

A machine learning model based on tumor and immune biomarkers to predict undetectable measurable residual disease (MRD) in transplant-eligible multiple myeloma (MM)

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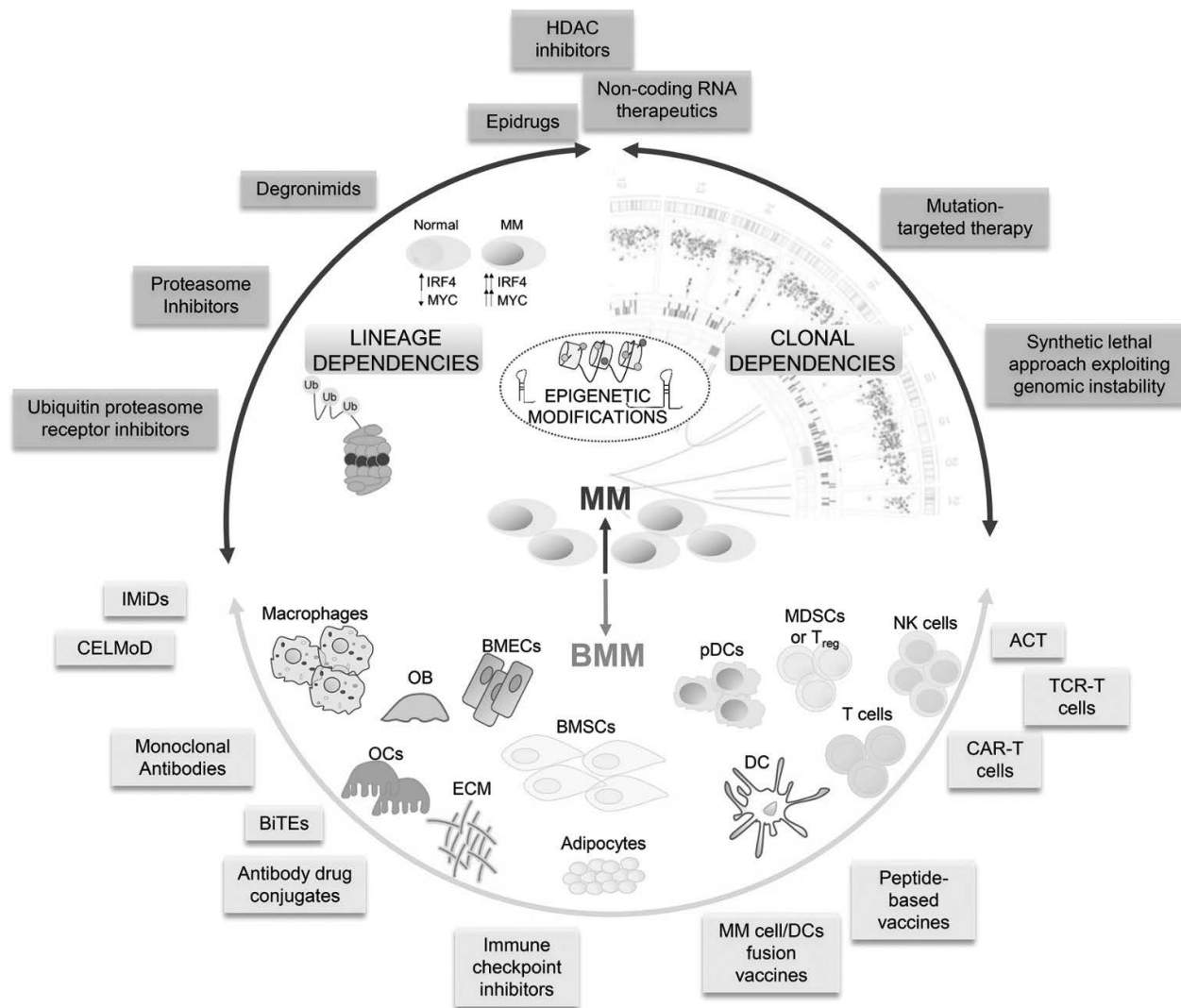
Saturday, September 11, 2021

Disclosures

- **Puig:** *Amgen, Celgene, Janssen, Takeda, The Binding Site:* honoraria; *Amgen, Celgene, Janssen, Takeda:* consulting or advisory; *Celgene:* speakers' bureau; *Celgene, Janssen, Amgen, Takeda:* research funding; *Amgen, Celgene, Janssen, Takeda:* travel accommodations and expenses.
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- **Lahuerta:** *Celgene, Takeda, Amgen, Janssen, Sanofi:* consulting or advisory role; *Celgene:* travel accommodations.
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- **Paiva:** *Adaptive, Amgen, BMS, Celgene, Janssen, Kite Pharma, Sanofi, Takeda:* honoraria for lectures from, and membership on advisory boards; *Celgene, EngMab, Roche, Sanofi, Takeda:* unrestricted grants; *BMS, Celgene, Janssen, Sanofi:* consultancy.
- The remaining authors declare they have no competing interests.

The (r)evolution of current therapies

Unmet need of biology-based individualized treatment



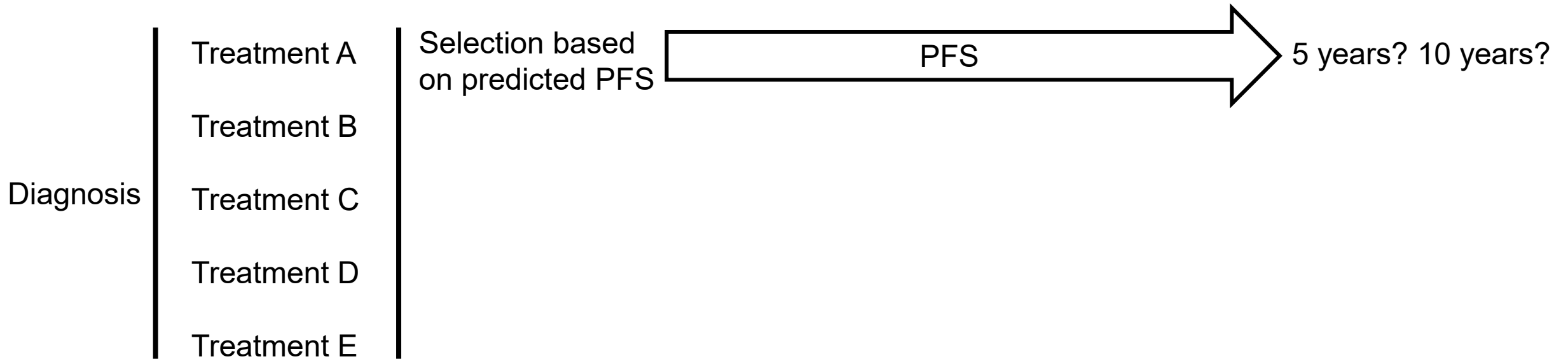
Possible models towards individualized treatment

How to select and confirm the success of treatment selection?



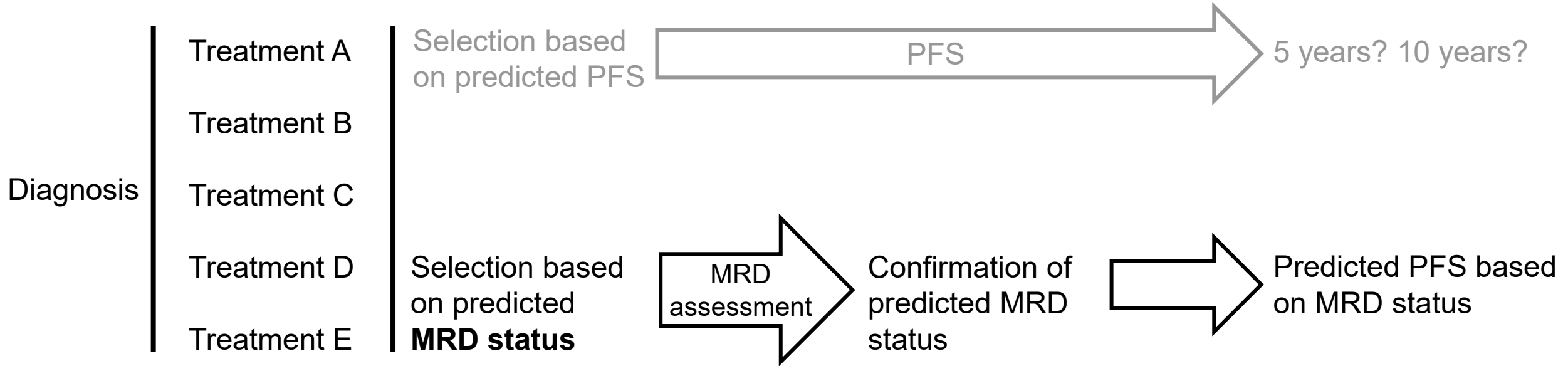
Possible models towards individualized treatment

