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CLINICAL APPLICABILITY OF PROPOSED ALGORITHM FOR IDENTIFYING INDIVIDUALS AT RISK FOR HEREDITARY HEMATOLOGIC MALIGNANCIES

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Over the past decade, more than 12 genes have been identified to cause hereditary predispositions to hematologic malignancies. These syndromes are characterized by an increased risk to develop myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or aplastic anemia (AA) at young ages, with various phenotypic features including peripheral cytopenias, immune dysfunction and skeletal defects. In 2013, Churpek et al. proposed a referral algorithm which consists of certain criteria for identifying leukemia patients who may benefit from genetic assessment for these hereditary syndromes. These criteria assess personal history of cytopenias, skin or nail abnormalities, immune deficiencies/atypical infections, and other associated clinical characteristics. The algorithm also assesses family history of leukemia and personal/family history of other malignancies.

Our study aimed to assess the applicability of these criteria on an unselected population of adults with leukemia by retrospective chart review at The University of Texas M.D. Anderson Cancer Center. These patients presented for initial consultation from March 1, 2014 to December 31, 2014. Six-hundred and eight individuals diagnosed with MDS/AML/AA were included in this study. Key demographic information was obtained from a clinical database maintained by the Department of Leukemia. The median age at diagnosis was 67 years, 387 (64%) were male, and at the time of data collection, 315 (51.8%) individuals were alive. Of the 608 individuals in this study, 334 (54.9%) were diagnosed with AML, 199 (32.7%) with MDS, 59 (9.7%) with MDS/MPD, and 16 (2.6%) with AA.

Regarding clinical/medical record documentation of referral criteria, three hundred and sixty-four (59.9%) individuals reported at least one first or second-degree relative with cancer. Thirty-one (5.1%) individuals reported a family history of leukemia, which was also the most consistently reported criteria in the medical record (n=580, 95.4%). Overall, 406 individuals (66.8%) had insufficient documentation to determine whether any criteria were met. Two hundred and two (33.2%) individuals met at least one of the proposed criteria for genetic counseling referral; however, only nine received a referral (4.5%) to genetic counseling. Increased documentation of the presence or absence of phenotypic features associated with these hereditary syndromes is necessary to better assess the applicability of these criteria, and to ensure that individuals receive appropriate referral for cancer genetics risk assessment.

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Introduction

Leukemia is the tenth most common malignancy in the United States with an estimated 60,140 new cases diagnosed in 2016 [1]. Familial occurrences of leukemia have been documented in the literature and first-degree relatives of individuals with leukemia carry an estimated 2.5-6 fold increased lifetime risk of leukemia depending on the type of leukemia in the family [6, 7]. In fact, approximately 10-20% of myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and aplastic anemia (AA) are related to newly-described hereditary predisposition syndromes [2-5].

Over the past decade, clinical investigations into families with multiple close relatives with leukemia have identified more than a dozen genes related to inherited predispositions to MDS and AML [3]. To date, genes associated with inherited MDS/AML syndromes include *ANKRD26, ATG2B, CEBPA, DDX41, ETV6, GATA2, GSKIP, RUNX1, SH2B3, SRP72* and *TP53*. Additional predisposition genes are also related to the inherited bone marrow failure syndromes (IBMFS), including Fanconi anemia (FA) caused by mutations in the Fanconi complementation groups (*FANCA, BRCA2, PALB2*, etc.) and dyskeratosis congenita (DC) caused by mutations in telomere maintenance genes (*TERT, TERC*) which have been associated with increased risks for AA, MDS, and AML. Together, these syndromes are characterized by significantly increased risk to develop MDS/AML/AA (30-100% lifetime risk) at younger ages (4-40 years old on average), with phenotypic characteristics including thrombocytopenia, other peripheral cytopenias, immune dysfunction, skeletal defects, and clinical bleeding in both adults and children [8, 9]. Additional phenotypes include primary lymphedema, deafness, cutaneous warts, low CD4/CD8 T cell ratio and mycobacterial infections [10-12], which can be seen in patients with germline *GATA2* mutations.

