



Algorithmic Diagnostic Approach and Spectrum of Hematological Malignancies in Patients with Germline Predisposition Syndromes

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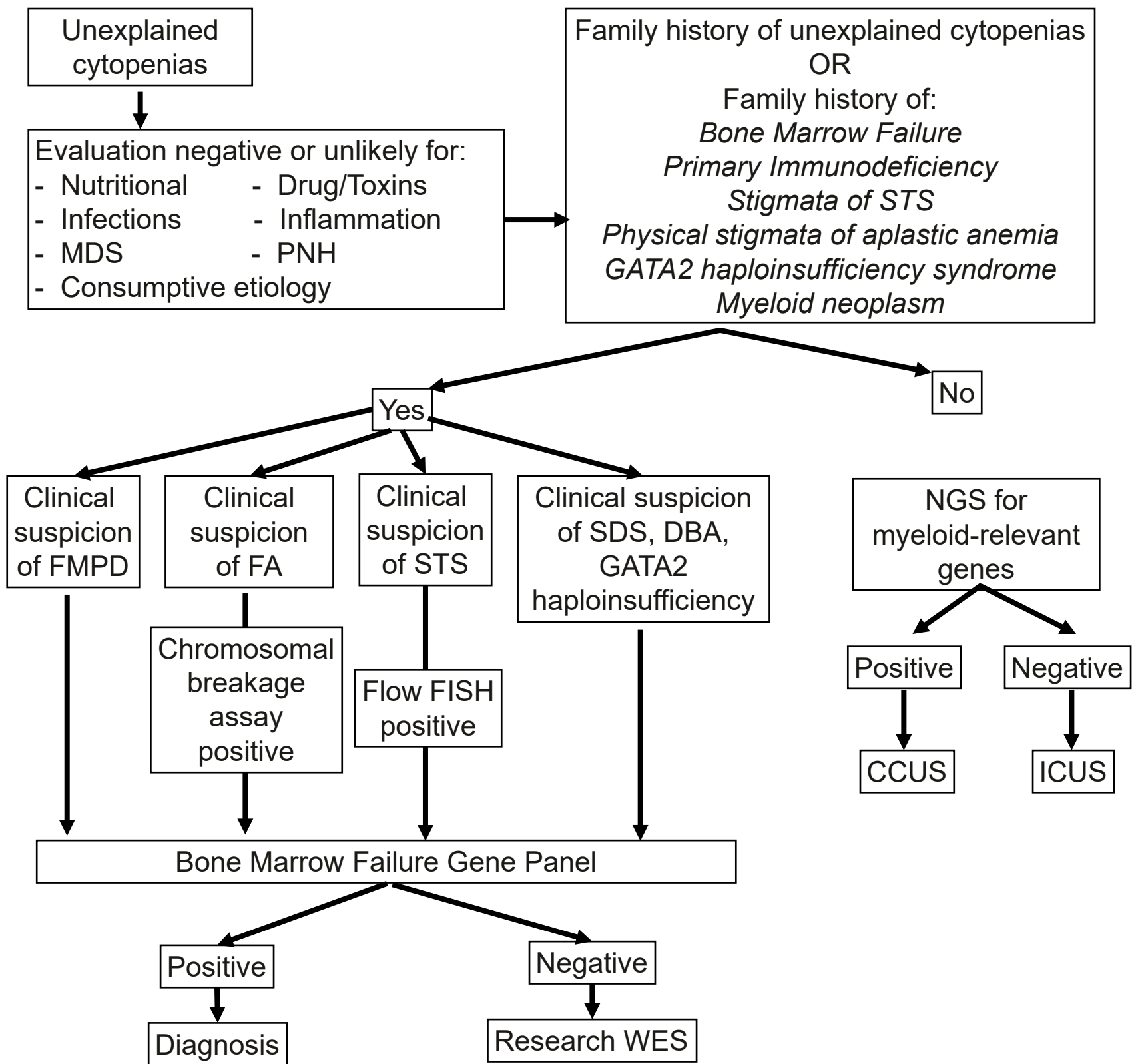
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Abstract