Confirmation of predicted PFS can only be done retrospectively



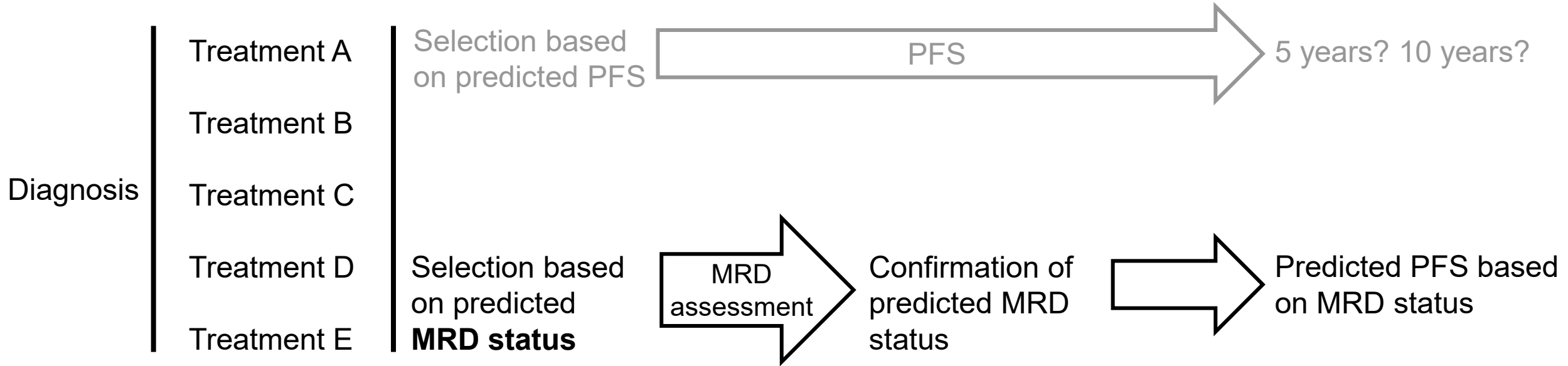
Possible models towards individualized treatment

Predicting undetectable MRD can be confirmed earlier



Possible models towards individualized treatment

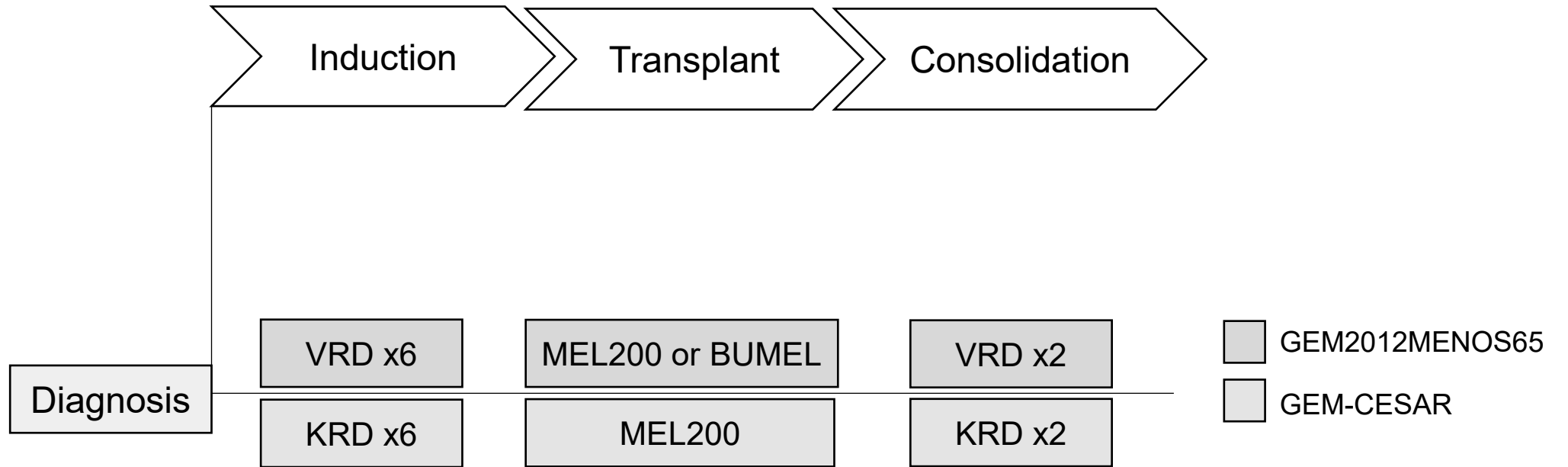
Predicting undetectable MRD can be confirmed earlier



This idea has not been investigated previously; therefore, we sought to explore this concept and define a machine learning model **to predict undetectable MRD in newly-diagnosed transplant-eligible MM patients**, treated with a standard of care.

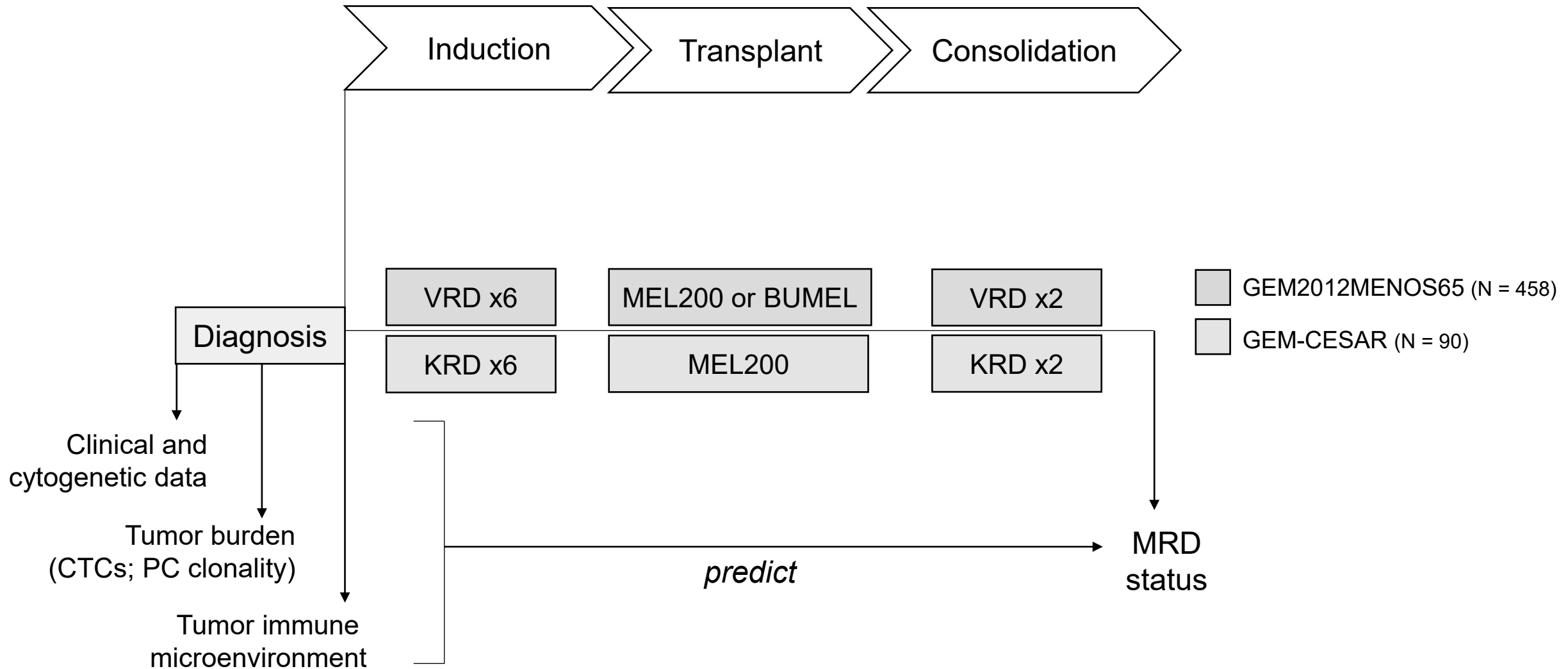
Methods. (I) GEM2012MENOS65 & GEM-CESAR trials used in the study

