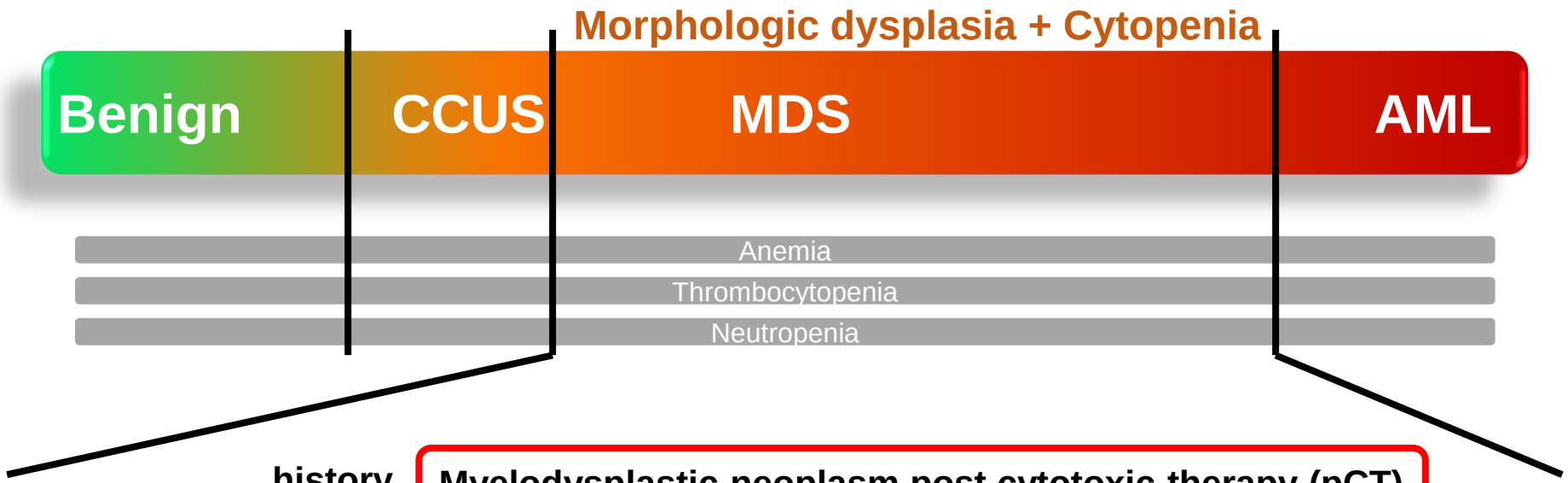
MDS – von der Diagnose zur Prognose

Constance Bär

MLL Münchner Leukämie Labor



history **Myelodysplastic neoplasm post cytotoxic therapy (pCT)**

Classification hierarchy

MDS with defining genetic abnormalities
MDS with low blasts and isolated 5q deletion
MDS with low blasts and *SF3B1* mutation
MDS with biallelic *TP53* inactivation

example:
MDS with bi*TP53* inactivation **- pCT**

MDS defined by morphology
MDS with low blasts
MDS, hypoplastic
MDS with increased blasts*

example:
MDS-IB1**- pCT**

*Exclude AML with defining genetic abnormalities as relevant

Die neue WHO (5th Edition, 2022)

Myelodysplastisches Syndrom (MDS)

Die neue WHO (5th Edition, 2022)

Myelodysplastische Neoplasie (MDS)

- **harmonisiert die Terminologie mit MPN**
- **unterstreicht den neoplastischen Charakter**

Die Klassifikation erkennt MDS grundsätzlich als eine Kategorie **klonaler hämatopoetischer Stammzellneoplasien** an, die durch Zytopenien und morphologische Dysplasie definiert und durch eine fortschreitend ineffektive Hämatopoese und ein erhöhtes Risiko einer akuten myeloischen Leukämie (AML) gekennzeichnet sind.

MDS – praktische Anwendung

MDS

1,931 MDS patients newly diagnosed according to WHO 2017

WHO 2017

51 patients

2.6 %

AML

WHO 2022 Diagnosis	n
AML with *NPM1* mutation	27
AML with *MECOM* rearrangement	21
AML with *KMT2A* rearrangement	1
AML with *DEK::NUP214* fusion	1
AML with *RBM15::MRTFA* fusion	1

WHO 2022

MLL Data

MDS – praktische Anwendung

36% female, 64% male

Median age: 75.8 years
(24.4 – 95.8 years)

07/2017 – 07/2022

1,880 newly diagnosed MDS

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Median age: 75.8 years
(24.4 – 95.8 years)

