A novel algorithm to identify, characterize and define the prognostic impact of complex catastrophic events in Multiple Myeloma

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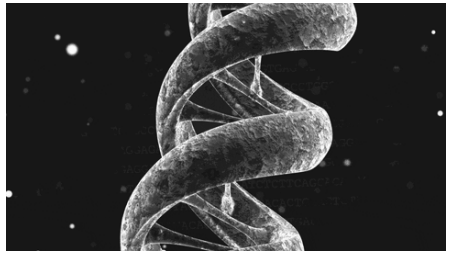
Conflict of interest

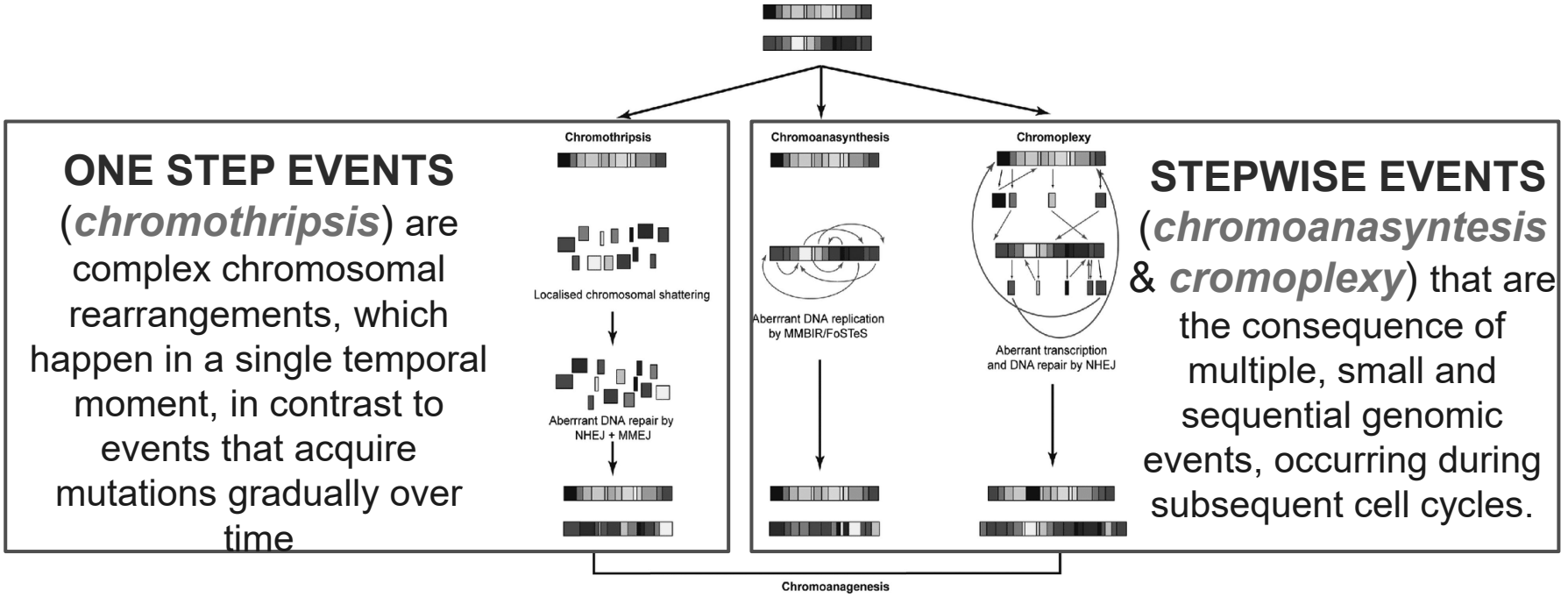
The authors declare no conflict of interests

Complex Catastrophic Events (CCEs)



➔ **neoplastic cells** are characterized by ***genomic instability***, which might cause the ***rapid evolution*** of the tumour

➔ ***chromoanagenesis*** = complex structural rearrangements leading to the formation of new aberrant chromosomes



ONE STEP EVENTS (***chromothripsis***) are complex chromosomal rearrangements, which happen in a single temporal moment, in contrast to events that acquire mutations gradually over time

