

# Myeloma XI genetics

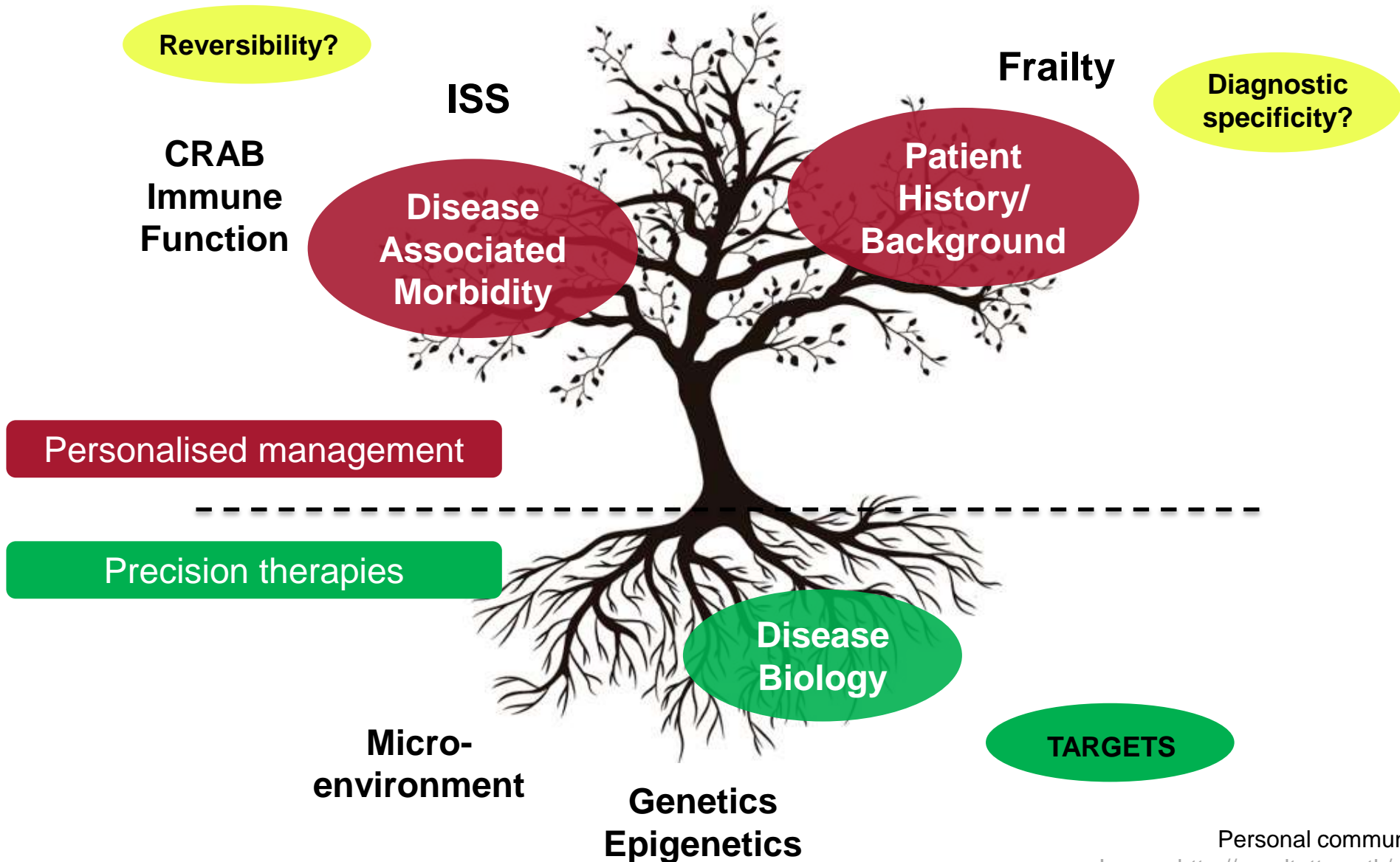
Dr Martin Kaiser

The Institute of Cancer Research & Royal Marsden Hospital, London, UK

