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# Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allogeneic Hematopoietic Stem-Cell Transplantation in Patients With Myelodysplastic Syndromes

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## ABSTRACT

**PURPOSE** Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only potentially curative treatment for patients with myelodysplastic syndromes (MDS). Several issues must be considered when evaluating the benefits and risks of HSCT for patients with MDS, with the timing of transplantation being a crucial question. Here, we aimed to develop and validate a decision support system to define the optimal timing of HSCT for patients with MDS on the basis of clinical and genomic information as provided by the Molecular International Prognostic Scoring System (IPSS-M).

**PATIENTS AND METHODS** We studied a retrospective population of 7,118 patients, stratified into training and validation cohorts. A decision strategy was built to estimate the average survival over an 8-year time horizon (restricted mean survival time [RMST]) for each combination of clinical and genomic covariates and to determine the optimal transplantation policy by comparing different strategies.

**RESULTS** Under an IPSS-M based policy, patients with either low and moderate-low risk benefited from a delayed transplantation policy, whereas in those belonging to moderately high-, high- and very high-risk categories, immediate transplantation was associated with a prolonged life expectancy (RMST). Modeling decision analysis on IPSS-M versus conventional Revised IPSS (IPSS-R) changed the transplantation policy in a significant proportion of patients (15% of patient candidate to be immediately transplanted under an IPSS-R-based policy would benefit from a delayed strategy by IPSS-M, whereas 19% of candidates to delayed transplantation by IPSS-R would benefit from immediate HSCT by IPSS-M), resulting in a significant gain-in-life expectancy under an IPSS-M-based policy ( $P = .001$ ).

**CONCLUSION** These results provide evidence for the clinical relevance of including genomic features into the transplantation decision making process, allowing personalizing the hazards and effectiveness of HSCT in patients with MDS.

## ACCOMPANYING CONTENT

 Appendix  
 Data Supplement

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## INTRODUCTION

Despite recent therapeutic progress, the only potentially curative treatment for patients with myelodysplastic syndromes (MDS) is allogeneic hematopoietic stem-cell transplantation

(HSCT), which is considered as a therapeutic option until age 70–75 years in eligible patients.<sup>1</sup> Its efficacy, however, is considerably limited by a non-negligible morbidity and mortality associated with the procedure, and therefore, an accurate patient selection is needed.<sup>1</sup> Several issues must be

## CONTEXT

### Key Objective

Are gene mutations relevant to improve the transplantation decision making process in patients with myelodysplastic syndromes (MDS) with respect to the definition of the optimal timing of the procedure?

### Knowledge Generated

In patients eligible for allogeneic hematopoietic stem-cell transplantation (HSCT), the Molecular International Prognostic Scoring System (IPSS-M, including both clinical and genomic features) improves the capability to define the optimal timing of the procedure compared with the currently available scores, thus allowing more effective personalized treatment strategies.

### Relevance (C.F. Craddock)

The IPSS-M provides important new information to guide both the role and optimal timing of allogeneic HSCT in the management of adults with MDS.\*

\*Relevance section written by JCO Associate Editor Charles F. Craddock, MD.

taken into account when considering HSCT and evaluating its benefits in individual patients with MDS, with the optimal timing of the procedure being a crucial question.<sup>2</sup>

Clinical decisions in MDS are currently based on the Revised International Prognostic Scoring System (IPSS-R), which includes clinical features and cytogenetic abnormalities.<sup>3</sup> There is clinical consensus to immediately perform HSCT in patients with higher-risk disease.<sup>4-6</sup> Conversely, as patients with lower-risk disease may experience long periods with stable disease after diagnosis, the morbidity and mortality related to HSCT would be unacceptably high for many of them. On the other hand, a number of studies have shown that advanced disease stage at transplantation is associated with inferior survival.<sup>4,6</sup> One of the major challenges in applying these evidences to make practical decisions is the large heterogeneity of the disease clinical course, especially in those patients diagnosed with lower-risk disease.<sup>3,7</sup> This heterogeneity is not efficiently captured by IPSS-R in all cases.<sup>7</sup>

In MDS, increasing efforts are ongoing to include somatic mutations that were shown to be valuable prognostic/predictive markers to improve clinical decision making.<sup>8-12</sup> Recently, a clinical-molecular prognostic model (Molecular IPSS, IPSS-M) was proposed, on the basis of hematologic parameters, cytogenetic abnormalities, and mutations of 31 MDS-related genes.<sup>13</sup> IPSS-M improves prognostic discrimination compared with IPSS-R and better predicts post-transplantation outcomes.<sup>14,15</sup>

In this study, we aimed to develop and validate a decision support system (DSS) to define the optimal timing of HSCT in patients with MDS on the basis of clinical and genomic information as provided by IPSS-M.<sup>16</sup> Moreover, we aimed to compare the outcome of transplantation policies on the basis of IPSS-M versus original IPSS-R and to measure the proportion of patients in which the optimal timing for HSCT

would change by introducing molecular information in the decision process.

## PATIENTS AND METHODS

### Study Populations and Procedures

The study was conducted by GenoMed4All<sup>17</sup> and Synthema<sup>18</sup> consortiums, with the support of EuroBloodNET<sup>19</sup> and International Consortium on MDS. The Humanitas Ethics Committee approved the study (ClinicalTrials.gov Identifier: [NCT04889729](https://clinicaltrials.gov/ct2/show/study/NCT04889729)). Informed consent was obtained from each participant.

Inclusion criteria were age  $\geq 18$  years, a diagnosis of primary MDS by WHO 2016<sup>20</sup> criteria, and available information on IPSS-M-related variables<sup>13</sup> collected at diagnosis for patients who did not undergo HSCT, before HSCT for patients who were transplanted up front, and before starting disease-modifying treatments for patients who underwent pre-HSCT cytoreduction.

Karyotypes were classified using International System for Cytogenetic Nomenclature Criteria. Mutation screening of MDS-related genes was performed on DNA from bone marrow mononuclear cells or blood granulocytes (Data Supplement, File S1 [online only]).

Patients were reclassified according to WHO 2022 and International Consensus Classification of Myeloid Neoplasms criteria.<sup>21,22</sup> IPSS-M score was calculated according to the original publication.<sup>13</sup>

### Statistical Analysis

Numerical variables were summarized by median and range; categorical variables were described with count and relative

frequency of patients in each category. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariable analyses were performed using Cox's proportional hazards regression models.

## Development of the DSS

The strategy to build the DSS is illustrated in [Figure 1](#) and described in detail in the companion methodologic paper.<sup>23</sup> First, we built cause-specific flexible parametric survival models in the study population to examine transition hazards for the risk of AML evolution, the risk of death without performing HSCT, the risk of relapse after HSCT, and the risk of death after HSCT in the absence of disease relapse and after relapse.<sup>24,25</sup> In the pre-HSCT models, the timescale used was time since the diagnosis of MDS, whereas for the post-HSCT models, it was defined as the time since HSCT. In both cases, age and disease risk category (by IPSS-M/IPSS-R) were used as explanatory variables. The time elapsed between the diagnosis of MDS and HSCT was considered as covariate in the post-HSCT models, which were further adjusted for disease-modifying therapies (hypomethylating agents, AML-like chemotherapy, or other) using the inverse probability of treatment weights.