Trials differ by disease stage and treatment

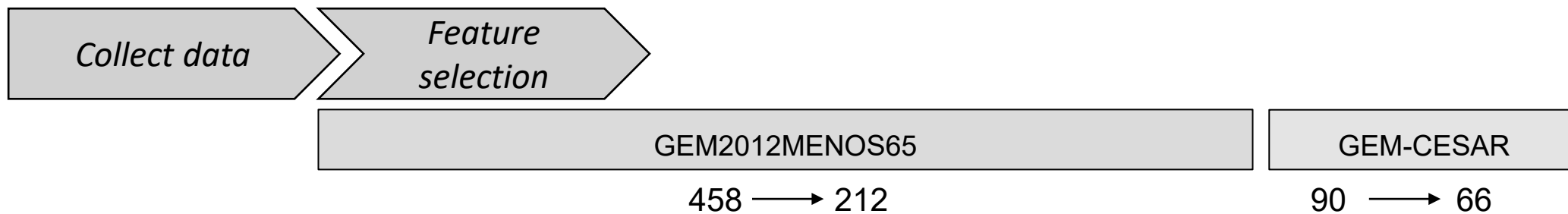


Methods. (I) GEM2012MENOS65 & GEM-CESAR trials used in the study

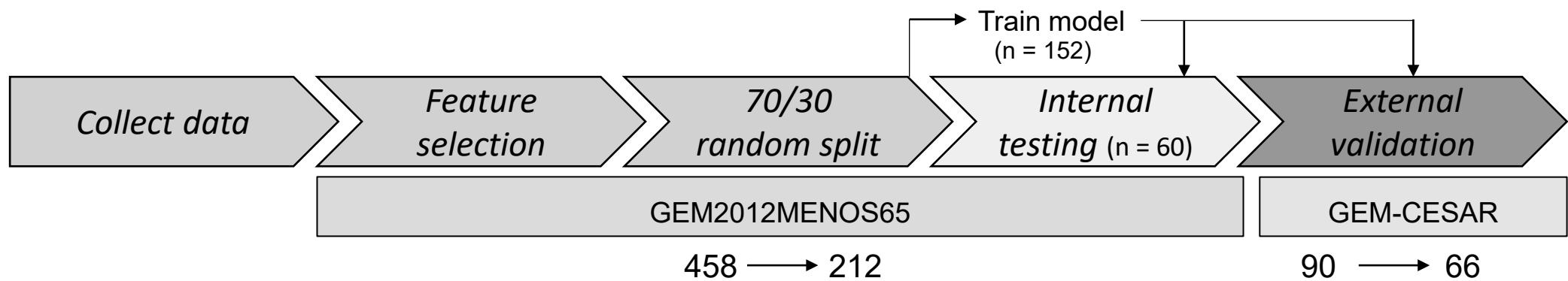
Trials differ by disease stage and treatment



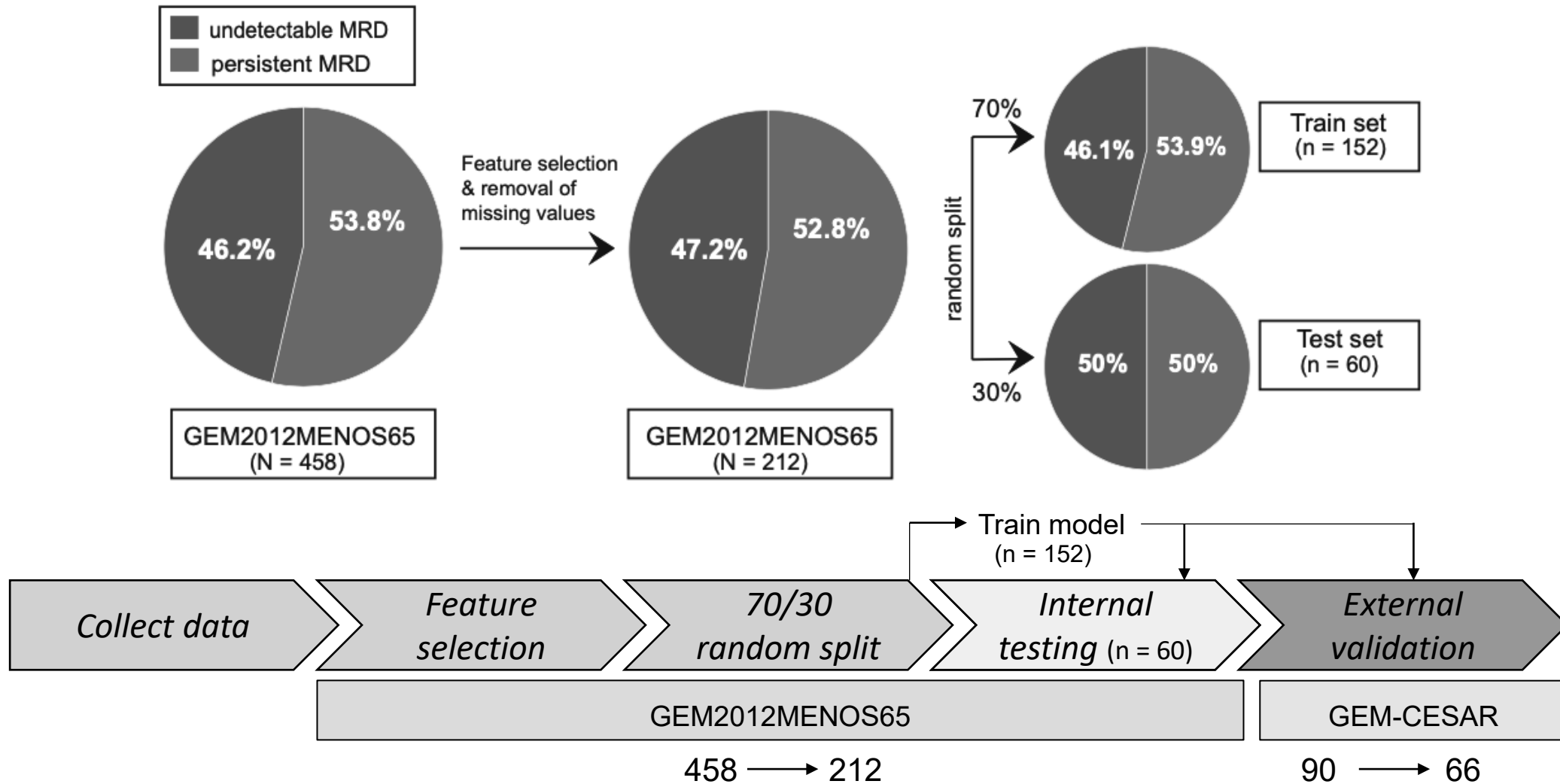
Methods. (II) Study workflow



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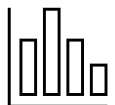