Recently, research has revealed that previously described conditions like FA and DC have more variable phenotypic expressivity than previously described, with 25-40% of individuals with FA, and 10-25% of individuals with DC, having no physical characteristics suggestive of these conditions [13, 14]. Additionally, individuals with IBMFS who do not show classic physical characteristics are more likely to have delayed diagnosis of MDS/AML/AA, often in adulthood [13]. This variability makes IBMFS difficult to diagnose in individuals who do not display the characteristic phenotype. Timely diagnosis is critical for treatment of MDS/AML/AA, as patients with IBMFS and familial AML/MDS syndromes have poor outcomes from hematopoietic stem cell transplantation (HSCT) due to use of a related donor with the same germline mutation and/or increased toxicity from high-intensity transplant conditioning regimens [15-17].

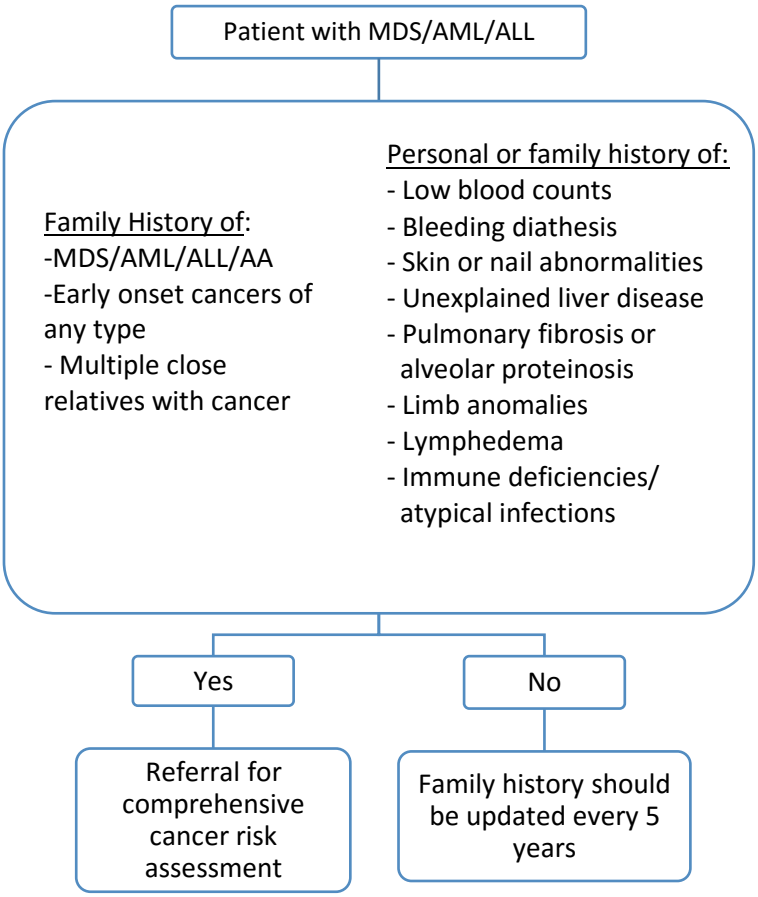
The complications arising from HSCT transplantation from a related donor illustrates the importance of a thorough family history for these at risk individuals. In 2014, the American Society of Clinical Oncology (ASCO) published an expert opinion statement regarding the collection and use of family history in oncology assessments and suggested that the minimum family history obtained should include cancer history of first- and second-degree relatives, including the type of primary cancer and age of diagnosis [14]. Although not all patients report an accurate family history, a study by Ziogas and Anton-Culver showed that most patient reports of family history are reliable, especially when reporting cancer history of first-degree relatives [18]. According to the ASCO statement, clinicians should be able to assess a family history to help determine if further evaluation for hereditary predisposition is warranted; however, a study by Sussner et al. revealed that only 1.7% of surveyed physicians felt they could accurately interpret a family history and make

appropriate recommendations [19, 20]. While previously considered exceedingly rare, the recent discovery of multiple hematologic malignancy predisposition syndromes requires increased clinical provider awareness. For optimal identification and appropriate referral of patients at risk of hereditary cancer syndromes, an accurate, detailed family history is critical to identify at-risk patients and families, as well as to help guide treatment and management.