The second part of the analysis involved the use of the cause-specific survival model estimates to develop a Semi-Markov multistate decision model on the basis of microsimulation.<sup>26</sup> This model compared various transplantation strategies on the basis of different timing of HSCT, conditionally on covariates of interest. A range of possible timings for HSCT, spanning from 1 to 36 months from the time of diagnosis, were considered. The decision model consisted of five states: MDS pre-HSCT, AML pre-HSCT, post-HSCT, disease relapse post-HSCT, and death. This microsimulation allowed us to simulate individual trajectories in continuous time between these health states, using random number generation. Given the profile of each patient (as a combination of age and IPSS-M/IPSS-R risk category), the probabilistic law used by the random number generator was determined by the transition hazards estimated from the data. The only exception was the transition from MDS pre-HSCT to post-HSCT, which was contingent on the specific transplantation strategy scenario. Only transplantation policies from MDS were studied, so the transition from AML pre-HSCT to post-HSCT was not considered.

The decision model on the basis of microsimulation can be thought of as simulating a hypothetical randomized clinical trial where patients are randomly assigned to receive HSCT at different time points since the diagnosis of MDS. In each trial arm (ie, a scenario within the microsimulation), transplant is performed on the basis of the assigned timing if the patient has not progressed to AML and is still alive.<sup>26</sup> In the decision model, this translates to all individuals transitioning to the post-HSCT state at the designated time determined by the simulation scenario, as long as they are not in the AML or death state.

Microsimulation was conducted over an 8-year time horizon. Results were used to estimate the average survival time for each combination of covariates, known as restricted mean survival time (RMST). In our context, RMST represents the expected time a patient spends in the model before reaching the death state and the RMST estimates were compared among different transplantation policies.<sup>26</sup> Finally, the optimal transplantation policy conditioned on the covariates of interest was defined as the 95% CI for the timing that maximized the average survival time. CIs were obtained incorporating probability sensitivity analysis within the microsimulation. In the probability sensitivity analysis, the parameters regulating the transition hazards were generated from a multivariate normal distribution, in accordance with the Maximum Likelihood Estimator theory. The results of the decision model were operationalized from a clinical perspective into two strategies: immediate HSCT if the lower bound of the optimum HSCT (95% CI) was below 12 months and delayed HSCT otherwise.

Average survival time was also estimated accounting for quality of life (QoL), using quality-adjusted life years (QALY). QoL adjustments were made by incorporating utilities into the estimation of life expectancy.<sup>5,27</sup> Utilities are numerical representations of the perceived value of a given health state and are expressed as values between 0 (equivalent to being dead) and 1 (perfect health). To account for worsening of QoL because of disease progression or transplant-related complications, we defined plausible utilities on the basis of previously published data. A QALY value of 0.85 was assigned to the evolution to AML. In patients receiving transplantation, the onset of chronic graft versus host disease resulted in a QoL reduction to 0.85. Therefore, a QALY value of 0.90 was set for post-HSCT survival.<sup>5,27</sup>

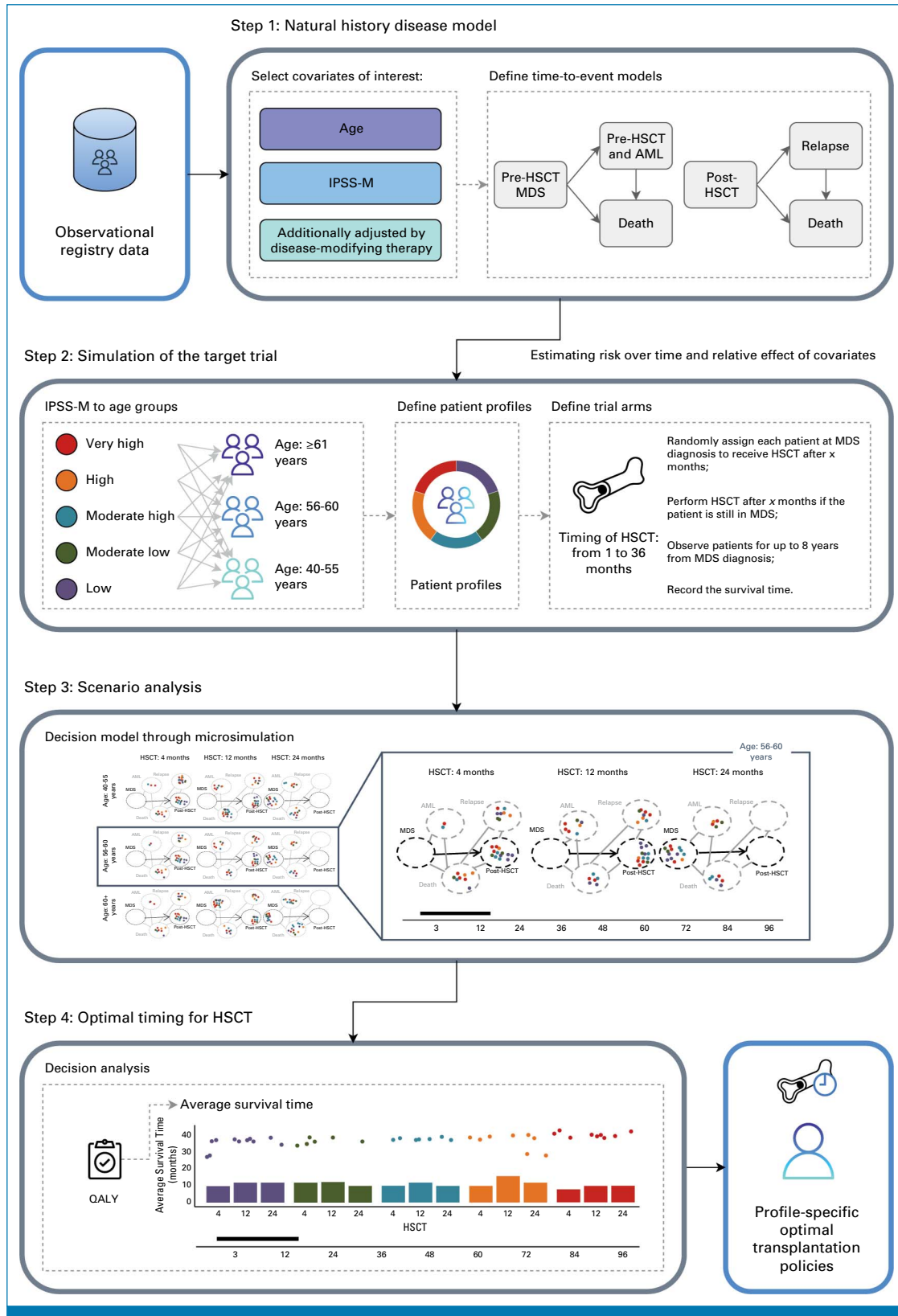
To compare the transplantation policies obtained using different scoring systems (IPSS-R/IPSS-M), we considered the samples of average survival times (RMST) for each replicated curve computed at the optimal transplantation timing conditioned on age and risk category. The two samples derived from analyses on the basis of IPSS-M and IPSS-R were compared using the t-test.

Statistical analyses were performed in the R software environment (Data Supplement, File S2).

