MOLECULAR AND CYTOGENETICS ABNORMALITIES IN ACUTE MEYLOID LEUKEMIA AT PUERTO RICO

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EN EL DÍA DEL AMOR Y LA AMISTAD ESCRIBE UN MENSAJE PARA LA UNIDAD Y LOS PACIENTES
AMOR
FORMULARIO DE TRIAGE DE PACIENTE
S M T - 12 D

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

FREE ACCESS | Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant | May 31, 2023

Molecular and cytogenetics abnormalities in acute myeloid leukemia at Puerto Rico.

Authors: William Doel Marrero-León, Hector R. Cintron-Colon, Steven Cruz-Rodriguez, William Caceres, Cristian I. Rodriguez-Arocho, and Alexis Cruz | AUTHORS INFO & AFFILIATIONS

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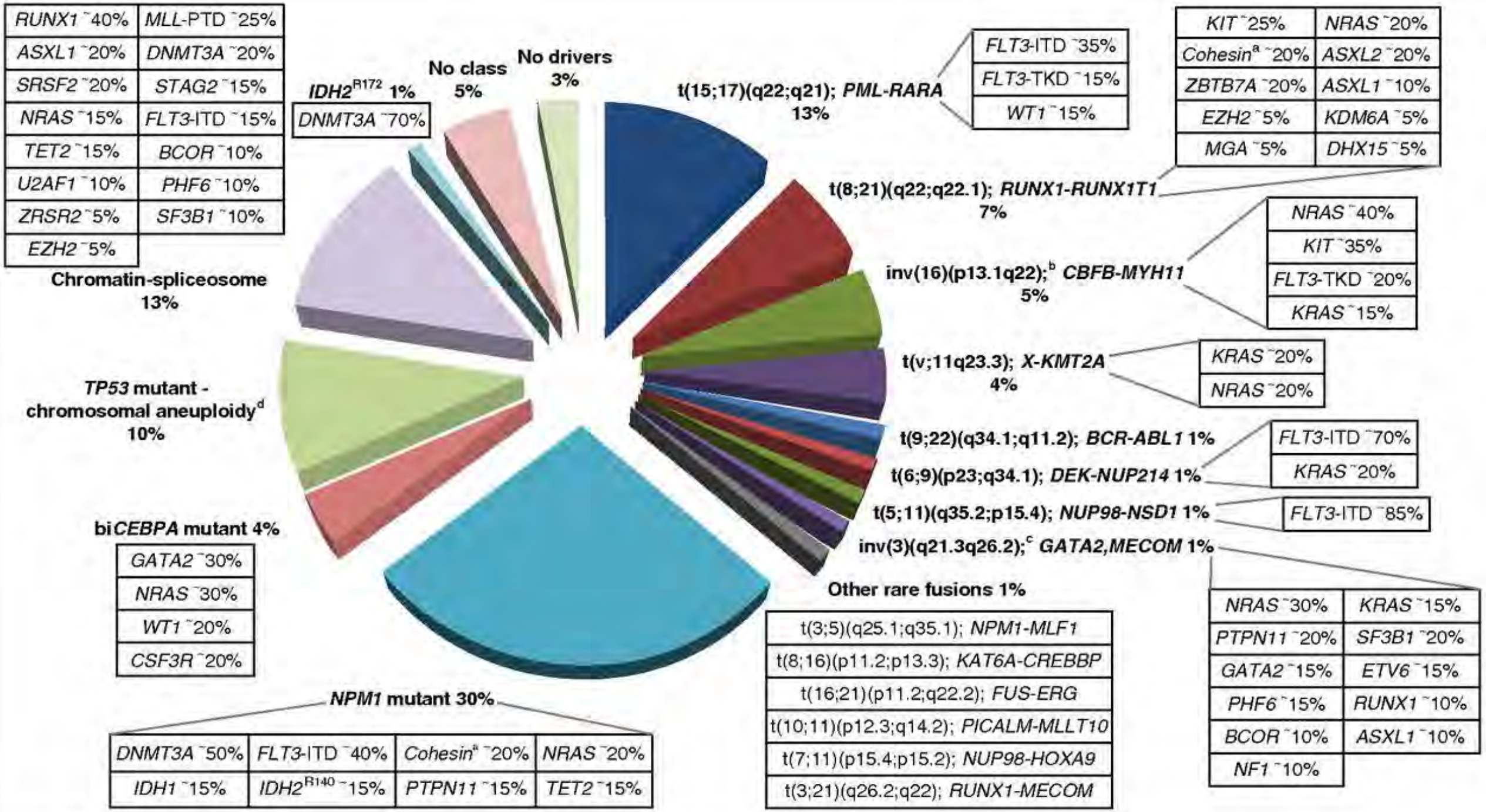
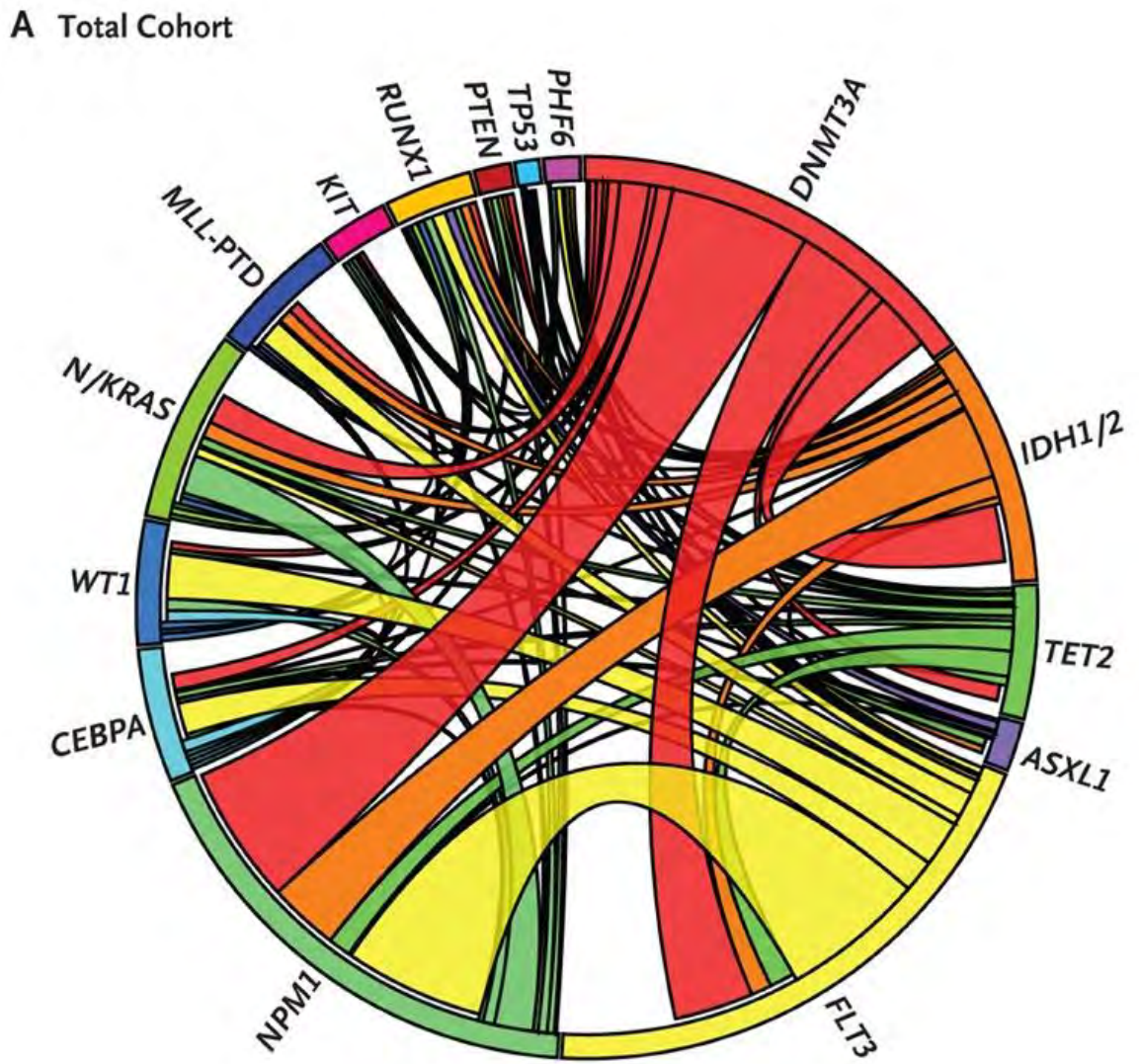
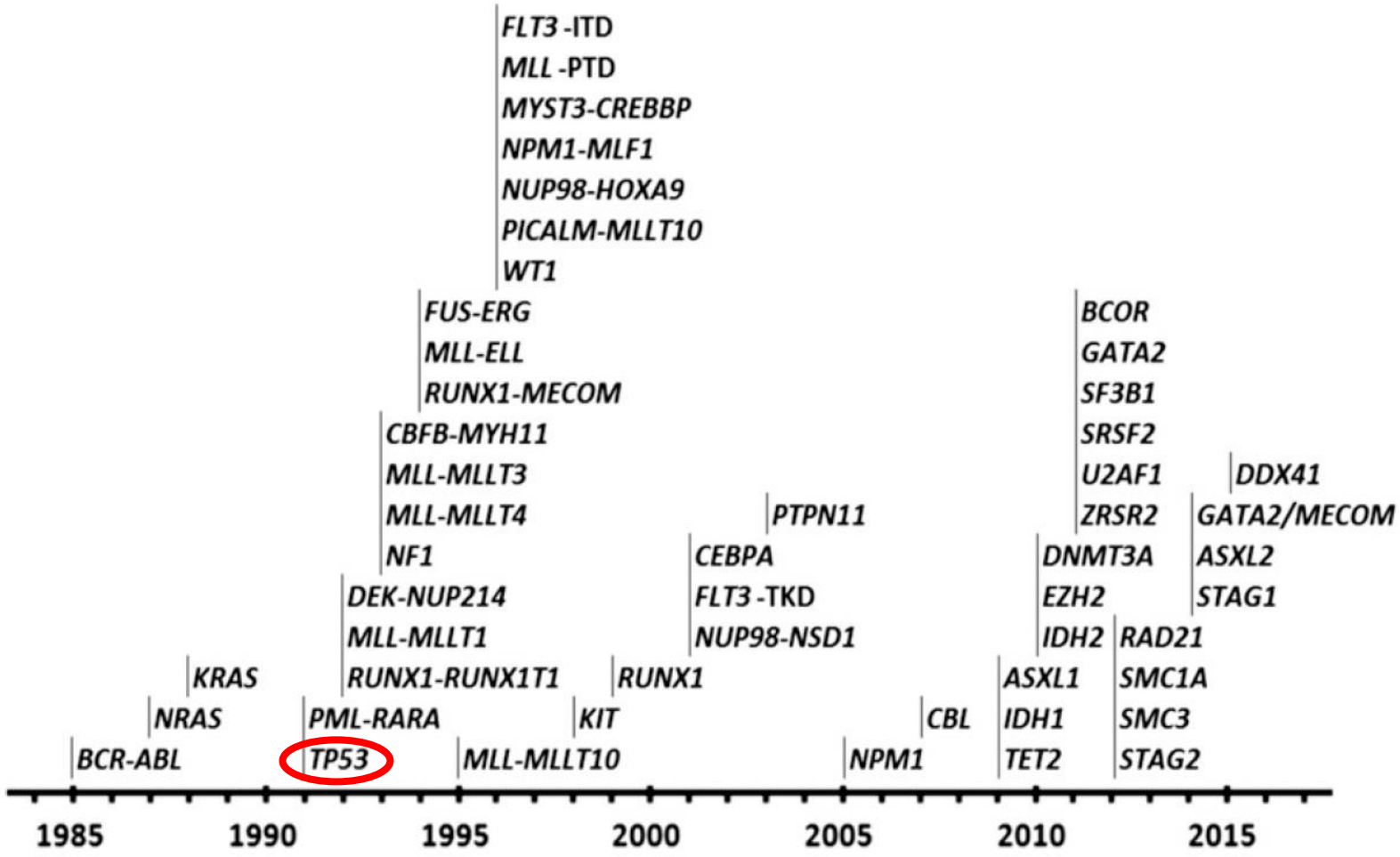

