Evaluation of Testing of Acute Leukemia Samples

Survey Result From the College of American Pathologists

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Purpose.—To survey physicians describing their current practice of test ordering in the diagnosis of acute leukemia (AL). The classification includes 23 subtypes of acute myeloid leukemia (AML) and 2 provisional entities, 5 subtypes of acute myeloid leukemia (ALL) and 4 provisional entities, 9 subtypes of acute lymphoblastic leukemia (ALL) and 14.2% (33) for ALL. In addition, fluorescence in situ hybridization studies were routinely performed by 81.2% (190 of 234) of respondents for AML and 85.0% (198 of 233) of respondents for ALL; other molecular studies were performed by 78.2% (183) for AML and 54.9% (128) for ALL; immunohistochemistry by 44.9% (105) for AML and 47.6% (111) for ALL; and cytochemistry by 24.8% (58) for AML and 14.2% (33) for ALL.

Conclusions.—While flow cytometry and karyotyping are routinely reported as being performed for the diagnosis of AL, there is marked variation in the reporting of testing patterns for other genetic studies, immunohistochemistry, and cytochemistry.

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**MATERIALS AND METHODS**

A baseline survey was designed by an expert panel from the CAP tasked with evaluating the impact of laboratory practice guidelines with a cooperative agreement from the Centers for Disease Control and Prevention (CDC). The survey development, analysis, and this article were supported by Cooperative Agreement S NU47OE000057-04-00 funded by the US CDC. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC or the Department of Health and Human Services. The cooperative agreement with CDC required preapproval of the survey instrument by the US Office of Management and Budget (OMB No. 0920-1067). The survey was conducted electronically through SurveyMonkey (Palo Alto, California) and included 23 questions on specimen types evaluated, ancillary testing performed, reporting practices, and participant demographics (see supplemental digital content at www.archivesofpathology.org in the August 2017 table of contents). Members of professional societies, including the CAP, Society for Hematopathology, ASH, and the European Association for Haematopathology, were asked to complete a survey describing their current practice of test ordering in the evaluation of AL. Members of the CAP who self-identified as hematopathologists were sent emails containing a link to the survey, and survey links were posted on the ASH Web site and posted on the listserv of the Society of Hematopathology. The CAP also promoted the survey with a news brief in CAP Today and in the CAP Pathology and Laboratory Quality Center Quarterly Newsletter, posts to social media outlets, a blog posting on CAP Connect, and an announcement on the CAP Web site. The survey was open June 8–July 24, 2015. Survey results were screened to exclude not applicable responses and the results were then tabulated. Statistical analyses using $\chi^2$ tests were used to investigate practice differences between university/academic medical centers and other institution types. Testing was also performed to investigate practice differences between university/academic medical centers and other institution types. Testing was also performed to investigate practice differences between university/academic medical centers and other institution types.

**RESULTS**

**Demographics**

Of 294 initial respondents in the survey who were asked if they examine bone marrow specimens and if they issue reports for the initial diagnosis of AL, 36 (12.2%) did not perform examinations, 192 (65.3%) examined bone marrow specimens for the initial diagnosis and subsequent testing, and 66 (22.4%) examined bone marrow specimens, but subsequent testing was sent to another laboratory. Of the remaining 258 survey respondents who did examine bone marrow specimens (88%), response rates per question varied from a maximum of 246 to a minimum of 150 respondents, depending on the survey question. The demographics of the responders are listed in Table 1. The majority of 249 responders (176, 70.7%) were board-certified hematopathologists, 63 (25.3%) were general pathologists, and 10 (4.0%) were hematologists and/or oncologists. Almost half of the respondents (113 of 246; 45.9%) practiced in university hospitals or academic centers. University/academic medical centers examined more bone marrows and issued reports for the initial diagnosis and subsequent testing of AL (84.1%; 95 of 113), compared to other practice settings (54.9%, 73 of 133; $P < .001$).