Results. (I) Identifying parameters associated with MRD

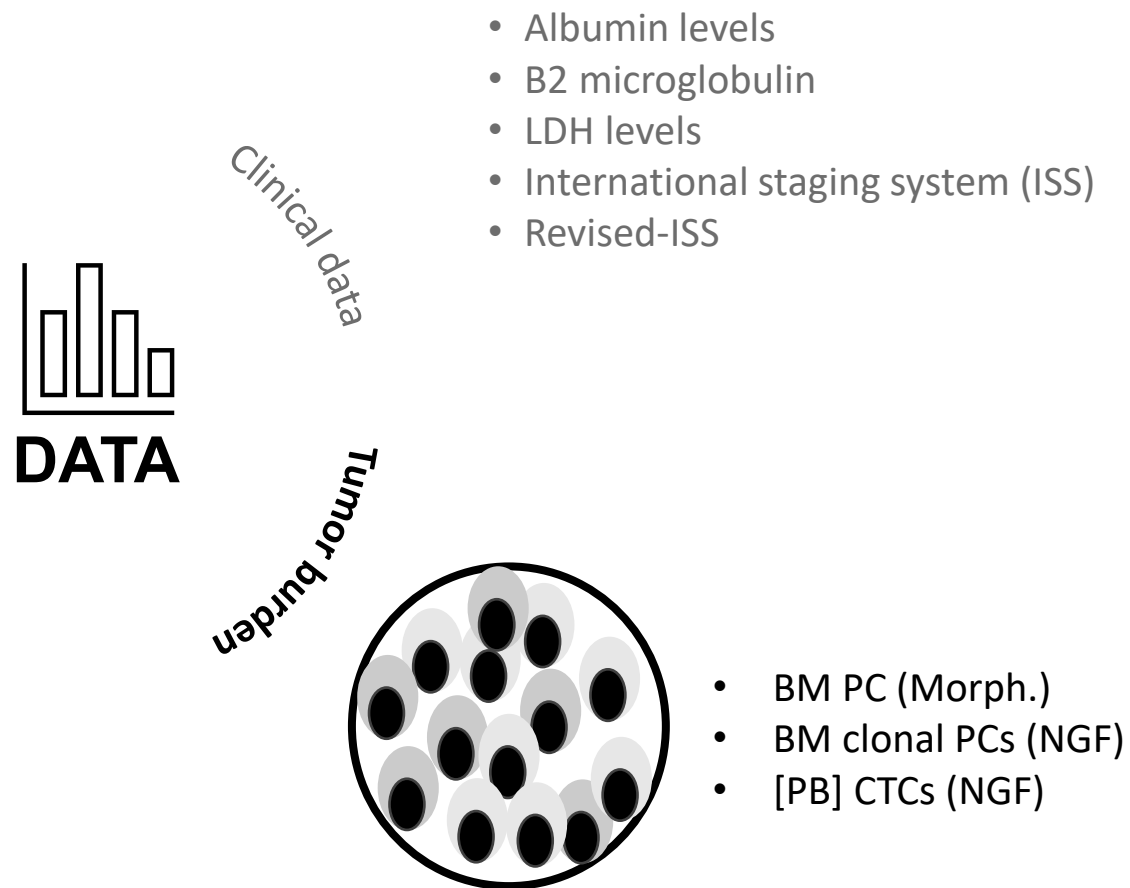


Clinical data

- Albumin
- B2 microglobulin
- LDH levels
- International staging system (ISS)
- Revised-ISS

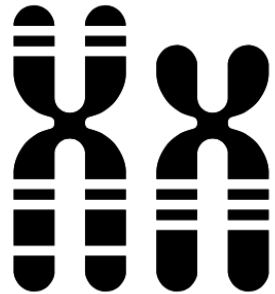


Results. (I) Identifying parameters associated with MRD



Results. (I) Identifying parameters associated with MRD

del(17p13)
IgH translocations;
t(4;14)
t(14;16)
del(17p13) and/or t(4;14)
Chromosome 1 abnormalities (1q/1p)



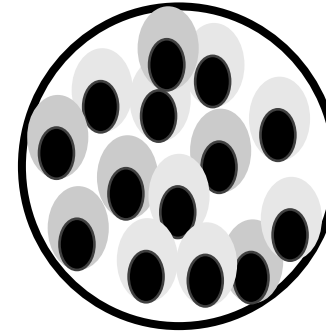
Cytogenetic profile



Clinical data

- Albumin levels
- B2 microglobulin
- LDH levels
- International staging system (ISS)
- Revised-ISS

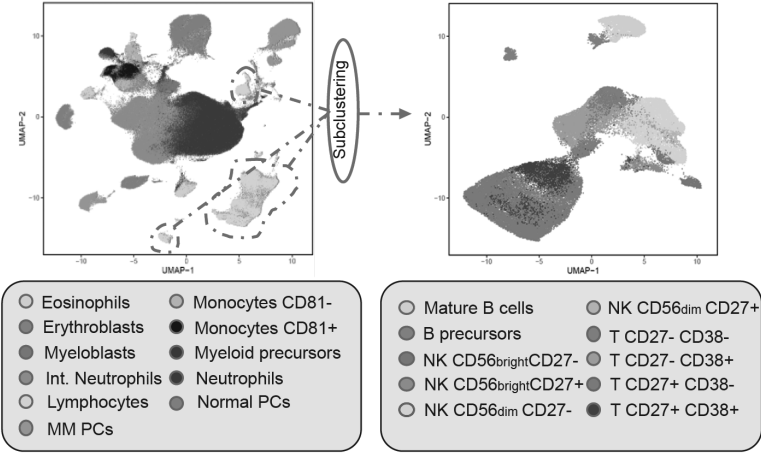
Tumor burden



- BM PC (Morph.)
- BM clonal PCs (NGF)
- [PB] CTCs (NGF)

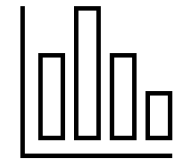


Results. (I) Identifying parameters associated with MRD



Immune microenvironment

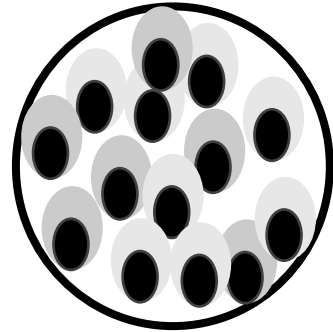
Clinical data



DATA

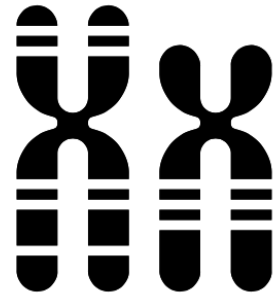
Cytogenetic profile

Tumor burden



- Albumin levels
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del(17p13)
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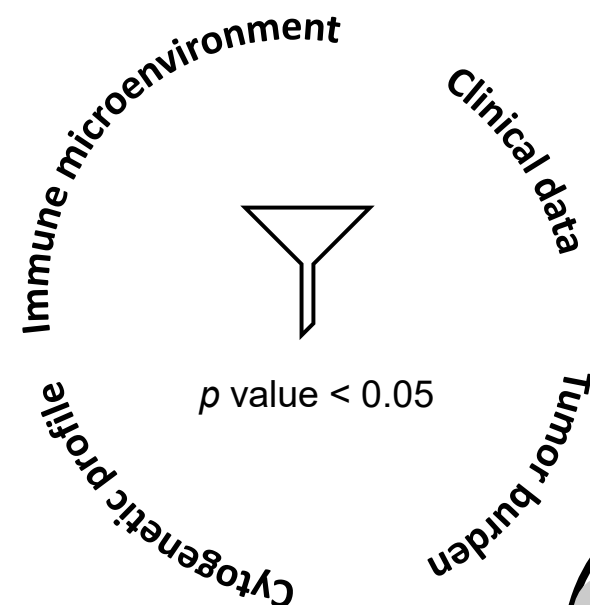
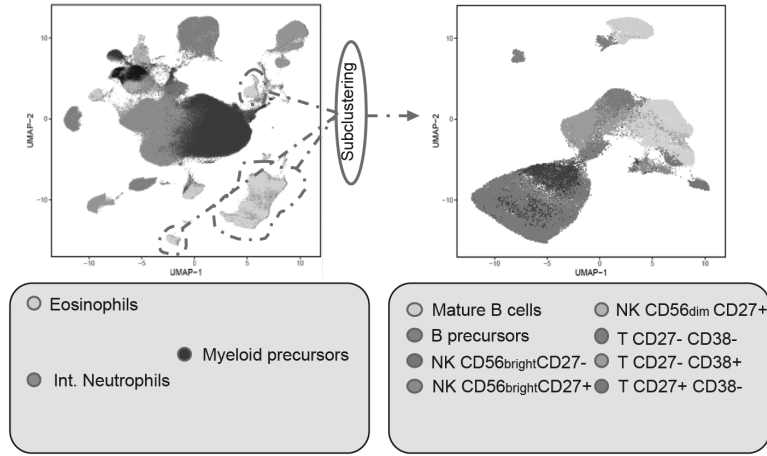
- BM PC (Morph.)
- BM clonal PCs (NGF)
- [PB] CTCs (NGF)



