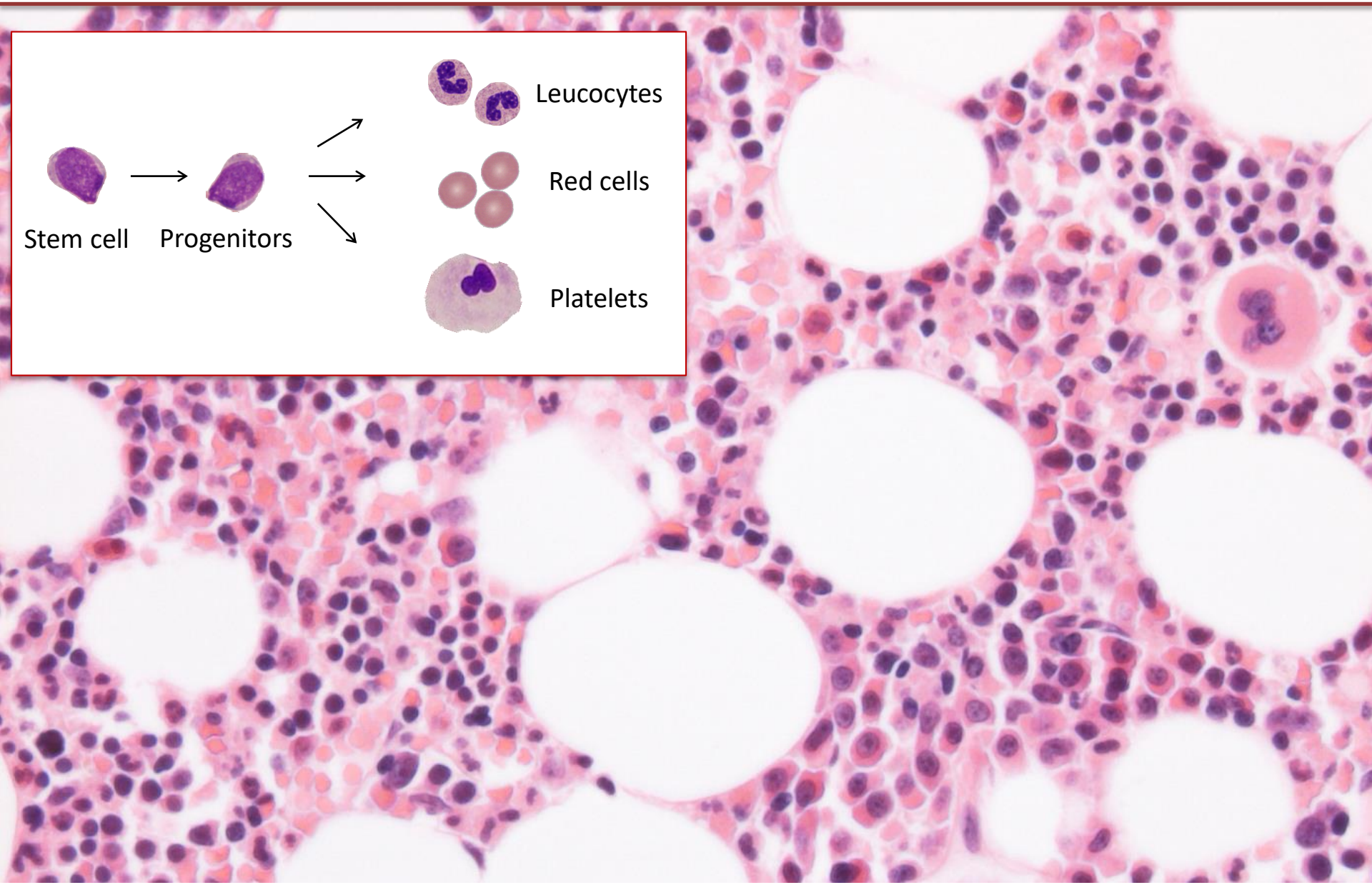
Towards personalised medicine in blood cancers