RUNX1 ~40%
MLL-PTD ~25%
ASXL1 ~20%
DNMT3A ~20%
SRSF2 ~20%
STAG2 ~15%
NRAS ~15%
FLT3-ITD ~15%
TET2 ~15%
BCOR ~10%
U2AF1 ~10%
PHF6 ~10%
ZRSR2 ~5%
SF3B1 ~10%
EZH2 ~5%
Chromatin-spliceosome 13%
IDH2R172 1%
DNMT3A ~70%
No class 5%
No drivers 3%
t(15;17)(q22;q21); PML-RARA 13%
FLT3-ITD ~35%
FLT3-TKD ~15%
WT1 ~15%
KIT ~25%
NRAS ~20%
Cohesin[a] ~20%
ASXL2 ~20%
ZBTB7A ~20%
ASXL1 ~10%
EZH2 ~5%
KDM6A ~5%
MGA ~5%
DHX15 ~5%
t(8;21)(q22;q22.1); RUNX1-RUNX1T1 7%
inv(16)(p13.1q22);[b] CBFB-MYH11 5%
NRAS ~40%
KIT ~35%
FLT3-TKD ~20%
KRAS ~15%
t(v;11q23.3); X-KMT2A 4%
KRAS ~20%
NRAS ~20%
t(9;22)(q34.1;q11.2); BCR-ABL1 1%
t(6;9)(p23;q34.1); DEK-NUP214 1%
FLT3-ITD ~70%
KRAS ~20%
t(5;11)(q35.2;p15.4); NUP98-NSD1 1%
FLT3-ITD ~85%
inv(3)(q21.3q26.2);[c] GATA2,MECOM 1%
NRAS ~30%
KRAS ~15%
PTPN11 ~20%
SF3B1 ~20%
GATA2 ~15%
ETV6 ~15%
PHF6 ~15%
RUNX1 ~10%
BCOR ~10%
ASXL1 ~10%
NF1 ~10%
Other rare fusions 1%
t(3;5)(q25.1;q35.1); NPM1-MLF1
t(8;16)(p11.2;p13.3); KAT6A-CREBBP
t(16;21)(p11.2;q22.2); FUS-ERG
t(10;11)(p12.3;q14.2); PICALM-MLLT10
t(7;11)(p15.4;p15.2); NUP98-HOXA9
t(3;21)(q26.2;q22); RUNX1-MECOM
TP53 mutant - chromosomal aneuploidy[d] 10%
biCEBPA mutant 4%
GATA2 ~30%
NRAS ~30%
WT1 ~20%
CSF3R ~20%
NPM1 mutant 30%
DNMT3A ~50%
FLT3-ITD ~40%
Cohesin[a] ~20%
NRAS ~20%
IDH1 ~15%
IDH2R140 ~15%
PTPN11 ~15%
TET2 ~15%


A Total Cohort
RUNX1
PTEN
TP53
PHF6
DNMT3A
KIT
MLL-PTD
N/KRAS
IDH1/2
WT1
TET2
CEBPA
ASXL1
NPM1
FLT3

Timeline of Genetic and Molecular Landscape in AML



Grimwade. Blood. 2016;127:29.