## RESULTS

### Clinical Characteristics of Patients and Stratification According to IPSS-M Criteria

Overall, 7,118 patients from 26 institutions across Europe and United States matched study inclusion criteria. Study participants included 4,397 men (62%) and 2,721 women (38%). The date range of diagnosis was from 2000 to 2018. Follow-up was updated on December 2020. Patients were stratified into a training cohort ( $n = 4,627$ , 65%) and a validation cohort ( $n = 2,491$ , 35%) balanced by age, sex,



**FIG 1.** DSS to define optimal timing of HSCT in patients with MDS stratified according to IPSS-M criteria. DSS, decision support system; HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-M, Molecular International Prognostic Scoring System; MDS, myelodysplastic syndromes; QALY, quality-adjusted life years.

country (EU v United States), disease category (by WHO 2016 criteria), and treatment (ie, receiving v not receiving HSCT). Clinical features of patients are reported in Table 1. Considering IPSS-M–related genomic features, 6,043 patients (85%) had one or more somatic mutations on the 31 IPSS-M–related genes (Data Supplement, File S3).

We analyzed the clinical outcomes for all IPSS-M categories in both training and validation cohorts. In patients who did not receive HSCT, IPSS-M categories showed significantly different probabilities of overall and leukemia-free survival ( $P < .001$ ); in patients who received HSCT, IPSS-M categories showed significantly different probabilities of post-transplantation overall survival and risk of disease relapse ( $P < .001$ ; Fig 2).

We then focused on patients treated with HSCT. In a multivariable analysis with probability of relapse as the end point, the following factors showed independent prognostic value: disease status at transplant (refractoriness to induction chemotherapy v complete remission, hazard ratio [HR], 1.28 [1.12–1.47];  $P = .003$ ) and type of conditioning regimen (patients receiving standard conditioning regimens showed a reduced probability of relapse, HR, 0.67 [0.52–0.89];  $P < .001$ ). Recipient age and human leukocyte antigen (HLA) match ( $\leq 7$  of 8 v 8 of 8) were significant risk factors for transplant-related mortality (HR, 1.02 [1.01–1.03];  $P < .001$  and HR, 1.37 [1.18–1.94];  $P = .005$ ). IPSS-M maintained an independent prognostic effect in predicting the probability of survival (HR, 1.21 [1.12–1.48];  $P < .0001$ ) and of relapse (HR, 1.36 [1.14–1.77];  $P < .0001$ ). In all these analyses, the variable cohort (training v validation) did not show any significant statistical effect. Overall, these results serve as a proof of concept that the integration of somatic mutations may improve the transplantation decision process in this clinical setting.

## Decision Analysis

A decision analysis for transplantation in MDS was developed on the training cohort, and its reliability was independently tested on the validation cohort.

We fitted a decision strategy in which patients with MDS were stratified according to IPSS-M. HSCT was not considered as a valuable option for those patients belonging to very low-risk category. The following patient age groups were considered: 40–55 years, 56–60 years, and  $\geq 61$  years. In our model, patients lost the eligibility to transplantation at age 70 years (because of few available information on HSCT outcome for older patients).

A detailed description of the optimal timing of HSCT (and 95% CI) in patients with MDS classified according to IPSS-M criteria is reported in the Data Supplement (File S4). In instances where the outcomes observed in the training cohort were not entirely replicated in the validation cohort, a caution in their interpretation is needed. Analyses

were adjusted for pretransplantation disease-modifying therapies (hypomethylating agents, AML-like chemotherapy, or other) and for QoL using QALY (the results before QALY adjustment are available in the Data Supplement, File S4).

In the training cohort (Fig 3A; Data Supplement, File S4), immediate transplantation was associated with a prolonged RMST in patients with moderate-high, high- and very-high IPSS-M risk categories across all age groups. These results were confirmed in the validation cohort (Fig 3B; Data Supplement, File S4). Patients in the training cohort with either low and moderate low IPSS-M risk benefited from a delayed transplantation policy (except for patients 61 years and older with a moderate-low risk). These results were partially replicated in the validation cohort (primarily encompassing patients age 40–55 years with low risk and 61 years and older with moderate risk, as outlined in the Data Supplement, File S4).

We performed a decision analysis focused on MDS with *TP53* mutations presenting a significant challenge for transplant decision making. We applied the 2022 WHO classification criteria<sup>21</sup> to categorize these patients into MDS with monoallelic ( $n = 372$ ) and biallelic *TP53* inactivation ( $n = 409$ ). The decision model was executed to determine the optimal timing of HSCT in these two categories. As illustrated in the Data Supplement (File S5), RMST was higher for patients with monoallelic *TP53* inactivation compared with biallelic inactivation, and in both populations, an immediate transplantation policy was associated with a prolonged life expectancy.

Then, we compared the outcome of transplantation policies on the basis of IPSS-M versus original IPSS-R and we measured the proportion of patients in which the optimal timing for HSCT would change by introducing molecular information in the decision analysis. Under an IPSS-R based policy, HSCT was not considered as valuable option for those patients belonging to very-low risk category. In the training cohort (as shown in Fig 4A; Data Supplement, File S4), immediate transplantation was associated with a prolonged RMST in patients belonging to high- or very-high-risk categories (regardless of age) and in those classified as intermediate risk (with the exception of patients age 40–55 years). These findings were confirmed in the validation cohort, except for younger patients with intermediate IPSS-R risk (Fig 4B; Data Supplement, File S4). Regarding patients with low-risk IPSS-R, results from the training cohort indicated that most patients benefited from a delayed transplantation policy (except for those 61 years and older), whereas in the validation cohort, immediate transplantation seems to be more advantageous for these patients.

A five-to-five comparison of IPSS-R and IPSS-M in the whole study population (in which we merged moderate-low and moderate-high to moderate risk in IPSS-M) resulted in

**TABLE 1. Clinical and Hematologic Characteristics and Transplant-Related Features of the Study Population, Stratified Into Training and Validation Cohorts (n = 4,627 and n = 2,491, respectively)**

Characteristic	Training Cohort	Validation Cohort	P
MDS natural history (no HSCT), No. (%)	(n = 3,502)	(n = 1,878)	
Demographic			
Male sex	2,177 (62.1)	1,132 (60.3)	NS
Age at diagnosis, years, range	73 (18-98)	72 (19-97)	NS
WHO 2022 category			
MDS-LB-5q-	203 (5.8)	113 (6)	
MDS-LB-SF3B1	686 (19.6)	331 (17.6)	
MDS-LB-RS	112 (3.2)	85 (4.5)	
MDS-LB	1,278 (36.5)	682 (36.3)	
MDS-IB1	473 (13.5)	267 (14.2)	
MDS-IB2	438 (12.5)	197 (10.5)	
MDS-biTP53	179 (5.1)	103 (5.5)	
MDS, with fibrosis	56 (1.6)	38 (2)	
MDS, hypoplastic	42 (1.2)	38 (2)	
AML	35 (1)	24 (1.3)	
IPSS-R risk group			
Very low	566 (16.2)	301 (16)	NS
Low	1,396 (39.9)	753 (40.1)	
Intermediate	685 (19.6)	370 (19.7)	
High	423 (12.1)	226 (12)	
Very high	432 (12.3)	228 (12.1)	
IPSS-M risk group			
Very low	352 (10.1)	182 (9.7)	NS
Low	1,196 (34.2)	646 (34.4)	
Moderately low	451 (12.9)	258 (13.7)	
Moderately high	369 (10.5)	184 (9.8)	
High	508 (14.5)	287 (15.3)	
Very high	626 (17.9)	321 (17.1)	
Disease-modifying treatment			
Yes	1,235 (35.3)	644 (34.3)	NS
No	2,267 (64.7)	1,234 (65.7)	
MDS Receiving HSCT, No. (%)	(n = 1,125)	(n = 613)	P
Clinical and hematologic characteristics			
Demographic			
Male sex	695 (61.7)	393 (64.1)	NS
Age at diagnosis, years, range	59.9 (18-77)	59 (18-78)	NS
WHO 2022 category			
MDS-LB-5q-	18 (1.6)	10 (1.6)	
MDS-LB-SF3B1	34 (3)	26 (4.2)	
MDS-LB-RS	21 (1.9)	12 (1.9)	
MDS-LB	297 (26.4)	144 (23.5)	
MDS-IB1	243 (21.5)	140 (22.8)	
MDS-IB2	368 (32.7)	193 (31.5)	
MDS-biTP53	59 (5.2)	53 (8.7)	
MDS with fibrosis	26 (2.3)	9 (1.4)	
MDS, hypoplastic	21 (1.9)	6 (0.9)	
AML	38 (3.4)	20 (3.3)	
IPSS-R risk group			
Very low	—	—	NS
Low	232 (20.6)	125 (20.4)	
Intermediate	284 (25.2)	138 (22.5)	
High	326 (29)	180 (29.4)	
Very high	283 (25.2)	170 (27.7)	