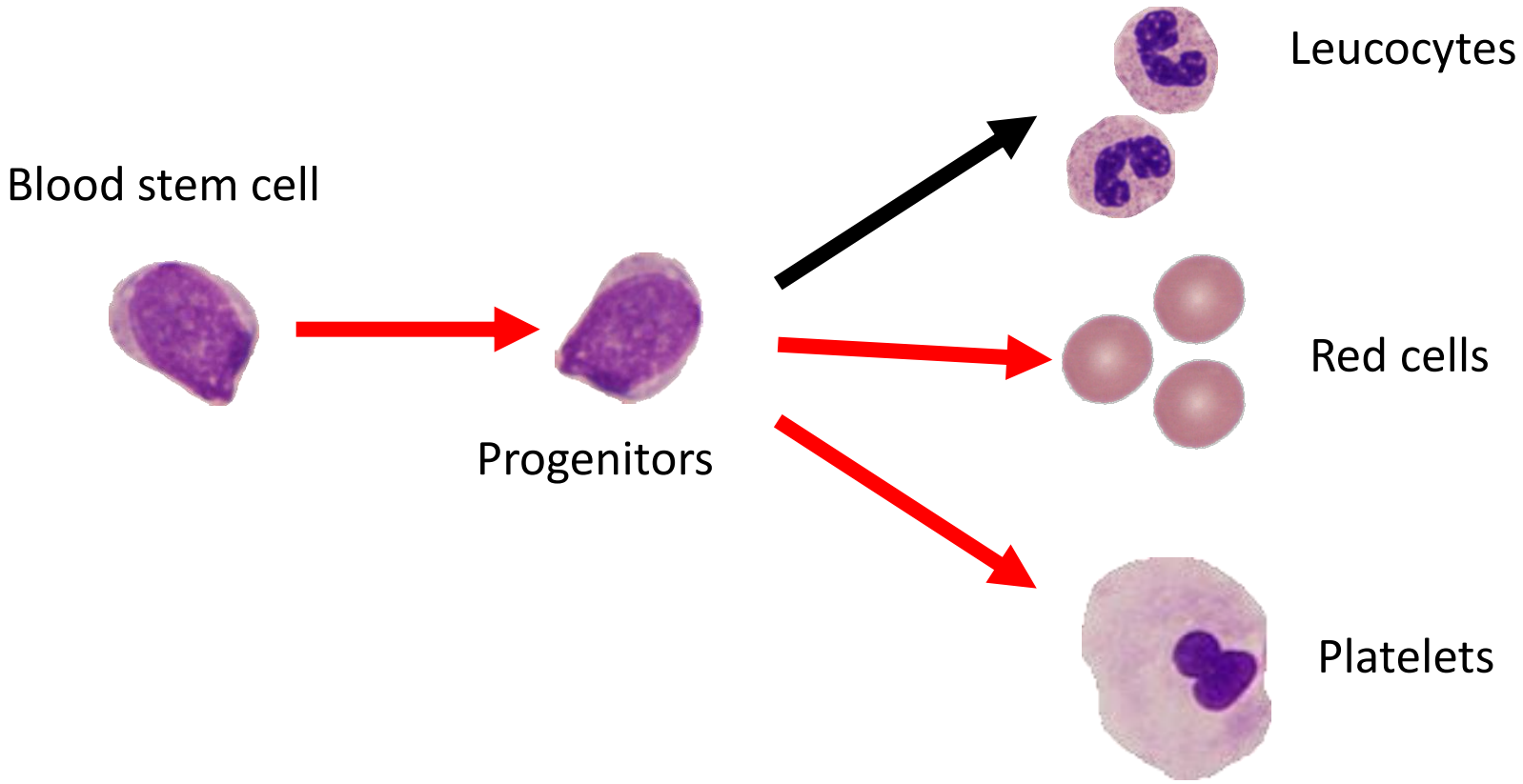
wellcome sanger institute

Jyoti Nangalia
CRUK Clinician Scientist

Haematopoiesis

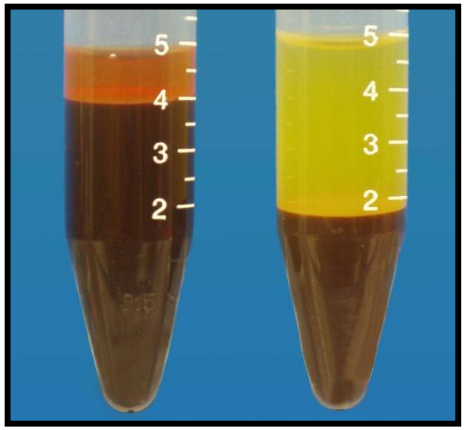


Myeloproliferative neoplasms

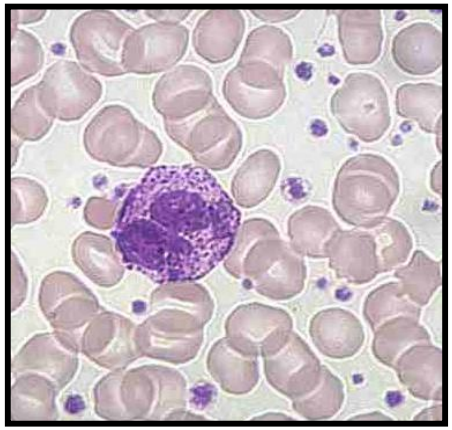


Myeloproliferative neoplasms

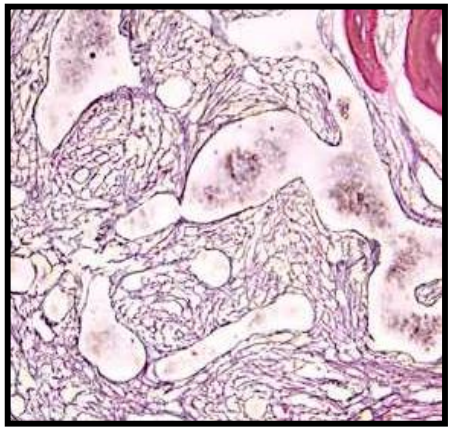
PV



ET

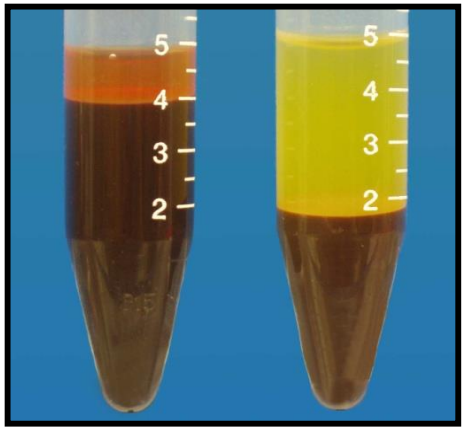
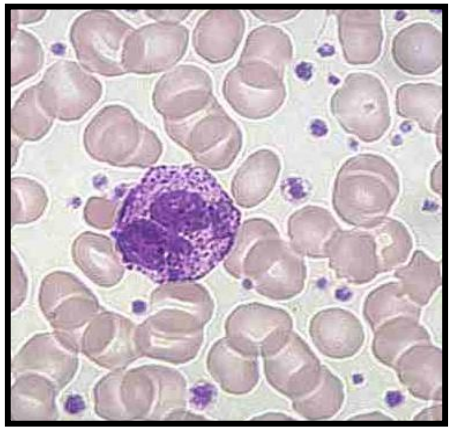
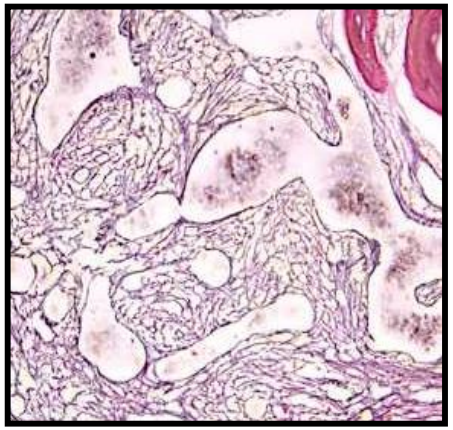


MF



- Prevalence in UK ~30,000
- Window on earliest stage of tumorigenesis
- Tractable – accessible tissue, chronic diseases, clonal analysis

Myeloproliferative neoplasms – *JAK2* mutations in majority

PV	ET	MF
		
JAK2: 98%	50-60%	50-60%

2005 → 2010

Identification of JAK2 mutation

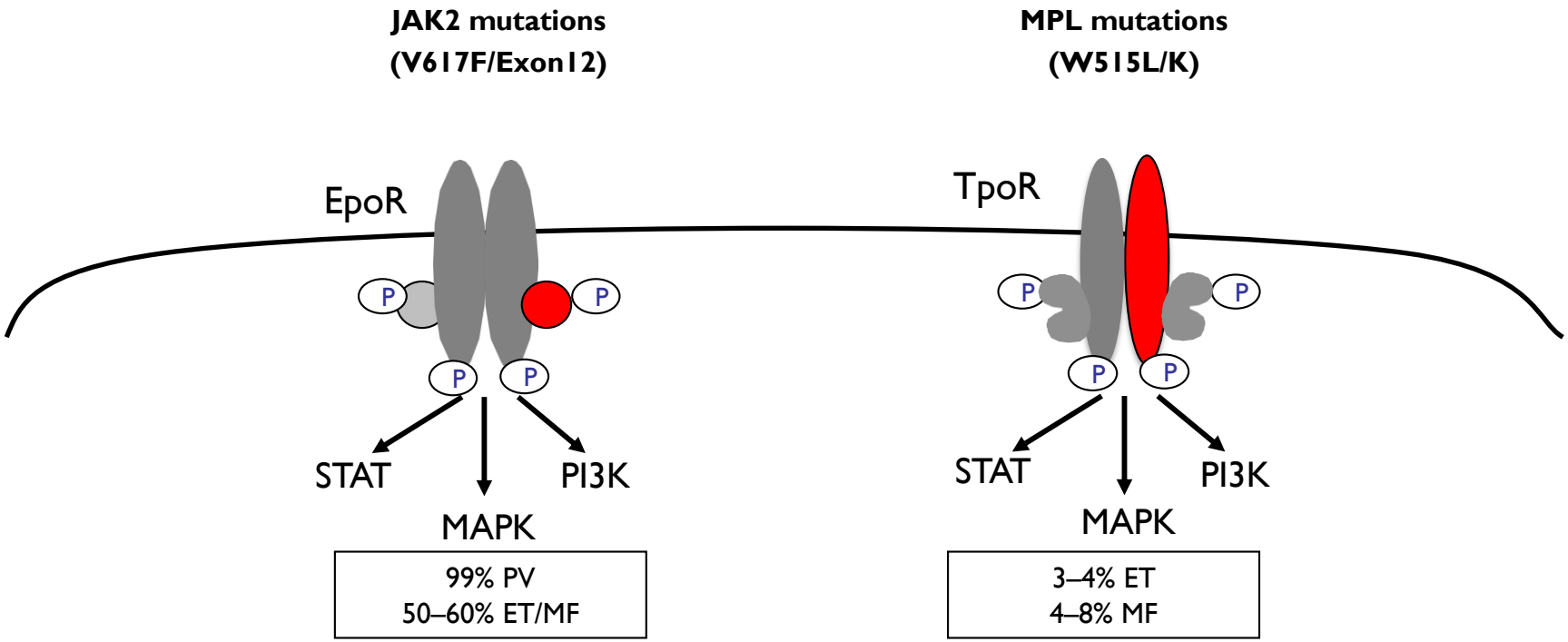
Recognition of new disease subtypes

Molecular testing in regional diagnostic service

Therapeutic JAK2 inhibitors

James et al, 2005; Baxter et al, 2005; Kralovics et al, 2005; Levine et al, 2005

Aberrant JAK/STAT signaling central to MPN



- Genome wide data lacking
- ? Pathogenic mechanism of 50% of ET and MF

James et al 2005; Levine et al 2005; Baxter et al 2005; Kralovics R, et al. *Blood* 2005;106:3374–3376; Scott et al 2007; Pikman Y, et al. *PLoS Med* 2006;3:e270; Beer et al 2008; Boyd et al 2010; Oh et al 2010; Lasho TL, et al. *N Engl J Med* 2010;363:1189–1190; Pardanani A, et al. *Leukemia* 2010;25:218–225; Sanada et al 2009; Grand et al 2009

Myeloproliferative neoplasms

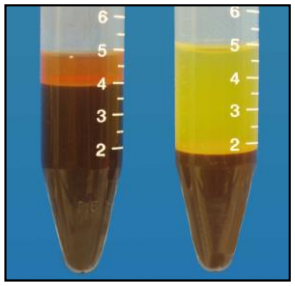
Disease specific challenges

- ***JAK2*** ^{V617F} in 95% PV but only 50% of ET and MF
- Genetic basis of disease was unknown in half of patients
- Clinical heterogeneity and overlap between subtypes
- Variable survival and disease progression unpredictable

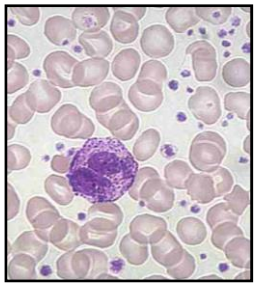
General challenge

- "How long have I had it for?" question

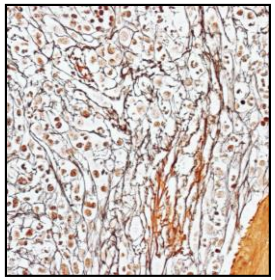
Polycythaemia vera (PV)



Essential thrombocythaemia (ET)



Myelofibrosis (MF)



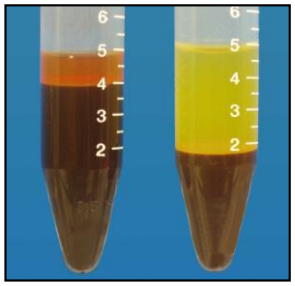
Clonal dynamics in myeloproliferative neoplasms

1. Detecting novel driver mutations

2. Integrating genomic and phenotypic heterogeneity to build a personalised outcome predictor

3. Studying the dynamics of clonal expansions in MPNs at the stem cell level

Polycythaemia vera (PV)



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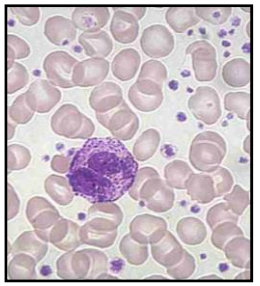

