

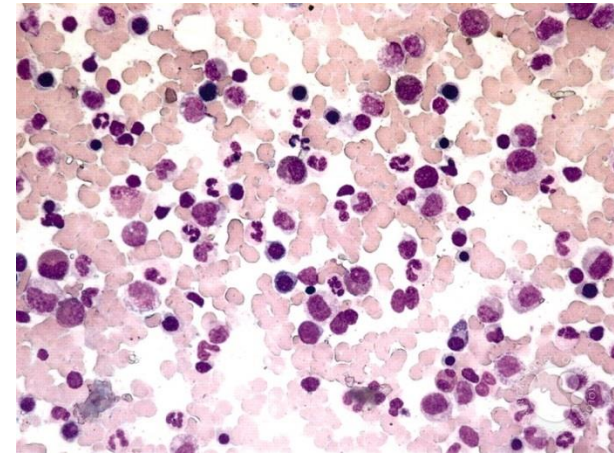
Noninvasive Diagnosis of Myelodysplastic Syndromes (MDS)

**H.S.Oster, S.Crouch, A.Smith,
... [EUMDS/MDS-RIGHT], ...
T. M.deWitte, and M.Mittelman**

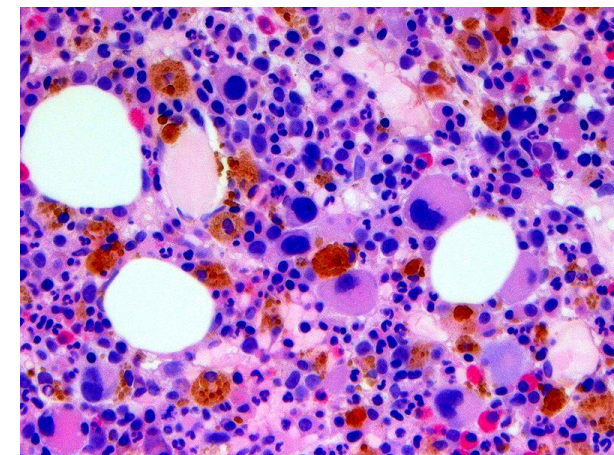
**Tel Aviv Medical Center/York University/
Radboud University/EUMDS**

Myelodysplastic Syndromes (MDS)

- Clonal hematopoietic stem cell disease
- Abnormal
 - differentiation, maturation, apoptosis
- Anemia – common
 - often treated with EPO
- Cytopenias:
 - WBC and Platelets
- Transformation
 - Acute Leukemia (20%-60%)



Normal bone marrow



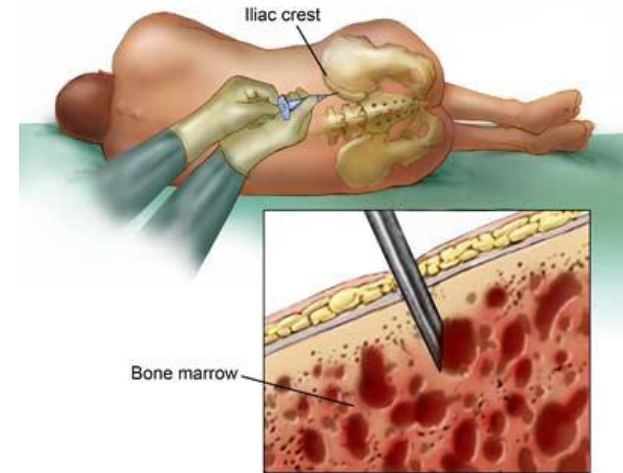
MDS bone marrow

MDS Diagnosis – gold standard

Bone marrow examination

But...

- Invasive
- Painful
- Possible bleeding (thrombocytopenia)
- Difficult for the older patients



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Aim of this study

Can we diagnose MDS noninvasively
in at least a portion of the patients?