07/2017 – 07/2022

1,880 newly diagnosed MDS

Defining history

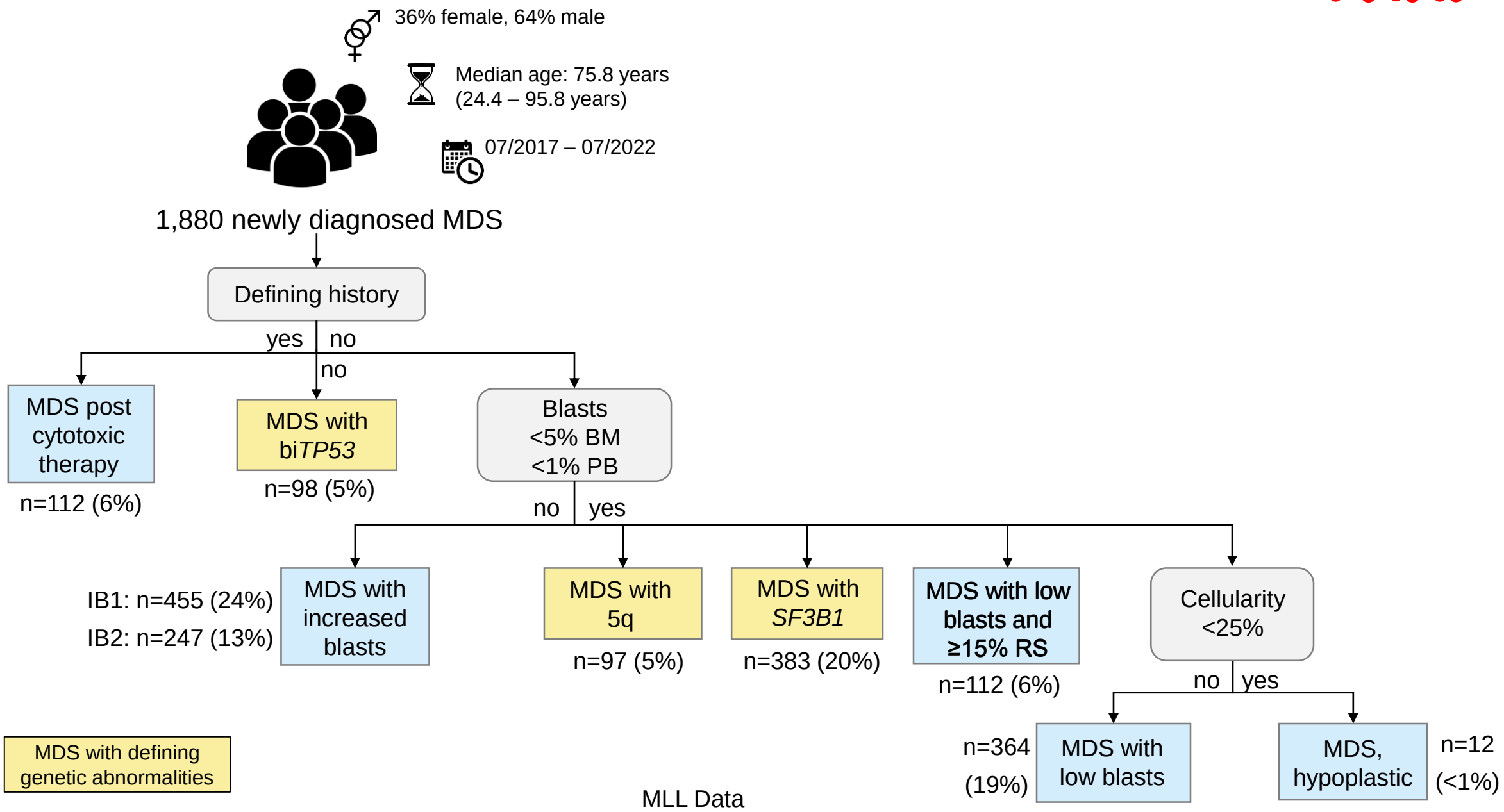
yes

MDS post cytotoxic therapy

n=112 (6%)

WHO 2022 diagnosis	n	freq
MDS-IB1	33	29%
MDS with bi*TP53*	26	23%
MDS-IB2	19	17%
MDS-LB	15	13%
MDS with low blasts and ≥15% RS	8	7%
MDS with *SF3B1*	8	7%
MDS with 5q	3	3%