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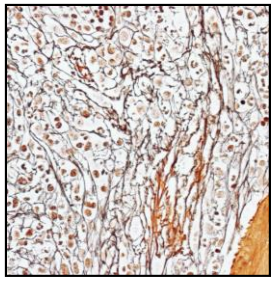
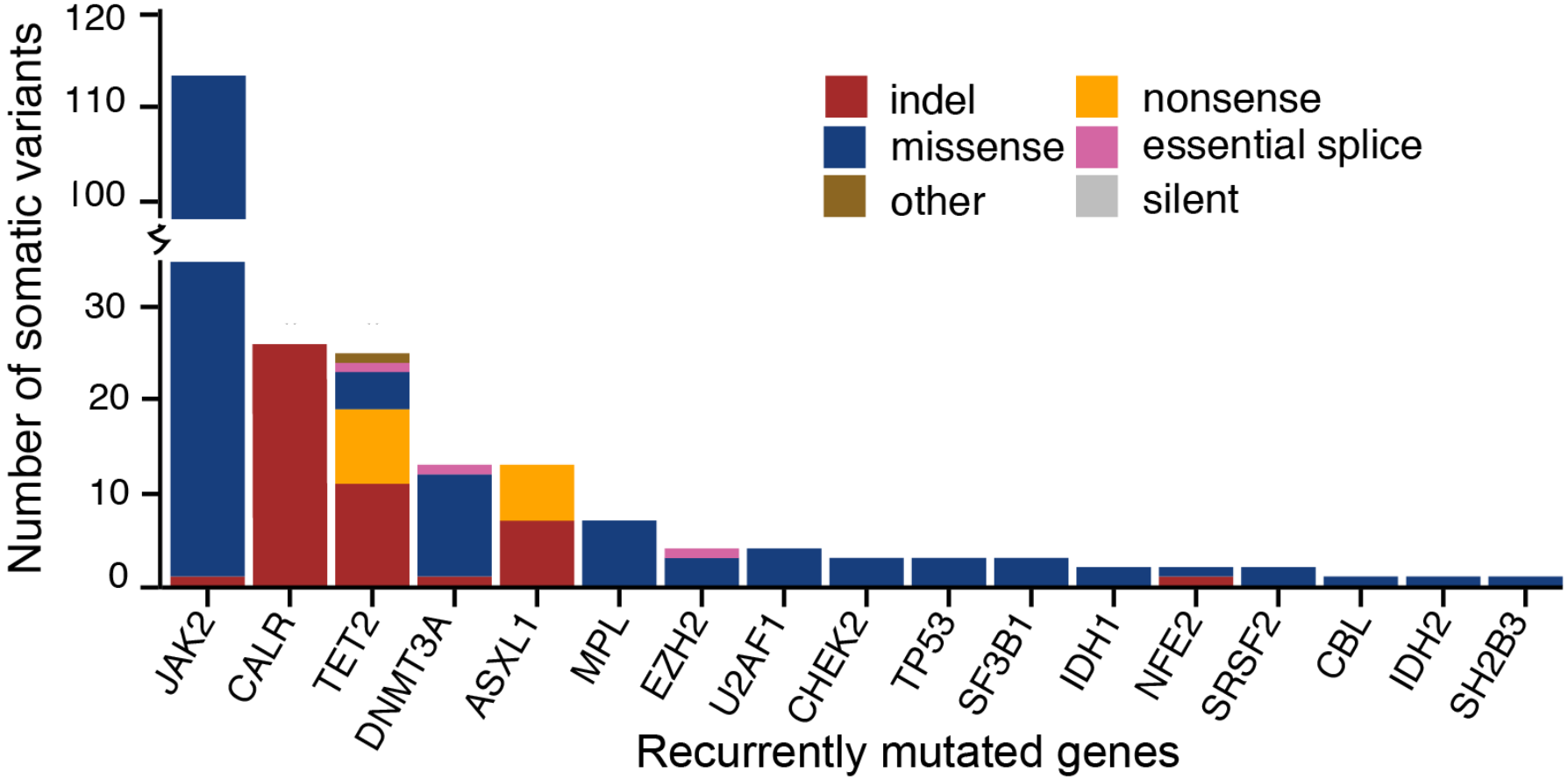


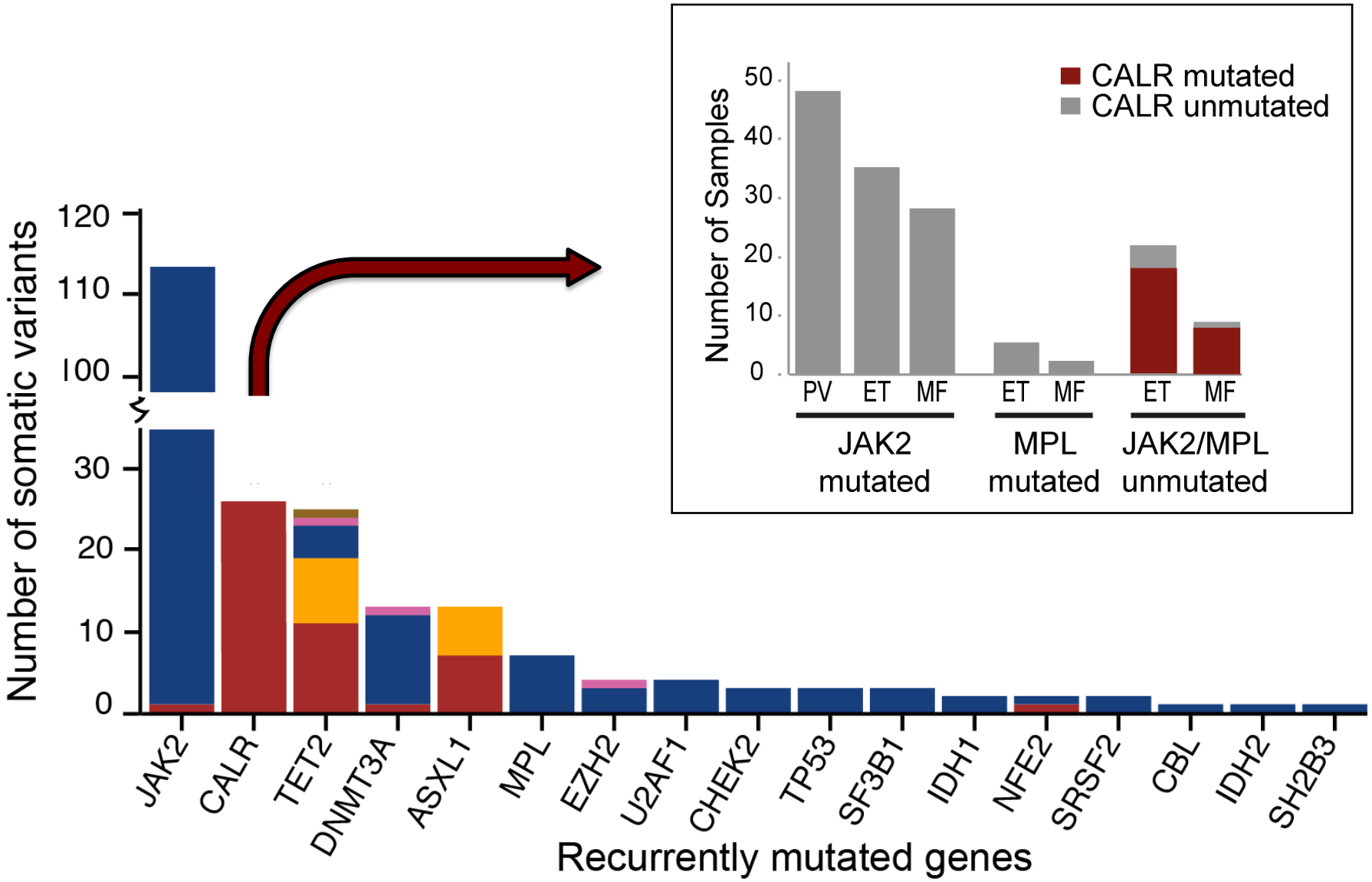
Nangalia and Massie *et al,* NEJM 2013; Grinfeld and Nangalia *et al*, NEJM 2018

Genomic heterogeneity in MPNs

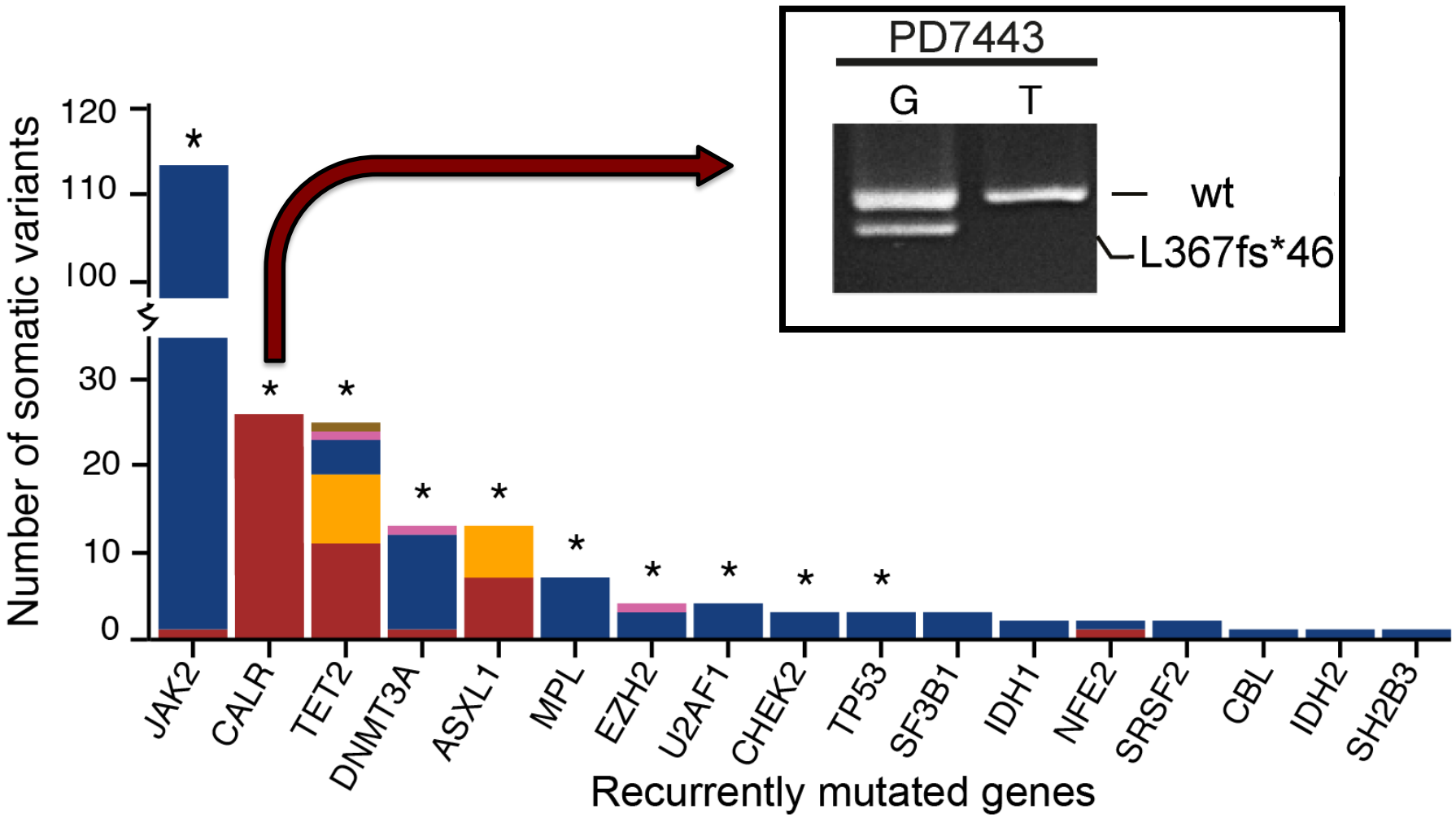
Whole-exome sequencing of tumour/normal matched pairs from 151 MPN patients