(continued on following page)

**TABLE 1.** Clinical and Hematologic Characteristics and Transplant-Related Features of the Study Population, Stratified Into Training and Validation Cohorts (n = 4,627 and n = 2,491, respectively) (continued)

Characteristic	Training Cohort	Validation Cohort	P
IPSS-M risk group			NS
Very low	—	—	
Low	271 (24.1)	137 (22.3)	
Moderately low	136 (12.1)	69 (11.3)	
Moderately high	169 (15)	86 (14)	
High	272 (24.2)	153 (25)	
Very high	277 (24.6)	168 (27.4)	
Pre-HSCT disease-modifying treatment			NS
Yes	696 (61.9)	409 (66.7)	
No	429 (38.1)	204 (33.3)	
Transplant-related features			
Time to HSCT, months, range	7.1 (1-226)	7.6 (1-185)	NS
Donor type, No. (%)			NS
HLA-identical sibling	361 (32.1)	170 (27.6)	
Matched unrelated donor	409 (36.4)	241 (39.4)	
Mismatched unrelated donor	239 (21.3)	149 (24.3)	
Mismatched related donor	103 (9.1)	46 (7.6)	
Cord blood	13 (1.1)	7 (1.1)	
Disease status at HSCT, No. (%)			NS
Up-front HSCT	423 (37.6)	207 (33.8)	
Complete response	309 (27.5)	194 (31.7)	
Active disease	393 (34.9)	211 (34.4)	
Conditioning regimen, No. (%)			NS
Standard conditioning regimen	682 (60.6)	368 (60.1)	
Reduced-intensity conditioning	443 (39.4)	245 (39.9)	

Abbreviations: HLA, human leukocyte antigen; HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-M, Molecular International Prognostic Scoring System; IPSS-R, Revised IPSS; MDS, myelodysplastic syndromes; MDS-5q, MDS with low blasts and isolated 5q deletion; MDS-bi*TP53*, MDS with biallelic *TP53* inactivation; MDS-IB1, MDS-IB2, MDS with increased blasts; MDS-LB, MDS with low blast; MDS-*SF3B1*, MDS with low blasts and *SF3B1* mutation; NS, not significant.

the restratification of 44% of patients. Of these, 29% were upstaged and 15% were downstaged.

We focused on patients younger than 70 years not belonging to IPSS-M very-low risk category, who were considered to be potentially eligible for HSCT (n = 3,172). Modeling decision analysis on IPSS-M (considering all risk categories) versus original IPSS-R in this population changed transplantation policy in a significant proportion of patients. Specifically, 15% of candidates to be immediately transplanted under an IPSS-R-based policy would benefit from a delayed strategy under an IPSS-M-based policy, whereas 19% of candidates to delayed transplantation by IPSS-R would benefit from immediate HSCT by IPSS-M. Overall, transplantation policy changed in 17% of cases after incorporating molecular features in the decision analysis (Fig 5). The comparison of the average conditional survival time for the optimal transplantation policies obtained using different scoring systems (IPSS-R/IPSS-M) resulted in a significant gain of RMST under an IPSS-M-based policy across all age groups (1.2 years;  $P = .001$ ), with an effect that was more relevant in patients with early

disease status (bone marrow blasts <10%, 1.8 years;  $P < .001$ ).

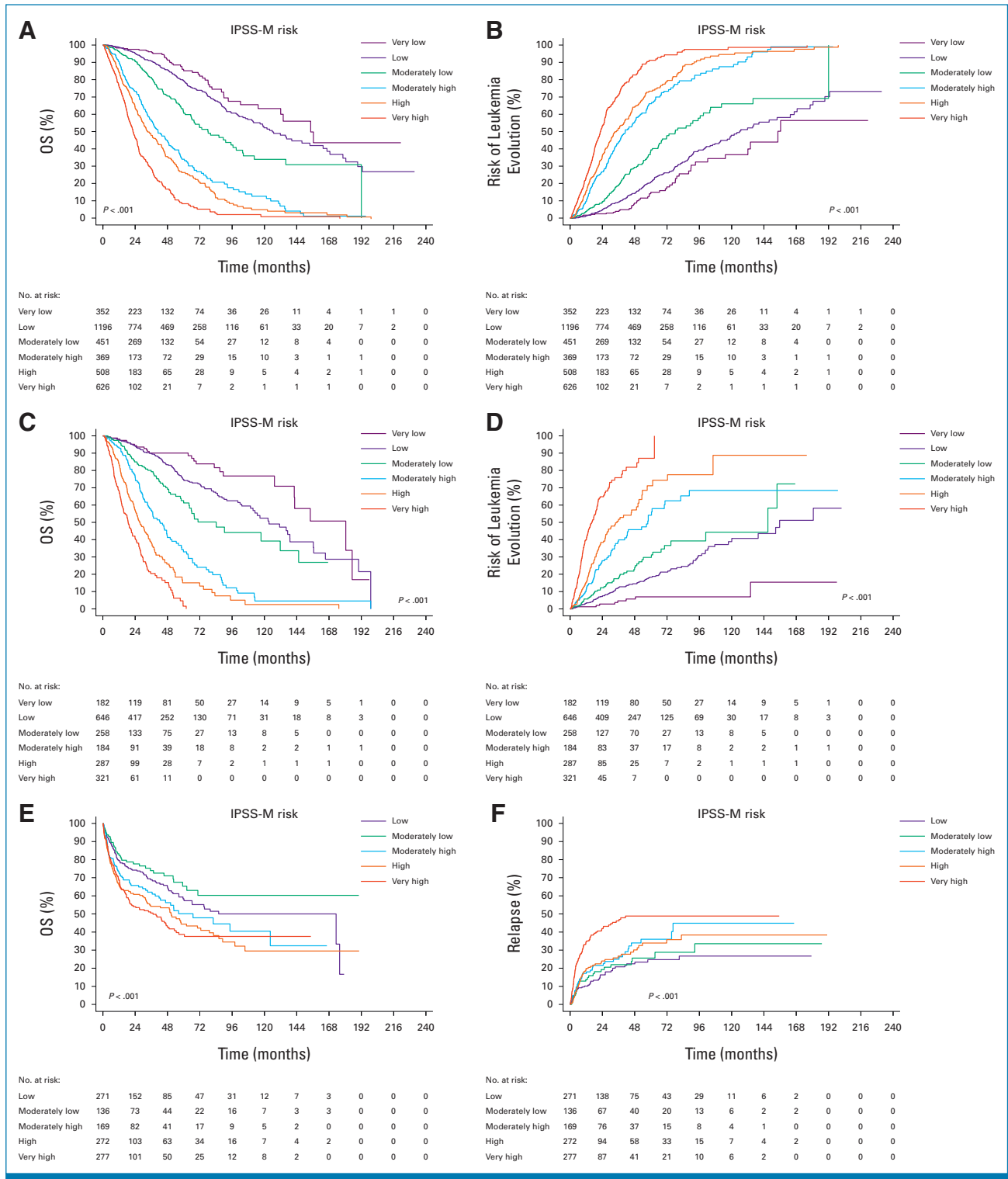
### Prototype Web Portal of the DSS for Transplantation in MDS

We have created a dedicated, publicly available tool to allow clinicians to become familiar with the DDS (HSCT Optimal Timing Calculator<sup>28</sup>), intended for research purpose only. This allows us to define the best timing for HSCT predicted on the whole study population on the basis of individual patient demographics, IPSS-R and IPSS-M information.

