ARTIFICIAL INTELLIGENCE

original reports

Synthetic Data Generation by Artificial Intelligence to Accelerate Research and Precision Medicine in Hematology

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abstract

PURPOSE Synthetic data are artificial data generated without including any real patient information by an algorithm trained to learn the characteristics of a real source data set and became widely used to accelerate research in life sciences. We aimed to (1) apply generative artificial intelligence to build synthetic data in different hematologic neoplasms; (2) develop a synthetic validation framework to assess data fidelity and privacy preservability; and (3) test the capability of synthetic data to accelerate clinical/translational research in hematology.

METHODS A conditional generative adversarial network architecture was implemented to generate synthetic data. Use cases were myelodysplastic syndromes (MDS) and AML: 7,133 patients were included. A fully explainable validation framework was created to assess fidelity and privacy preservability of synthetic data.

RESULTS We generated MDS/AML synthetic cohorts (including information on clinical features, genomics, treatment, and outcomes) with high fidelity and privacy performances. This technology allowed resolution of lack/incomplete information and data augmentation. We then assessed the potential value of synthetic data on accelerating research in hematology. Starting from 944 patients with MDS available since 2014, we generated a 300% augmented synthetic cohort and anticipated the development of molecular classification and molecular scoring system obtained many years later from 2,043 to 2,957 real patients, respectively. Moreover, starting from 187 MDS treated with luspatercept into a clinical trial, we generated a synthetic cohort that recapitulated all the clinical end points of the study. Finally, we developed a website to enable clinicians generating high-quality synthetic data from an existing biobank of real patients.

CONCLUSION Synthetic data mimic real clinical-genomic features and outcomes, and anonymize patient information. The implementation of this technology allows to increase the scientific use and value of real data, thus accelerating precision medicine in hematology and the conduction of clinical trials.

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ASSOCIATED CONTENT

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Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Personalized medicine combines established clinical-pathologic parameters with advanced genomic profiling to develop innovative diagnostic, prognostic, and therapeutic strategies.[1] Hematology has been rapidly transformed by genome characterization and is the forefront to reap the benefits of personalized medicine for patient management.[1]

The clinical implementation of personalized medicine requires the availability of a great amount of real-world data, including clinical features, genomics, treatments, and outcomes.[2-4] Collecting such information in large patient populations is challenging, especially when facing rare diseases with heterogeneous clinical/molecular background. Additionally, real data often have imbalances or lack/incomplete information.[5,6] Finally, there are many issues concerning patient privacy that may prevent use of data outside specific contexts and that are to be accounted for.[7]

One approach that can circumvent these issues is the creation of synthetic data. Synthetic data are artificial data generated by a model trained to learn the essential characteristics of a real source data set.[8,9] Synthetic data building techniques attempt to ensure that the generated data are neither a copy nor a representation of the real data, setting the grounds to data sharing without violating the current legislation on privacy.[8,9] Moreover, synthetic

CONTEXT

Key Objective

Are synthetic data able to recapitulate real clinical-genomic features and clinical outcomes, and to guarantee privacy preservability? Can this technology accelerate clinical/translational research in hematology?

Knowledge Generated

We developed a new technology on the basis of generative artificial intelligence that allows to generate synthetic patient cohorts with high clinical fidelity and privacy performances. We created a prototype web portal for synthetic data generation to help clinicians to be familiar with this new technology.

Relevance

This technology allows the resolution of lack/incomplete information and data augmentation starting from real patients. Synthetic data generate new knowledge to accelerate both translational research and the conduction of clinical trials.

data allow to increase insufficient information obtained from real patients by data augmentation and data integration, thus potentially solving issues related with small sample size and clinical/molecular class imbalance.[10]

Overall, synthetic data may overcome many of the pitfalls of real data, allowing for faster, less expensive, and more scalable access to information that is representative of the underlying source and privacy-preserving.[8-11] Synthetic data is a growing technology[8] and it is expected that in the next 2-3 years, >60% of the data used in research and development process across different domains (including life sciences) will be synthetically generated.[12]

In this project, we addressed the issue of clinical validation and research utility of synthetic data in hematology. To this purpose, we aimed to (1) apply innovative synthetic data generation methods to real-world data sets of different hematologic malignancies including comprehensive clinical and genomic information; (2) develop a synthetic validation framework (SVF) to evaluate data fidelity and privacy preservability; and (3) test the capability of synthetic data to accelerate translational and clinical research.

As a paradigmatic use case, we focused on myeloid malignancies, which are rare neoplasms with high clinical heterogeneity and complex genomic background and that include patients with unmet clinical needs.[13]

METHODS

Study Populations

The study was conducted by GenoMed4All and Synthema European consortia and supported by EuroBloodNET, the European Reference Network on rare hematologic diseases. Written informed consent was obtained from each participant. The Humanitas Ethics Committee approved the study. This study was registered at ClinicalTrials.gov (identifier: NCT04889729).

All the study procedures were compliant with the 2021 WHO guidance on ethics and governance of artificial intelligence for health.[14]

Inclusion criteria were age ≥18 years, a diagnosis of myeloid neoplasm (either myelodysplastic syndromes [MDS] or AML) according to WHO 2016 criteria,[15] and information available on demographics, clinical features, mutational screening/chromosomal abnormalities, treatment, and survival. Overall, 7,133 patients were included.

Generative Model for Synthetic Data

Artificial intelligence (AI)–based generative models are characterized by multi-layer neural networks that are able to generate samples (patients) by learning the distribution of a set of real data.[16] In this context, generative adversarial networks (GANs)[17] create simulation scenarios where models and processes interact to create completely new data sets of events. GANs consist of two networks: the generator and the discriminator. These two networks are trained adversarially. The generator creates artificial outputs that are passed to the discriminator along with real data, while the discriminator is tasked to identify which outputs were real and which were fake. The final goal here is to reach equilibrium, in which the generated samples follow the same distribution as the real data. When this happens, the discriminator can do no better than random guessing.[16] Conditional GANs are variants of GANs where a label is added as a parameter to the input of the models to create more realistic data by learning specific correlations.[18] In this study, we implemented a conditional Wasserstein's tabular GAN[18] with gradient penalty[19] that ensures high performance in modeling large data sets with complex distribution and interactions among different features. We adopted different preprocessing steps and training strategies to properly prepare the input data and optimize the training steps.

Development of a Synthetic Validation Framework

A SVF was developed to evaluate fidelity and privacy preservability of the newly generated synthetic data.

We assessed the quality of the following data types: demographics, clinical features, genomics (evaluated as categorical variables), and clinical outcomes (probability of overall survival and leukemia-free survival). Distribution, correlation, and principal component analysis evaluation were then assessed on all data types. Descriptive statistics and pairwise association analyses were carried out. We calculated a clinical synthetic fidelity (CSF) and a genomic synthetic fidelity (GSF) as the average of multiple metric tests adopted; optimal threshold was considered ≥85% in both systems.

Real and synthetic patients were stratified by hierarchical Dirichlet clustering[20] to identify genomic associations and subgroups. Survival analyses were performed with Kaplan-Meier curves. We implemented Cox proportional hazard and L1-penalized Cox regression models to define features with significant impact on survival probability.[20,21] Model discrimination was assessed using Harrell's concordance index.[22]

To assess the privacy preservability and evaluate the risk associated with synthetic datasets of resampling a patient from a synthetic record, we first measured the exact matches between synthetic and original data (identical match share [IMS]). Moreover, we calculated the distance to closest record that measures the absolute distances between synthetic records to their nearest original records, and we then calculated the nearest neighbor distance ratio (NNDR), that is, the ratio of the distances of each synthetic record to the nearest and to the second nearest neighbors, that allows to compare inliers and outliers in the population on an equal base.[23] Optimal range for NNDR was considered from 0.60 to 0.85 (value closer to 0.50 indicating a significant loss of similarity of the synthetic patients compared with the real ones that can affect the fidelity of synthetic data; value closer to 1.00 indicating an excess of similarity of synthetic data with respect to the real ones, thus possibly affecting the privacy preservability).[23]

Explainability of AI algorithms was assessed by Shapley Additive Explanations (SHAP), a method to explain individual predictions on the basis of the game theoretically optimal Shapley values.[24]

Experimental Setup

We tested synthetic data generation process in different experimental settings (Fig 1).

In *setting A*, we investigated the capability of the generative model to create a synthetic reproduction of real data with high grade of fidelity on clinical/genomic features, clinical outcomes, and with high privacy preservability. We used 2043 patients with MDS from GenoMed4All cohort[20] to train and test the model.

In *setting B*, we tested the capability of the model to overcome lack/incomplete information in real data and to allow data augmentation; moreover, we assessed the generalizability of the model's performances across different clinical settings. We considered three different populations: 2,043 MDS from GenoMed4All cohort[20]; 2,957 MDS from the International Working Group for Prognosis in MDS (IWG-PM) cohort,[21] and 1,002 AML from GenoMed4All cohort.[20] In all experiments, we calculated fidelity and privacy metrics.

In *setting C*, we investigated if the generation of synthetic data can accelerate translational research. Starting from a MDS cohort available in 2014 (N = 944),[25] we generated a 300% augmented synthetic data set. We aimed to recapitulate and anticipate in this cohort of synthetic patients the most relevant and recent insights in personalized medicine (ie, the definition of a new molecular MDS classification and of a molecular scoring system, developed on 2,043 and 2,957 real patients in 2022, respectively).[20,21]

In *setting D*, we generated synthetic patients to be used as a control arm in clinical trials, thus possibly accelerating clinical development of new drugs/new indications of existing drugs. Starting from 187 MDS treated with luspatercept into a multicenter clinical trial,[26] we generated a new synthetic cohort of the same size. Then, we tested the capability of newly generated synthetic patients to recapitulate all the clinical end points of the original study.

RESULTS

Creation of a Synthetic, Reliable, and Private Reproduction of Real Data (Setting A)

We used 2,043 real MDS from GenoMed4All cohort[20] to generate a new cohort of 2,043 synthetic patients. The model showed high-fidelity performances for both clinical and genomic features (CSF = 93%; GSF = 90%; Fig 2 and Appendix Fig A1). We then applied Dirichlet processes to compare complex interactions and broad dependencies among genomic features in real versus synthetic patients and we obtained highly comparable results; explainability analysis (SHAP) showed that similar features drive patients' classification in both data sets (Appendix Fig A2).

Synthetic patients had comparable survival outcomes with respect to the real ones. When applying the reference scoring system for MDS prognostication (Revised International Prognostic Scoring System), the probability of survival of the five risk categories between synthetic and real patients was comparable (Fig 3).

We build a CoxPH model including all features of prognostic relevance with a unique binary covariate (indicating the belonging of the patient to the real or the synthetic data set) that obtained a *P* value of .742, suggesting that there is no significant difference in the survival probability between the two cohorts in a multivariable setting (Fig 3). Concordances obtained for the different category included in the model (demographics, clinical, and genomics) were comparable in both cohorts. Considering the global concordance of the model, we obtained similar results with the model fitted on real versus synthetic data (0.736 ± 0.012 *v* 0.769 ± 0.012; Fig 3).