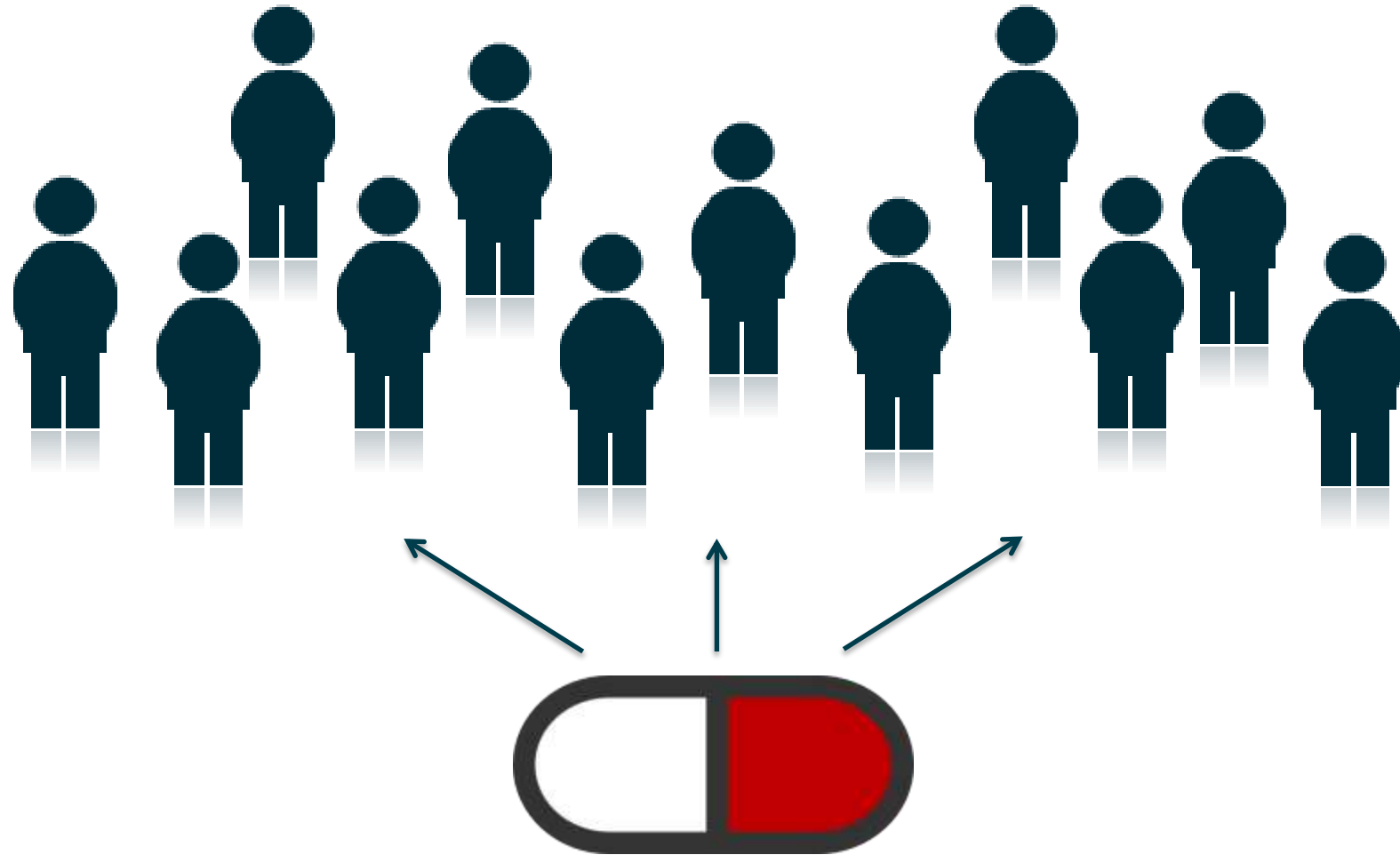
UKMF Autumn Day, 08/11/2018



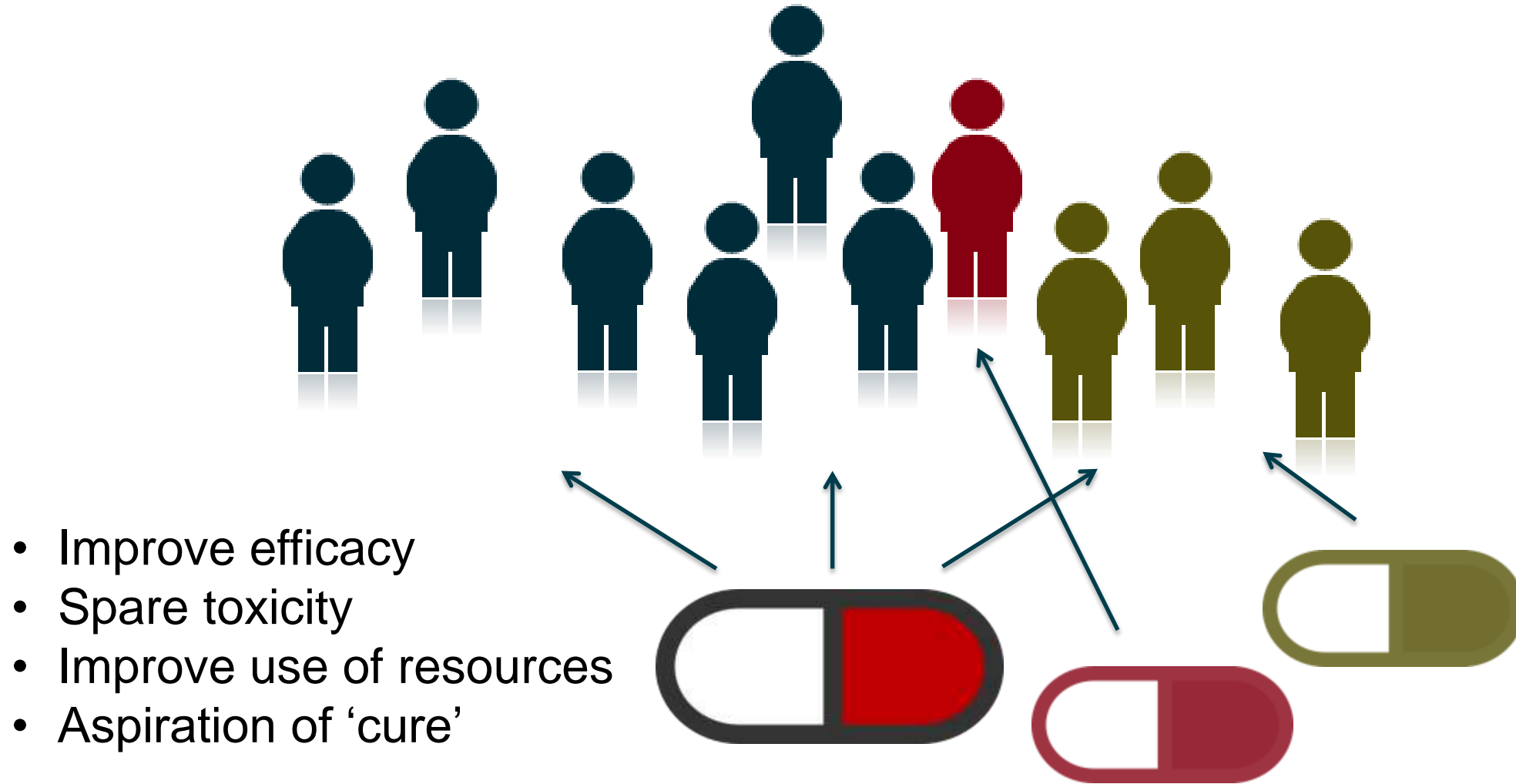
# Challenge: background and disease morbidity