Stage I: Logistic regression (LoR)

MDS patients: 48

Control patients: 63

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Control patients: 63

$$Y = \frac{e^{(B_1X_1+B_2X_2+\dots+B_6X_6+C)}}{1 + e^{(B_1X_1+B_2X_2+\dots+B_6X_6+C)}}$$

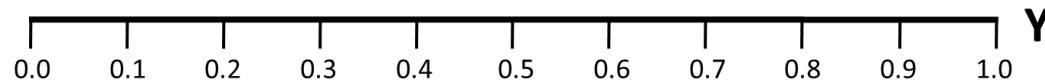
- Gender (X_1)
- Age (X_2)
- Hb (X_3)
- MCV (X_4)
- WBC (X_5)
- Platelets (X_6)

Stage I: Logistic regression (LoR)

MDS patients: 48
Control patients: 63

$$Y = \frac{e^{(B_1X_1+B_2X_2+\dots+B_6X_6+C)}}{1 + e^{(B_1X_1+B_2X_2+\dots+B_6X_6+C)}}$$

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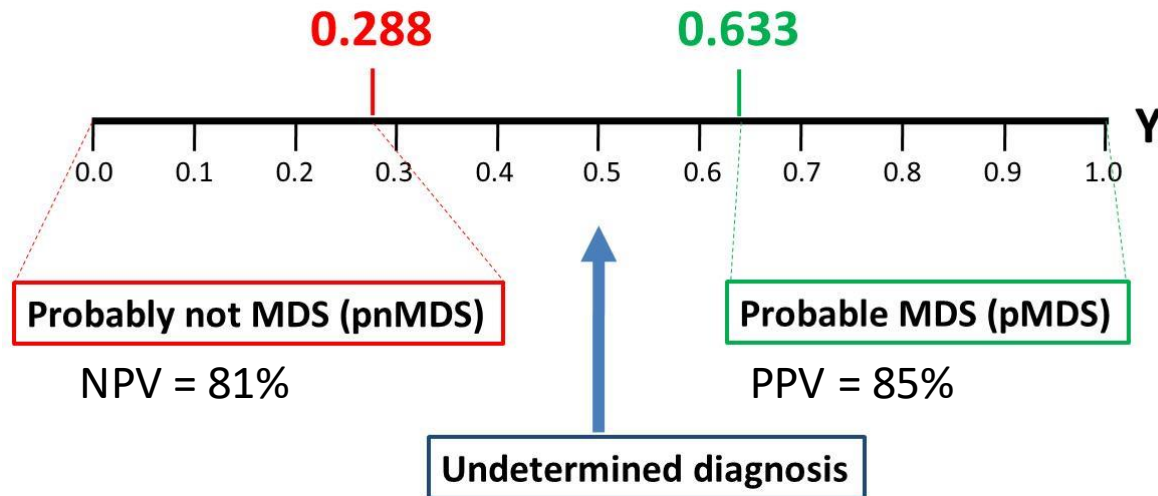


Probably not MDS (pnMDS)

Probable MDS (pMDS)

Stage I: Logistic regression (LoR)

- Area under ROC curve (AUC) = 0.748
- Two cutoffs:



Approximately 50% could benefit from noninvasive diagnosis

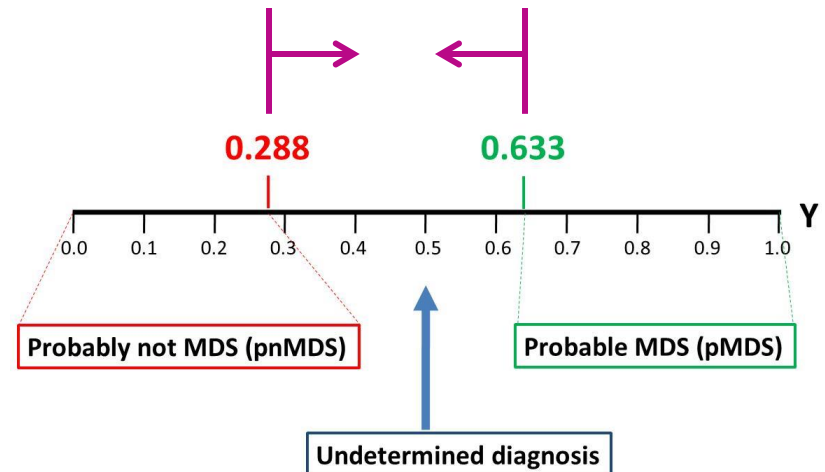
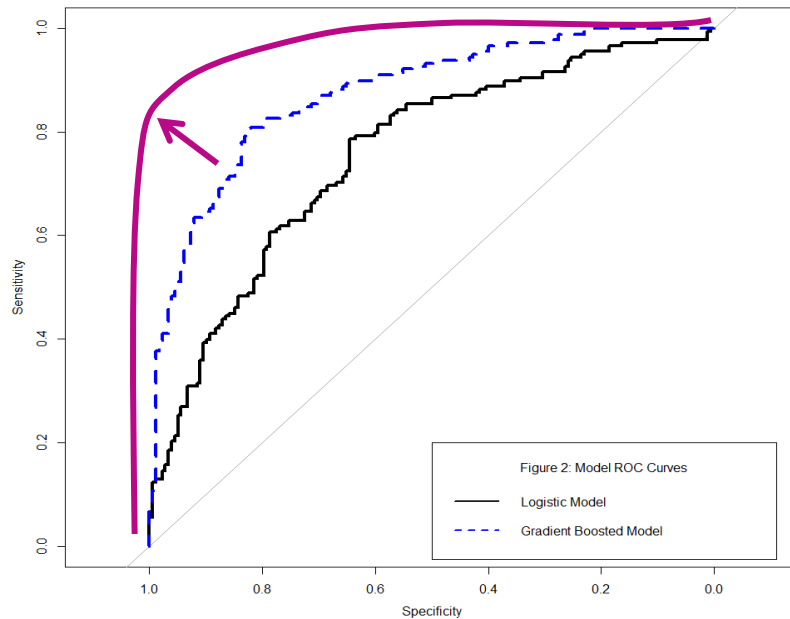
(Oster et al. *Leuk & Lymph* 2018: 59; 2222)