Transplantation and Cellular Therapy 30 (2024) 143–154

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

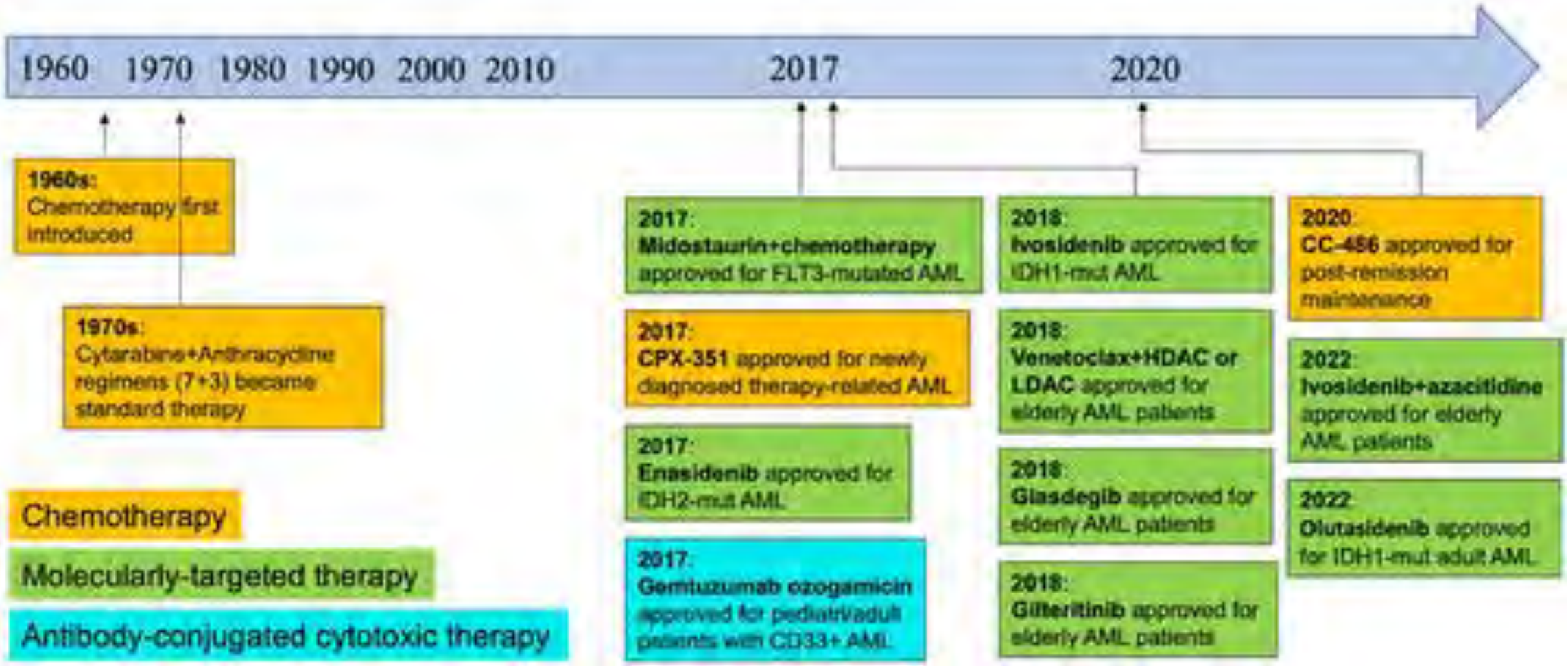
Guideline

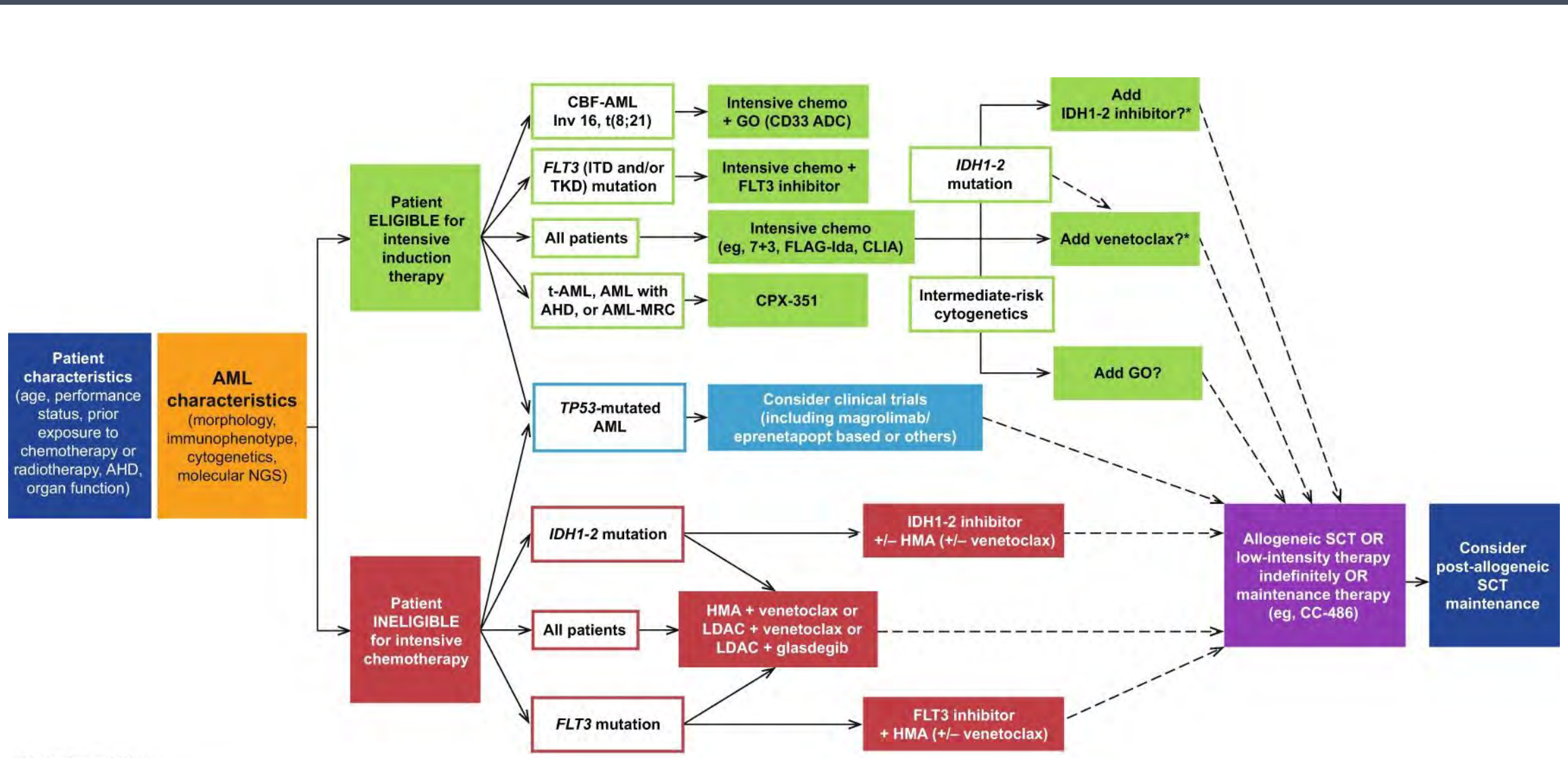
Genetic Findings of Potential Donor Origin following Hematopoietic Cell Transplantation: Recommendations on Donor Disclosure and Genetic Testing from the World Marrow Donor Association

