Molecular-Based Ecosystem to Improve Personalized Medicine in Chronic Myelomonocytic Leukemia

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ABSTRACT

PURPOSE Chronic myelomonocytic leukemia (CMML) is a rare myeloid neoplasm characterized by clinical heterogeneity and is associated with poor outcomes. To date, limited molecular information has been incorporated into disease classification and risk stratification. We aimed to integrate genomic features into the clinical decision-making process for CMML.

PATIENTS AND METHODS We analyzed a retrospective cohort of 3013 patients with CMML (training set) and a prospective population of 516 patients (validation set). Using an innovative framework for multimodal data analysis, we developed molecular-based disease taxonomy and prognostication.

RESULTS Unsupervised clustering identified nine entities with distinct genomic features and outcomes ($P < .001$), including splicing machinery, transcription factors, signal transduction and tyrosine kinase pathways aberrations, and high-risk molecular signatures. Notably, 15% of patients showed molecular/clinical overlap with other myeloid neoplasms. We integrated molecular and clinical information to build the international CMML Prognostic Scoring System (iCPSS), incorporating mutations in nine genes together with hematologic parameters and cytogenetic abnormalities. The iCPSS identified five groups with distinct probability of overall and leukemia-free survival in both training and validation cohorts ($P < .001$), outperforming existing prognostic models. Importantly, 55% of patients were reassigned to higher or lower risk groups by the iCPSS. Decision analysis demonstrated that iCPSS could refine the optimal timing of allogeneic transplantation at the individual level; compared with conventional prognostic tools, iCPSS-based decision modeling changed transplantation strategy in 31% of cases, resulting in a significant gain-in-life expectancy for eligible patient population ($P < .001$). A federated learning platform was implemented to enable continuous, privacy-preserving model update across multiple centers.

CONCLUSION Molecular information improves CMML classification and prognostication, supports more effective clinical decision making, and potentially refines the design of clinical trials.

ACCOMPANYING CONTENT

Editorial, p. 1567

Appendix

Data Sharing Statement

Data Supplement

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INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a rare myeloid neoplasm predominantly affecting individuals older than 70 years.[1] The disease phenotype is characterized by features of both myelodysplastic syndromes (MDS) and myeloproliferative neoplasms, variably expressed across individual patients.[2] Peripheral blood monocytosis is the hallmark of the disease, and there is an inherent risk of transformation into AML. Allogeneic stem cell transplantation (hematopoietic

CONTEXT

Key Objective

Are gene mutations relevant to improve the classification, prognostication, and clinical decision making in patients with chronic myelomonocytic leukemia (CMML)?

Knowledge Generated

The CMML molecular taxonomy identifies biologically distinct CMML entities characterized by specific genomic profiles, clinical outcomes, and variable overlap with other myeloid neoplasms. The international CMML Prognostic Scoring System (iCPSS) provides superior prognostic discrimination across all major clinical end points compared with existing models. In patients undergoing allogeneic hematopoietic stem cell transplantation, iCPSS more accurately identifies transplant-eligible patients—particularly at early disease stages—optimizes timing of transplantation, and improves prediction of post-transplant relapse risk.

Relevance *(C. Craddock)*

The iCPSS represents an important advance in disease prognostication in CMML. At a time of increasing transplant options the iCPSS provides important new data allowing more accurate identification of patients who may benefit from allogeneic stem cell transplantation and informs decision making regarding transplant timing.*

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

stem cell transplantation [HSCT]) is the only potentially curative treatment; however, most patients are not eligible because of older age or comorbidities.[3] Hypomethylating agents (HMA) are the only approved drugs for patients who are not candidate for HSCT, with limited clinical benefit.[4-6]

Advancements in the characterization of genomic information have transformed the study of myeloid neoplasms.[7-10] A wide range of somatic mutations has been described in CMML implicating multiple cellular processes such as transcription regulation, RNA splicing, and signal transduction. Importantly, specific mutational profiles have been shown to correlate with clinical presentation, disease progression, and survival.[11,12]

Despite these advancements, the integration of molecular information into clinical practice in CMML remains limited, with current classification systems lacking entity definitions based on molecular profiles. Existing prognostic models variably incorporate genomic data,[7-9,13-17] the prognostic contribution of individual gene mutations can vary substantially, and tangible effects in patient management are not clear.[13-17] Comprehensive analyses of large patient populations and innovative methodologies are warranted to better estimate the combined effect of clinical features, cytogenetic abnormalities, and gene mutations on clinical outcomes.

In this study, we developed and validated a molecular ecosystem to support personalized medicine in CMML, based on disease molecular taxonomy (as an input for a molecular classification) and an innovative prognostic score tied to a specific and relevant treatment choice for patients with CMML (ie, HSCT). To address challenges and facilitate broad adoption, in this project we (1) used a framework to extract meaningful information from available data[18]; (2) analyzed a large, retrospective cohort with clinical and genomic annotation to capture disease heterogeneity; (3) validated findings in a prospective population with centralized genomic screening for consistency and reproducibility; (4) assessed the clinical utility of the developed tools in influencing clinical decision making, with a focus on HSCT[19,20]; and (5) established a sustainable framework for extending the prospective evaluation of these tools, potentially enabling iterative updates in response to evolving standards of care.[21]

PATIENTS AND METHODS

Study Population and Procedures

The study was conducted by the international CMML Prognostic Scoring System Alliance (iCPSS) and approved by the Ethics Committee at Humanitas Research Hospital (ClinicalTrials.gov identifier: NCT04889729). Informed consent was obtained from all participants.

The training cohort was a retrospective, multicentric population of adult patients diagnosed with CMML per WHO 2016 classification.[7] A prospective international cohort with centralized sequencing (Moffitt Cancer Center, Tampa, FL) was used for validation. Demographic, clinical, and genomic data were collected at diagnosis time, before any treatment administration. Ancillary cohorts and their role in this project are described in the Data Supplement (Fig S1, online only).

Statistical Methods

Analyses were conducted using MOSAIC,[18] an innovative framework for classification and prognostication in rare diseases. The molecular taxonomy was defined via unsupervised clustering to inform a hierarchical classification algorithm. Selected comparisons were performed with patients with MDS and AML from the ancillary cohorts.

The iCPSS prognostic score was developed using overall survival (OS) as the outcome measure. Candidate variables included mutations in 43 genes, hematologic parameters, cytogenetic risk,[22] age, and sex.

A federated-learning platform was developed for continuous update using real-world data.[21] Federated-learning allows multiple centers to collaboratively train models without centralizing patient-level data: participating institutions represent *worker* nodes that train algorithms locally and share coefficients with a *manager* node for final aggregation, thus aligning with data protection regulations.[23]

The iCPSS was used to develop a decision support system for optimal timing of HSCT. The methodology is described in previous works by this group.[19,20] Treatment policies were defined as *immediate transplantation* if optimal timing's 95% CI was <6 months or *delayed* otherwise. The results were

TABLE 1. Baseline Characteristics of Patients in the Main Retrospective Cohort and Prospective Validation Cohort

Characteristic	Main Cohort (n = 3,013)	Validation Cohort (n = 516)	*P*
Sex, No. (%)			.8
Male	2,024 (67)	346 (68)	
Female	989 (33)	170 (32)	
Age at diagnosis, years, median (IQR)	70 (62-77)	71 (65-77)	.001
WHO 2016 classification, No. (%)			.002
CMML-0	1,511 (50)	212 (42)	
CMML-1	917 (30)	187 (37)	
CMML-2	585 (19)	106 (21)	
WHO 2022 classification, No. (%)			.4
CMML-1	2,428 (81)	399 (79)	
CMML-2	585 (19)	106 (21)	
FAB phenotype, No. (%)			<.001
Myelodysplastic	1,833 (61)	226 (45)	
Myeloproliferative	1,180 (39)	259 (51)	
Unknown	0 (0)	22 (4.3)	
WBC count, $\times 10^3/\mu L$, median (IQR)	10 (6-21)	15 (8-31)	<.001
Absolute neutrophil count, $\times 10^3/\mu L$, median (IQR)	5 (3-11)	8 (3-19)	<.001
Absolute monocyte count, $\times 10^3/\mu L$, median (IQR)	2.2 (1.4-4.4)	2.9 (1.6-6.6)	<.001
Hemoglobin concentration, g/dL, median (IQR)	11.0 (9.2-12.7)	10.9 (9.2-12.9)	>.9
Platelet count, $\times 10^3/\mu L$, median (IQR)	109 (61-191)	111 (60-178)	.7
Peripheral blast count (%), median (IQR)	0 (0-1.00)	0 (0-1.00)	.007
Bone marrow blast count (%), median (IQR)	4.0 (2.0-8.0)	4.0 (2.0-8.0)	.2
Normal karyotype, No. (%)	1,794 (71)	335 (73)	.5
Complex karyotype, No. (%)	70 (2.3)	11 (2.4)	>.9
Sum of gene mutations, median (IQR)	3.0 (2.0-4.0)	3.0 (2.0-3.0)	.3
CPSS-mol risk, No. (%)			<.001
Low	452 (15)	110 (21)	
Intermediate-1	725 (24)	128 (25)	
Intermediate-2	1,151 (38)	199 (39)	
High	685 (23)	79 (15)	
Treatment with HMA, No. (%)	307 (10)	129 (25)	<.001
Allogeneic HSCT, No. (%)	829 (28)	44 (12)	<.001

NOTE. *P* values compare differences between cohorts using the chi-square or Fisher exact test for categorical variables and the *t* test or Mann-Whitney U test for continuous variables. CMML-0/1/2 refer to WHO 2016 classification based on blast percentage; CMML-1/2 refer to WHO 2022 classification. FAB phenotype classification distinguishes myelodysplastic versus myeloproliferative variants.
Abbreviations: CMML, chronic myelomonocytic leukemia; CPSS-mol, Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System incorporating molecular data; FAB, French-American-British; HMA, hypomethylating agents; HSCT, hematopoietic stem cell transplantation.

