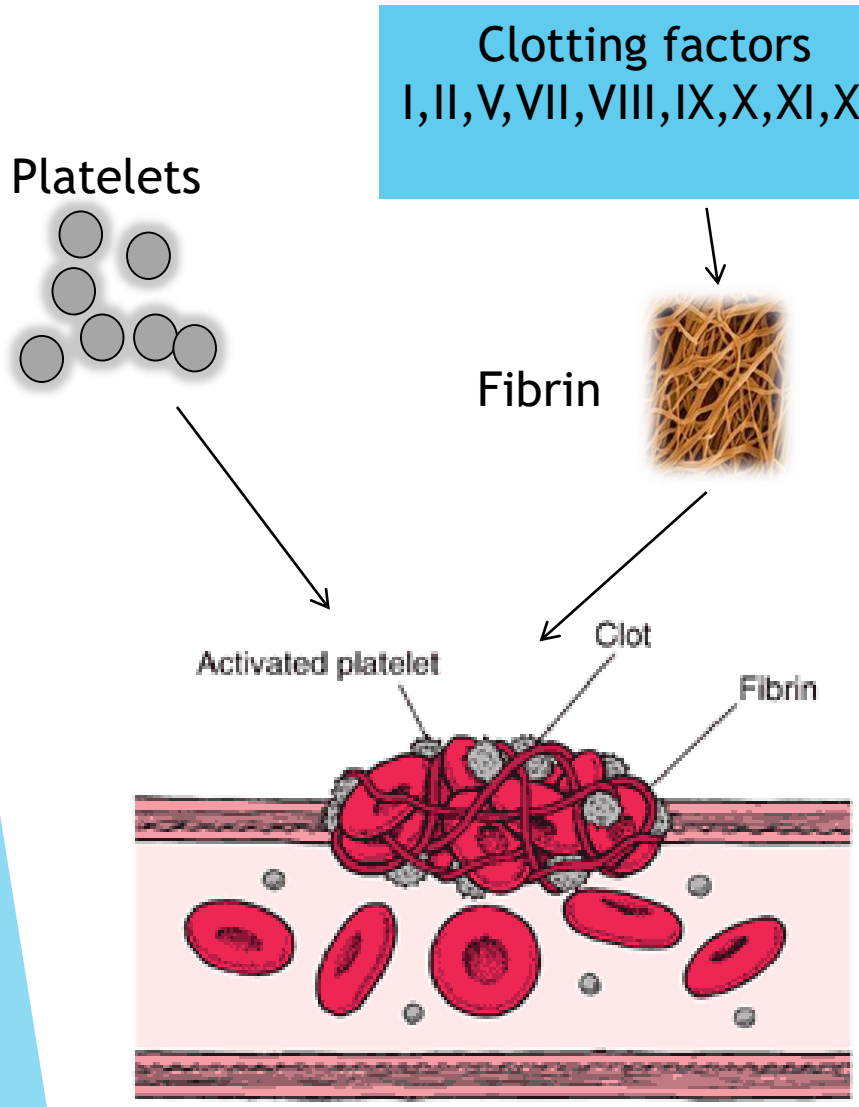


>>results in progressive tissue damage

IMPORTANT TO CONSIDER THE POSSIBILITY OF AMYLOIDOSIS

REQUIRES A MODIFIED APPROACH TO TREATMENT WITH DIFFERENT GOALS

Bleeding and bruising in WM

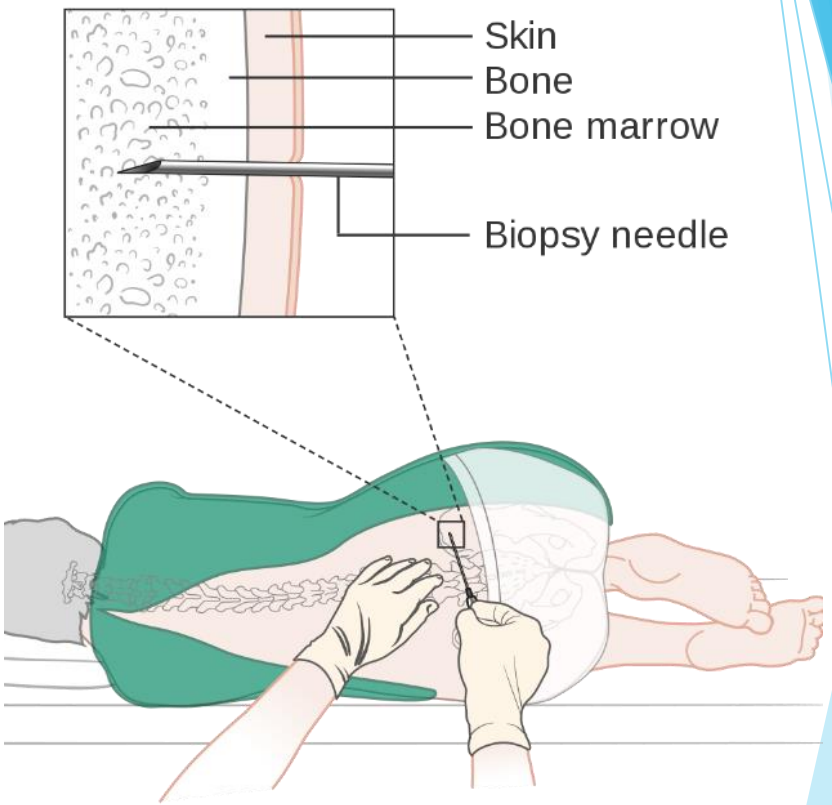


- Platelets
  - Production reduced
  - Immune destruction (ITP)
  - Impaired function
- Clotting factors
  - IgM interference
  - Acquired hemophilia
  - Acquired von Willebrand's disease (vWD)