Angharad Pryce[1], Eefke Van Eerden[2], Meghann Cody[3], Jason Oakes[3], Anna DeSalvo[3], Sarah Bannon[4], Catherine Burlton[1], Rachel Pawson[5], Warren Fingrut[6], Francisco Barriga[7], Jane Ward[8], Charlotte Ingram[8], Michael Walsh[6], Khaled El-Ghariani[9], Sunday Ocheni[10], Laura Machin[11,12], David Allan[13], Thilo Mengling[14], Chloe Anthias[1,15,*]

2022 ELN risk classification by genetics at initial diagnosis*

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ *CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • –5 or del(5q); –7; –17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]


1960 1970 1980 1990 2000 2010 2017 2020
1960s: Chemotherapy first introduced
1970s: Cytarabine+Anthracycline regimens (7+3) became standard therapy
2017: Midostaurin+chemotherapy approved for FLT3-mutated AML
2017: CPX-351 approved for newly diagnosed therapy-related AML
2017: Enasidenib approved for IDH2-mut AML
2017: Gemtuzumab ozogamicin approved for pediatr/adult patients with CD33+ AML
2018: Ivosidenib approved for IDH1-mut AML
2018: Venetoclax+HDAC or LDAC approved for elderly AML patients
2018: Glasdegib approved for elderly AML patients
2018: Gilteritinib approved for elderly AML patients
2020: CC-486 approved for post-remission maintenance
2022: Ivosidenib+azacitidine approved for elderly AML patients
2022: Olutasidenib approved for IDH1-mut adult AML
Chemotherapy
Molecularly-targeted therapy
Antibody-conjugated cytotoxic therapy


Patient characteristics (age, performance status, prior exposure to chemotherapy or radiotherapy, AHD, organ function)
AML characteristics (morphology, immunophenotype, cytogenetics, molecular NGS)
Patient ELIGIBLE for intensive induction therapy
CBF-AML Inv 16, t(8;21)
Intensive chemo + GO (CD33 ADC)
FLT3 (ITD and/or TKD) mutation
Intensive chemo + FLT3 inhibitor
All patients
Intensive chemo (eg, 7+3, FLAG-Ida, CLIA)
t-AML, AML with AHD, or AML-MRC
CPX-351
IDH1-2 mutation
Intermediate-risk cytogenetics
Add IDH1-2 inhibitor?*
Add venetoclax?*
Add GO?
TP53-mutated AML
Consider clinical trials (including magrolimab/ eprenetapopt based or others)
Patient INELIGIBLE for intensive chemotherapy
IDH1-2 mutation
IDH1-2 inhibitor +/– HMA (+/– venetoclax)
All patients
HMA + venetoclax or LDAC + venetoclax or LDAC + glasdegib
FLT3 mutation
FLT3 inhibitor + HMA (+/– venetoclax)
Allogeneic SCT OR low-intensity therapy indefinitely OR maintenance therapy (eg, CC-486)
Consider post-allogeneic SCT maintenance
*Under investigation

Age-Adjusted Incidence Rates by County , in Puerto Rico.