### DISCUSSION

A growing number of elderly patients with MDS are undergoing disease-modifying treatments, including HSCT.<sup>1</sup> Findings from prospective biologic assignment studies according to donor availability suggest that HSCT can improve the survival of patients with advanced MDS age 50-75 years compared with nontransplant strategies.<sup>29-31</sup> Furthermore, the introduction of reduced-intensity





**FIG 2.** (A-D) Probability of overall survival and risk of leukemia evolution in the nontransplant study population stratified into training (A,B) and validation (C,D) cohorts. (E-H) Probability of post-transplantation survival and risk of disease relapse after transplant in the study population stratified into training (E,F) and validation (G,H) cohorts. OS, overall survival. (continued on following page)

conditioning regimens has notably reduced transplant-related mortality, providing valuable clinical benefit in patients older than 60 years.<sup>32,33</sup> In recent years, there has

been a rise in the use of HLA-mismatched related donors, taking advantage of improvements such as the administration of post-transplant cyclophosphamide as a graft-versus-

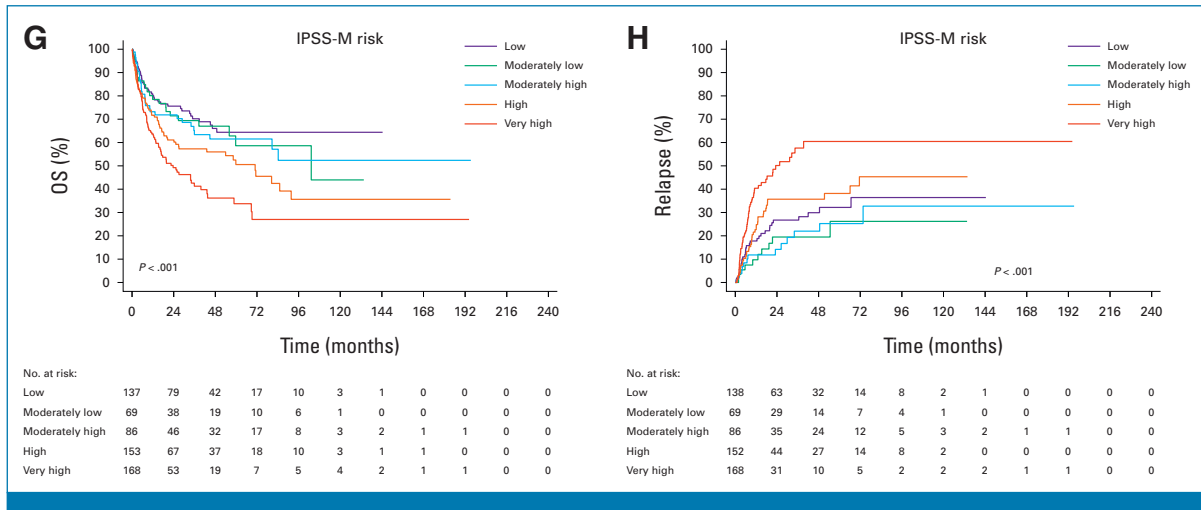


FIG 2. (Continued).

host disease prophylaxis; according to available clinical evidence, haploidentical HSCT is a suitable option for patients with MDS lacking an HLA-matched donor.<sup>34</sup> Despite these advances increasing the eligibility for transplantation, certain issues still need to be addressed to maximize the effectiveness of HSCT in MDS and a crucial question revolves around determining the optimal timing of the procedure, especially in patients without advanced disease.<sup>1,35</sup>

The development of a more accurate prognostic system is essential to improve personalized medicine strategies for patients with MDS.<sup>1,2,10,13</sup> Accordingly, there is currently a shift from conventional prognostic models on the basis of clinical/hematologic parameters (IPSS-R) to next-generation tools complemented by the introduction of molecular features (IPSS-M), which better capture the heterogeneous disease biology and patient clinical outcomes.<sup>13-15</sup> The clinical implementation of IPSS-M is expected to result in a more effective selection of candidates to disease-modifying therapies (including HSCT) and to refine the optimal timing of intervention at the individual patient level.<sup>13-15</sup>

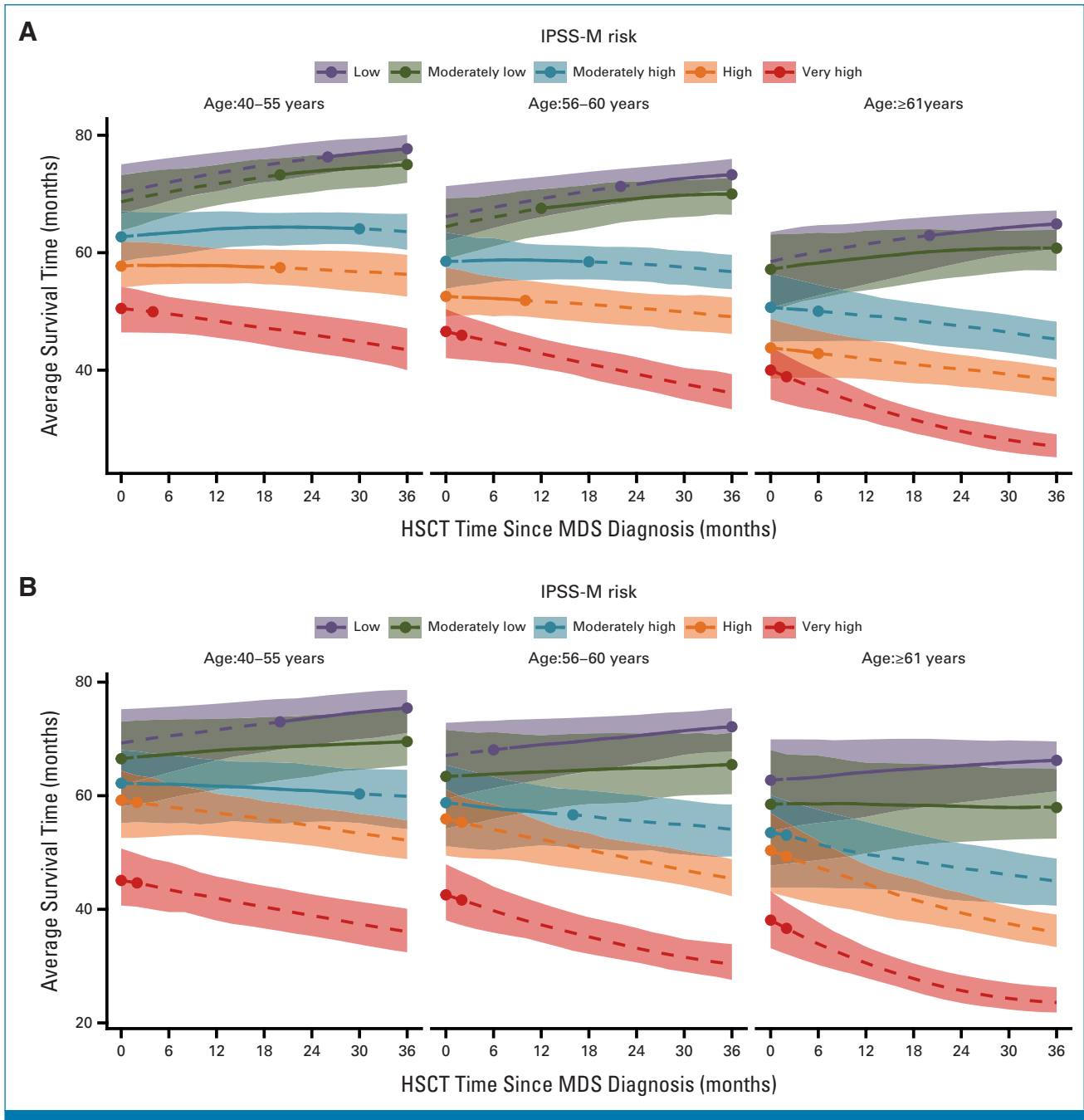
This study specifically addressed the issue of defining the optimal timing of HSCT, by incorporating molecular information (as assessed by IPSS-M) in the decision process. Using an innovative DSS, we provided evidence that IPSS-M may allow for a more precise and effective treatment strategy compared with the conventional IPSS-R. Importantly, all the results were validated in an independent patient population.