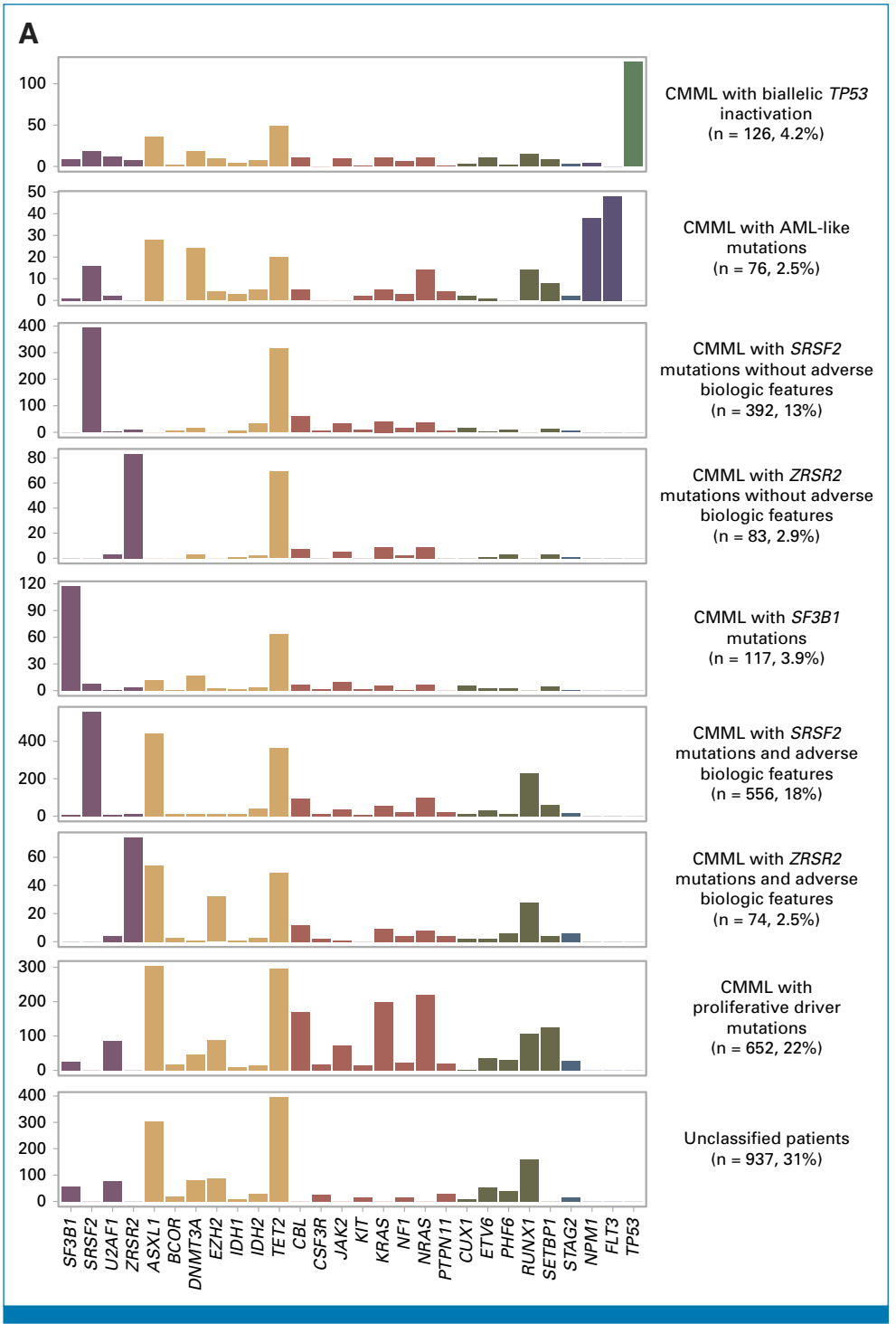

FIG 1. Molecular and clinical characteristics of CMML taxonomy classes and their association with clinical outcomes. (A) Distribution of gene mutations across CMML molecular taxonomy classes. Bar heights represent patient absolute counts for each gene. (B) Heatmap showing significant associations between CMML taxonomy classes and clinical features. Color intensity represents percentage of patients with each feature; asterisks indicate statistical significance (*FDR < 0.05, **FDR < 0.01). Light gray indicates nonsignificant associations (FDR > 0.05). (C) OS by CMML taxonomy class subtype. Data shown as median survival with 25th-75th percentile ranges. (D) LFS by CMML taxonomy class. Data shown as median survival with 25th-75th percentile ranges. CMML, chronic myelomonocytic leukemia; FDR, false discovery rate; LFS, leukemia-free survival; OS, overall survival. (continued on following page)

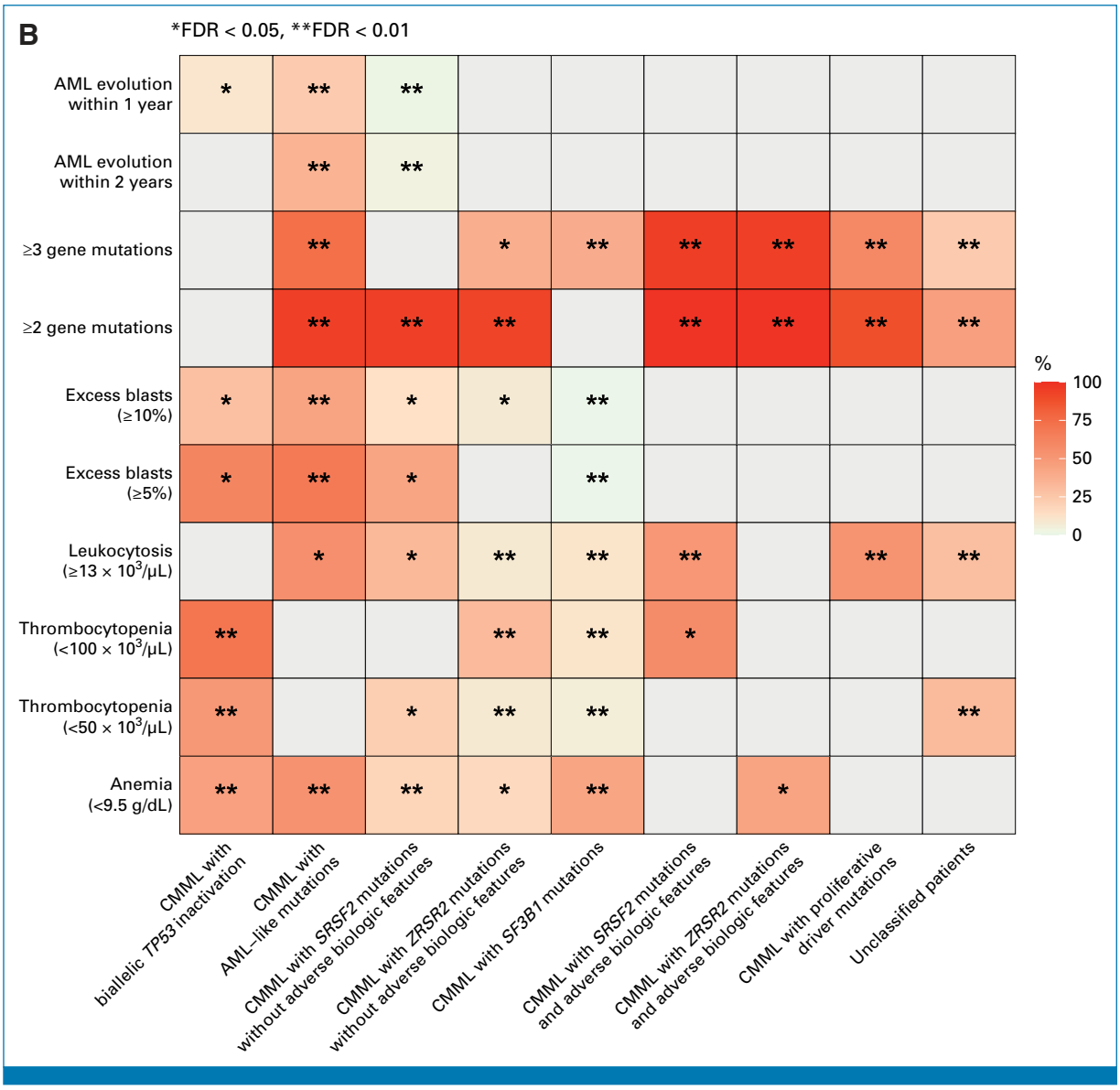

FIG 1. (Continued).