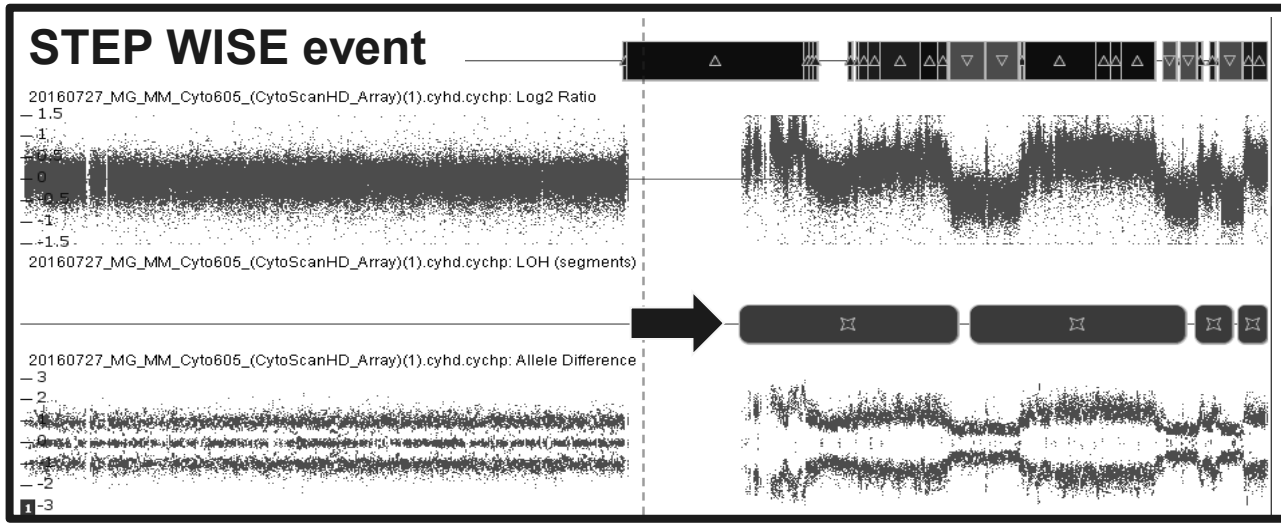
STEPWISE EVENTS (***chromoanasyntesis*** & ***cromoplexy***) that are the consequence of multiple, small and sequential genomic events, occurring during subsequent cell cycles.

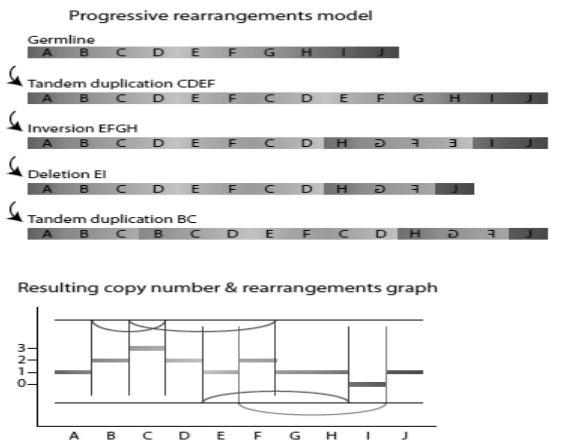
chromoanagenesis incidence = ***2-3%*** in all tumours