CALR mutations in the majority of *JAK2*-unmutated MPNs

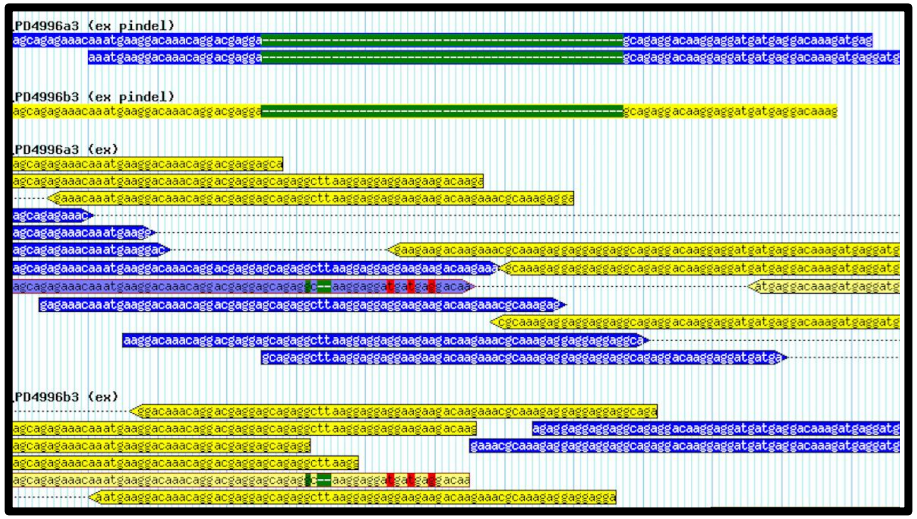


CALR mutations are somatically acquired

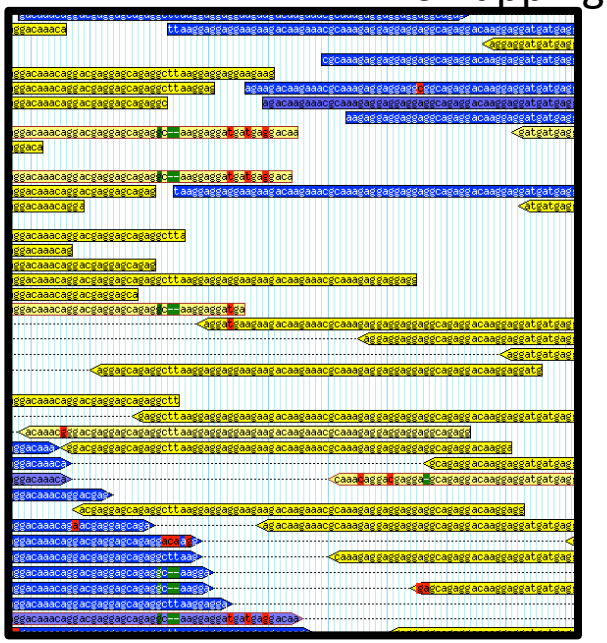


Difficulties detecting *CALR* mutations

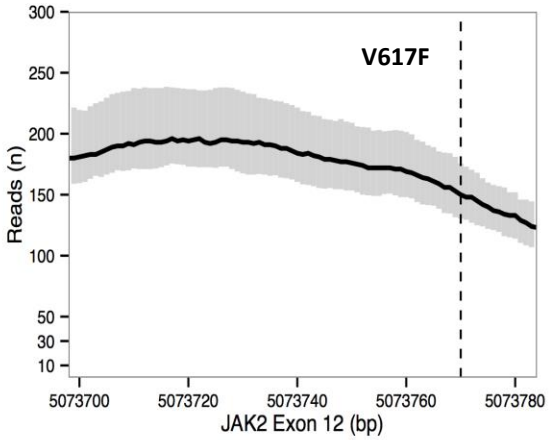
Buccal

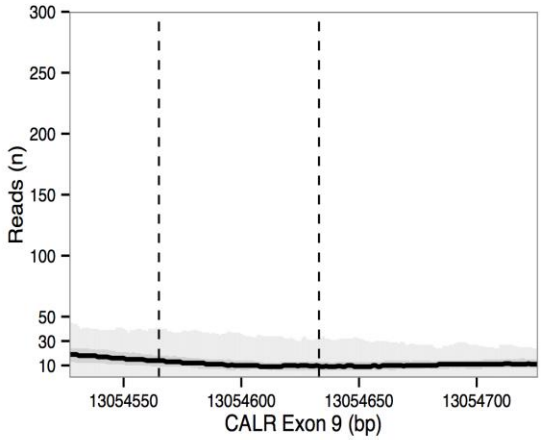


Mismapping

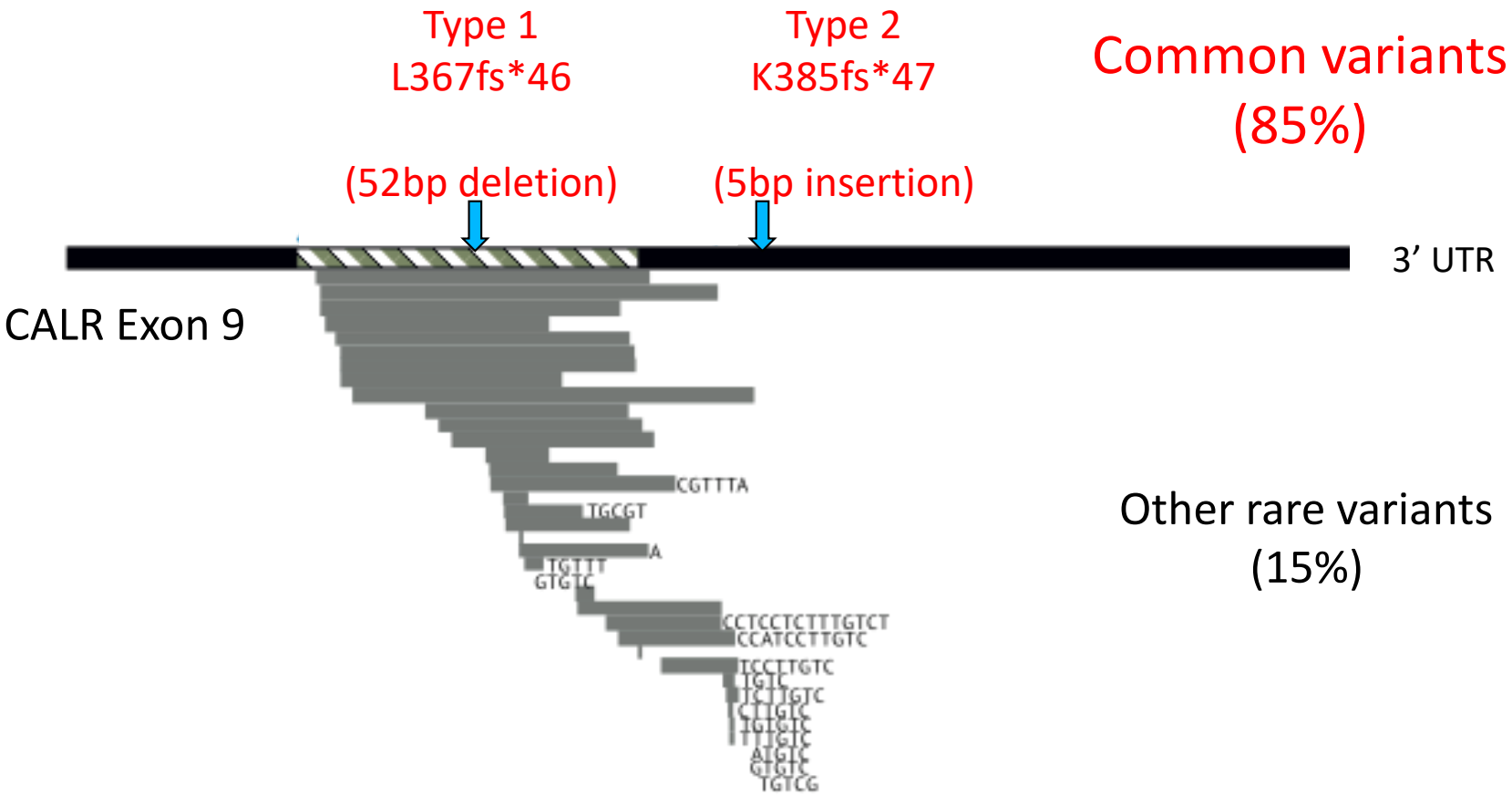


Low coverage





How do CALR mutations drive MPNs?



Nangalia et al NEJM 2013

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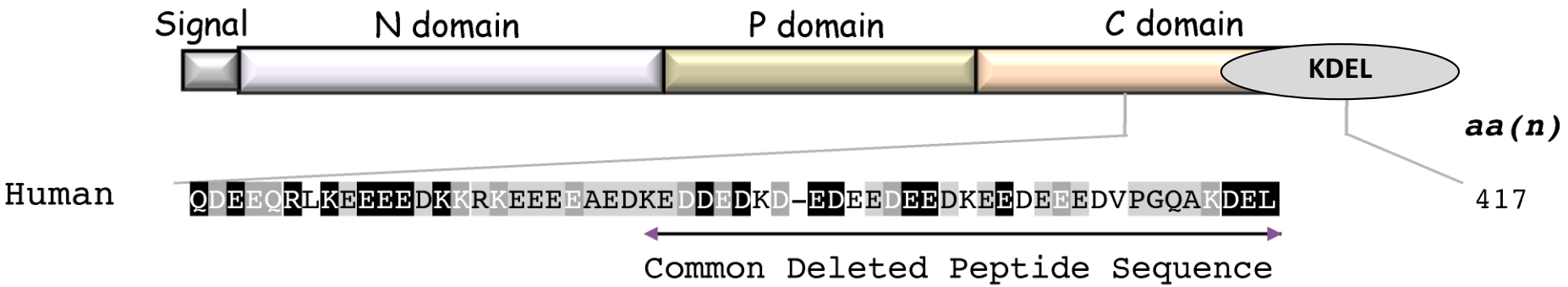