**Testing Performed on AML and ALL Specimens**

As shown in Table 2, morphologic assessment, flow cytometric analysis, conventional cytogenetics, and fluorescence in situ hybridization (FISH) studies were performed for both AML and ALL specimens at a similarly high rate. While the survey did not specifically separate peripheral blood smear from bone marrow aspirate smear morphologic assessment, peripheral blood smear morphology was included as a component of the final bone marrow report by a high percentage of survey respondents (Table 3). A much lower percentage of participants indicated that they

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**Table 1. Respondent Demographics**

| Demographics                           | No. (%) |
|----------------------------------------|---------|
| Practice setting                       | n = 246 |
| University hospital/academic medical center | 113 (45.9) |
| Voluntary, nonprofit hospital          | 68 (27.6) |
| For-profit hospital                    | 19 (7.7)  |
| National/corporate/reference laboratory | 14 (5.7)  |
| City/county/state hospital             | 9 (3.7)   |
| Regional/local independent laboratory (except clinic or group practice and not owned by a national corporation[s]) | 8 (3.3) |
| Veterans hospital                      | 8 (3.3)   |
| Office laboratory                      | 2 (0.8)   |
| Other                                  | 5 (2.0)   |
| Specialty                              | n = 249 |
| Hematopathology                        | 176 (70.7) |
| Pathology                              | 63 (25.3) |
| Hematology and/or oncology             | 10 (4.0)  |

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**Table 2. Tests Performed on Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) Specimens**

| Tests (multiple responses allowed) | AML Specimens n = 234 No. (%) | ALL Specimens n = 233 No. (%) |
|-----------------------------------|-------------------------------|-------------------------------|
| Morphologic assessment            | 234 (100.0)                  | 232 (99.6)                    |
| Flow cytometric analysis          | 232 (99.1)                   | 229 (98.3)                    |
| Conventional cytogenetics (karyotype) | 225 (96.2)                | 225 (96.6)                    |
| FISH studies for unique translocations  | 190 (81.2)                 | 198 (85.0)                    |
| Molecular testing                 | 183 (78.2)                   | 128 (54.9)                    |
| Iron staining                      | 168 (71.8)                   | 138 (59.2)                    |
| Immunohistochemistry              | 105 (44.9)                   | 111 (47.6)                    |
| Reticulin staining                 | 66 (28.2)                    | 61 (26.2)                     |
| Cytochemical studies (MPO, Sudan black, NSE) | 58 (24.8)                 | 33 (14.2)                     |
| PAS staining                       | 29 (12.4)                    | 26 (11.2)                     |
| Other                             | 6 (2.6)                      | 4 (1.7)                       |

Abbreviations: FISH, fluorescence in situ hybridization; MPO, myeloperoxidase; NSE, nonspecific esterase; PAS, periodic acid–Schiff.

**Table 3. Components of the Final Bone Marrow Report in Acute Leukemia**

| Report Results                           | No. (%) |
|------------------------------------------|---------|
| Bone marrow morphologic assessment       | 191 (97.0) |
| Flow cytometry results                   | 191 (97.0) |
| Cytogenetics                             | 188 (95.4) |
| FISH                                      | 187 (94.9) |
| Peripheral blood smear morphology        | 182 (92.4) |
| Bone marrow aspirate/touch preparation   | 182 (92.4) |
| Molecular genetic studies                | 180 (91.4) |
| CBC with differential                     | 174 (88.3) |
| Other                                     | 11 (5.6) |

Abbreviations: CBC, complete blood count; FISH, fluorescence in situ hybridization.

* This includes results after all addenda have been issued.
used immunohistochemistry for testing in AML (234 respondents) and ALL (233 respondents), (45% [105] and 48% [111], respectively), but results were similarly concordant. Use of a reticulin stain was also similarly low among both groups (28% [66] and 26% [61] for AML and ALL, respectively). Very few respondents indicated the use of a periodic acid–Schiff stain for either group (12% [29] and 11% [26] for AML and ALL, respectively). Discordant results for AML versus ALL were present for molecular testing, iron staining, and cytochemistry, with the utilization of these tests seen at higher rates for AML than ALL specimens (78% [183] versus 55% [128] for molecular testing, \( P < .001 \); 72% [168] versus 59% [138] for iron staining, \( P = .004 \); 25% [58] versus 14% [33] for cytochemistry, \( P = .004 \).