With the identification of these predisposition genes, researchers have sought to understand how frequently these germline mutations occur in patients with leukemia. DiNardo et al. identified germline mutations associated with a hereditary cancer syndrome in 18% of patients with hematologic malignancies referred for genetic testing [2, 21]. Another study by Churpek et al. in 2016 illustrated a similar frequency of germline mutations (11-24%) in patients with hematologic malignancies referred for genetic testing [2]. Notably, germline mutations in hematologic malignancies appear to show similar prevalence to germline mutations in solid tumors such as breast and colon cancers for which genetic risk assessment has become routine.

In 2013, Churpek et al. proposed clinical detection and management criteria for patients and family members with familial MDS/AML/AA predisposition syndromes (Figure 1).

Figure 1. Proposed Algorithm for identifying individuals for referral for comprehensive cancer risk assessment



These criteria assess personal or family history of cytopenias, the presence of skin, nail, or limb abnormalities, unexplained liver disease, pulmonary fibrosis/alveolar proteinosis, lymphedema and immune deficiencies/atypical infections. Additionally, the algorithm assesses family history of acute lymphocytic leukemia (ALL)/MDS/AML/AA and other malignancies. Individuals meeting these criteria warrant referral to genetic counseling for comprehensive cancer risk assessment.

To date, no studies have sought to evaluate the clinical applicability of these criteria to an unselected adult population of leukemia patients. We aim to assess the proposed algorithm against a large unselected cohort of patients with MDS/AML/AA to determine if

the characteristics needed to identify these patients for genetic counseling and risk assessment are reported in the medical record. Identifying these individuals is of utmost importance for personalized treatment strategies to maximize positive outcomes and minimize toxicity.

Materials and Methods

Patient Selection

We identified 613 individuals seen as new patients in the Department of Leukemia at The University of Texas M.D. Anderson Cancer Center between March 1, 2014 to December 31, 2014 with a diagnosis of MDS, AML, or AA. Five individuals were excluded either due to age (<18 years old) at the time of their initial appointment, no leukemia diagnosis, or no medical records available for review, leaving 608 individuals for analysis. Medical history and pathology were obtained from a prospectively-maintained clinical database within the Department of Leukemia. Personal and family history, genetic testing performed, and referral criteria from the Churpek et al. algorithm were obtained by electronic medical record chart review. A somatic 28-gene panel was performed for all 608 patients and this information was used to assess for double mutant (dm) somatic mutation carriers. To ensure adequate data capture, chart review procedure included assessment of the first five and last five leukemia department provider's notes, and the leukemia department providers' history and physical notes (H&P).

Statistical Analyses

Patient demographics, clinicopathologic characteristics, and personal and family history variables were analyzed. We evaluated 608 patients with MDS/AML/AA for the proposed criteria (Figure 1) to determine if they met the proposed criteria, and whether eligible patients were recommended for cancer genetic risk assessment. The statistical significance between cohorts was determined using the chi-squared test and Fisher's exact test for categorical variables, Wilcoxon rank sum test for continuous variables and nonparametric test for trend for ordered variables. All analyses were performed in STATA (v.13.1, College Station, TX). *P*-value <0.05 was set for statistical significance. This study was approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center and by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston. A waiver of informed consent was obtained.

Results

Demographics

Clinical data and demographic information from 608 individuals diagnosed with AML/MDS/AA seen at our institution from March 1, 2014-December 31, 2014 are described in Table 1.