Context: Germline predisposition syndromes (GPS) are genetic disorders that increase the risk of all types of malignancies, with a growing list of genes associated specifically with hematological malignancies. Although many of these conditions have syndromic features, some GPS patients present without identifiable traits. We have established a hematology GPS clinic that uses an algorithmic approach to diagnose GPS patients. **Objective:** To illustrate the heterogeneity of GPS and the benefits of an algorithmic approach to identify non-syndromic GPS patients. **Design:** Medical records were reviewed retrospectively from patients diagnosed with GPS at our institution from 1994 to 2018. Prospectively, we investigated new pediatric and adult patients with GPS from 2017 to 2020 using an algorithmic approach summarized as follows: 1) Evaluation of relevant family history, 2) phenotype-specific functional assays (telomere measurement, breakage assay, erythrocyte adenosine deaminase testing), 3) germline genetic testing through a custom-designed gene panel, and 4) research whole exome sequencing for negative cases. Both a detailed explanation of the algorithm and the methodology for genetic variant interrogation are included in Mangaonkar et al. MC Proc 2019. **Setting:** This study was carried out at the Division of Hematology at Mayo Clinic. **Patients or Other Participants:** GPS was investigated in pediatric and adult patients with one or more first-degree relatives with hematological/visceral malignancies, in those with antecedent thrombocytopenia, or in those with specific features indicative of inherited bone marrow failure (IBMF) (short telomere syndromes, GATA2 haploinsufficiency, Fanconi anemia, Schwachman-Diamond syndrome). **Main Outcomes Measures:** Number of patients diagnosed with GPS both retrospectively and prospectively were tallied and compared. **Results:** A total of 144 individuals were included in the study divided as follows: 27 (19%) presented with hematological malignancy with precedent thrombocytopenia, 28 (19%) without precedent thrombocytopenia, 72 (50%) showed IBMF, and 17 (12%) showed general cancer predisposition syndrome. Eighty-five patients were retrospectively included, while 59 were prospectively evaluated through our algorithmic approach. Among retrospective patients, 7.1% (6 patients) did not present syndromic features, while this value increased to 14.7% (9 patients) when using the algorithmic approach. **Conclusions:** By using an algorithmic approach, we can identify a higher percentage of GPS patients without syndromic features.

Figure1



Diagnostic algorithm followed by our clinic. Adapted from Mangaonkar et al. MC Proc 2019. Nutritional causes include deficiencies of iron, B12, copper, folate, and pyridoxine. A wide array of drugs, toxins, infections, and inflammatory etiology is considered at the discretion of the referring hematologist. Consumptive etiology includes splenomegaly and various causes of intravascular and extravascular hemolysis. CCUS: clonal cytopenia of undetermined significance; DBA: Diamond-Blackfan anemia; FA: Fanconi anemia; Flow-FISH: flow cytometry-fluorescent in situ hybridization; FMPD: familial myeloid predisposition syndromes; GATA2: GATA-binding factor 2; ICUS: idiopathic cytopenia of undetermined significance; MDS: myelodysplastic syndromes; NGS: next-generation sequencing; PNH: paroxysmal nocturnal hemoglobinuria; SDS: Shwachman-Diamond syndrome; STS: short telomere syndrome; WES: whole-exome sequencing

Table 1

Characteristics of patients identified in the study and summary of malignant transformation associated with each predisposition syndrome. AML: acute myeloid leukemia; CCUS: clonal cytopenias of undetermined significance; CHIP: clonal hematopoiesis of indeterminate potential; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia; DLBCL: diffuse large B-cell lymphoma; F: female; JMML: juvenile myelomonocytic leukemia; M: male; MDS: myelodysplastic syndrome; MDS/MPN-U: myelodysplastic/myeloproliferative neoplasm, unclassifiable; MPN-ET: myeloproliferative neoplasm, essential thrombocythemia; NHL: Non-Hodgkin lymphoma; T-ALL: T-cell acute lymphoblastic leukemia; T-LPD: T-cell lymphoproliferative disease; TPLL: T-cell prolymphocytic leukemia