Model improvement

Improve the AUC



Narrow the undetermined region



More patients could benefit from noninvasive diagnosis of MDS

Improved model (Stages II and III)

- More patients
 - MDS:
 - Israel MDS registry (>260)
 - European MDS registry (>2600)
 - Controls: Ichilov pathology data base
- More variables
- Better model
 - **Gradient Boosted Model (GBM)**
 - Much more complex than LoR
 - Takes into account the interactions among variables
- Collaboration with York University

Improved model

- Stage II (ASH 2017)
 - Patients:
 - MDS: 178
 - Controls: 178
 - Gradient Boosted Model (GBM)
 - Number of variables: 6 variables
- **Stage III (ASH 2018)**
 - Patients:
 - MDS: **502**
 - Controls: **502**
 - **Gradient Boosted Model (GBM)**
 - Number of variables: **10** variables

A

Age →
Gender →
Hb →
WBC →
PLT →
MCV →

$$Y = \frac{e^{(B_1X_1 + B_2X_2 + \dots + B_6X_6 + C)}}{1 + e^{(B_1X_1 + B_2X_2 + \dots + B_6X_6 + C)}}$$

X_i ($i=1 \dots 6$) – Each variable
 B_i ($i=1 \dots 6$) – Relative weights of X_i
 C – A constant