In terms of privacy metrics, the IMS analysis showed that none of the real patients were copied in the synthetic dataset; moreover, we obtained good results for NNDR (0.64), indicating adequate distance to real data and poor privacy risk.[23]

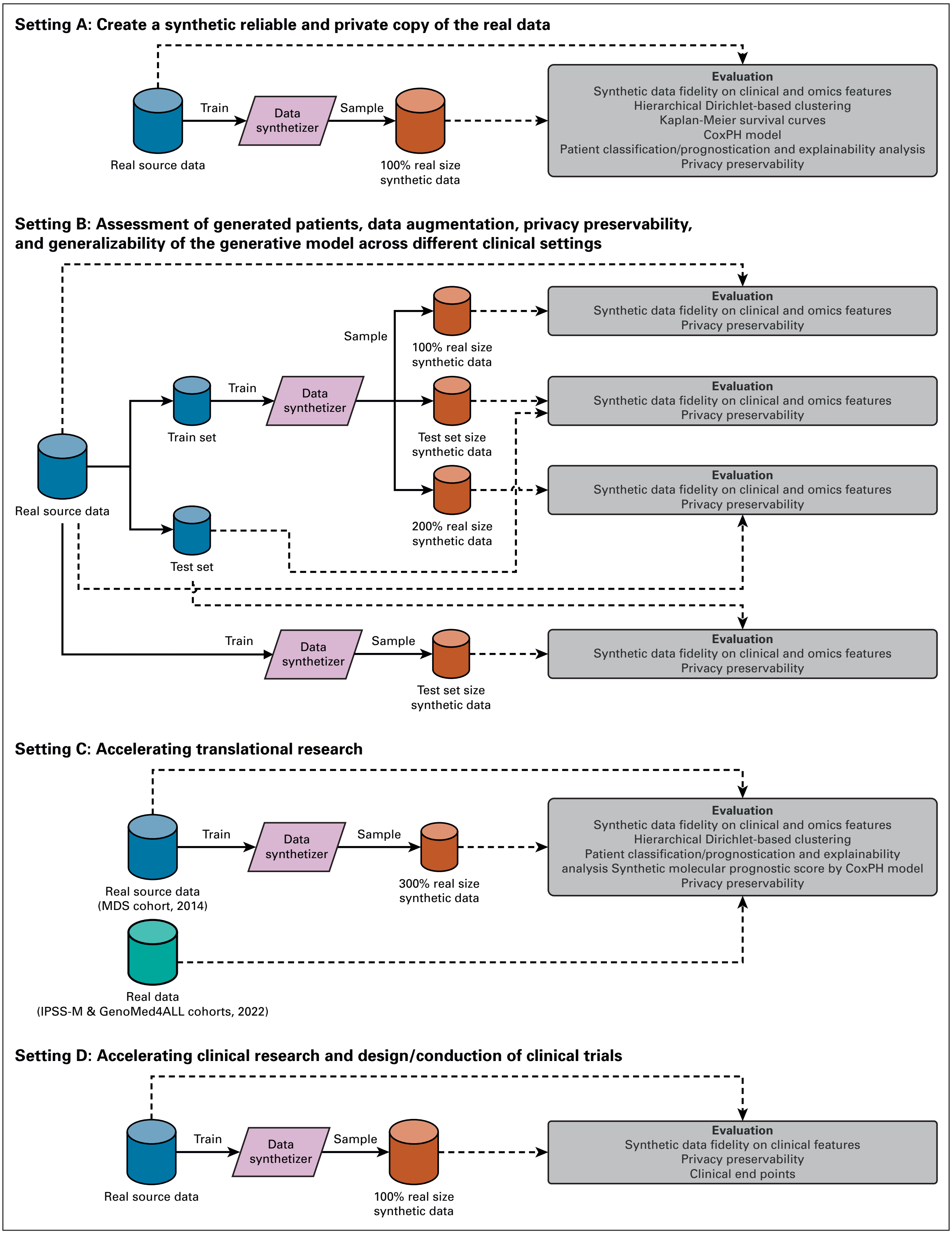

Setting A: Create a synthetic reliable and private copy of the real data
Real source data
Train
Data synthetizer
Sample
100% real size synthetic data
Evaluation
Synthetic data fidelity on clinical and omics features
Hierarchical Dirichlet-based clustering
Kaplan-Meier survival curves
CoxPH model
Patient classification/prognostication and explainability analysis
Privacy preservability
Setting B: Assessment of generated patients, data augmentation, privacy preservability, and generalizability of the generative model across different clinical settings
Real source data
Train set
Test set
Train
Data synthetizer
Sample
100% real size synthetic data
Test set size synthetic data
200% real size synthetic data
Evaluation
Synthetic data fidelity on clinical and omics features
Privacy preservability
Train
Data synthetizer
Sample
Test set size synthetic data
Setting C: Accelerating translational research
Real source data (MDS cohort, 2014)
Train
Data synthetizer
Sample
300% real size synthetic data
Real data (IPSS-M & GenoMed4ALL cohorts, 2022)
Evaluation
Synthetic data fidelity on clinical and omics features
Hierarchical Dirichlet-based clustering
Patient classification/prognostication and explainability analysis Synthetic molecular prognostic score by CoxPH model
Privacy preservability
Setting D: Accelerating clinical research and design/conduction of clinical trials
Real source data
Train
Data synthetizer
Sample
100% real size synthetic data
Evaluation
Synthetic data fidelity on clinical features
Privacy preservability
Clinical end points

FIG 1. Overview of experimental settings to validate synthetic data. Setting A: Create a synthetic reliable and private copy of the real data. Setting B: Assessment of generated patients, data augmentation, privacy preservability, and generalizability of the generative model across different clinical settings. Setting C: Accelerating translational research. Setting D: Accelerating clinical research and design/conduction of clinical trials. IPSS-M, Molecular International Prognostic Scoring System; MDS, myelodysplastic syndromes.

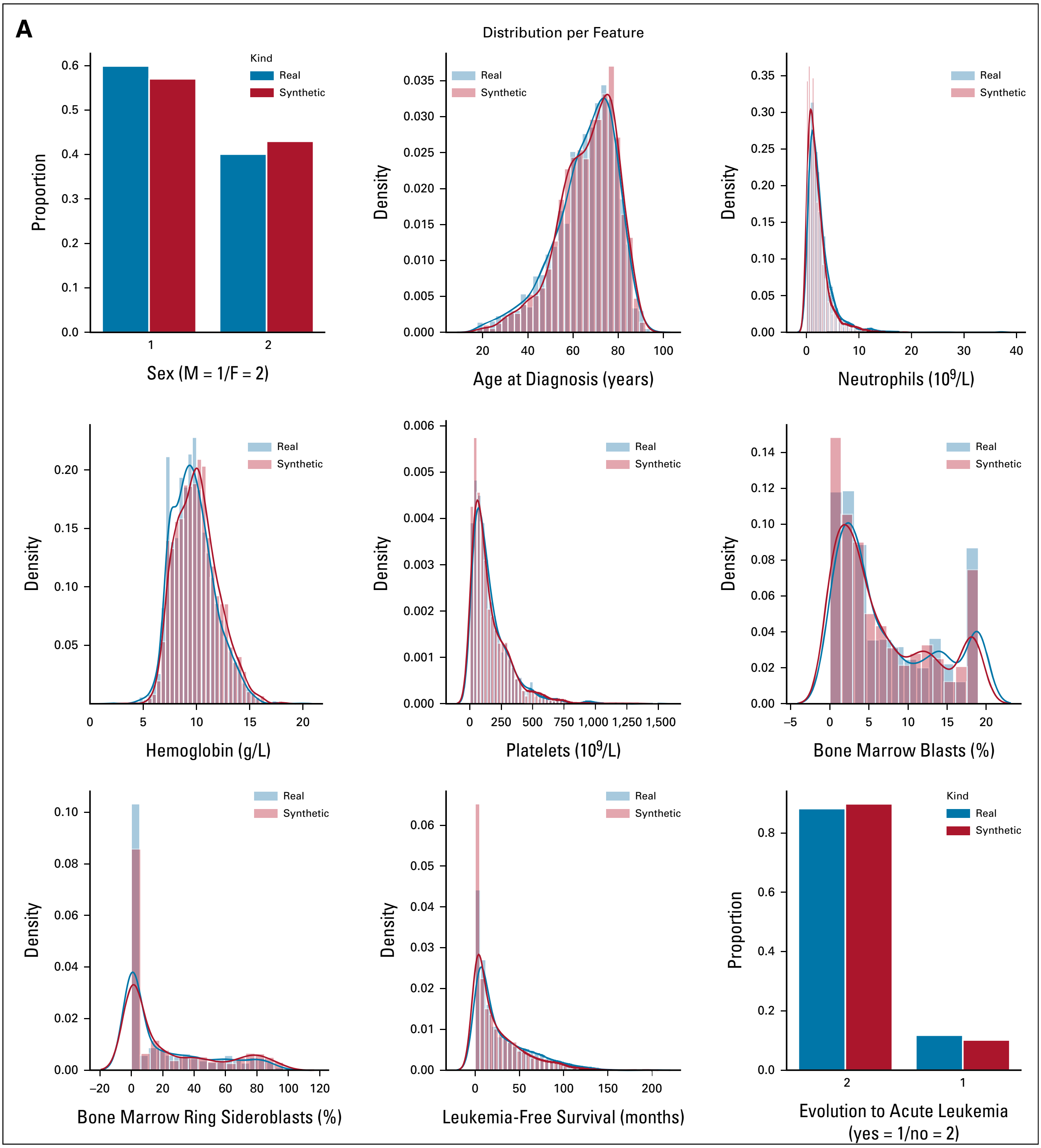


FIG 2. SVF on synthetic MDS cohort (N = 2,043), as performed in setting A. (A) Distributions for clinical, demographic, and survival features. Blue illustrates the real data, while red illustrates the synthetic data. (B) Frequency of recurrently mutated genes and chromosomal abnormalities. (C) Pairwise association among genes and/or cytogenetics abnormalities. In the upper triangle, for each couple of genomic abnormalities, the numbers of patients showing mutation co-occurrences are illustrated using a blue and white color scale. In the lower triangle, the gene-gene co-occurrence and mutual exclusivity is assessed using odds ratio, illustrated using a green and yellow color scale according to odds ratio values. All results in (A), (B), and (C) are referring to one MDS synthetic data set of 2,043 patients generated. Detailed results are reported in the Data Supplement. (D) Synthetic data fidelity calculated by SVF on clinical, demographic, and genomic features and patient survival. Average over three training and sampling replications on MDS cohort of 2,043 patients. MDS, myelodysplastic syndromes; SVF, synthetic validation framework. (continued on following page)