# Current treatment status



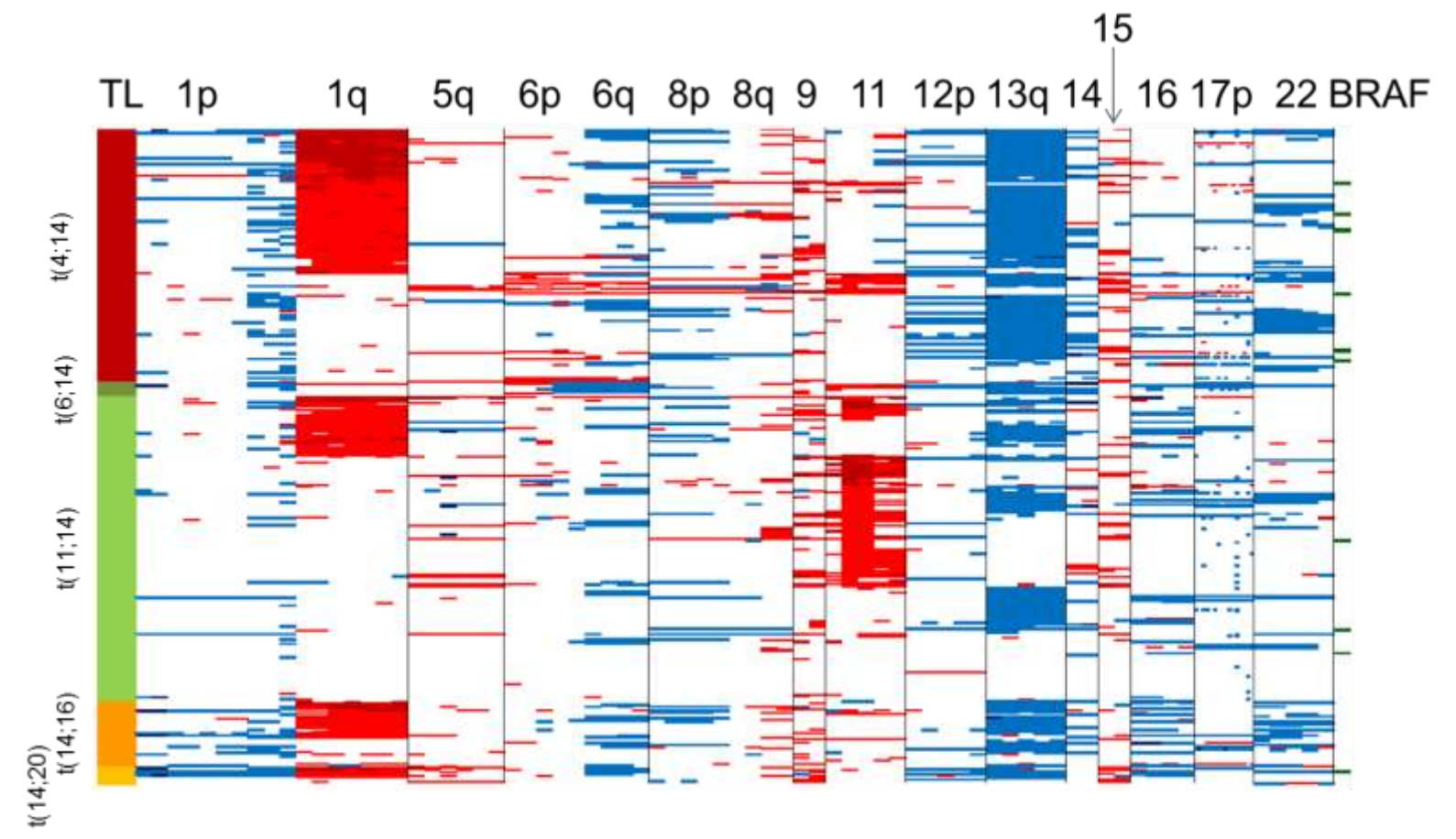
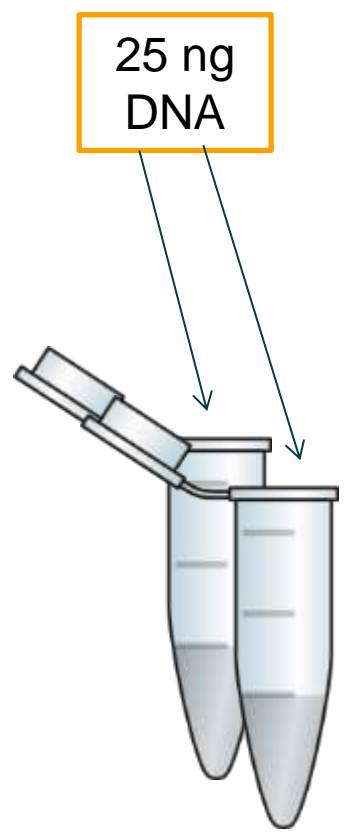
# Stratified treatment approach



## Molecular markers for stratified medicine

# Accessible molecular biomarker profiling

## MLPA



→ Sensitivity/specificity equal to FISH (MRC Myeloma IX)  
 → Used in standard-of-care genetic laboratories

# Meta-analysis of 1,905 NDMM (Myeloma IX & XI)

**Myeloma IX**  
n=869

**Myeloma XI**  
n=1,036

**Combined**  
n=1,905  
HRs OS

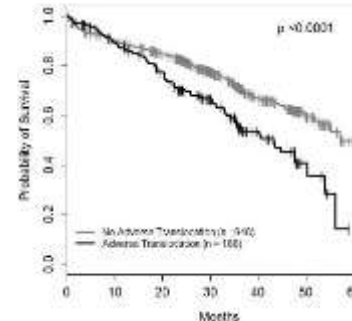
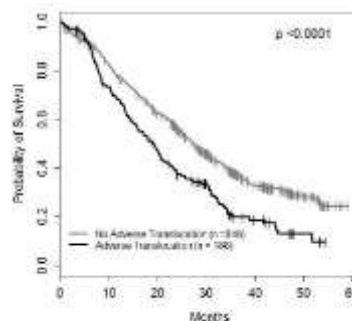
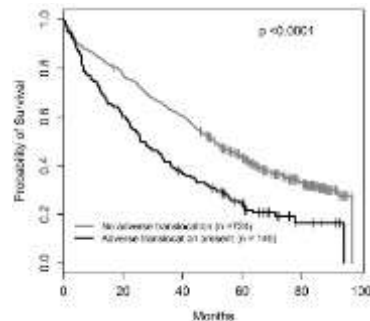
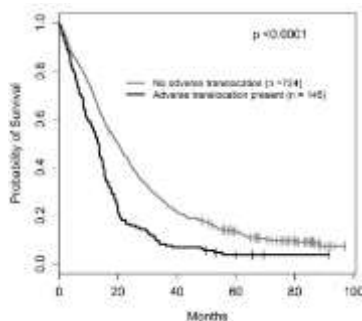
**PFS**

**OS**

**PFS**

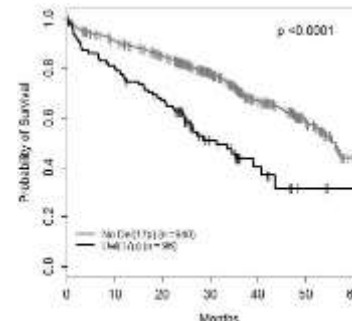
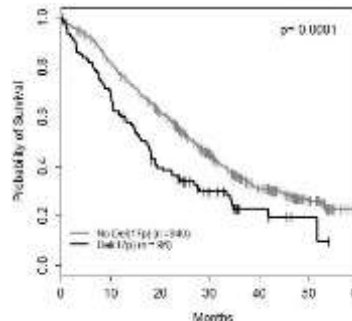
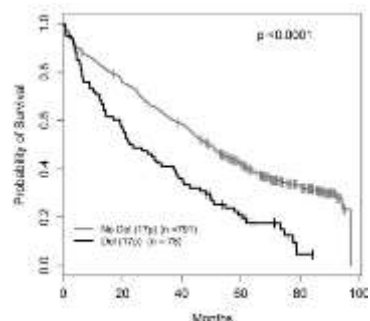
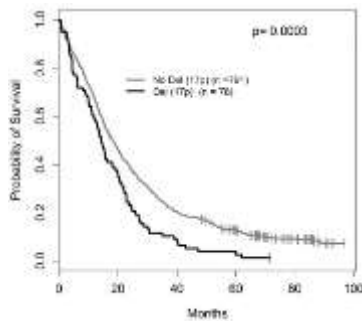
**OS**

**Adverse TL**



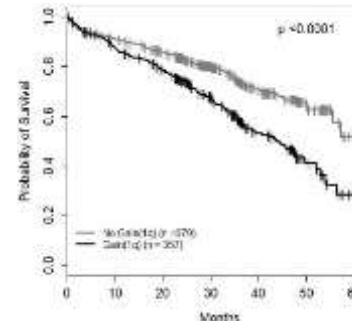
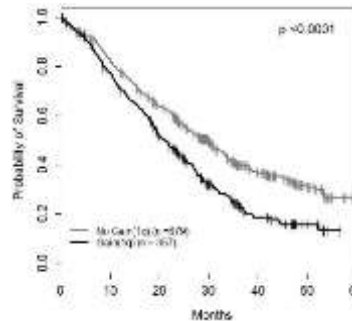
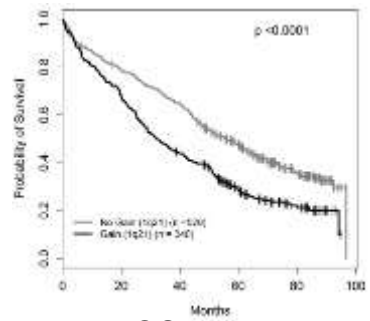
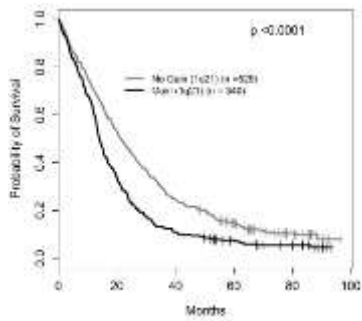
**1.73**  
( $P=1.63 \times 10^{-11}$ )

