Chronic Lymphocytic Leukaemia
Biology, genetics and prognosis

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AUCKLAND DISTRICT HEALTH BOARD
Te Toka Tumai

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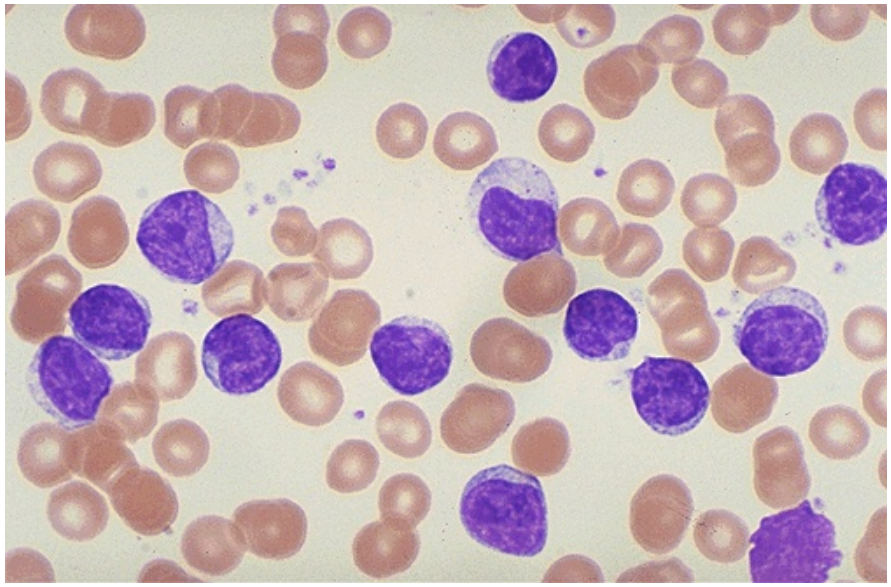
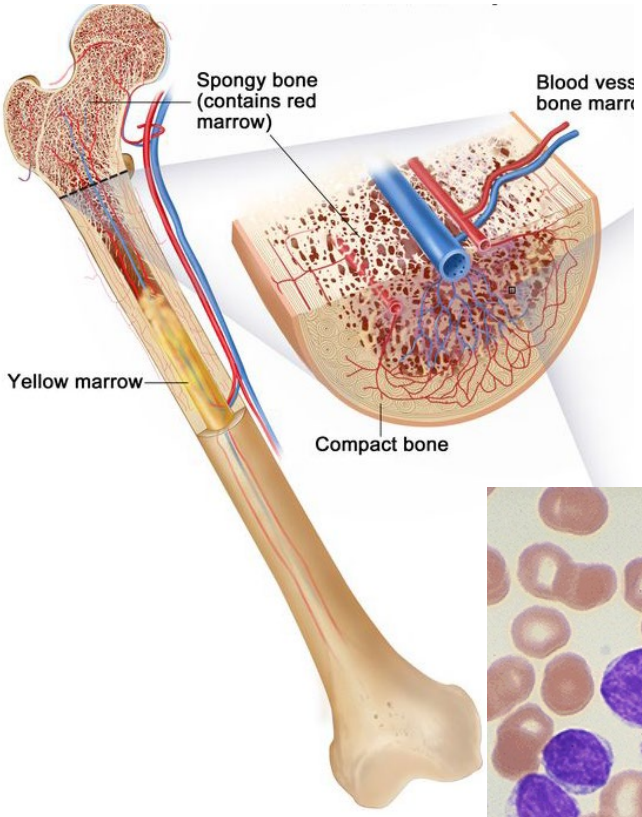
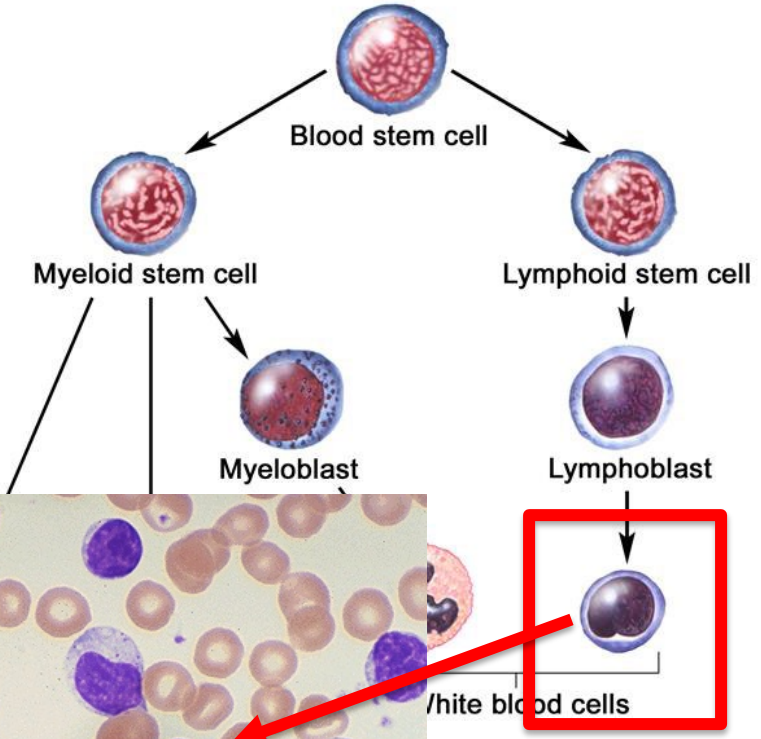
What is chronic lymphocytic leukaemia?

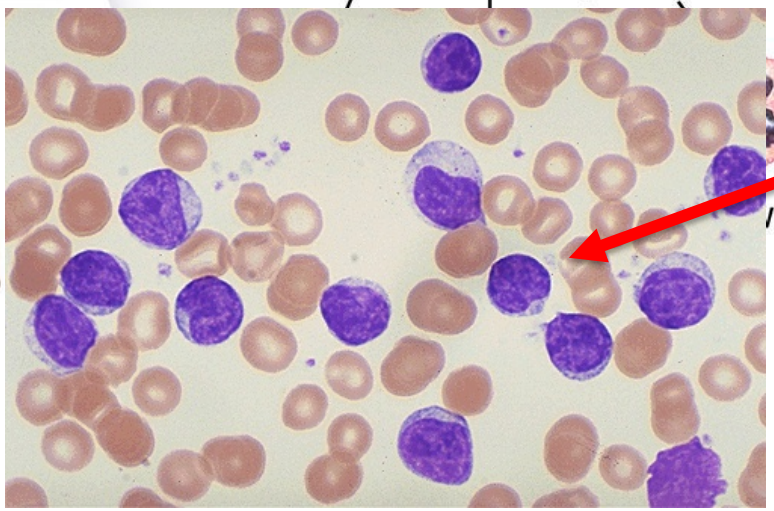
CLL is a low grade lymphoproliferative blood cancer caused by an accumulation of monoclonal B lymphocytes in the bone marrow, blood, lymph nodes and spleen



What is chronic lymphocytic leukaemia?