preliminarily validated in a simulated scenario with synthetic data generated with established algorithms and assessed for clinical fidelity with respect to real patients.[24,25]

The detailed methodology of this study is reported in the Data Supplement (pp. 3-11, Fig S2).

RESULTS

Study Populations

Patient characteristics from the retrospective (N = 3,013) and prospective (N = 516) cohorts are described in Table 1. The median follow-up was 4.1 and 4.9 years, respectively (Data Supplement, Figs S3 and S4). The genomic landscape of the cohorts is reported in the Data Supplement (Figs S5 and S6).

CMML Molecular Taxonomy

We defined nine classes with distinct genomic and clinical features (Fig 1), encompassing 2,076 (69%) patients in the retrospective cohort. Two classes were defined by isolated splicing factor mutations, *SRSF2* (n = 392, 13%) and *ZRSR2* (n = 83, 3%), frequently comutated with *TET2* (82%). These patients predominantly exhibited myelodysplastic features, mild cytopenias, low marrow blast counts (<5%), and favorable outcomes (median OS, 5.4 and 8.2 years). By contrast, two classes combined *SRSF2* (n = 556, 18%) or *ZRSR2* (n = 74, 2%) with adverse-risk mutations (*ASXL1*, *EZH2*, *RUNX1*). These patients more often showed proliferative features, higher blast counts (≥10%), inferior survival (median OS, 3.3 and 2.7 years; $P < .001$), and increased AML transformation (17% *v* 10% for *SRSF2*; 19% *v* 7% for *ZRSR2*; $P < .001$). A distinct class with *SF3B1* mutations without

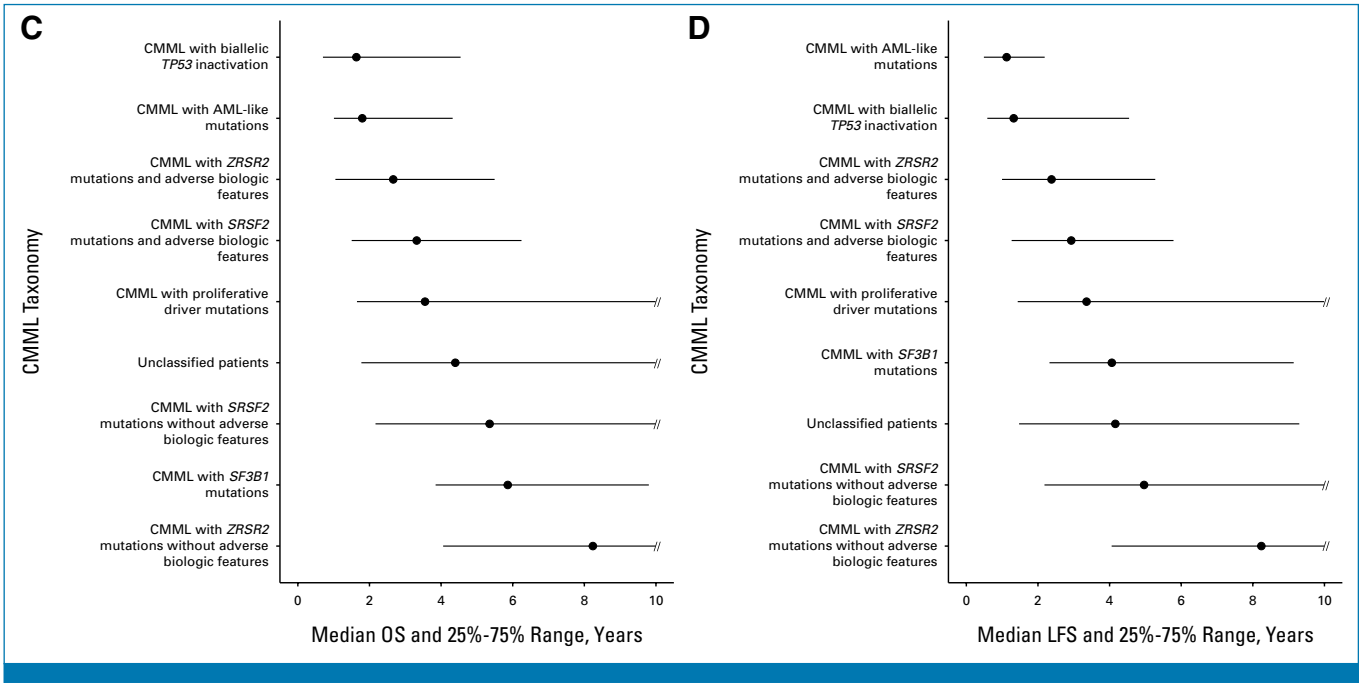

FIG 1. (Continued).

adverse comutations (n = 117, 4%) frequently harbored *TET2* (54%) or *DNMT3A* (15%) mutations and showed marked dysplasia, anemia, low blast counts, and outcomes comparable with splicing-only classes (median OS, 5.9 years). Four classes defined by proliferative driver mutations (*NRAS*, *KRAS*, *CBL*, *JAK2*, *SETBP1*) were grouped into a single subtype (n = 652, 22%), characterized by a proliferative phenotype, mild anemia, and intermediate survival (median OS, 3.6 years). Two high-risk classes were defined by biallelic *TP53* mutations (n = 126, 4.2%) or AML-like mutations (*NPM1*/*FLT3*; n = 76, 2%). These classes showed increased blast counts, high AML transformation rates (16.7% and 39.5%), and the poorest survival (median OS, 1.6 and 1.8 years).

A hierarchical algorithm was developed to assign newly diagnosed patients to the nine molecular classes (Fig 2). Additional characteristics and a comparison with the prospective cohorts for classes with a sufficient number of patients are reported in the Data Supplement (Tables S1-S9).

We then compared patients with CMML in the *SF3B1*, *SRSF2*, *TP53*, and AML-like classes with ancillary MDS and AML cohorts. Both patients with CMML and MDS with *SF3B1* mutations showed isolated anemia (Data Supplement, Table S10) and comparable survival (P = .21, Data Supplement, Fig S7). Patients with CMML with *SRSF2* mutations, with or without adverse features, shared dysplastic phenotypes (Data Supplement, Tables S11 and S12) and similar outcomes with MDS counterparts (Data Supplement, Figs S8 and S9). Despite phenotypic differences (Data Supplement, Tables S13 and S14), patients with CMML with biallelic *TP53* mutations had survival comparable with patients with MDS/AML (P = .08; Data Supplement, Figs S10 and S11). Patients with CMML with AML-like mutations (*NPM1*/*FLT3*, Data Supplement, Table S15) demonstrated survival similar to patients with AML (P = .95, Data Supplement, Fig S12). Overall, 15% of patients with CMML showed genomic, clinical, and outcome overlap with other well-defined myeloid malignancies.

The iCPSS

After feature selection, the iCPSS risk score was developed using a nonpenalized Cox model with hematologic parameters (white blood cells, hemoglobin, platelets, marrow blasts), CPSS cytogenetic risk,[20] and mutational status of *ASXL1*, *DNMT3A*, *EZH2*, *RUNX1*, *SETBP1*, *STAG2*, *TET2*, *TP53*, and *U2AF1* genes (Data Supplement, Tables S16 and S17).

