

CORRESPONDENCE



Genetic Profiling in Acute Myeloid Leukemia

TO THE EDITOR: In their article on the prognostic relevance of integrated genetic profiling in patients with acute myeloid leukemia (AML), Patel et al. (March 22 issue)¹ propose an elaborate risk-stratification system for refining prognosis for patients with intermediate-risk AML. This stratification is based on mutational analysis by DNA sequencing of 10 individual leukemia genes in addition to standard karyotyping. However, even ignoring the impracticality of such an analysis, we consider this risk stratification to be overly complicated and unjustified. Instead, on the basis of the report's supplementary data, we believe that only two genes are worthy of mutational screening, *DNMT3A* and *MLL*. Mutations in either of these genes predict adverse outcomes independent of other mutations, including internal tandem duplication in *FLT3* (*FLT3*-ITD), as reported previously.² Moreover, *DNMT3A* and *MLL* mutations define a biologic subgroup of AML patients typically presenting with myelomonocytic or blastic morphology and marked leukocytosis³ who may benefit from escalation of induction chemotherapy with dose-intensified daunorubicin.⁴ We propose that rapid identification of unfavorable mutations in *DNMT3A* and partial tandem duplication in *MLL* (*MLL*-PTD) alone is required for guiding optimal treatment in patients with newly diagnosed AML.

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No potential conflict of interest relevant to this letter was reported.

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2. Ley TJ, Ding L, Walter MJ, et al. *DNMT3A* mutations in acute myeloid leukemia. *N Engl J Med* 2010;363:2424-33.
3. Yan XJ, Xu J, Gu ZH, et al. Exome sequencing identifies somatic mutations of DNA methyltransferase gene *DNMT3A* in acute monocytic leukemia. *Nat Genet* 2011;43:309-15.
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THE AUTHORS REPLY: As the correspondents suggest, the addition of diagnostic testing for mutations in *DNMT3A* and *MLL*-PTD to karyotypic evaluation would improve prognostication in patients with AML. However, restricting molecular studies to these two genes would not capture all patients with molecularly defined unfavorable-risk disease. Specifically, 41% of patients with risk that is unfavorable on the basis of our integrated genetic classification would remain in the intermediate-risk cohort without additional mutational data. We recognize that full-length resequencing of a set of informative genes in the clinical setting is a labor-intensive effort. However, with the plummeting cost of sequencing, focused next-generation sequencing is now a potentially viable

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option for mutational studies. The goal of our study was to identify all genes known to be mutated in AML with potential clinical relevance when integrated with current cytogenetic evaluation and to validate their prognostic relevance. Given the increasing affordability of sequencing technology, we believe that the cost of identifying each additional patient who would benefit from more detailed mutational profiling, as compared with the more limited diagnostic eval-

uation suggested by the correspondents, is completely justifiable.

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Since publication of their article, the authors report no further potential conflict of interest.

Device Closure for Stroke with Patent Foramen Ovale

TO THE EDITOR: Furlan et al. (March 15 issue)¹ report no benefit from the closure of a patent foramen ovale in patients with cryptogenic stroke. Several issues deserve comment.

First, it is unclear how many study patients truly had cryptogenic stroke (30% had hypertension and 20% smoked, which suggests that some may have had lacunar strokes). It is of interest that most of the recurrent strokes (81%) were not considered to be clearly cryptogenic (including some that may have been explained by lacunar infarction in patients with risk factors). Second, among patients with shunts of moderate or substantial size, the estimated reduction in risk of stroke is 35%. The decision to include patients at low risk may have diluted the actual protective effect of the device in patients at higher risk.

Furthermore, the protocol specified the use of antiplatelet agents in the closure group, although 97 of the patients in this group had previously been taking warfarin. Was warfarin withdrawn in the closure group while being allowed in some patients in the medical-therapy group? Patent foramen ovale closure is associated with a risk of atrial fibrillation that is eight times as high as that among patients assigned to medical therapy. This issue may be critical, since double antiplatelet therapy has been shown to be inferior to warfarin in patients with atrial fibrillation.²

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Several factors could limit the translation of CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) into clinical practice. Some patients with large redundant atrial septal aneurysms were excluded, although such aneurysms are an important risk factor for recurrent embolism.¹ The STARFlex device (NMT Medical) is no longer available; the rates of residual shunt and thrombus associated with this device were higher than those associated with other devices.² Patients at highest risk for recurrence may have been treated outside the trial or may have received other devices. In addition, the complication rate is much higher and the success rate lower in CLOSURE I than has been previously reported.³ Finally, it is an underpowered trial; thus, the possibility of clinical benefit from closure cannot be ruled out.

In our opinion, this trial demonstrates the importance of patient selection (i.e., excluding patients with alternative causes of stroke) and the need to concentrate the use of these interventions at high-volume centers with low rates of procedural complications and high success rates. Such centers can complete the ongoing randomized trials that will contribute information additional to that provided by CLOSURE I