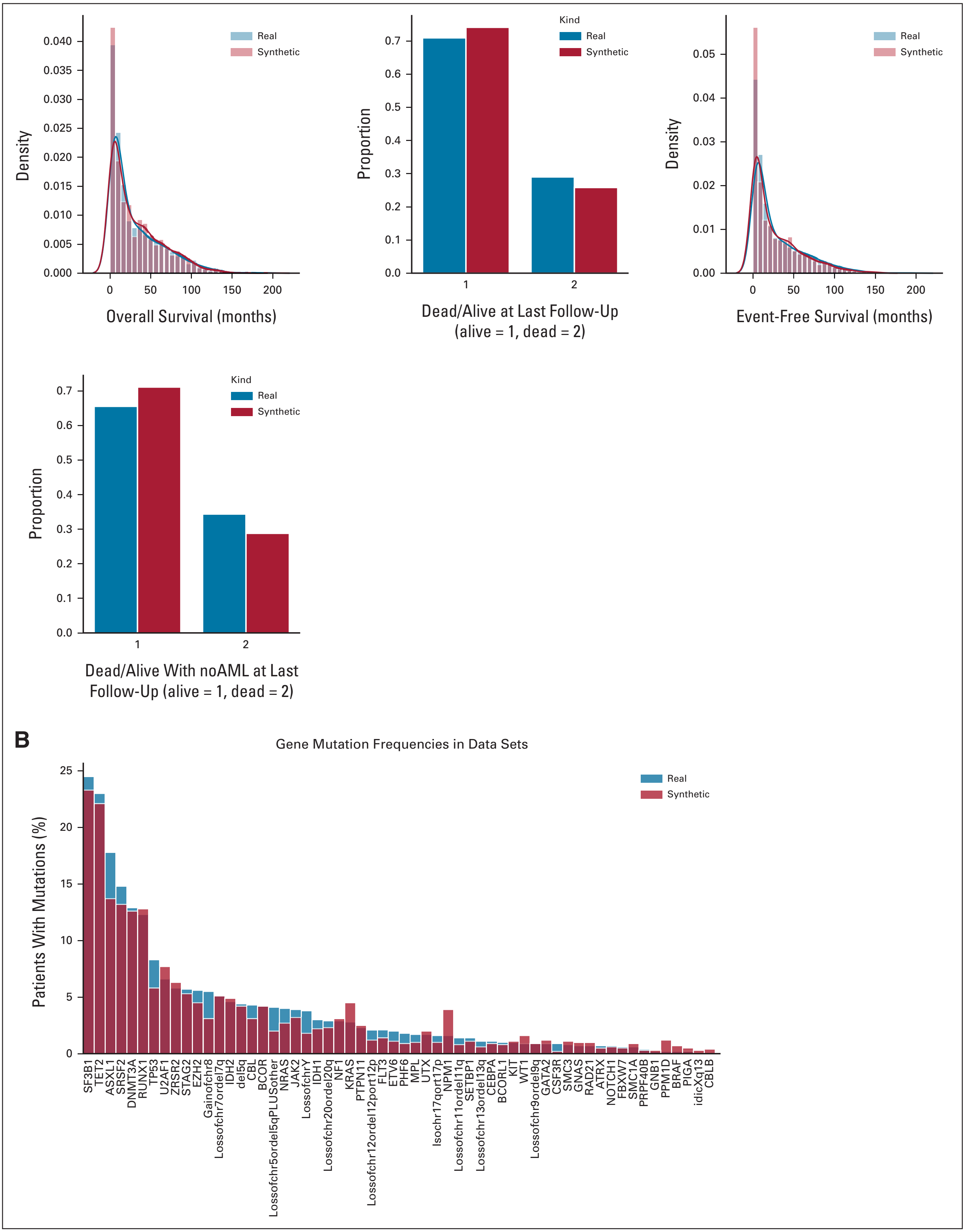


FIG 2. (Continued).

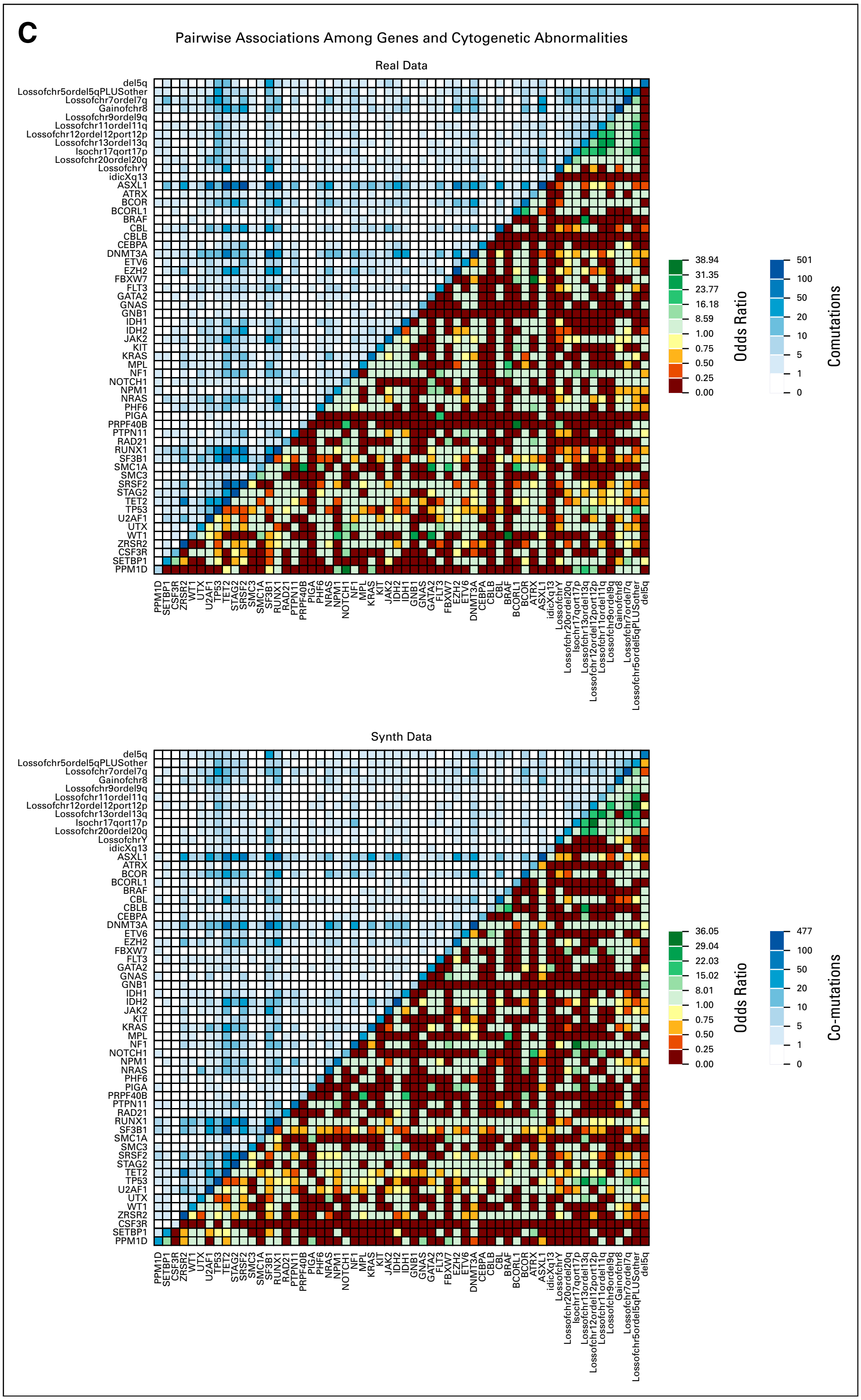
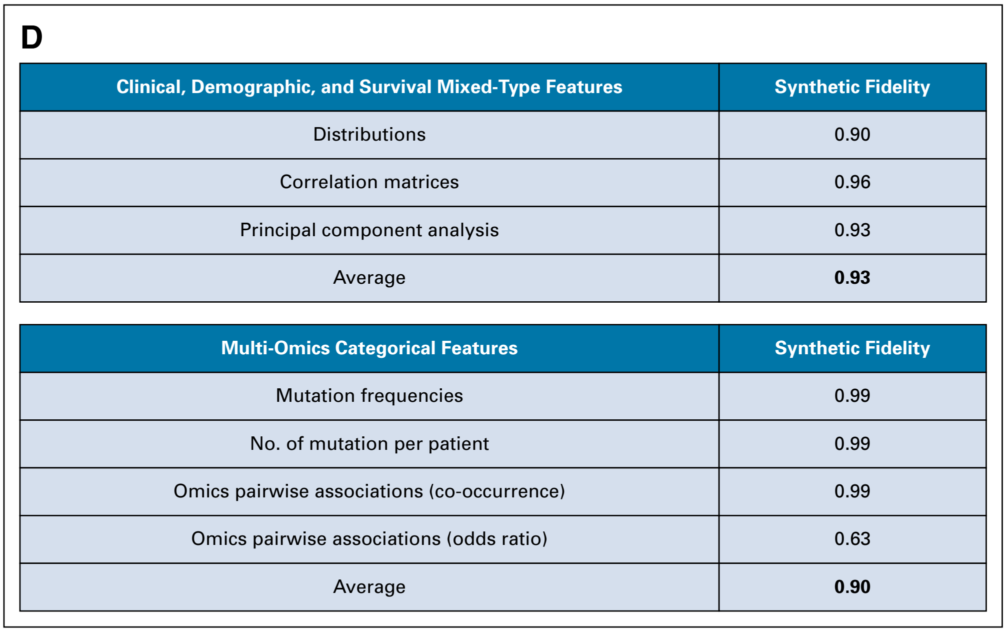


FIG 2. (Continued).



Clinical, Demographic, and Survival Mixed-Type Features	Synthetic Fidelity
Distributions	0.90
Correlation matrices	0.96
Principal component analysis	0.93
Average	**0.93**

Multi-Omics Categorical Features	Synthetic Fidelity
Mutation frequencies	0.99
No. of mutation per patient	0.99
Omics pairwise associations (co-occurrence)	0.99
Omics pairwise associations (odds ratio)	0.63
Average	**0.90**

FIG 2. (Continued).

Resolution of Lack/Incomplete Information, Data Augmentation, Privacy Preservability, and Generalizability of the Model Across Different Clinical Settings (Setting B)

Starting from the MDS GenoMed4all cohort (N = 2,043),[20] we trained the model with a set of a smaller size (including 70% of the patients) and then with a set with 30% of missing information across all features. We obtained the same high-fidelity performances as in setting A, in which synthetic patients were generated form the whole real data set (CSF and GSF were >90% in both experiments).