Table 1. Patient Demographics (n=608)

Clinical Characteristics	n (%)
Median (IQR), age at diagnosis, years	67 (56-73)
Male sex	387 (64)
Vital status, living	315 (51.8)
Race/Ethnicity	
White	478 (78.6)
Hispanic	47 (7.7)
Black	38 (6.3)
Unknown	22 (3.6)
Asian	18 (3)
Other	5 (0.8)
Leukemia Diagnosis	
AML	334 (54.9)
MDS	199 (32.7)
MDS/MPD	59 (9.7)
AA	16 (2.7)
Personal History of Cancer	
None	410 (67.4)
Prostate	37 (6.1)
Breast	32 (5.3)
Basal cell carcinoma	32 (5.3)
Lymphoma	29 (4.7)
Colon	12 (2.0)
Other	56 (9.2)
Family History of Cancer*	
≥1 FDR	304 (50%)
≥1 SDR)	121 (19.9%)
None	183 (30.1%)

IQR: Inter Quartile Range
AML: Acute Myeloid Leukemia; MDS: Myelodysplastic syndrome; MPD: Myeloproliferative disorder; AA: Aplastic anemia
FDR: First-degree relative; SDR: Second-degree relative
*Family history of cancer does not include family history of hematologic malignancies

The median age at diagnosis was 67 years, 387 (64%) were male, and at the time of data collection, 315 (51.81%) individuals were still living. Four hundred and seventy-eight (78.6%) individuals in the cohort reported their ethnicity as non-Hispanic white. The majority of patients in our cohort had AML (n=334, 54.9%). Forty-three (7.1 %) individuals

had favorable MDS/AML cytogenetics, 278 (45.7%) had intermediate cytogenetics, and 174 (28.6%) had unfavorable cytogenetics. One hundred and thirteen (18.6%) individuals had unknown cytogenetics results.

One hundred and ninety-eight (32.6%) individuals had a personal history of an additional primary cancer diagnosis prior to their leukemia diagnosis. Breast cancer, prostate cancer, and basal cell carcinoma of the skin were the three most common, comprising 51.1% of total prior primary malignancies reported. For analysis of somatic mutation status, 29 (4.8%) individuals were found to have $\geq$2 somatic mutations in one of three genes known to be associated with hereditary hematologic malignancies, *CEBPA, RUNX1* and *GATA2*.

Criteria documentation and cancer genetics referral

We evaluated the presence, absence, or unreported status of the referral criteria proposed by Churpek et al. among the 608 patients [Table 2].

Table 2. Documentation of the evaluated personal and family history criteria (n=608)

	Present n (%)	Absent n (%)	Unreported n (%)
Personal History Criteria			
Skin/nail abnormalities	39 (6.4)	524 (86.2)	45 (7.4)
Anemia	19 (3.1)	259 (42.6)	330 (54.3)
Thrombocytopenia	23 (3.8)	235 (38.7)	350 (57.5)
Neutropenia	2 (0.3)	124 (20.4)	482 (79.3)
Limb anomalies	7 (1.2)	70 (11.5)	531 (87.3)
Pulmonary fibrosis/ alveolar proteinosis	22 (3.6)	7 (1.2)	579 (95.2)
Unexplained liver disease	11 (1.8)	10 (1.7)	587 (96.5)
Lymphedema	10 (1.6)	2 (0.3)	596 (98.1)
Immune deficiencies/atypical infections	5 (0.8)	3 (0.5)	600 (98.7)
Family History Criteria			
Leukemia	31 (5.1)	549 (90.3)	28 (4.6)
Cancer	364 (59.9)	216 (35.5)	28 (4.6)
Other Cytopenias	11 (1.8)	10 (1.6)	587 (96.6)
Thrombocytopenia	7 (1.2)	7 (1.2)	594 (97.6)

Personal history of blood count abnormalities had an unreported frequency ranging from 54.3% (n=300) for anemia to 79.2% (n=482) for neutropenia. Physical characteristics (skin/nail abnormalities, unexplained liver disease, pulmonary fibrosis/alveolar proteinosis, limb anomalies, lymphedema, immune deficiencies/atypical infections) had the highest unreported rate. Prior history of immune deficiencies/atypical infections was unreported for 98.7% (n=600) of individuals, while skin/nail abnormalities were usually reported (n=563, 92.6%). Only 3.5% (n=21) of individuals had documentation for family history of other cytopenias. Similarly, only 2.4% (n=14) had family history of thrombocytopenia reported. The criterion with the highest reported documentation was family history of leukemia, noted in 95.4% (n=580) of individuals.