→ Y

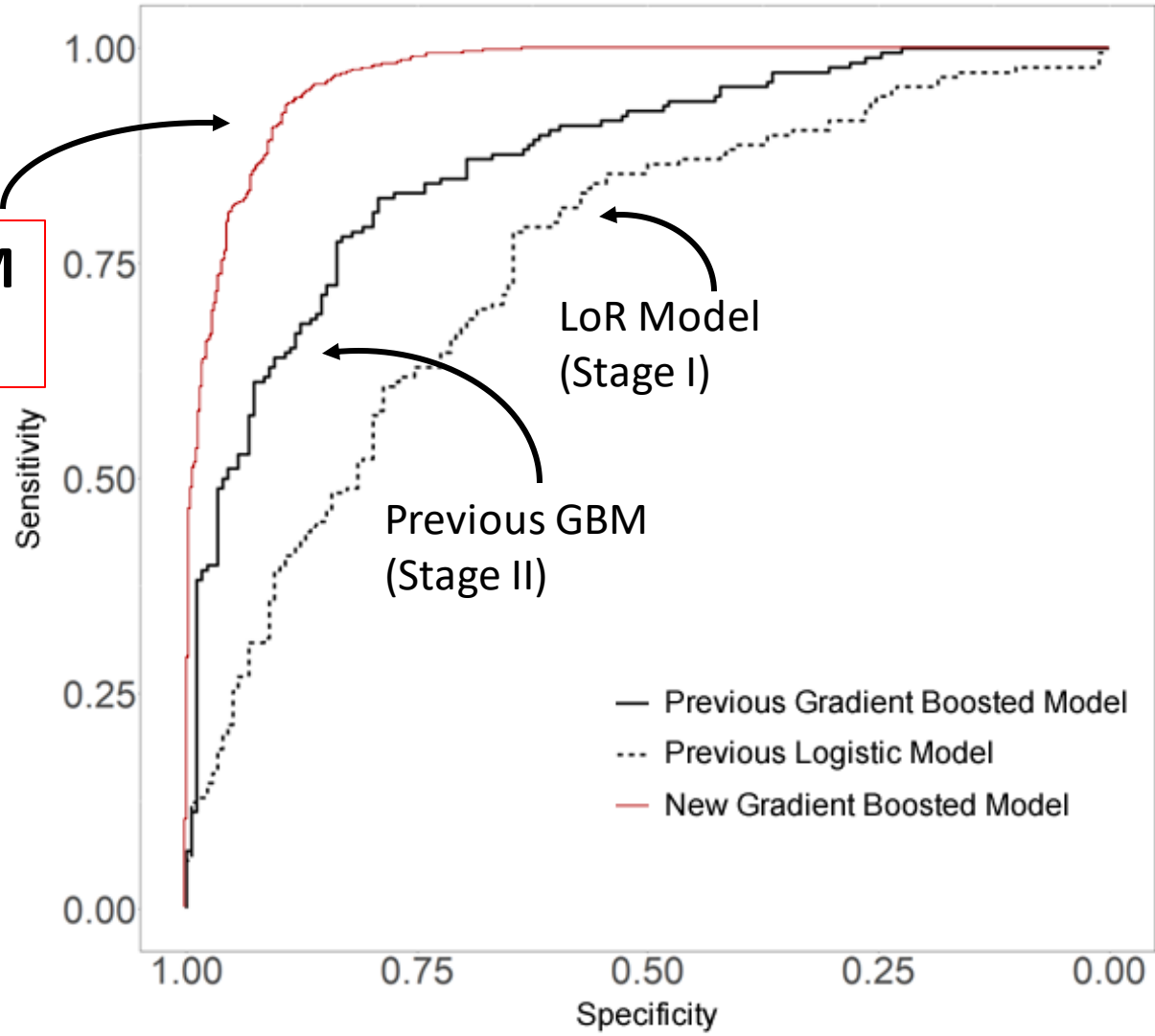
B

Age →
Gender →
Hb →
WBC →
PLT →
MCV →
Neutrophils →
Monocytes →
Glucose →
Creatinine →

GBM algorithm
computation

→ GBM
Score

**New GBM
(Stage III)**



AUC = 0.97 (95% CI 0.96-0.98)

Noninvasive MDS diagnosis, in practice

shiny.york.ac.uk/mds



Noninvasive MDS diagnosis, in practice

MDS Predictive Modelling

Disclaimer

This web application is experimental, and should not be used in the diagnosis of any medical condition.

What is the age of the patient? (In years)

Sex (M/F)

Male

Female

Haemoglobin Count?

White Blood Count?

Platelet Count?

Mean Corpuscular Volume?

Neutrophil Count?

Monocyte Count?

Blood Glucose Concentration?

Creatinine?

Calculate

shiny.york.ac.uk/mds



Noninvasive MDS diagnosis, in practice

MDS Predictive Modelling

Age = 75

Hemoglobin = 10.5

Platelets = 125

Neutrophils = 0.9

Glucose = 100

Sex = Male

WBC = 3.1

MCV = 101

Monocytes = 0.2

Creatinine = 1.1

Neutrophil Count?

Blood Glucose Concentration?