**Morphologic Assessment of Acute Leukemia**

The morphologic assessment of AL typically included bone marrow cellularity (100%, n = 233), the blast percentage from the aspirate smear or touch preparation (99.6%; 232), specific or unique morphologic features of leukemia (eg, Auer rods) (99.6%; 232), the presence of any additional findings of importance (eg, necrosis, fibrosis) (97.4%; 227), the presence of dysplasia (96.6%; 225), and the adequacy of aspirate smears/touch preparations (94.8%; 221). Assessment of ring sideroblasts was included 78.5% (183) of the time. A manual count on the bone marrow aspirate smear or touch preparation was used as the primary method to determine the blast percentage 80.7% (188 of 233) of the time, with far fewer respondents using an estimated percentage of blasts from the aspirate smear/touch preparation (6.9%; 16 of 233), flow cytometry data (6.9%; 16 of 233), or an immunohistochemical-derived blast count on the core biopsy or clot sections (5.6%; 13 of 233). Respondents in academic settings performed a manual count on the aspirate smear/touch preparation at a higher rate (90.6%; 96 of 106) than other settings (73.1%, 87 of 119; \( P = .008 \)). When enumerating blasts, more participants counted 500 cells, versus 200 cells, or 100 cells (Figure). The morphologic assessment of dysplasia was performed qualitatively (55.4%; 128 of 231) or semiquantitatively (35.5%; 82 of 231), with a minority of respondents using a percentage (9.1%; 21 of 231).

**Test-Ordering Practices**

Ancillary tests for the initial diagnosis of AL showed a broad range of responses to a series of statements (Table 4). A standardized testing algorithm was used in many laboratories with 76.6% (157 of 205) of respondents answering “always” or “sometimes.” A number of respondents indicated that testing is always at the discretion of individual pathologists (39.9%; 79 of 198), although most indicated that this was sometimes true (55.6%; 110 of 198). Most respondents also indicated that testing is sometimes at the discretion or request of individual clinicians (67.2%; 127 of 189), with a minority indicating that this was always true (21.2%; 40 of 189). The majority of 191 respondents answered that testing is ordered after discussion with the clinician sometimes (81.2%; 155). Specimens are sent to a reference laboratory for ancillary tests most of the time, as based on a sum of “always” and “sometimes” responses (81.3%; 157 of 193).

**Molecular and Genetic Testing**

Molecular and genetic testing, other than karyotype analysis, in adult and pediatric ALL were queried in 2 questions summarized in Table 5. Most respondents routinely tested for \( BCR-ABL1 \) fusions and \( MLL \) (now known as \( KMT2A \)) translocations in both adult and pediatric patients, and almost half (47.9% [103 of 215] for adults and 48% [72 of 150] for children) performed quantitative polymerase chain reaction for \( BCR-ABL1 \) when that fusion was detected. Most pediatric ALL samples were also studied for \( ETV6-RUNX1 \) translocations (81.3%; 122 of 150), which are not usually detectable by karyotypic analysis. Interestingly, 102 of 215 respondents (47.4%) reported testing for \( ETV6-RUNX1 \) in adult ALL samples, an uncommon translocation in this age group. Testing for trisomy 4 and 10 was relatively common (44.7%; 67 of 150) in pediatric ALL. Other genetic subgroup testing was not commonly performed for ALL in either age group.

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**Table 4. Ordering of Ancillary Tests on Bone Marrows for the Diagnosis of Acute Leukemia**