**Del(17p)**



**2.10**  
( $P=8.86 \times 10^{-14}$ )

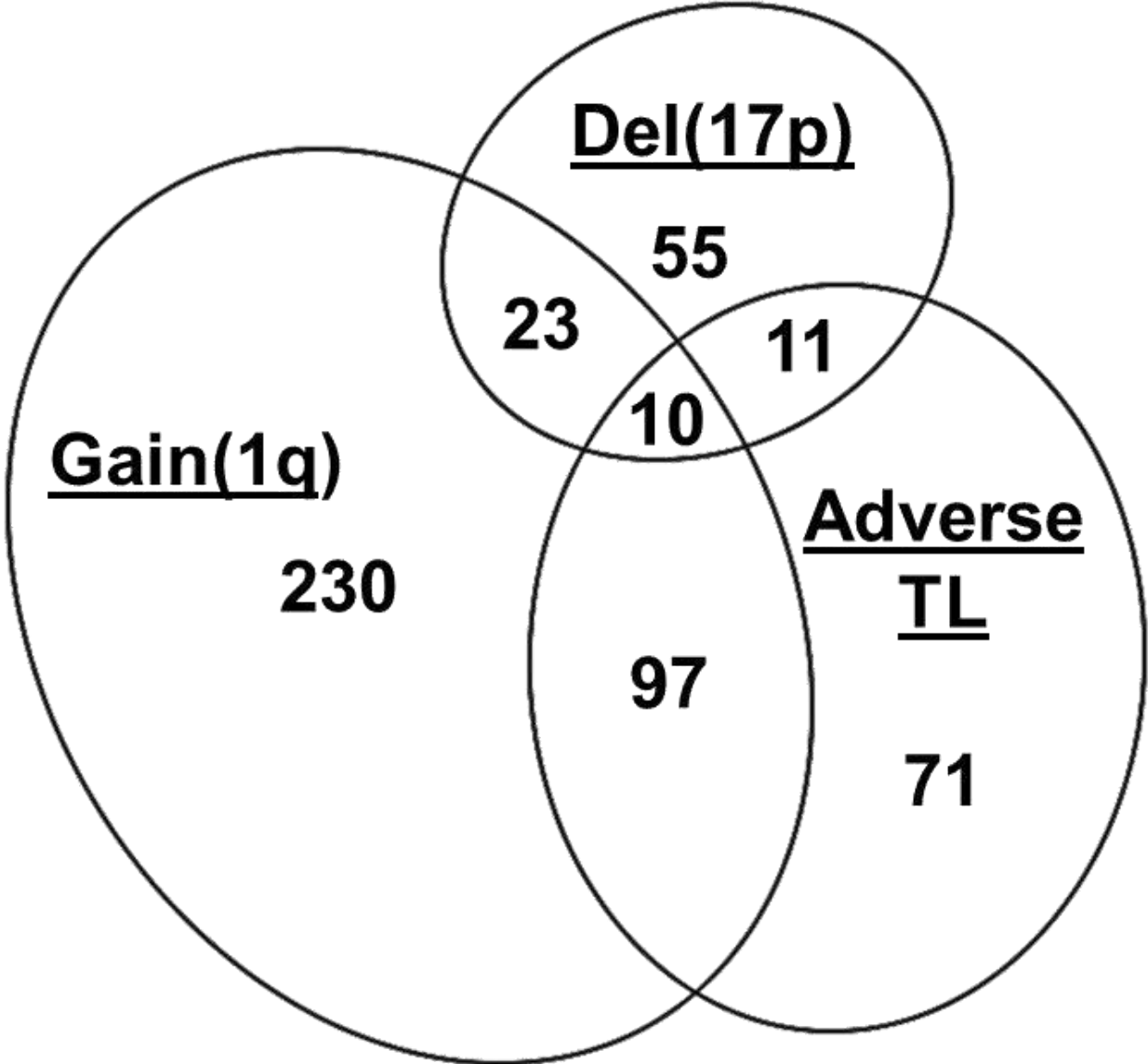
**Gain(1q)**



**1.68**  
( $P=2.18 \times 10^{-14}$ )



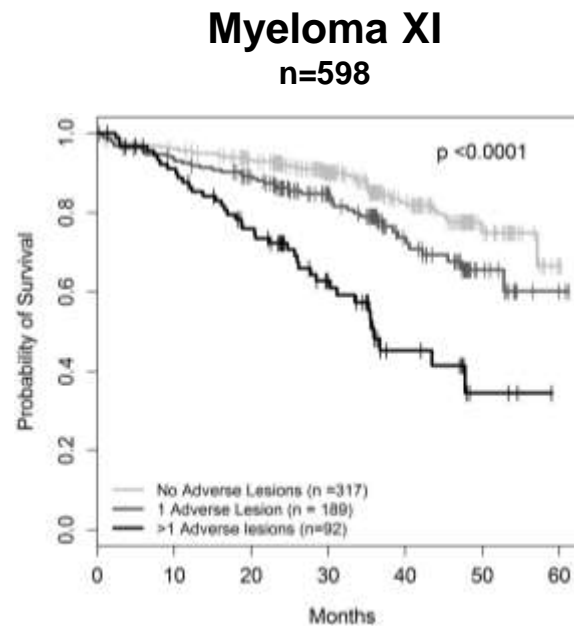
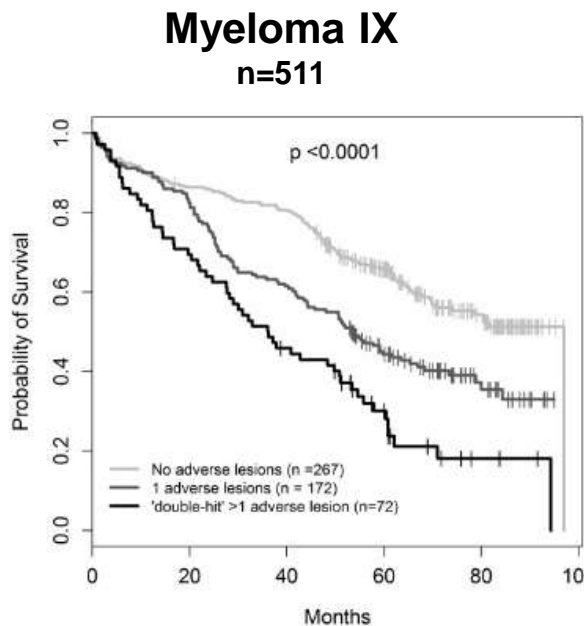
# High-risk lesions inter-relationship



TL, translocation.