Among patients diagnosed in an early disease stage (low-risk IPSS-R), those with higher-risk mutational profiles according to IPSS-M should be considered for an earlier transplant procedure than those suggested by the conventional scoring system (IPSS-R). Conversely, delayed HSCT may maximize life expectancy for patients with lower-risk mutational profiles according to IPSS-M, who may experience a prolonged period

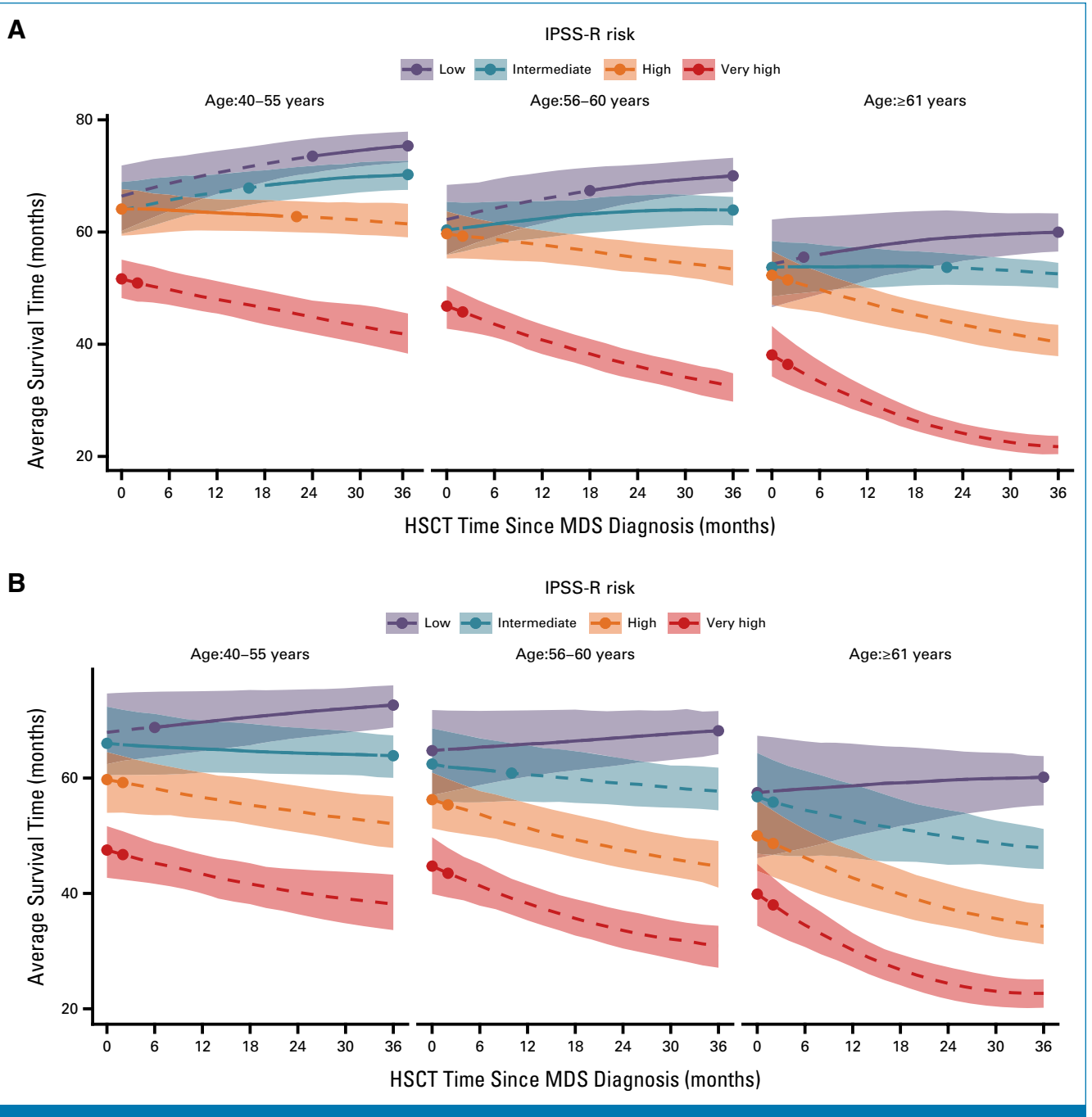
of stable disease.<sup>13-15</sup> Moreover, patients with intermediate IPSS-R may benefit from a more efficient stratification by IPSS-M,<sup>13-15</sup> providing a clearer distinction between those who should immediately be transplanted if eligible (ie, moderate high/high IPSS-M) and those for whom a delayed procedure is suitable (ie, moderate-low IPSS-M). In higher-risk patient categories defined by molecular features (such as *TP53*-mutated MDS),<sup>9,21,22</sup> prospective biologic assignment studies suggested that HSCT can improve the survival in comparison with hypomethylating agents.<sup>30</sup> Our analysis indicates in addition that in these patients, irrespective of the presence of mono- versus biallelic inactivation, blast count, and severity of cytopenia, HSCT should be performed immediately to maximize the effectiveness of the procedure.