MDS – praktische Anwendung



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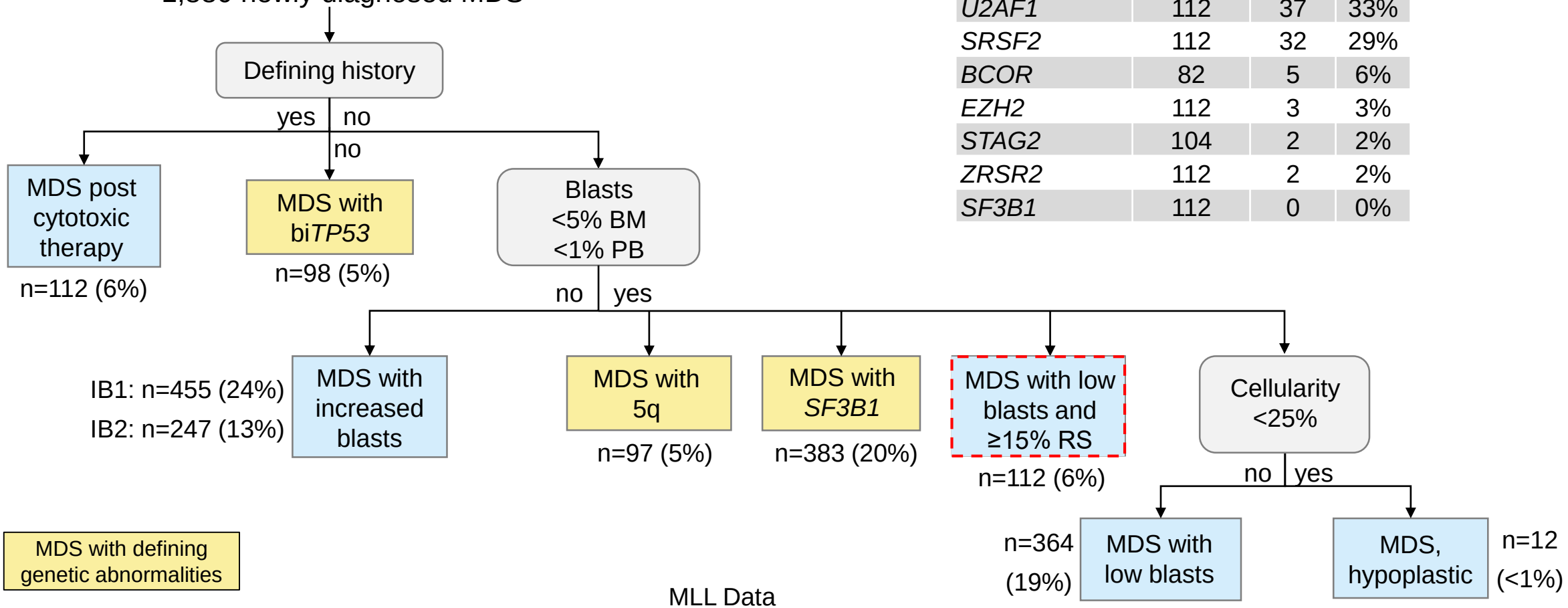
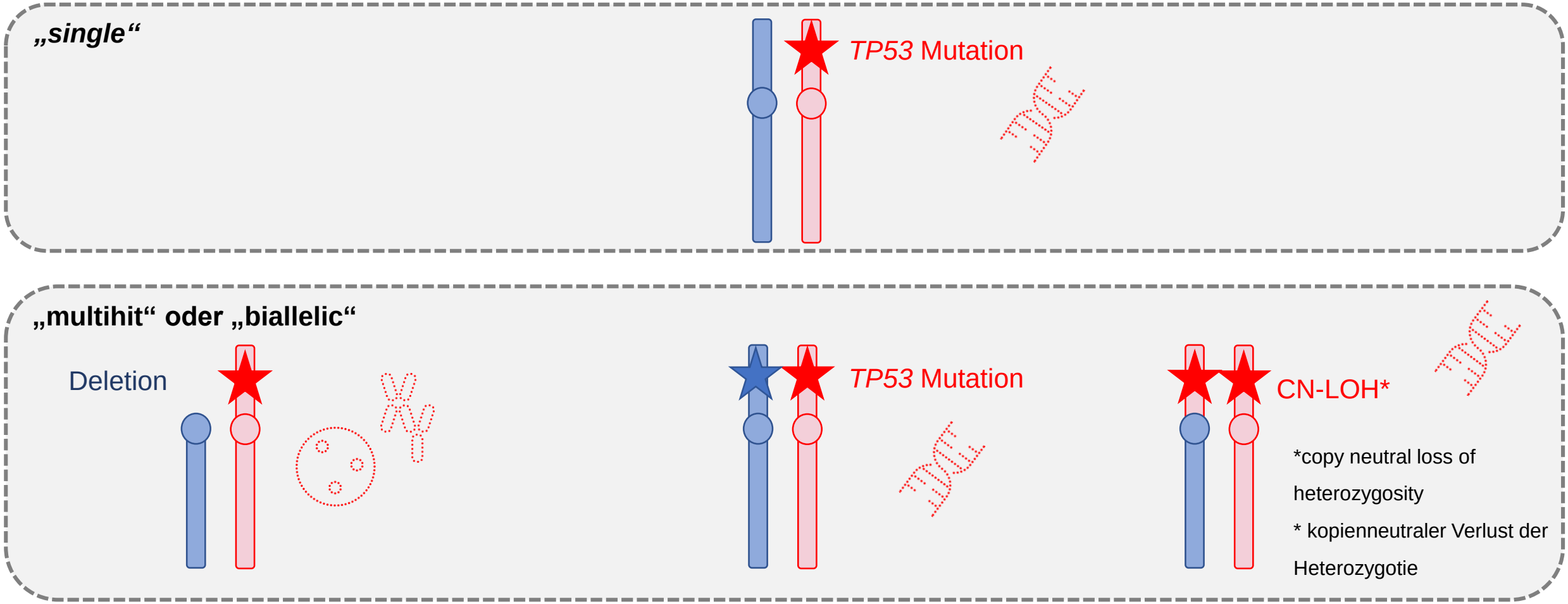


Gene	analysed	mut	freq
ASXL1	112	40	36%
U2AF1	112	37	33%
SRSF2	112	32	29%
BCOR	82	5	6%
EZH2	112	3	3%
STAG2	104	2	2%
ZRSR2	112	2	2%
SF3B1	112	0	0%

MLL Data

Was bedeutet „*TP53* multihit“ oder „biallelic *TP53* inactivation“



ICC- International Consensus Classification

15 SEPTEMBER 2022

blood®
Special Report

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Daniel A. Arber,[1] Attilio Orazi,[2] Robert P. Hasserjian,[3] Michael J. Borowitz,[4] Katherine R. Calvo,[5] Hans-Michael Kvasnicka,[6] Sa A. Wang,[7] Adam Bagg,[8] Tiziano Barbui,[9] Susan Branford,[10] Carlos E. Bueso-Ramos,[7] Jorge E. Cortes,[11] Paola Dal Cin,[12] Courtney D. DiNardo,[7] Hervé Dombret,[13] Eric J. Duncavage,[14] Benjamin L. Ebert,[15] Elihu H. Estey,[16] Fabio Facchetti,[17] Kathryn Foucar,[18] Naseema Gangat,[19] Umberto Gianelli,[20] Lucy A. Godley,[1] Nicola Gökbuget,[21] Jason Gotlib,[22] Eva Hellström-Lindberg,[23] Gabriela S. Hobbs,[3] Ronald Hoffman,[24] Elias J. Jabbour,[7] Jean-Jacques Kiladjian,[13] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.-C. Loh,[25] Bob Löwenberg,[26] Elizabeth Macintyre,[27] Luca Malcovati,[28] Charles G. Mullighan,[29] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Elli Papaemmanuil,[33] Francesco Passamonti,[28] Kimmo Porkka,[34] Ching-Hon Pui,[29] Jerald P. Radich,[35] Andreas Reiter,[36] Maria Rozman,[37] Martina Rudelius,[38] Michael R. Savona,[39] Charles A. Schiffer,[40] Annette Schmitt-Graeff,[41] Akiko Shimamura,[15,42] Jorge Sierra,[43] Wendy A. Stock,[1] Richard M. Stone,[15] Martin S. Tallman,[44] Jürgen Thiele,[45] Hwei-Fang Tien,[46] Alexandar Tzankov,[47] Alessandro M. Vannucchi,[48] Paresh Vyas,[49] Andrew H. Wei,[50] Olga K. Weinberg,[51] Agnieszka Wierzbowska,[52] Mario Cazzola,[28] Hartmut Döhner,[53] and Ayalew Tefferi[19]

ICC - WHO 2022

Zeidan, *et. al*; 2022, Leukemia

Finding consistency in classifications of myeloid neoplasms:

a perspective on behalf of the International Workshop for Myelodysplastic Syndromes

Table 2. Comparison of key components included in ICC and WHO 2022 definitions of MDS.