# 'Double-hit' genetics in younger, fitter patients

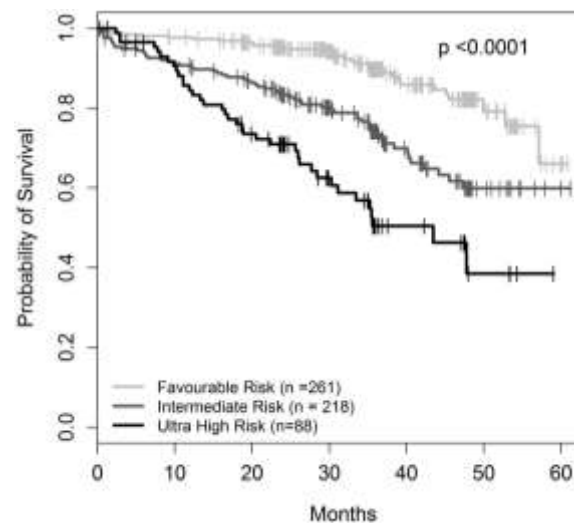
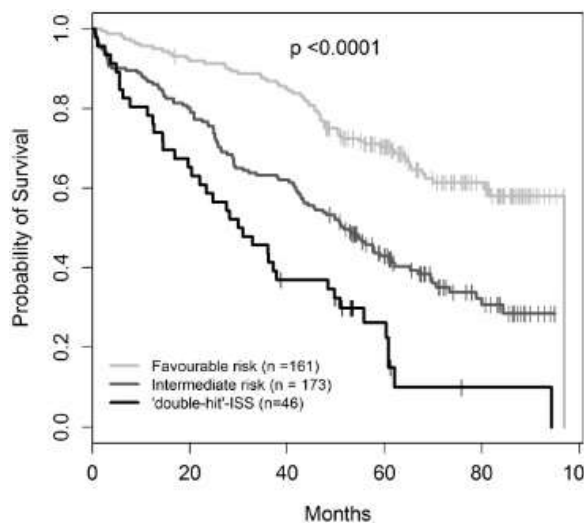
'double-hit'



**Combined**  
n=1,109  
HRs OS

**3.19**  
( $P=1.23 \times 10^{-18}$ )

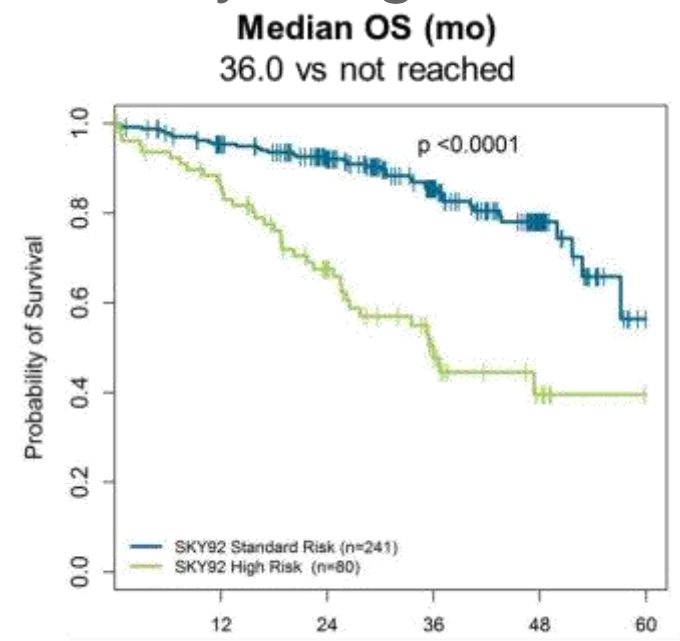
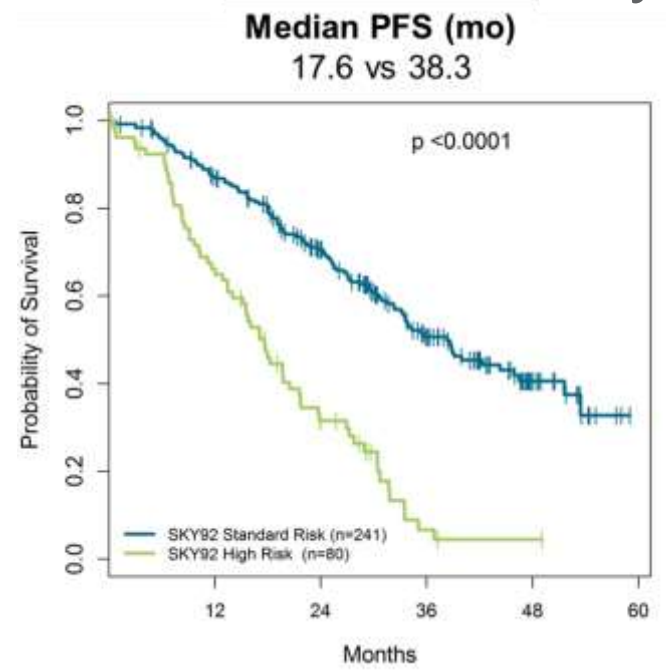
'double-hit'-ISS