P.J Stephens et al.; 2011 Jan , Cell
M.N.H. Luijten et al; 2018; Sep; Mutat. Res

CCEs in Multiple Myeloma

STEP WISE event

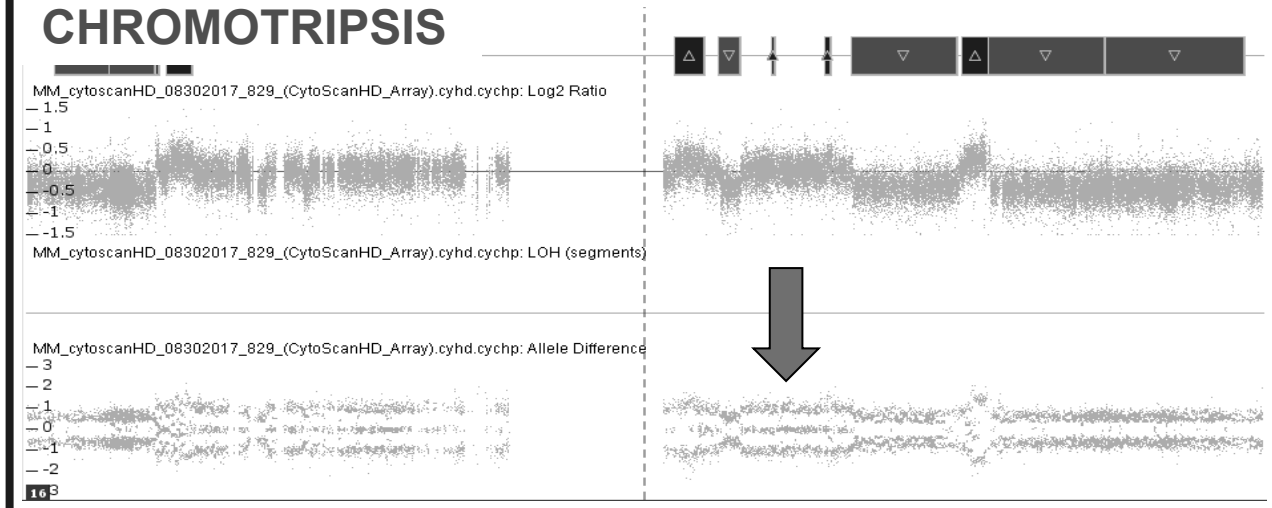


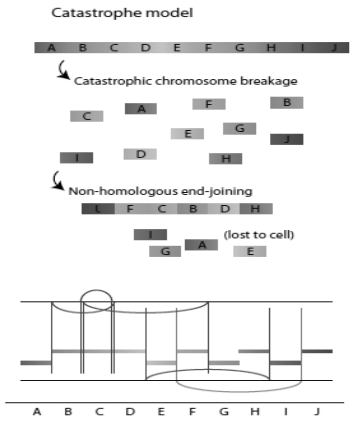


>3 CN state

LOH in 2N region

CHROMOTRIPSIS

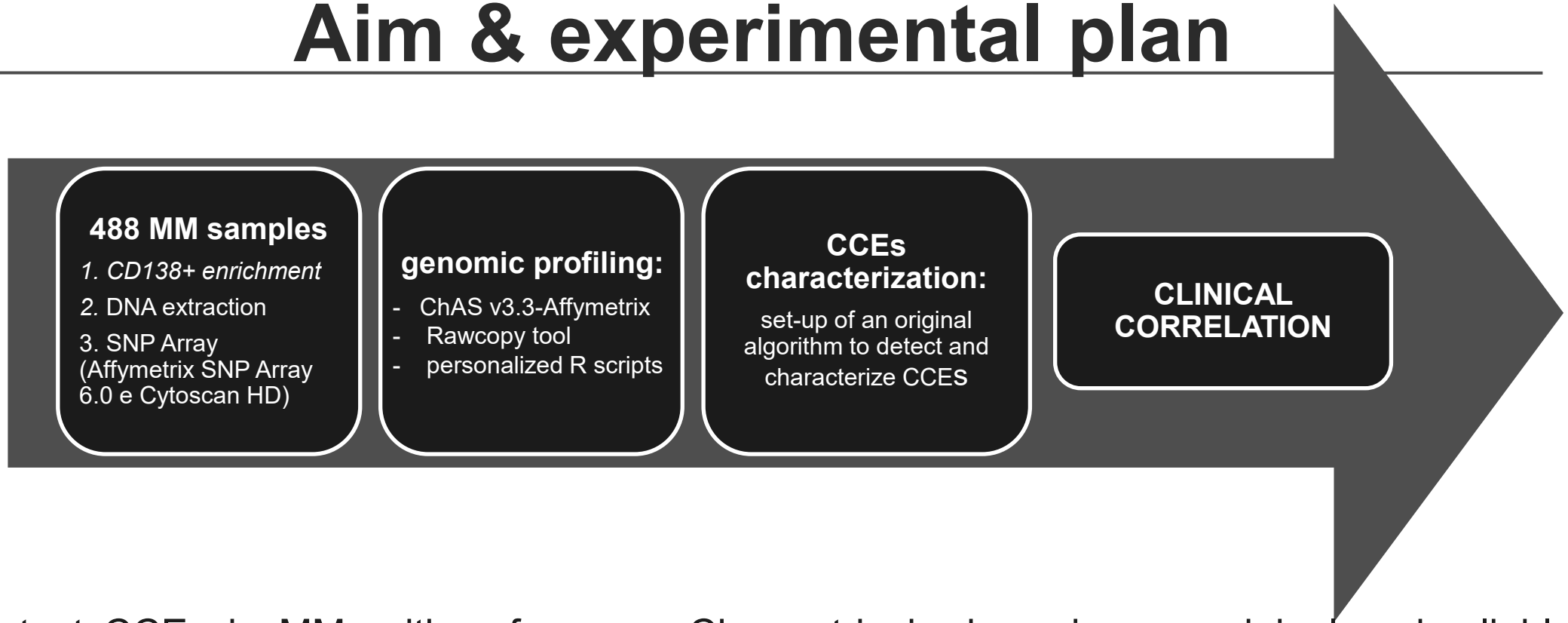




<3 CN state

HETEROZIGOSITY in 2N region