	Syndrome/Phenotype	Total Cases [Probands]	Sex	Median Age at Diagnosis of Predisposition Syndrome (Range)	Malignant Transformations	Median Age at Transformation (Range)	Median Follow-up (Range)	Outcomes
Inherited bone marrow failure syndrome	Bloom Syndrome	1 [1]	F – 1	3 years	Burkitt Lymphoma – 1 DLBCL – 1 CCUS – 1	19 years	502 months	Alive – 1
	Diamond Blackfan Anemia	11 [11]	F – 5 M – 6	3.5 months (2 months – 41 years)	--	--	245 months (0-555)	Alive – 7 Deceased – 4
	Severe Congenital Neutropenia	5 [5]	M – 5	19 years (2-28)	CCUS – 1	28 years	22 months (0-207)	Alive – 5
	Fanconi Anemia	18 [18]	F – 12 M – 6	16 years (7 months – 61 years)	AML – 4 MDS – 2	19.5 years (1-32)	24 months (0-345)	Alive – 14 Deceased – 4
	Schwachman-Diamond Syndrome	5 [4]	M – 5	8.5 years (9 months – 17 years)	AML – 1 CCUS – 1	21 years (13-29)	34 months (0-352)	Alive – 4 Deceased – 1
Hematologic predisposition syndrome with antecedent thrombocytopenia	Short Telomere Syndrome	32 [28]	F – 12 M – 20	30 years (2-75)	AML – 1 MDS – 2	54.5 years (41-65)	15.5 months (0-302)	Alive – 23 Deceased – 9
	Thrombocytopenia 2 (ANKRD26)	6 [2]	F – 2 M – 4	51 years (15-72)	CMML – 1 MDS – 1	67 years (62-72)	18.5 months (0-64)	Alive – 5 Deceased – 1
	Thrombocytopenia 5 (ETV6)	2 [2]	M – 2	26 years (23-29)	--	--	35.5 months (1-70)	Alive – 2
	X-linked Thrombocytopenia (GATA1)	1 [1]	M – 1	Unknown	--	--	Unknown	Alive – 1
	Congenital Amegakaryocytic Thrombocytopenia	3 [1]	M – 3	10 years (2-14)	--	--	17 months	Alive – 3
Hematologic predisposition syndrome without antecedent thrombocytopenia	RUNX1-Familial Platelet Disorder	15 [11]	F – 6 M – 9	56 years (1 month – 71 years)	AML – 2 CHIP – 1 MDS – 2 CCUS – 1 CMML – 3 MDS – 1	63.5 years (3-71)	9.5 months (0-120)	Alive – 15
	Noonan Syndrome-like Disorder	1 [1]	F – 1	10 years	--	--	7 months	Alive – 1
	Familial AML	1 [1]	F – 1	35 years	AML – 1	24 years	2 months	Alive – 1
	Familial Myeloproliferative/ Lymphoproliferative Neoplasms (DDX41)	10 [6]	F – 4 M – 6	61 years (35-79)	Follicular NHL – 1 AML – 3 MDS – 3	63 years (46-78)	2 months (0-13)	Alive – 9 Deceased – 1
	GATA2-mediated susceptibility to MDS and AML	16 [10]	F – 10 M – 6	30.5 years (4 months – 56 years)	AML – 5 MDS – 4 CCUS – 2	30 years (7-50)	42.5 months (0-116)	Alive – 12 Deceased – 4
General cancer predisposition syndrome	Heterozygous Germline ATM Predisposition	3 [3]	M – 3	44 years (37-59)	DLBCL – 1 T-PLL – 1	50.5 years (42-59)	3 months (0-11)	Alive – 1 Deceased – 2
	Ataxia-Telangiectasia	7 [7]	F – 4 M – 3	4.5 years (2-8)	Burkitt Lymphoma – 1 Follicular NHL – 1 T-ALL – 1 T-LPD – 1	17 years (11-21)	104.5 months (16-230)	Alive – 3 Deceased – 4
	CHECK2-related Cancer Predisposition Syndrome	2 [2]	F – 2	35.5 years (35-36)	CML – 1	35 years	8.5 months (5-12)	Alive – 2
	Neurofibromatosis Type 1	1 [1]	M – 1	Unknown	JMML – 1	4 years	Unknown	Alive – 1
	Nijmegen Breakage Syndrome	1 [1]	M – 1	1 year	--	--	179 months	Alive – 1
	Melanoma-Pancreatic Cancer Syndrome	1 [1]	M – 1	59 years	CMML – 1	69 years	128 months	Alive – 1
	Li-Fraumeni Syndrome	2 [2]	F – 2	40 years (27-53)	MPN-ET – 1 MDS – 1	40.5 years (27-54)	50 months (3-97)	Alive – 2