GEM2012MENOS65

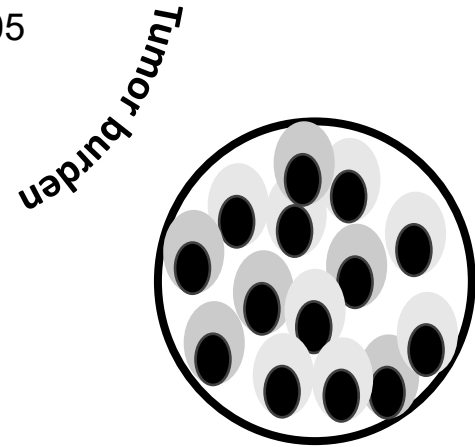
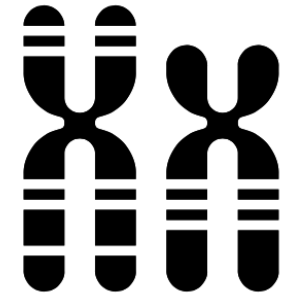
Results. (I) Identifying parameters associated with MRD

Univariate analyses to identify variables significantly associated with MRD status



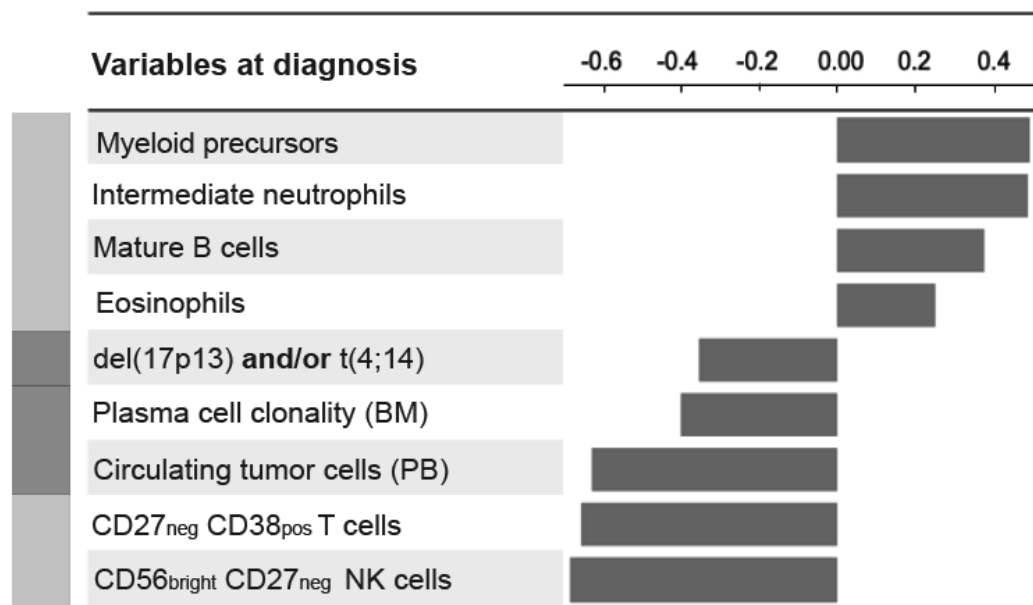
- Albumin levels
- B2 microglobulin
- **LDH levels**
- International staging system (ISS)
- Revised-ISS

del(17p13)
IgH translocations;
 t(4;14)
 t(14;16)
 del(17p13) and/or t(4;14)
 Chromosome 1 abnormalities (1q/1p)



- BM PC (Morph.)
- **BM clonal PCs (NGF)**
- [PB] CTCs (NGF)

Results. (II) Logistic regression algorithm



- Immune microenvironment
- Cytogenetic abnormalities
- Tumor burden

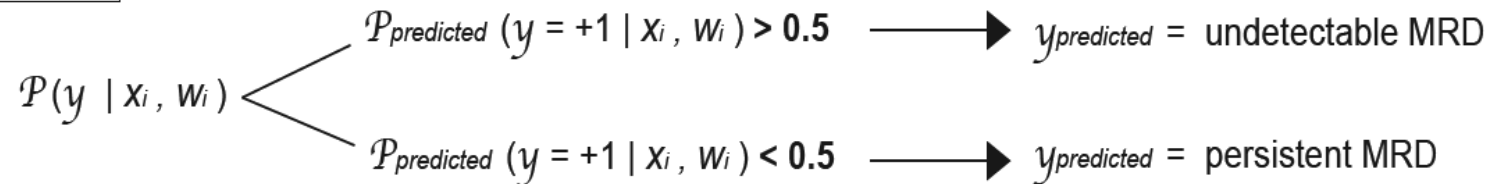
Results. (II) Logistic regression algorithm

Variables at diagnosis	-0.6	-0.4	-0.2	0.00	0.2	0.4	1	0	Input $h(x_i)$	x	Coefficient weights (w)
Myeloid precursors							> 0.21	≤ 0.21	1 or 0		+ 0.497
Intermediate neutrophils							> 36.33	≤ 36.33	1 or 0		+ 0.490
Mature B cells							> 1.75	≤ 1.75	1 or 0		+ 0.379
Eosinophils							> 1.76	≤ 1.76	1 or 0		+ 0.252
del(17p13) and/or t(4;14)							positive	negative	1 or 0		- 0.351
Plasma cell clonality (BM)									(X - 11.01) / 13.71		- 0.398
Circulating tumor cells (PB)							> 0.735	≤ 0.735	1 or 0		- 0.629
CD27 ^{neg} CD38 ^{pos} T cells							> 0.61	≤ 0.61	1 or 0		- 0.656
CD56 ^{bright} CD27 ^{neg} NK cells							> 0.04	≤ 0.04	1 or 0		- 0.685
Logistic regression intercept									1		+ 0.237

Immune microenvironment
 Cytogenetic abnormalities
 Tumor burden

$$P_{\text{predicted}}(y = +1 | X_i, W_i) = \frac{1}{1 + e^{-\sum w h(x_i)}}$$

$$= \sum_{i=1} w h(x_i)$$



Results. (II) Logistic regression algorithm

Interactive webpage to facilitate its use in clinical practice

del(17p13) and/or t(4;14)

Ex. positive or negative

Plasma cell clonality

Ex. 0.24

Absolute number of circulating tumor cells [PB]