Common Novel Peptide Sequence

Deletions

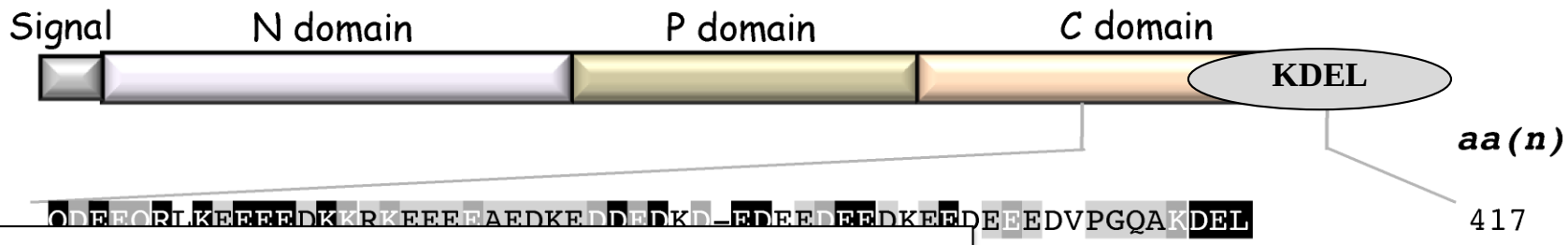
L367fs*46	QDEE	QRTRRMMRTKMRMRRMRRTRRKMRRKMSPARPRTSCREACLOGWTEA	411
E370fs*43	QDEEQRLKE	VMRTKMRMRRMRRTRRKMRRKMSPARPRTSCREACLOGWTEA	411
E370fs*48	QDEEQRLKE	QRTRRMMRTKMRMRRMRRTRRKMRRKMSPARPRTSCREACLOGWTEA	416

Insertions

K385fs*47	QDEEQRLKEEEEDKKRKEEE EAED (NC)	RRMMRTKMRMRRMRRTRRKMRRKMSPARPRTSCREACLOGWTEA	430
K385fs*47	QDEEQRLKEEEEDKKRKEEE EAED (LC)	RRMMRTKMRMRRMRRTRRKMRRKMSPARPRTSCREACLOGWTEA	430

Nangalia et al NEJM 2013

How do CALR mutations drive MPNs?



Human ...EDVPGQAKDEL 417

...ide Sequence

...el Peptide Sequence

Del

L36... RKMSPARPRTSCREACLOGWTEA 411

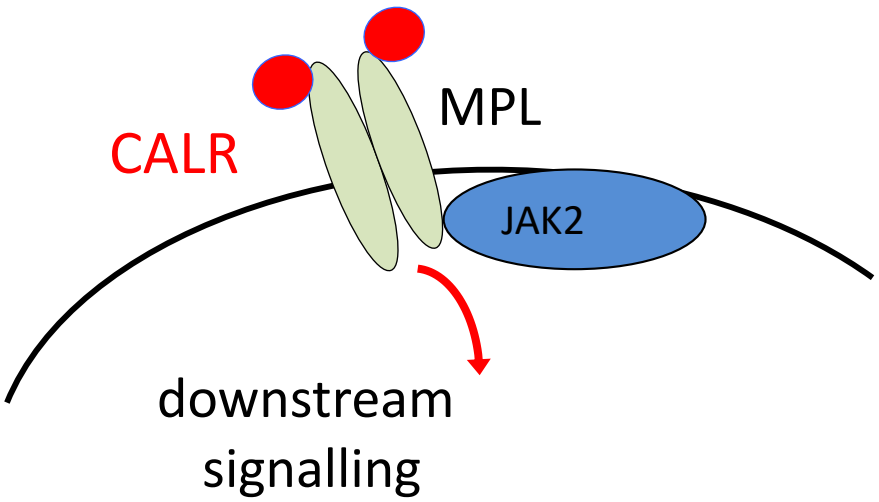
E37... RKMSPARPRTSCREACLOGWTEA 411

E37... RKMSPARPRTSCREACLOGWTEA 416

Ins

K38... RKMSPARPRTSCREACLOGWTEA 430

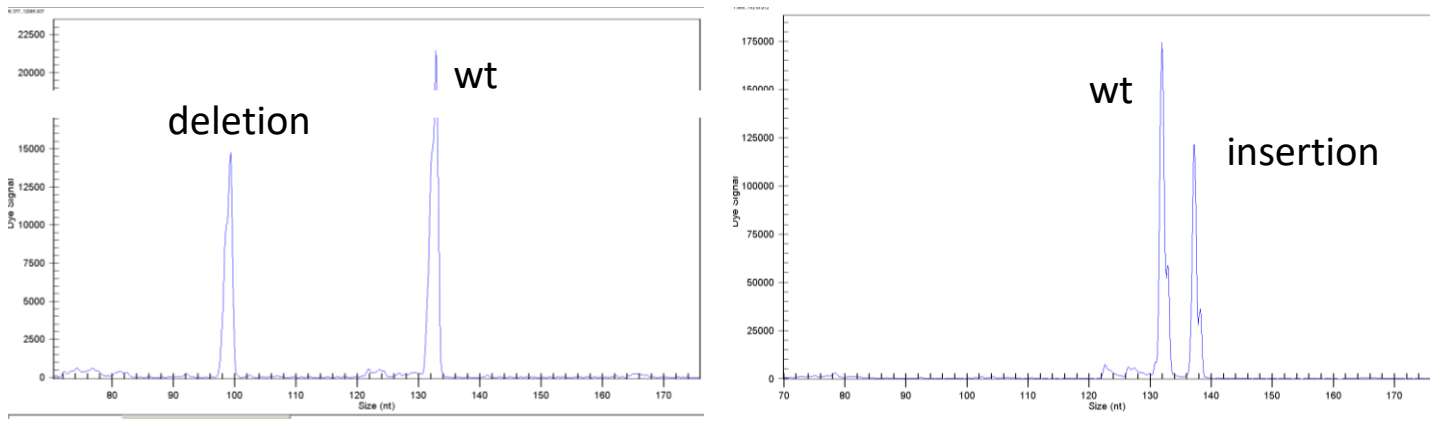
K38... RKMSPARPRTSCREACLOGWTEA 430



Chachoua et al. Blood 2015
Marty et al. Blood 2015;
Elf et al. Cancer discovery 2016

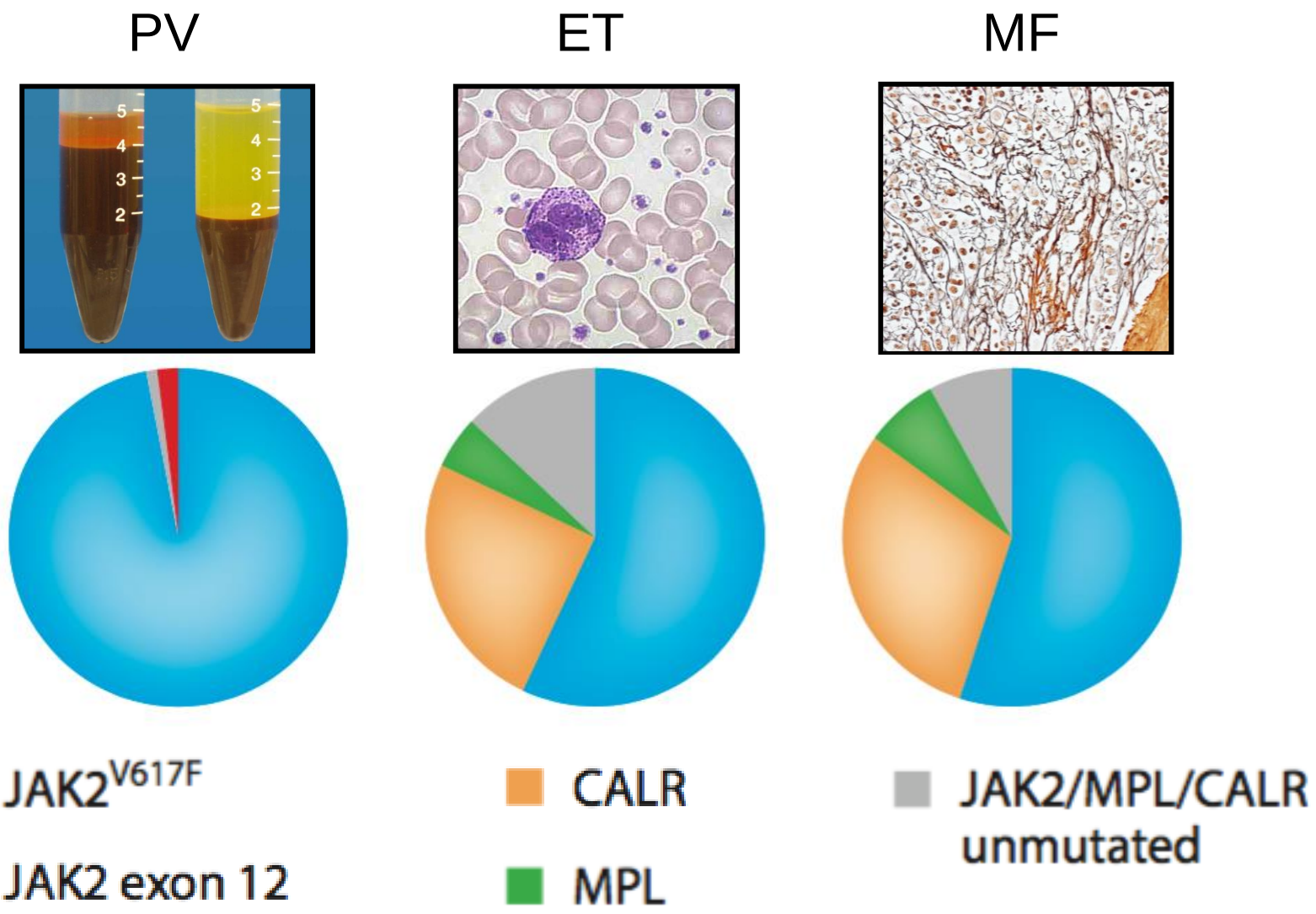
Nangalia et al NEJM 2013

Rapid clinical impact – new diagnostic test



Fragment size analysis for CALR.
Mutation testing in regional diagnostic service and international guidelines