Figure 2

Genes carrying genetic variants identified in the cohort described, classified by function and subcellular compartment

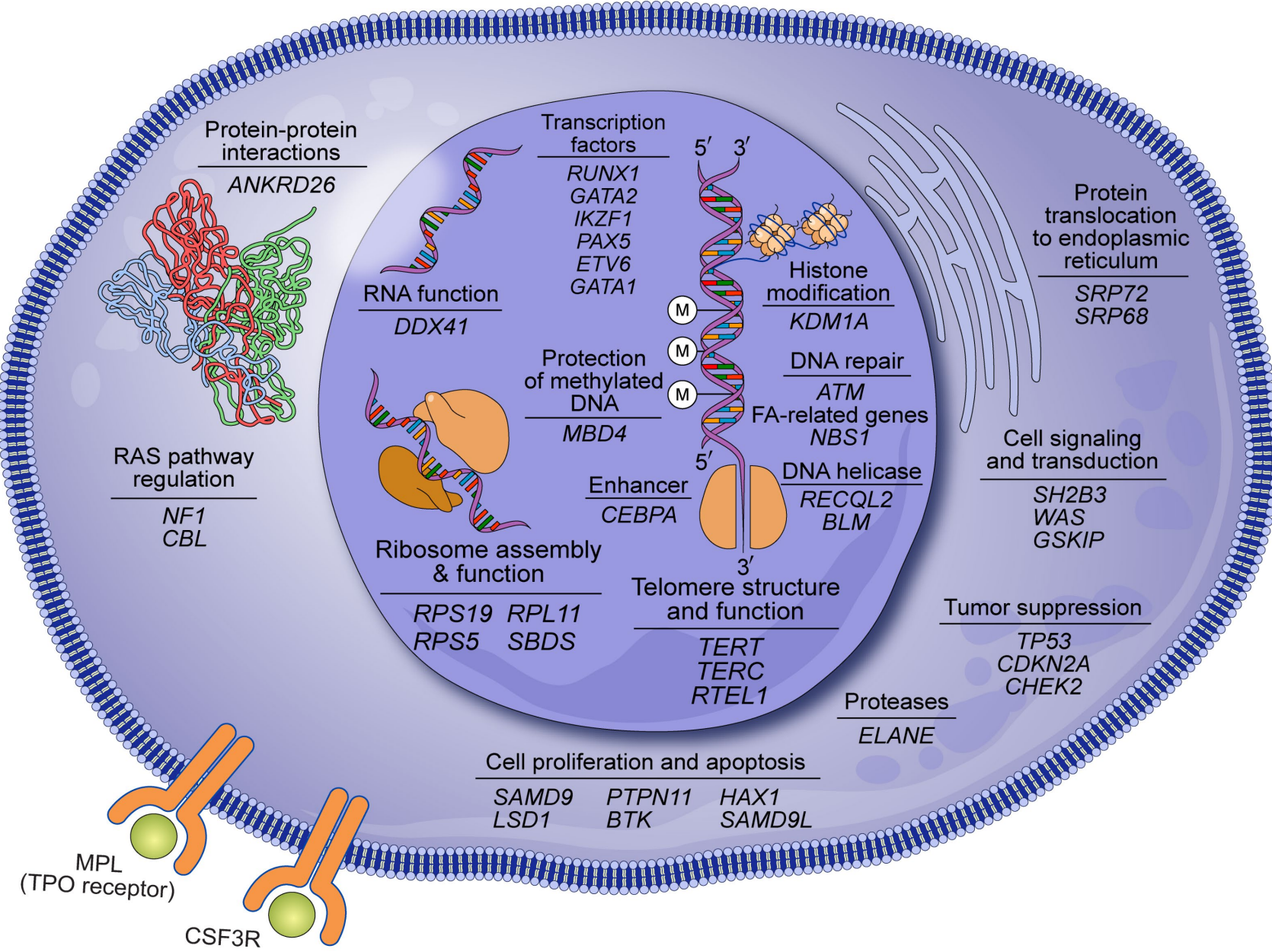
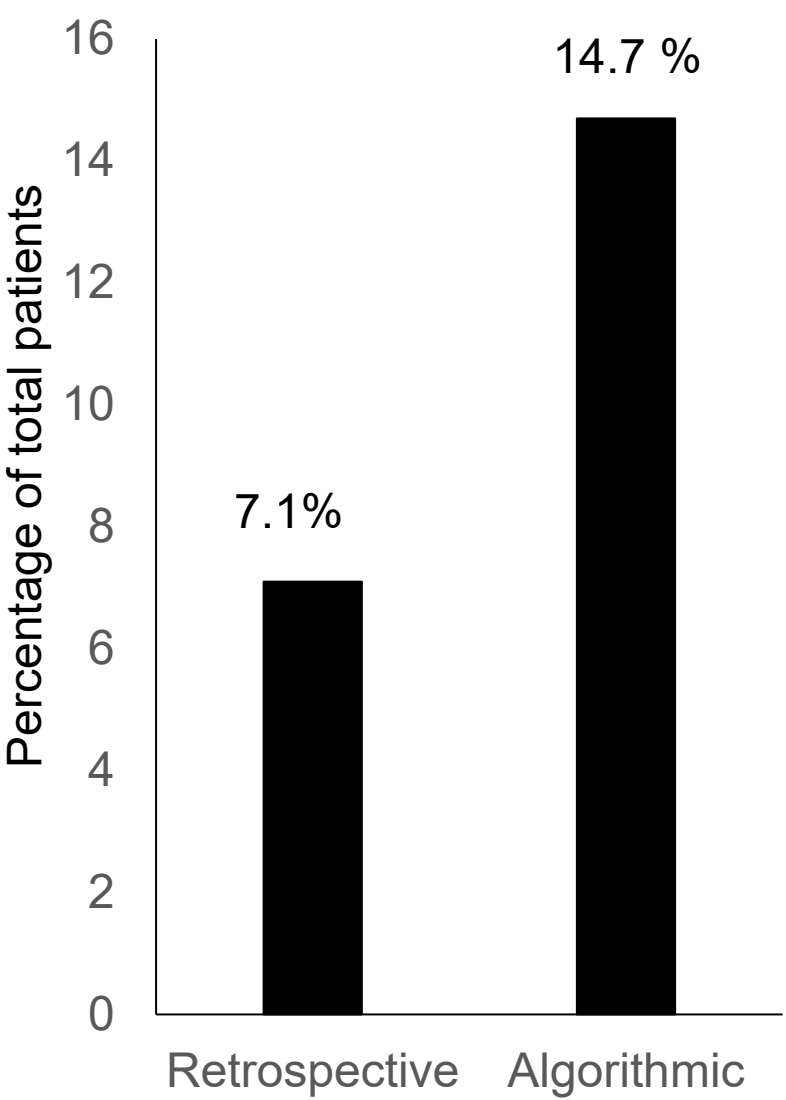


Figure 3

Using an algorithmic approach, we were able to identify 14.7% of non-syndromic patients with genetic predisposition syndrome, compared to 7.1% of patients analyzed retrospectively



Conclusion

By using an algorithmic approach, we can identify a higher percentage of genetic predisposition syndrome patients without syndromic features.

Acknowledge

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References

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- St Martin et al. Am J Hematol, 2021