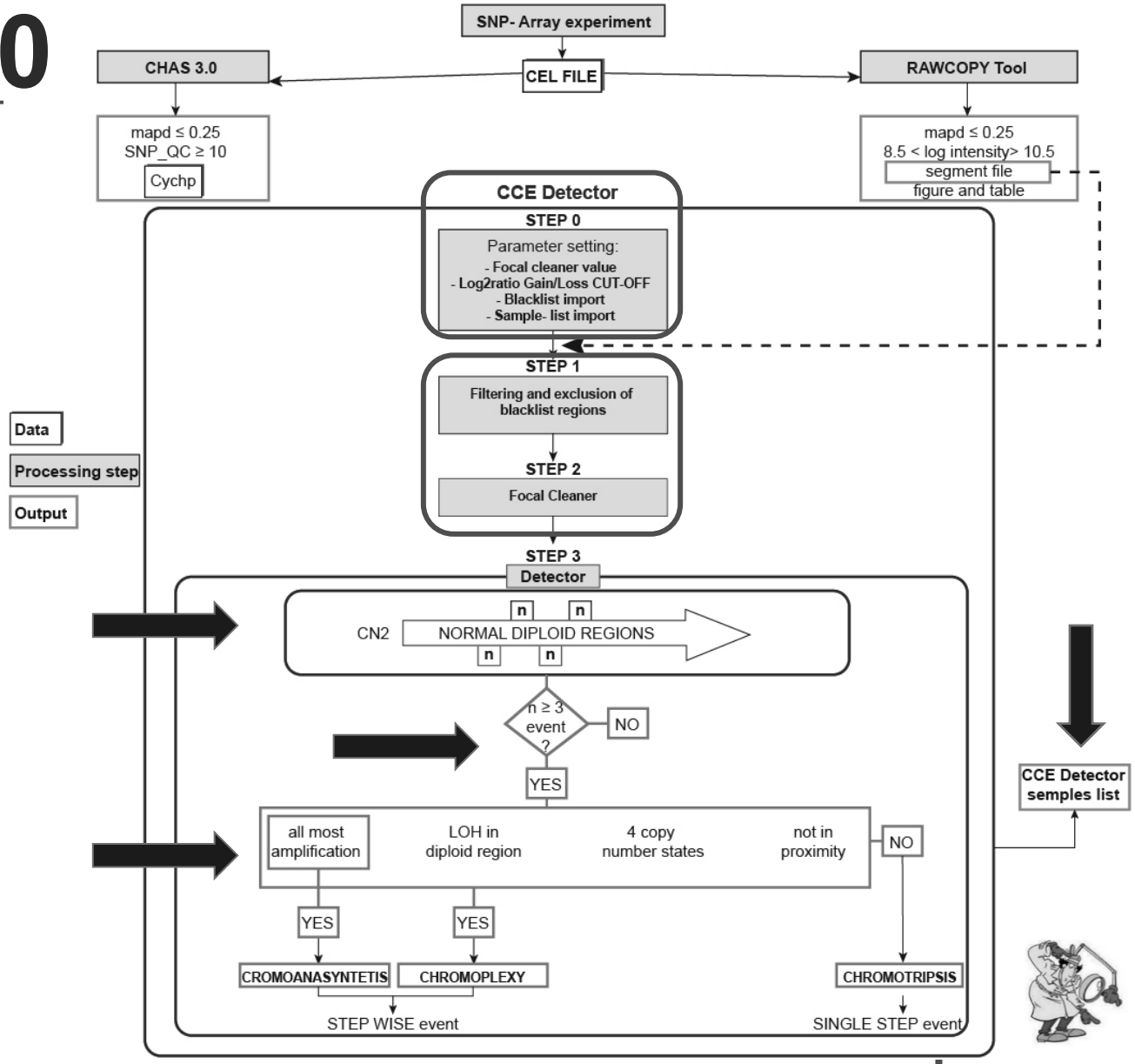
Aim & experimental plan



1. to detect CCEs in MM, with a focus on Chromotripsis, by using an original and reliable bio-informatic algorithm
2. to characterize the genetic and genomic context of Chromotripsis
3. to correlate the presence of Chromotripsis with patient prognosis