The retrospective cohort was stratified as very low (504, 17%), low (1,249, 41%), intermediate (528, 18%), high (508, 17%), and very high (223, 7%) risk. The risk classes displayed a significantly different probability of OS (9.8 years for very low, 1.1 years for very high, P < .001), leukemia-free survival (LFS, 9.2-1.0 year, P < .001), and cumulative incidence of AML (median not reached, P < .001, Fig 3 and Data Supplement, Fig S13). Discrimination according to Harrell and Uno concordance index (c-index) for iCPSS was 0.71 and 0.7 for OS, 0.7 and 0.69 for LFS. Model performances were compared with Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System incorporating molecular data (CPSS-mol),[14] Mayo Molecular Model,[15] Groupe Francophone des Myelodysplasies Model,[16] BLAST-Mol,[17] and IPSS-M.[26] Pairwise testing with other risk stratification scores showed consistent and statistically significant improvement for the iCPSS

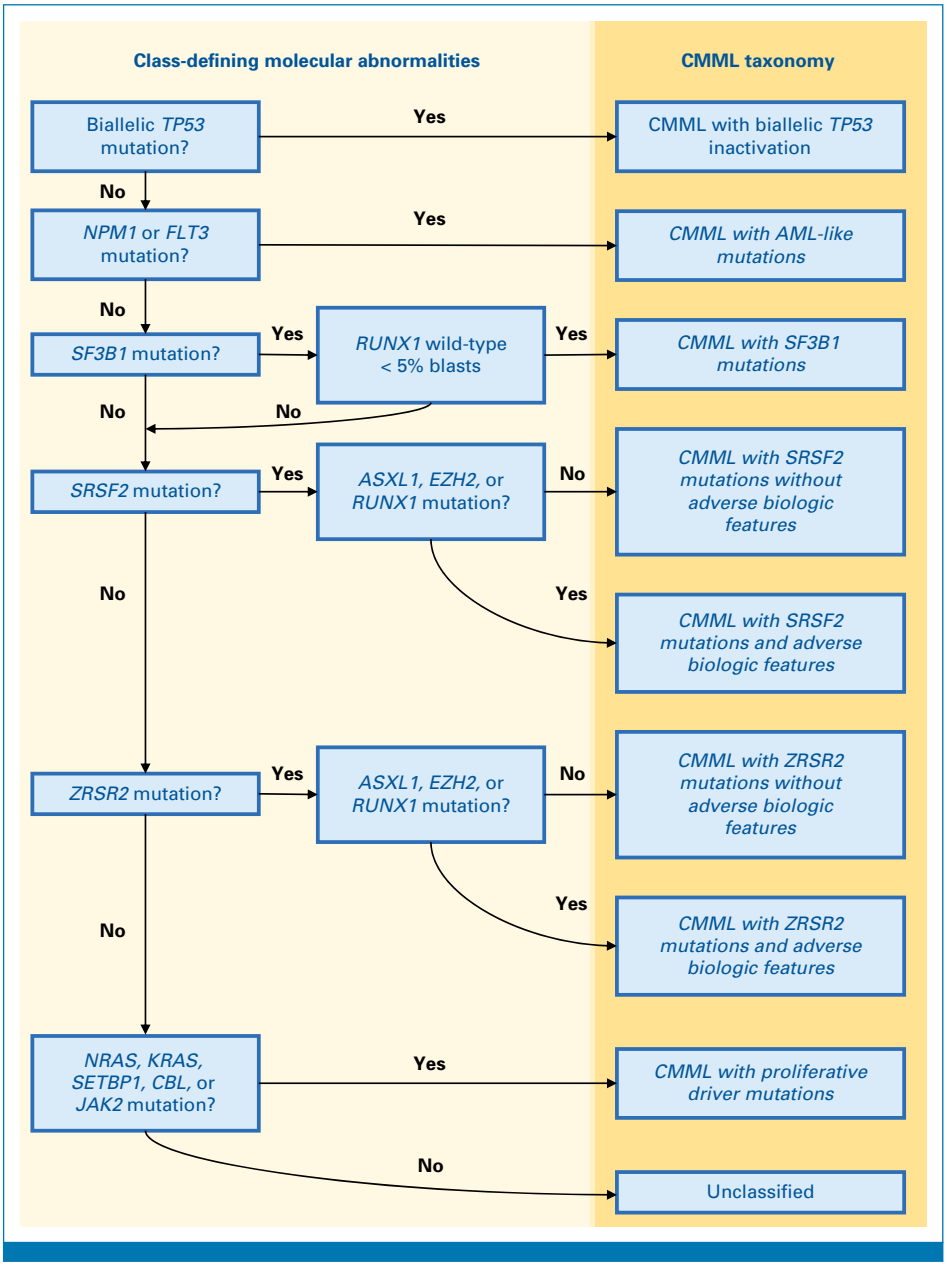

FIG 2. Molecular classification algorithm for CMML taxonomy. Decision tree showing the hierarchical approach to classify CMML patients based on class-defining molecular abnormalities. Patients are sequentially evaluated for specific mutations starting with biallelic *TP53* inactivation (defined by the presence of two or more TP53 mutations or one mutation with VAF ≥ 50%), followed by AML-like mutations (*NPM1*, *FLT3*), splicing factor mutations (*SF3B1*, *SRSF2*, *ZRSR2*), and proliferative driver mutations (*NRAS*, *KRAS*, *SETBP1*, *CBL*, *JAK2*). For *SRSF2* and *ZRSR2* mutations, classification is further refined based on the presence or absence of adverse biologic features (*ASXL1*, *EZH2*, or *RUNX1* mutations). Patients not meeting criteria for any defined class are designated as unclassified. CMML, chronic myelomonocytic leukemia; VAF, variant allele frequency.

(adjusted $P < .001$, Fig 3G and Data Supplement, Figs S14-S16). Beyond disease-specific scores, IPSS-M showed performance comparable with that of iCPSS in cases with a myelodysplastic phenotype, whereas its accuracy was reduced in patients with myeloproliferative features (Data Supplement p.33).

In the prospective cohort, iCPSS showed robust stratification of OS, LFS, and cumulative incidence of AML ($P < .001$). Harrell and Uno c-index were 0.72 and 0.71 for OS, 0.73 and 0.72 for LFS, respectively, outperforming alternative scores (Fig 3H).

Compared with CPSS-mol, 1,671 (55%) patients in the retrospective cohort were restratified, with 1,064 (35.3%) downstaged and 607 (20.1%) upstaged (Fig 4). Similarly, 315 (61%) patients in the prospective cohort were restratified

