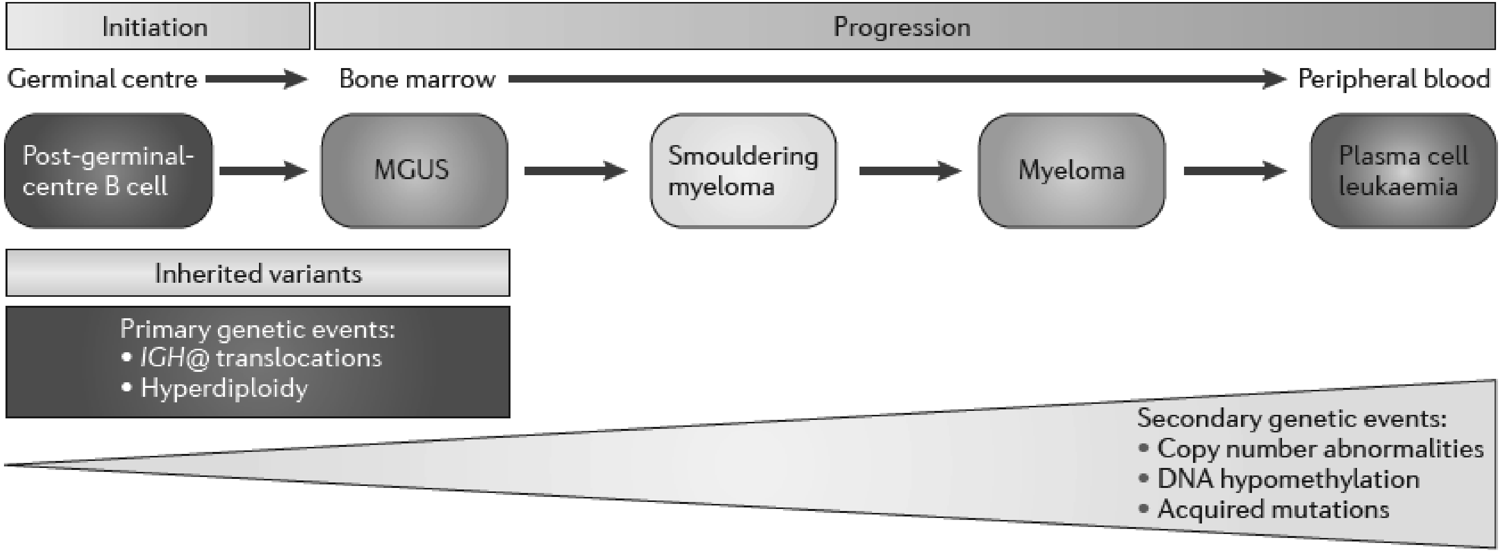
Division of Hematology/Oncology

Genomic Evolution – germinal B cell to MGUS/SMM/MM

Dr Brian Walker
bw75@iu.edu

September 8th 2021 IMW18

INDIANA UNIVERSITY SCHOOL OF MEDICINE



Initiation

Progression

Germinal centre → Bone marrow → Peripheral blood

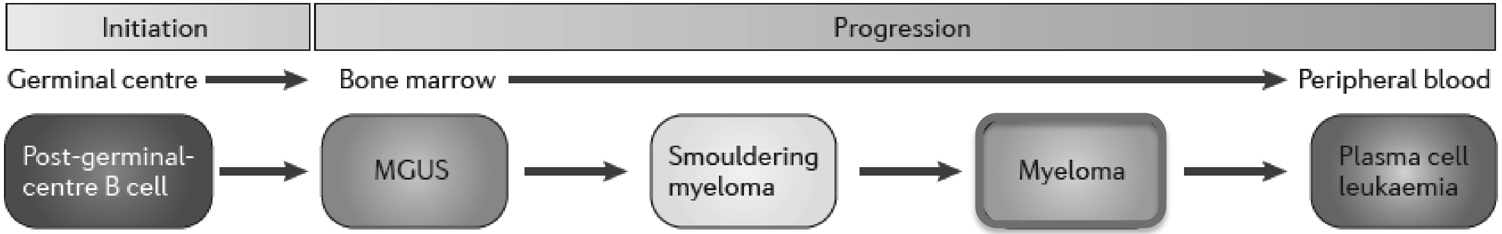
Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia

Inherited variants

Primary genetic events:
- *IGH@* translocations
- Hyperdiploidy

Secondary genetic events:
- Copy number abnormalities
- DNA hypomethylation
- Acquired mutations