C.C.E. detector 3.0

- count of the CN changes as compared to the diploid region (2N)
- if the total number of CN changes is >3, it continues with detection and categorization of the event
- the events are categorized according to the reported guidelines
- the file output includes a list of detected events and their chromosomal position for each individual sample



Frequency & co-segregation

Diagnosis 488 pts			Chromotripsis
			46
			9%

chromotripsis **events are mainly carried by specific chromosomes**

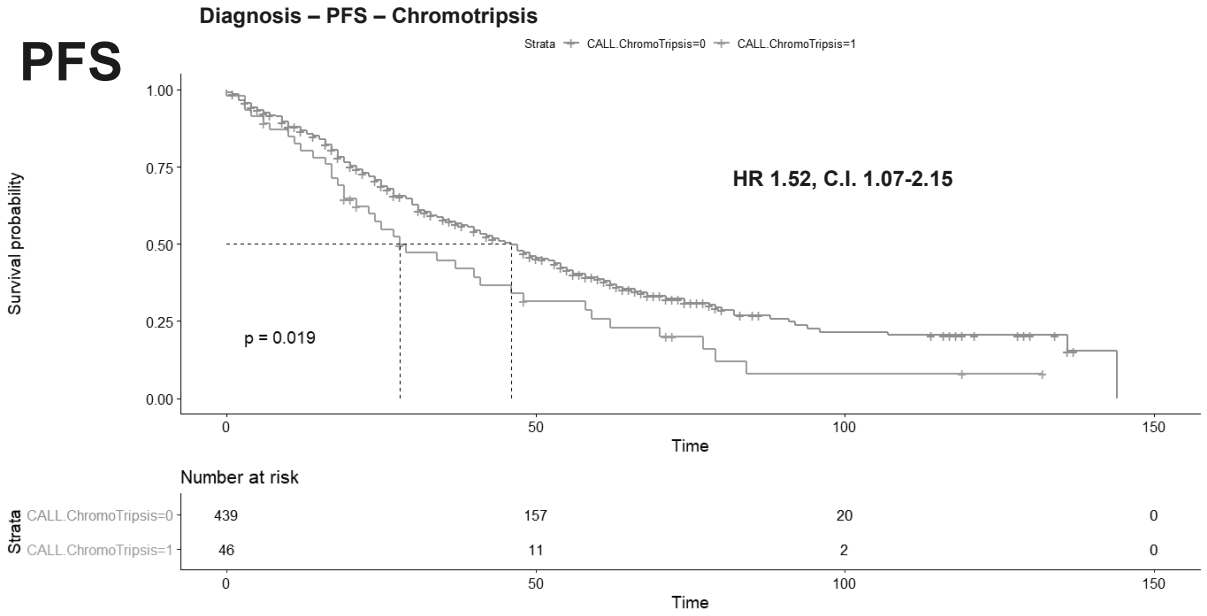
Chromosonal aberration	Targeted gene		
del chr 17p	**17p**		
	del *TP53*		
	mut *TP53*		
del chr 1p			
	del *CDKN2C*		
	del *FAF1*		
amp chr 1q			
	amp *CKS1B*		
Traslocations		**0.002**	**3.4**
t(4;14)		**0.003**	**2.01**
t(14;20)		**0.01**	**8**
t(14;16)		**0.04**	**3.55**