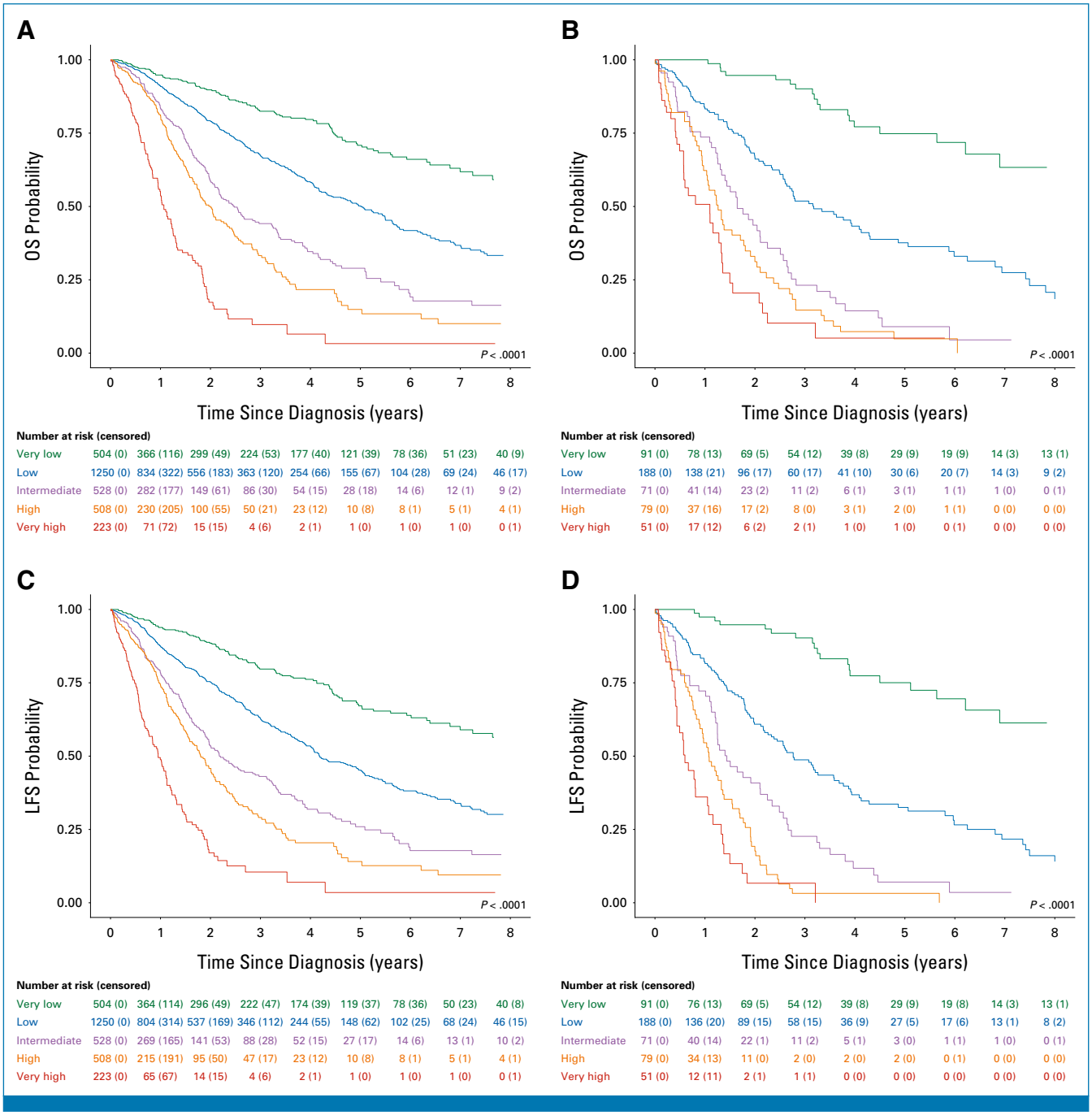

FIG 3. Survival outcomes and model performance by iCPSS risk stratification in retrospective and prospective cohorts. Kaplan-Meier estimates of OS in the (A) retrospective and (B) prospective cohorts and LFS in the (C) retrospective and (D) prospective cohorts, with *P* values from log-rank tests. (E and F) Cumulative incidence functions for transformation to AML in the retrospective and prospective cohorts, respectively, treating death before AML as a competing event; *P* values were obtained using the Gray test. (G, H) Display Uno's concordance index for OS (green bars) and LFS (red bars), estimated using inverse probability of censoring weighting to account for censoring; error bars represent 95% bootstrap CIs and q-values are Holm-adjusted *P* values from Wald statistics, with standard errors estimated from the bootstrap distribution. Analyses are stratified by iCPSS risk groups (very low, low, intermediate, high, very high). CMML, chronic myelomonocytic leukemia; CPSS-mol, Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System incorporating molecular data; iCPSS, International CMML Prognostic Scoring System; GFM, Groupe Francophone des Myélodysplasies Model; LFS, leukemia-free survival; MMM, Mayo Molecular Model; OS, overall survival. (continued on following page)

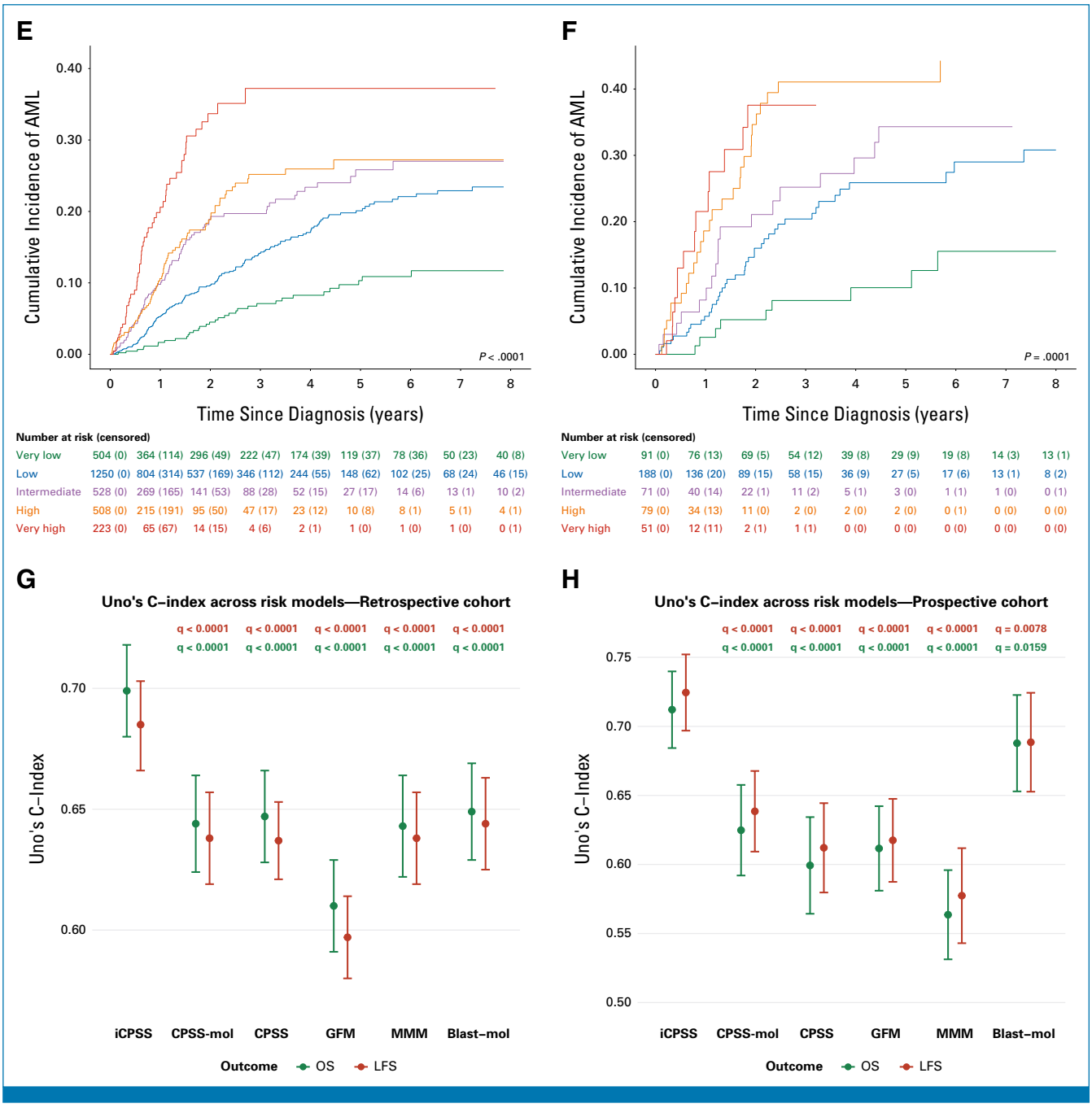

FIG 3. (Continued).

(Data Supplement, Fig S17). Outcomes for restaged patients were better predicted by iCPSS (Data Supplement, Fig S18).

To facilitate clinical adoption, the iCPSS can be computed by accessing a web calculator,[27] with optional handling of missing genetic information (Data Supplement, pp. 36-38, Figs S19-S23). The distribution of iCPSS risk classes according to the molecular taxonomy is reported in the Data Supplement (Fig S24).

Finally, we implemented a proof-of-concept federated learning platform across three centers.[21] Using an unbalanced distribution of the retrospective cohort across the federated nodes, the retrained iCPSS achieved performance comparable with the centralized repository (Harrell c-index 0.7, Data Supplement, Table S18 and Fig S25).

Investigation of Oligomonocytic CMML

The clinical significance of molecular taxonomy and iCPSS was investigated in a cohort of 337 classified as oligomonocytic CMML (Data Supplement, pp. 42-45, Table S19, Figs S26 and 27).