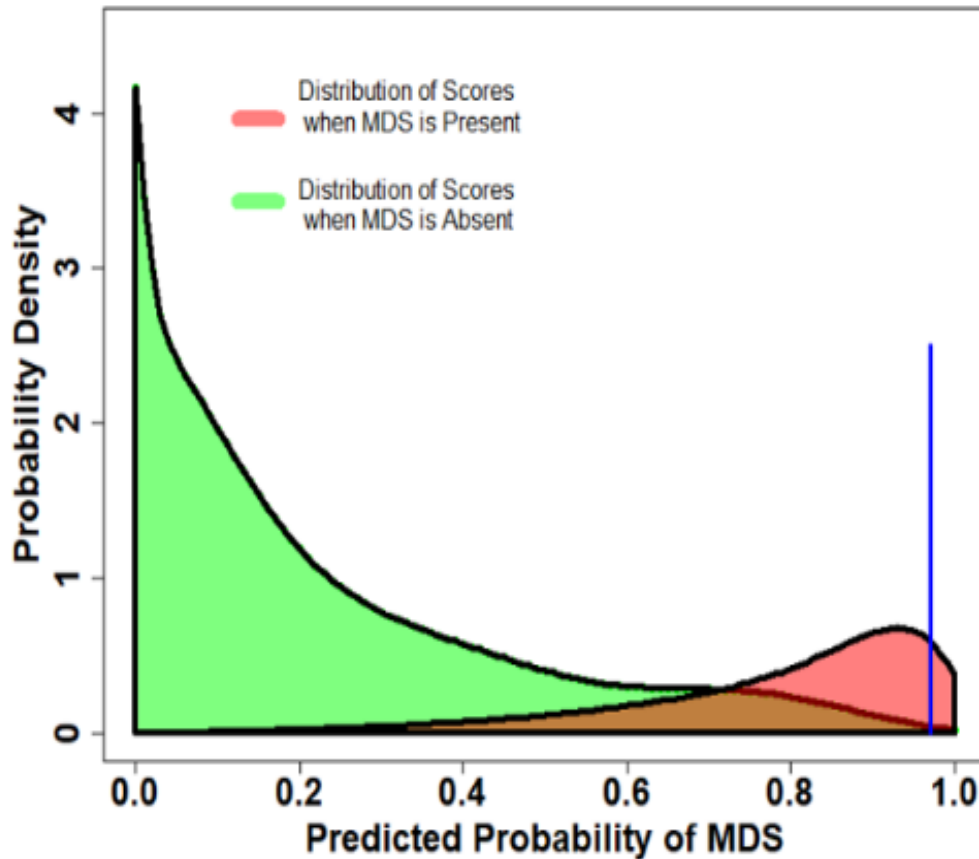
Monocyte Count?

Creatinine?

shiny.york.ac.uk/mds



Noninvasive MDS diagnosis, in practice



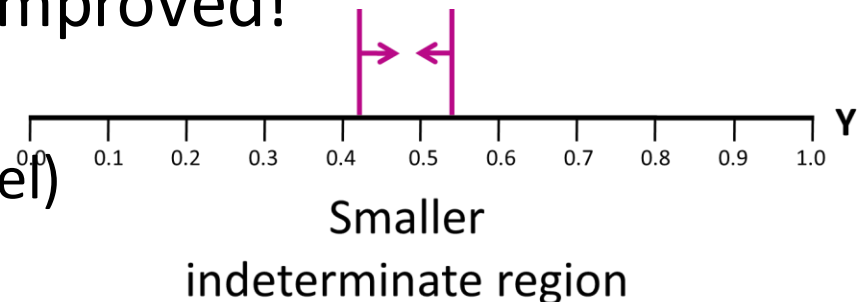
Probable MDS
(pMDS)

shiny.york.ac.uk/mds



Model Quality

- One cut-off (AUC = 0.97): improved!
 - Sensitivity = 88%
 - Specificity = 95%
- Two cut-offs
 - 90% PPV (above upper cut-off)
 - 95% NPV (below lower cut-off)
 - Indeterminate region: improved!
 - 14% of the patients
 - (50% in our earlier model)



Noninvasive MDS diagnosis, in practice

MDS Predictive Modelling

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White Blood Count?

Platelet Count?

Mean Corpuscular Volume?

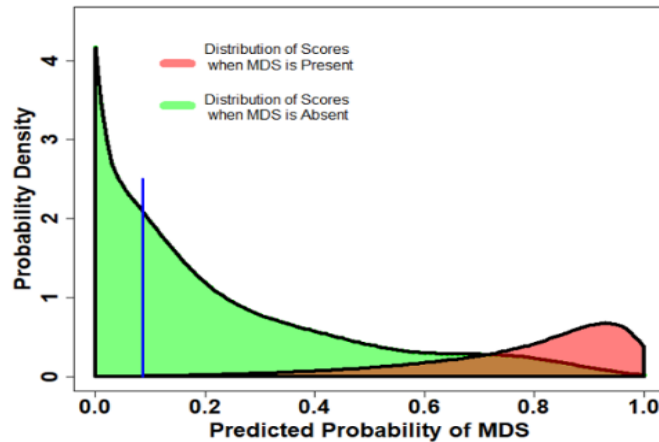
Neutrophil Count?

Monocyte Count?

Blood Glucose Concentration?

Creatinine?

Probably not MDS (pmMDS)



MDS Predictive Modelling

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What is the age of the patient? (In years)

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 Male
 Female

Haemaglobin Count?

White Blood Count?

Platelet Count?

Mean Corpuscular Volume?