Ex. 1.45

Myeloid Precursors

Ex. 1.63

CD56bright CD27neg NK cells

Ex. 0.23

Eosinophils

Ex. 2.34

CD27neg CD38pos T cells

Ex. 0.35

Mature B cells

Ex. 2.53

Intermediate neutrophils

Ex. 40.6

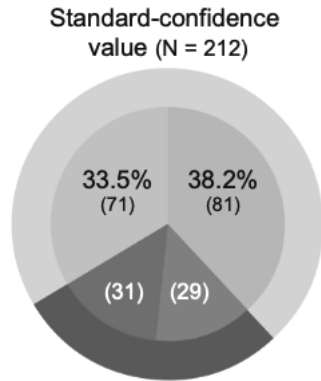
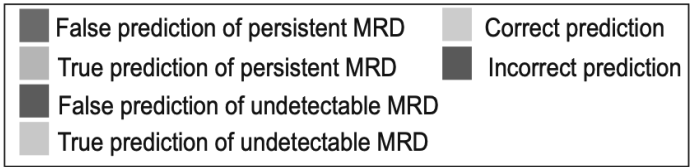
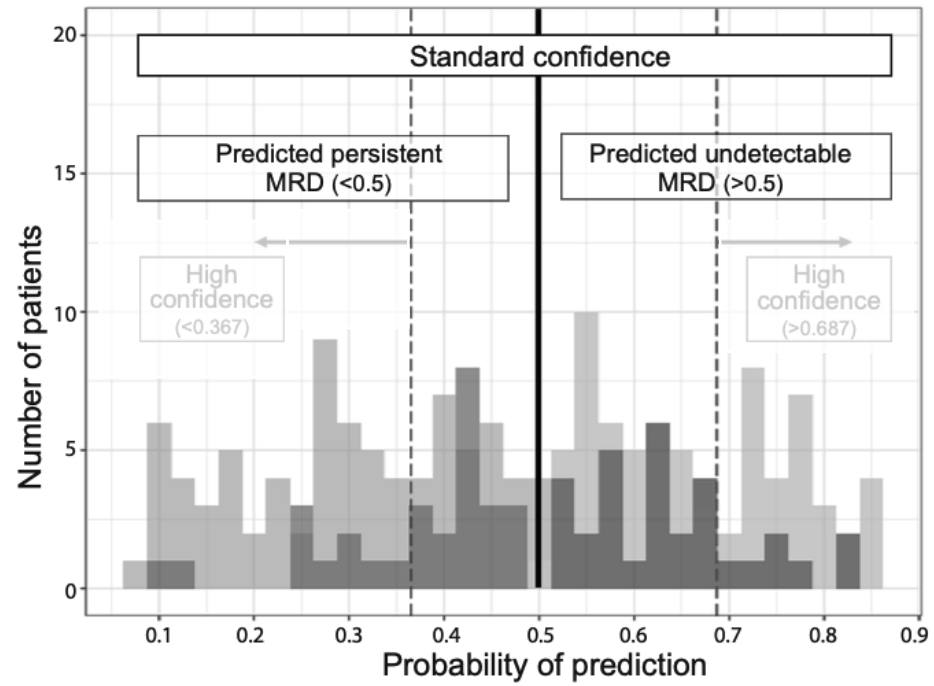
Predicting undetectable MRD in newly-diagnosed multiple myeloma

Your prediction is undetectable MRD, with a probability of 70.1% of undetectable MRD

<http://www.MRDpredictor.com>

Results. (III) The accuracy of the algorithm

Probability distributions

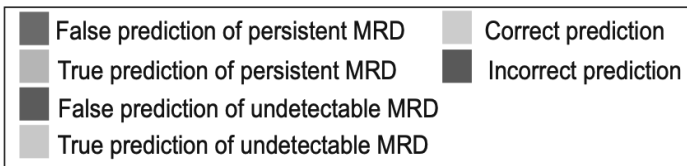
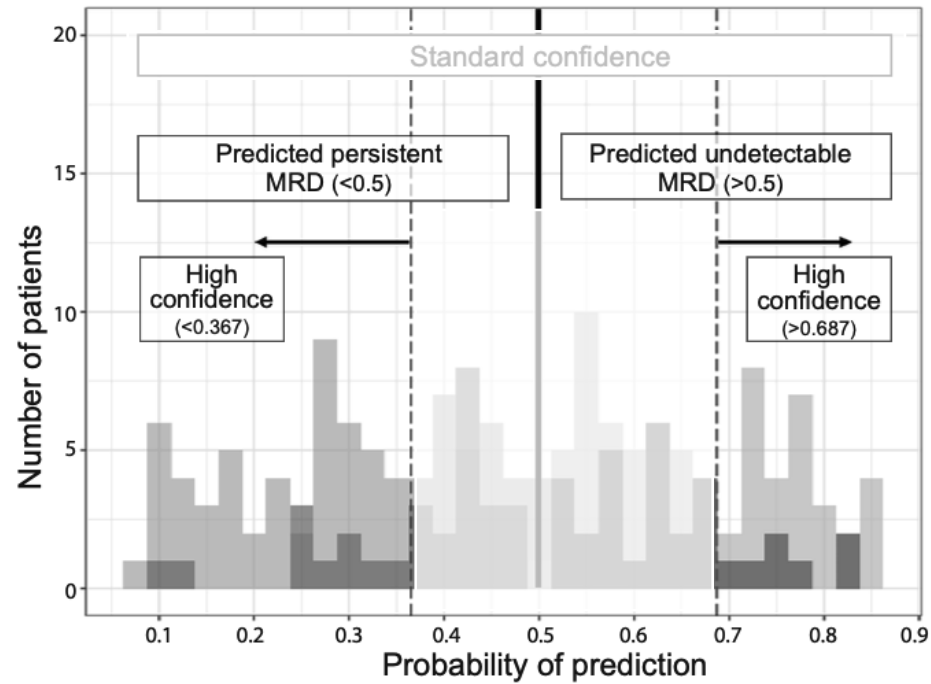


Accuracy = 71.7%

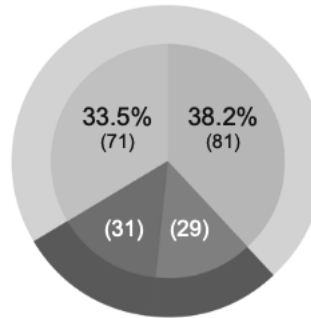


Results. (III) The accuracy of the algorithm

Probability distributions

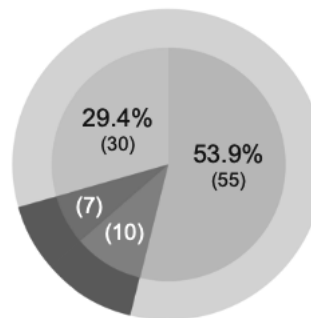


Standard-confidence value (N = 212)



Accuracy = 71.7%

High-confidence value (N = 102)

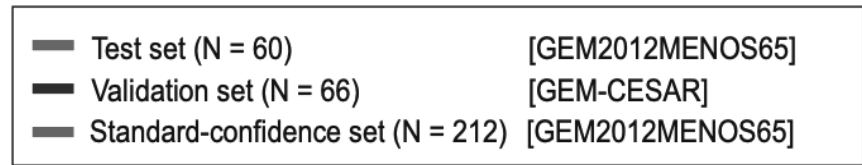
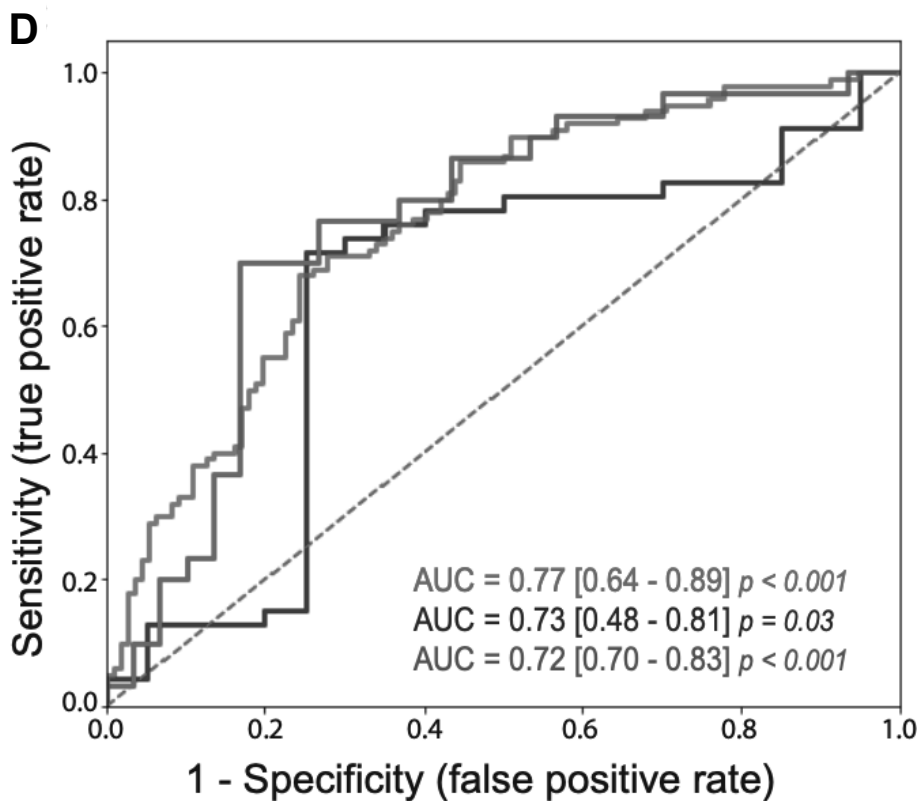