Position	p_value
chr 1p	<0.001
chr2q	<0.001
chr 11q	<0.001
chr 22q	<0.001

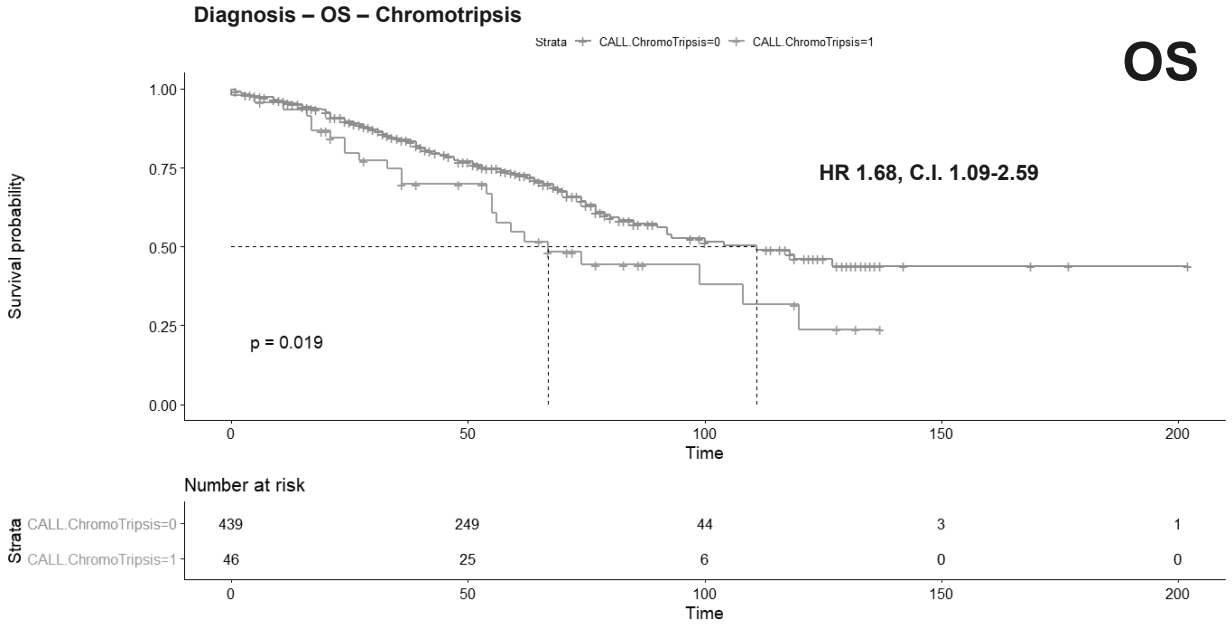
	p-value	HR
	0.009	5.24
	0.013	2.27
	0.03	2.75
	0.02	3.52
	>0.001	3.05
	0.009	2.35
del *XBP1*	>0.001	4.68