Morgan, Walker & Davies *Nat Rev Cancer* 2012 **12**:335

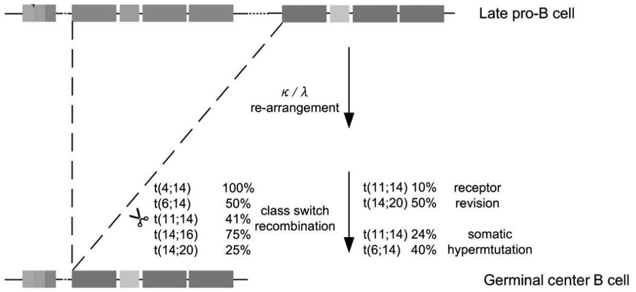


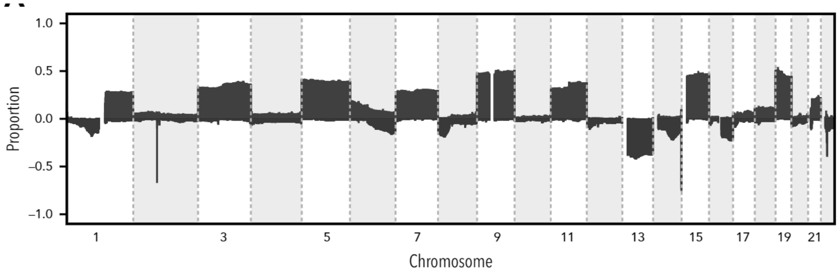
Initiation

Progression

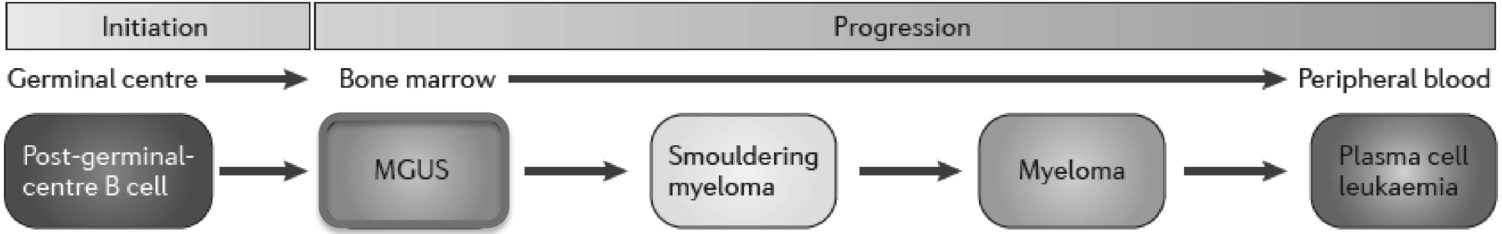
Germinal centre → Bone marrow → Peripheral blood

Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia





Morgan, Walker & Davies *Nat Rev Cancer* 2012 **12**:335



Initiation

Progression

Germinal centre → Bone marrow → Peripheral blood

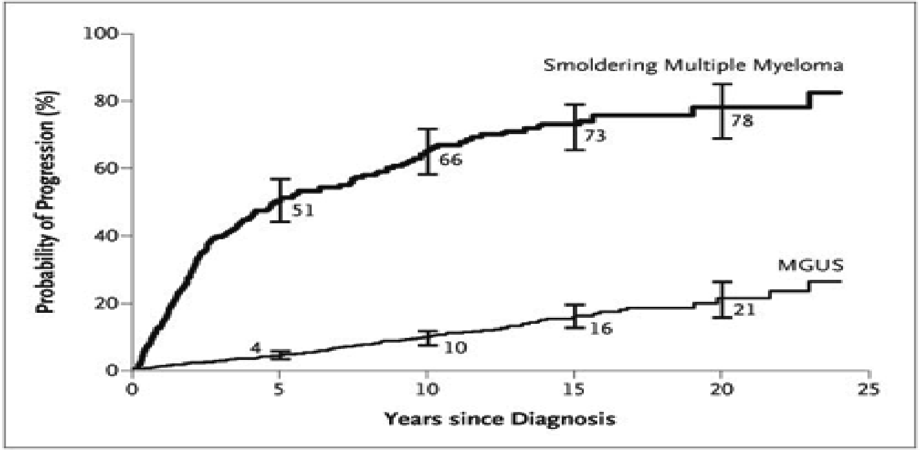
Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia

?

When does MGUS start?