Dimopoulos Blood 1994

Perkins Blood 1970

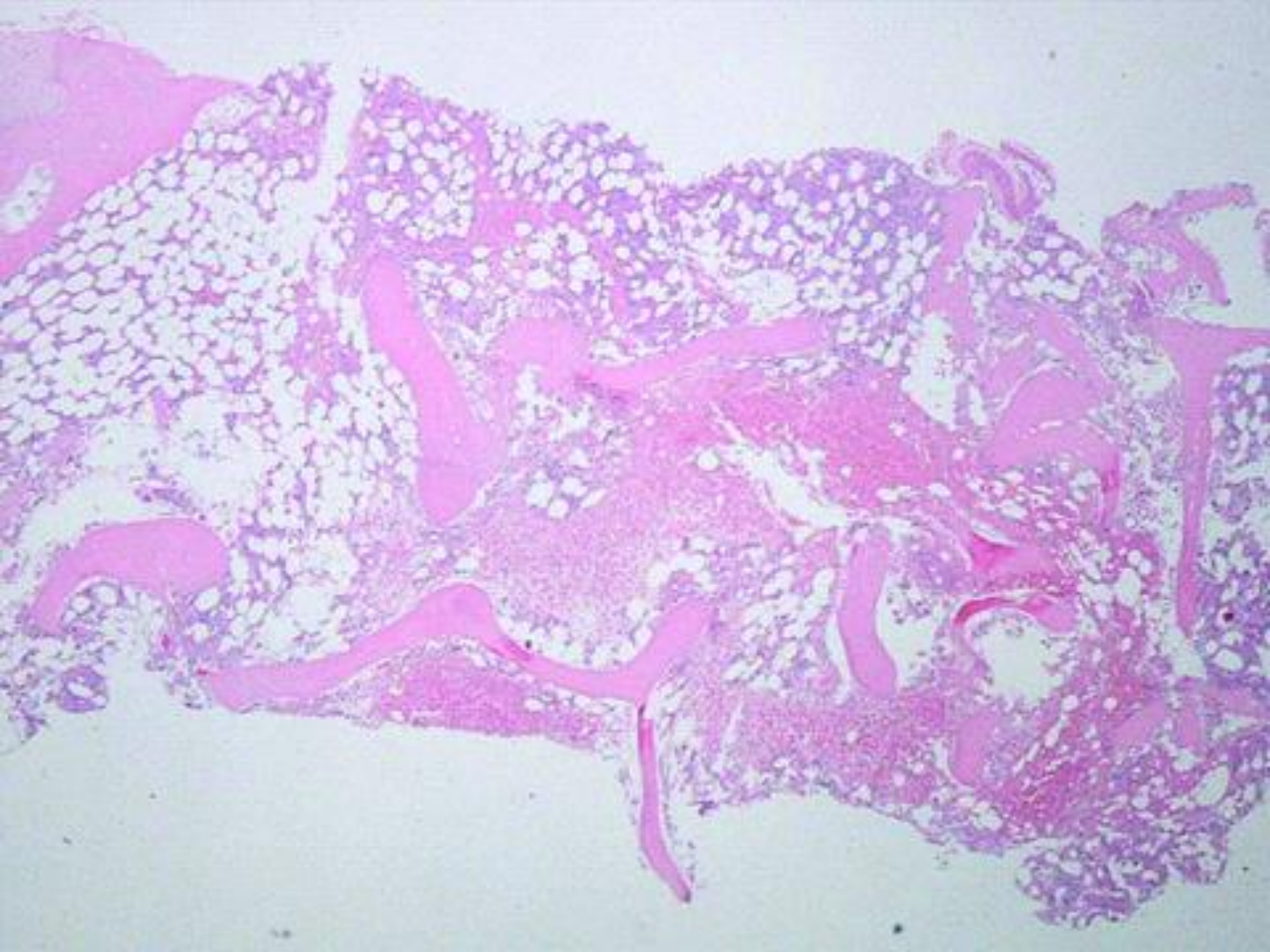
Diagnosis of WM



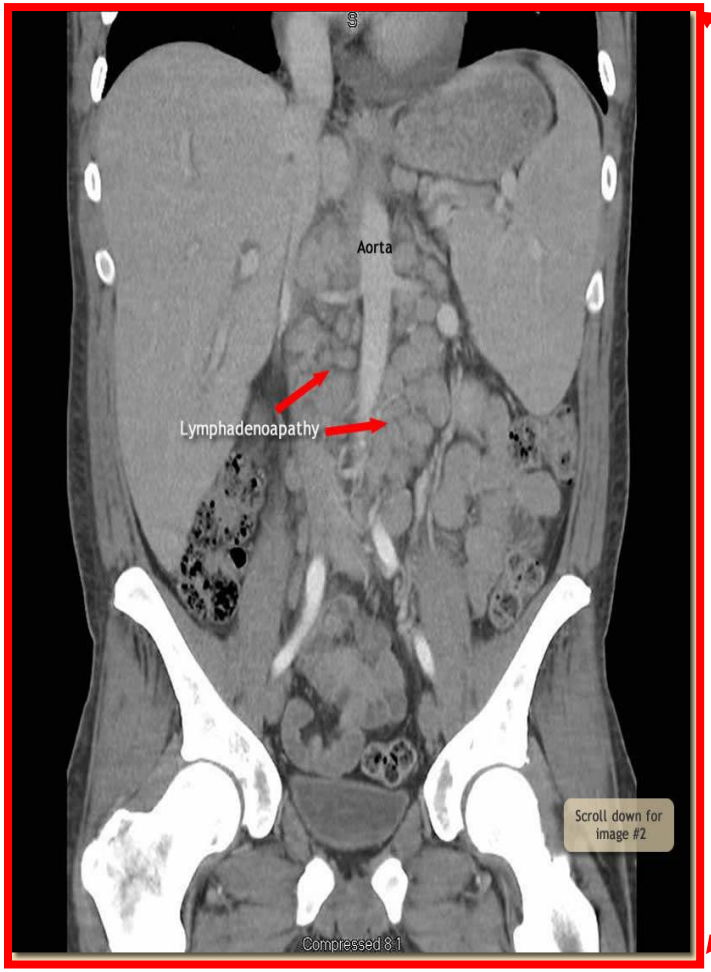
Bone marrow biopsy

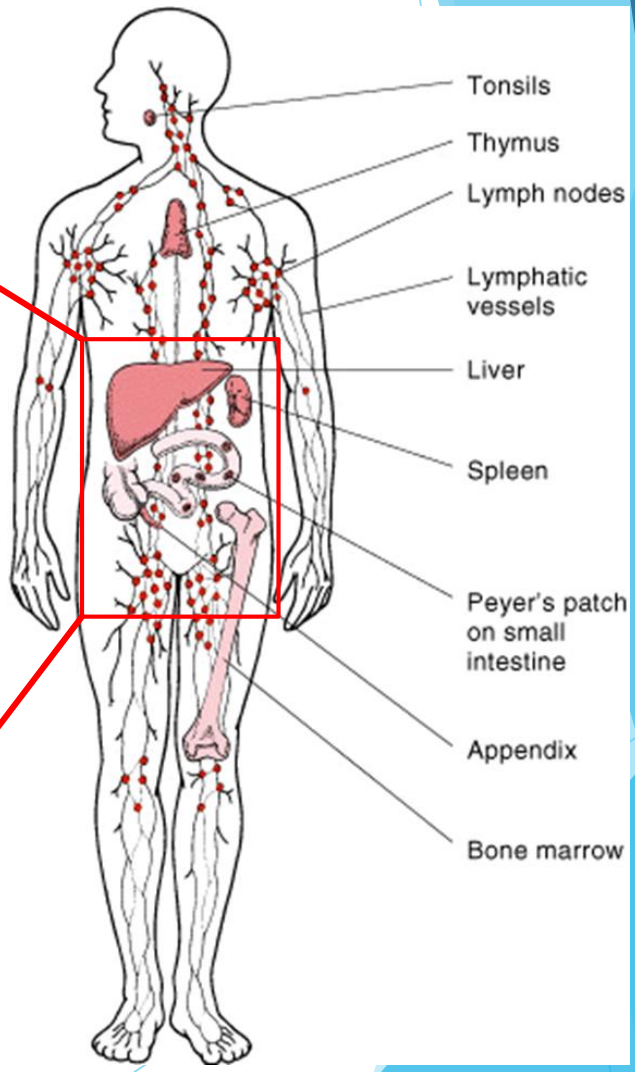
to assess the cellular burden

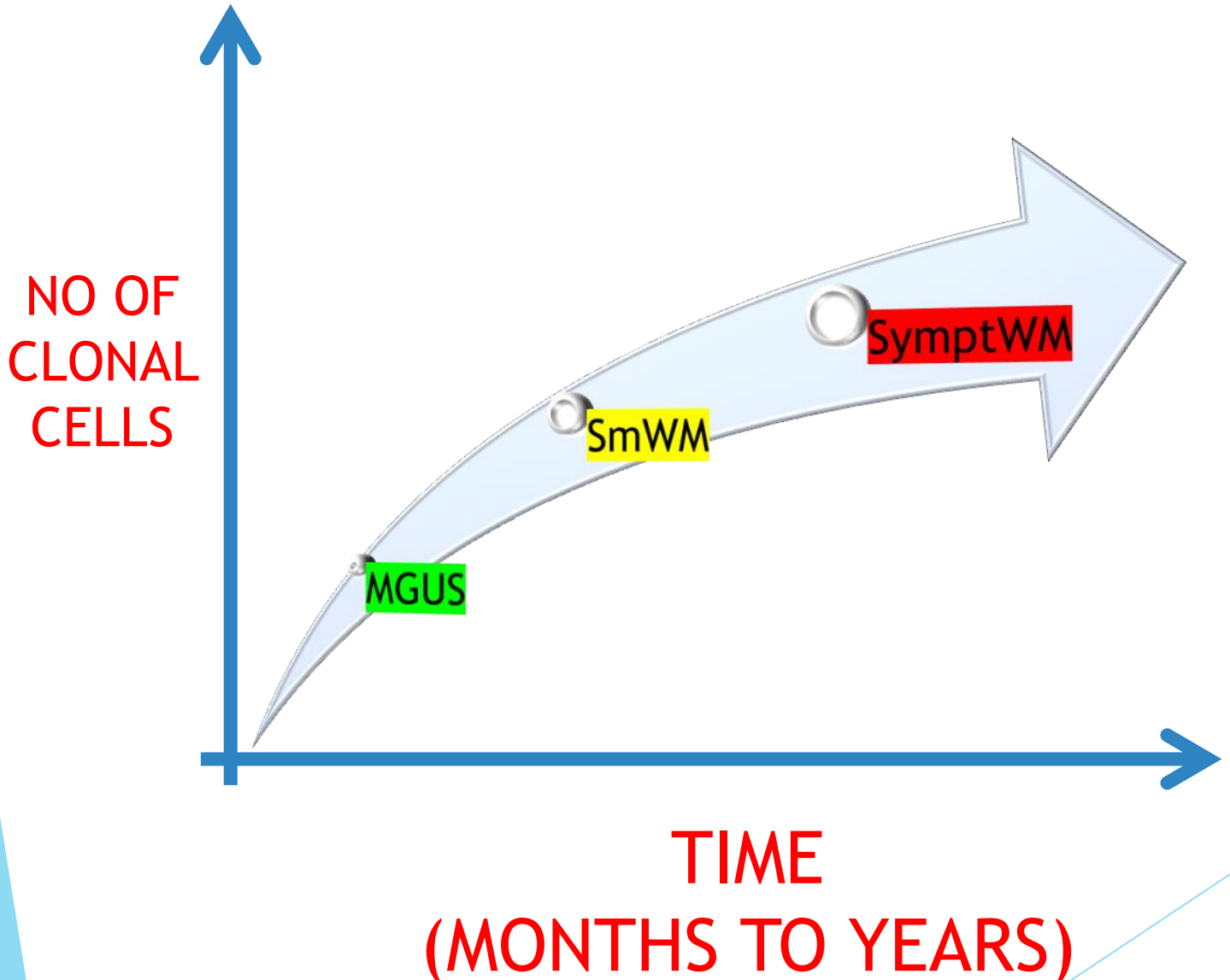
Black and Decker version



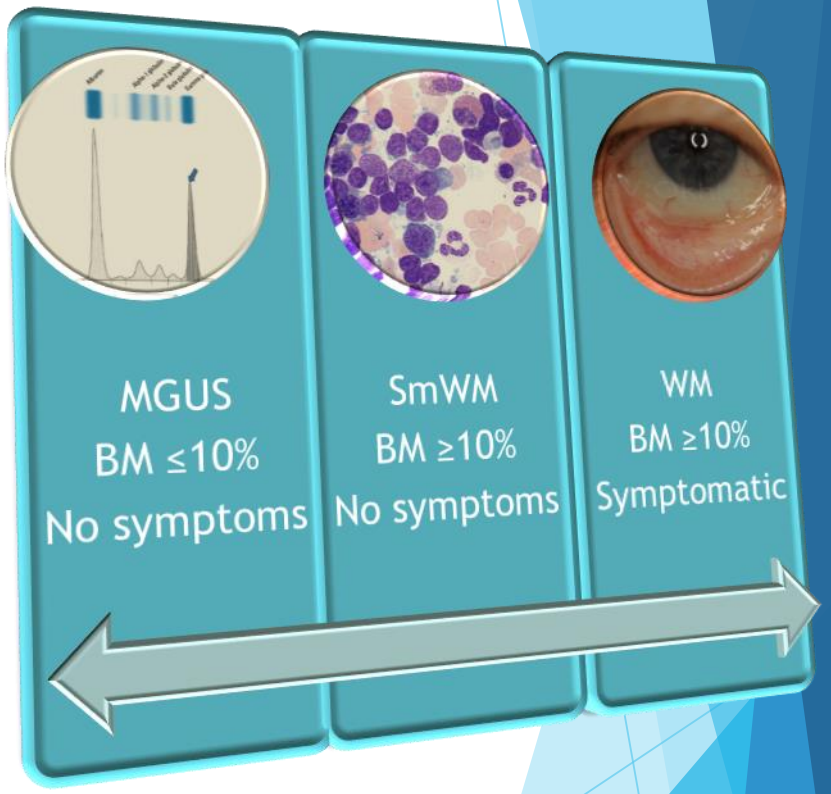
Radiology- to assess lymph nodes and spleen






NO OF CLONAL CELLS
MGUS
SmWM
SymptWM
TIME
(MONTHS TO YEARS)

MGUS (Monoclonal gammopathy of uncertain significance) vs Smouldering WM vs Symptomatic WM