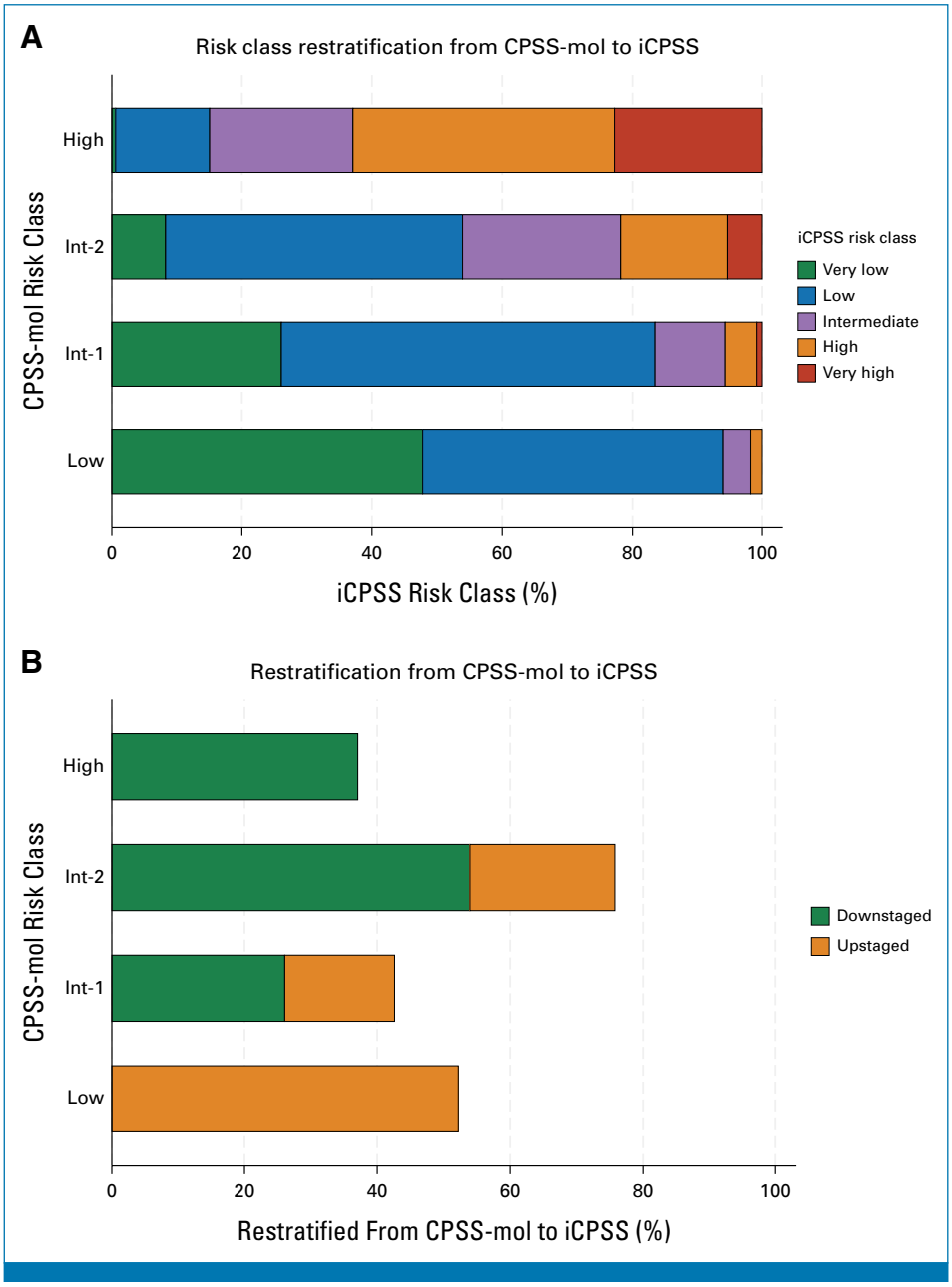

FIG 4. Risk restratification from CPSS-mol to iCPSS in the retrospective cohort. (A) Distribution of iCPSS risk classes within each CPSS-mol risk category. Stacked bars show the percentage of patients in each CPSS-mol risk group (low, Int-1, Int-2, high) that were reclassified into iCPSS risk categories (very low, low, intermediate, high, very high). (B) Overall restratification patterns showing the proportion of patients within each CPSS-mol risk category that were downstaged (green) or upstaged (orange) when classified by iCPSS. CMML, chronic myelomonocytic leukemia; CPSS-mol, Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System incorporating molecular data; iCPSS, International CMML Prognostic Scoring System.

Evaluation of the Clinical Impact of iCPSS

In retrospective patients who underwent HSCT (n = 829), iCPSS significantly stratified post-HSCT OS and relapse risk (both $P < .001$), with a clear separation between lower- and higher-risk groups (Fig 5). In multivariable models adjusting for age, sex, time to HSCT, donor type, disease status, and conditioning, iCPSS remained independently associated with overall and relapse-free survival (hazard ratio [HR], 1.34 and 1.54, respectively, $P < .001$). Compared with CPSS-mol, iCPSS reclassified 55% of transplanted patients, including 23% upstaged and 32% downstaged.

We developed a decision support system[19,20] to define the optimal timing of HSCT based on iCPSS risk (Fig 5C). Microsimulation analyses showed that immediate HSCT

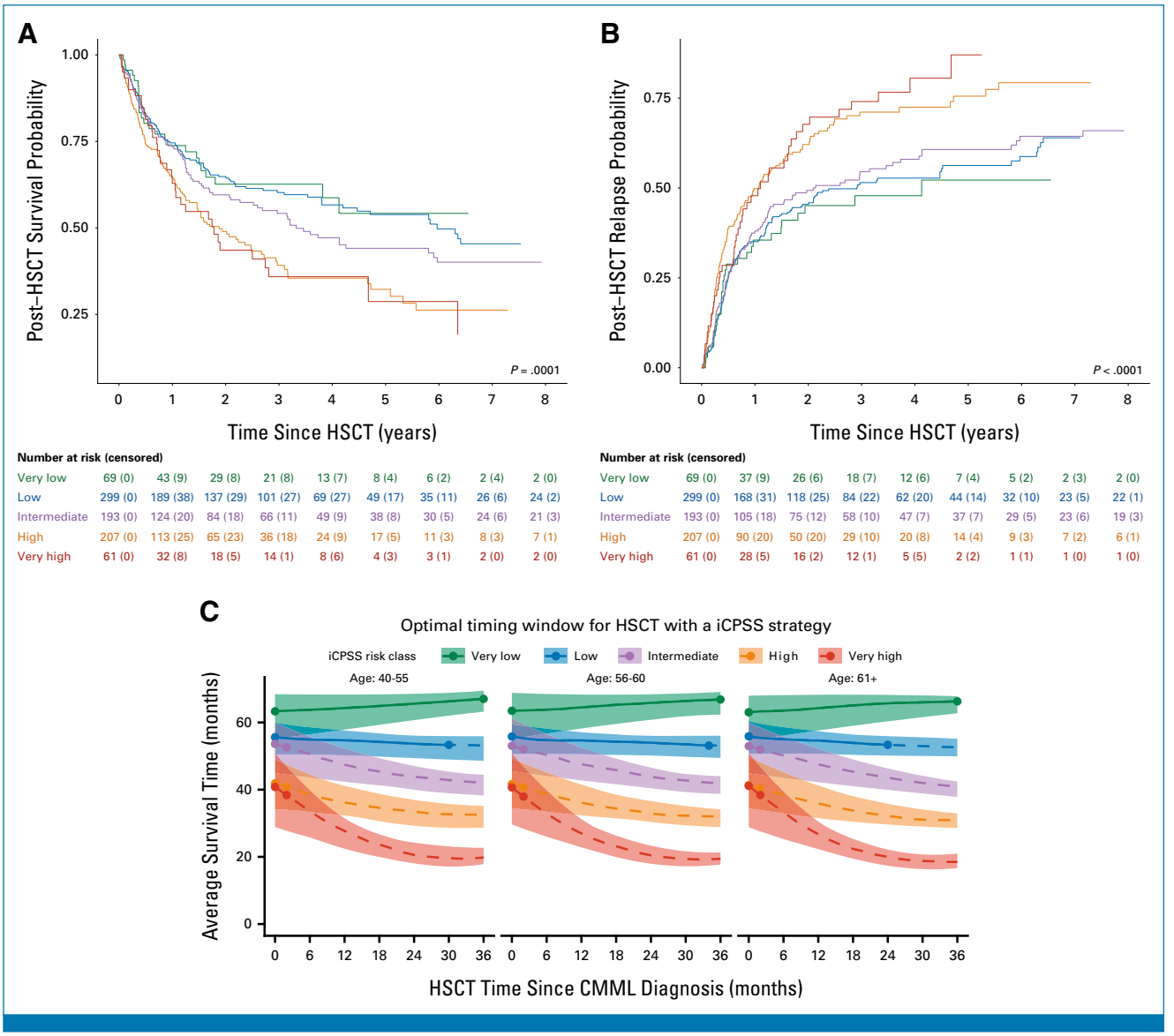

FIG 5. Decision support analysis for optimal HSCT timing in CMML using iCPSS risk stratification. (A) OS post-HSCT stratified by iCPSS risk groups. (B) Cumulative incidence of relapse post-HSCT by iCPSS risk groups. (C) Semi-Markov microsimulation model results showing optimal timing windows for HSCT across age groups (40-55, 56-60, 61+ years) and iCPSS risk categories. Solid lines represent optimal time windows to maximize quality of life-adjusted survival. (D) Alluvial diagram comparing HSCT timing recommendations between CPSS-mol–based and iCPSS-based strategies, showing reclassification of 27.4% of patients from delayed to immediate HSCT and 36.6% from immediate to delayed HSCT. (E) Kaplan-Meier analysis of OS post-HSCT in the main retrospective cohort, comparing patients transplanted within optimal timing windows (green) versus nonoptimal timing (red), demonstrating superior post-HSCT survival with optimal timing for HSCT. CMML, chronic myelomonocytic leukemia; CPSS-mol, Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System incorporating molecular data; HSCT, hematopoietic stem cell transplantation; iCPSS, International CMML Prognostic Scoring System; OS, overall survival. (continued on following page)

(≤6 months from diagnosis) maximized restricted mean survival time (RMST) in intermediate, high, and very high risk, whereas delayed HSCT was favored in very low- and low-risk patients, irrespective of age (Data Supplement, pp. 46-49, Tables S20 and S21, Figs S28 and S30).