| Ancillary Test Ordering | Total No. of Responses | Always No. (%) | Sometimes No. (%) | Never No. (%) |
|-------------------------|------------------------|----------------|------------------|--------------|
| Our laboratory uses a standard testing algorithm | 205 | 90 (43.9) | 67 (32.7) | 48 (23.4) |
| Testing is at the discretion of individual pathologists | 198 | 79 (39.9) | 110 (55.6) | 9 (4.5) |
| Testing is at the discretion/request of individual clinicians | 189 | 40 (21.2) | 127 (67.2) | 22 (11.6) |
| Testing is ordered after discussion with the clinician | 191 | 21 (11.0) | 155 (81.2) | 15 (7.9) |
| Specimens are sent to a reference laboratory for ancillary tests | 193 | 71 (36.8) | 86 (44.6) | 36 (18.7) |
Other than karyotype analysis, molecular testing for PML–RARA fusions and mutations of FLT3, NPM1, CEBPA, and KIT were most commonly performed in cases of AML (Table 6). PML–RARA testing was reportedly performed 97.7% (213 of 218) of the time for all or selected patients suspected of having acute promyelocytic leukemia. Testing for mutations in FLT3 and NPM1 was performed for all patients by 51.4% (109 of 212) and 46.9% (98 of 209) of respondents, respectively, and for selected cases by 45.8% (97 of 212) and 47.8% (100 of 212) and 46.9% (98 of 209) of respondents, respectively. CEBPA mutation testing was performed in all cases 35.7% (74 of 207) of the time and in selected cases 55.6% (115 of 207) of the time. KIT mutations, which are common in core-binding factor leukemias that include those with t(8;21)(q22;q22.1) and mutations, which are common in core-binding factor KIT, and next-generation sequencing panels, were tested in 16.3% (32 of 196) of all cases of AML and 75.5% (148 of 212) of the time.

A subset of respondents (38.8%; 83 of 214) reported that they performed molecular genetic testing, in addition to testing for PML–RARA fusions and mutations of FLT3, NPM1, CEBPA, and KIT. Based on the 81 comments reported with the survey, this additional testing included primarily FISH panels for recurrent karyotype abnormalities in AML (n = 18) and next-generation sequencing panels that included genes in addition to FLT3, NPM1, and CEBPA (n = 34). Although referring to different types of testing in AML, a subset of respondents indicated that additional testing was performed always by 34.6% (27 of 78) of this subgroup, usually by 33.3% (26 of 78), sometimes by 24.4% (19 of 78), and rarely in 7.7% (6 of 78).

**Reporting Practices**

In the initial report of the first diagnosis of AL, morphologic assessment and flow cytometry were frequently included in the report, while FISH and molecular genetic testing were less frequently included. Peripheral blood smears, aspirate smears, bone marrow core biopsies, and flow cytometry were all evaluated in the initial report always or nearly always (76%–99%) at least 89.9% of the time, while FISH and molecular genetic testing were evaluated always or nearly always 40.8% (91 of 223) and 32.9% (74 of 225) of the time, respectively. Morphologic evaluation of the clot section and touch imprints were evaluated in the initial report always or nearly always 73.4% (171 of 233) and 58% (134 of 231) of the time, respectively. These percentages increased in the final report after all addenda had been issued. The final report contained descriptions of morphologic assessment, flow cytometry, FISH, molecular studies, and cytogenetics at least 91% (197 of 216) of the time (Table 3).

Participants were queried about practices of incorporating ancillary test results and prognostic statements from ancillary testing into the final report of AL. The majority of 225 responders (150; 66.7%) issue addendum reports as ancillary test results are received, 47 (20.9%) issue a preliminary diagnosis of AL and render a final diagnosis once all ancillary testing is completed, and 28 (12.4%) do not render an additional report as ancillary testing is reported separately. There was no difference in reporting practice between participants from university/academic medical centers versus other sites (P = .51). Incorporating a summary statement into the final report regarding the prognostic significance of ancillary testing was always done by 31 of 197 responders (15.7%), was sometimes done by 132 (67.0%), and was never done by 34 (17.3%).

**DISCUSSION**

A literature search on the subject of testing practices for the diagnosis of AL yielded few results and highlights a lack of information on these practice patterns among physicians. This survey offers an in-depth analysis on current testing patterns.

With respect to tests performed on AML and ALL specimens, there were similar rates of morphologic assessment, flow cytometric analysis, and karyotyping being performed, reflecting a similar diagnostic approach to AL among all responders. FISH studies for unique translo-
molecular genetic testing for that 97.7% of respondents reported performing FISH or promyelocytic leukemia. Recently published algorithms should be performed in all cases of suspected acute promyelocytic leukemia, but this testing should be performed in all cases of suspected acute promyelocytic leukemia. Recently published algorithms will likely help guide future FISH testing. There were also significant differences in the rates of molecular testing performed in AML versus ALL, and this is likely due to the greater availability of next-generation sequencing panels for AML. The low level of testing performed for cytology reflects the general trend for analyzing myeloperoxidase by flow cytometry instead of the manual cytochemical myeloperoxidase staining. Despite this, cytology is performed more frequently in AML than ALL, which likely reflects the practice of some laboratories performing a cytochemical test to confirm a diagnosis of AML initially. Iron staining is also performed more frequently in AML than ALL; this may be due to the examination for ring sideroblasts on the iron stain, a finding found more frequently in certain subtypes of AML.