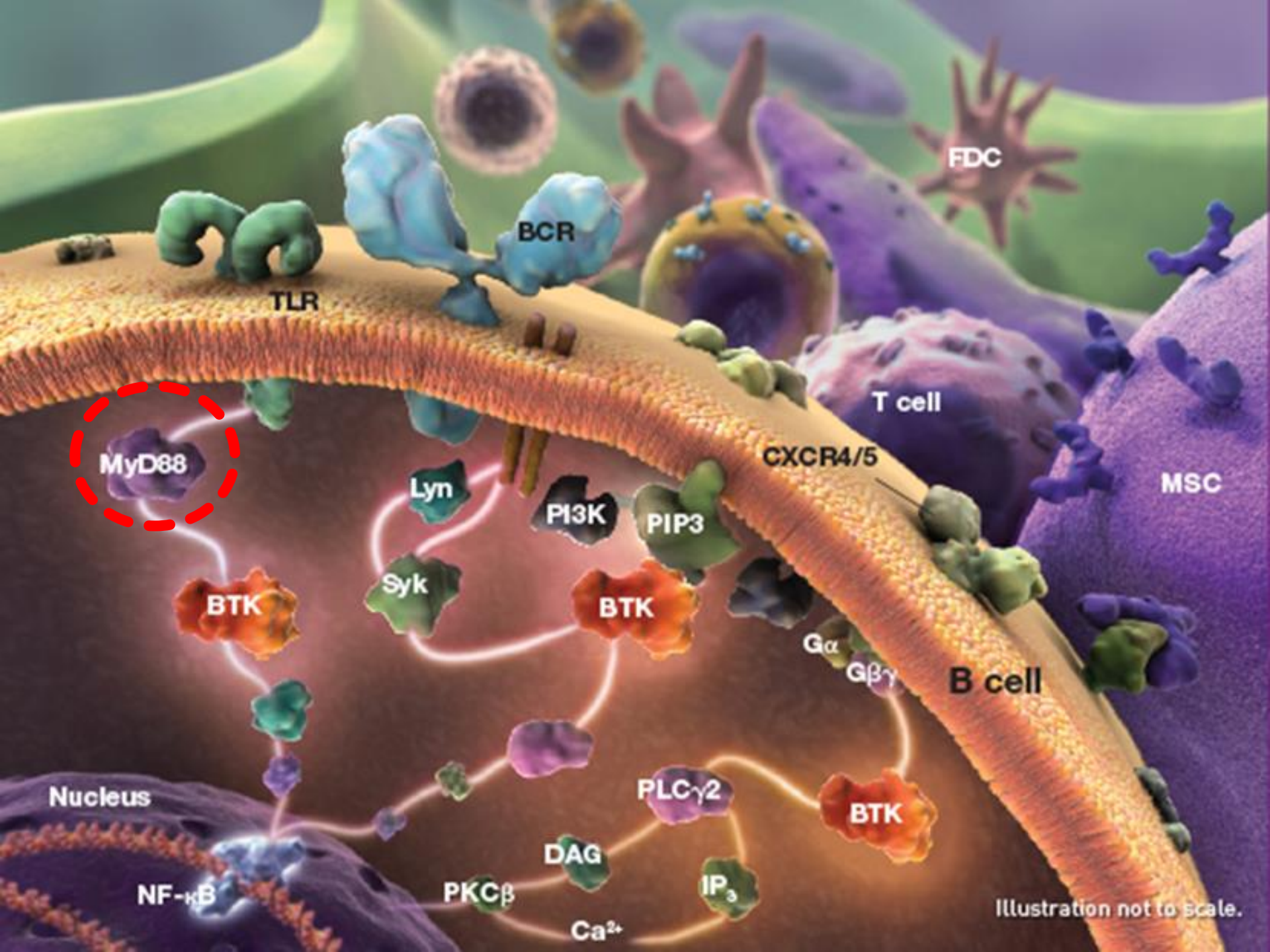
- Presence of IgM paraprotein in blood
- = IgM **Monoclonal gammopathy**
- **(MGUS)**
  - 3% in the >70 years; 5% in >80 years
- Results from a gradual accumulation of

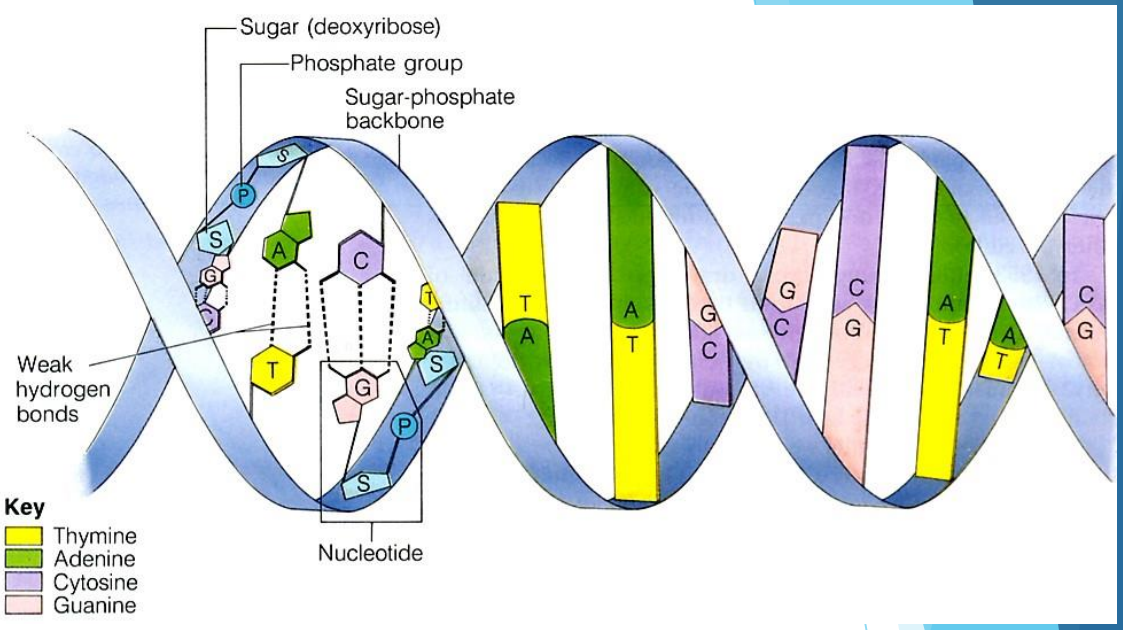
  clonal cells* in the bone marrow
- If asymptomatic, **not** affecting organs or rapidly changing

  then **no need for intervention**

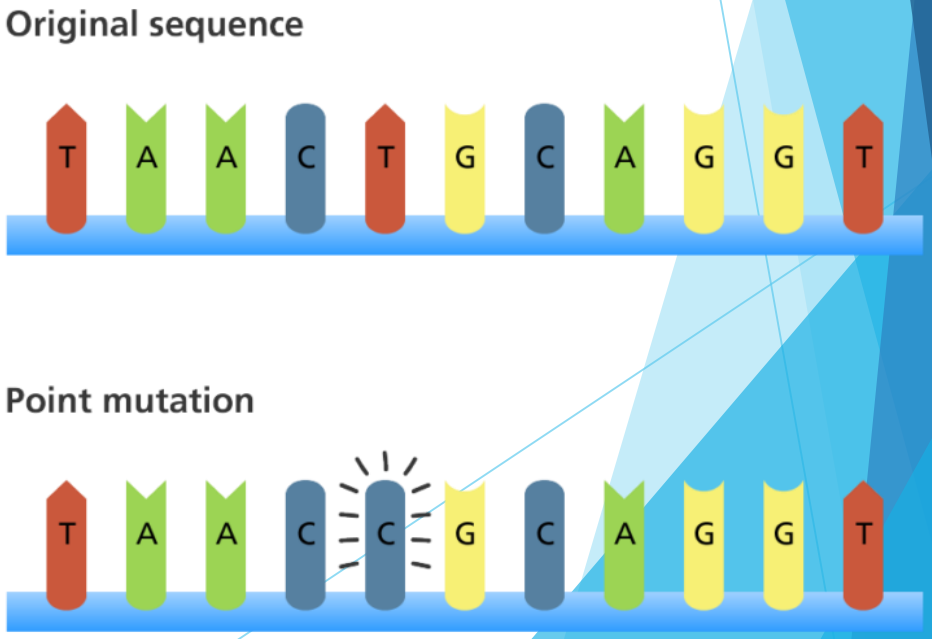
*One of a kind

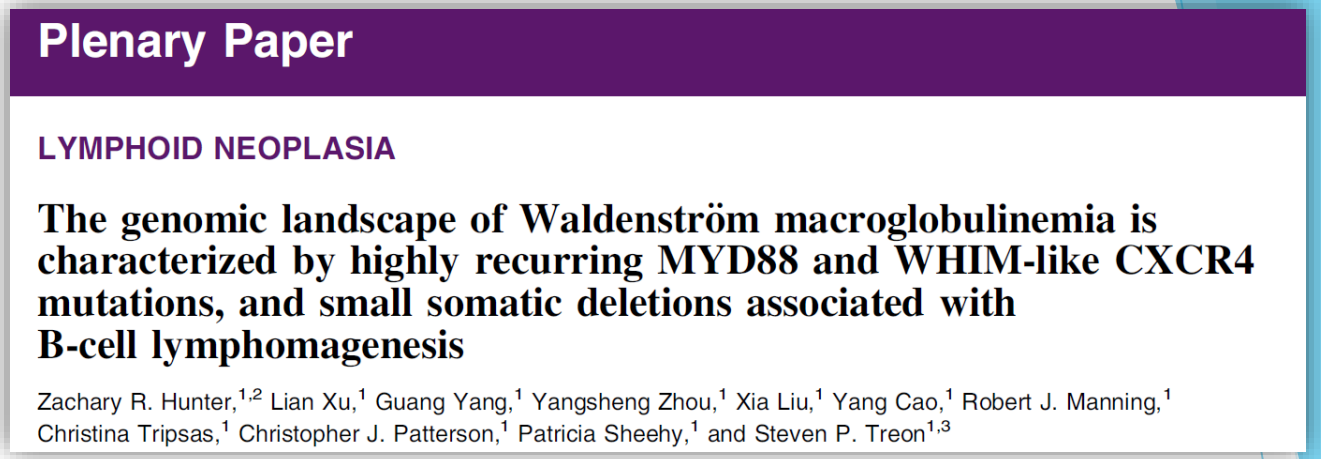
MYD88 etc.


FDC
BCR
TLR
T cell
MyD88
CXCR4/5
MSC
Lyn
PI3K
PIP3
Syk
BTK
BTK
Gα
Gβγ
B cell
Nucleus
PLCγ2
BTK
DAG
NF-κB
PKCβ
IP3
Ca2+
Illustration not to scale.



- In WM, the most common mutation occurs in MYD88 gene.
- Over 90 percent of patients carry this mutation in the WM cells.
- MYD88 L265P mutation turns on growth and survival pathways including Bruton tyrosine kinase (BTK), the target of ibrutinib.
- There are other mutations (not L265P) that confer similar characteristics





Plenary Paper

LYMPHOID NEOPLASIA

The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter,[1,2] Lian Xu,[1] Guang Yang,[1] Yangsheng Zhou,[1] Xia Liu,[1] Yang Cao,[1] Robert J. Manning,[1] Christina Tripsas,[1] Christopher J. Patterson,[1] Patricia Sheehy,[1] and Steven P. Treon[1,3]

- The second most frequently mutated gene in WM is *CXCR4*, which occurs in about 30-40% of cases
- Almost exclusively present in MYD88-mutated WM
- Mutations of this gene, which are known to play a key role in the trafficking of immune cells in the body
- In WM, mutations of *CXCR4* turn on growth and survival pathways
- WM cells with some mutations of the CXCR4 gene also show resistance to Ibrutinib

blood

When to treat WM?

Not everyone needs treatment

- Smoldering Waldenström's Macroglobulinaemia (SWM) is an intermediate state in which the IgM monoclonal protein is ≥ 30 g/L and/or a bone marrow contains ≥ 10% LPL cells
- These patients may progress to symptomatic WM, amyloidosis or lymphoma at a rate of 6% in the first year, 39% at 3 years, 59% at 5 years and 68% at 10 years.

Alexanian R, Weber D, Delasalle K, Cabanillas F, Dimopoulos M
Semin Oncol. 2003 Apr; 30(2):206-10.

Indications for treatment (guide for doctors)

Clinical indications	Laboratory indications
Signs and symptoms associated with hyperviscosity	Hemoglobin <10 g/dL
Moderate to severe peripheral neuropathy	Platelet count $<100\times10^9$/dL
AL amyloidosis	Hemolytic anemia
Symptomatic cryoglobulinemia	
Constitutional symptoms, Raynaud's phenomenon, and arthralgia	
Bulky or symptomatic lymphadenopathy	
Symptomatic organomegaly	

Abbreviation: AL, amyloid light-chain.