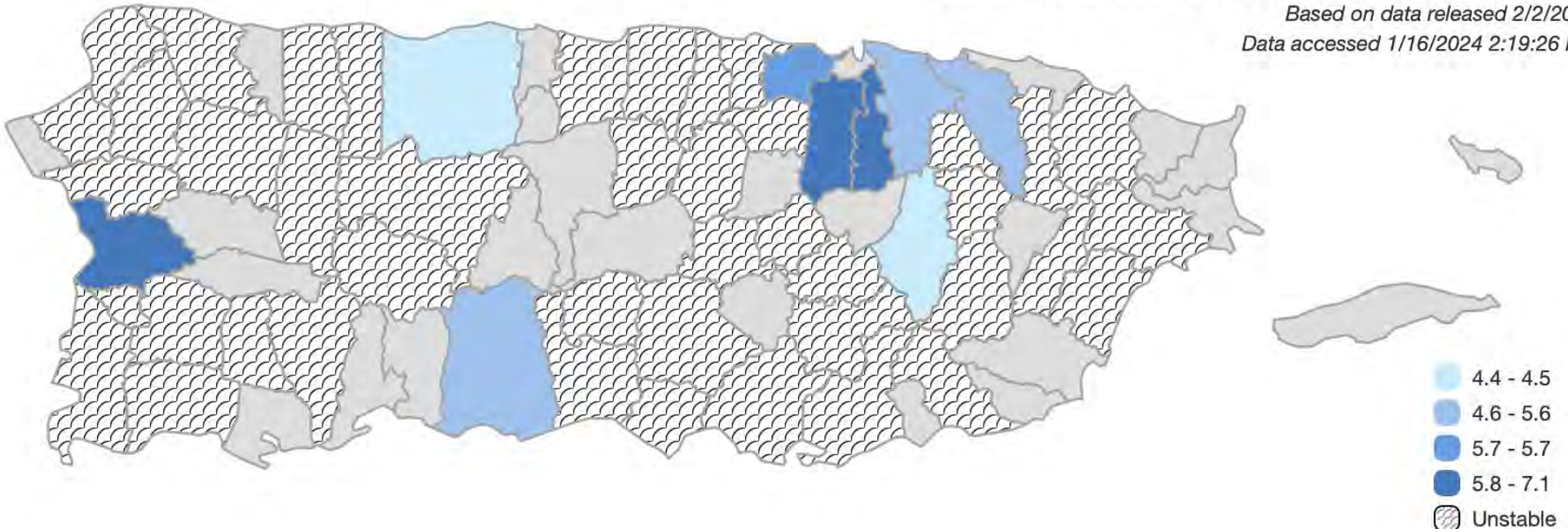
Myeloid and Monocytic Leukemia , 2015-2019

All rates are per 100,000 population.

Rates are age-adjusted to the 2000 PR Std Population (19 age groups)

Based on data released 2/2/2022

Data accessed 1/16/2024 2:19:26 PM



CYTOGENETICS AND MOLECULAR

OBJECTIVE

The San Juan City Hospital-hematology oncology department is one of the major referral centers on the island for initial evaluation and management of AML.

Retrospective study was to identify the most common cytogenetic and molecular abnormalities present in our population.

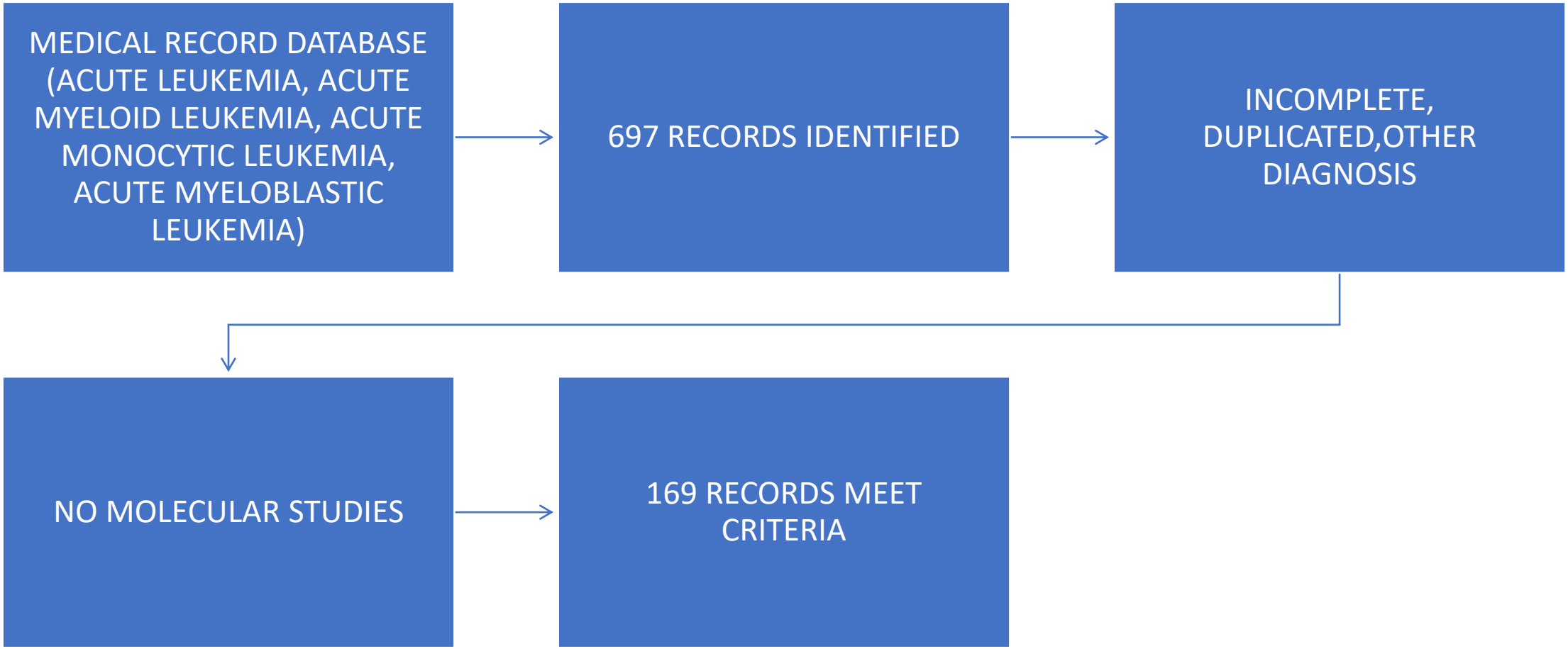
METHODS

Examined the frequency of molecular markers in newly diagnosed (ND) patients with AML. Patients that were at least 18 years of age or older with cytogenetic and molecular analysis.