Then we generated a 200% augmented data set of synthetic MDS patients, resulting into a high fidelity of the model (CSF = 91%; GSF = 89%) that was maintained when comparing the synthetic data sets with the real test set never seen by the model during the training phase (CSF = 90%; GSF = 88%).

When considering a more complex data set (IWG-PM MDS cohort, N = 2,604) including a higher number of genomic features (245 *v* 65), we obtained comparable fidelity performances to the previous experiments (CSF = 93%; GSF = 93%).

Importantly, a similar trend was noted by replicating all these experiments in a cohort of 1,002 synthetic patients with AML generated form an equal number of real subjects (CSF > 90%; GSF > 88% in all cases), thus providing evidence for a generalizability of the generative model across different clinical settings.

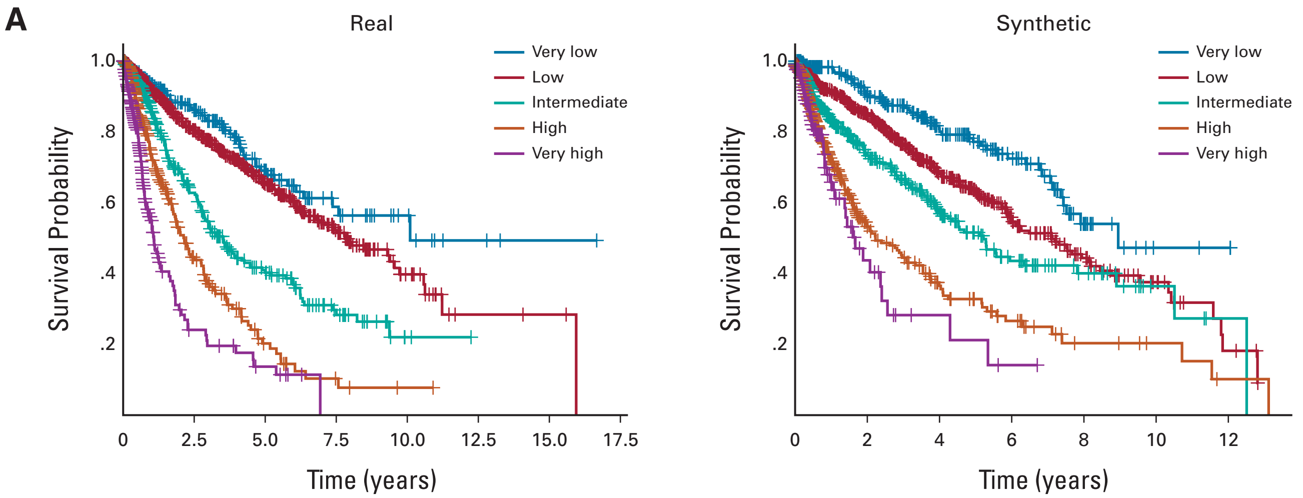
In terms of privacy metrics, in all experiments on the three different synthetic patient populations, the IMS analysis showed that none of the real patients were copied in the synthetic data sets; moreover, we obtained similar good distance results in all experiments for NNDR (values from 0.60 to 0.71).

Accelerating Translational Research by Synthetic Data (Setting C)

Starting from a MDS cohort available in 2014 (N = 944),[25] we generated a 300% augmented synthetic data set of 2,832 patients. Fidelity and privacy performances were comparable with previous experiments (CSF = 92%; GSF = 89%; NNDR = 0.62). We aimed to recapitulate and anticipate in this cohort of synthetic patients the most relevant insights in the field of personalized medicine (ie, the definition of new molecular MDS classification provided on a cohort of 2,043 real patients[20] and the definition of the Molecular International Prognostic Scoring Systems [IPSS-M], defined on a cohort 2,897 real patients[21]).

First, Dirichlet processes were applied to synthetic data to define genomic-based clinical entities, resulting in the identification of the same eight disease categories described in a real cohort of 2,043 patients in 2022. Patients' classification into clinical groups followed a similar distribution as the real cohort, and explainability analysis (SHAP) also showed that similar features drive the patients' classification in both data sets (Fig 4 and Appendix Fig A3).

As a second experiment, we applied a L1-penalized Cox regression model to the synthetic data set of 2,832 patients to generate a molecular prognostic score (synthetic IPSS-M). After feature selection, we developed a prognostic tool on the synthetic cohort and compared it with IPSS-M developed on real patients. The comparison of the two scores reveals the same feature extraction and the identification of six risk categories with comparable probability of overall survival and leukemia-free survival (Fig 5 and Appendix Fig A4).



No. at risk:

Very low	197	118	57	24	9	3	1	0
Low	578	329	174	68	18	3	2	0
Intermediate	328	126	56	21	2	0	0	0
High	281	55	14	4	1	0	0	0
Very high	215	16	6	0	0	0	0	0

No. at risk:

Very low	255	163	96	55	16	3	2
Low	655	379	194	90	42	16	4
Intermediate	451	170	87	38	17	4	1
High	406	82	39	19	7	4	1
Very high	134	13	4	1	0	0	0

B

Measurement	Real Data				Synthetic Data			
	Clinical	CNA	Demographics	Genetics	Clinical	CNA	Demographics	Genetics
Concordance	0.683	0.555	0.581	0.654	0.708	0.544	0.601	0.722
Std(c-d)	0.012	0.009	0.012	0.012	0.012	0.010	0.012	0.012

FIG 3. Patient classification and survival analysis on the synthetic MDS cohort (N = 2,043), as performed in setting A. (A) Kaplan-Meier survival probability curves obtained from the real (left) and synthetic (right) populations, stratified according to IPSS-R risk categories. The *P* values of the log-rank test are calculated, confirming the hypothesis of no difference in survival probabilities between real and synthetic patients for every IPSS-R risk group. (B) Partial concordance and standard error for each category of variables obtained from the mixed-effect CoxPH models fitted on the real and synthetic cohorts. CNA, copy number alteration; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes.

Accelerating Clinical Research and Conduction of Clinical Trials by Using Synthetic Data (Setting D)

We investigated the possibility to use a synthetic data set as a comparison group in a clinical trial. We therefore aimed to replicate a real patient cohort from a multicenter study including 187 patients with MDS who were treated with luspatercept.[26]

Eligible patients were age 18 years or older and had an MDS with ring sideroblasts; were receiving regular red blood cells transfusions; and were refractory to erythropoiesis-stimulating agent therapy. Primary end point was transfusion independence (TI) for ≥8 weeks during weeks 1-24; key secondary end point was TI for ≥12 weeks during both weeks 1-24 and 1-48.

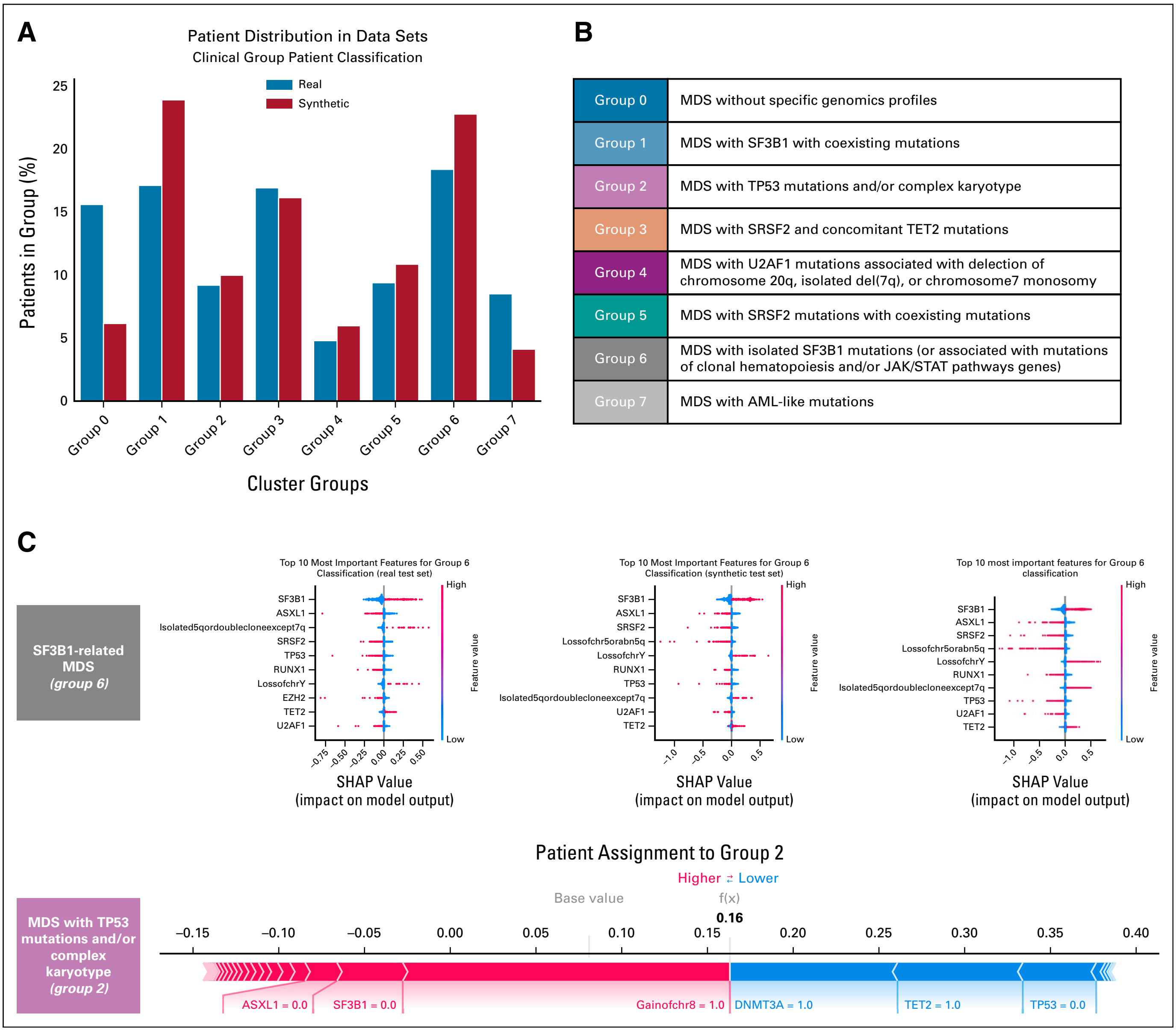
We generated a synthetic cohort (N = 187) from the patients included in the study using all data for training, and we compared the synthetic end points with the original study results. All the characteristics and metrics of the synthetic cohort were comparable with respect to the original data set, as shown in Figure 6 and Appendix Figure A5, with high efficient coefficient of privacy preservability (NNDR = 0.71).

Generator of Synthetic Data

To help clinicians to be familiar with generative AI to build synthetic data, we have created a prototype web portal[27] that allows to generate synthetic patients starting from 2,957 real MDS of IWG-PM cohort.[21] This portal allows to generate synthetic cohorts with different sizes, to verify the performance of the newly generated data (fidelity and privacy preservability), and to download the synthetic data set for research use.