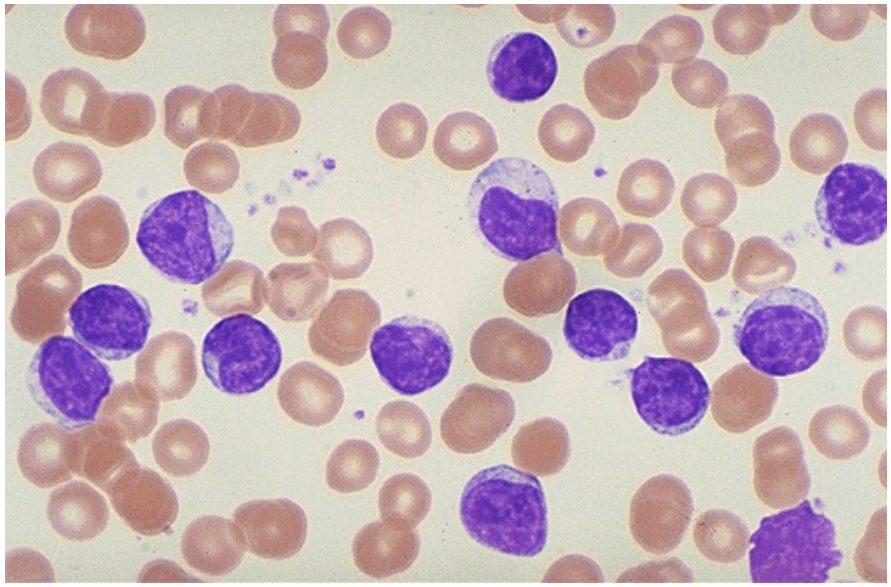




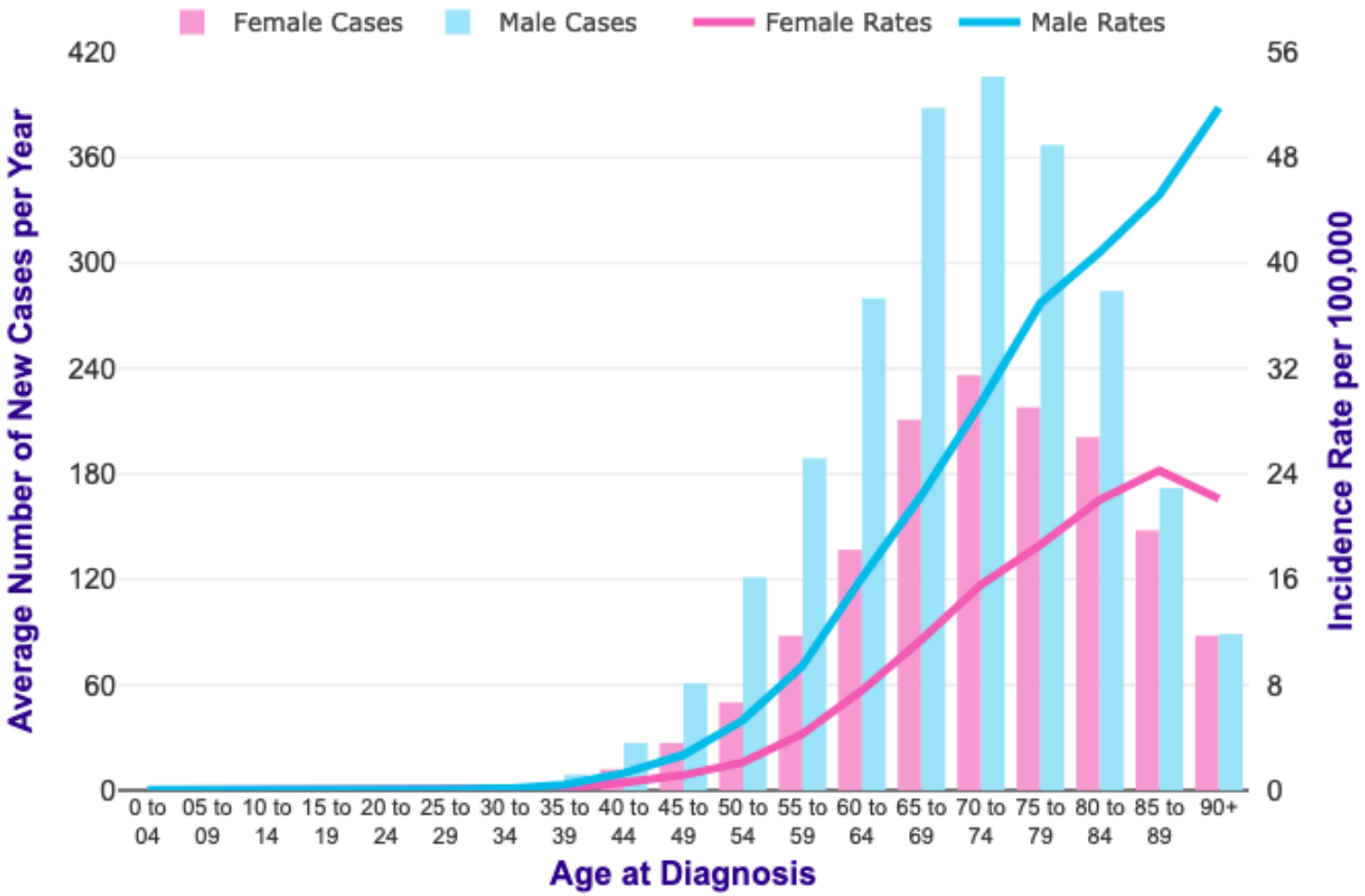
What is chronic lymphocytic leukaemia?

CLL is the most frequent leukaemia in Western countries including NZ

- Incidence of 4 per 100,000 population
- Median age 70 - 75; M > F

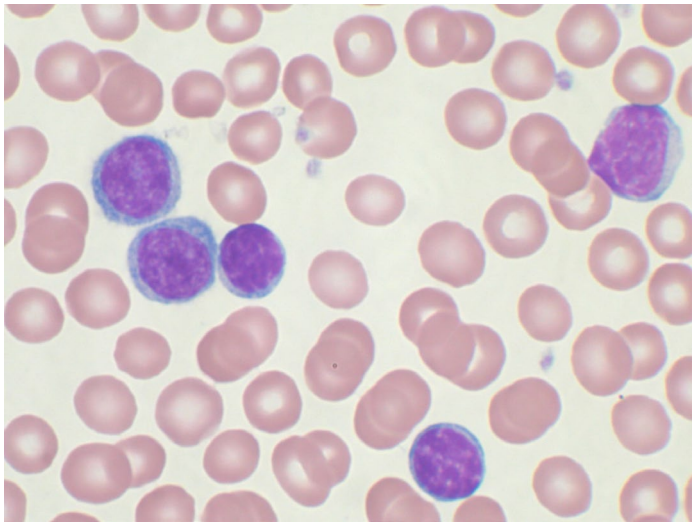


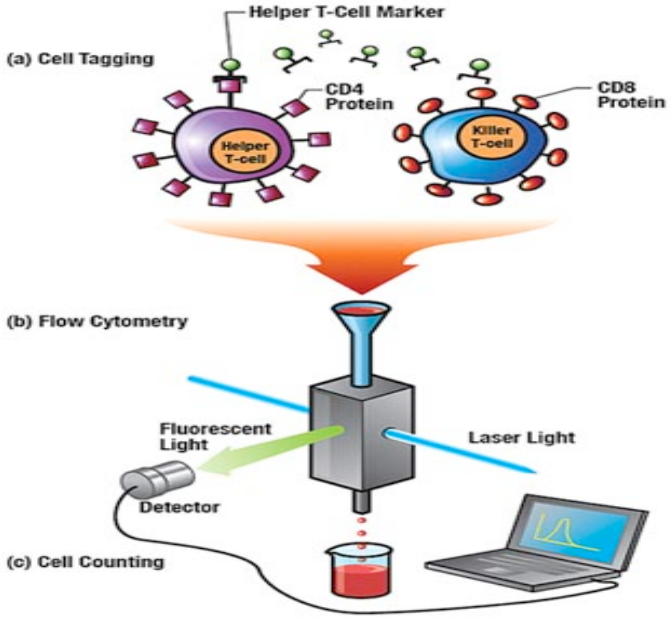
Age and Incidence of CLL



UK Cancer Registry 2015 - 17

Diagnosis of CLL





Full blood count and blood film analysis

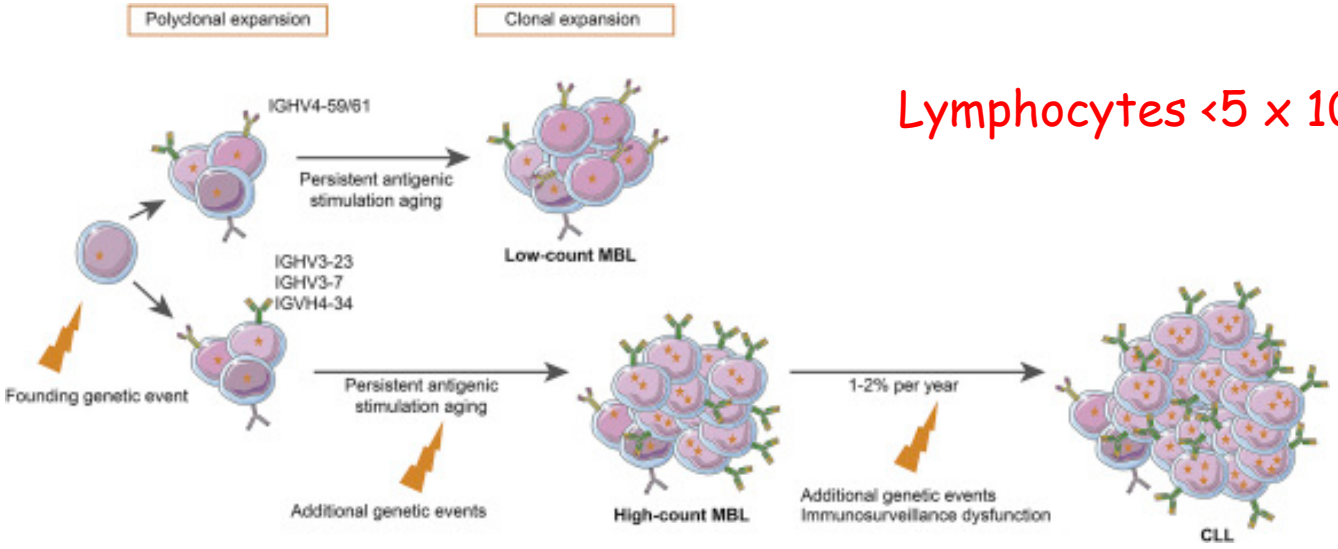
Cell marker studies "Immunophenotype"

Monoclonal B cell population with expression of CD5 and co-expression of B cell markers CD19, CD20, CD23

Diagnosis of CLL

All cases of CLL preceded by a pre-malignant phase called **Monoclonal B cell Lymphocytosis**

Present in 5% of the population age > 60, with 1-2% progressing to CLL each year



Lymphocytes <5 x 10^9/L

What causes CLL?

Increased understanding of the genomic landscape and the spelling mistakes / mutations in the genetic code of the CLL cells

A permissive microenvironment in the bone marrow and lymph nodes to support the CLL cells

No clearly established environmental risk factors identified to date

Increased risk of CLL in first degree relatives of patients

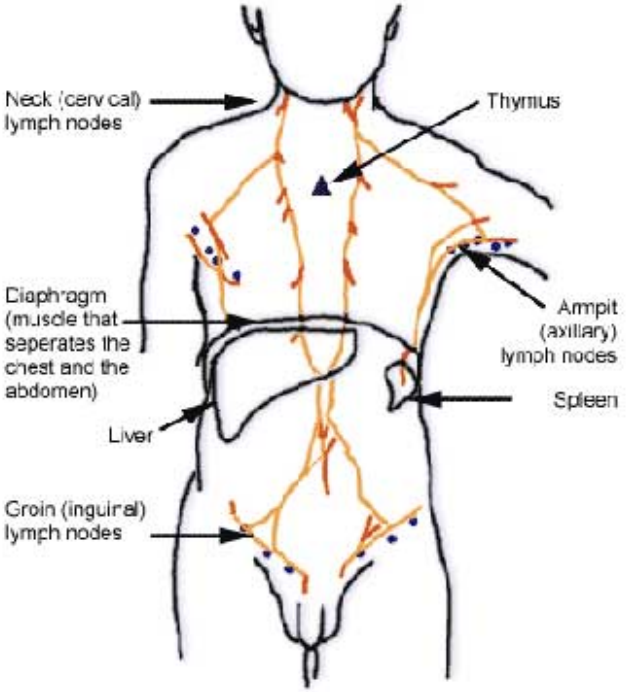
Is there a familial risk in CLL?