Overall, modeling decision analysis on IPSS-M versus IPSS-R changed the transplantation policy for a considerable proportion of patients (17%), resulting in a significant gain in life expectancy under an IPSS-M-based policy across all age groups. This underscores the clinical relevance of including genomic screening information in the transplantation decision making process. The clinical importance of the IPSS-M implementation is underlined in addition by previous observations that it efficiently captures the probability of relapse after HSCT, potentially refining the choice of the optimal conditioning regimen at an individual patient level and improving the identification of patients who can be considered for pre-emptive treatments of disease recurrence.<sup>14,15</sup>

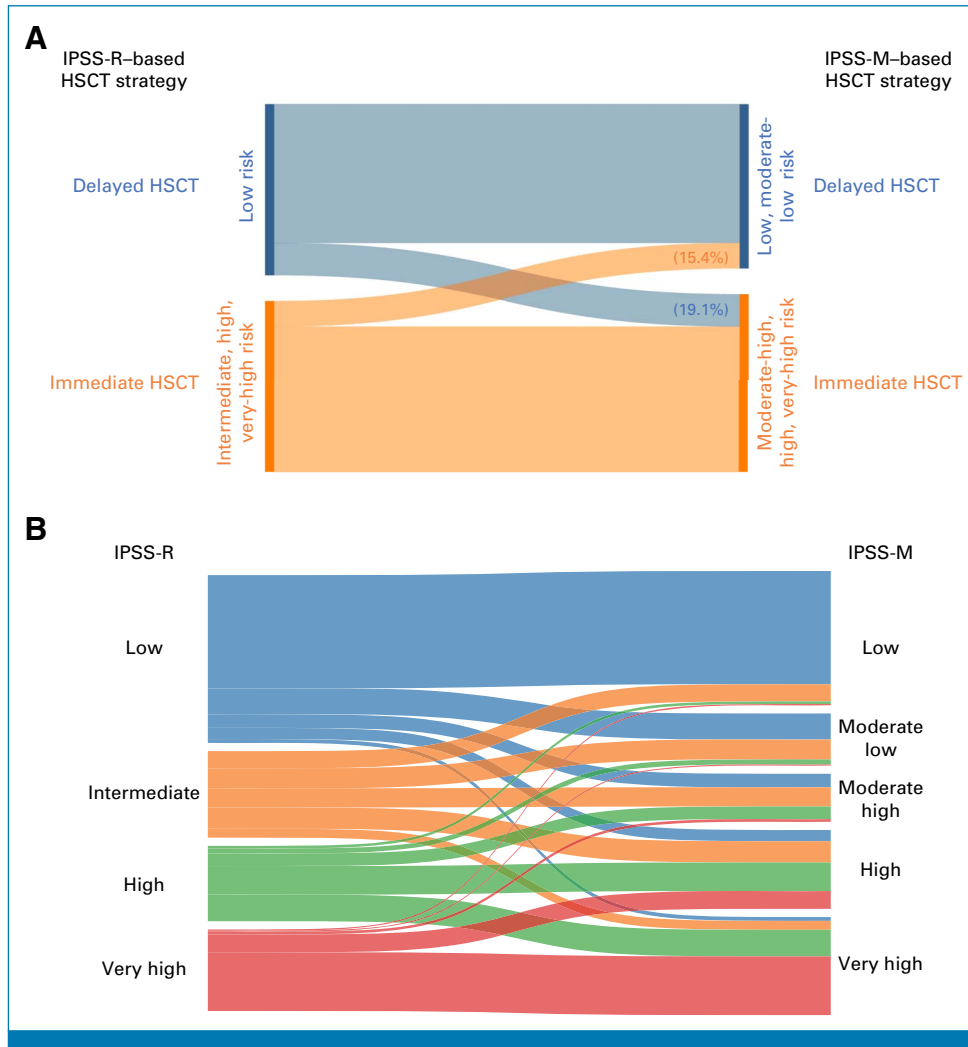
We acknowledge that molecular testing is not yet routine globally because of cost, infrastructure, and reimbursement considerations; in this context, in a previous work, we analyzed the accuracy of IPSS-M prediction when one or more molecular features are missing and defined a minimum data set of 15 relevant genes associated with high accuracy of IPSS-M prediction, thus facilitating the implementation of the score into a real-world clinical setting.<sup>14</sup>



**FIG 3.** IPSS-M–based transplantation policy in patients with MDS ((A) training cohort; (B) validation cohort). The decision model on the basis of microsimulation can be thought of as simulating a hypothetical randomized clinical trial where patients are randomly assigned to receive HSCT at different time points on diagnosis of MDS (in the x-axis). Results were used to estimate the average survival time (RMST, in the y-axis) over an 8-year time horizon. The primary emphasis in our decision analysis is on the shape of the curves, which captures the underlying relationship between HSCT timing and the corresponding RMST for different patient profiles. Hence, the width of the 95% CIs depicted as the colored area on the y-axis provides essential information about the overall probability of survival for a patient with a specific age and molecular profile but is of lesser significance for the final results and interpretation of the decision analysis. The interpretation of the figure is centered around the shape of the curves rather than the height or range of the curves themselves. It is therefore important to consider the 95% CI with respect to the optimal policies (on the x-axis), which, for each age group and IPSS-M category, defines the optimal transplantation policy (denoted with a solid line). QoL adjustments were made by incorporating utilities into the estimation of average survival time. The optimal timing for HSCT and the corresponding 95% CI from the model are presented in tabular format in the Data Supplement (File S4). HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-M, Molecular International Prognostic Scoring System; MDS, myelodysplastic syndromes; QoL, quality of life; RMST, restricted mean survival time.



**FIG 4.** IPSS-R–based transplantation policy in patients with MDS ((A) training cohort; (B) validation cohort). The decision model on the basis of microsimulation can be thought of as simulating a hypothetical randomized clinical trial where patients are randomly assigned to receive HSCT at different time points on diagnosis of MDS (in the x-axis). Results were used to estimate the average survival time (RMST, in the y-axis) over an 8-year time horizon. The primary emphasis in our decision analysis is on the shape of the curves, which captures the underlying relationship between HSCT timing and the corresponding RMST for different patient profiles. Hence, the width of the 95% CIs depicted as the colored area on the y-axis provides essential information about the overall probability of survival for a patient with a specific age and molecular profile but is of lesser significance for the final results and interpretation of the decision analysis. The interpretation of the figure is centered around the shape of the curves rather than the height or range of the curves themselves. It is therefore important to consider the 95% CI with respect to the optimal policies (on the x-axis), which, for each age group and IPSS-R category, defines the optimal transplantation policy (denoted with a solid line). QoL adjustments were made by incorporating utilities into the estimation of average survival time. HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; QoL, quality of life; RMST, restricted mean survival time.



**FIG 5.** Comparison of IPSS-R versus IPSS-M transplantation policy. (A) Whole MDS population potentially eligible for HSCT ( $n = 3,172$ ); (B) detailed description of change of transplantation policy at the individual patient level, according to the risk restratification by IPSS-M criteria. HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-M, Molecular International Prognostic Scoring System; IPSS-R, Revised IPSS; MDS, myelodysplastic syndromes.

Health care on the basis of the best available clinical evidence can lead to a higher quality of care. While randomized clinical trials provide the highest level of evidence for comparing different treatment policies, the optimal timing of HSCT cannot be addressed by randomized studies.<sup>1</sup> Clinical DSS is a technology that uses patient-specific data to provide medical knowledge at the point of care. It is considered an important quality improvement intervention to cover areas of the decision making process where conclusive evidence from a trial is lacking.<sup>16,36</sup> Our DSS uses data from a large patient population to define the best timing for HSCT on the basis of patient demographics and IPSS-R/IPSS-M information. It provides a proof of concept for the clinical relevance of including molecular features for a personalized assessment of the hazards and effectiveness of HSCT, with a clinical value that is maximized in elderly patients who

represent a significant challenge for transplant decision making. The clinical implementation of such a system is expected to improve the objectivity of clinical decisions and adherence to clinical evidence by health care providers.<sup>16,36</sup>

Finally, we would like to address the possible limitations of the study. A dynamic validation of IPSS-M is still lacking,<sup>13</sup> and in our analysis, clinical and genomic features of the nontransplantation cohort were only available at diagnosis. Consequently, the model did not account for disease progression from lower- to higher-risk MDS, which is typical of the natural course of the disease. Moreover, the existing DSS could be refined by incorporating additional information potentially relevant for transplantation decisions such as comorbidity, HLA-matching, conditioning regimen, and donor-related features.<sup>1</sup>

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C.A.T., C.G., M.R., N.G., and C.G. contributed equally to this work as first authors. R.K., F.I., and M.G.D.P. contributed equally to this work as last senior authors.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## DATA SHARING STATEMENT

Requests for access to data from the study should be addressed to GenoMed4All/Synthema scientific committees (please contact M.G.D.P. at [matteo.della\\_porta@hunimed.eu](mailto:matteo.della_porta@hunimed.eu)). All proposals requesting data access will need to specify how the data will be used, and all proposals will need the approval of the GenoMed4All/Synthema scientific committees before data release.