DISCUSSION

In this study, we showed that synthetic data may (1) efficiently recapitulate statistical properties and complex interactions between clinical and genomic features in hematologic malignancies; (2) replicate reliable estimates of survival and effectiveness of specific treatments;



Group 0	MDS without specific genomics profiles
Group 1	MDS with SF3B1 with coexisting mutations
Group 2	MDS with TP53 mutations and/or complex karyotype
Group 3	MDS with SRSF2 and concomitant TET2 mutations
Group 4	MDS with U2AF1 mutations associated with delection of chromosome 20q, isolated del(7q), or chromosome7 monosomy
Group 5	MDS with SRSF2 mutations with coexisting mutations
Group 6	MDS with isolated SF3B1 mutations (or associated with mutations of clonal hematopoiesis and/or JAK/STAT pathways genes)
Group 7	MDS with AML-like mutations

FIG 4. Definition of a molecular classification on augmented synthetic MDS cohort starting from 944 patients available in 2014, as performed in setting C. (A) Evaluation of the real (blue) and synthetic (red) patients' distribution considering genomic groups classification. (B) Genomic group definition according to Bersanelli et al.[20] (C) SHAP summary plot analysis on the top 10 most important features for a real test set, a synthetic test set, and a complete augmented synthetic data set for the genomic group 6. Below is the force plot showing the importance of the most relevant features in assigning a synthetic patient to genomic group 2. MDS, myelodysplastic syndromes; SHAP, Shapley Additive Explanations.

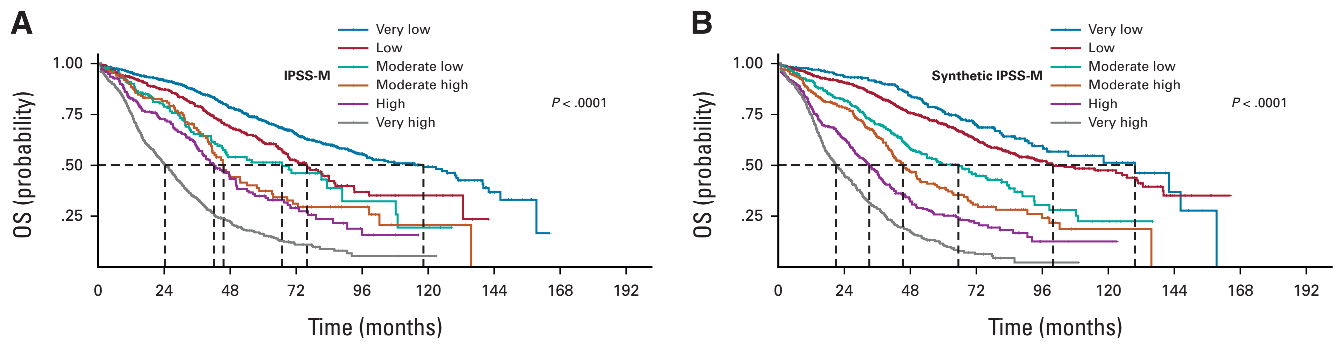
(3) overcome lack/imbalance of information of real data; and (4) allow effective data augmentation.

The implementation of this technology may allow to increase the scientific use and value of real data, and it is expected to accelerate precision medicine in hematology and the conduction of clinical trials.

To help clinicians to be familiar with this new technology, we created a prototype web portal that allows to generate synthetic data from a real data set of patients with clinical and genomic information, and that provides a report of the quality of the newly generated synthetic patients.

The implementability of synthetic data in translational and clinical research depends on two main properties: (1) fidelity, ie, the newly generated data should be plausible and preserve structural properties of the real data; (2) privacy, that is, it should be possible to precisely quantify how much information about the original data is revealed through the releasing of the synthetic sample.[28,29]

The use of generative AI rapidly increased the implementation of synthetic data in life sciences in past years.[8-10] As an example, SyntheticMass hosts over one million synthetic patient records from the state of Massachusetts.[30] In



No. at risk:

IPSS-M									
—	1,074	884	587	317	125	53	11	0	0
—	379	267	155	70	23	9	0	0	0
—	149	101	45	22	5	3	0	0	0
—	155	100	36	20	9	2	0	0	0
—	236	133	58	19	6	0	0	0	0
—	746	308	91	21	3	2	0	0	0

No. at risk:

Synthetic IPSS-M									
—	312	266	193	109	45	15	4	0	0
—	964	768	483	250	94	44	7	0	0
—	326	218	111	50	14	6	0	0	0
—	286	172	72	30	13	2	0	0	0
—	381	192	64	22	4	2	0	0	0
—	470	177	49	8	1	0	0	0	0

C

Measurement	Synthetic IPSS-M Risk Category					
	Very Low	Low	Moderate Low	Moderate High	High	Very High
Patients, No. (%)	312 (11)	964 (35)	326 (12)	286 (10)	381 (14)	470 (17)
Hazard ratio (95% CI) – LFS	0.5 (0.26-0.82)	1.0 Reference	2.0 (1.37-2.97)	2.5 (1.7-3.77)	5.4 (3.9-7.5)	9.9 (7.4-13.3)
Median LFS (months)	-	-	-	-	66.9	49.7
Hazard ratio (95% CI) – OS	0.77 (0.6-0.97)	1.0 Reference	1.8 (1.5-2.22)	2.5 (2.03-3.03)	3.9 (3.3-4.6)	6.4 (5.4-7.5)
Median OS (months)	129.7	100	65.5	45.3	33.1	21

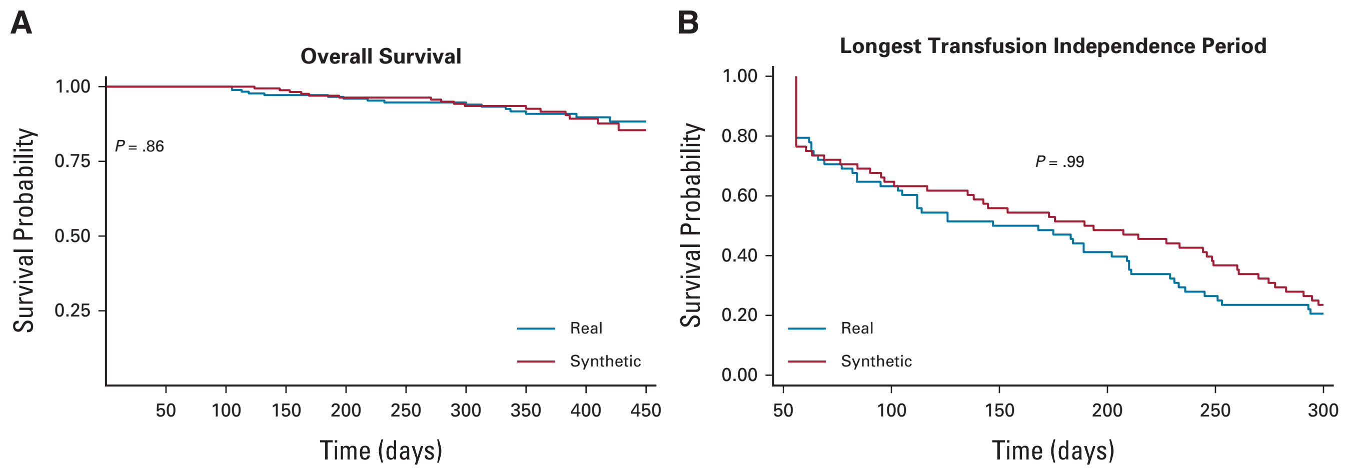
	IPSS-M Risk Category					
	Very Low	Low	Moderate Low	Moderate High	High	Very High
Patients, No. (%)	1,074 (39)	379 (14)	149 (5.4)	155 (5.6)	236 (9)	746 (27)
Hazard ratio (95% CI) – LFS	0.5 (0.3-0.7)	1.0 Reference	1.6 (0.9-2.7)	1.3 (0.7-2.3)	2.4(1.6-3.8)	5.3 (3.7-7.6)
Median LFS (months)	-	-	-	-	-	55.9
Hazard ratio (95% CI) – OS	0.66 (0.5-0.8)	1.0 Reference	1.37 (1.0-1.8)	1.7 (1.3-2.2)	2 (1.6-2.6)	3.9 (3.2-4.7)
Median OS (months)	118.3	76	66.9	45.6	42.2	24.4

FIG 5. Survival analysis on synthetic molecular prognostic score generated (synthetic IPSS-M) performed in setting C. (A) Kaplan-Meier probability estimates of OS for synthetic patients with MDS are represented and stratified by IPSS-M risk categories as defined by Bernard et al.[21] *P* value is from log-rank test. (B) Kaplan-Meier probability estimates of OS for synthetic patients with MDS are represented and stratified by synthetic IPSS-M risk categories. *P* value is from log-rank test. (C) Percentage of patients in each IPSS-M risk category (both synthetic and original) with the HRs for each outcome, and the median survival for each patient class, where values could be calculated. HR, hazard ratio; IPSS-M, Molecular International Prognostic Scoring System; LFS, leukemia-free survival; MDS, myelodysplastic syndromes; OS, overall survival.

Europe, synthetic data sets that mimic a part of the Netherlands Cancer Registry and Public Health England's Cancer Registration are now available for research purposes.[31,32] The creation of a synthetic data bank makes the information accessible while also streamlining the data sets that medical research teams have to work with. But, there are limitations: the more complex the data query, the more approximate the results; in particular, the generation of high-fidelity synthetic patients with comprehensive clinical and genomic information reproducing complex interactions among different data layers is still a challenge.[8-10]

In this study, we used an optimized method (conditional GAN)[17-19] to recapitulate clinical and genomic properties of real patients with myeloid neoplasms, which are rare diseases characterized by large clinical and biological heterogeneity.[13,15] The methodologic advantage of conditional GAN allowed us to face specific challenges in research on rare diseases (such as lack/imbalance of data) and we provided evidence for a high generalizability of the performances of the model across different clinical settings.

Synthetic data require an extensive validation of their reliability in recapitulating properties of real patients.[8-10,28-30] We therefore created a SVF to perform a clear fidelity analysis of clinical, survival, and genomic information and that may represent a solid basis to define the quality of a newly generated synthetic data set. Moreover, we implemented a comprehensive approach for data explainability,[24] thus facilitating the clinical interpretation of the results of deep learning analysis on synthetic data.