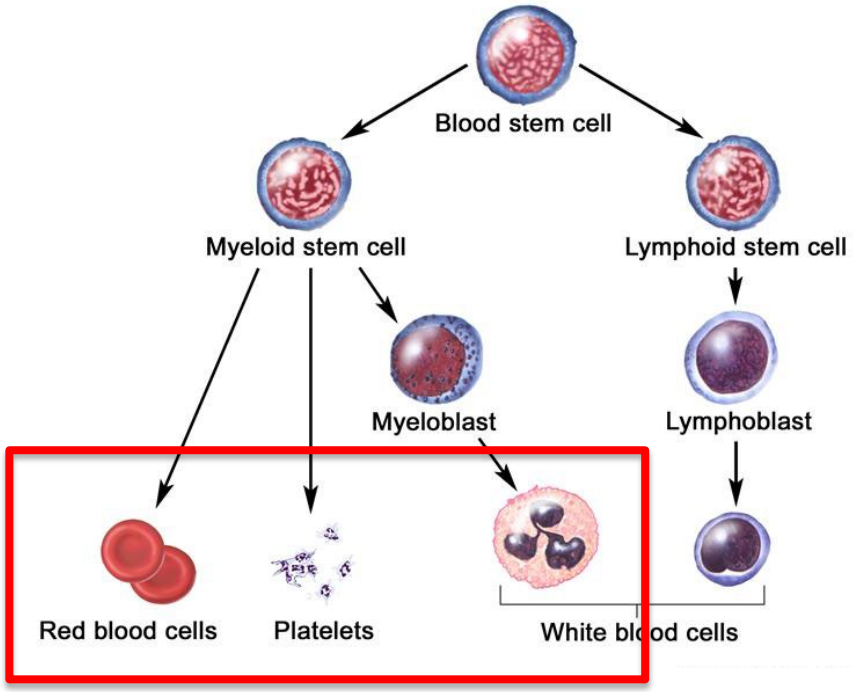
No single predisposition gene identified unlike breast and colon cancer

Likely to be interaction of multiple genes and variations within those genes

Risk for relatives remains very low

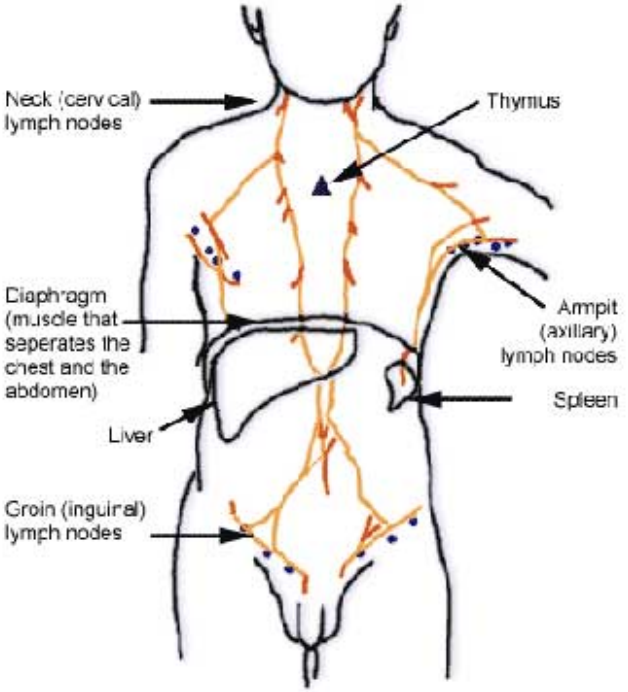
Presentation of CLL

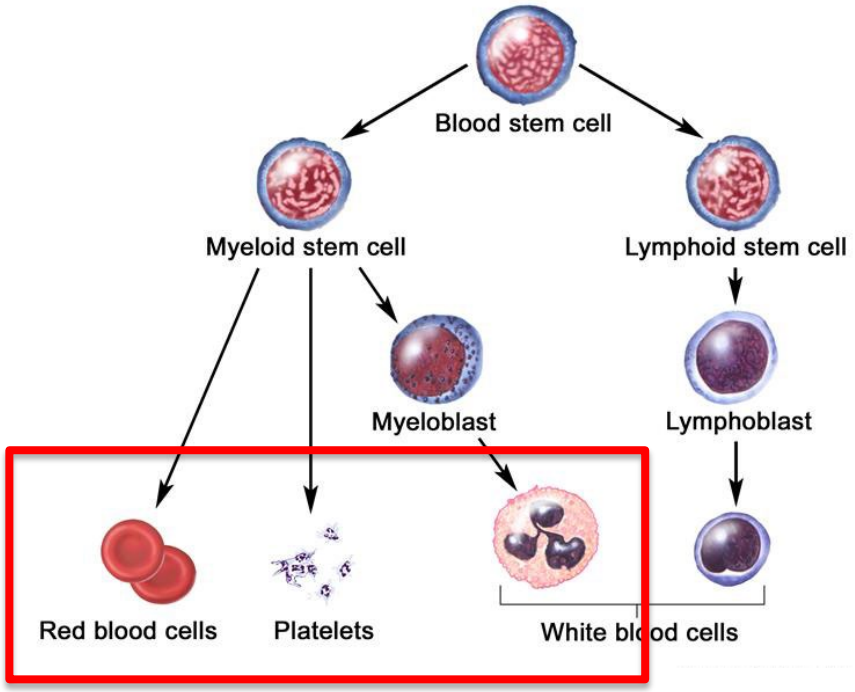




Raised lymphocyte count in the peripheral blood
Suppression of the normal blood counts (in red box)
Enlarged lymph nodes and / or spleen

Presentation of CLL





70% of patients early stage of disease at presentation with no anaemia or thrombocytopenia and no significantly enlarged nodes

Predicting outcome in CLL

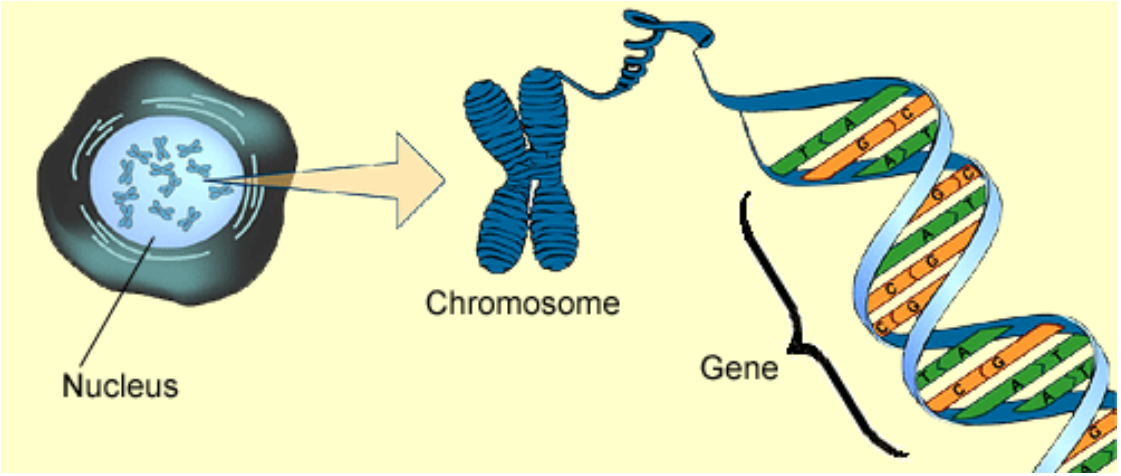
Recent discoveries in genetic alterations in CLL

The importance of the immunoglobulin gene mutation status

Incorporating these findings into new prognostic scores for patients

The increasing role of measuring minimal residual disease

Personalized Haematology



Chronic Lymphocytic Leukaemia

Improved understanding of the mutations / spelling mistakes that occur in the genes of the CLL cells

Treatment decisions made based on the different mutations found in each case of CLL