Family history of MDS/AML/AA

Thirty-one (16.2%) individuals who met criteria reported a family history of MDS/AML/AA or acute lymphoblastic leukemia (ALL) (Table 3).

Table 3. Family History of Leukemia (n=31)

Cancer Family History	FDR (n=17) n, %	SDR (n=17) n, %
AML	2 (6.5)	3 (9.7)
MDS	3 (9.7)	1 (3.2)
ALL	0 (0)	1 (3.2)
AA	1 (3.2)	1 (3.2)
Unknown leukemia	11 (35.5)	11 (35.5)

FDR, first-degree relative; SDR, second degree relative
AML: Acute Myeloid Leukemia; MDS: Myelodysplastic syndrome; MPD: Myeloproliferative disorder; AA: Aplastic anemia

Two individuals reported 2 first-degree relatives with leukemia, and two individuals reported 2 second-degree relatives with leukemia, totaling 34 family members with reported hematologic malignancies in this cohort. The majority of reported family members with leukemia did not have a specified subtype of leukemia documented. Five (16.1%) had a first or second-degree relative with AML, four (12.9%) with MDS and two with AA (6.5%).

Comparison between individuals who met criteria and those who could not be determined

Overall, 406 (66.8%) individuals had insufficient documentation to determine whether any criteria were met. Two hundred and two (33.2%) individuals met at least one of the proposed criteria for genetic counseling referral. Due to insufficient documentation, no individuals were classified as not meeting criteria [Table 4].

Table 4. Comparison between patients who met criteria and could not be determined

Characteristics	Met Criteria (n=202) n (%)	Could not be Determined (n=406) n (%)	*p*-value
Median (IQR) age at diagnosis, years	66 (56-73)	67 (56-73)	0.407
Male sex	126 (62.4)	261 (64.3)	0.655
Race			0.475
White/Caucasian	163 (80.7)	315 (77.6)	
Unknown	21 (10.4)	48 (11.8)	
Black	12 (5.9)	26 (6.4)	
Asian	6 (3)	12 (3)	
Middle Eastern	0 (0)	5 (1.2)	
Diagnosis			0.250
AML	100 (49.5)	234 (57.6)	
MDS	76 (37.6)	123 (30.3)	
MDS/MPD	20 (9.9)	39 (9.6)	
AA	6 (3)	10 (2.5)	
Personal History of Cancer			
Breast	18 (8.9)	14 (3.4)	0.006
Prostate	11(5.4)	26 (6.4)	0.721
Lymphoma	11(5.4)	18 (4.4)	0.553
Basal Cell Carcinoma	10 (5.0)	22 (5.4)	1.00
Other	27 (13.4)	41 (10.1)	
None	125 (61.9)	285 (70.3)	
Family History of Cancer			
BREAST			
FDR	30	39	0.058
SDR	13	19	0.441
LUNG			
FDR	25	35	0.151
SDR	16	17	0.060
PROSTATE			
FDR	24	27	0.042
SDR	5	8	0.768
COLON			
FDR	18	19	0.048
SDR	7	15	1.000

IQR: Inter Quartile Range
AML: Acute Myeloid Leukemia; MDS: Myelodysplastic syndrome; MPD: Myeloproliferative disorder; AA: Aplastic anemia
FDR: First-degree relative; SDR: Second-degree relative
*Family history of cancer does not include family history of hematologic malignancies

There was no significant difference between patient's age or sex at diagnosis and whether they met criteria (p=0.407, p=0.655). Seventy-seven (38.1%) individuals who met criteria had a prior malignancy. Prior history of breast cancer was associated with whether an individual met criteria for cancer genetics referral (p=0.006). For our study, those who met criteria solely based on their personal history of breast cancer were diagnosed with breast cancer before age 45 as individuals diagnosed with breast cancer before age 45 meet National Comprehensive Cancer Network (NCCN) guidelines for genetic risk assessment.