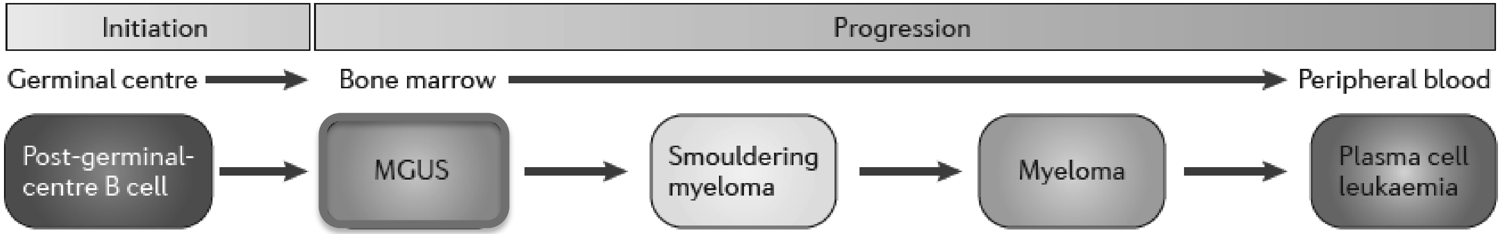
Examine mutation rates

Clock-like mutations correlate with age
Myeloma initiation at 20-30 years of age



Rustad et al. *Nat Commun 2020*

Kyle et al. *NEJM 2007*



Initiation

Progression

Germinal centre → Bone marrow → Peripheral blood

Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia

IGH translocations are present

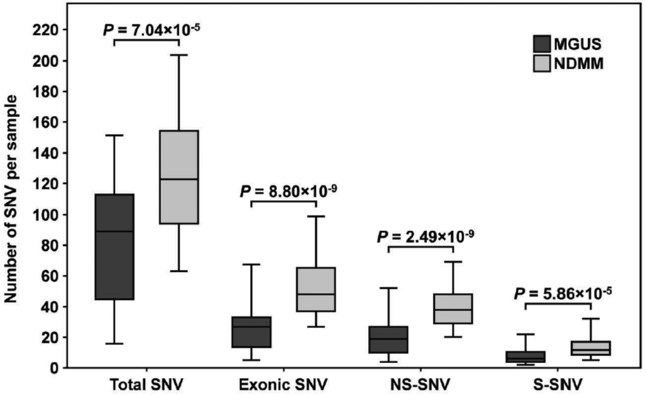
97% of patients have mutations

Mutations happen first, followed by CNAs

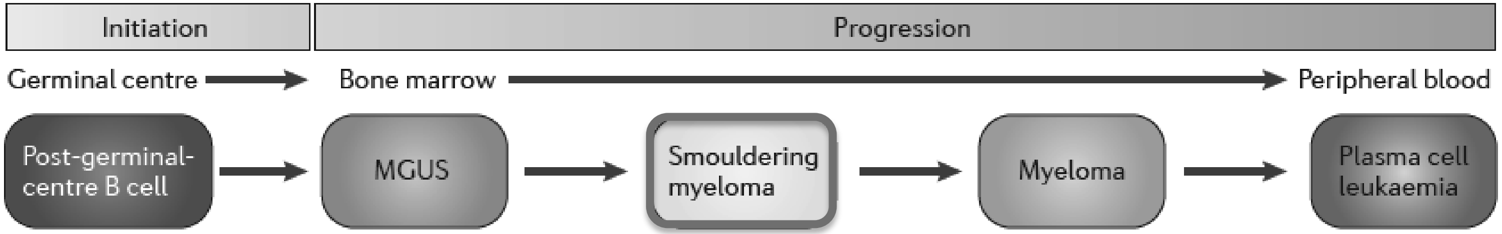
Common mutations can be present
KRAS, NRAS, DIS3, etc.