**4.79**  
( $P=5.10 \times 10^{-23}$ )

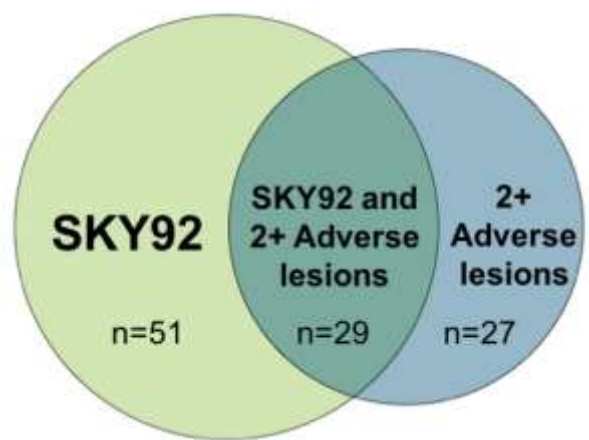


# GEP SKY92 MMProfiler – Myeloma XI younger, fitter patients

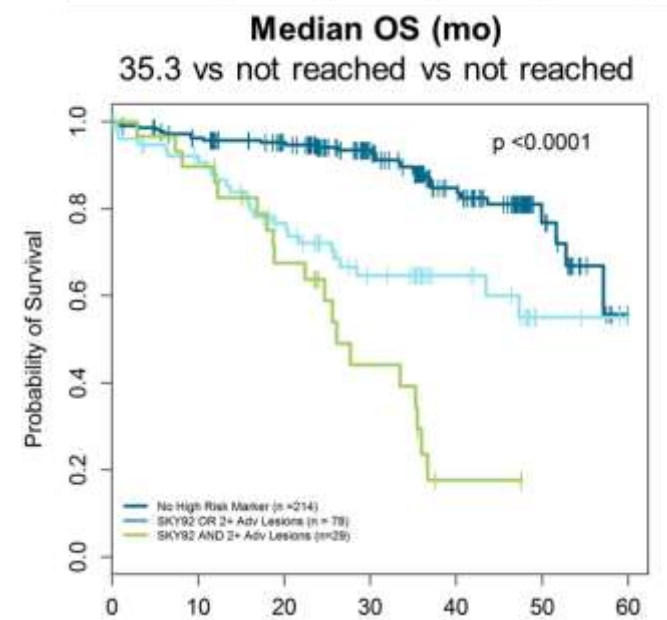


**HR OS**

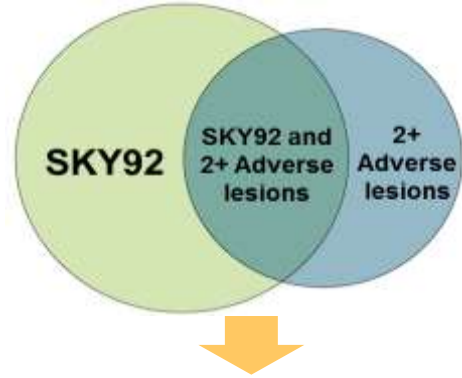
**4.0 ( $P=4.06 \times 10^{-9}$ )**



**33% (107/321 pts)**



# Penta-therapy to counteract rapid disease evolution



Molecularly & clinically matched  
High Risk group Myeloma XI/XI+

Induction  
Single Vel-augmented ASCT  
Consolidation 1:  
6 cycles  
Consolidation 2:  
12 cycles  
Maintenance  
until progression