Period of 4 years (2019-2022).

Demographic, bone marrow biopsy, cytogenetics, and molecular markers were obtained from electronic medical record at our institution with institutional review board approval.

METHODS

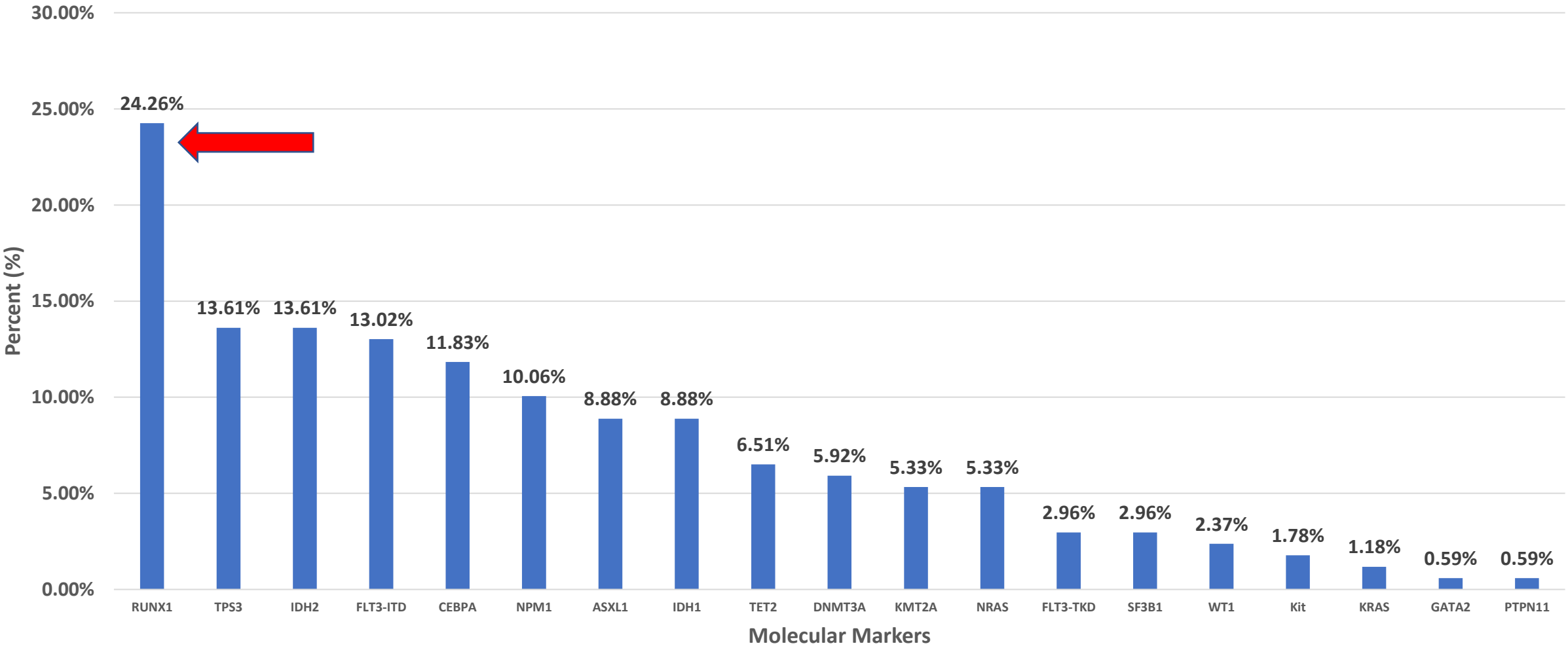

MEDICAL RECORD DATABASE (ACUTE LEUKEMIA, ACUTE MYELOID LEUKEMIA, ACUTE MONOCYTIC LEUKEMIA, ACUTE MYELOBLASTIC LEUKEMIA)
697 RECORDS IDENTIFIED
INCOMPLETE, DUPLICATED,OTHER DIAGNOSIS
NO MOLECULAR STUDIES
169 RECORDS MEET CRITERIA

RESULTS

- 169 PATIENTS
- FEMALE: 56.21%
- MALE 43.79%
- AGE AT DX 58.10


ELN Criteria
32 (18.93%)
49 (28.99%)
88 (52.07%)
Fav
Int
Adv

MOLECULAR MARKERS



RUNX1

Regulation and differentiation of normal hematopoietic stem cells.

Mutation of RUNX1 leads to impaired hematopoiesis and ultimately leukemia.

Poor outcome observed in AML expressing RUNX1.

Germline RUNX1 mutations result in the well-described autosomal-dominant familial platelet disorder with predisposition to hematologic malignancies.