Progressive symptoms and diminished patient well-being should be the trigger

Not specific cut-off of IgM

Aberykoon JP, et al. *Cancer Manag Res*. 2017; 9:73–83.

Key issues regarding treatment

When to treat?	Objectives	How to treat?
LPL cells have accumulated excessively in BM causing anaemia	Take back control of bone marrow	Intensively enough to do the job without excessive toxicity
LPL cells have expanded lymph nodes and spleen or extramedullary sites resulting in consequences	Shrink abnormally enlarged tissues and organs	Intensively enough to do the job without excessive toxicity
IgM is causing symptomatic high blood viscosity	To lower IgM level as soon as possible	Plasma exchange and treatment that works rapidly
IgM is causing immunological spin-offs such as neuropathy, cold agglutinin disease	To neutralize the activity of the rogue antibody	Ideally more subtle treatment that produces a complete response

In all cases….

REMEMBER THE TREATMENT OBJECTIVES
Fitness of patient
Wishes of patient
Minimise toxicity/ burden of treatment
Maximise benefit of each treatment
Use treatments judiciously
Don’t give unnecessary treatment

Chemotherapy + Rituximab (finite number of weeks)
vs
Continuous therapy e.g. Ibrutinib

Add maintenance for deeper effect?

Orderly and appropriate sequence

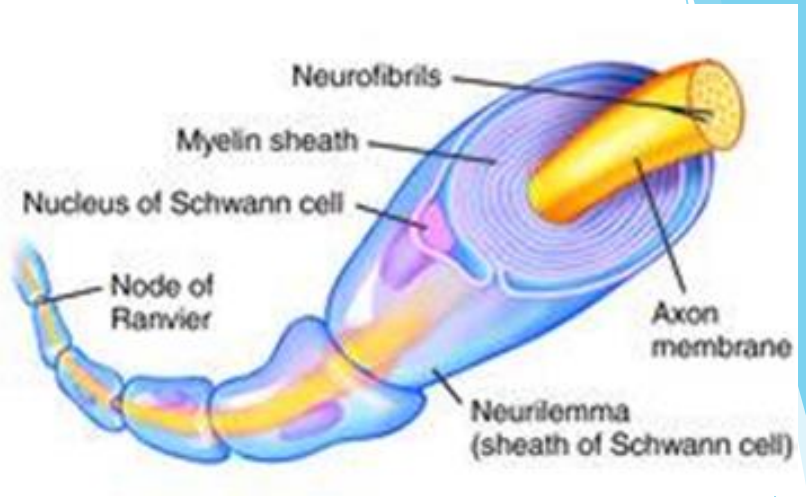
Too much treatment increases the risk of infections

How to measure response to treatment?

Complete Response	**CR**	Disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy / organomegaly (confirmed by CT scan), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required at least 6 weeks apart with a second immunofixation.
Partial Response	**PR**	A ≥50% reduction of serum monoclonal IgM concentration on protein electrophoresis and ≥ 50% decrease in adenopathy/organomegaly on physical examination or on CT scan. No new symptoms or signs of active disease.
Minor Response	**MR**	A ≥ 25% but < 50% reduction of serum monoclonal IgM by protein electrophoresis. No new symptoms or signs of active disease.
Stable Disease	**SD**	A <25% reduction and <25% increase of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM.
Progressive Disease	**PD**	A ≥25% increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥ 38.4°C, drenching night sweats, ≥ 10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloidosis) attributable to WM.

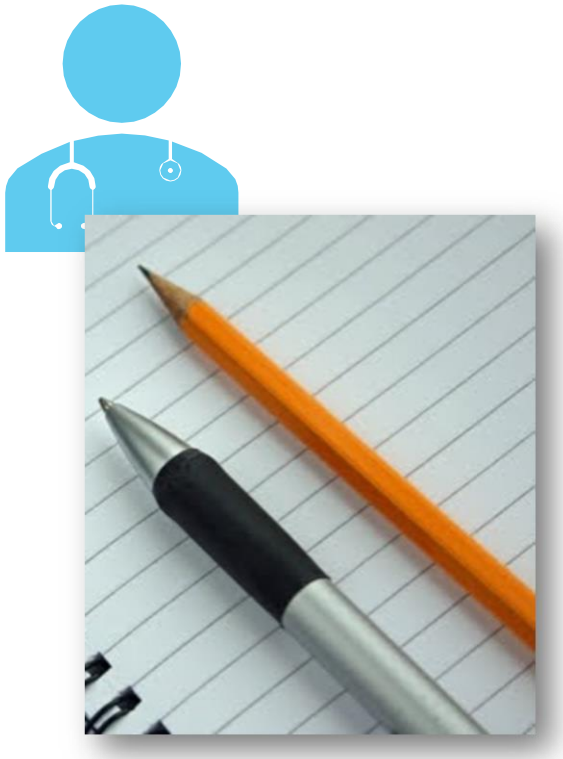
Special situations: involvement of the nervous system

Nerve damage: peripheral neuropathy



- Neuropathies associated with IgM paraprotein present variously as
  - Anti-MAG mediated peripheral neuropathy
  - Peripheral neuropathy without anti-MAG antibodies
  - IgM-associated peripheral neuropathy with ganglioside antibodies
- Although there are aspects of these disorders that are distinct, the symptoms are often similar

Assessing Neuropathy

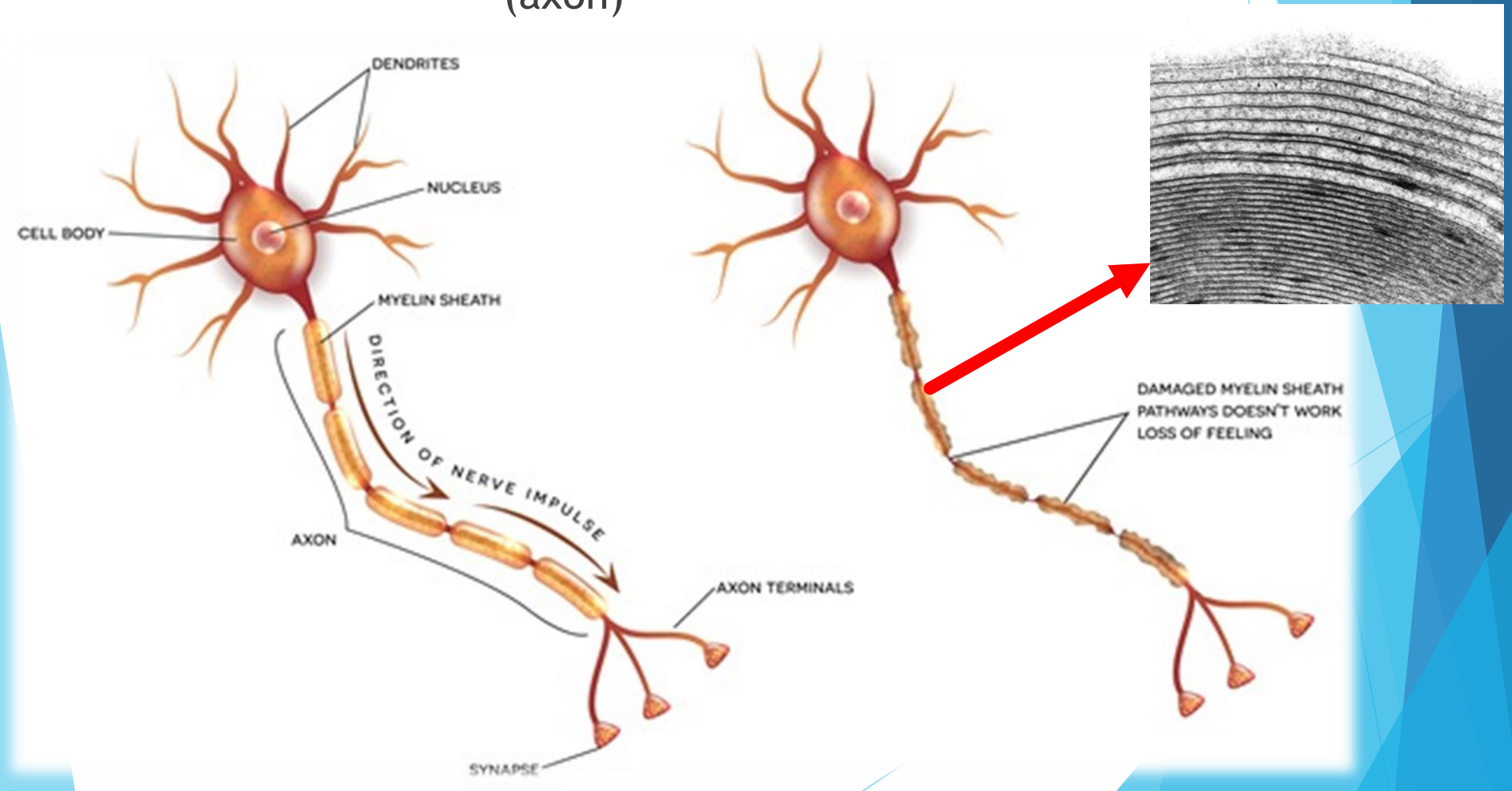


- Nature of symptoms, spatial distribution
- Speed of onset
- Rate of change
- Effect on functional abilities
- Motor/ sensory/ autonomic features

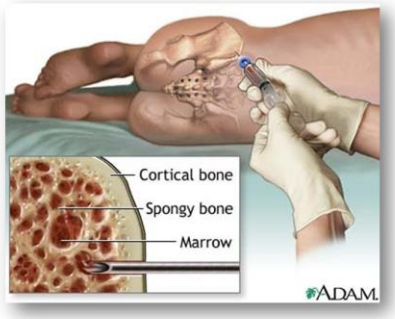
- Examination to confirm neurological picture and provide a baseline for future comparison
  - Features of amyloid- bruising, oedema, cardiac insufficiency, postural drop in BP
  - Features of cryoglobulins- acrocyanosis, livedo reticularis, ulcers
- Examination to confirm haematological picture: MGUS vs WM
  - Lymphadenopathy
  - Splenomegaly

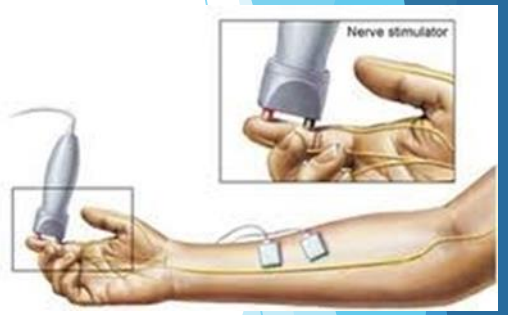
Myelin Associated Glycoprotein

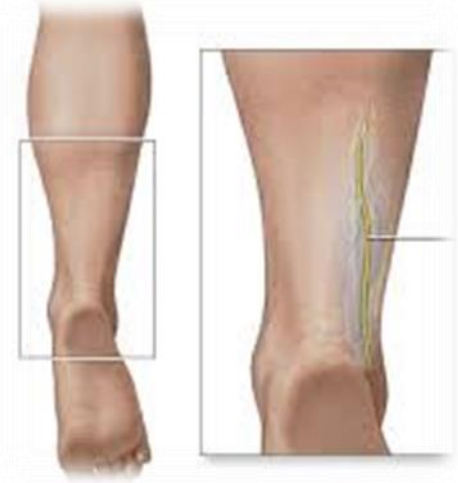
- MAG is a glycoprotein localised in “Schwann cells” on the innermost myelin wrap, directly across from the axon surface
- Some IgM antibodies target MAG and damage the insulation (myelin sheath) of the nerve fibre (axon)