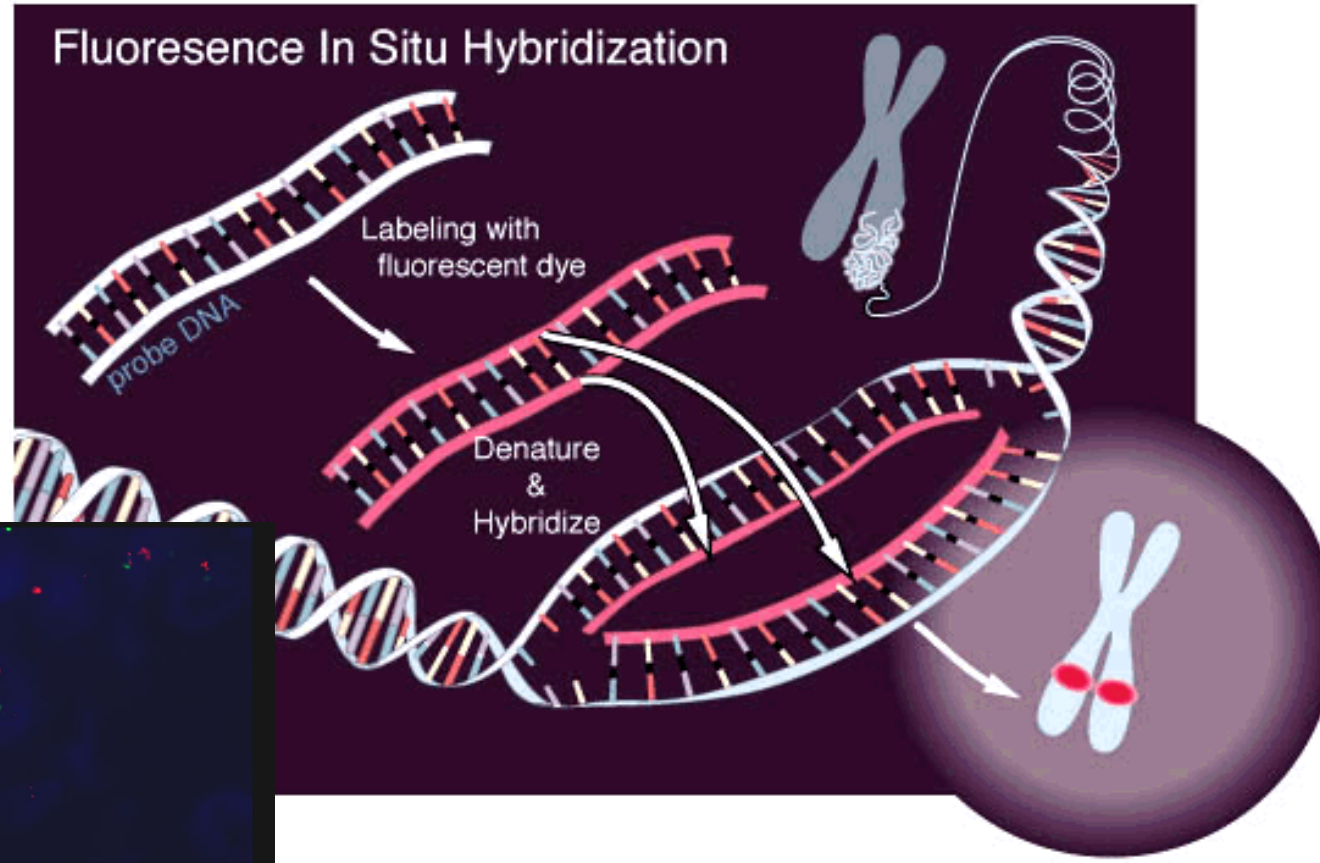
FISH studies in CLL

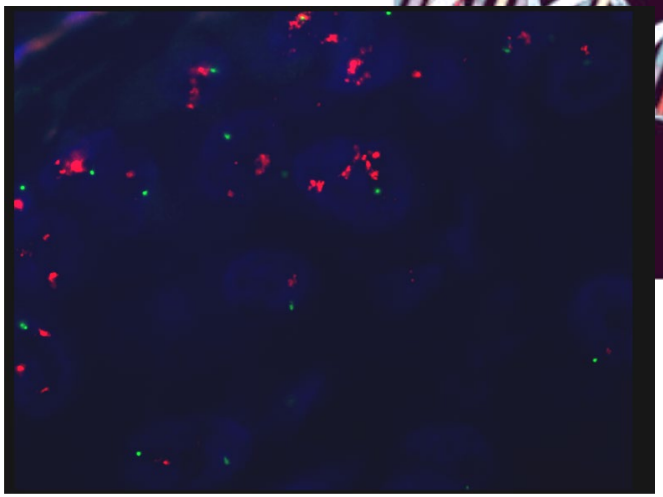
FISH is an acronym for ...

Fluorescence *In Situ* Hybridization

This technique exploits the ability of a fluorescent labelled DNA molecule to bind specifically to DNA

FISH studies in CLL



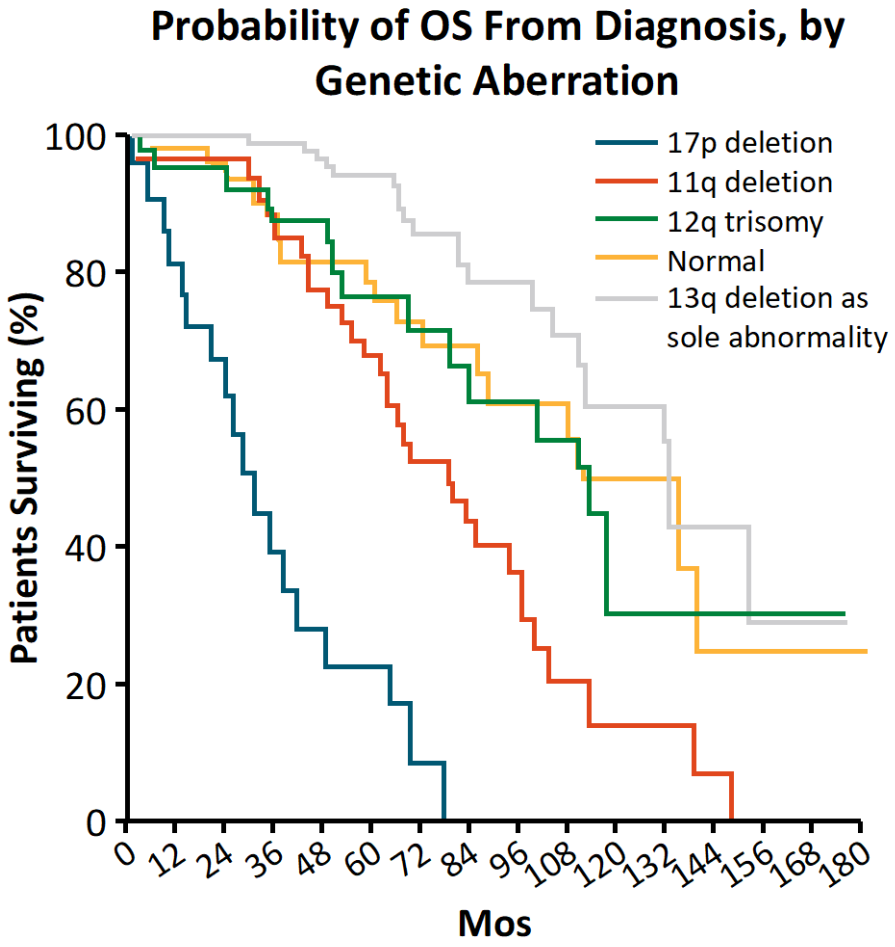


FISH studies in CLL

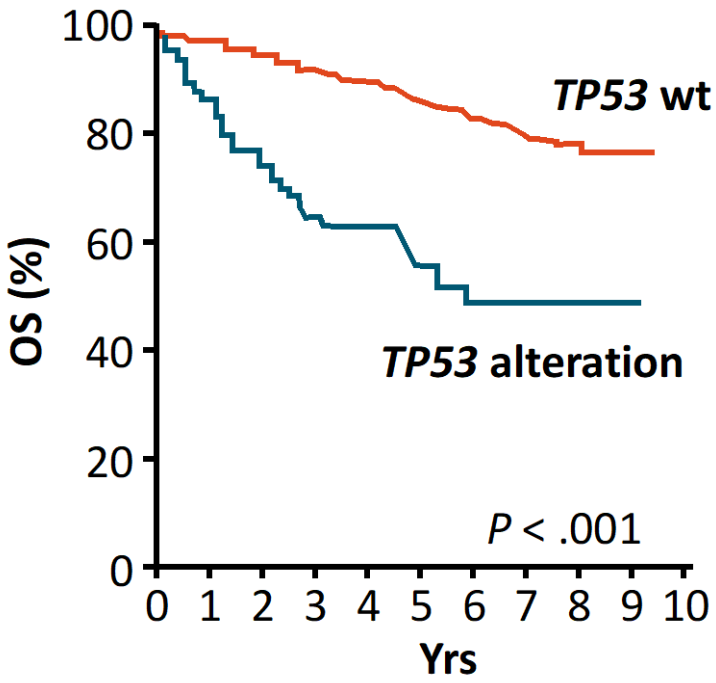
Four chromosomes analyzed:

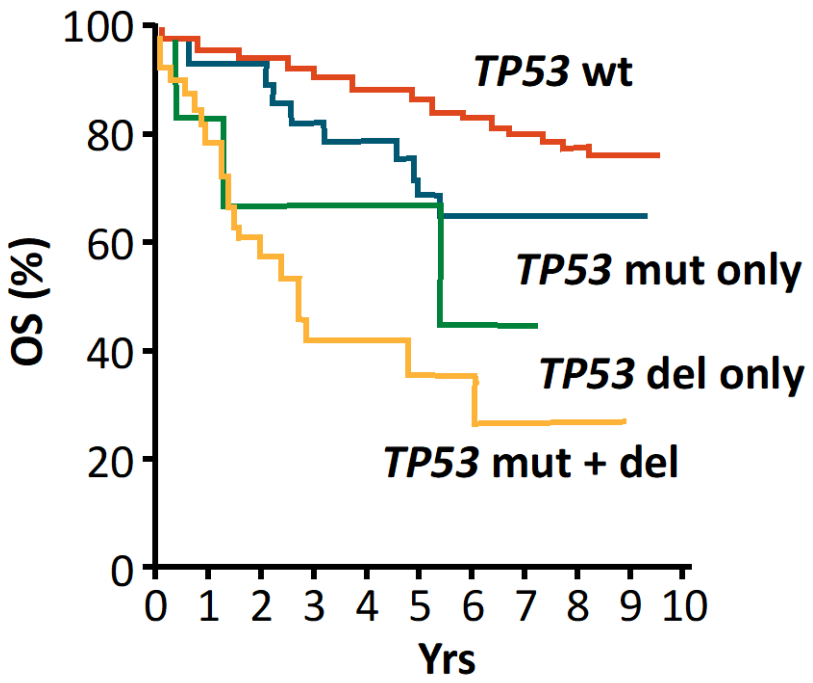
- Del 13q 55%
- Trisomy 12 20%
- Del 11q 25%
- Del 17p 5 – 8%

TP53 gene
Add sequencing gene
if FISH negative



Impact of *TP53* mutations

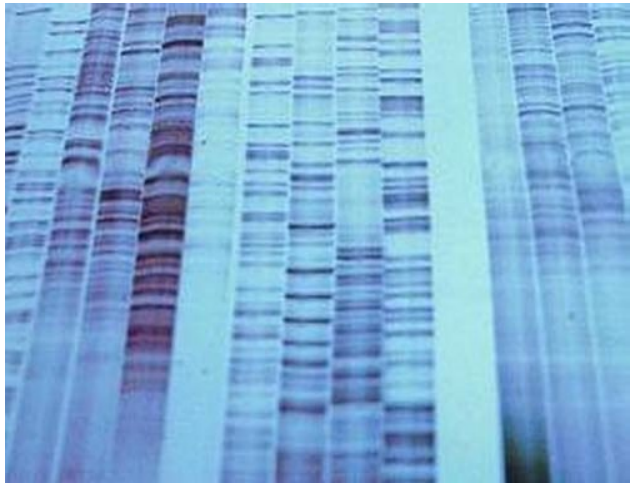




Poor response to conventional therapy eg FCR
Good responses to novel agents Ibrutinib and Venetoclax
Venetoclax funded by Pharmac