No biallelic deletions in TSGs.
CDKN2C, TP53, CYLD, BIRC2/3

No *TP53* mutations or *MYC* abnormalities



Mikulasova et al. *Haematologica 2017*

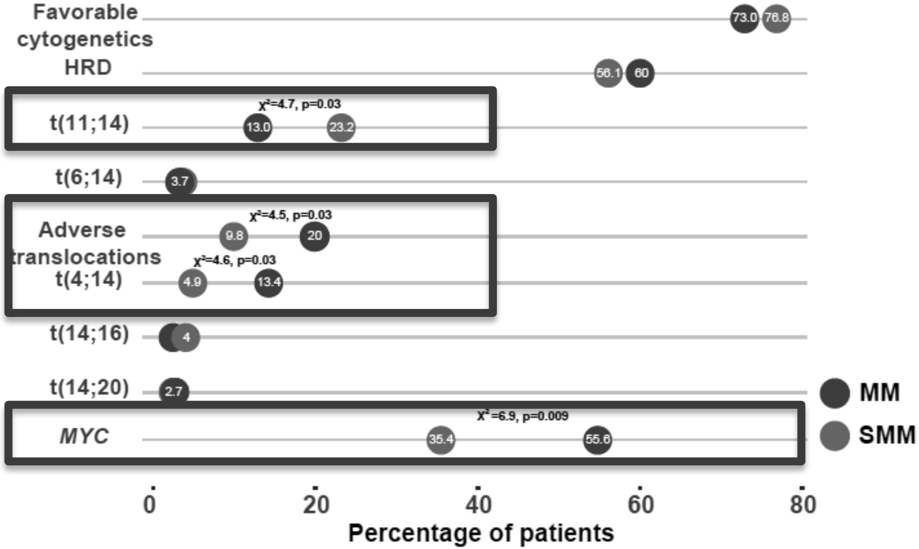


Initiation

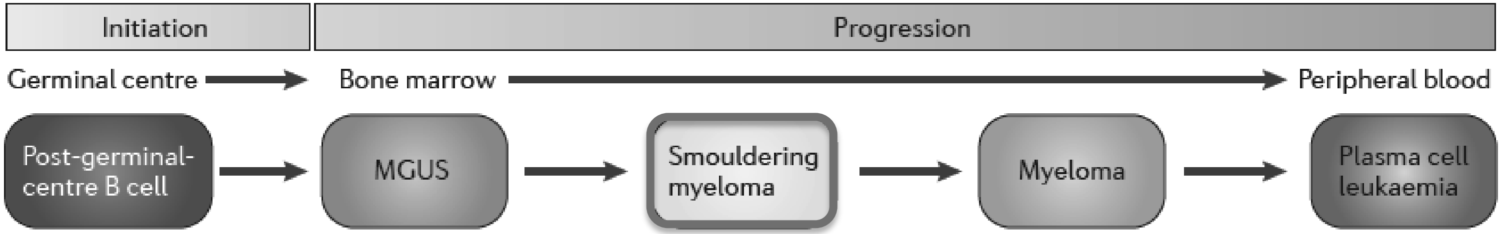
Progression

Germinal centre → Bone marrow → Peripheral blood

Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia



Boyle, Walker et al. Nature Commun. 2021

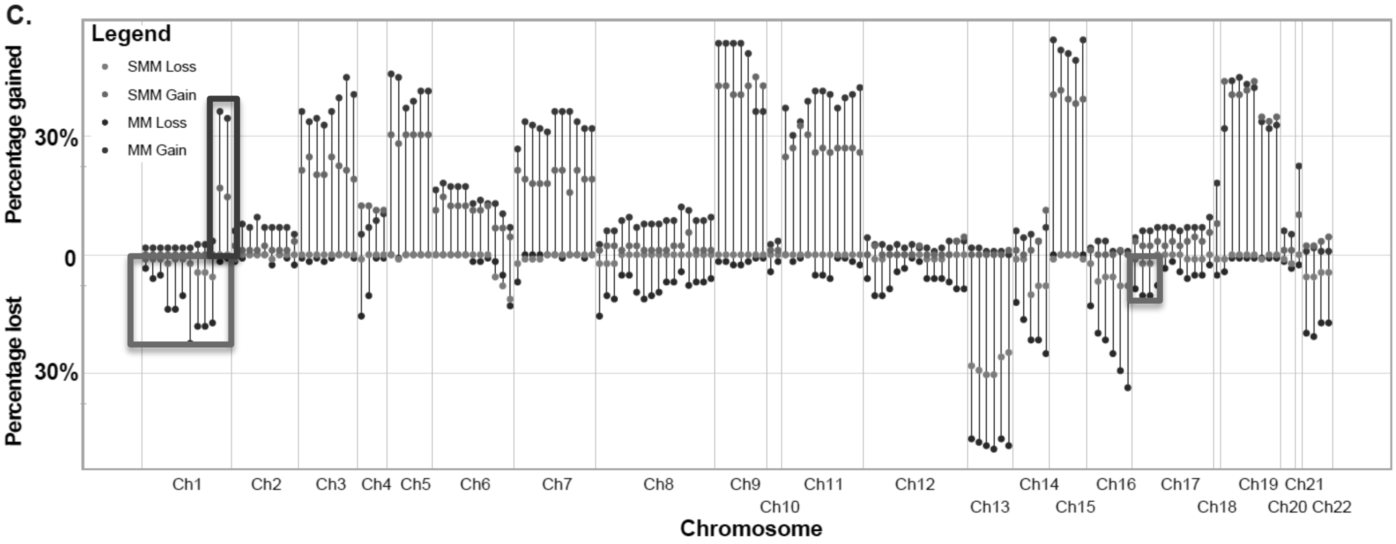


Initiation

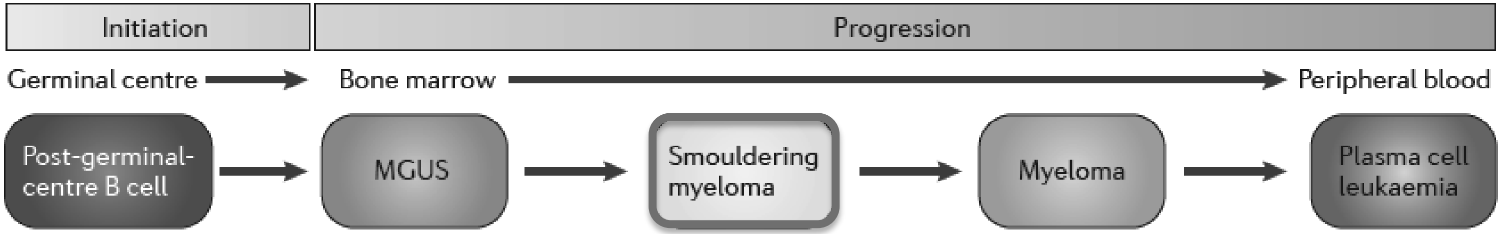
Progression

Germinal centre → Bone marrow → Peripheral blood

Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia



Boyle, Walker et al. Nature Commun. 2021

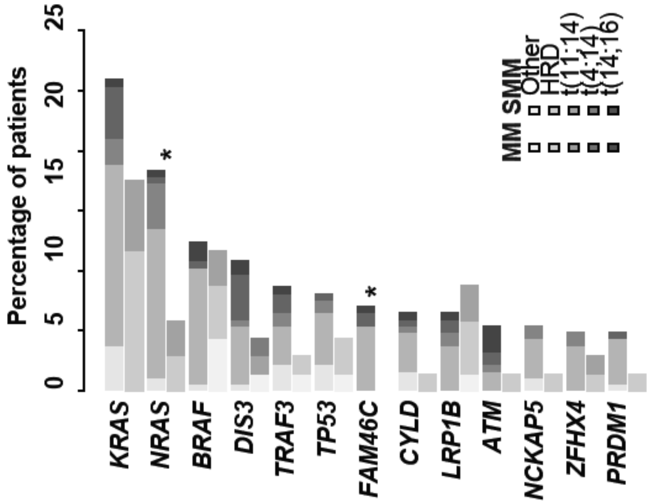


Initiation

Progression

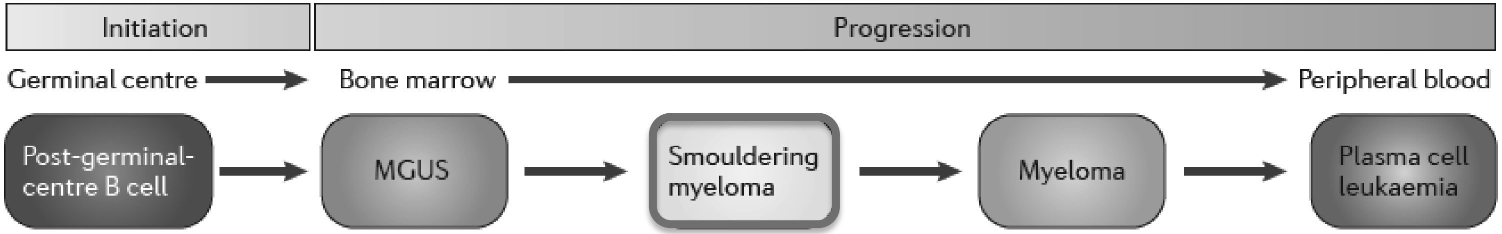
Germinal centre → Bone marrow → Peripheral blood

Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia



- *NRAS* and *FAM46C* mutations detected at significantly lower frequencies in SMM
- Mutations in *FAM46C* completely absent in SMM

Boyle, Walker et al. Nature Commun. 2021

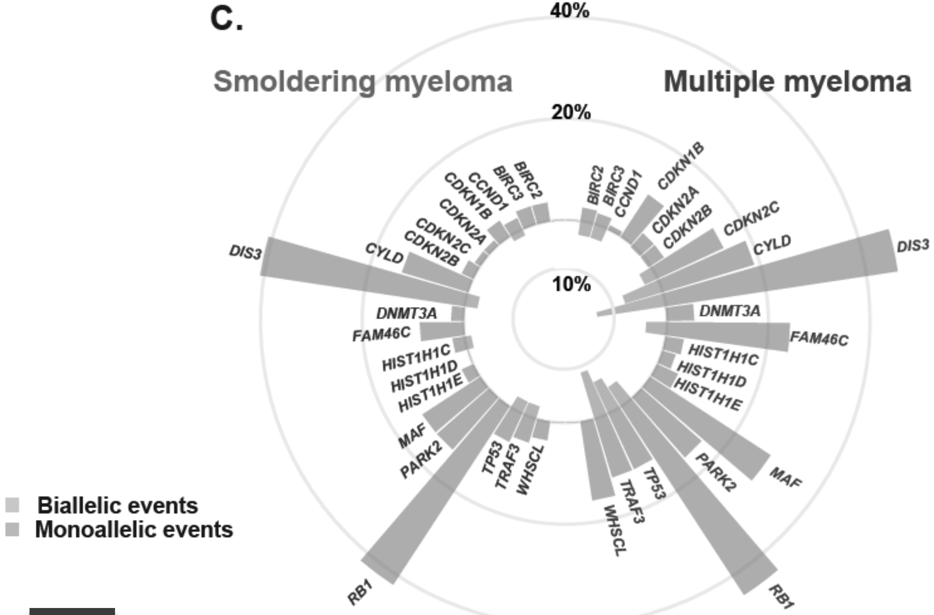


Initiation

Progression

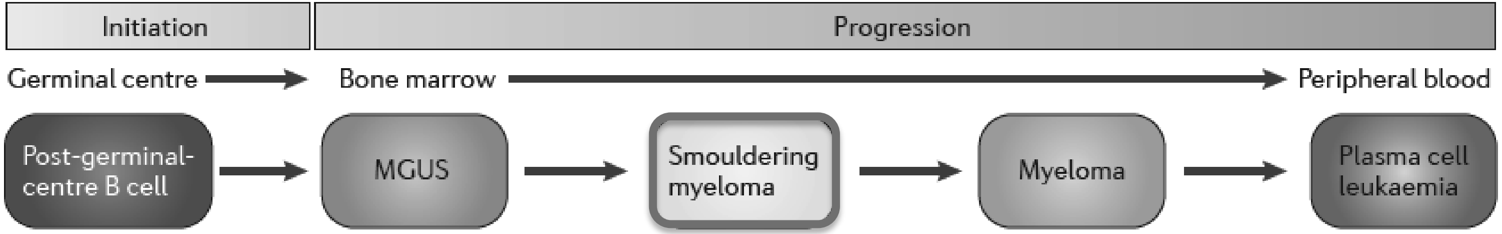
Germinal centre → Bone marrow → Peripheral blood

Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia



- Total of 103 (64/223 pts) biallelic events identified in MM, compared to 8 (8/82 pts) in SMM, $\chi^2=10.9$, p=0.001
- 1.2% SMM patients with Biallelic *TP53*, compared to 8.1% in MM
- 2% SMM with Biallelic *DIS3*, compared to 5% in MM
- Biallelic inactivation may be a hallmark mechanism in the transition to MM

Boyle, Walker et al. Nature Commun. 2021

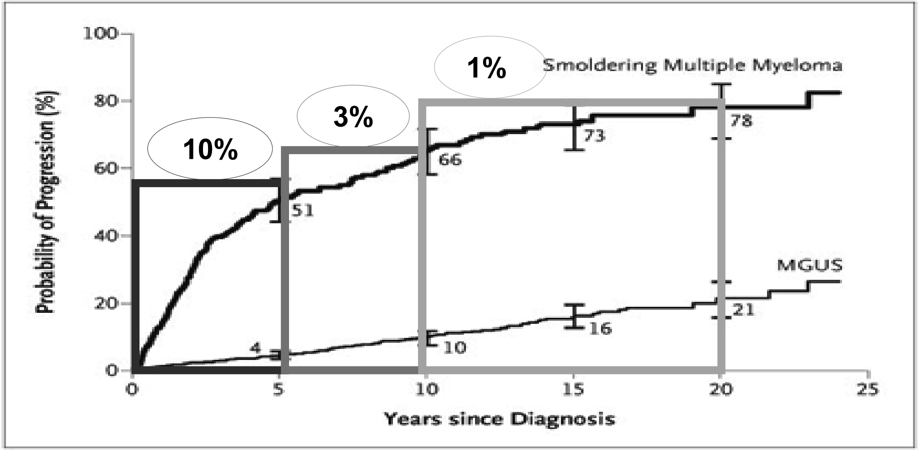


Initiation

Progression

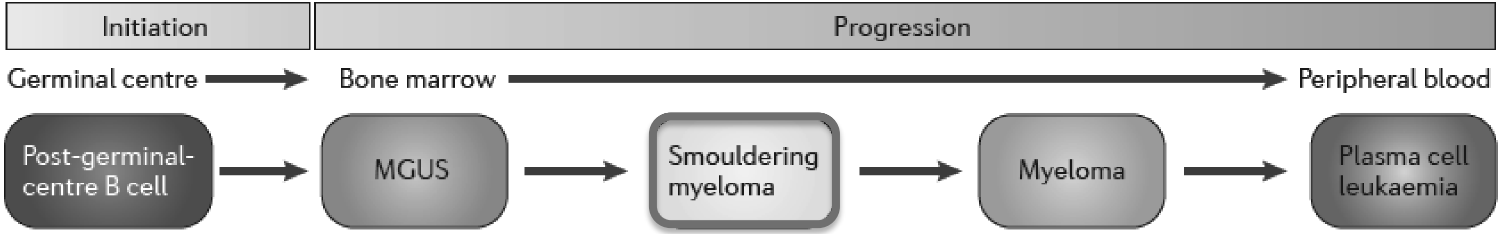
Germinal centre → Bone marrow → Peripheral blood

Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia



Are there any genomic risk factors predicting progression to active disease?