C

Clinical End Point	Real Data	Synthetic Data	*P*
RBC-TI ≥ 8 weeks 1-24	56 (31.5)	56 (31.5)	1.0
Longest transfusion indepence period, weeks, median (range)	195 (56-490)	280 (56-490)	< .05
RBC-TI ≥ 8 weeks 1-48	68 (38.2)	61 (34.3)	.50
RBC-TI ≥ 12 weeks 1-24	36 (20.2)	41 (23.0)	.60
RBC-TI ≥ 12 weeks 1-48	51 (28.7)	46 (25.8)	.63
Reduction ≥ 4 RBC	62 (34.8)	63 (35.4)	1.0
Reduction ≥ 50%	77 (43.3)	72 (40.4)	.66
AML evolution	4 (2.2)	6 (3.4)	.75
Discontinued patients	74 (41.6)	82 (46.1)	.64

FIG 6. Comparison of clinical trial end points between real and synthetic patients, as performed in setting D. (A) Kaplan-Meier survival probability curves compared for real and synthetic patients' overall survival. (B) Kaplan-Meier curves of longest transfusion independence period for real and synthetic patients. The *P* values of the log-rank test are calculated, confirming the hypothesis of no difference in survival probabilities between real and synthetic cohorts. (C) Study end point comparison between real and synthetic cohorts. RBC-TI, rate of red blood cell transfusion independence.

Sharing data has the potential to improve decision making and accelerate research and innovation.[2-4,11] At the same time, many data are highly sensitive and sharing them may violate fundamental rights guarded by modern privacy regulations.[7,11] Anonymization (where potentially identifiable variables are removed) is one way to make data available; however, intensive anonymization can degrade the data to the extent that they are no longer fit for purpose. Moreover, several reidentification attempts on anonymized data have been successful and have harmed public and regulators' trust in such methods.[33,34] We showed that generative AI can guarantee a high privacy preservability of newly generated synthetic data. We focused on analyzing the distance between the real and synthetic patients and we showed that there was enough distance between the real and synthetic patients to avoid the risk of revealing sensitive information from the training data and not too far away to maintain correlations of the source real population.[23]

We provided evidence that synthetic data can accelerate translational research in hematology. Since the first publication on clinical relevance of gene mutations in MDS, it took several years to collect real large patient populations for defining a molecular classification and molecular prognostic score.[20,21] By generating synthetic data from a relative small cohort of patients available in 2014,[25] we were able to recapitulate the definition of genomic-based subgroups and of a molecular prognostic score as described in real cohorts many years later.[20,21]

Finally, synthetic patients could be used in the future to improve the conduction of clinical trials. The use of synthetic control arms may reduce clinical trial costs and duration. Moreover, using a synthetic control arm may ensure that all participants receive the active treatment, thus eliminating patient concerns about treatment assignment.[35]

Secondary analyses of data from clinical trials can provide new insights compared with the original publications.[36] In this context, our findings suggest that generative AI can create synthetic patients that efficiently reproduce clinical characteristics and efficacy end points of the original study and that can be promptly available for secondary analyses.

As a possible improvement of our approach, recently, GAN technology was optimized to generate synthetic patients with time-series records and longitudinal evaluation of treatment response (multilabel time-series GAN [MTGAN]).[37] MTGAN can preserve temporal information by developing a temporally correlated generation process, thus finally increasing the generation quality of uncommon diseases and the performance of predictive models.

To maximize the impact of this technology in accelerating precision medicine in hematology, it will be relevant to develop regulatory frameworks involving synthetic data and to define standards for synthetic data quality and privacy preservability.[8,12]

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EQUAL CONTRIBUTION

G.C. and M.G.D.P. are last senior authors.

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DATA SHARING STATEMENT

To help clinicians to be familiar with generative AI to build synthetic data, we have created a prototype web portal (https://sdg-webserver-cloudrun-xkb3corsxq-ew.a.run.app/) that allows to generate synthetic patients starting from 2,957 real MDS of IWG-PM cohort. This portal allows to generate synthetic cohorts with different sizes, to verify the performance of the newly generated data (fidelity and privacy preservability), and to download the synthetic dataset for research use.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Patents, Royalties, Other Intellectual Property: Part of a patent for a TFR-2 antibody (Rauner et al Nature Metabolics 2019)
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APPENDIX

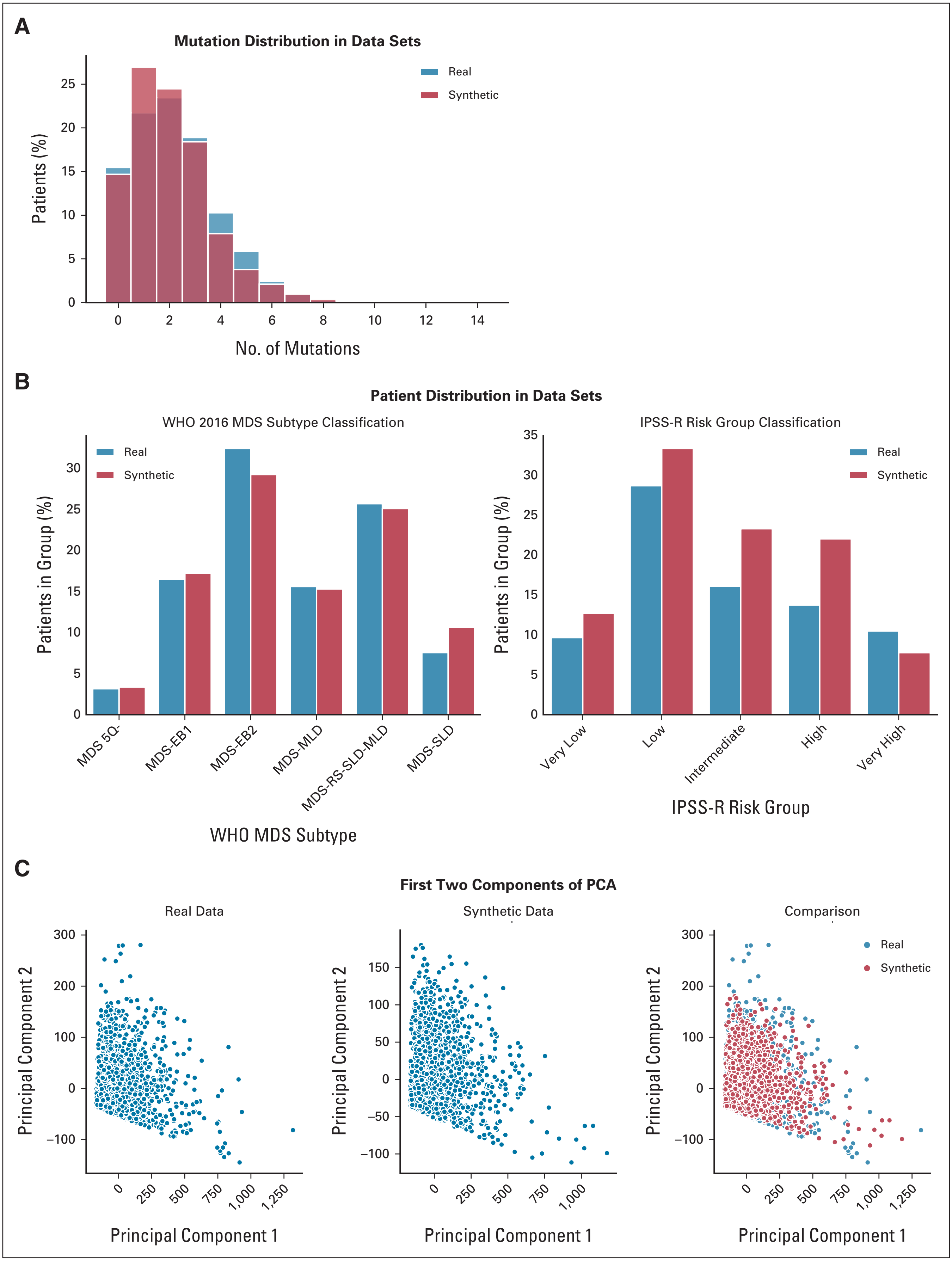

A
Mutation Distribution in Data Sets
Real
Synthetic
Patients (%)
0
5
10
15
20
25
0
2
4
6
8
10
12
14
No. of Mutations
B
Patient Distribution in Data Sets
WHO 2016 MDS Subtype Classification
Real
Synthetic
Patients in Group (%)
0
5
10
15
20
25
30
MDS 5Q-
MDS-EB1
MDS-EB2
MDS-MLD
MDS-RS-SLD-MLD
MDS-SLD
WHO MDS Subtype
IPSS-R Risk Group Classification
Real
Synthetic
Patients in Group (%)
0
5
10
15
20
25
30
35
Very Low
Low
Intermediate
High
Very High
IPSS-R Risk Group
C
First Two Components of PCA
Real Data
Principal Component 2
−100
0
100
200
300
0
250
500
750
1,000
1,250
Principal Component 1
Synthetic Data
Principal Component 2
−100
−50
0
50
100
150
0
250
500
750
1,000
Principal Component 1
Comparison
Real
Synthetic
Principal Component 2
−100
0
100
200
300
0
250
500
750
1,000
1,250
Principal Component 1

FIG A1. SVF on synthetic MDS cohort (N = 2,043), as performed in setting A. (A) Distributions of the patients according to the number of recurrently mutated genes and chromosomal abnormalities. (B) Evaluation of the real (blue) and synthetic (red) patients' distribution considering WHO 2016 classification and IPSS-R risk value. (C) PCA for clinical, demographic, and survival features. (D) Correlation matrices for clinical, demographic, and survival features, indicating the interdependencies per column on real and synthetic data sets. All results are referring to one MDS synthetic data set of 2,043 patients generated. Detailed results are reported in the Data Supplement. IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; PCA, principal component analysis; SVF, synthetic validation framework.