	ICC [5]	WHO 2022 [3]
MDS/AML overlap category for patients with 10–19% bone marrow or peripheral blood blasts	Included	Not included; patients should be classified as MDS-IB2
Dysplasia and ring sideroblasts as diagnostic criteria	≥10% dysplasia required for diagnosis; distinction between single- and multilineage dysplasia maintained; select molecular features enable diagnosis without dysplasia (e.g., monosomy 7). Ring sideroblasts no longer impact diagnosis.	≥10% dysplasia required for diagnosis; no distinction between single- and multi-lineage dysplasia. Ring sideroblasts still used for diagnosis of MDS cases lacking SF3B1 mutation or with unknown SF3B1 status.
MDS with fibrosis and hypoplastic MDS	Not included	Included as MDS-f and MDS-h
Molecular characteristics as disease-defining features	Addition of biallelic *TP53* mutations, SF3B1 mutation, and various AML-defining genetic alterations	Addition of biallelic *TP53* mutations, SF3B1 mutation, and various AML-defining genetic alterations; name change to myelodysplastic neoplasms

Verzicht auf willkürliche Schwellenwerte

(molekulare) genetische Charakterisierung

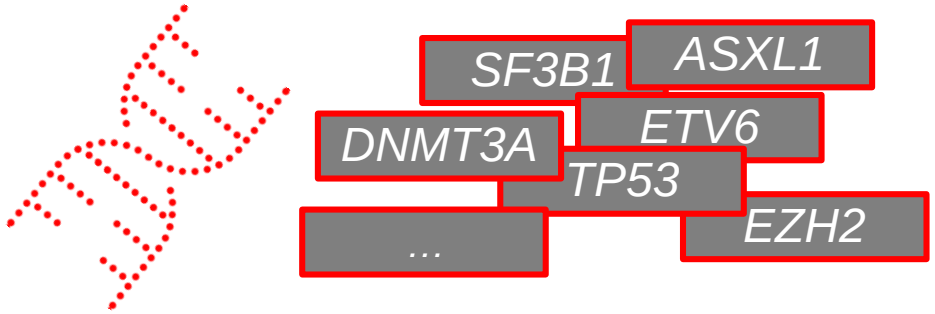
Prognose

IPSS (Greenberg *et al*, 1997)
- Bone marrow blasts
- Number of cytopenias
- Cytogenetics

IPSS-R (Greenberg *et al*, 2012)
- Bone marrow blasts
- Hb/Platelets
- ANC
- Cytogenetics

IPSS-M (Bernard *et al*, 2022)
- Bone marrow blasts
- Hb/Platelets
- Cytogenetics
- **31 genes**

1997 **2012** **2021 2022**



Personalized prediction models (Nazha *et al,* and Bersanelli *et al.* both 2021)
- **Molecular genetics**
- ….

Greenberg et al. Blood, 1997; Greenberg et al. Blood, 2012;
Bernard et al. NEJM Evidence, 2022; Nazha et al. JCO, 2021; Bersanelli et al. JCO, 2021

IPSS-M

Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	–0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	–0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{5q}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	–0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

AML

NICHT berücksichtigt:

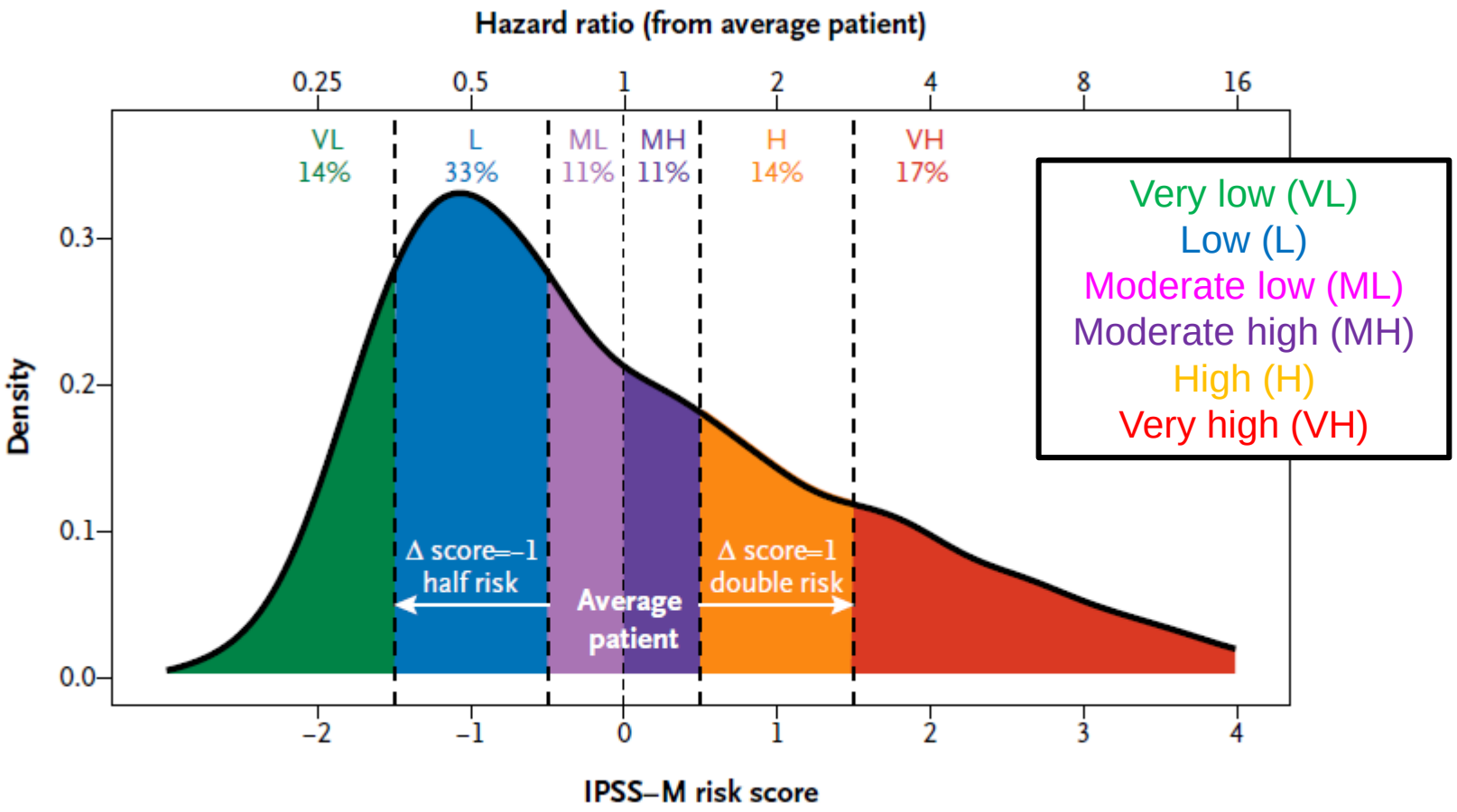
- Alter
- ANC
- Geschlecht
- MDS Typ

E. Bernard *et al.*, NEJM evidence, 2022

IPSS-M

"The IPSS-M score was built as a weighted sum of prognostic variables observed for each patient."

- jeder Patient bekommt einen Wert
- 0 steht für einen hypothetischen Durchschnittspatienten
- Werte von -1, 1 oder 2 entsprechen dem halben, doppelten oder vierfachen Risiko im Vergleich zum Durchschnittspatienten



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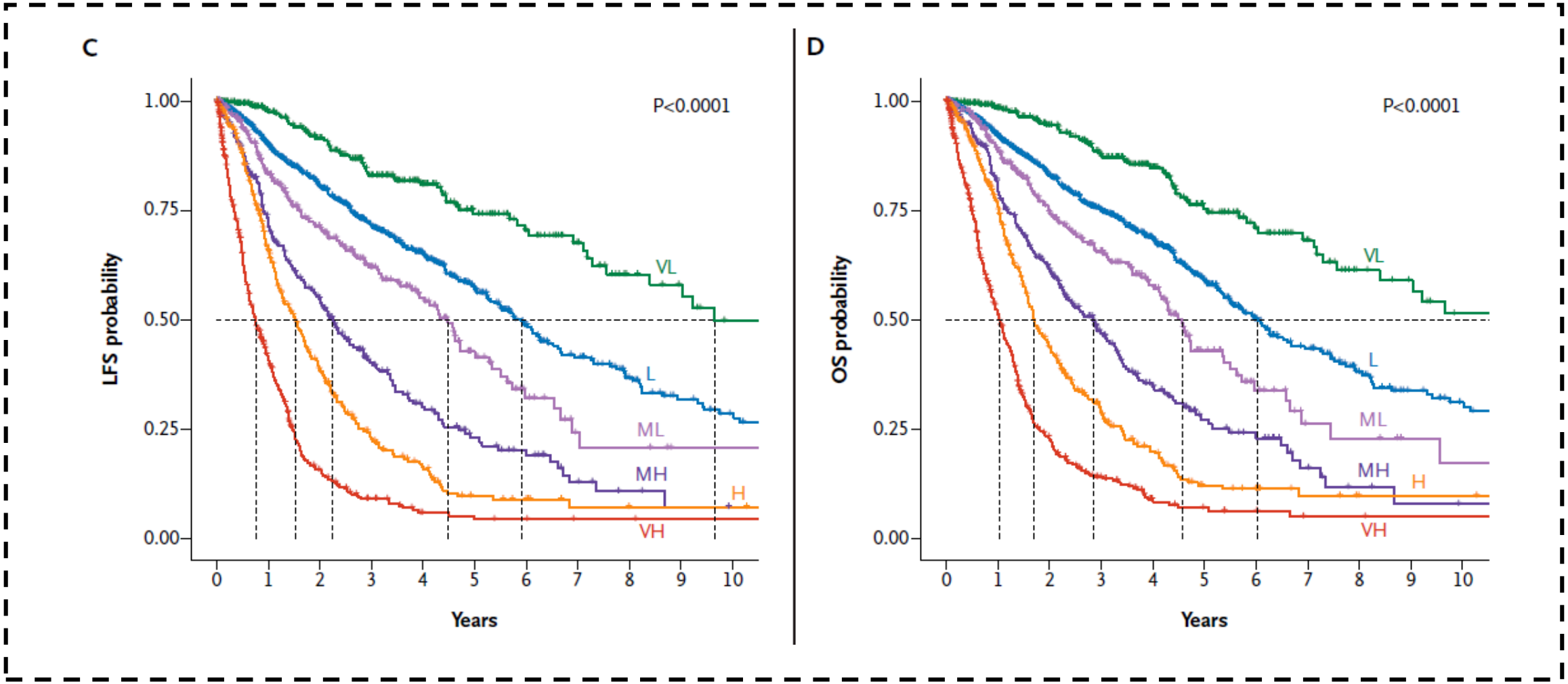
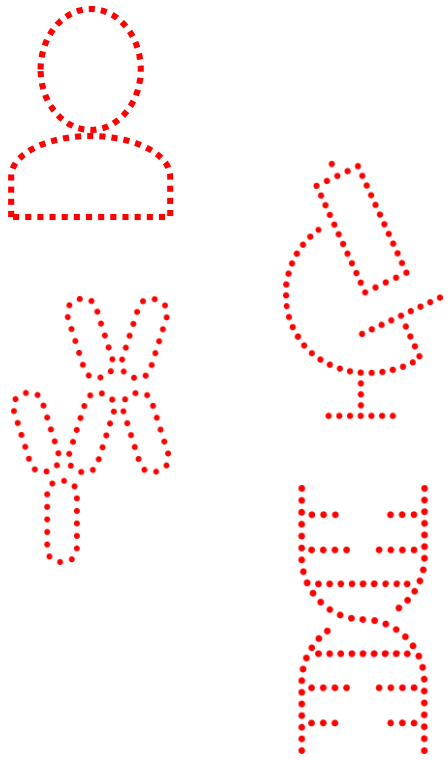
IPSS-M