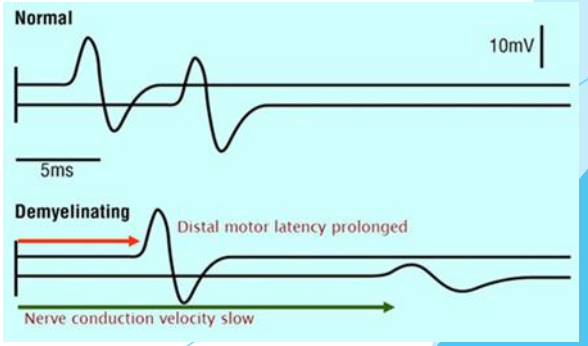


Investigations









Anti-MAG neuropathy treatment:

Who, when, what for

- Only if there is a progressive functional impact: case-by-case decision
- Short disease duration (<2 years), active progression at time of treatment might predict response[1].
- The depth of optimal haematological remission is not known[2].
- Complete elimination of the clonal IgM is probably not practical or possible.
- Stability rather than improvement is the most likely outcome of treatment

1. Treon SP 2010
2. Benedetti et al 2007

Anti-MAG neuropathy Therapeutic options

IVIG may have limited benefit in the short term (timescale of weeks)

Steroids alone are not effective, but may be beneficial in combination with other agents such as **cyclophosphamide**.

Purine analogues (Fludarabine and Cladribine) have demonstrated a modest improvement in some studies, and although tolerance of these agents was reported as good, the studies were small[3,4].

For occasional patients with rapidly worsening neuropathy especially with signs of motor disability, **combinations of active agents** or even high dose therapy and **stem cell transplantation** have been attempted.

Anti-MAG neuropathy: Rituximab

There are several non-randomised studies of Rituximab in anti-MAG-PN reporting positive benefit in small groups of patients.

Five studies reported a worsening of the PN following Rituximab, possibly related to an IgM flare.

Two RCTs of Rituximab have been negative in their primary outcome measures

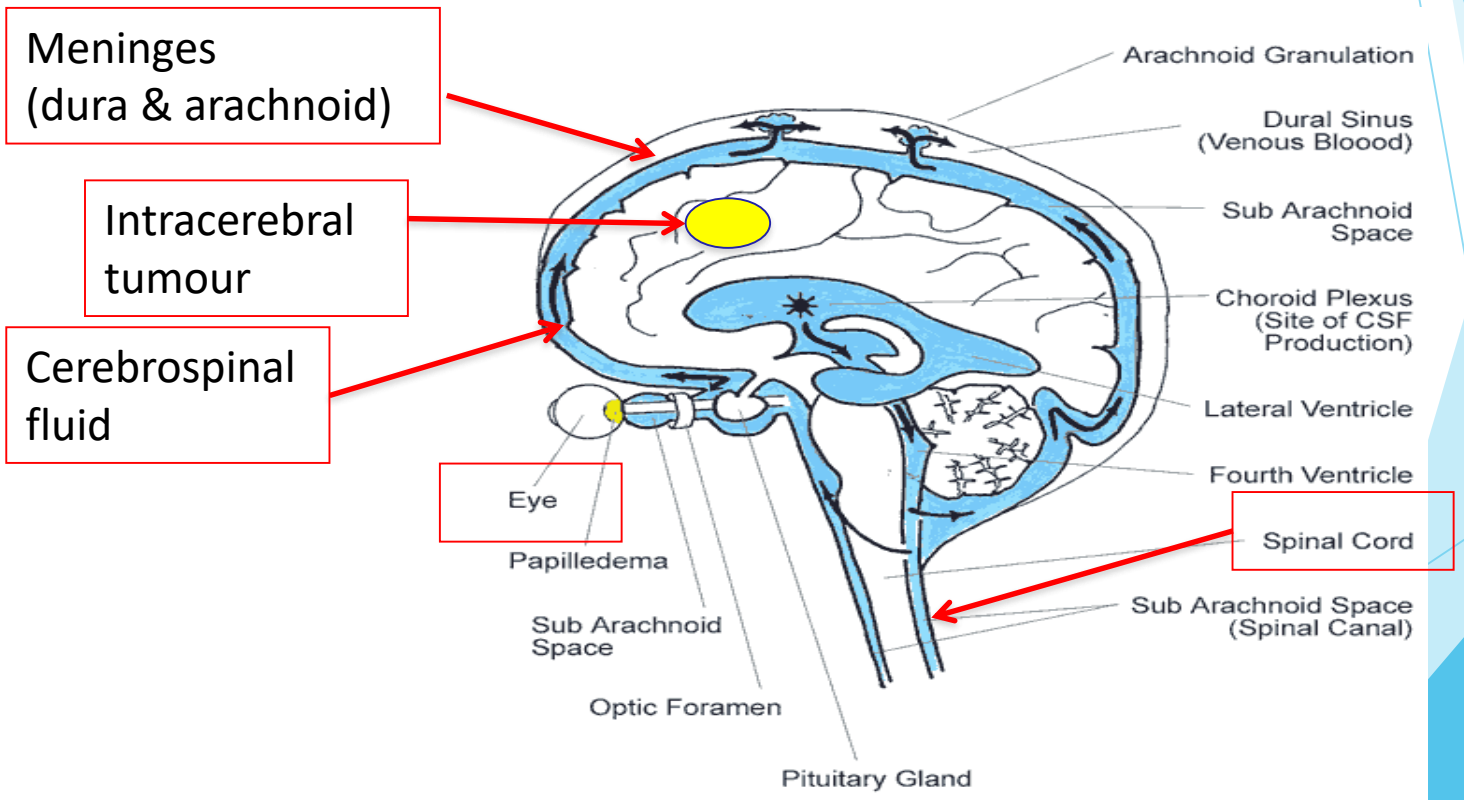
Secondary outcome measures including patient impression of change were positive and a systematic review highlights significant therapeutic benefit.

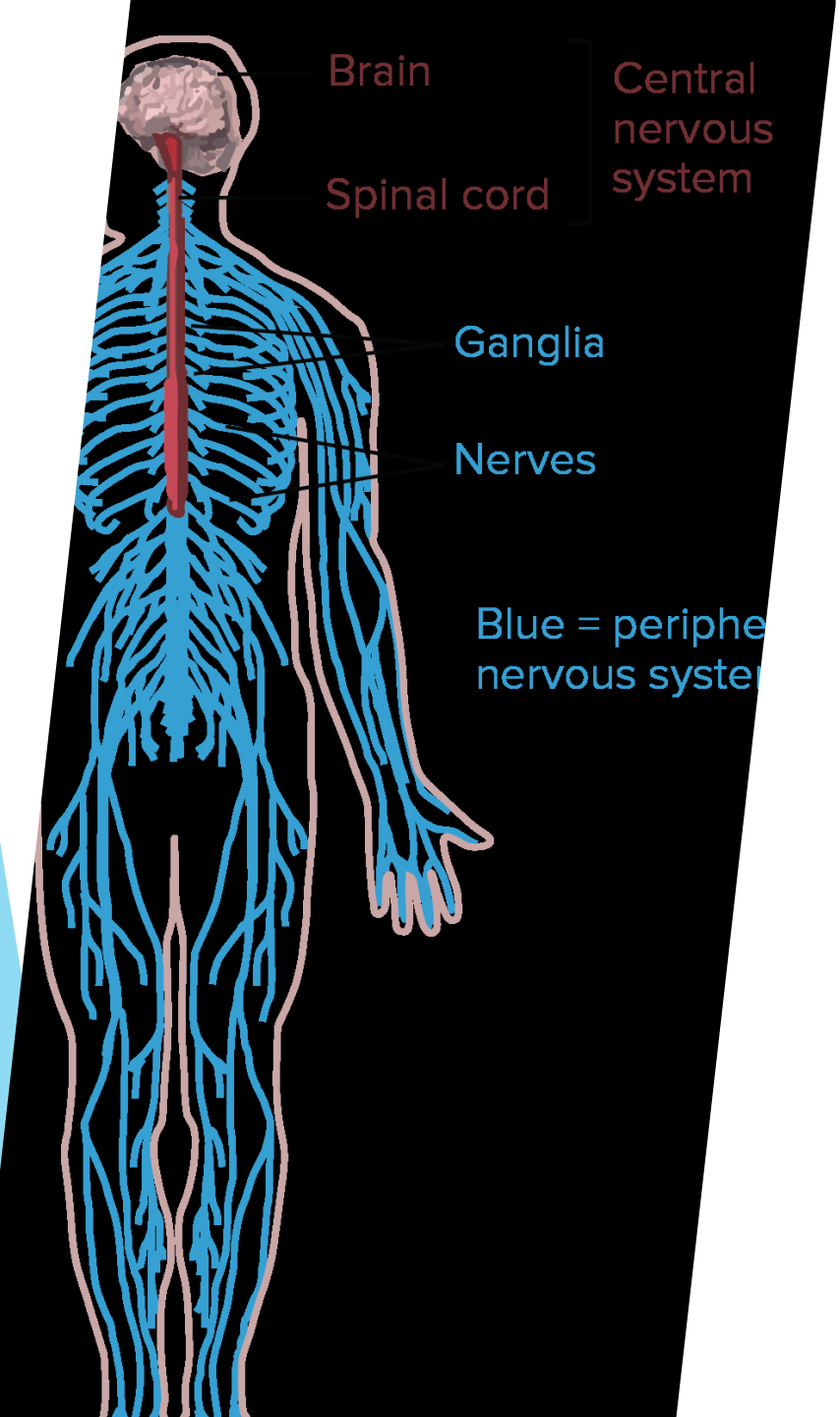
Factors predictive of a response to Rituximab in anti-MAG-PN remain to be elucidated.