Progress in Genomic Technology

1990



600 bases per day

270 000 years per human genome

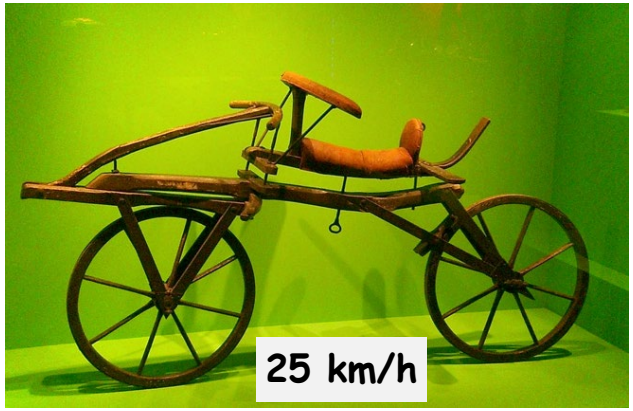
200 million fold

2020

120,000,000,000 bases per day

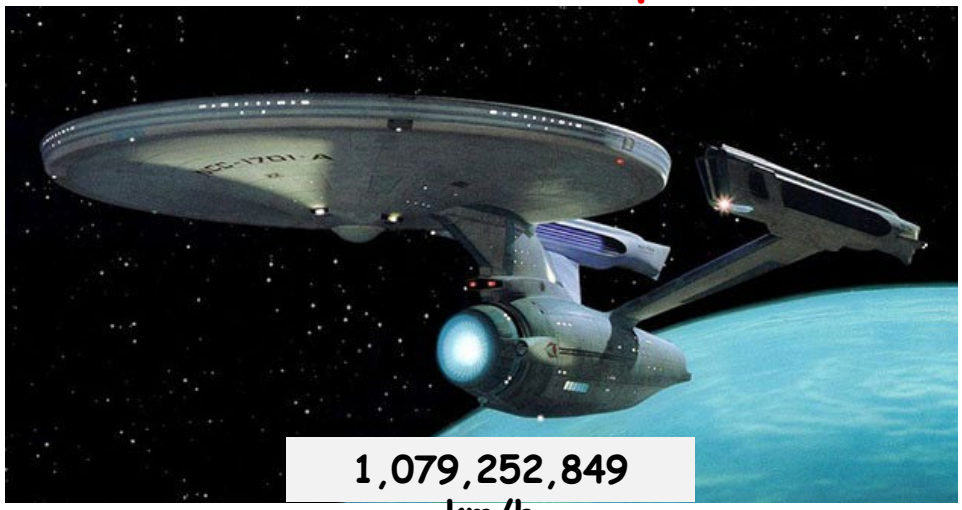
1 day per human genome

Progress in Genomic Technology



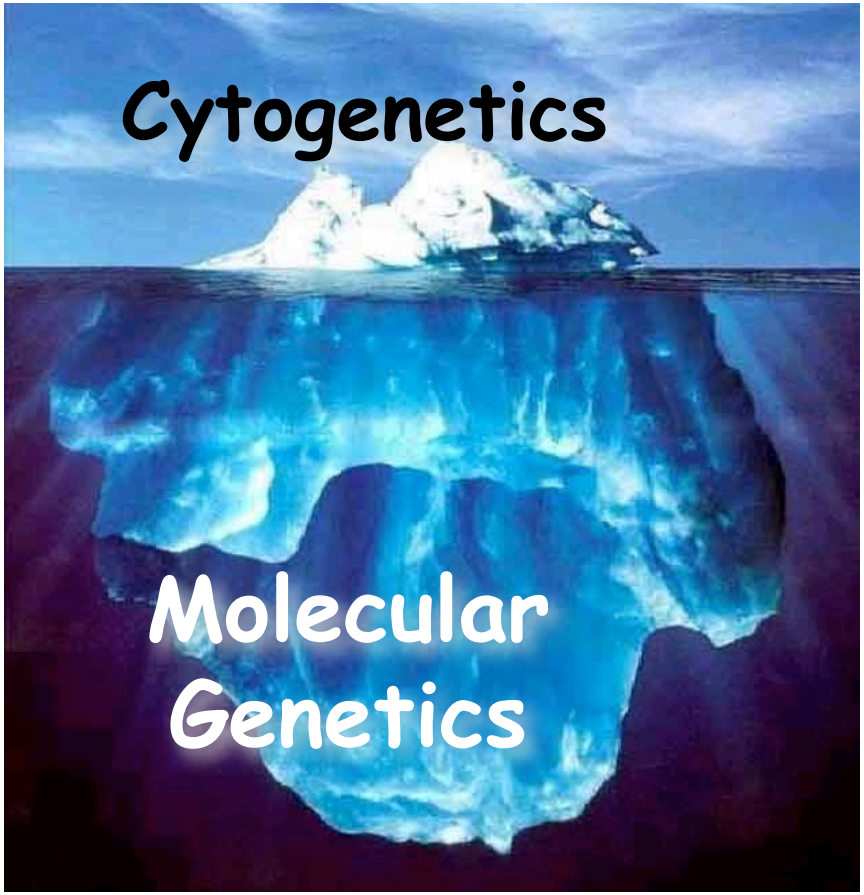
10 fold increase in speed

40 million fold increase in speed

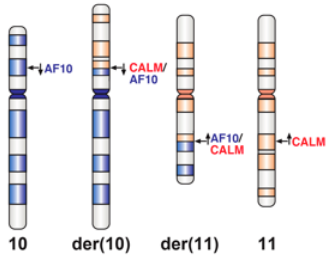


4 million fold increase in speed

Genetics of leukaemia