Phenotypic driver mutations in MPNs



Clonal heterogeneity and evolution in MPN

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2. Integrating genomic and phenotypic heterogeneity to build a personalised outcome predictor

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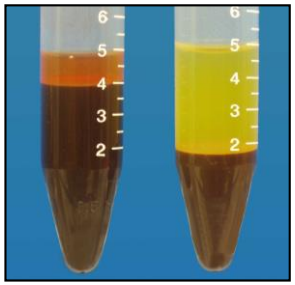

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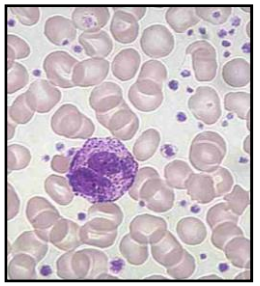

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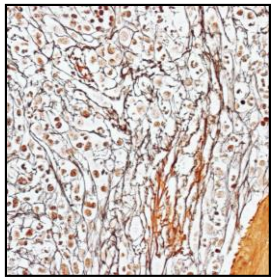


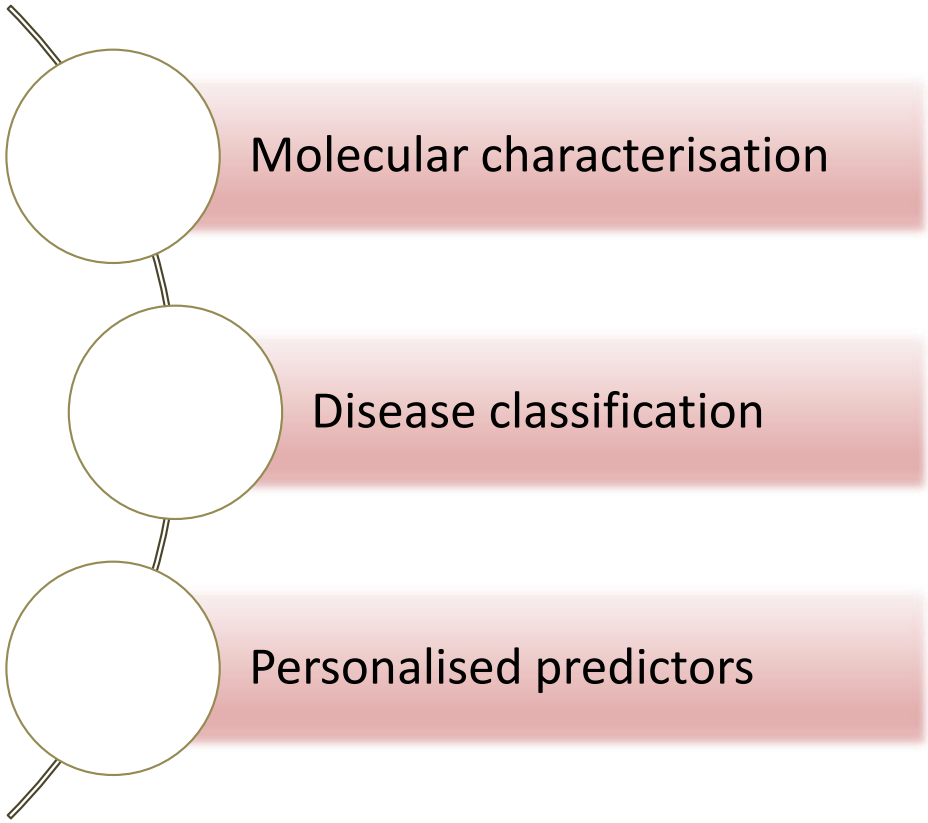
Study plan

Cohort
- 2040 MPN patients
- UK, Ireland, Italy, Denmark

Genomic characterisation
- 70 genes → 34 myeloid drivers
- Copy number from SNPs
- Germline predisposition

Clinical data
- Baseline laboratory
- Prior thrombosis
- Disease transformation
- Patient outcome

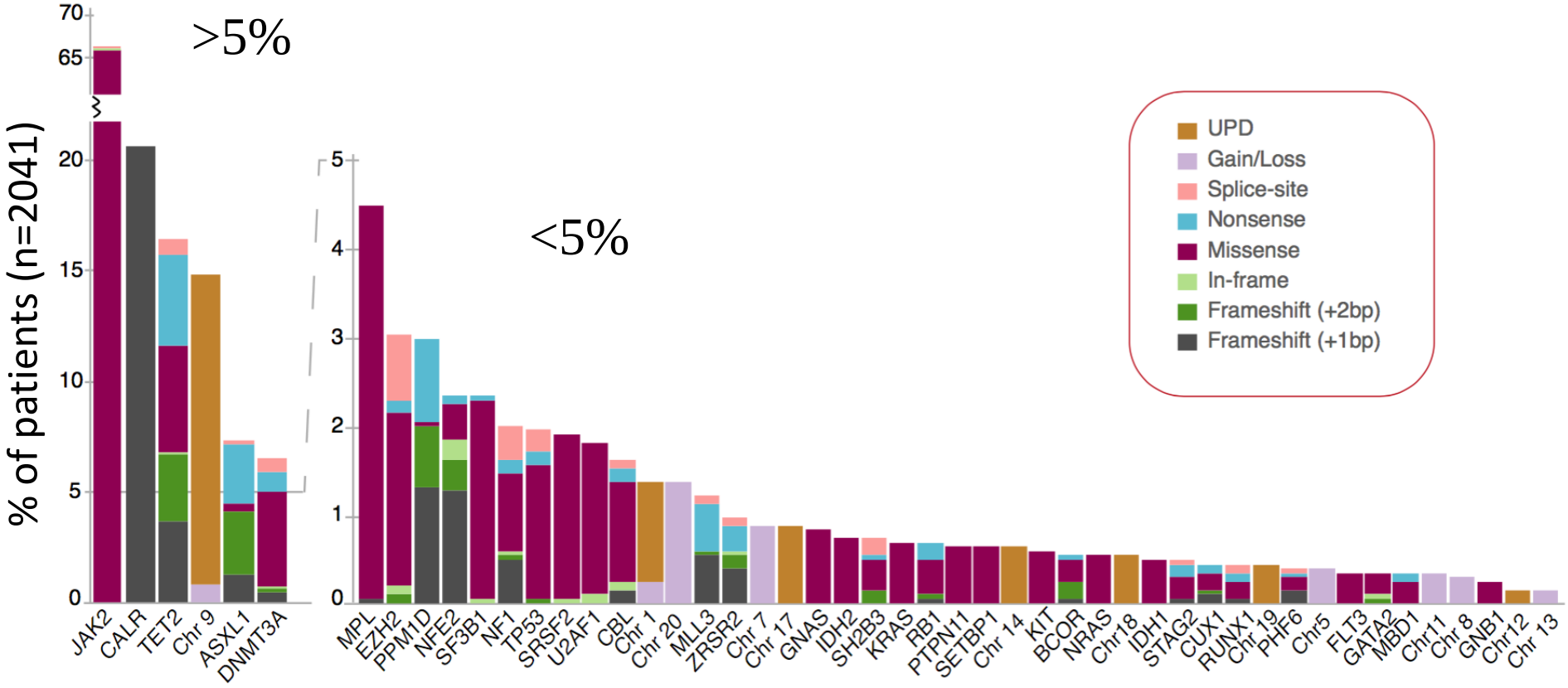
Validation cohort
- University of Florence (515)