Relative to a CPSS-mol strategy, iCPSS-guided recommendations altered HSCT timing in 31% of patients; 27% of patients candidate to be immediately transplanted under a CPSS-mol–based policy would benefit from a delayed strategy by iCPSS, while 36% of candidates to delayed transplantation by CPSS-mol would benefit from immediate HSCT by iCPSS (Fig 5). RMST comparisons in patients ≤70 years demonstrated a significant survival advantage for the iCPSS-based strategy across age groups ($P = .001$).

These results were preliminarily validated in a simulated scenario using synthetic data (Data Supplement, pp. 50-52, Tables S22-S24, Figs S31-S33).

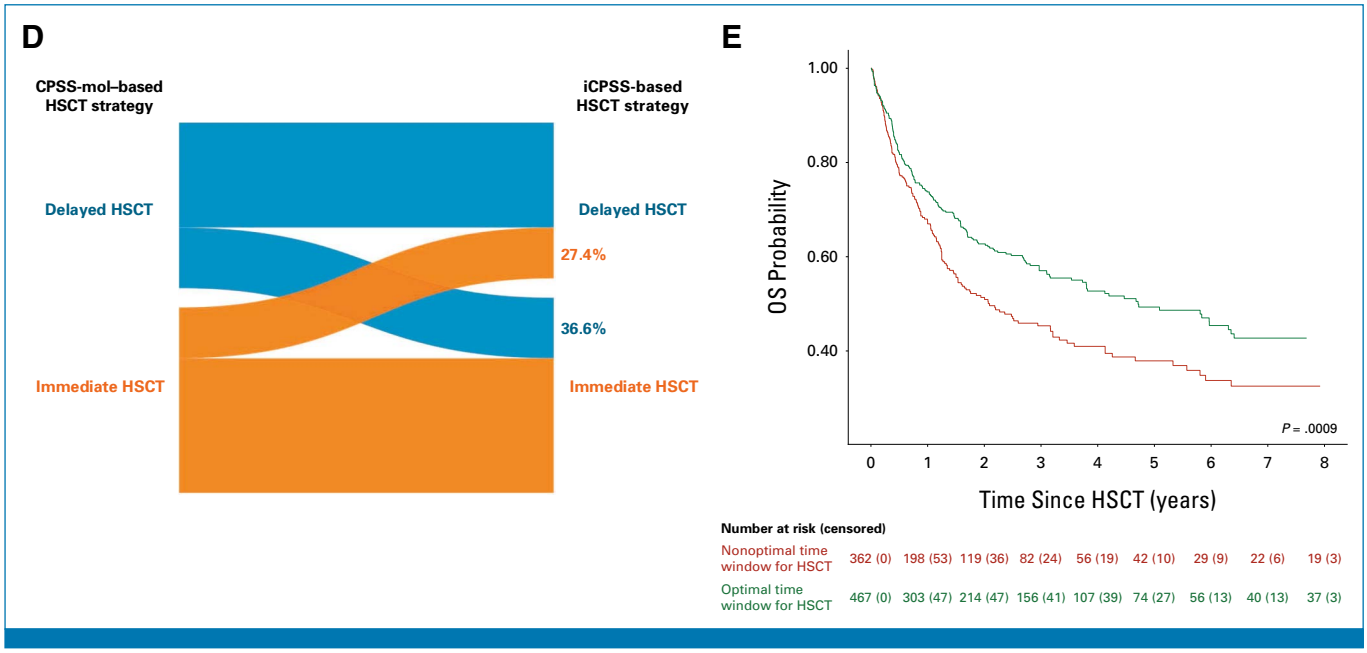

FIG 5. (Continued).

In the retrospective cohort, only 56% of patients underwent HSCT within the iCPSS-recommended time window by iCPSS. Transplantation within this window was associated with superior survival, corresponding to a median gain of 2.2 years ($P < .001$, Fig 5). The prognostic benefit of receiving HSCT within the optimal window remained significant in a multivariate model adjusting for recipient age and sex, donor type, disease status at transplant, and conditioning regimen (HR, 1.4, $P < .001$).

DISCUSSION

Here, we proposed and validated a molecular ecosystem for CMML that has the potential to significantly advance personalized clinical decision making.

The aims and clinical utility of molecular taxonomy and iCPSS are distinct, although both contribute to clinical decision making. The molecular taxonomy described here identifies groups of patients with CMML who share common molecular pathogenesis, thereby providing a foundation for a genetically informed disease classification.[28,29] Defining molecularly homogeneous groups is crucial for elucidating disease biology as well as the determinants of disease progression and treatment response. CMML molecular taxonomy is therefore expected to represent a framework for future correlative studies and exploratory analyses within clinical trials.[30] On the other hand, iCPSS prognostic score combine clinical and molecular variables to estimate patient outcomes and to guide risk-adapted therapeutic strategies.[28,30] Importantly, there is no direct equivalence between molecular groups and iCPSS prognostic risk categories, indicating that they provide complementary information. For instance, two patients belonging to distinct molecular groups according to CMML taxonomy may both be classified as low risk by iCPSS despite having biologically different disease; conversely, iCPSS is able to refine risk stratification within individual molecular groups.

The molecular taxonomy identified nine groups of patients with shared molecular pathogenesis.[11,12,23] The observation that a non-negligible proportion of patients with CMML display molecular overlap with other myeloid neoplasms despite minor phenotypic discrepancies raises the importance of defining the hierarchical relevance of genomic versus morphologic features in the classification of disease entities.[28-31] For example, *SF3B1*-mutated CMML shared clinical and prognostic features with *SF3B1*-mutated MDS, highlighting similar molecular biology,[32] and potentially suggesting the use of MDS-approved therapies (luspatercept) in *SF3B1*-mutated CMML, which often present symptomatic anemia.[33] Indeed, using a taxonomy-based stratification, 17% of patients with CMML could potentially access approved therapies for MDS or AML.[34] Furthermore, our observation that *TP53*-mutated myeloid neoplasms with biallelic inactivation show the same dismal prognosis across different disease categories reinforces the concept of defining a distinct clinical entity based on *TP53* mutational landscape.[35,36]

CMML taxonomy is also a potentially valuable tool for the development of innovative clinical trials. Conventional trial designs face substantial limitations in rare myeloid neoplasms and often fail to account for the underlying biological heterogeneity within a given clinical diagnosis.[37] Recent evidence showed that a therapeutic approach guided by patient biology result in longer survival compared with

standard treatment assignment based on conventional diagnostic features.[38] A taxonomy-based framework may therefore offer a foundation for innovative, molecularly driven trial designs that enroll patients according to shared molecular profiles, even across different clinical diagnoses.[34]

Risk stratification is of crucial importance in a patient-centered approach to the treatment of CMML.[39] Patients with lower-risk CMML are candidates for treatments aimed at ameliorating cytopenias or cytosis and improving quality of life, while higher-risk patients should be considered for therapies capable of altering the natural disease course and prolonging survival, namely HSCT.[3]

For over two decades, individual risk assessment and treatment decisions have relied mainly on prognostic models that were not disease-specific or incorporated limited and heterogeneous molecular information.[13-16,40] To address this gap, we developed and validated the iCPSS, a personalized, interpretable, and reproducible prognostic tool that integrates the mutational status of nine genes involved in disease pathophysiology. Notably, the iCPSS also offers a flexible and transparent approach for handling missing data. Compared with existing models, the iCPSS demonstrated superior prognostic accuracy across all long-term clinical end points and reclassified nearly 50% of patients with CMML, offering more precise risk categorization.

Among the multitude of existing scores for CMML,[13-17] clinical implementation should prioritize tools that have the potential to change patient management and thereby generate tangible benefits. In this context, iCPSS may have a concrete impact by guiding the management of patients who are candidates for HSCT, the only potentially curative approach for this disease.[3,41-43]

Our findings showed that in the low/intermediate-1 CPSS-mol risk groups, 15% of patients were reclassified into less favorable prognostic categories by iCPSS (high/very-high risk). Thus, iCPSS is expected to result in a more effective selection of candidates to disease-modifying therapies (including HSCT) among patients with early-stage disease.