Chromotripsis is predictive of clinical outcome

PFS



OS



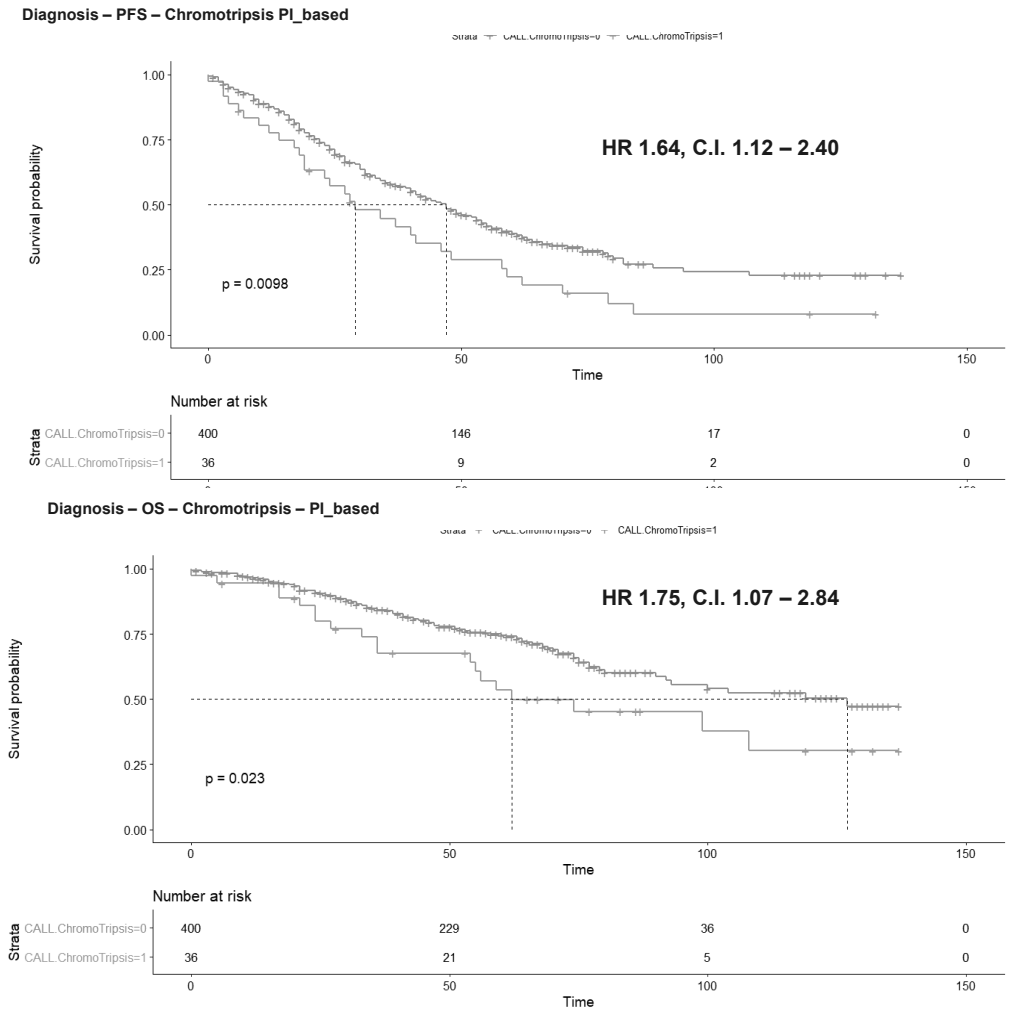
multivariate analysis

Event	p.value	C.I
CALL.ChromoTripsis	0.04601 *	1.0065 - 2.055
del *TP53* (17p13.1)	0.2854	0.4945 - 1.230
T(4;14)	0.00591 **	1.1275 - 2.041

Event	p.value	C.I
CALL.ChromoTripsis	0.0387 *	1.0246 - 2.490
del *TP53* (17p13.1)	0.2766	0.3298 - 1.373
T(4;14)	0.0011 **	1.2897 - 2.771

the impact of chromotripsis on PFS and OS is ***independent*** from other adverse prognostic factors

PI-based therapy & chromotripsis



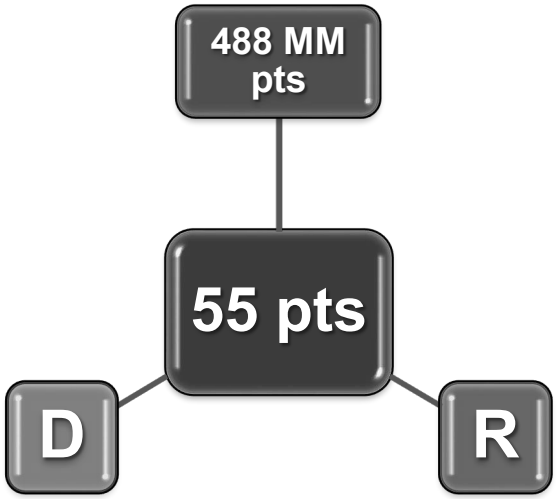
Masaki R. et al, 2016, Int J Hematol
Sinan X. et al., 2021,Cell and Molecular life Sciences

➔ ***ER stress pathway*** deregulation is related to the decrease of response to PI-based therapy