RUNX1 in 5-10% of patients at a median age of 68 years old.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2016 VOL. 374 NO. 23

Genomic Classification and Prognosis in Acute Myeloid Leukemia

Elli Papaemmanuil, Ph.D., Moritz Gerstung, Ph.D., Lars Bullinger, M.D., Verena I. Gaidzik, M.D., Peter Paschka, M.D., Nicola D. Roberts, B.Sc., Nicola E. Potter, Ph.D., Michael Heuser, M.D., Felicitas Thol, M.D., Niccolo Bolli, M.D., Ph.D., Gunes Gundem, Ph.D., Peter Van Loo, Ph.D., Inigo Martincorena, Ph.D., Peter Ganly, B.M., B.Ch., Ph.D., Laura Mudie, B.Sc., Stuart McLaren, B.Sc., Sarah O'Meara, B.Sc., Keiran Raine, M.Sc., David R. Jones, M.Sc., Jon W. Teague, B.Sc., Adam P. Butler, B.Sc., Mel F. Greaves, Ph.D., Arnold Ganser, M.D., Konstanze Döhner, M.D., Richard F. Schlenk, M.D., Hartmut Döhner, M.D., and Peter J. Campbell, M.B., Ch.B., Ph.D.

Other class-defining lesions				
t(x;11), not *MLLT3–MLL*	37 (2)	1.4 (1.0–2.1)	0.06	0.2
ASXL1	70 (5)	1.3 (1.0–1.6)	0.04	0.2
ZRSR2	13 (1)	1.3 (1.0–1.7)	0.04	0.2
RUNX1	133 (9)	1.1 (0.9–1.3)	0.5	0.8
t(9;11), *MLLT3–MLL*	18 (1)	0.8 (0.4–1.4)	0.5	0.7
IDH2^{R172}	39 (3)	0.8 (0.6–1.0)	0.07	0.2
t(8;21), *RUNX1–RUNX1T1*	63 (4)	0.7 (0.4–1.0)	0.03	0.2

Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia

The Cancer Genome Atlas Research Network

Characteristic	Value
Mutation — no./total no. (%)	
NPM1	54/200 (27)
FLT3	56/200 (28)
DNMT3A	51/200 (26)
IDH1 or *IDH2*	39/200 (20)
NRAS or *KRAS*	23/200 (12)
RUNX1	19/200 (10)
TET2	17/200 (8)
TP53	16/200 (8)
CEBPA	13/200 (6)
WT1	12/200 (6)
PTPN11	9/200 (4)
KIT	8/200 (4)
Loss of 5 or del(5q)	16/195 (8)
Loss of 7 or del(7q)	20/195 (10)
11q23	7/195 (4)
t(15;17)	18/195 (9)
t(8;21)	7/195 (4)
inv(16)	12/195 (6)

Open Access Article

Clinical Outcomes and Co-Occurring Mutations in Patients with *RUNX1*-Mutated Acute Myeloid Leukemia

by Maliha Khan [1], Jorge Cortes [1], Tapan Kadia [1], Kiran Naqvi [1], Mark Brandt [1], Sherry Pierce [1], Keyur P. Patel [2], Gautam Borthakur [1], Farhad Ravandi [1], Marina Konopleva [1], Steven Kornblau [1], Hagop Kantarjian [1], Kapil Bhalla [1] and Courtney D. DiNardo [1,*]

[1] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[2] Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS | NOVEMBER 28, 2023

High Frequency of RUNX1 Mutation in Acute Myeloid Leukemia at Puerto Rico

William D. Marrero, Hector R Cintron-Colon, Steven Cruz, Cristian I. Rodriguez-Arocho, William Caceres, Courtney D. DiNardo, Alexis M. Cruz-Chacon

Blood (2023) 142 (Supplement 1): 5985.

https://doi.org/10.1182/blood-2023-173450

RUNX 1

- MEAN AGE: 56.08 (+/- 15.80)

- GENDER

MALE: 46.15%

FEMALE: 53.85%

VAF: 40%

RUNX1 and TP53: 19%

RUNX and complex cytogenetics: 41%

Germline Predisposition

SPECIAL REPORT | SEPTEMBER 22, 2022

Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN

Hartmut Döhner, Andrew H. Wei, Frederick R. Appelbaum, Charles Craddock, Courtney D. DiNardo, Hervé Dombret, Benjamin L. Ebert, Pierre Fenaux, Lucy A. Godley, Robert P. Hasserjian, Richard A. Larson, Ross L. Levine, Yasushi Miyazaki, Dietger Niederwieser, Gert Ossenkoppele, Christoph Röllig, Jorge Sierra, Eytan M. Stein, Martin S. Tallman, Hwei-Fang Tien, Jianxiang Wang, Agnieszka Wierzbowska, Bob Löwenberg

Blood (2022) 140 (12): 1345–1377.

A variant is deemed germline if:

- it is detected in DNA derived from a tissue source not likely to undergo somatic mutation frequently and at a variant allele frequency consistent with the germline (generally 30–60%); or
- it is identified in ≥2 relatives at a variant allele frequency consistent with the germline.

CONCLUSION

YOUNGER PATIENTS WITH AML

HIGH INCIDENCE OF RUNX1

HIGHER VAF FOR RUNX1

POSSIBILITY OF GERMLINE MUTATION, NEED TO BE CONSIDER

Hematology & Oncology

San Juan City Hospital
VA Caribbean Healthcare System