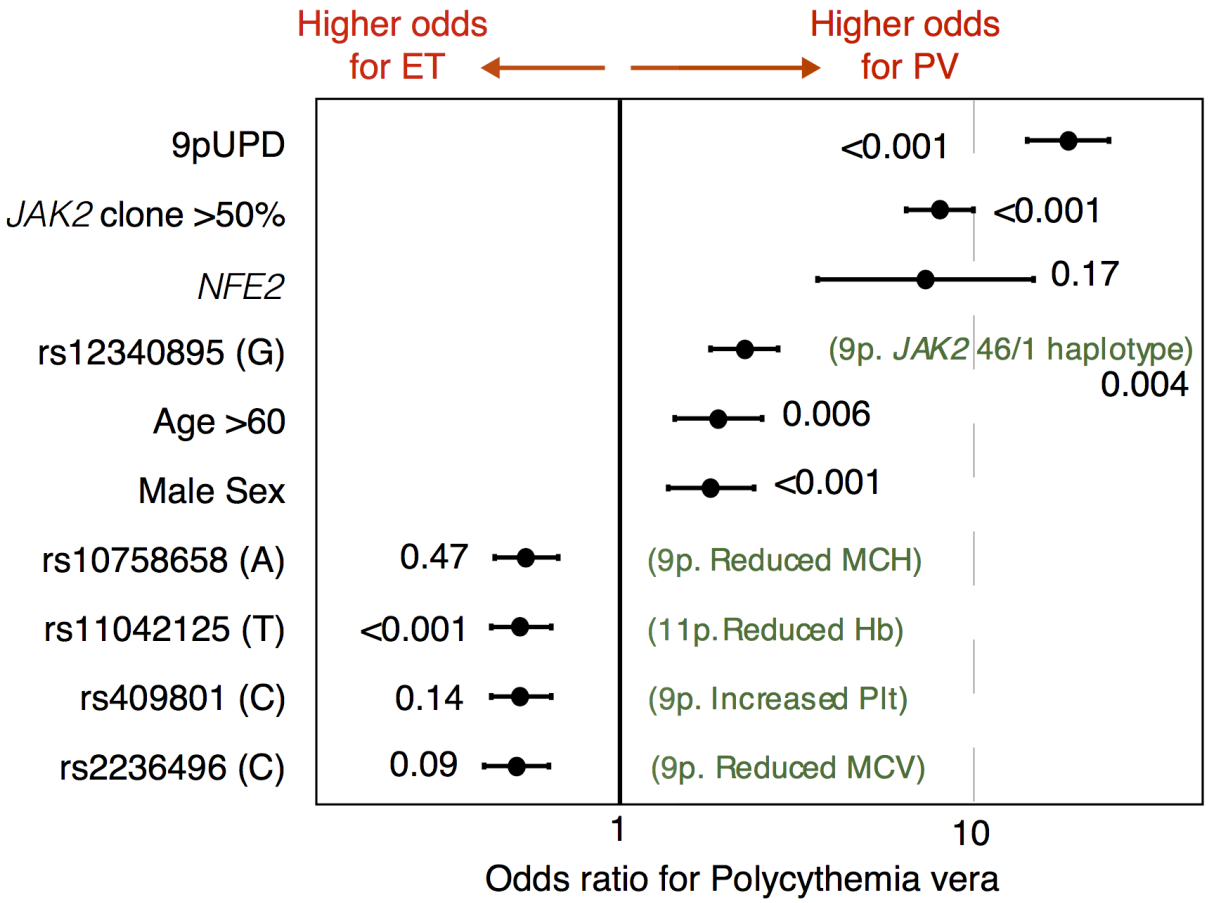
Jacob Grinfeld

Tony Green
Peter Campbell

Genetic landscape



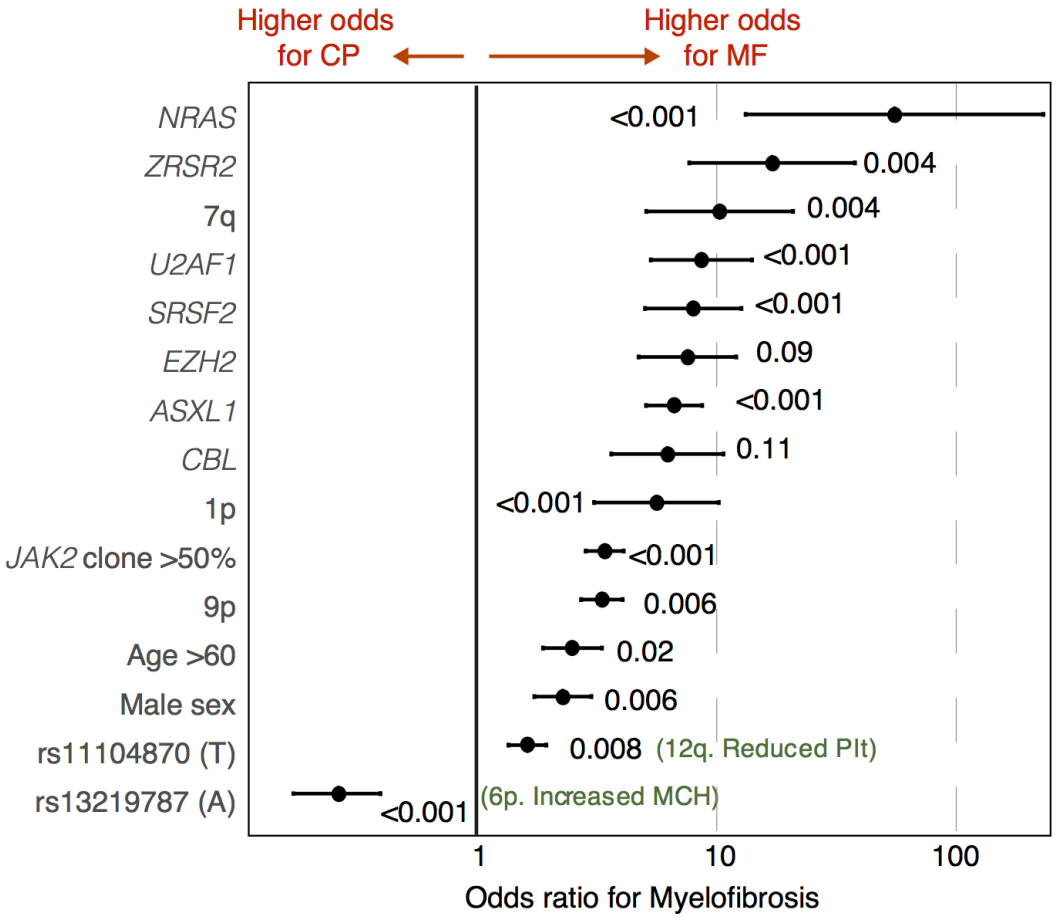
Determinants PV versus ET (*JAK2*^{V617F} context)



N=1078

Grinfeld, Nangalia et al NEJM 2018

Determinants of MF



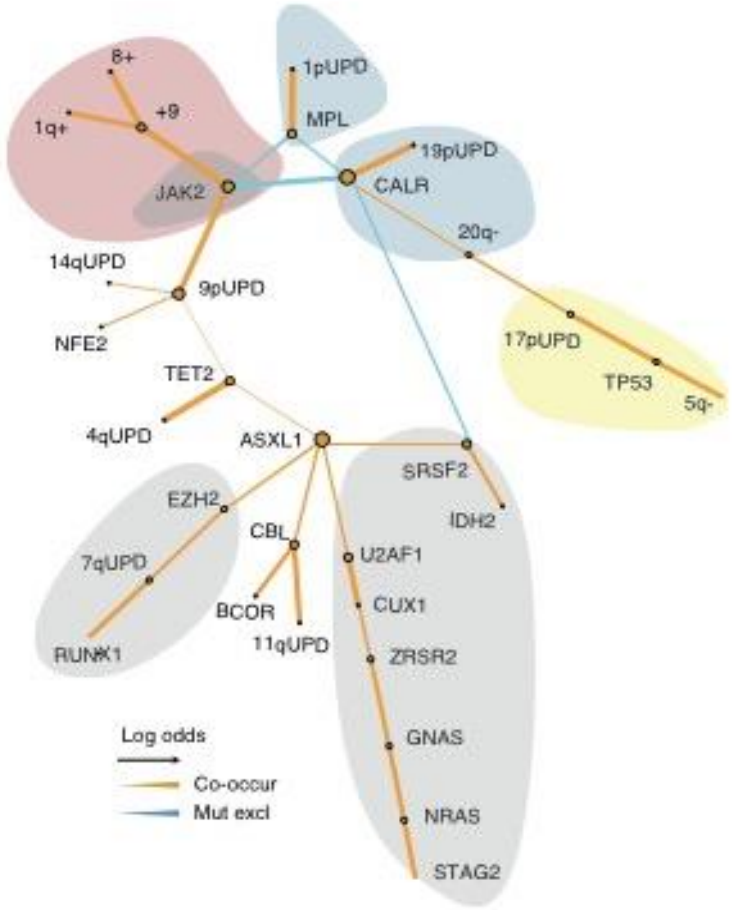
N=2004

Grinfeld, Nangalia et al NEJM 2018

Genomic subgroups of MPN

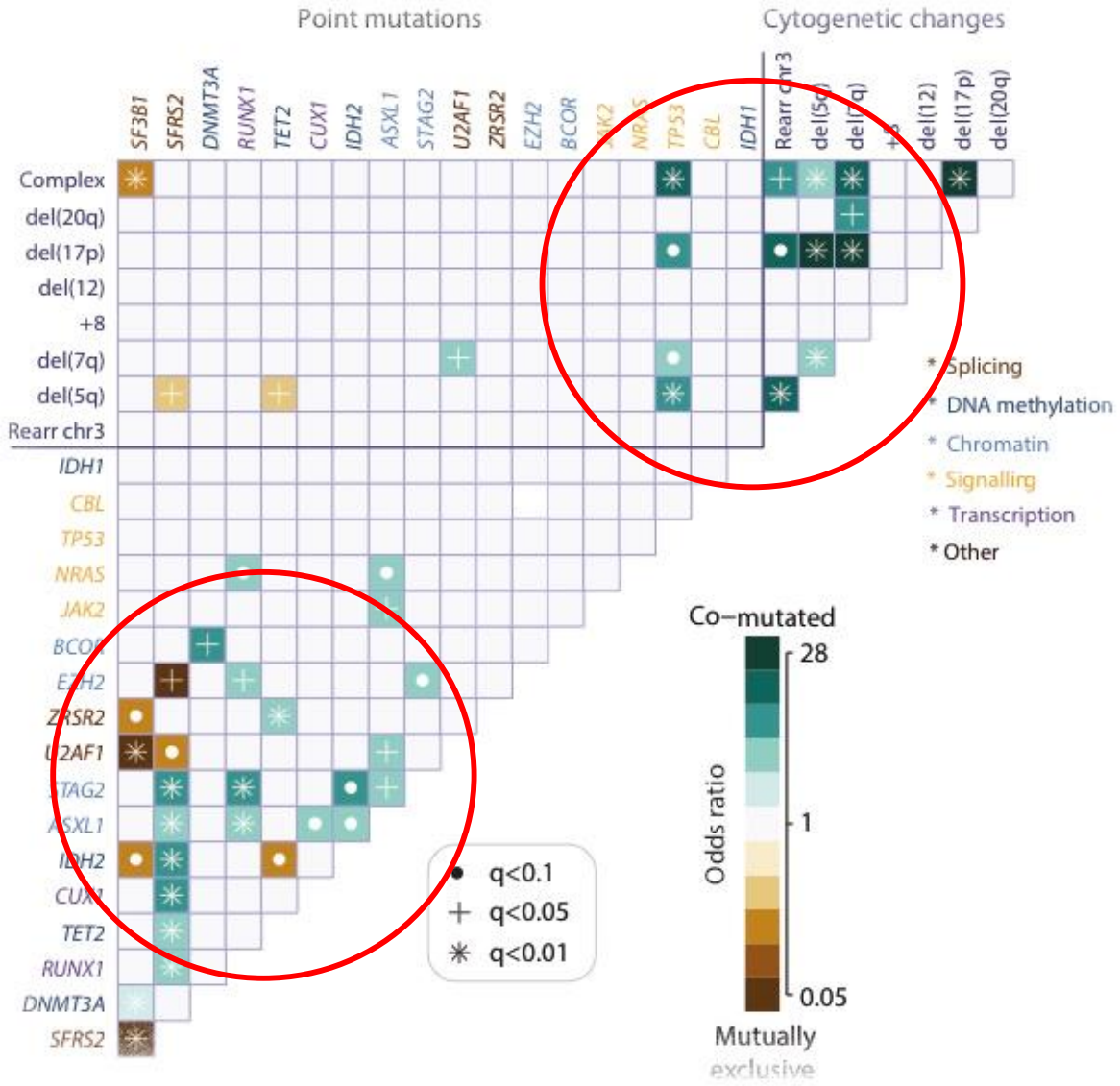
- Patterns of co-occurrence and mutual exclusivity
- Less inter-observer variability
- Reproducible and objective

Reflects causative disease biology….