E. Bernard *et al.*, NEJM evidence, 2022

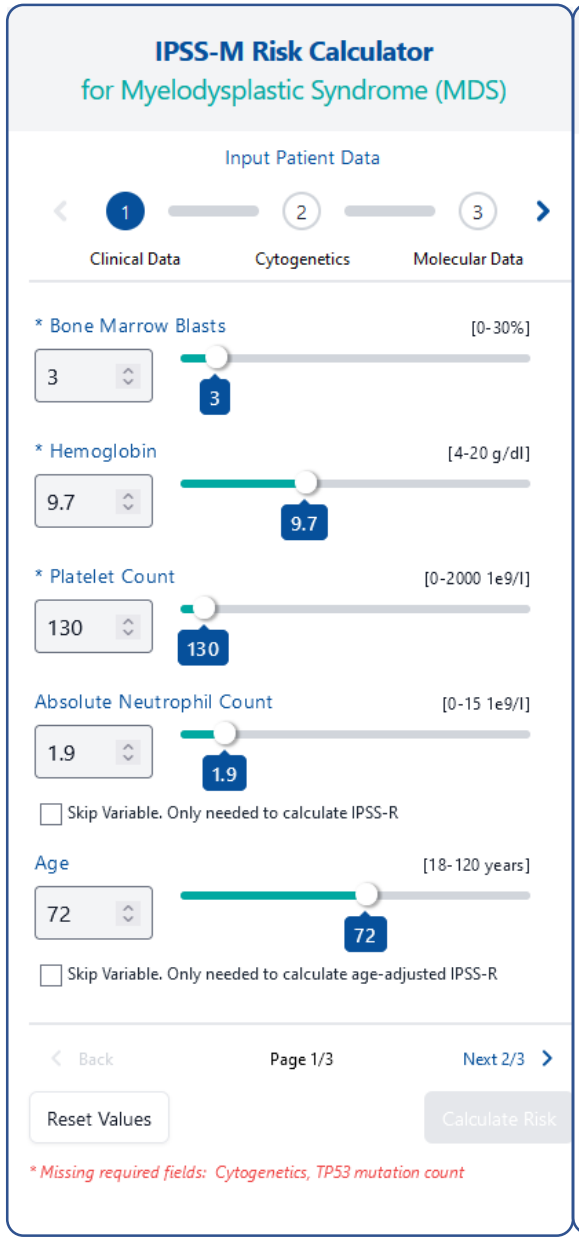
Wie wird der IPSS-M verwendet?

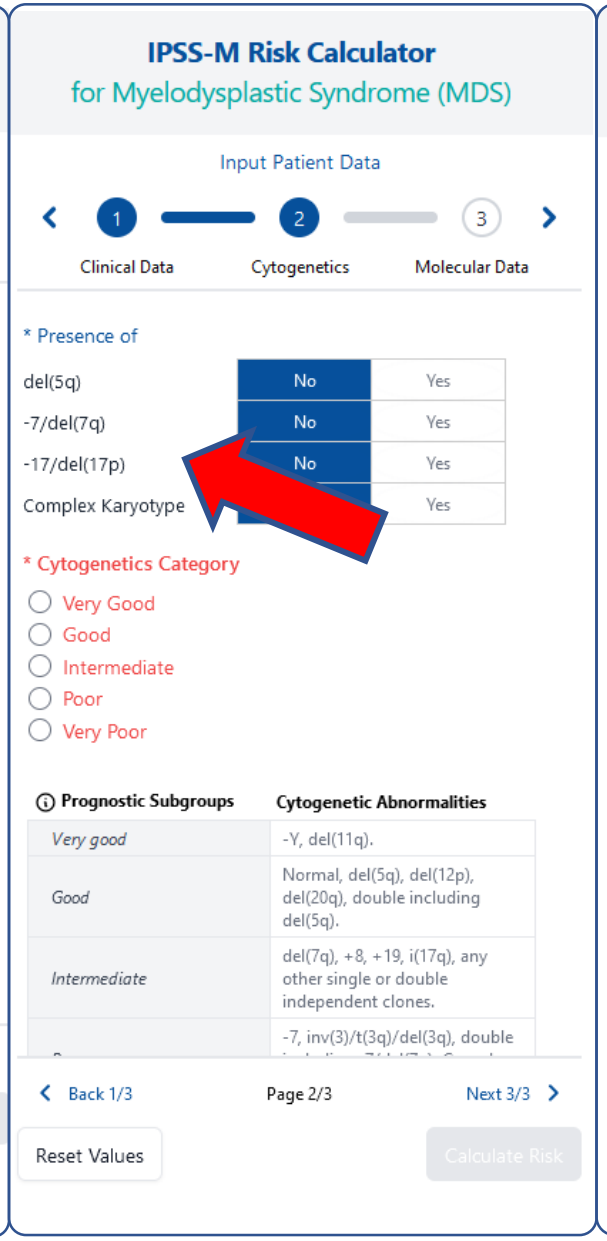
1. Hämoglobin
2. Thrombozyten
3. % Blasten (KM)
4. Zytogenetik nach dem IPSS-R
5. Molekulargenetik für 31 Gene