**Dara-CVRd**

**Velcade-HD-MEL+ASCT**

**Dara-VRd**

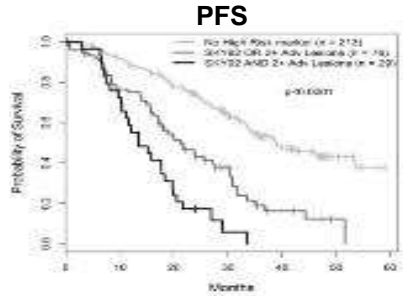
**Dara-VR**

**Dara-R**

**Bayesian design**



**MRD-neg  
Progression**



**PFS + PFS2  
comparison**

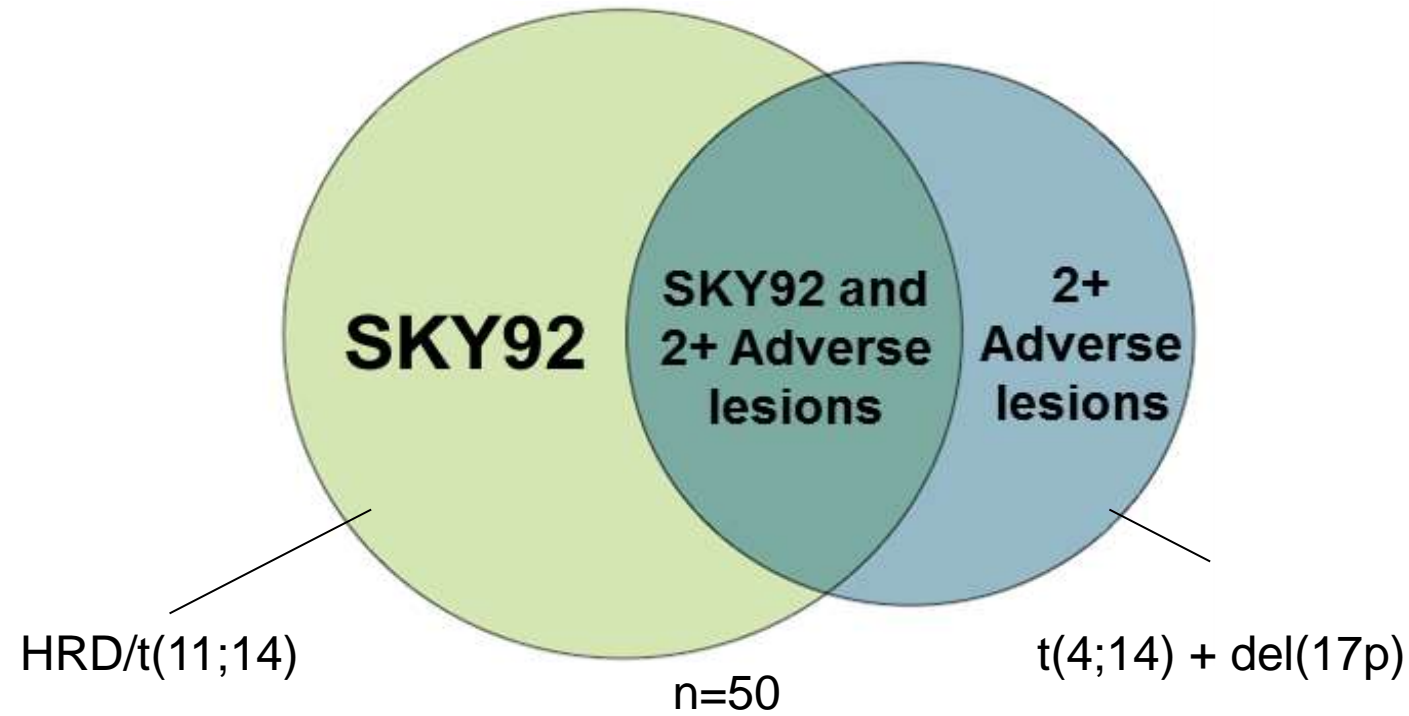


**CTD/CRD/  
KCRD**

**HD-MEL+ASCT**

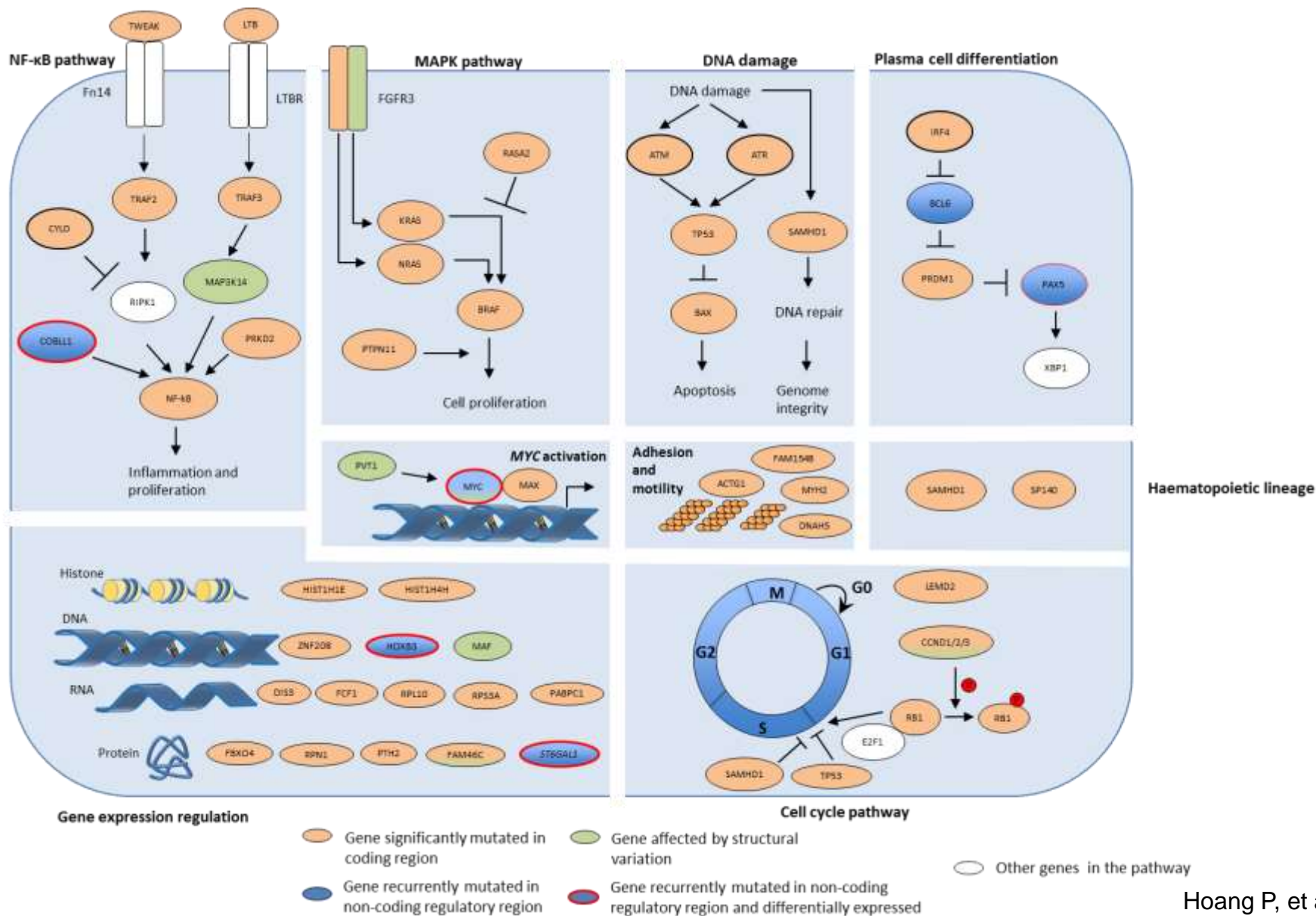
**Maintenance**

# Highly successful recruitment



**Questions – please contact Matthew Jenner and Martin Kaiser**

# Characterising the mutational landscape

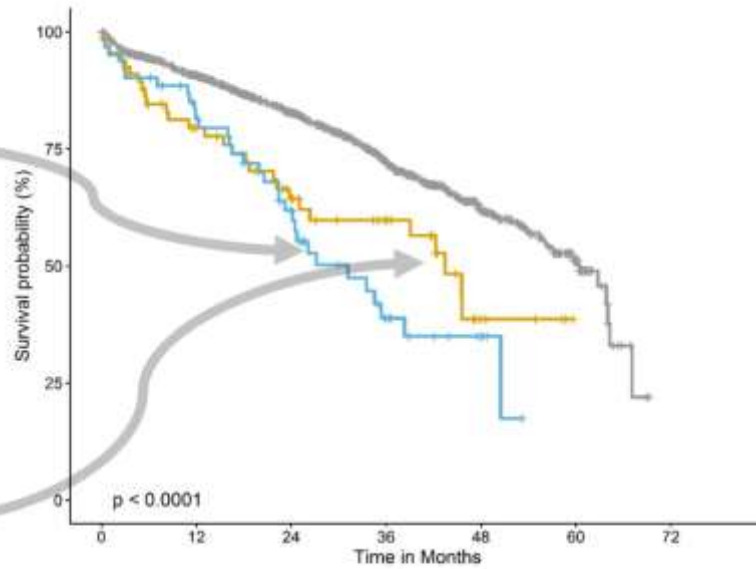
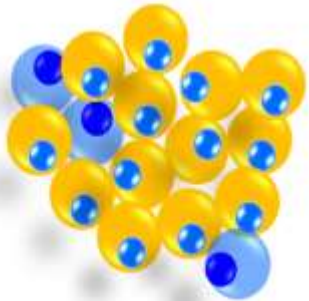