Queries regarding the blast count showed interesting results. Responders reported that the primary method for determining the blast percentage in bone marrow is the manual blast count performed on aspirate smears/touch preparations. While the result reported is high (80.7%; 188 of 233), one could argue that this is not high enough given the WHO recommendation for performing a morphologic blast count on all new ALs. Specifically, it is well known that the blast count from flow cytometry may overestimate or underestimate the blast count owing to lysis of erythroid cells or hemodilution, for example. A small number of cases do require immunohistochemistry to estimate a blast count in AL due to fibrosis, and other technical reasons. In terms of counting blasts, the WHO recommends that 500 cells be enumerated, but our data show only slightly more than half of responders routinely doing this (52.7%; 99 of 188).

With respect to molecular and genetic testing, some centers seem to be performing unnecessary ETV6-RUNXI and iAMP21 (intrachromosomal amplification of chromosome 21) FISH testing in adults with ALL, abnormalities that are uncommon in this age group. The reported percentage for iAMP21 testing in pediatric ALL (18.7%) is surprisingly low, since this finding can be identified with the FISH assay for ETV6-RUNXI. This finding suggests a lack of familiarity with this fairly recently identified poor prognostic indicator in pediatric ALL. The recent description of BCR-ABL1–like ALL will probably result in an increase in future testing for other abnormalities associated with this poor-prognosis ALL type, such as CRLF2 translocations, which were uncommonly tested for in this survey.

The difference in mutation studies in AML appears to reflect, in part, variation in practice regarding ordering such studies at diagnosis in all cases versus waiting for karyotype results before ordering such testing. The latter approach tends to focus on performing mutation studies only for patients with normal karyotypes. KIT testing is of limited to no utility outside of the potential prognostic significance in adult core-binding factor leukemias. The testing of KIT mutations by 32 of 196 laboratories (16.3%) for all patients could reflect the use of gene panels that are becoming more common in diagnostic laboratories. The survey did not gather specific methodology data for this question, which might clarify if this represents overuse of an individual molecular assay or a gene panel analysis. Recent data on the frequency and prognostic significance of gene mutations and combinations of mutations in AML will certainly impact future testing.

The report of 34 respondents who routinely perform next-generation sequencing panels in AML probably reflects a trend that will increase as these gene panels become more readily available.

Examination of test-ordering practices shows that most responders sometimes or always use a standard testing algorithm, reflecting a trend among physicians to use evidence-based algorithms in practice. Testing appears to be at the discretion of pathologists and clinicians, with most testing ordered after discussion with the clinician (92.1% [176 of 191] always/sometimes). Most responders also use a reference laboratory for all or some ancillary testing. This likely reflects the fact that specialized testing for AL is not available in many laboratories, even those in academic or university settings.

Finally, we discuss reports issued by survey participants. Reports issued initially correspond to testing results that are immediately available including the peripheral blood smear, bone marrow aspirate and core biopsy, and flow cytometric analysis. Final reports are integrated and include all testing performed, as recommended by the WHO. The high rate of using integrated reports may also reflect an academic bias by our responders.

Limitations of the survey include a potential bias of respondents, inaccuracy due to self-reporting, and a lack of detailed knowledge by some respondents for certain testing practices. The demographics of the survey participants show a heavy preponderance of pathologists, specifically hematopathologists, and thus, the data do not provide robust test-ordering patterns among hematologists and/or oncologists. A large proportion of survey responders also include physicians practicing at university or academic medical centers, and thus, results may not be generalizable to physicians in other practice settings. There are also limitations of the data capture of self-reporting by pathologists opting to receive email from CAP’s system, in addition to the online survey being promoted by various other resources. Also, the data reported by respondents may not actually reflect practice owing to biases discussed above. Finally, as no accurate denominator is available, the response rate cannot be determined. Next steps include an assessment of practice patterns of testing in AL after the CAP-ASH guidelines have been implemented.

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