Several factors must be carefully considered when evaluating the potential benefits of HSCT in individual patients with CMML, with the optimal timing of the procedure being a crucial question.[3,19,44,45] The iCPSS enabled a refined, patient-specific definition of the optimal timing for transplantation. Its high predictive accuracy has significantly improved the ability to distinguish patients who are more likely to benefit from early versus delayed HSCT, leading to a change in treatment recommendation in one third of patients. This results in a significant gain in life expectancy in a simulated scenario, when compared with a CPSS-mol–based approach. Moreover, patients who underwent HSCT within the optimal time window defined by the iCPSS-based decision model experienced superior post-transplant OS compared with those transplanted outside the optimal window. Finally, iCPSS was able to efficiently capture the probability of relapse, thus potentially refining the choice of the optimal conditioning regimen at the individual patient level[46-48] and improving the identification of subjects with high risk of transplantation failure that can be considered for preemptive treatments of disease recurrence.[49]

Overall, these findings emphasize the value of molecularly informed strategies in therapeutic decision making for CMML, define the priority of genomic alterations to be included in routine screening as clinically informative, and offer a practical framework for personalized transplantation policies aimed at maximizing both survival and quality of life.

The study has some limitations, primarily that the evidence is based on retrospective data collection and on molecular information obtained using diverse platforms. For these reasons, further prospective validation of the results is recommended. However, we mitigated potential bias by including large and geographically diverse study populations, as well as a prospective validation cohort with centralized molecular analyses. Moreover, we adopted a technological framework to maximize the accuracy of the developed tools according to available data.[18] In addition, innovative technologies such as federated learning—which enables collaboration among multiple centers without the need for direct data sharing—[21,23] and synthetic data[24,25,50] may provide a sustainable strategy to ensure that the developed tools remain responsive to changes in clinical practice and to offer preliminary evidence for validation in cases with limited availability of data.

At a broader level, the implementation of innovative technological frameworks can accelerate the generation of new evidence, particularly benefiting rare cancers, which account for over 20% of human malignancies and for which data are limited, sparse across different institutions, and nonharmonized.[18,51] The implementation of these technologies is also expected to optimize the clinical management of patients with currently available therapies—enhancing the objectivity and reproducibility of decision making, which is known to be particularly low in rare cancers—[51] and to provide a knowledge base for designing innovative studies guided by molecular information.

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Requests for access to data from the study should be addressed to iCPSS Alliance Scientific Committee (please contact M.G.D.P. at matteo.della_porta@hunimed.eu). All proposals requesting data access will need to specify how the data will be used, and will need the approval of the iCPSS alliance scientific committee before data release.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Molecular-Based Ecosystem to Improve Personalized Medicine in Chronic Myelomonocytic Leukemia

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Speakers' Bureau: Incyte
Research Funding: Jazz Pharmaceuticals, Aprea Therapeutics (Inst)

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Leadership: MLL Munich Leukemia Laboratory
Stock and Other Ownership Interests: MLL Munich Leukemia Laboratory

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Consulting or Advisory Role: Bristol Myers Squibb, Taiho Oncology, Curis, Ascentage Pharma, SERVIER, Takeda, Keros Therapeutics
Research Funding: Novartis, AbbVie, Bristol Myers Squibb, Genentech, Curis, Rigel, Taiho Oncology, Zentalis, Chordia Therapeutics, Takeda, GlaxoSmithKline, Ascentage Pharma, SERVIER, AstraZeneca

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Research Funding: Amgen (Inst), Janssen (Inst), Novartis (Inst), BerGenBio (Inst), Celgene (Inst), Curis (Inst)
Patents, Royalties, Other Intellectual Property: Part of a patent for a TFR-2 antibody (Rauner et al. Nature Metabolics 2019)
Travel, Accommodations, Expenses: Celgene

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Honoraria: Novartis, Keros Therapeutics, Bristol Myers Squibb/Celgene, AbbVie
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Travel, Accommodations, Expenses: Gilead Sciences, Novartis

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Research Funding: Novartis (Inst), NIH (Inst), Apellis Pharmaceuticals (Inst), Alexion Pharmaceuticals (Inst), SOBI (Inst)

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Honoraria: Gilead/Forty Seven, Epizyme, SERVIER, Geron, Keros Therapeutics, NeoGenomics Laboratories, Bristol Myers Squibb/Celgene, Caris Life Sciences
Consulting or Advisory Role: NeoGenomics Laboratories, Takeda, Gilead/Forty Seven, Epizyme, Geron, SERVIER, Caris Life Sciences
Patents, Royalties, Other Intellectual Property: A patented signature for prognostic gene mutations in MDS was licensed to Genoptix 15 years ago

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Travel, Accommodations, Expenses: Novartis, Jazz Pharmaceuticals, Therakos

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Consulting or Advisory Role: Ryvu Therapeutics, Bristol Myers Squibb, PharmaEssentia, Calytrix, Geron, Rigel, Treadwell Therapeutics
Research Funding: Astex Pharmaceuticals (Inst), Incyte (Inst), ALX Oncology (Inst), Prelude Therapeutics (Inst)
Patents, Royalties, Other Intellectual Property: Product license—Boehringer-Ingelheim (minority owner)
Travel, Accommodations, Expenses: Taiho Oncology

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Consulting or Advisory Role: Bristol Myers Squibb
Research Funding: Bristol Myers Squibb

Guillermo Sanz
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Research Funding: Novartis (Inst), Bristol Myers Squibb/Celgene (Inst), Janssen (Inst), Takeda (Inst), Amgen (Inst), Menarini (Inst), Bayer (Inst), Pfizer (Inst)

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Speakers' Bureau: Pfizer
Research Funding: Celgene, Novartis, MorphoSys, GlaxoSmithKline

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Research Funding: Celgene (Inst)
Travel, Accommodations, Expenses: Janssen-Cilag, Celgene, Jazz Pharmaceuticals

Amer M. Zeidan
Honoraria: AbbVie, Otsuka, Pfizer, Bristol Myers Squibb, Agios, Boehringer Ingelheim, Novartis, Astellas Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Takeda, Epizyme, Geron, Akeso Biopharma, ALX Oncology, Amgen, BeiGene, BioCryst, Celgene, Chiesi, Faron Pharmaceuticals, Genentech, Gilead Sciences, GlycoMimetics, Hikma Pharmaceuticals, Janssen, Karyopharm Therapeutics, Keros Therapeutics, Kura Oncology, Kyowa Kirin International, lava therapeutics, Mendus, Notable Labs, Orum Therapeutics, Regeneron, Rigel, Schrodinger, SERVIER, Shattuck Labs, Sumitomo Pharma Oncology, Syndax, Syros Pharmaceuticals, Treadwell Therapeutics, Vincerx Pharma, Zentalis
Consulting or Advisory Role: AbbVie, Otsuka, Pfizer, Celgene, Bristol Myers Squibb, Agios, Boehringer Ingelheim, Novartis, Astellas Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Takeda, Epizyme, Geron, Akeso Biopharma, ALX Oncology, Amgen, Astex Pharmaceuticals, BeiGene, BioCryst, Chiesi, Faron Pharmaceuticals, Genentech, Gilead Sciences, GlycoMimetics, Hikma Pharmaceuticals, Janssen, Karyopharm Therapeutics, Keros Therapeutics, Kura Oncology, Kyowa Kirin International, lava therapeutics, Mendus, Notable Labs, Orum Therapeutics, Regeneron, Rigel, Schrodinger, SERVIER, Shattuck Labs, Sumitomo Pharma Oncology, Syndax, Syros Pharmaceuticals, Treadwell Therapeutics, Vincerx Pharma, Zentalis
Research Funding: Celgene (Inst), Bristol Myers Squibb (Inst), AbbVie (Inst), Astex Pharmaceuticals (Inst), Takeda (Inst), Novartis (Inst), Amgen, Geron, Kura Oncology, Otsuka, Shattuck Labs, Syros Pharmaceuticals

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Speakers' Bureau: SERVIER, PharmaEssentia, SOBI, Rigel
Research Funding: Bristol Myers Squibb/Celgene (Inst)
Travel, Accommodations, Expenses: Jazz Pharmaceuticals, Bristol Myers Squibb, PharmaEssentia

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Research Funding: BMS GmbH & Co. KG (Inst), AbbVie (Inst), Jazz Pharmaceuticals (Inst)

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Consulting or Advisory Role: Kura Oncology (Inst)
Research Funding: Stemline Therapeutics (Inst), Epigenetix (Inst), Solu Therapeutics (Inst), Kura Oncology (Inst), Polaris (Inst)

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Speakers' Bureau: Novartis, Taiho Pharmaceutical, Blueprint Medicines
Research Funding: Incyte (Inst), Bristol Myers Squibb (Inst), Kura Oncology (Inst)

No other potential conflicts of interest were reported.

APPENDIX 1. iCPSS ALLIANCE

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