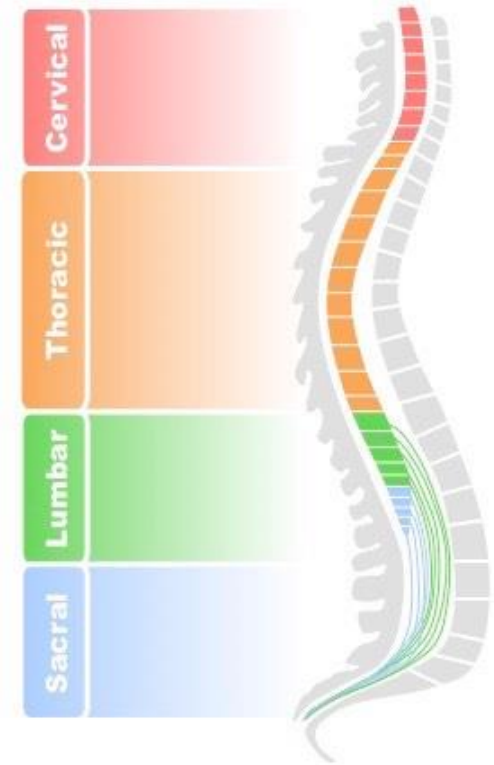
Bing Neel syndrome

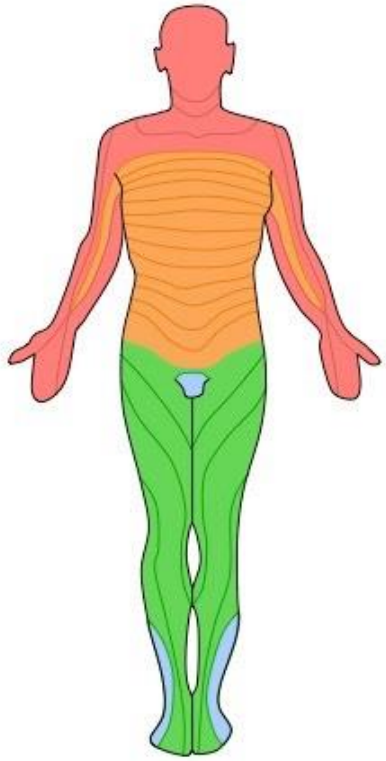
Definition

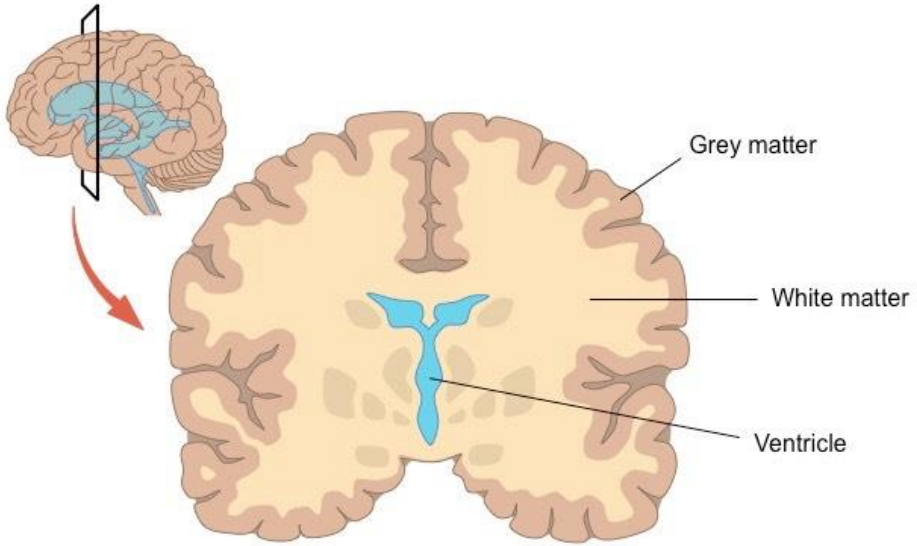
Infiltration of WM cells in the central nervous system.




Brain
Spinal cord
Central nervous system
Ganglia
Nerves
Blue = periphe
nervous syste


Cervical
Thoracic
Lumbar
Sacral




Grey matter
White matter
Ventricle

Who gets BNS?

- ≈ 1% of all WM patients
- Lack of clinical awareness, under-reporting?
- No prospective studies, ±150 pts reported in literature
  - 2 publications with 34 and 44 pts, respectively
- Can be presenting symptom of WM ≈ 15-36%
- Can be present without any other evidence of active/progression of systemic WM

Simon et al Haematologica 2015 , 1587-1594
Castillo et al, Br J Haematol, 2016 , 709-15

BNS in patients with known WM: pitfalls!

- The median time from WM to BNS diagnosis was 3 and 8.9 years (range 0 to 24.7 years)
- For 71% of the 28 patients previously diagnosed with WM, BNS occurred independently of a systemic progression of WM
- At the time of BNS diagnosis, seven patients were actively receiving therapy, of which six were responding to their current therapy based on serum IgM level reduction.

Simon et al Haematologica 2015 , 1587-1594
Castillo et al, Br J Haematol, 2016 , 709-15

Clinical picture is extremely variable without any specific signs or symptoms

- ✓ Altered mental status , including memory loss
- ✓ Cranial nerve disorder
- ✓ Paraplegia/paralysis
- ✓ Unsteady gait

30-50%

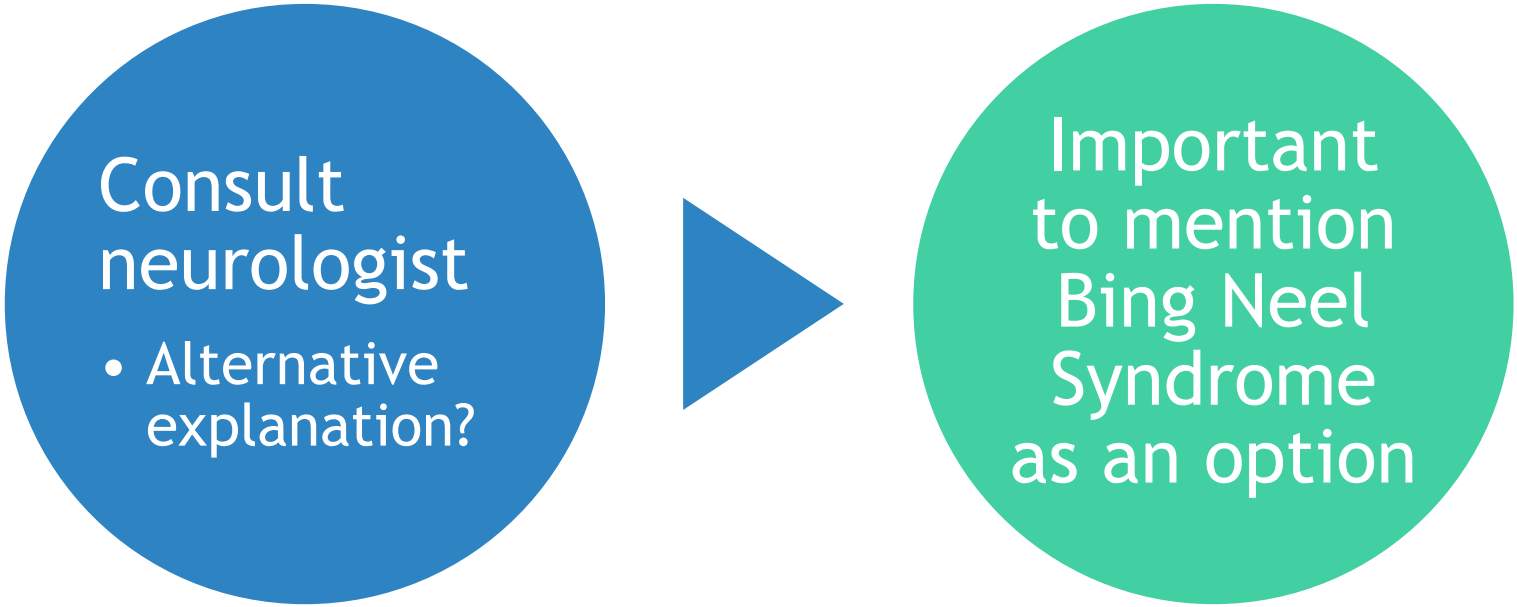
- ✓ Headache
- ✓ Paresthesia
- ✓ Seizures
- ✓ Limb pain

20-30%

- ✓ Psychiatric symptoms
- ✓ Blurry vision
- ✓ Hearing loss

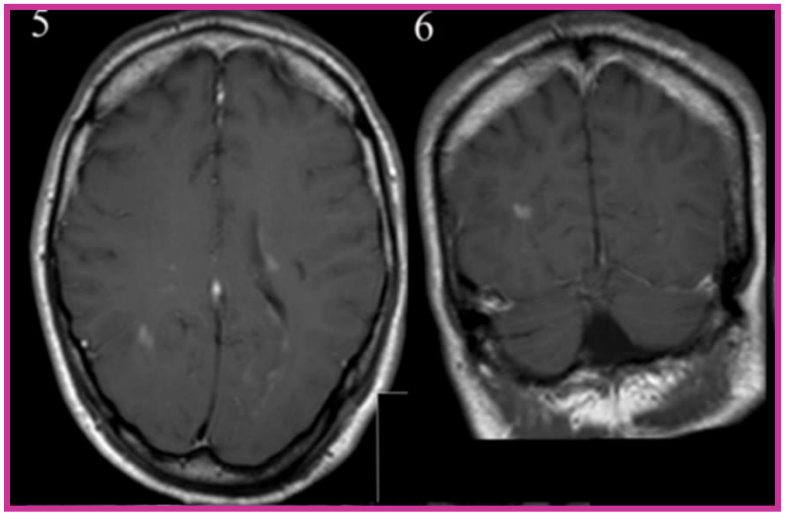
10-20%

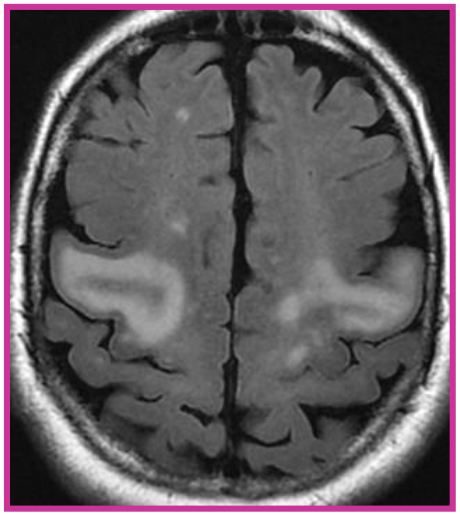
Suspected BNS: Step 1

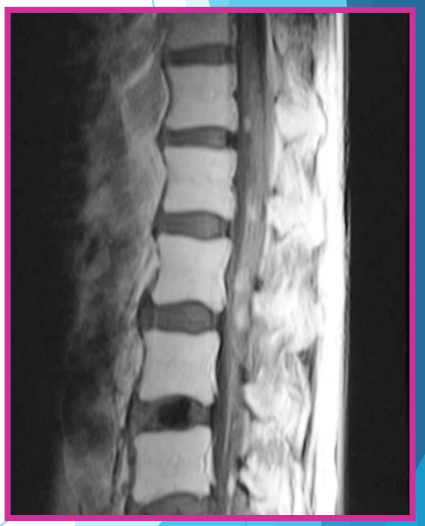


Step 2: Radiology = MRI

Radiological findings	Prevalence of radiological findings (*N* and %)
Leptomeningeal involvement	17/24 patients or 70.8%
Dural involvement	9/24 patients or 37.5%
Parenchymal involvement	10/24 patients or 41.7%

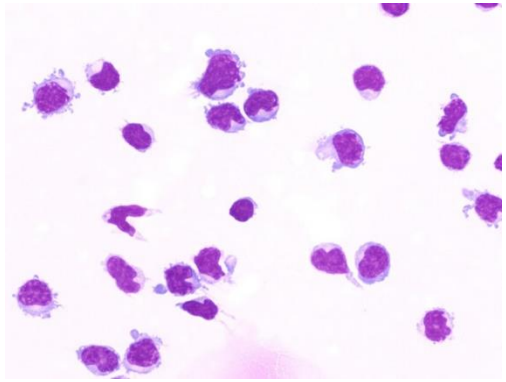


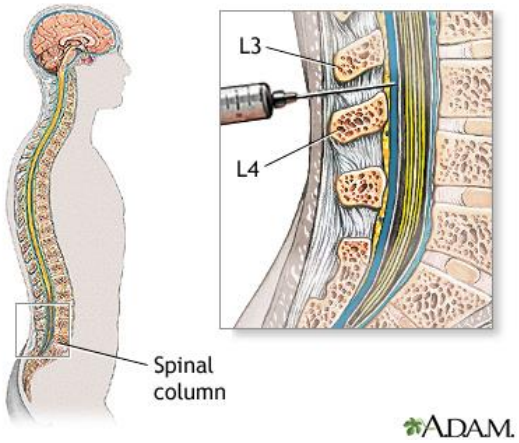




Fitsiori et al, European Radiology, 2018.
Imaging spectrum of Bing–Neel syndrome: how can a radiologist recognise this rare neurological complication of Waldenström's macroglobulinemia?