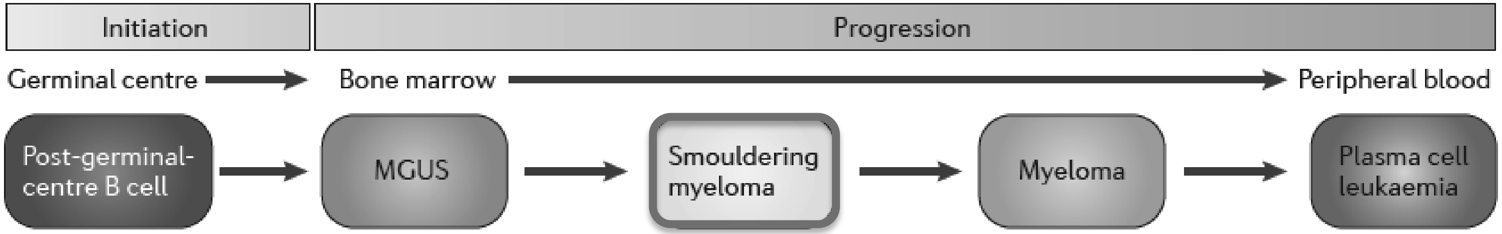
Kyle R. N Engl J Med 2007; 356:2582-90

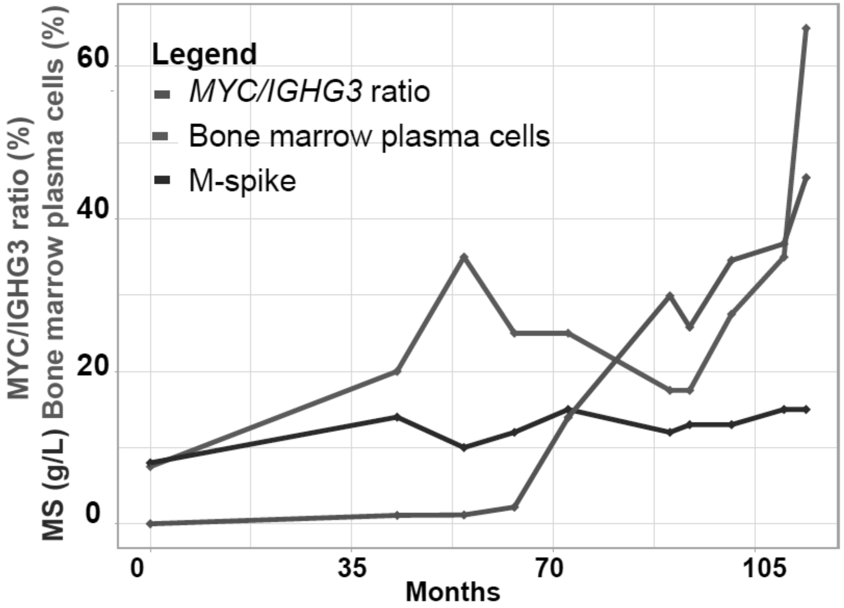


Markers associated with a short time to progression to MM

	Mutations	***CNAs***	***MYC***	***IMWG***
Boyle et al.	*KRAS*	del6q		+
Bustoros et al.	*KRAS/NRAS* *TP53/ATM/ATM*	Biallelic deletion	+	+
Misund et al	*DIS3*		+	

N.B. 1q+, del(1p), del(13q), etc. not associated with TTP





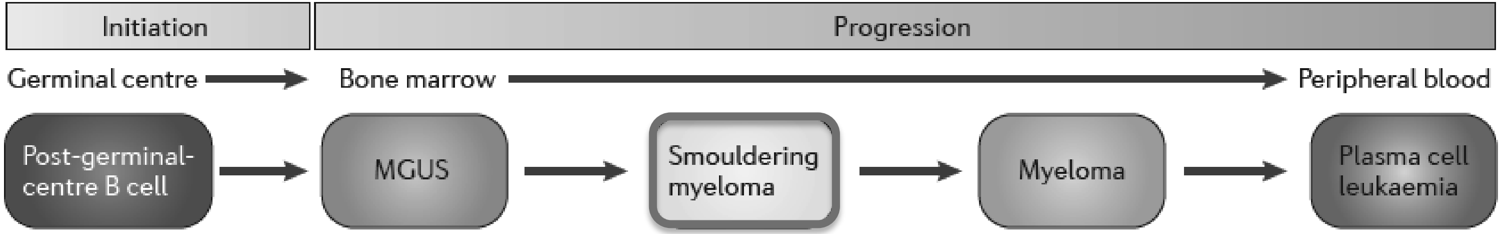
Detected at t(*MYC*) in one patient, >70 months after SMM diagnosis

Used digital PCR to determine the evolution of the t(*MYC*), compared to the V(D)J rearrangement

t(*MYC*) was undetectable at SMM diagnosis and appeared in a subclone (1%) 3 years later, has increased steadily over time and reached 45% of the tumor cells 8.2 years from diagnosis

Increase in t(MYC) clone coincided with an increase in bone marrow plasma cells

Boyle, Walker et al. Nature Commun. 2021



Initiation | Progression

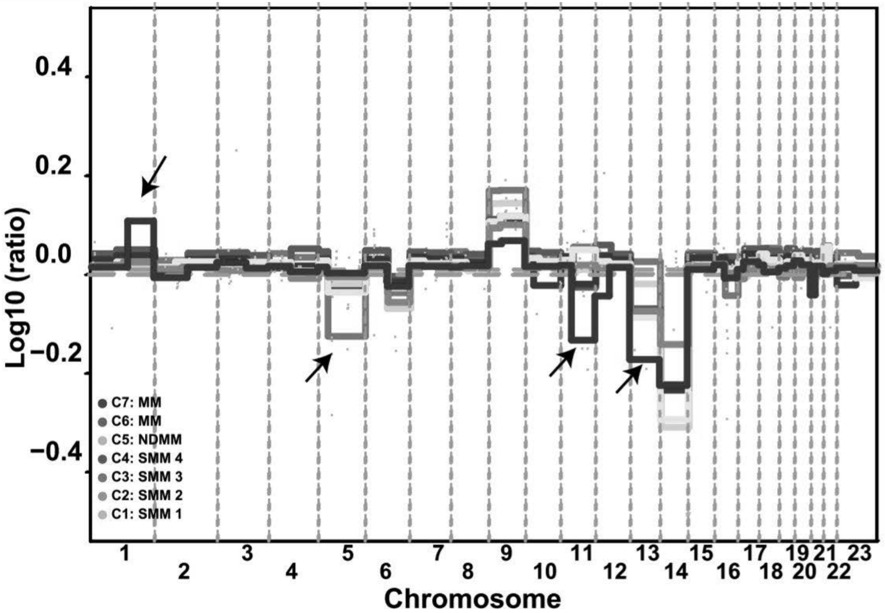
Germinal centre → Bone marrow → Peripheral blood