Accuracy = 83.3%



Results. (III) The accuracy of the algorithm

Receiver operating characteristic curves

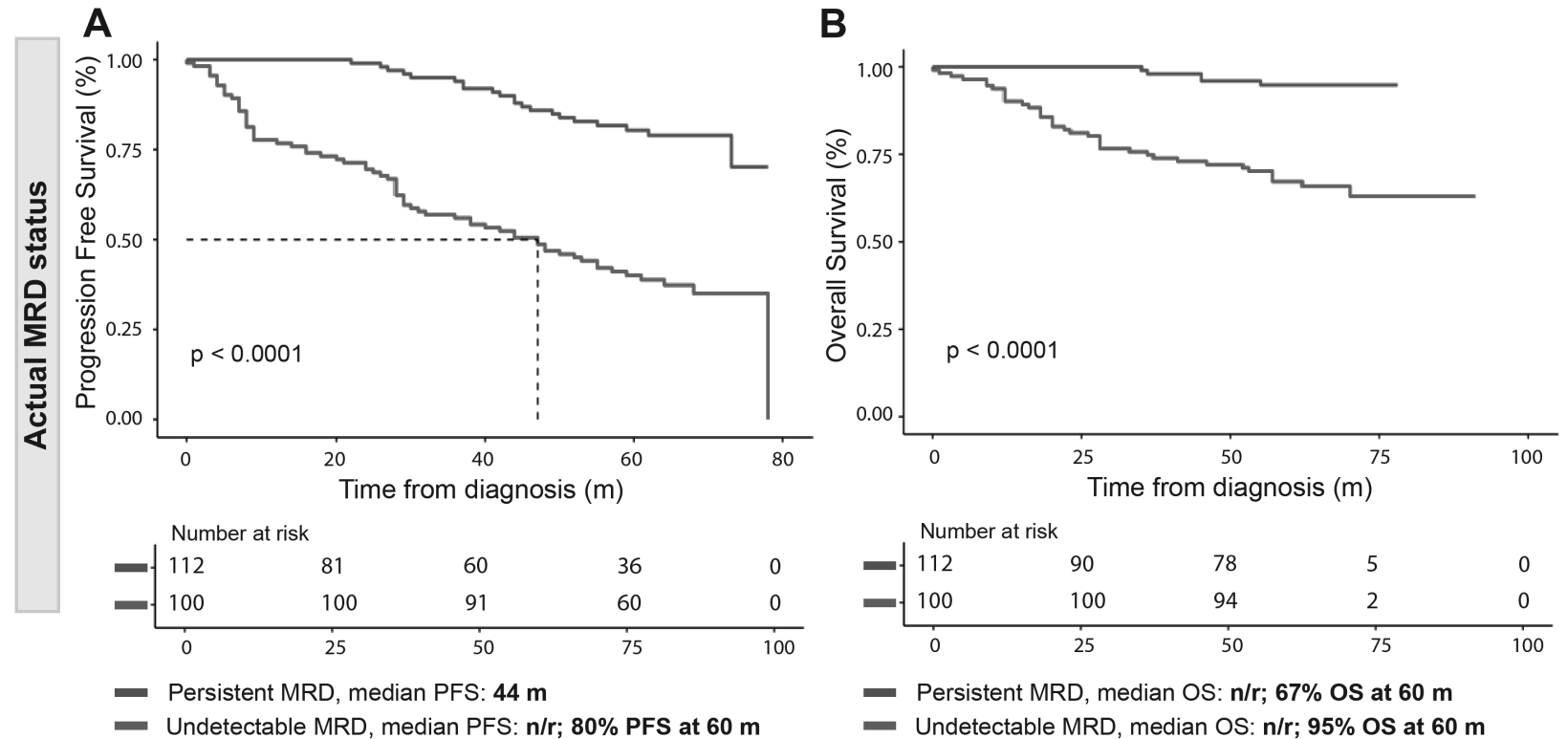


GEM2012MENOS65

GEM-CESAR

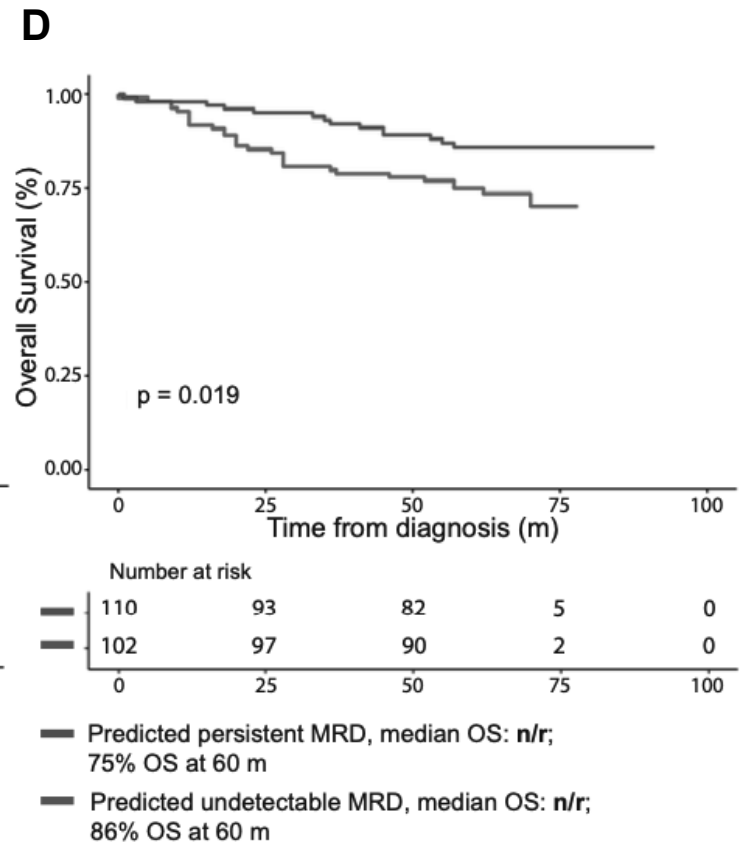
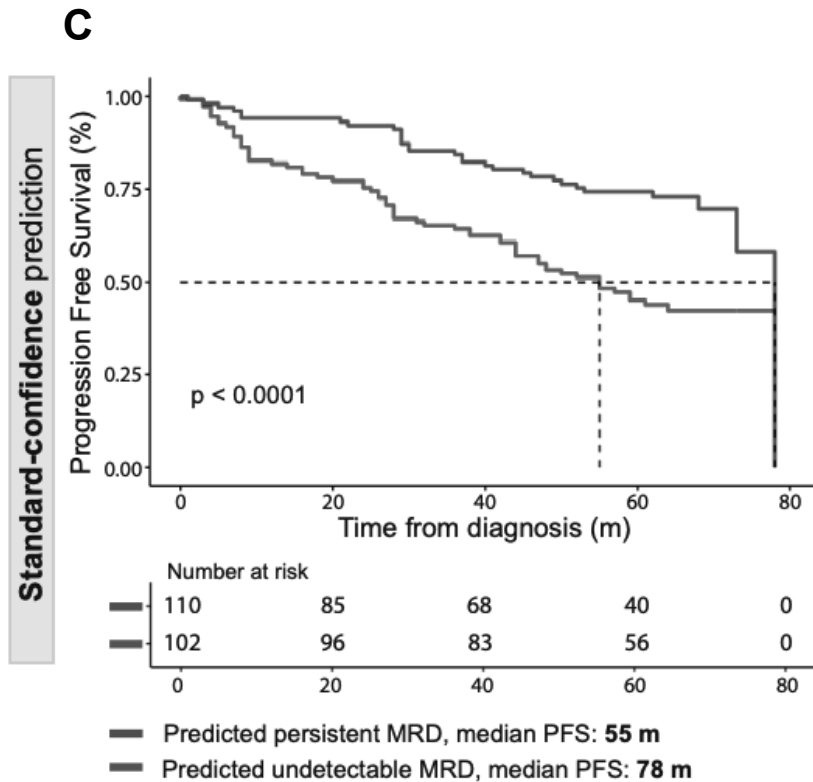
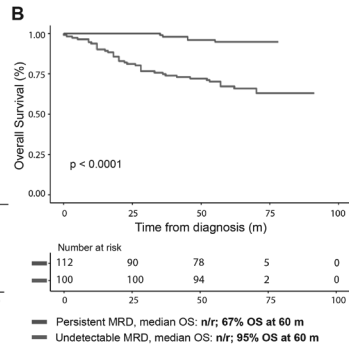
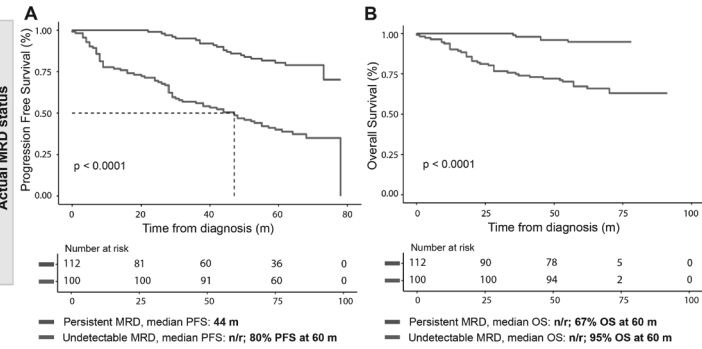
Results. (IV) Prognostic value of the model