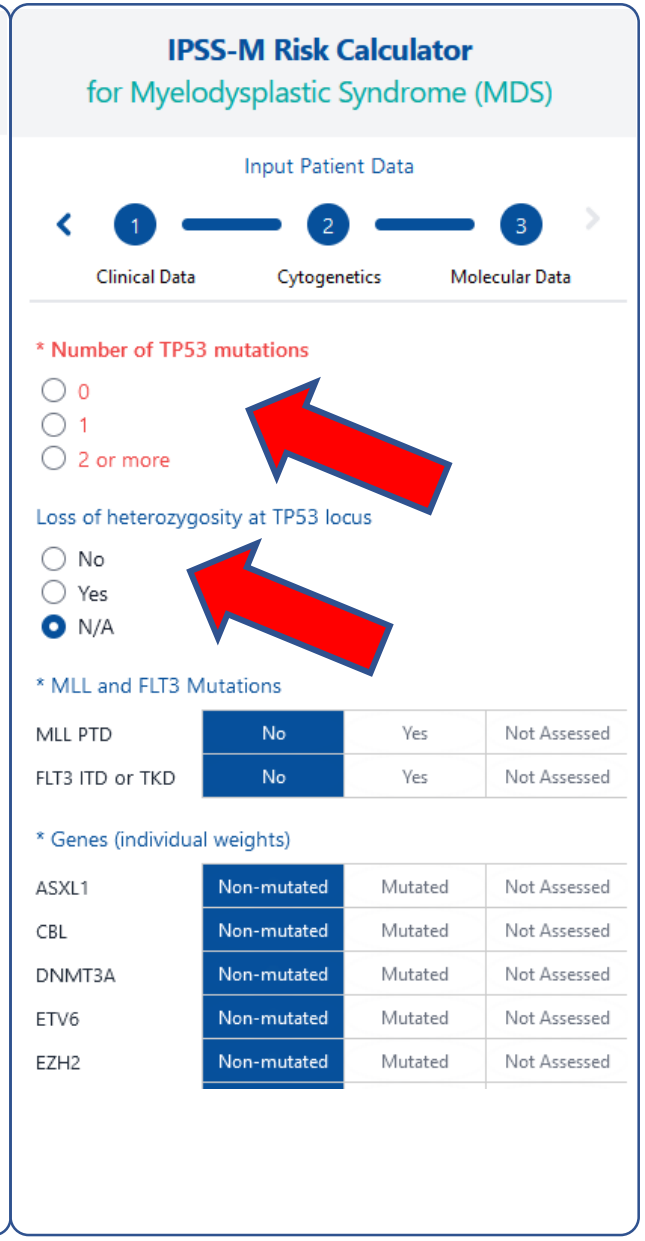


https://mds-risk-model.com/

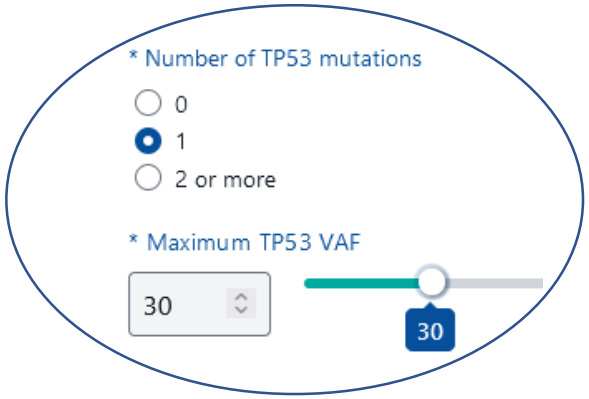
Wie wird der IPSS-M verwendet?