Five hundred and eighty (95.4%) patients had documentation of family history information in their medical record. Three hundred and four (50%) individuals had at least one first-degree relative (FDR) with cancer documented in their medical record. One hundred and twenty-one individuals (19.9%) had at least one second-degree relative (SDR) with cancer documented in their medical record [Table 1]. Individuals that had a first- and second-degree relative with the same malignancy were included in both calculations. The most commonly documented malignancies among FDRs were breast, lung, and prostate cancers, comprising 41.5% of total malignancies reported among FDRs (n=180). Additionally, having a FDR with prostate, colon, or ovarian cancer was a significant factor in whether or not an individual met criteria (p=0.042, p=0.048, p=0.000). The most commonly reported malignancies among SDRs were breast, lung, and colon cancers, comprising 50.9% of total malignancies reported in SDRs (n=87).

Referral to genetic counseling

Of the 202 individuals that met at least one criteria for a cancer genetics referral according to the proposed algorithm, 166 (82.2%) met one criteria, 30 (14.8%) met 2, 5 (2.5%) met 3, and only one patient (0.5%) met 4 criteria [Table 5].

Table 5. Referral criteria and subsequent referral to genetic counseling (n=202)

	Number of criteria met			
	1	2	3	4
Referred to genetics (n=9)	4 (2.4)	4 (13.3)	1 (20)	0 (0)
Not referred to genetics (n=193)	162 (97.6)	26 (86.7)	4 (80)	1 (100)

p=0.002

Only 9 patients (4.5%) who met criteria received a referral for clinical cancer genetics risk assessment The difference between number of criteria met and the likelihood for subsequent genetics referral was statistically significant (p=0.002) with those meeting more criteria being less likely to have been referred to genetics.

Additional Criteria

In addition to the criteria proposed by Churpek et al., we assessed the somatic mutation profile within this MDS/AML/AA cohort. In our cohort, 29 (4.8%) individuals were found to have $\geq$2 somatic mutations in three genes known to be associated with hereditary hematologic malignancies and tested within our current myeloid malignancy panel: *CEBPA*, *RUNX1* and *GATA2*. Of 10 individuals with $\geq$2 *CEBPA* mutations, only four met one of the proposed Churpek et al. criteria. One patient with biallelic *GATA2* mutations met two criteria. Of the 18 patients with $\geq$2 *RUNX1* mutations, five met one of the referral criteria. We also assessed young age at MDS/AML/AA diagnosis, specifically individuals diagnosed

prior to age 40. In our cohort, 66 (10.85%) individuals were diagnosed ≤40 years. Of those, only 17 (%) met at least one of the Churpek criteria.

Discussion

We reviewed the medical records of 608 individuals to evaluate the criteria proposed by Churpek et al. to a large unselected adult leukemia population. The median age of diagnosis for our cohort (67 years) is consistent with the median age of diagnosis of leukemia within the general population (66 years [1]). Of note, in the two years since these individuals presented to The University of Texas M.D. Anderson Cancer Center, only 51.8% are alive, consistent with the poor long-term outcomes of MDS and AML in older patients, which have a 5-year survival rate of 26.9% [1]. The high mortality rate within a short time period illustrates the importance of prompt assessment and referral for genetic counseling and testing in this unique cancer population. Due to the otherwise low documentation of the majority of the referral criteria, individuals in this cohort met referral criteria based primarily on a personal/family history of malignancies. Those with a personal history of breast cancer, or a FDR diagnosed with prostate, colon or ovarian cancer, were more likely to meet criteria. This is consistent with current national guidelines that recommend genetic counseling referrals based on family history of these specific malignancies (i.e. *BRCA1* and *BRCA2* evaluation). While not directly related to assessing for inherited leukemia syndromes, it is important to note that personal and family history of non-hematologic malignancies are referenced in the Churpek algorithm and should be assessed according to the ASCO guidelines, and followed up by appropriate cancer genetics evaluation (14).