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## REFERENCES

- de Witte T, Bowen D, Robin M, et al: Allogeneic hematopoietic stem cell transplantation for MDS and CMML: Recommendations from an international expert panel. *Blood* 129:1753-1762, 2017
- Malcovati L, Hellström-Lindberg E, Bowen D, et al: Diagnosis and treatment of primary myelodysplastic syndromes in adults: Recommendations from the European LeukemiaNet. *Blood* 122:2943-2964, 2013
- Greenberg PL, Tuechler H, Schanz J, et al: Revised International Prognostic Scoring System for myelodysplastic syndromes. *Blood* 120:2454-2465, 2012
- Cutler CS, Lee SJ, Greenberg P, et al: A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: Delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood* 104:579-585, 2004
- Della Porta MG, Jackson CH, Alessandrino EP, et al: Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the Revised International Prognostic Scoring System. *Leukemia* 31:2449-2457, 2017
- Della Porta MG, Alessandrino EP, Bacigalupo A, et al: Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. *Blood* 123:2333-2342, 2014
- Della Porta MG, Tuechler H, Malcovati L, et al: Validation of WHO classification-based Prognostic Scoring System (WPSS) for myelodysplastic syndromes and comparison with the Revised International Prognostic Scoring System (IPSS-R). A study of the International Working Group for Prognosis in Myelodysplasia (IWG-PM). *Leukemia* 29:1502-1513, 2015
- Papaemmanuil E, Gerstung M, Malcovati L, et al: Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* 122:3616-3699, 2013
- Bernard E, Nannya Y, Hasserjian RP, et al: Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med* 26:1549-1556, 2020
- Bersanelli M, Travaglino E, Meggendorfer M, et al: Classification and personalized prognostic assessment on the basis of clinical and genomic features in myelodysplastic syndromes. *J Clin Oncol* 39:1223-1233, 2021
- Della Porta MG, Galli A, Bacigalupo A, et al: Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol* 34:3627-3637, 2016
- Lindsley RC, Saber W, Mar BG, et al: Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med* 376:536-547, 2017
- Bernard E, Tuechler H, Greenberg PL, et al: Molecular International Prognostic Scoring System for myelodysplastic syndromes. *NEJM Evid* 1:EVIDoa2200008, 2022
- Sauta E, Robin M, Bersanelli M, et al: Real-world validation of Molecular International Prognostic Scoring System for myelodysplastic syndromes. *J Clin Oncol* 41:2827-2842, 2023
- Gurnari C, Gagelmann N, Badbaran A, et al: Outcome prediction in myelodysplastic neoplasm undergoing hematopoietic cell transplant in the molecular era of IPSS-M. *Leukemia* 37:717-719, 2023
- Sutton RT, Pincock D, Baumgart DC, et al: An overview of clinical decision support systems: Benefits, risks, and strategies for success. *NPJ Digit Med* 3:17, 2020
- GENOMED4ALL: Genomics for next generation healthcare. [www.genomed4all.eu](http://www.genomed4all.eu)
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- Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 127:2391-2405, 2016
- Khoury JD, Solary E, Abal O, et al: The 5th edition of the World Health Organization Classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. *Leukemia* 36:1703-1719, 2022
- Arber DA, Orazi A, Hasserjian RP, et al: International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. *Blood* 140:1200-1228, 2022
- Gregorio C, Sperafico M, D'Amico S, et al: Personalized timing for allogeneic stem-cell transplantation in hematological neoplasms: A target trial emulation approach using multi-state modeling and microsimulation. *J Clin Cancer Inform* 10.1200/CCI.23.00205
- Jackson C, Jackson MC: Package 'flexsurv'. Flexible parametric survival and multi-state models, 2018. <https://cran.r-project.org/web/packages/flexsurv/flexsurv.pdf>
- Royston P, Parmar MKB: Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 21:2175-2197, 2002
- Incerti D, Jansen JP: HESIM: Health economic simulation modeling and decision analysis. *arXiv:2102.09437*, 2021.10. 48550/arXiv:2102.09437
- Bush NE, Donaldson GW, Haberman MH, et al: Conditional and unconditional estimation of multidimensional quality of life after hematopoietic stem cell transplantation: A longitudinal follow-up of 415 patients. *Biol Blood Marrow Transplant* 6:576-591, 2000
- Center for Accelerating Leukemia/Lymphoma Research: Clinical and genomic-based Decision Support System to define the optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndromes. <https://cdss-webserver.shinyapps.io/HSCT-Optimal-Timing-Calculator/>
- Kröger N, Sockel K, Wolschke C, et al: Comparison between 5-azacytidine treatment and allogeneic stem-cell transplantation in elderly patients with advanced MDS according to donor availability (VidazaAllo study). *J Clin Oncol* 39:3318-3327, 2021
- Versluis J, Saber W, Tsai HK, et al: Allogeneic hematopoietic cell transplantation improves outcome in myelodysplastic syndrome across high-risk genetic subgroups: Genetic Analysis of the Blood and Marrow Transplant Clinical Trials Network 1102 study. *J Clin Oncol* 41:4497-4510, 2023
- Nakamura R, Saber W, Martens MJ, et al: Biologic assignment trial of reduced-intensity hematopoietic cell transplantation based on donor availability in patients 50-75 years of age with advanced myelodysplastic syndrome. *J Clin Oncol* 39:3328-3339, 2021
- Kröger N, Iacobelli S, Franke GN, et al: Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: A prospective randomized phase III study of the EBMT (RICMAC trial). *J Clin Oncol* 35:2157-2164, 2017
- Koreth J, Pidala J, Perez WS, et al: Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: An international collaborative decision analysis. *J Clin Oncol* 31:2662-2670, 2013
- Robin M, Porcher R, Ciceri F, et al: Haploidentical transplant in patients with myelodysplastic syndrome. *Blood Adv* 1:1876-1883, 2017
- Campagna A, Della Porta MG: Mutational screening to improve the transplantation decision-making process in MDS. *Hematology Am Soc Hematol Educ Program* 2023:73-76, 2023
- Vasey B, Nagendran M, Campbell B, et al: Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. *Nat Med* 28:924-933, 2022

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

### Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allogeneic Hematopoietic Stem-Cell Transplantation in Patients With Myelodysplastic Syndromes

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## APPENDIX 1. GENOMED4ALL, SYNTHEMA, GRUPO ESPAÑOL DE SÍNDROMES MIELODISPLÁSICOS (GESMD), FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE (FISIM) AND EUROBLOODNET CONSORTIUMS' AUTHOR LIST

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