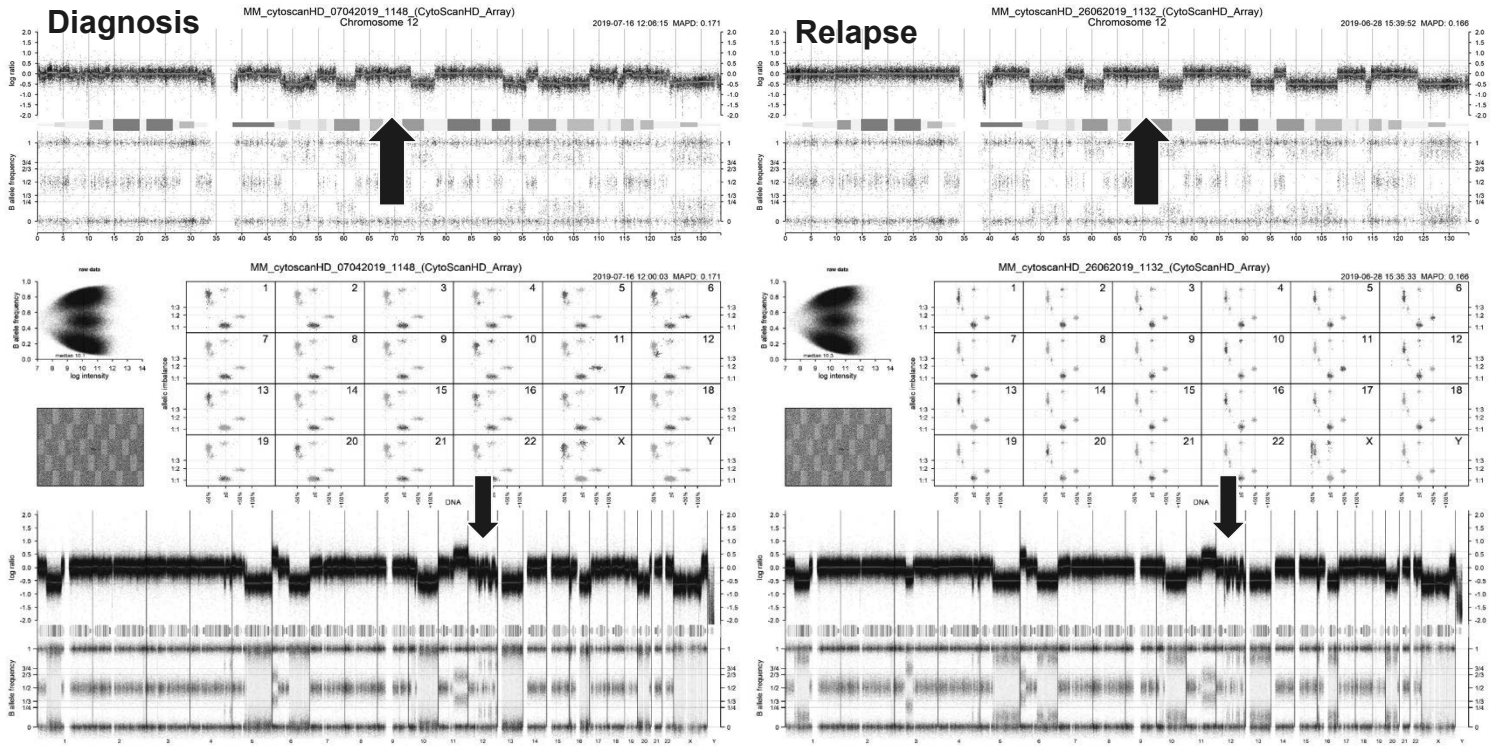
ER STRESS pathway's gene			
Targeted gene	**chr position**	**p_value**	**HR**
amp *XBP1*	22q12.1	ns	ns
del *XBP1*	**22q12.1**	**>0.001**	**4.68**
amp *ATF4*	**22q13.1**	**0.03**	**6.05**
del *ATF4*	**22q13.1**	**0.01**	**3.01**
amp/del *ATF6*	1q23.3	ns	ns
amp/del *CRBN*	3p26.2	ns	ns
amp/del *DDIT3 (CHOP)*	12q13.3	ns	ns
amp/del *EIF2AK3 (PERK)*	2p11.2	ns	ns
amp/del *ERN1 (IRE1a)*	17q23.3	ns	ns

➔ **CNAs** in ***2 genes*** of the ***ER stress pathway*** correlates with the presence of chromotripsis

Chromotripsis & Clonal Evolution



Chromotripsis		
Diagnosis Clonal Subset 55 pts	n° event	4
	% events	7%
Relapse Clonal Subset 55 pts	n° event	4
	% events	7%



➔ **Chromothripsis** is detectable as clonal event in **MGUS** and **SMM** that will progress to multiple myeloma.

➔ **Chromothripsis** is conserved over time after precursor progression and at relapse after treatment, as clonal, without any significant changes in its structure and copy number profile.

Maura F et al, 2021, Semin Cell Dev Biol

Conclusions

1. ***CCEs Dectector 3.0*** highlights and characterizes CCEs across the whole genome

2. CCEs frequency was ***36%***; chromotripsis frequency was ***9%***

3. chromotripsis ***significantly impact*** PFS and OS of newly diagnosed MM patients

4. chromotripsis events significantly correlate with CNAs in ***TP53***, ***XBP1***, ***ATF4***

5. in the genome throughout MM course, thus suggesting their key-role in driving disease progression

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