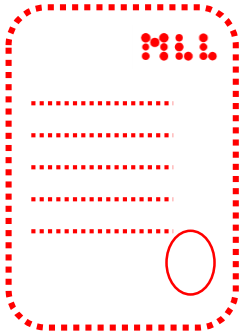






TP53 multi

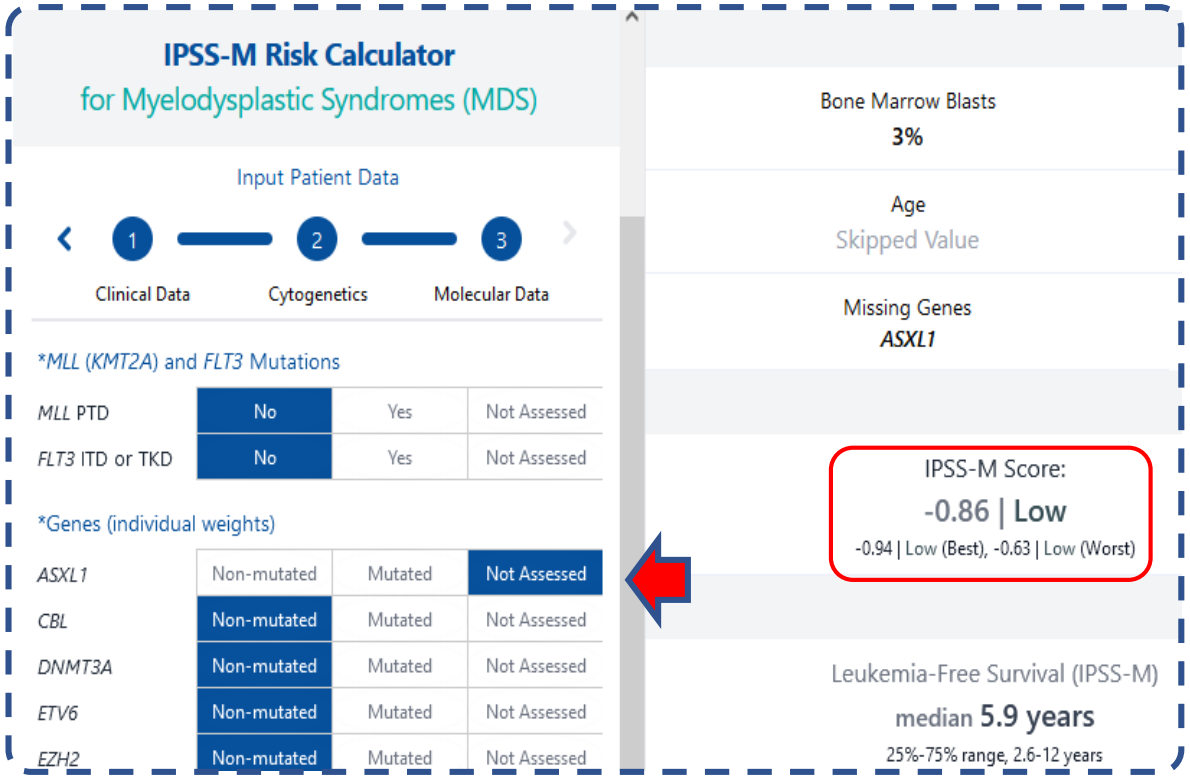


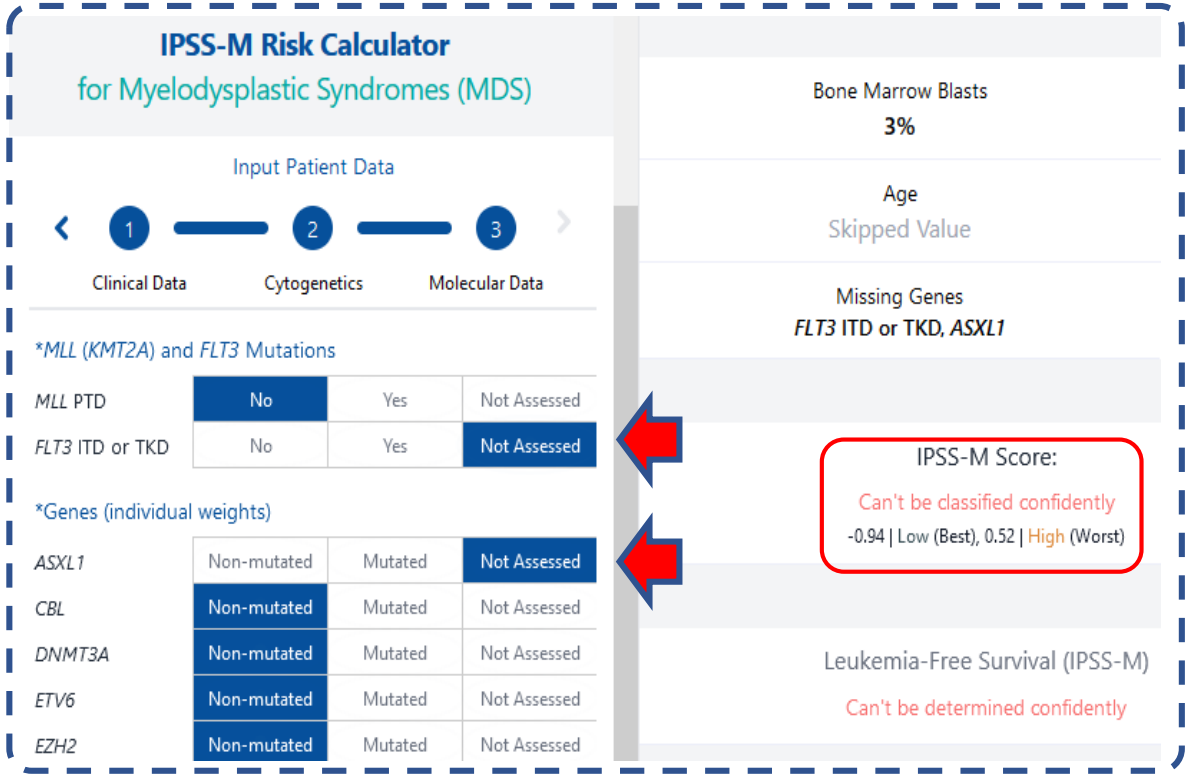


Anhang:
Veränderungen (Tier 1 oder 2)

Gene	Exon	[…]	Protein	VAF
TP53	08	[…]	p.Arg273Leu	30

Wie wird der IPSS-M verwendet?





Zusammenfassung

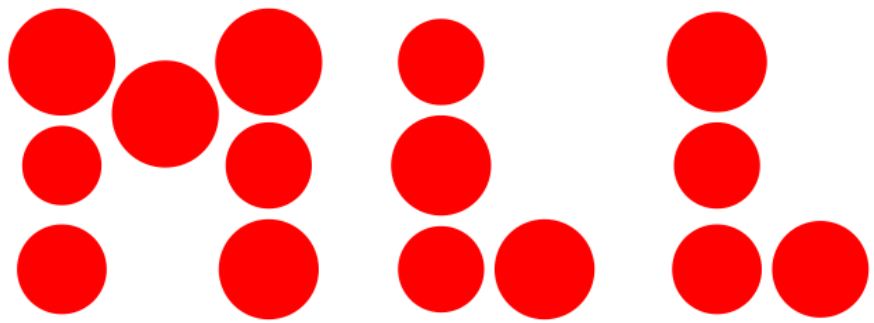
„Blue Book“ WHO 5th Edition und ICC Guidelines

- Grenzwert (Blastenzahl) weicht zunehmend einer genetischen Klassifikation

WHO 5th Edition:

- hierarchische Klassifikation (Genetik → Morphologie)
- Myelodysplastisches Syndrom (MDS) → Myelodysplastische Neoplasie (MDS)
- t-MDS → Myelodysplastic neoplasm post cytotoxic therapy (pCT):

  CAVE: pCT wird an die Klassifikation angehängt

Prognose Scores:

- IPSS-M und andere beinhalten nun molekulargenetische Veränderungen