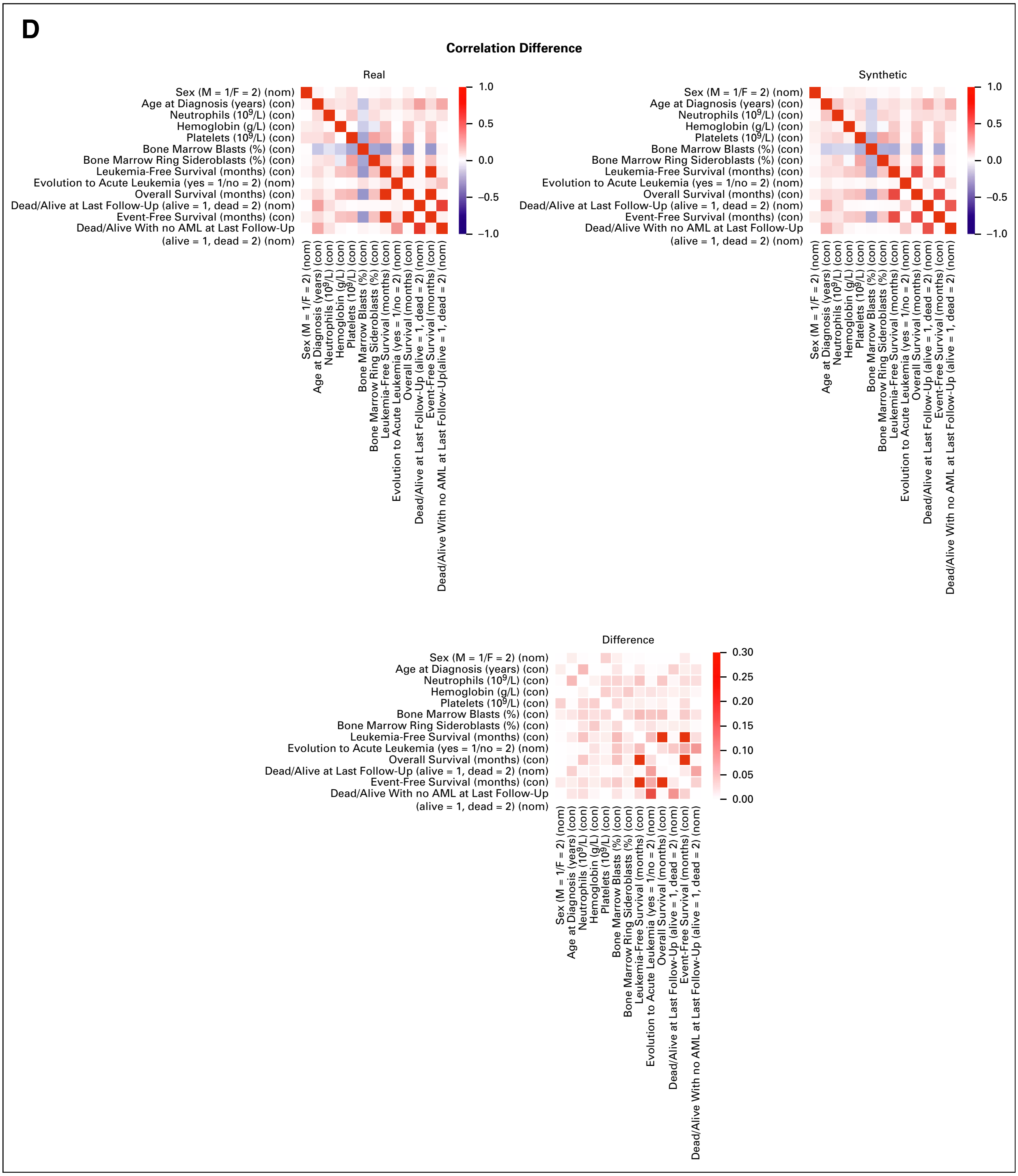
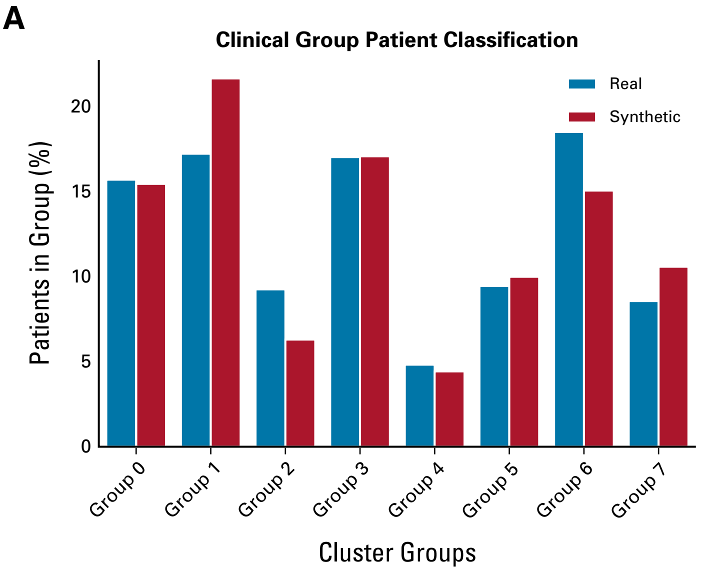


FIG A1. (Continued).



B

Component 1	Component 2	Component 3	Component 4	Component 5
SF3B1	U2AF1	SRSF2	TP53	DNMT3A
TET2	ASXL1	ASXL1	Lossofchr5ordel5qPLUSother	BCOR
DNMT3A	Lossofchr7ordel7q	RUNX1	Lossofchr7ordel7q	IDH1
del5q	SETBP1	TET2	Lossofchr12ordel12port12p	FLT3
JAK2	Lossofchr20ordel20q	STAG2	Gainofchr8	NPM1

Component 1	Component 2	Component 3	Component 4	Component 5	Component 6
SF3B1	U2AF1	SRSF2	TP53	DNMT3A	BCOR
TET2	ASXL1	ASXL1	Lossofchr5ordel5qPLUSother	IDH1	TET2
DNMT3A	RUNX1	TET2	Lossofchr7ordel7q	WT1	RUNX1
MPL	EZH2	RUNX1	Lossofchr12ordel12port12p	NPM1	SF3B1
del5q	ZRSR2	IDH2	Isochr17qort17p	GATA2	DNMT3A

FIG A2. Patient classification and survival analysis on synthetic MDS cohort (N = 2,043), as performed in setting A. (A) Evaluation of the real (blue) and synthetic (red) patients' distribution considering clinical groups. Patient assignment was made by using a multiclass classifier (MLP) trained on the clinical groups identified in the EuroMDS cohort. (B) Components from the Dirichlet process on real data (above) and for the synthetic ones (below). Only the top five anomalies have been reported per cluster, decreasingly sorted by importance. (C) SHAP summary plot analysis on the top 10 most important features for real (left) and synthetic (right) for the genomic group defined as MDS with SF3B1 mutation. Below is the force plot showing the features importance in assigning a synthetic patient to this genomic group. MDS, myelodysplastic syndromes; MLP, multilayer perceptron; SHAP, Shapley Additive Explanations. (continued on following page)

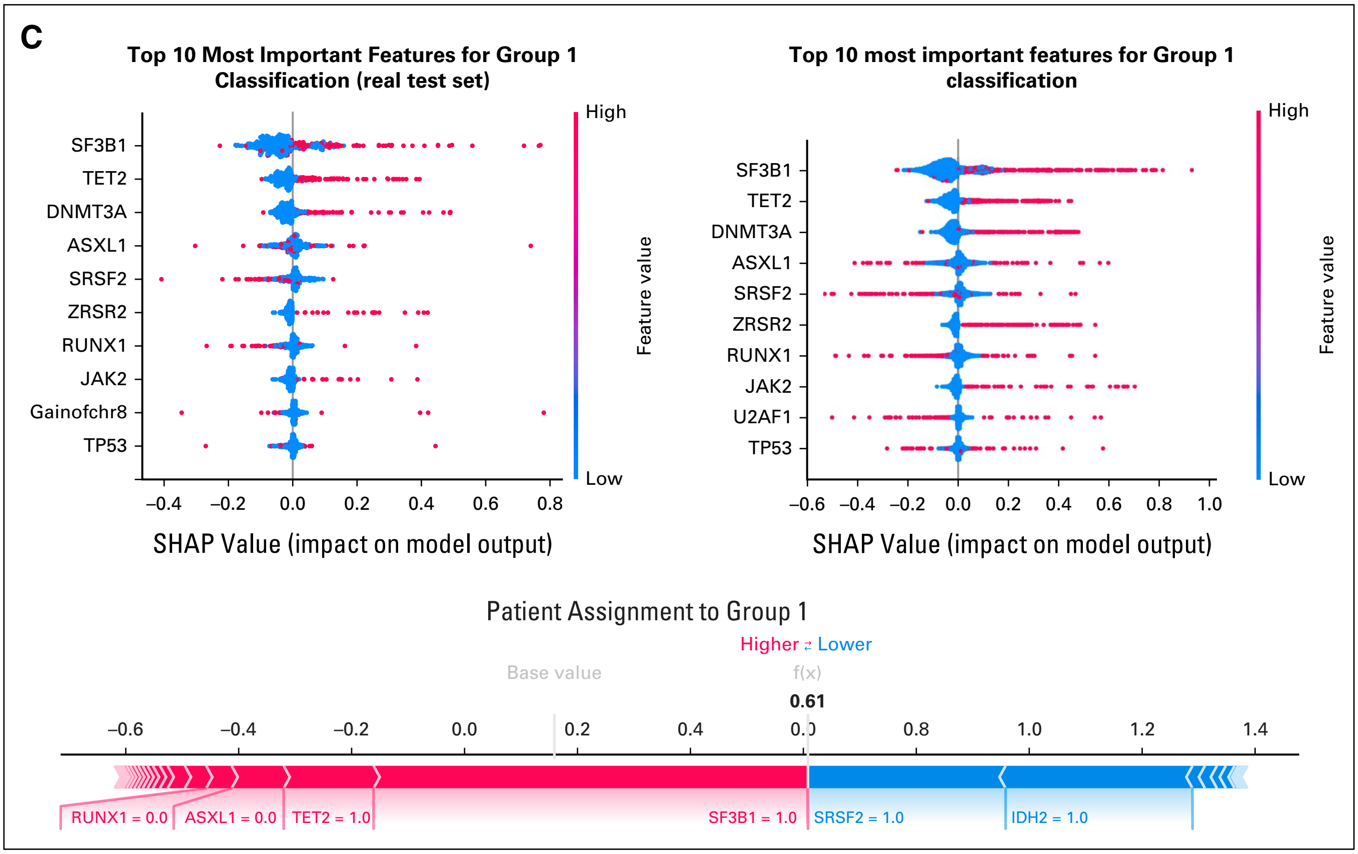


FIG A2. (Continued).