Step 3: lumbar puncture > cerebrospinal fluid (CSF)





- CSF analysis;
  - **Cell count (lymphocytosis)**
  - **Morphology**
  - **Total protein**
  - **Flow cytometry**
  - **Molecular testing**
    - *MYD88*^{L265P} mutation
    - VDJ rearrangement
  - Protein electrophoresis and immunofixation
- Brain or meningeal biopsy is rarely required

Therapy for BNS: CNS penetrating chemotherapy

Methotrexate

- ≥ 3 g/m²: cytotoxic conc in CSF, > 1 g/m2 in brain parenchyma, blood-CSF conc. 30:1

Cytarabine

- Intermediate to high dosing ≥ 2 g/m²

High dose intensive schemes as used in primary CNS lymphoma

Purine analogues

- Fludarabine
- Cladribine
- Bendamustine

- Pass blood brain barrier
- Can be damaging to nerves

Targeted Therapy

- BTK inhibitors cross the blood brain barrier
- Higher doses may be needed

Welcome to the

The Rory Morrison Registry

Rory Morrison

- WMUK is a unique not for profit organisation, also a registered charity, developed jointly to bring WM patients and medical professionals closer together to improve the treatment of WM
- Medical board of doctors treating WM in the UK together with patient representatives
- Annual WMUK doctor/ patient forums
- Point of contact for patients and families
- WMUK is also involved in patient advocacy at UK and EU levels
- We work closely with the IWMF, Lymphoma Action, Myeloma UK
- Develop and maintain links with Pharma companies

WMUK Projects

- Key role to put the UK on the map and participate in clinical trials of novel agents

- With support from patients and families, and that of other bodies such as the IWMF and Pharma we launched an ambitious funding package for
-
  - the **Rory Morrison Registry**

  - a **Biobank** at University College Hospital in London (jointly with the IWMF)

  - sponsorship of a **research projects**

Rory Morrison Registry (RMR)

- Increasing role for novel therapies in WM
- Important to capture '***real world data***' to establish the landscape of WM in the UK and to assess the impact of newer treatments
- Funding for the Rory Morrison Registry (RMR) project was made possible by generous donations to WMUK
- Demographics, diagnosis, treatment and patient reported outcomes (PRO)
- The RMR has been acknowledged as a valuable resource by NHS England's **Final Appraisal Determination for Ibrutinib for relapsed/refractory Waldenström's (2017): IBRUTINIB on CANCER DRUGS FUND (CDF)**

WMUK

UK Point of Contact for Waldenström's Macroglobulinemia

Reg. Charity no 1149692

The Rory Morrison Waldenström's Macroglobulinaemia UK Clinical Data Registry

www.wmuk.org.uk

e:info@wmuk.org.uk

The clinical registry of treatment outcomes for those with WM gathers information from any registered UK doctor treating WM so the disease may be better understood and treatment improved. WMUK is a unique charitable alliance of doctors, patients, nurses and carers fighting WM. The Registry is dedicated to the memory of founder member Rory Morrison, the much-loved BBC Radio 4 broadcaster who died in 2013. His former BBC colleague Charlotte Green is our Patron.

DENDRITE CLINICAL SYSTEMS

For technical support please email national-support@e-dendrite.com or call + 44 1491 411 288

Login

Register

Demonstration database only

Enter the live database here

The WM Registry has already received generous grant funding from the following, but more funding is welcome for its upkeep.

janssen

idera

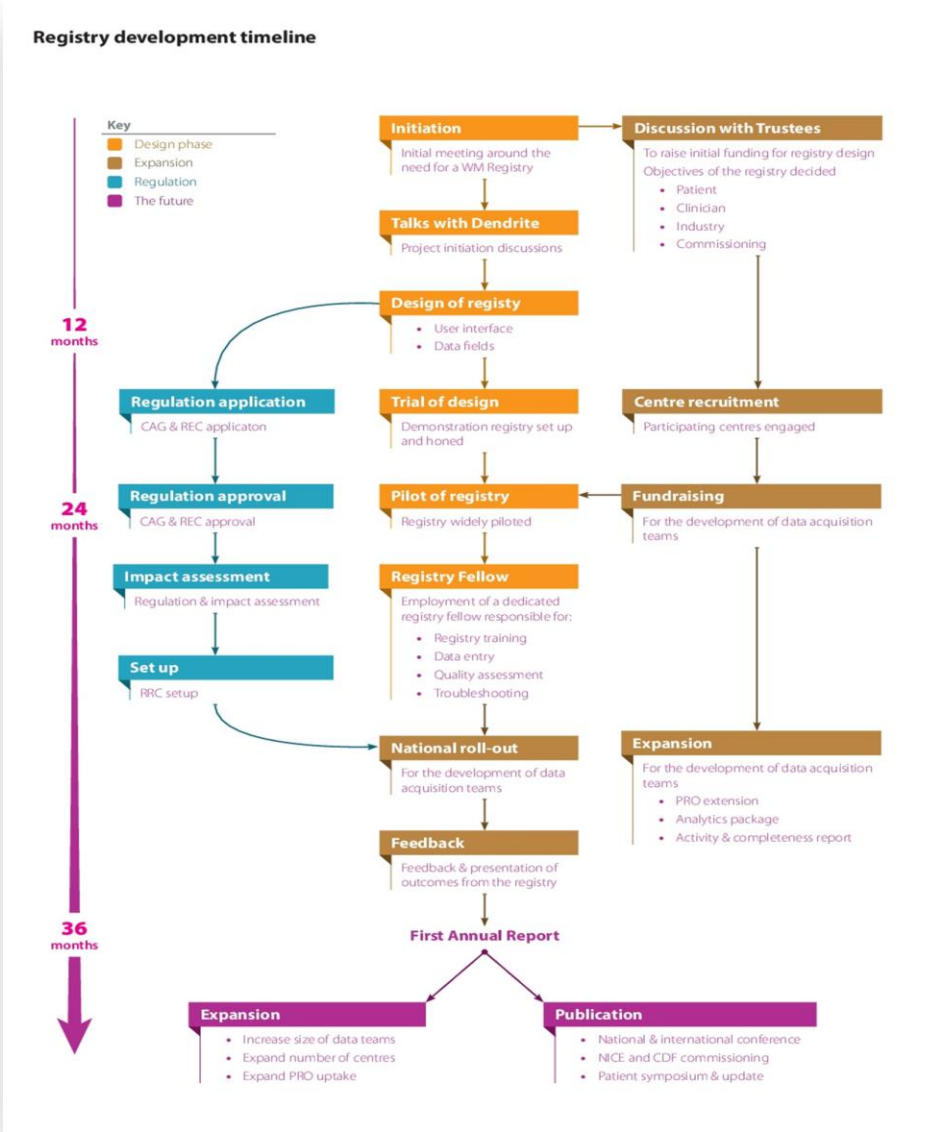
GILEAD

Advancing Therapeutics. Improving Lives.

Binding Site

Timeline

- The initial 12 month phase
  - defining the objectives of the Registry
  - designing the structure of the Registry
  - fundraising for the expansion of the Registry
- The second 12 month phase
  - obtaining regulatory and ethical approval
  - development of the data acquisition teams at the registered centres
  - Subsequent successful pilot at UCLH followed national rollout in January 2018



Data in the Registry

- In total 579 patients are currently registered from 19 hospitals; this includes 8 patients who have specifically signed up to the Patient Reported Outcomes extension despite their hospital not yet being registered with the Registry.

- In total 11 centres are formally registered, with 5 centres undergoing registration at present.

- So far 6 centres have regularly entered data; the remaining centres have been hampered by delays in local processing and resource allocation.

Demographics and diagnosis

- Traditionally, WM is perceived as a condition of elderly, Caucasian males.
- Findings from the Registry would suggest that there is a very significant younger population developing WM: over 35% were diagnosed in their thirties, forties or fifties.

- Similarly, the ratio of male : female patients was closer to 1.6 : 1 suggesting a very significant female population with WM or IgM associated condition.

- 51% of patients presented with symptoms of WM relating to paraprotein production (peripheral neuropathy, hyperviscosity or haemolytic anaemia) or lymphomatous related conditions such as anaemia, lymphadenopathy or B symptoms (fevers, night sweats and weight loss)