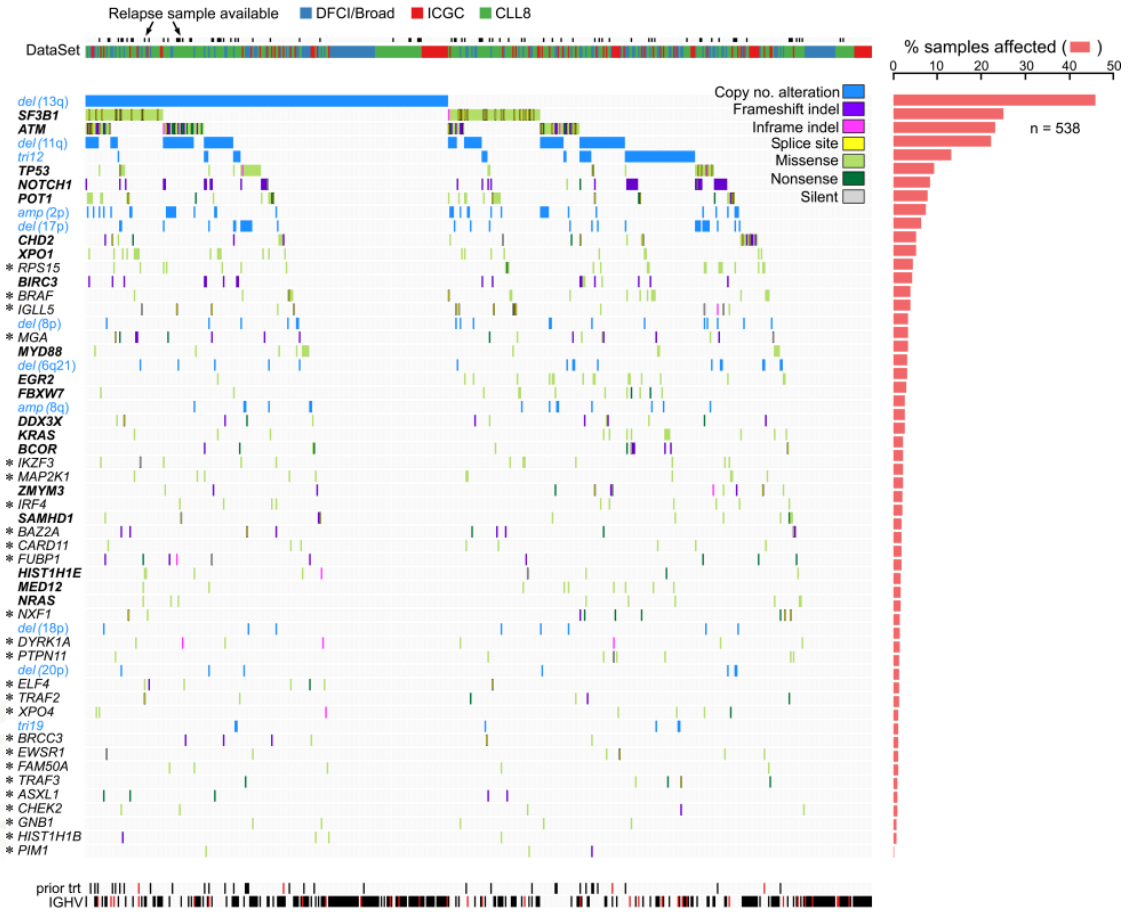


Translocations



Gene Sequencing

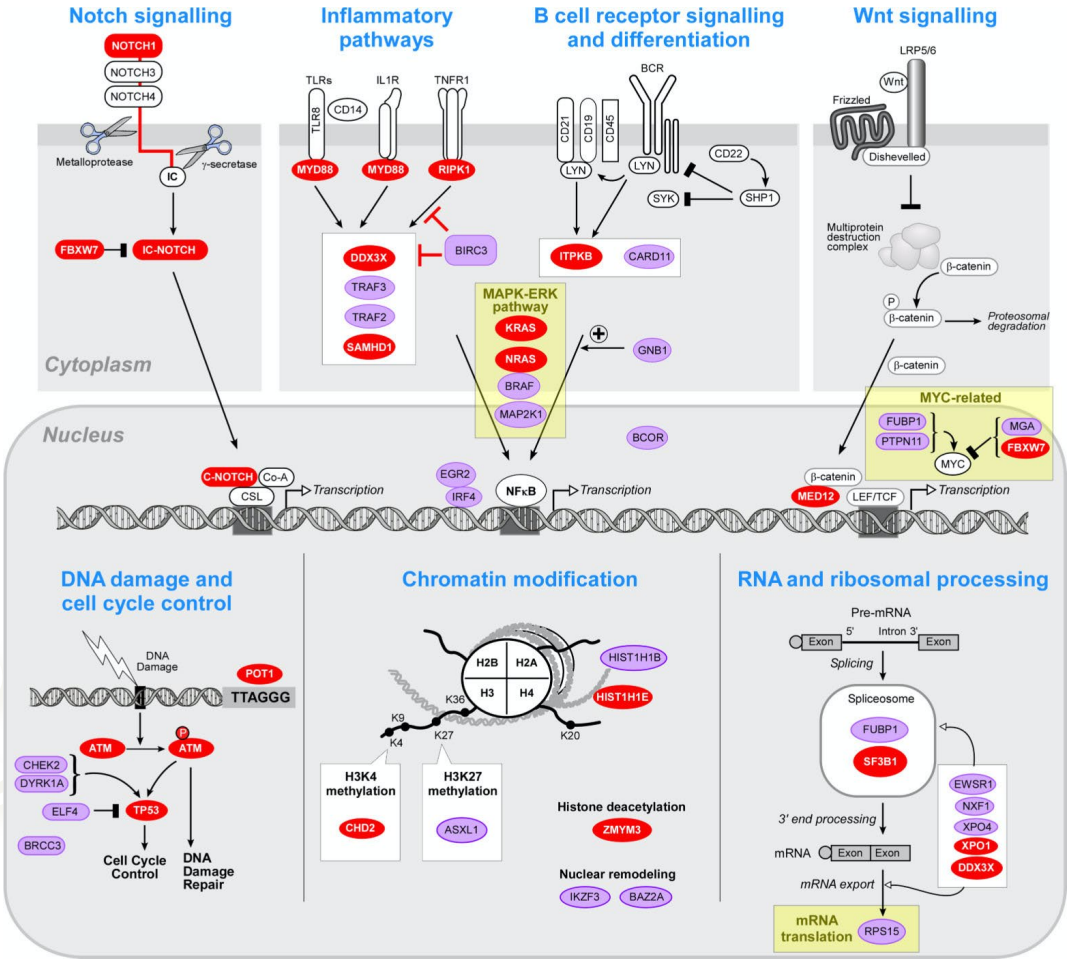
Genetics of CLL



538 patients with CLL whole exome sequencing
44 recurrently mutated genes

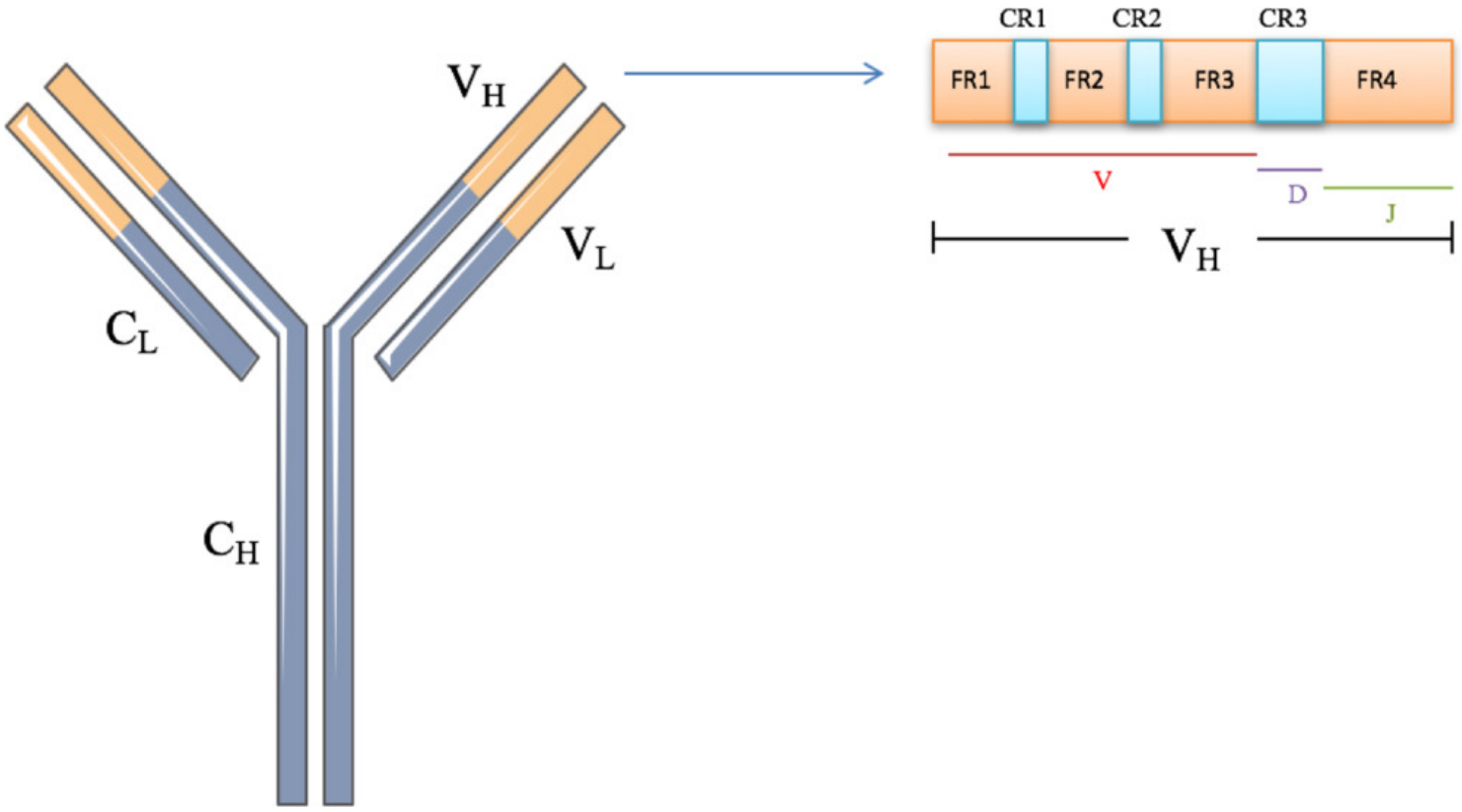
Landau et al Nature 2015

Genetics of CLL and Treatment



Landau et al Nature 2015

Impact of IGVH Mutation Status



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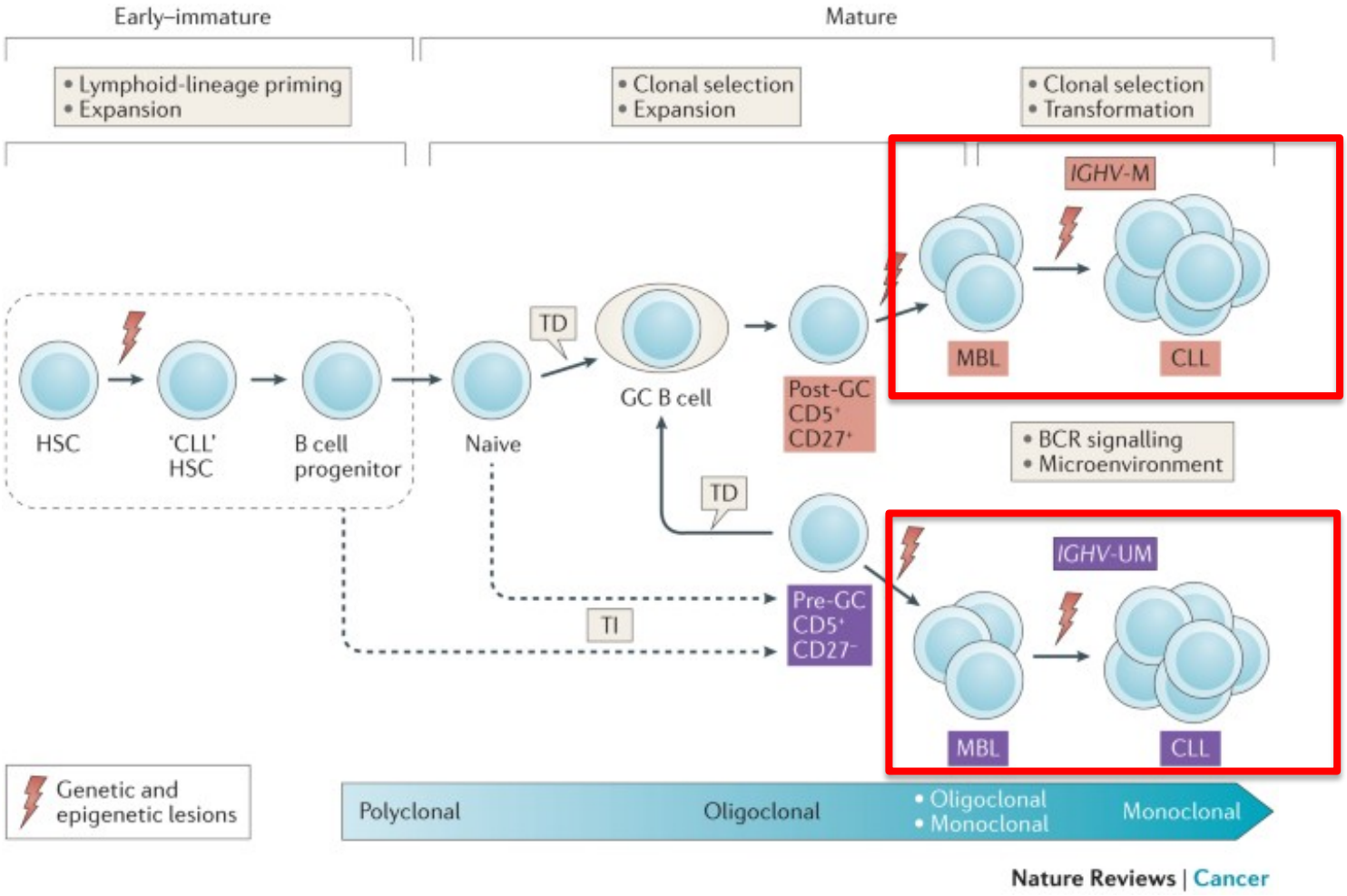