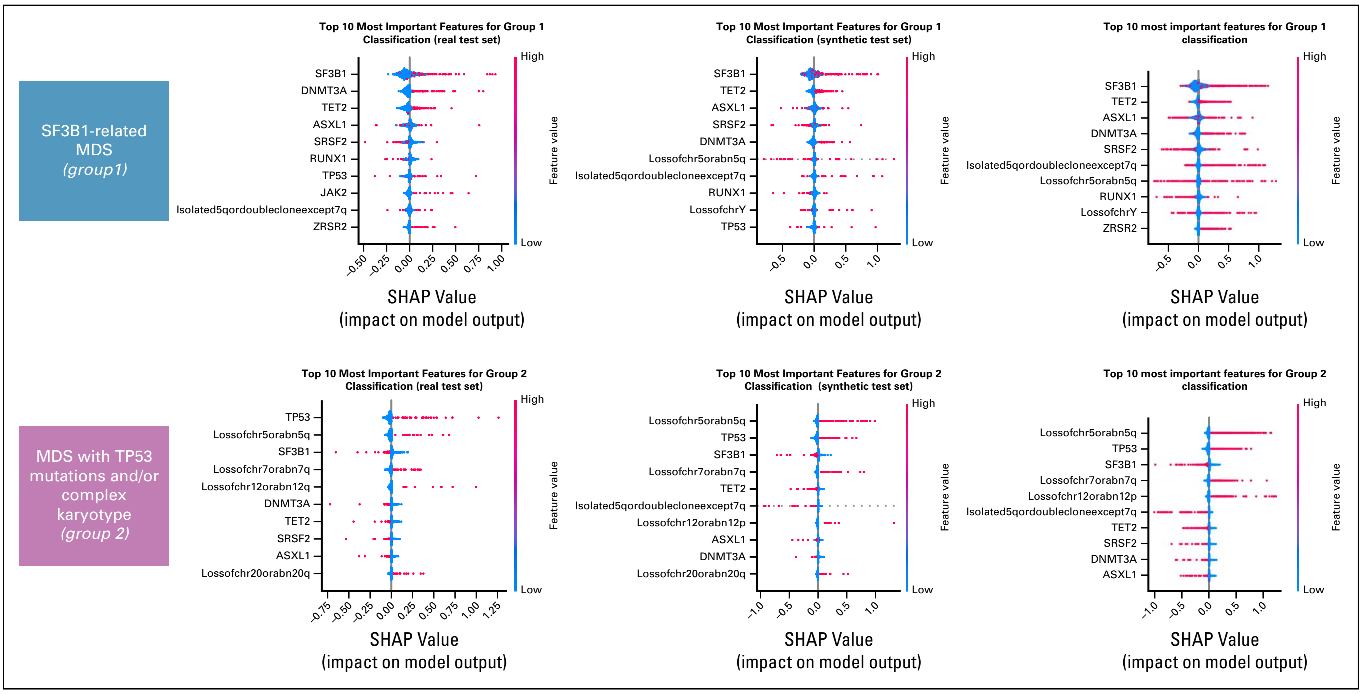


FIG A3. Definition of a molecular classification on augmented synthetic MDS cohort starting from 944 patients available in 2014, as performed in setting C. SHAP summary plot analysis on the top 10 most important features for a real test set, a synthetic test set, and a complete augmented synthetic data set for the genomic groups 1 and 2. MDS, myelodysplastic syndromes; SHAP, Shapley Additive Explanations.

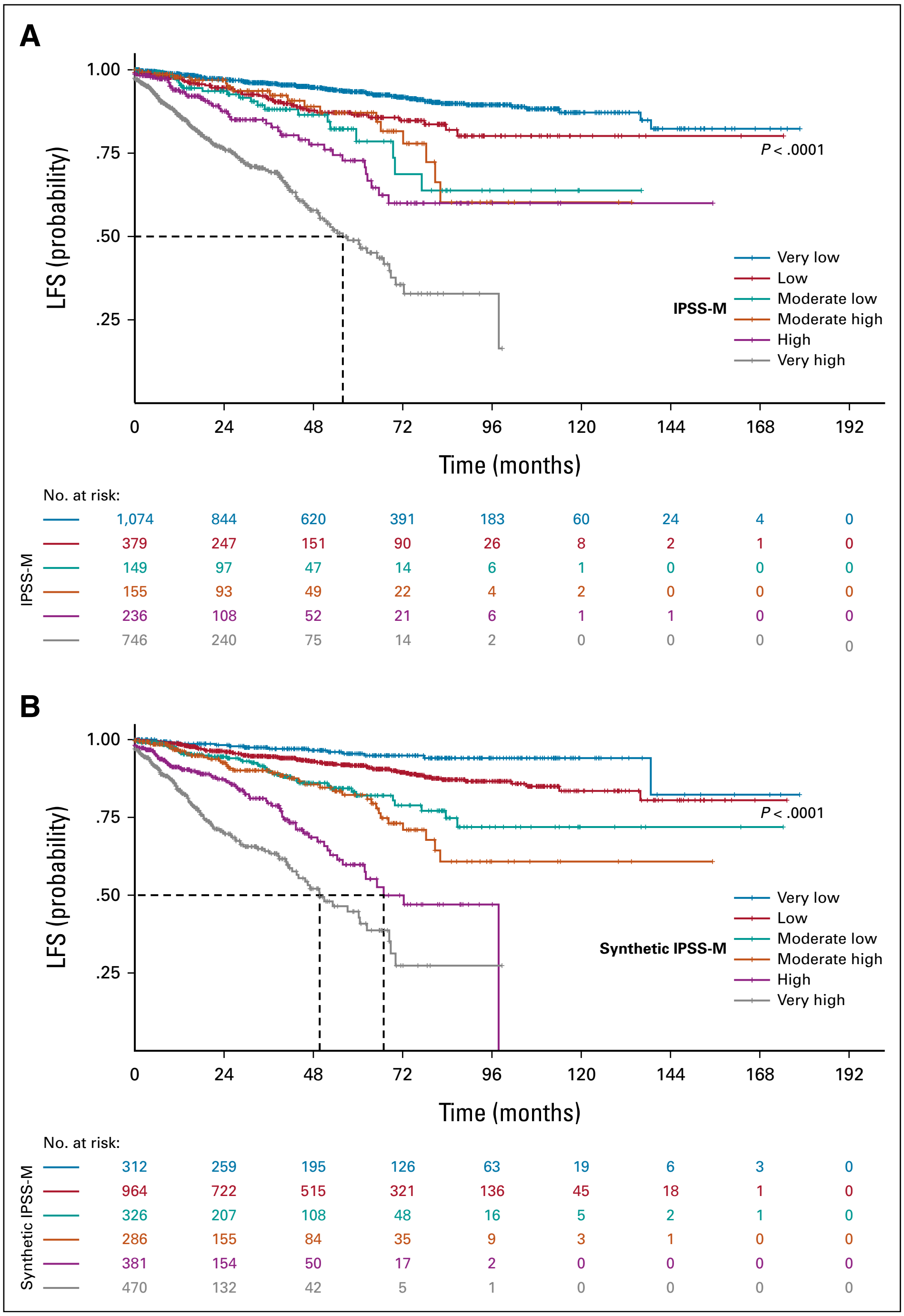
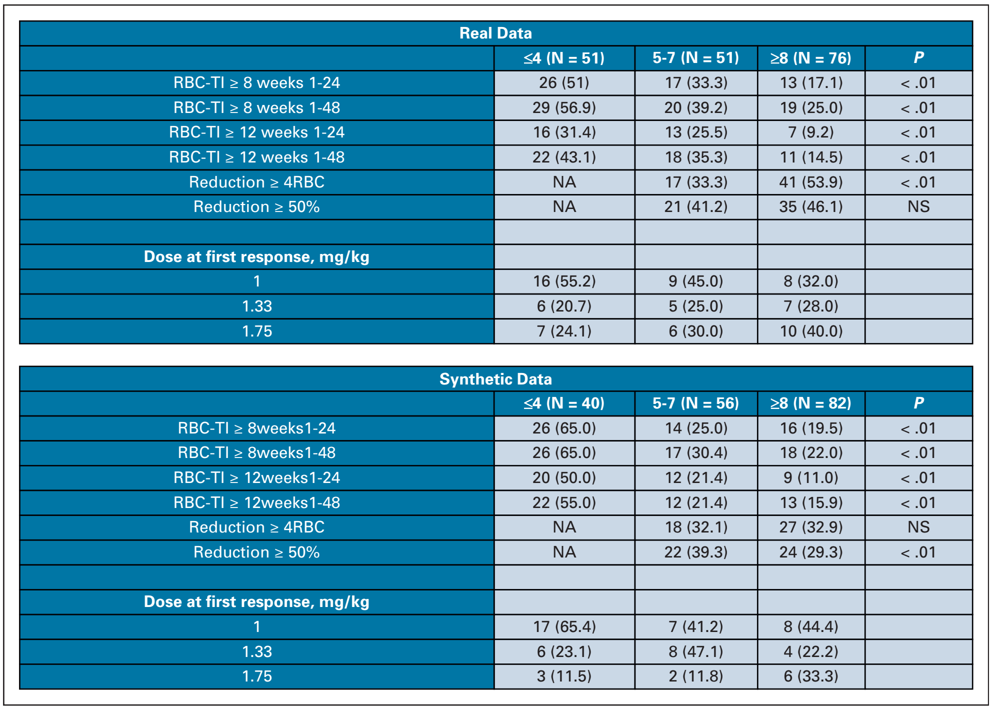


FIG A4. Survival analysis on synthetic molecular prognostic score generated (synthetic IPSS-M) performed in setting C. (A) Kaplan-Meier probability estimates of LFS for synthetic MDS patients are represented and stratified by IPSS-M risk categories as defined by Bernard et al.[21] *P* value is from log-rank test. (B) Kaplan-Meier probability estimates of LFS for synthetic MDS patients are represented and stratified by synthetic IPSS-M risk categories. *P* value is from log-rank test. IPSS-M, Molecular International Prognostic Scoring System; LFS, leukemia-free survival; MDS, myelodysplastic syndromes.



Real Data				
	≤4 (N = 51)	5-7 (N = 51)	≥8 (N = 76)	*P*
RBC-TI ≥ 8 weeks 1-24	26 (51)	17 (33.3)	13 (17.1)	< .01
RBC-TI ≥ 8 weeks 1-48	29 (56.9)	20 (39.2)	19 (25.0)	< .01
RBC-TI ≥ 12 weeks 1-24	16 (31.4)	13 (25.5)	7 (9.2)	< .01
RBC-TI ≥ 12 weeks 1-48	22 (43.1)	18 (35.3)	11 (14.5)	< .01
Reduction ≥ 4RBC	NA	17 (33.3)	41 (53.9)	< .01
Reduction ≥ 50%	NA	21 (41.2)	35 (46.1)	NS
Dose at first response, mg/kg				
1	16 (55.2)	9 (45.0)	8 (32.0)	
1.33	6 (20.7)	5 (25.0)	7 (28.0)	
1.75	7 (24.1)	6 (30.0)	10 (40.0)	

Synthetic Data				
	≤4 (N = 40)	5-7 (N = 56)	≥8 (N = 82)	*P*
RBC-TI ≥ 8weeks1-24	26 (65.0)	14 (25.0)	16 (19.5)	< .01
RBC-TI ≥ 8weeks1-48	26 (65.0)	17 (30.4)	18 (22.0)	< .01
RBC-TI ≥ 12weeks1-24	20 (50.0)	12 (21.4)	9 (11.0)	< .01
RBC-TI ≥ 12weeks1-48	22 (55.0)	12 (21.4)	13 (15.9)	< .01
Reduction ≥ 4RBC	NA	18 (32.1)	27 (32.9)	NS
Reduction ≥ 50%	NA	22 (39.3)	24 (29.3)	< .01
Dose at first response, mg/kg				
1	17 (65.4)	7 (41.2)	8 (44.4)	
1.33	6 (23.1)	8 (47.1)	4 (22.2)	
1.75	3 (11.5)	2 (11.8)	6 (33.3)	

FIG A5. Comparison of clinical trial end points between real and synthetic patients, as performed in setting D. Response rate and dose at first response, stratified by baseline transfusion burden, in both real and synthetic cohorts. RBC-TI, rate of red blood cell transfusion independence.