# Mapping disease evolution

Near-Clonal TP53 deletion

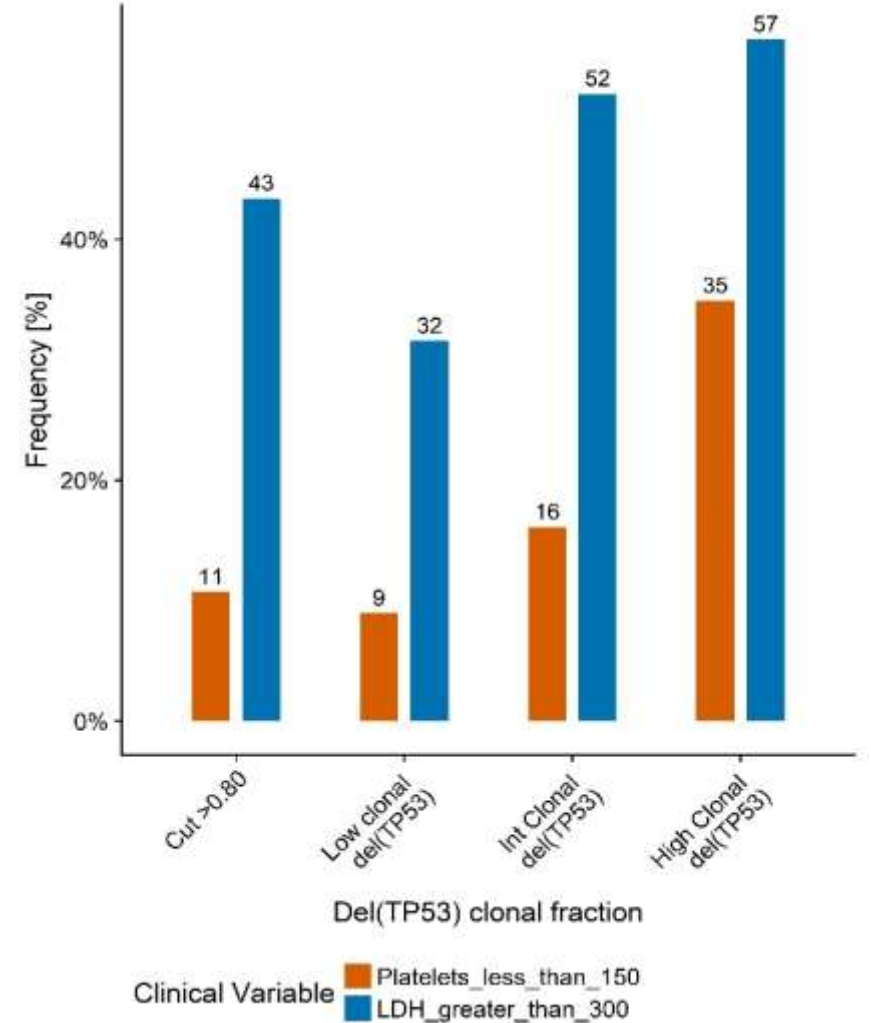


Sub-clonal TP53 deletion



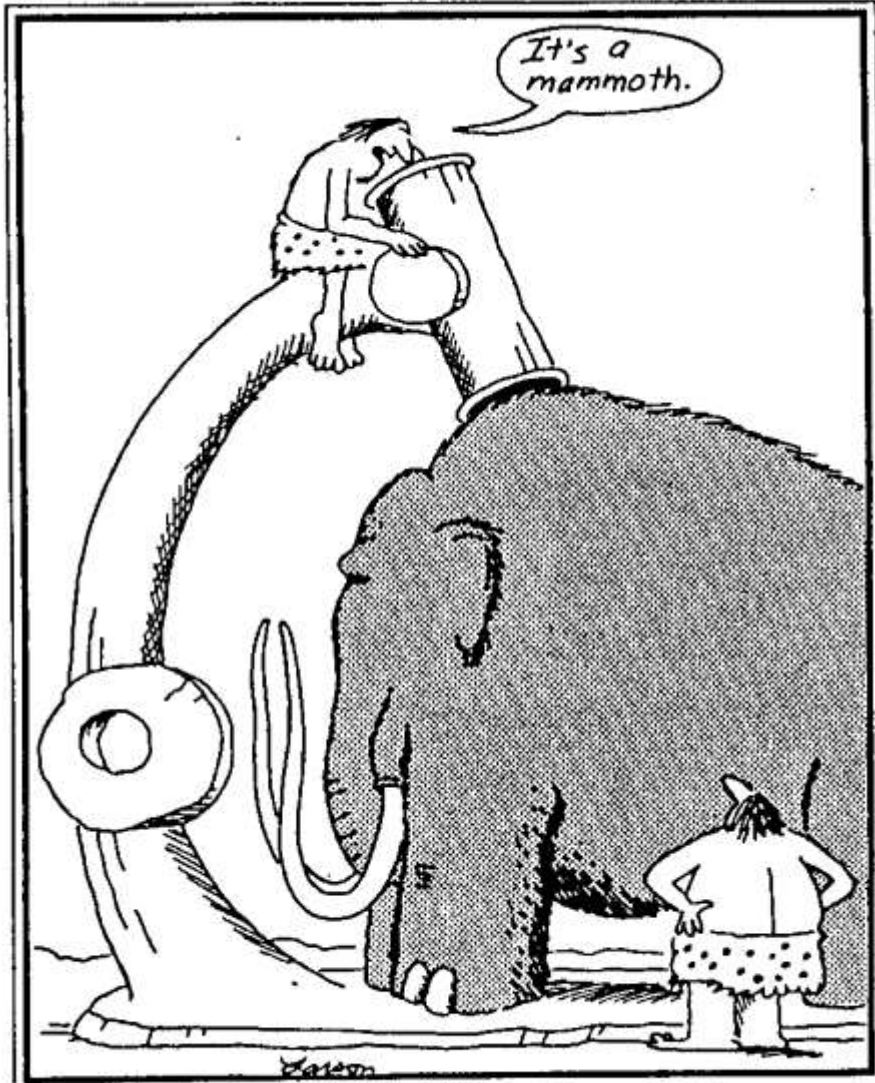
 TP53 not deleted  
 Deleted TP53

Clinical changes associated with increasing size of TP53 deleted clone

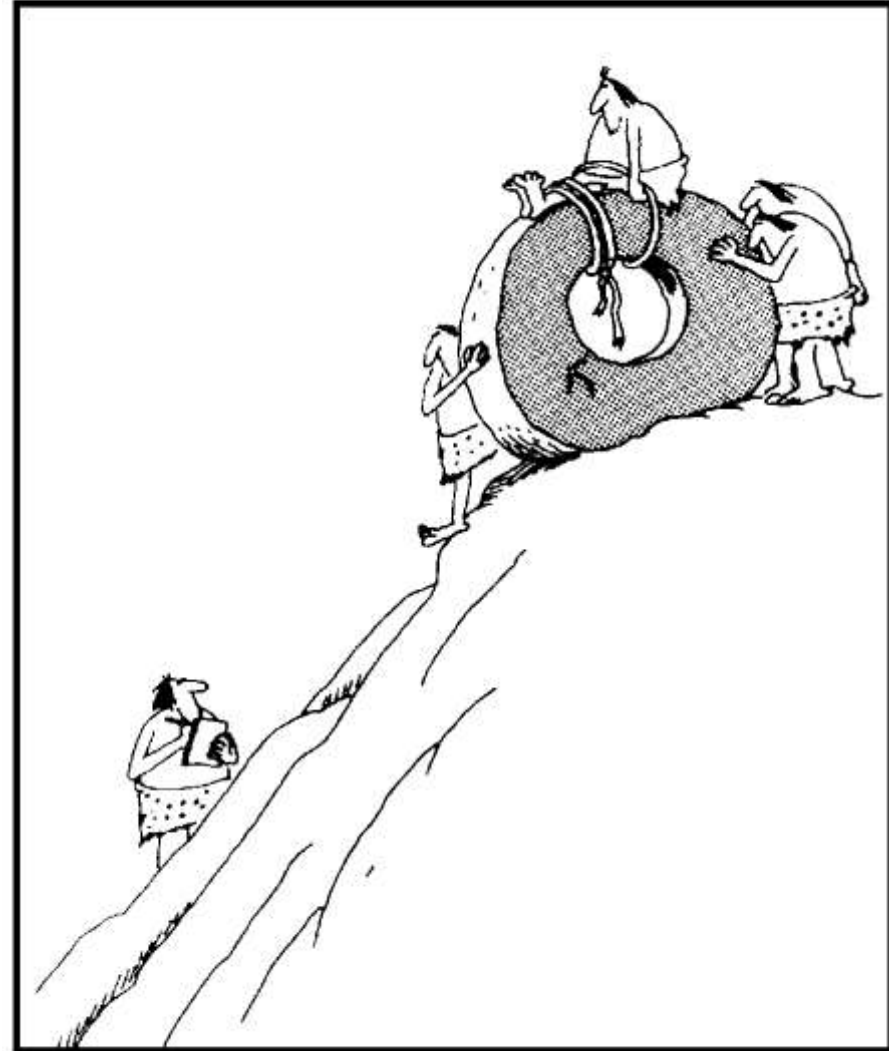




# Issues in cancer genetics...



Early microscope



Early experiments in transportation





in partnership with  
*The ROYAL MARSDEN*  
NHS Foundation Trust

Myeloma Lab:

Martin Kaiser

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Vallari Shah

David Johnson

Sidra Ellis

Jack Kendall

Amy Price

Karen Menezes

Scott Kimber

Fabio Mirabella

Biomedical Research  
Council

Christina Messiou



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Samantha Hinsley  
Roger G Owen  
Gordon Cook



Matthew Jenner



Mark Drayson  
Guy Pratt

Graham Jackson



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Questions?