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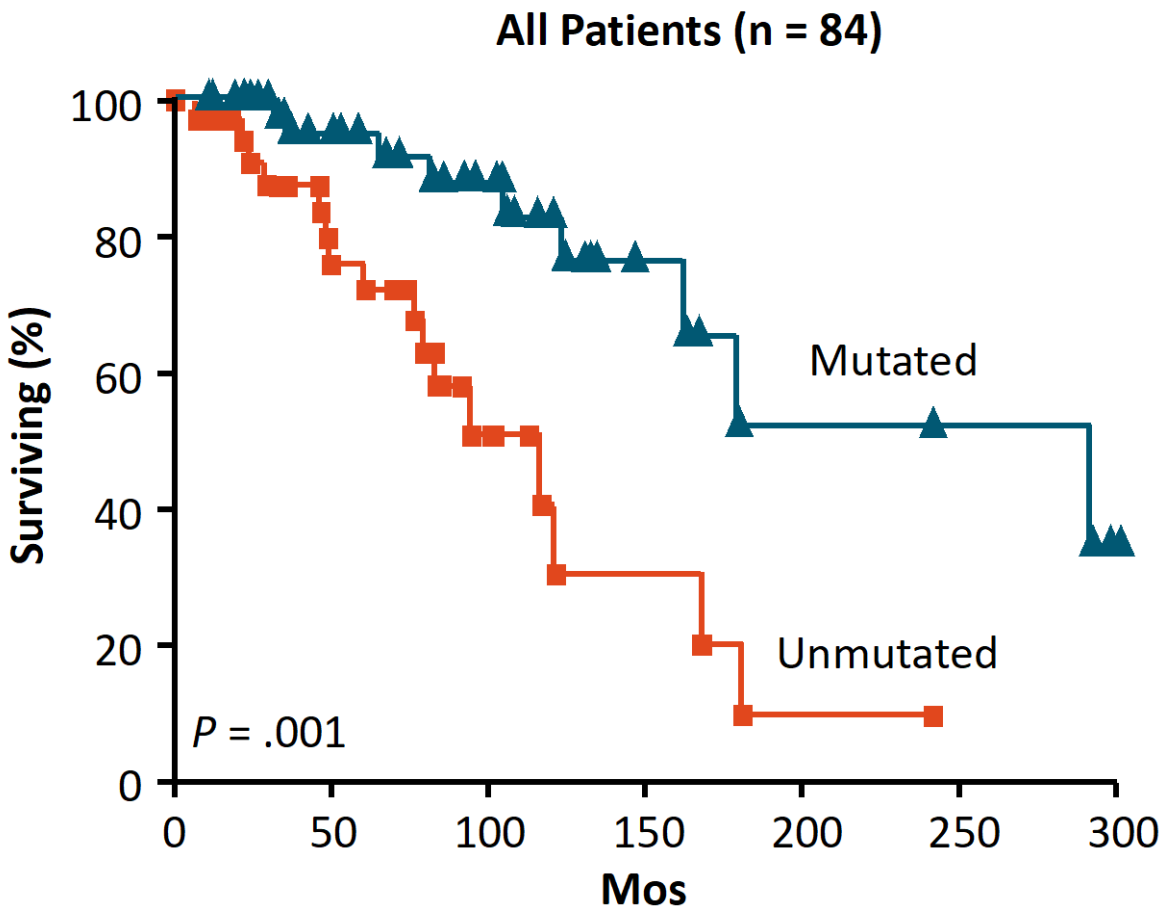


Hamblin et al Blood 1999

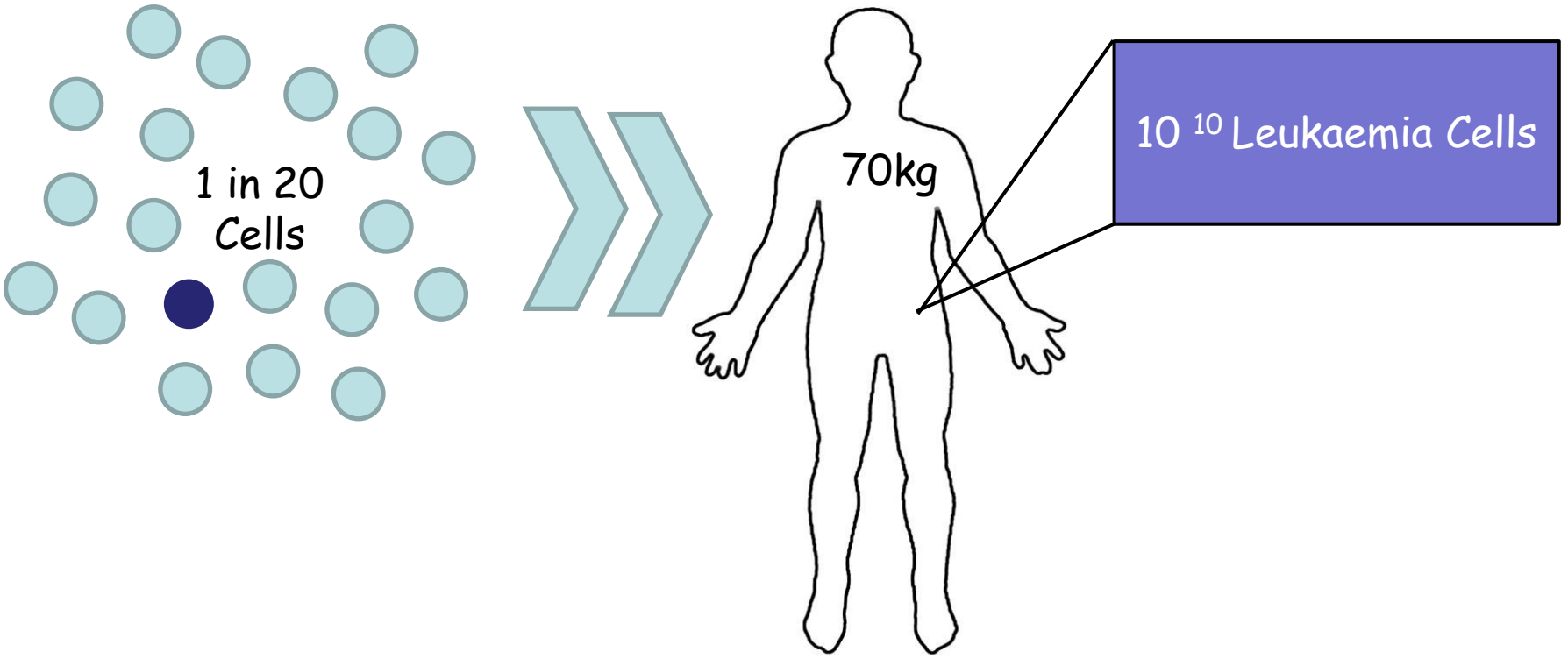
Integration of biologic markers into clinical staging

Prognostic factor	Points
Del17p on FISH or *TP53* mutation	4
Unmutated *IGHV* genes	2
Serum β2 microglobulin >3.5 mg/L	2
Rai stage I–IV	1
Age >65 years	1

Cumulative CLL-IPI score	Risk category	5-year TFS[a]
0–1	Low risk	78%
2–3	Intermediate risk	54%
4–6	High risk	32%
7–10	Very high risk	0%