Genomic subgroups transcend traditional myeloid categories

MDS



Papaemmanuil *et al,,* Blood 2013

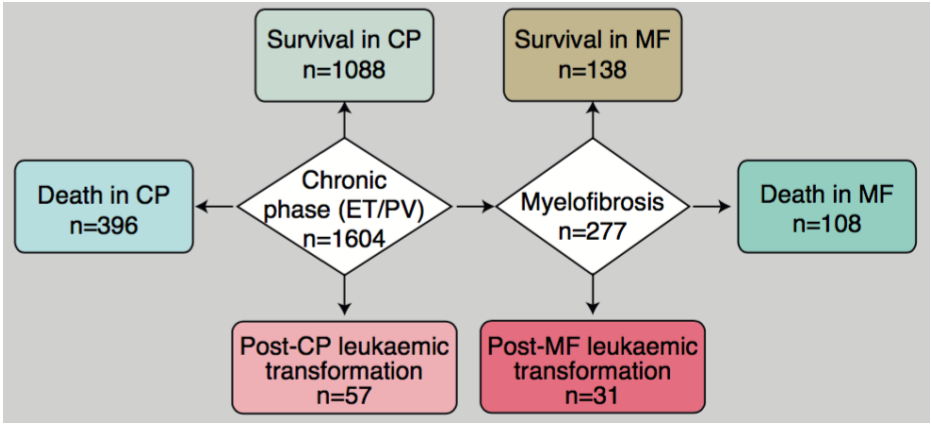
Personalised patient prognosis

Demographic

- Age at diagnosis
- Gender

Clinical

- Blood counts at diagnosis
- Splenomegaly
- Prior thrombosis
- MPN classification
  - Chronic phase (PV v ET)
  - Myelofibrosis
- Cohort

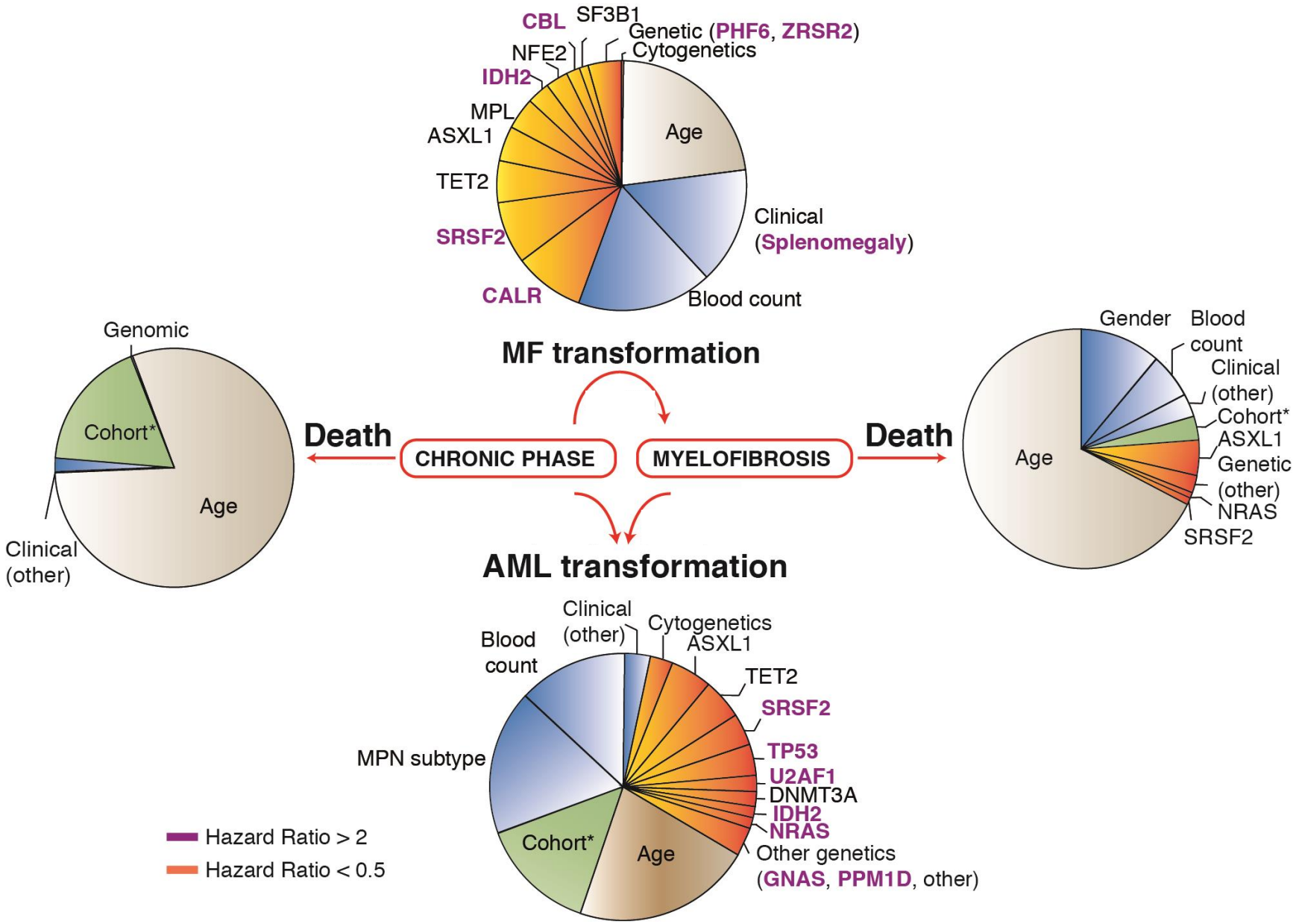


Genomic data

- 34 myeloid drivers
- 16 copy number changes

63 VARIABLES

Determinants of outcome in MPN

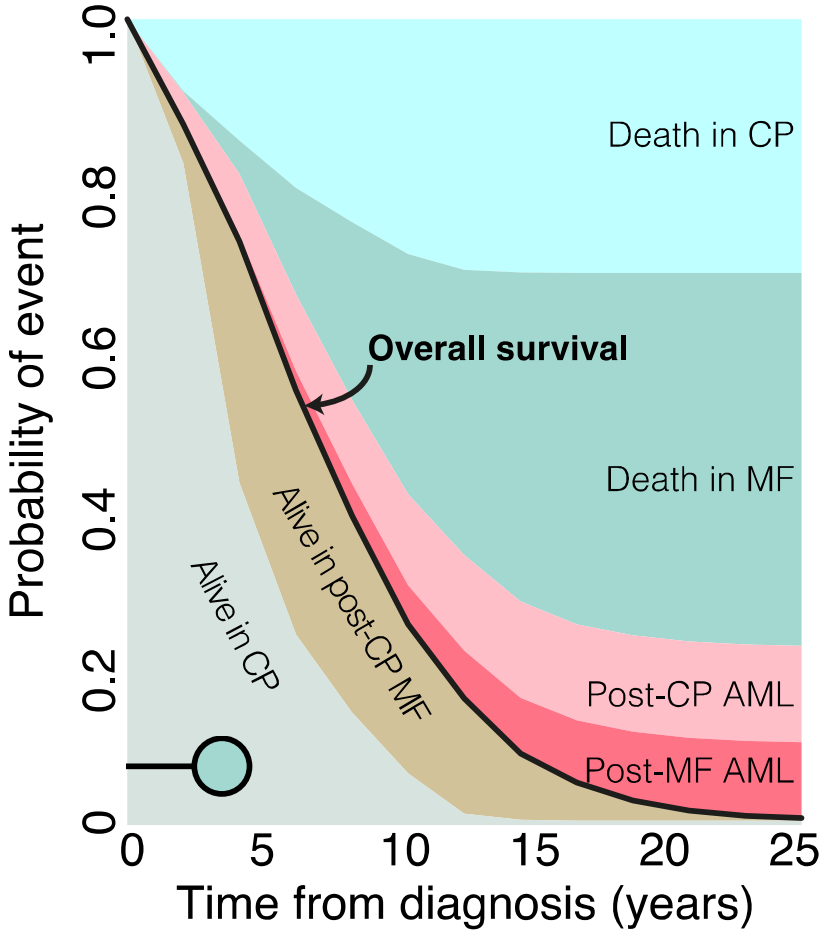


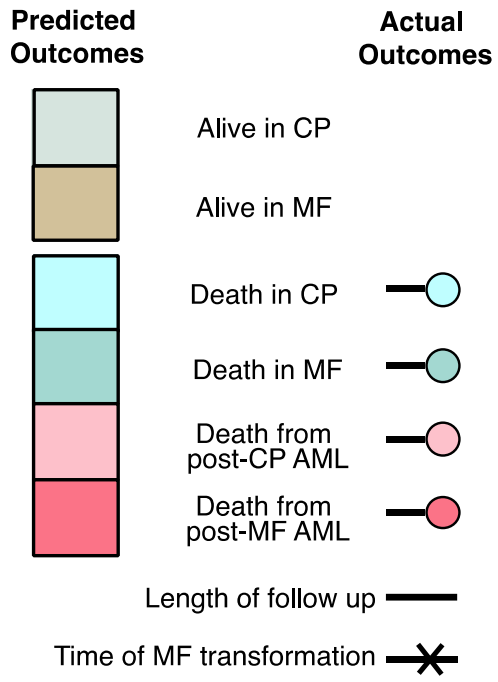
Personalised patient prognosis

ET
79yr
Female

Hb 104g/l
WCC 8.4x10^9/l
Plt 2300x10^9/l

CALR
SRSF2
IDH2
18q LOH





Acknowledgements

Nangalia group
Nick Williams
Joe Lee

Jacob Grinfeld
Moritz Gerstrung

Peter Campbell Group
Kevin Dawson
Adam Butler
Jon Teague

Tony Green Group
Charlie Massie

Addenbrookes
Anna Godfrey
Joanna Baxter, CBSB
Phyllis Paterson, MPN clinic

PT1 trial team and patients

Clinical collaborators
Claire Harrison
Mary-Frances McMullin
Nick Cross
Alessandro Vannucchi
Paula Guglielmelli

CANCER RESEARCH UK

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