The criteria proposed by Churpek et al. are the only published screening criteria to help identify individuals at increased risk for inherited leukemia predisposition syndromes. National society guidelines, like those from the National Comprehensive Cancer Network (NCCN), are lacking. The absence of published guidelines and the relative novelty of these hereditary leukemia syndromes likely contributed to the poor documentation of these criteria items in the medical record. As illustrated in Table 5, the vast majority of patients in this cohort have multiple missing variables, including personal or family history characteristics such as thrombocytopenia, limb anomalies and immune deficiencies/atypical infections. This could partially be due to study design wherein information had to be stated unequivocally (i.e. documentation of pertinent negatives) to be considered present or absent from the medical record. Interestingly, the two most frequently reported criteria were family history of leukemia and personal history of skin/nail abnormalities. Typically, family history and physical exam are integral to an initial medical consultation. Additionally, physical exam documentation is a required component of History & Physical medical record documentation and therefore may have contributed to the increased reporting of skin/nail abnormalities.

Only 4.5% of patients who met at least one-referral criteria received a genetics referral. The trends seen in Table 6 illustrate that as the number of criteria increased, so did the percentage of patients referred. The lack of cancer genetics referrals, coupled with the lack of documented personal and family history criteria makes it difficult to assess the true applicability of the criteria.

One principal researcher reviewed all 608 charts and human error cannot be excluded as a possible limitation of this study. Additionally, study design was a possible limitation to this study. Only the first five and last five leukemia providers' notes and H&Ps were

examined for review. Some clinical documents, as well as charts from other specialties, were not reviewed. Criteria may have been documented in those charts but not obtained for this study. Racial demographics were skewed and not representative of the general population. Additionally, this study was solely comprised of individuals seen at The University of Texas M.D. Anderson Cancer Center, a tertiary referral center, and may not be representative of patients diagnosed with leukemia across the United States. However, this did provide a large population of individuals with MDS/AML/AA from which to analyze.

In addition to the criteria proposed by Churpek et al., we assessed the somatic mutation profile within this MDS/AML/AA cohort. Current literature suggests that about 7-11% of somatic double mutant *CEBPA (*dm*CEBPA)* mutations are actually present in the germline [22, 23]. While the exact frequency of somatic *RUNX1* mutations found to be germline is unknown, a two hit hypothesis for *RUNX1* mutations has been proposed that could lead to the development of acute leukemia [24]. This is important considering 6 individuals in this study with biallelic *CEBPA* mutations met no additional testing criteria, but have an increased risk for an inherited susceptibility. Based on previous estimates, it is likely that at least one individual in the cohort had a germline *CEBPA* mutation. We propose that considering ≥2 somatic mutations in *CEBPA, RUNX1* and *GATA2* as an additional referral criterion may be warranted, as it would potentially increase the detection of individuals who otherwise have no additional indications for genetic risk assessment. Additionally, the presence of a variant allele frequency suggestive of germline inheritance (~50%) is an important question for future analysis regarding identifying patients at risk for germline mutations. We also assessed young age at MDS/AML/AA diagnosis, specifically individuals diagnosed prior to age 40 since individuals with IBMFS are at a significantly

increased risk to develop BMF before the age of 40 [16]. We propose that age dx $\leq$40 and/or the presence of $\geq$2 somatic mutations should be considered as additional criteria when assessing leukemia patients for referral for cancer genetics risk assessment.

Suggestions to increase documentation include incorporating criteria assessment into the EMR, or obtaining information directly from patients via a short intake form/questionnaire. Further studies need to assess the applicability of these criteria and may benefit from including suggested additional criteria like molecular testing results and age of diagnosis prior to age 40. Further studies are needed to determine which combination of criteria yields the highest association with subsequent positive germline testing results. National guidelines for referral criteria for inherited leukemia susceptibility syndromes would likely increase detection of families with hereditary predispositions to hematologic malignancies.

Conclusion

One-third of individuals met at least one criteria for a cancer genetics referral based on the proposed algorithm, while the remainder could not be determined based on insufficient information present in the medical record. Ultimately, only nine individuals presenting during this nine-month interval meeting criteria received genetic counseling referrals. The presence or absence of proposed criteria must be documented in the medical record in order to assess clinical applicability in the leukemia population. Increased and timely detection of these families is important, as it would allow for more tailored transplant donor selection, treatment, anticipatory guidance counseling, and increased screening for at risk family members.

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