Post-germinal-centre B cell → MGUS → Smouldering myeloma → Myeloma → Plasma cell leukaemia

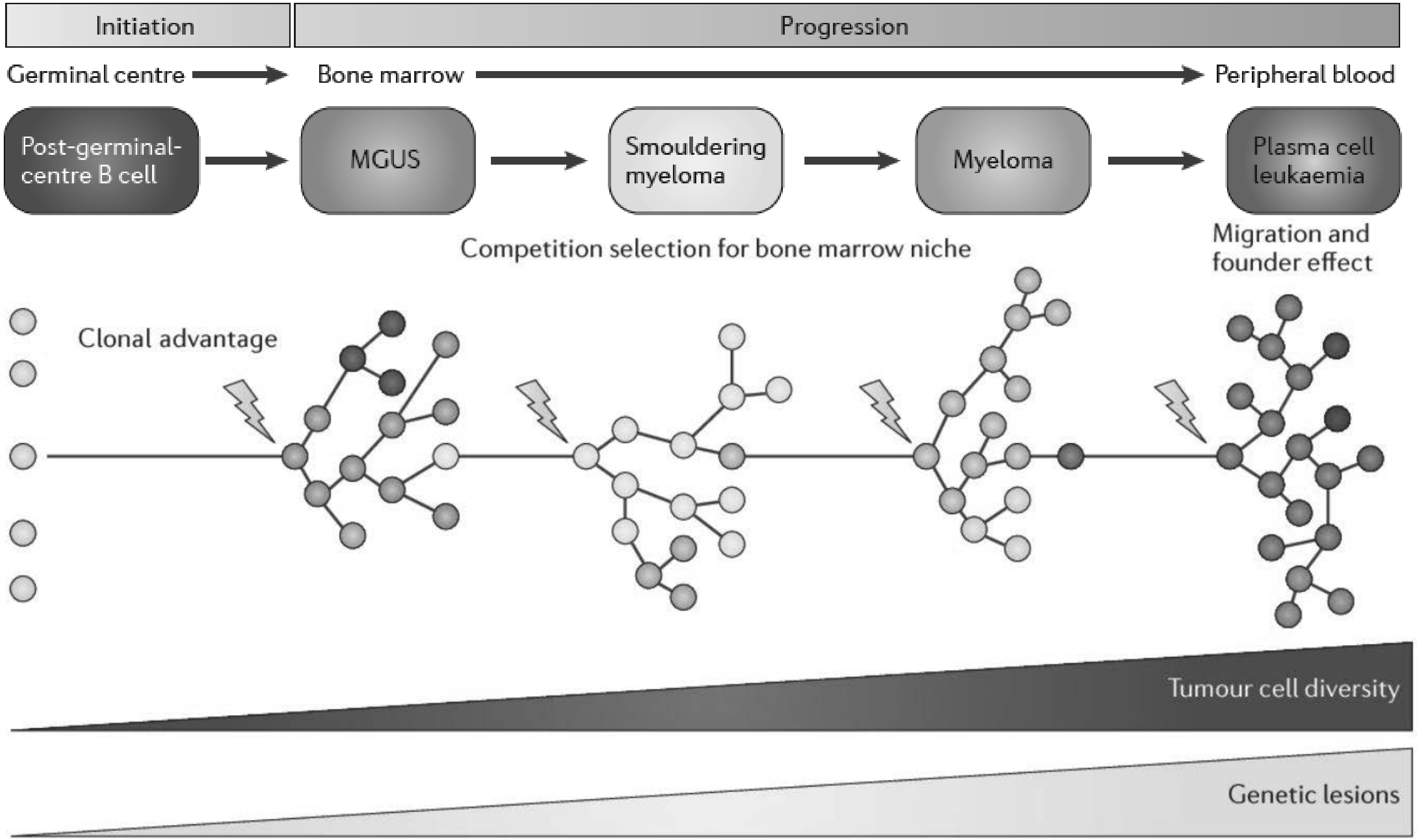
Serial analysis of samples from patients progressing from SMM to MM

Clonal dominance over time shows changes in copy number

SMM patients are not static and require regular monitoring for high-risk genomic markers.



Boyle, Walker et al. Leukemia. 2021


Initiation
Progression
Germinal centre
Bone marrow
Peripheral blood
Post-germinal-centre B cell
MGUS
Smouldering myeloma
Myeloma
Plasma cell leukaemia
Competition selection for bone marrow niche
Migration and founder effect
Clonal advantage
Tumour cell diversity
Genetic lesions

Sabine Wenzel
Parvathi Sudha
Enze Liu
Nathan Becker

Rafat Abonour
Mohammad Abu Zaid
Fabiana Perna
David Roodman
Attaya Suvannasankha
Melissa Stanley

UAMS

Aneta Mikulasova
Eileen Boyle

Ruslana Tytarenko
Purvi Patel
Shayu Deshpande
Cody Ashby
Chris Wardell

Bart Barlogie

NYU

Faith Davies
Gareth Morgan

LEUKEMIA & LYMPHOMA SOCIETY®