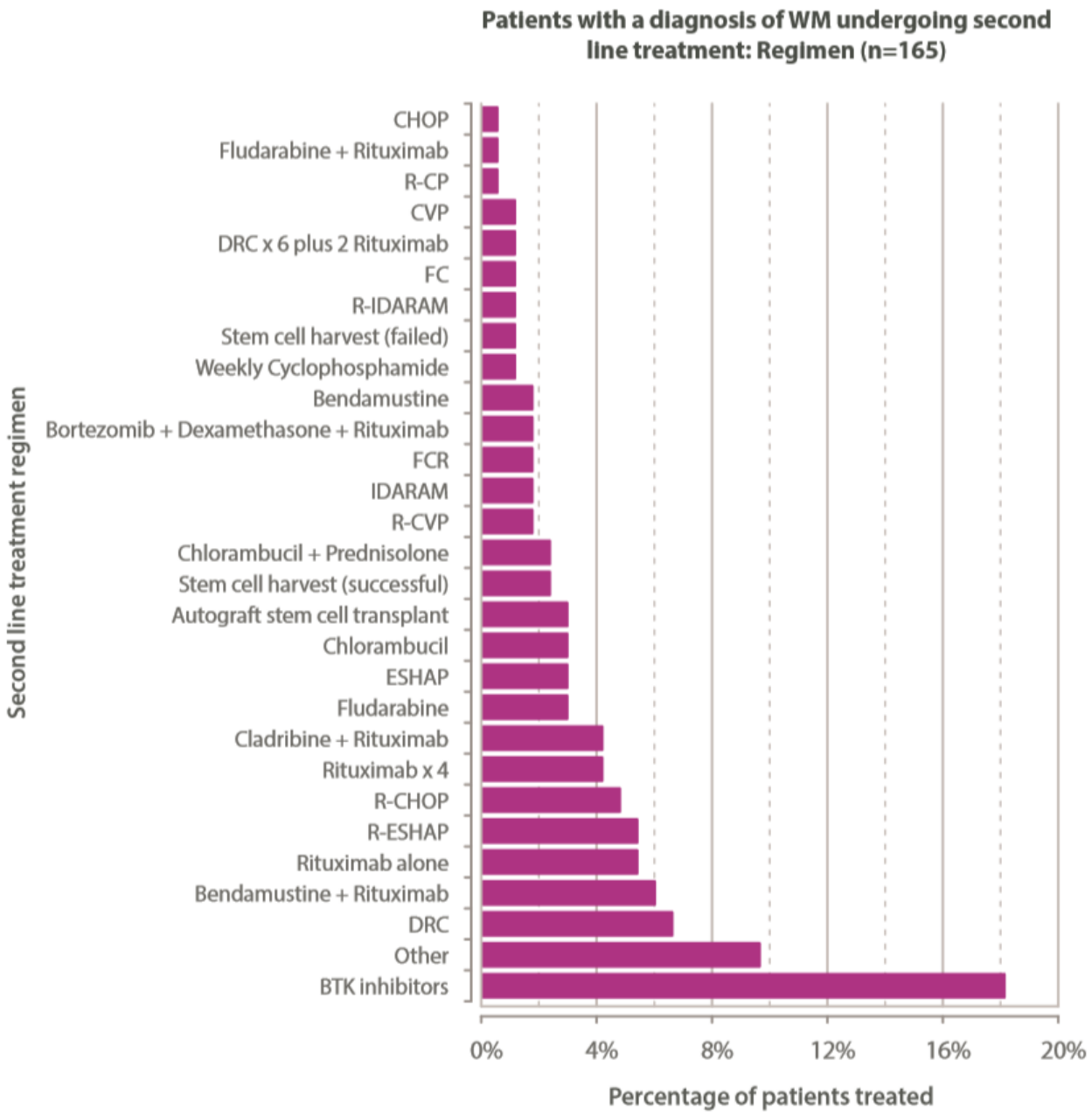
- The remaining 49% entered the active monitoring programme (watch and wait).

Treatment

- The time from diagnosis to treatment varies hugely (median 4 months, but ranging from months to years)
- Most strikingly is the variety of treatments (over 26) used as first line therapy and how these have changed with time.

Patients with WM undergoing first line treatment: treatment regimen

Regimen	Year of diagnosis							
	Not recorded	<2000	2000-2004	2005-2009	2010-2012	2013-2015	2016-2018	All
Allograft stem cell transplant	0	1	1	0	0	0	0	2
Bendamustine	0	0	0	0	0	1	1	2
Bendamustine + Rituximab	0	0	1	1	6	19	14	41
Bortezomib + Dexamethasone + Rituximab	0	0	1	0	2	0	1	4
BTK inhibitors	0	0	1	0	0	1	1	3
Chlorambucil	0	2	8	10	2	1	0	23
Chlorambucil + Rituximab	0	0	0	0	4	1	2	7
Chlorambucil and Prednisolone	0	0	0	2	0	0	0	2
CHOP	0	2	2	2	0	0	0	6
Cladribine + Rituximab	0	0	2	3	4	2	0	11
CP	0	0	0	0	1	0	0	1
CVP	0	0	1	0	2	1	0	4
DRC	1	0	4	6	12	19	9	51
DRC x 6 plus 2 Rituximab	0	0	0	3	5	6	3	17
FC	0	1	1	2	2	0	0	6
FCR	0	0	1	4	2	2	1	10
Fludarabine	0	2	0	1	0	0	0	3
Fludarabine + Rituximab	0	0	0	1	0	0	0	1
MATRIX	0	0	0	0	0	0	2	2
Other	0	4	5	8	6	15	4	42
R-CHOP	0	2	1	12	10	5	0	30
R-CP	0	0	0	1	2	3	0	6
R-CVP	0	0	0	2	7	1	1	11
Rituximab alone	0	0	0	0	1	3	1	5
Rituximab x4	0	0	1	6	5	6	3	21
Weekly Cyclophosphamide + Prednisolone	0	0	0	1	0	0	0	1
Unspecified	0	0	0	0	1	1	0	2
All	**1**	**14**	**30**	**65**	**74**	**87**	**43**	**314**


Patients with a diagnosis of WM undergoing second line treatment: Regimen (n=165)
Second line treatment regimen
CHOP
Fludarabine + Rituximab
R-CP
CVP
DRC x 6 plus 2 Rituximab
FC
R-IDARAM
Stem cell harvest (failed)
Weekly Cyclophosphamide
Bendamustine
Bortezomib + Dexamethasone + Rituximab
FCR
IDARAM
R-CVP
Chlorambucil + Prednisolone
Stem cell harvest (successful)
Autograft stem cell transplant
Chlorambucil
ESHAP
Fludarabine
Cladribine + Rituximab
Rituximab x 4
R-CHOP
R-ESHAP
Rituximab alone
Bendamustine + Rituximab
DRC
Other
BTK inhibitors
0%
4%
8%
12%
16%
20%
Percentage of patients treated

Outcomes

- Based on the Registry, median overall survival in patients presenting with symptomatic WM is 18.5 years and even longer in asymptomatic patients.

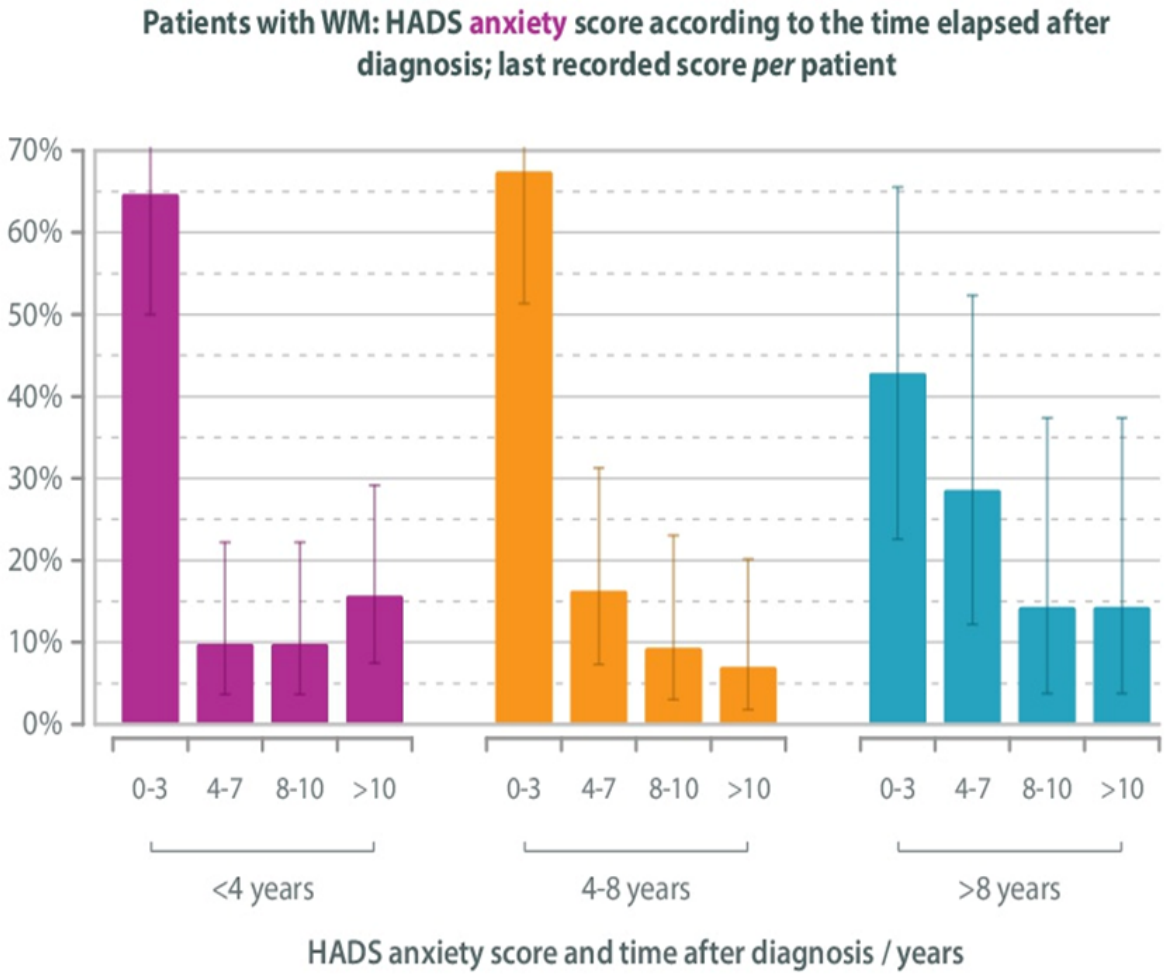
- This needs to be taken in the context of the data limitations, but would suggest a promising outcome for patients with WM, even for those who present symptomatically.

- Complications from WM such as high grade transformation have been noted in the analysis, but other complications, for example recurrent infections or treatment complications, will form part of a more comprehensive analysis of the Registry in the future.

Patient reported outcomes

- Health related Quality of Life (HrQoL) and Patient Reported Outcomes (PRO) are multi-dimensional concepts reflecting the physiological, psychological and social influences of the disease and its treatment from the patient's perspective.
- Quality of life in WM is of paramount importance due to its chronic relapsing nature, the lack of sufficient information regarding the personal impact of various chemotherapy treatments, and the paradigm shift offered by novel therapies, many of which are administered continuously until progression
- Since WM is chronic condition with an unpredictable course, the mental health of patients is of critical importance.
- The **Hospital Anxiety and Depression Score (HADS)** is a validated method to assess the prevalence of anxiety and depression. Scores between 8 and 10 suggest moderate anxiety and above 10 confirm a diagnosis of anxiety

The chart below demonstrates results from the HADS questionnaire received from 63 patients through both hand-written forms and online submission. Irrespective of time from diagnosis, anxiety can be present in between 10% and 20% of the population. This significant cohort may benefit from specific referral to cancer support services and psychological support.



- Planned expansion of the Rory Morrison Registry is currently underway to increase the number of centres registered and patients registered for the PRO extension.
- Continued updates to the Registry include capturing treatment complications and the role of supportive care.
- With further data entry and patient/centre registration the Registry will be used as a hypothesis generating tool alongside its surveillance and observational capabilities.
- The Registry is still in its infancy, but this first report demonstrates the potential of a the Rory Morrison Registry to truly capture the '*real world data*' and understand the landscape of WM in the United Kingdom for the benefit of patients.

Take home messages

- WM is a rare and very varied disease
- Confusing terminology – that confuses patients and doctors
- Most patients are at W+W stage
- Although incurable, generally responds very well to treatment
- Great progress being made with many new treatment options

This work is supported by grants from the International Waldenström's Macroglobulinemia Foundation (IWMF) and Waldenström's Macroglobulinaemia United Kingdom (WMUK) and the generosity and support of patients and their families, without who this project would not have been possible