PFS and OS based on actual MRD outcomes



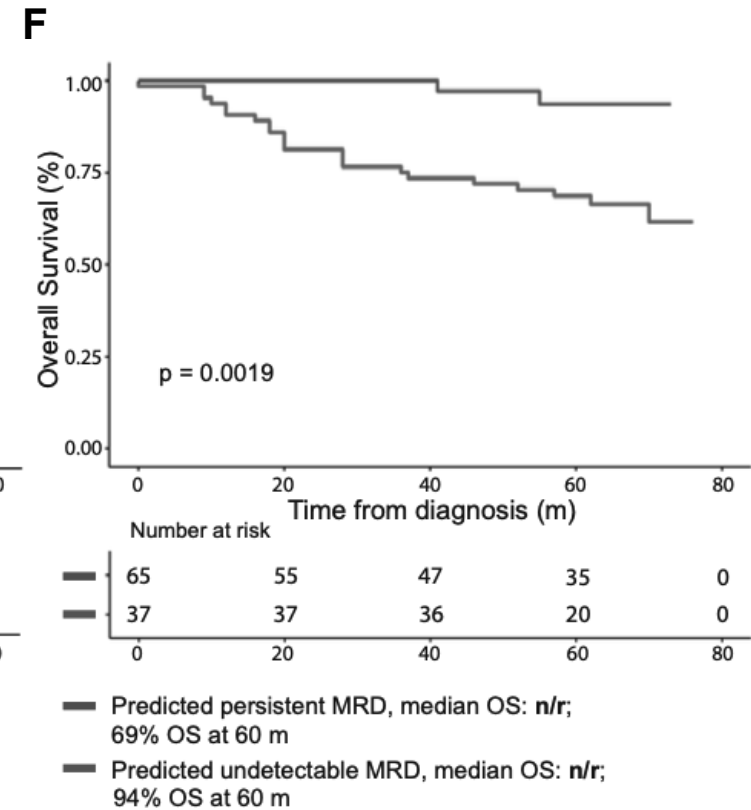
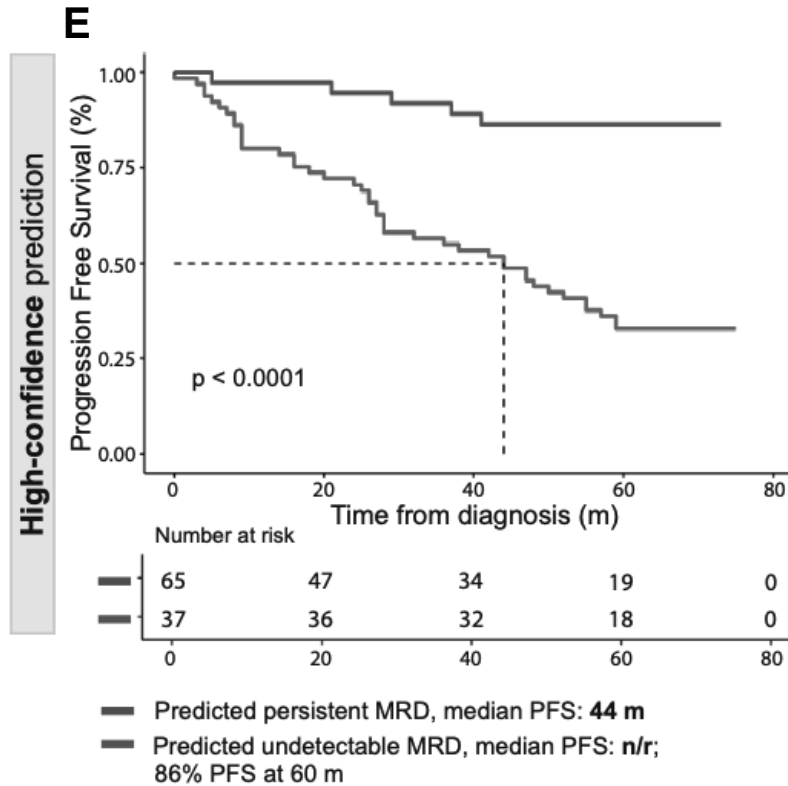
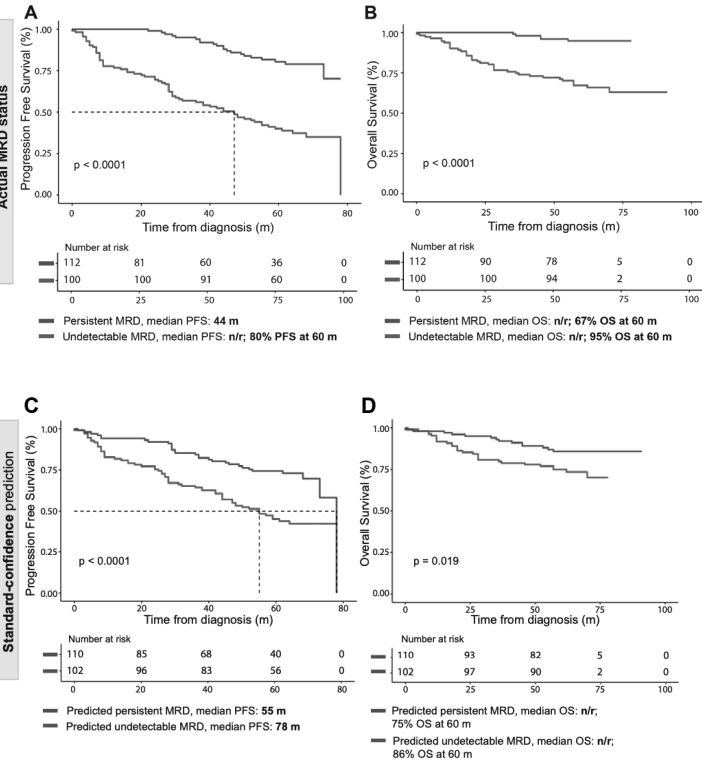
Results. (IV) Prognostic value of the model

PFS and OS based on MRD predicted outcomes; *standard-confidence* predictions (n = 212)



Results. (IV) Prognostic value of the model

PFS and OS based on MRD predicted outcomes; *high-confidence* predictions (n = 102)



Conclusions

- We demonstrated that it is possible to predict patients' MRD status with significant accuracy, using an integrative, weighted model based on machine learning algorithms.
- These findings should stimulate other investigators to further validate this model and define new ones in other treatment scenarios.
- Finally, selecting a regimen based on probable MRD outcomes, and confirming soon after if that probability was accurate, is a possible new approach towards individualized treatment in MM.

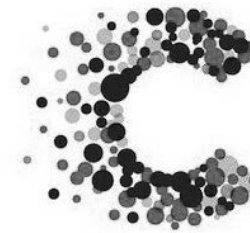
Thank you!



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