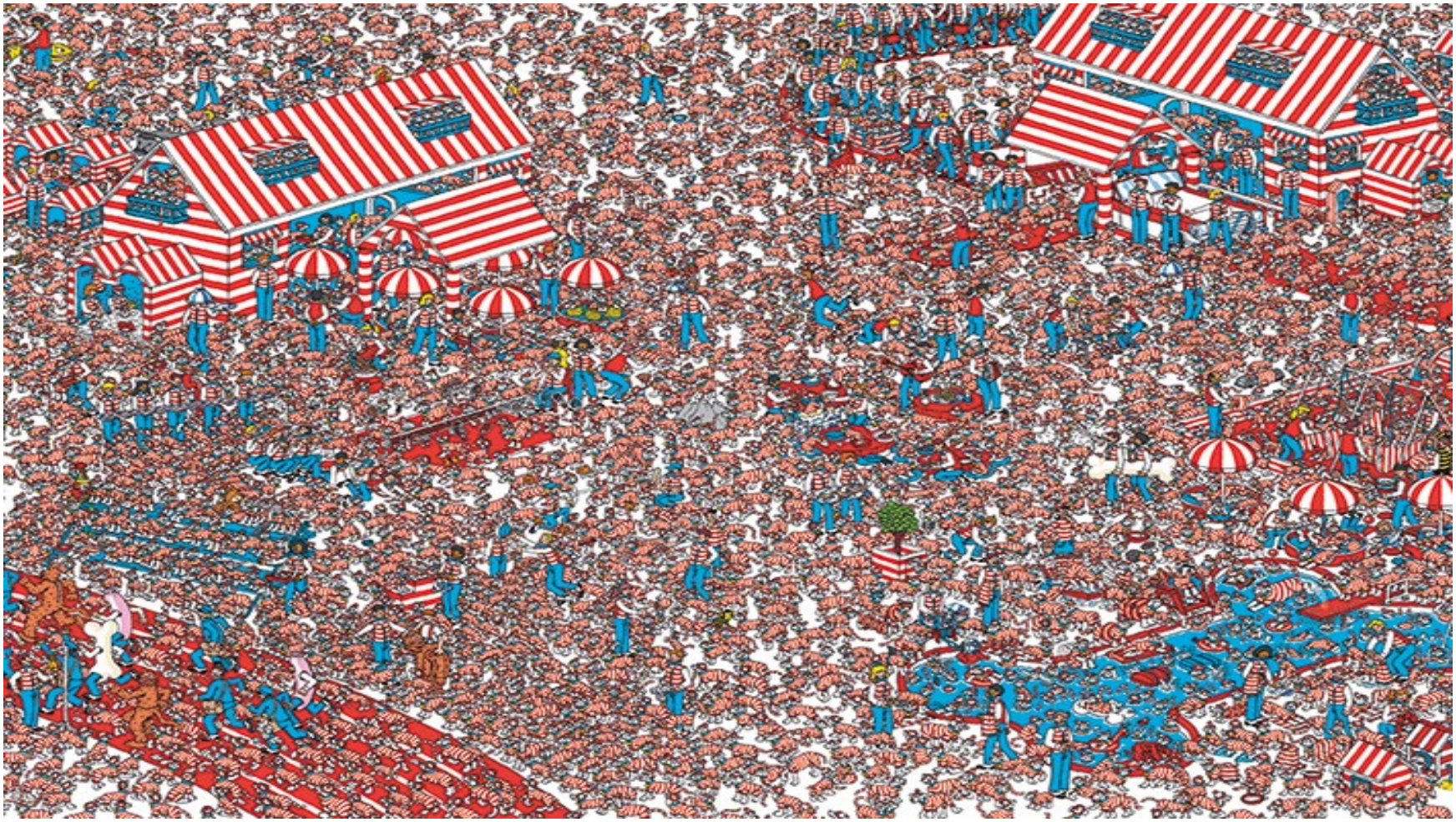
CLL-IPI Lancet Oncology 2016

Minimal residual leukaemia

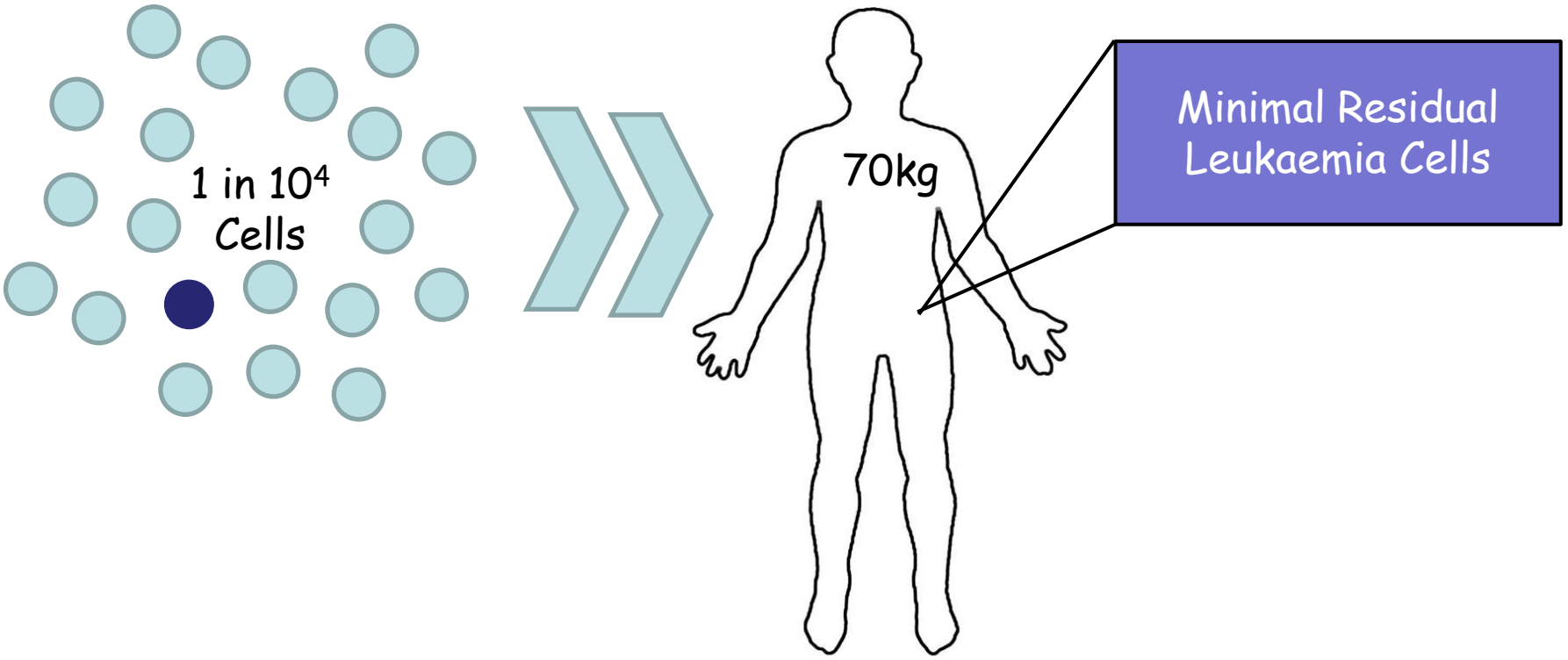


Remission is defined normal blood count, normal bone marrow and resolution of lymphadenopathy

Detection of Minimal Residual Disease (MRD)

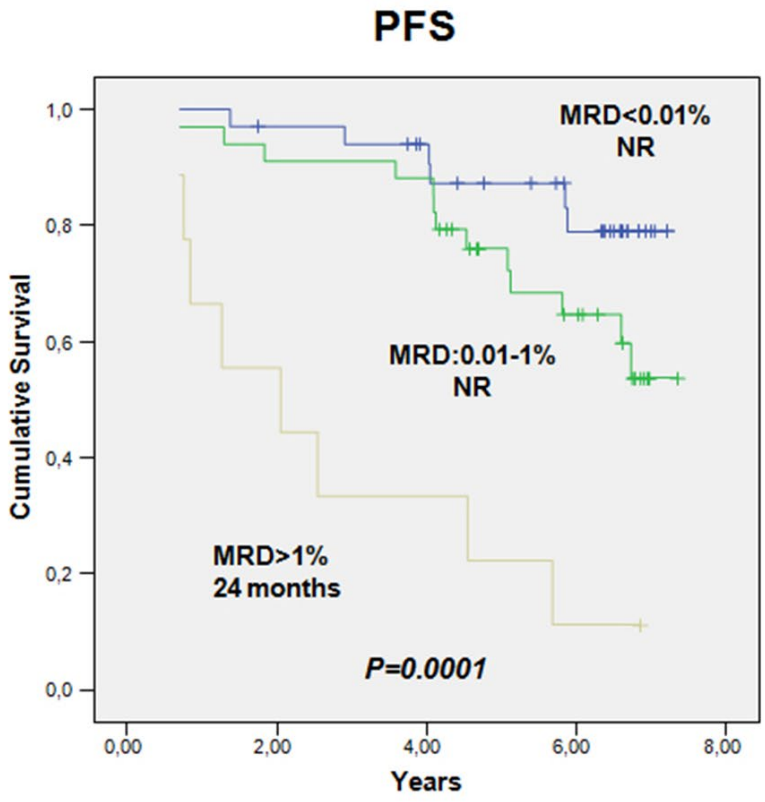


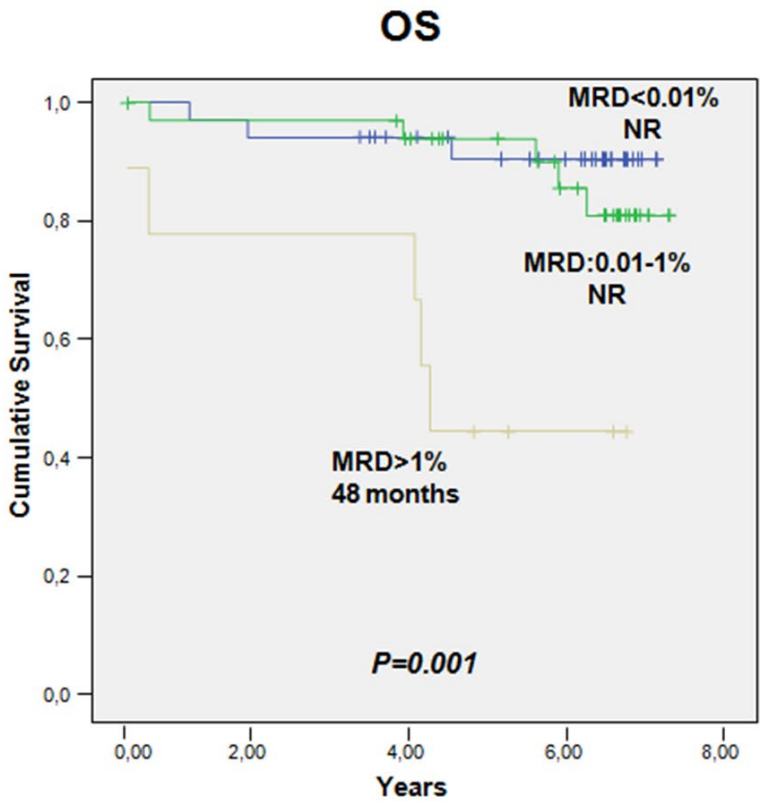
Detection of MRD in CLL by Flow Cytometry



Monitor patients post therapy
Improved outcomes if MRD negative

Prognostic Impact of MRD in CLL





Garcia-Marco et al Haematologica 2019

Biology of CLL Conclusions

Significant advances in understanding the genetics and biology of CLL

- Impact of TP53 status
- Impact of IGVH mutation status
- Emerging data from genomic sequencing studies

Moving into contemporary practice

Emerging role of MRD monitoring

Thank you

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our mission is to care, our vision is to cure

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FACULTY OF MEDICAL AND HEALTH SCIENCES

The Family of

Marijana Kumerich