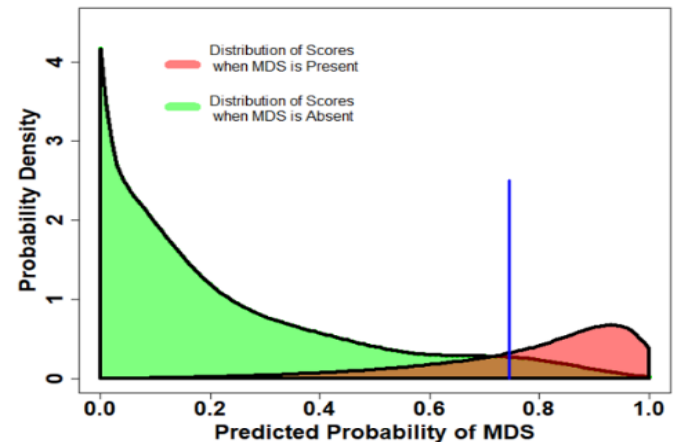
Neutrophil Count?

Monocyte Count?

Blood Glucose Concentration?

Creatinine?

Indeterminate



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Noninvasive MDS diagnosis, in practice

MDS Predictive Modelling

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What is the age of the patient? (In years)

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Platelet Count?

Mean Corpuscular Volume?

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Monocyte Count?

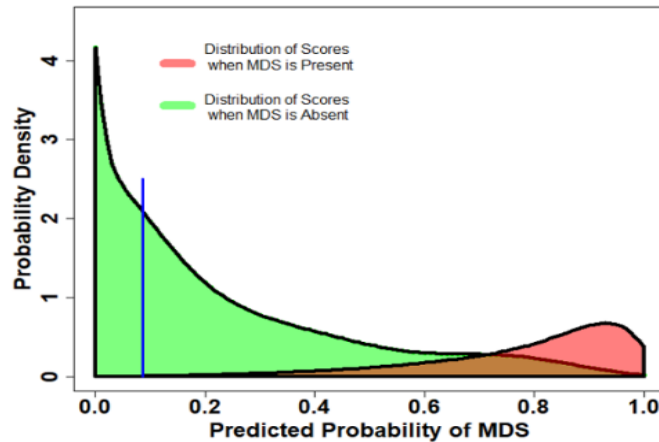
Blood Glucose Concentration?

Creatinine?

Calculate

Probably not MDS (pnMDS)

Probably not MDS (pnMDS)



MDS Predictive Modelling

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What is the age of the patient? (In years)

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Monocyte Count?

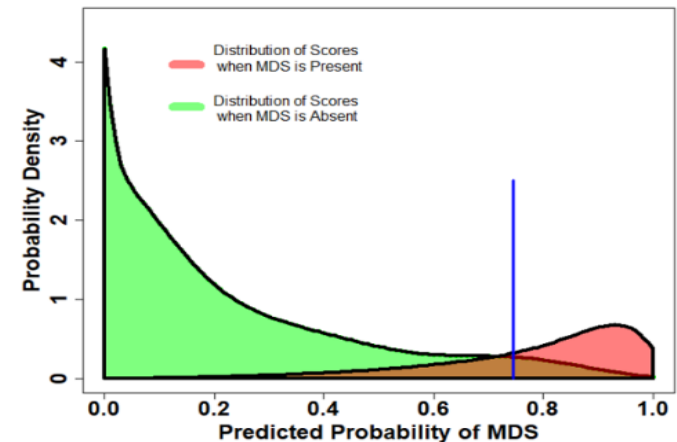
Blood Glucose Concentration?

Creatinine?

Calculate

Indeterminate

Indeterminate



shiny.york.ac.uk/mds

Future Work

- Complete/improve (internet, cellphone...) and publish
- Improve the model – stage IV
 - Increase numbers of patients and variables
- Incorporate additional peripheral blood parameters
 - **Flow cytometry**
 - **Genetic info**
- Use the model for other purposes
 - Prognosis
 - Follow up

Summary and Conclusions

- **Stage 1:**
 - 6 variables, (48 and 63 patients), LoR model
 - Diagnose/exclude MDS in 50% of patients.
- **Stage 2:**
 - GB model, 178 and 178 patients
 - Model improvement
- **Stage 3:**
 - 10 variables, 502 and 502 patients, GB model diagnosed
 - PPV = 90%; NPV = 95%
 - **Diagnose/exclude MDS in 86% of patients.**
- **Conclusion:** For most patients, MDS can be diagnosed or ruled out noninvasively without a bone marrow examination.

Thank you

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Thank you