toxic regimen might be larger in elderly patients with APL, since an older age remains a prominent negative prognostic factor because of the high death rate associated with both induction therapy and consolidation therapy.[2,3] We would be grateful if the authors could provide information on the efficacy and safety of the regimen of ATRA plus arsenic trioxide among elderly patients in the current trial.

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

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THE AUTHORS REPLY: With respect to elderly patients, the upper age limit in our study was under 71 years. Therefore, we can provide data on the 35 patients between the ages of 60.1 years and 70.2 years who were included in the trial. A total of 16 patients were assigned to receive ATRA plus arsenic trioxide, and 19 were assigned to receive ATRA plus chemotherapy. There were no significant between-group differences in the main presenting features (age, white-cell and platelet counts, fibrinogen level, and coagulopathy). The 24-month event-free survival rates were 100% in the group receiving ATRA plus arsenic trioxide and 84.2% in the group receiving ATRA plus chemotherapy (P=0.40). No patients died and 1 patient had a relapse at 27 months in the group receiving ATRA plus arsenic trioxide. In the group receiving ATRA plus chemotherapy, 3 patients died (1 during induction from the differentiation syndrome and 2 during consolidation from pulmonary embolism and bronchopneumonia). We are further investigating the important issue raised by Miura et al. by analyzing an extended series of elderly patients in our study with prolonged follow-up.

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Since publication of their article, Dr. Lo-Coco reports having received honoraria as a speaker for Lundbeck, and Dr. Platzbecker's disclosure form has been updated to include receiving honoraria as a speaker for Teva. No further potential conflict of interest relevant to this letter was reported.

Genomic Landscapes and Clonality of De Novo AML

TO THE EDITOR: In reviewing the analysis of the genomic and epigenomic landscapes of de novo acute myeloid leukemia (AML) by the Cancer Genome Atlas Research Network (May 30 issue),[1] we were struck by an apparent discrepancy in the reported clonal architecture of the AML samples as compared with that reported by Ding et al.[2] (an average of one to two distinct clones identified vs. four or more). This discrepancy may reflect the limited depth of the sequencing analysis performed in the more recent study.[1] More important, the authors do not reveal which mutations occur in the founding clone, as would be expected for an initiator of disease, and which occur in minor clones, which subsequently drive disease. For instance, *FLT3* mutations that are present at diagnosis frequently disappear at relapse, which suggests that these mutations are unlikely to represent initiators of disease in AML.[3] In contrast, *DNMT3A* mutations present at diagnosis appear to occur exclusively in the major AML clone, as would be expected in an initiator of AML, but are not, it seems, lost (or indeed gained) at relapse.[4] Such information on these and other genes would allow the identification of initiating mutations that may serve as therapeutic Achilles' heels and biomarkers of residual disease in AML.[5]

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THE AUTHORS REPLY: We agree that it is important to understand whether mutations are responsible for the initiation of AML or cooperate with initiating mutations to cause disease progression or relapse.[1,2] Whereas initiating mutations may be more likely to appear in founding clones, cooperating mutations might appear either in founding clones or subclones derived from founding clones. In our study, it was not possible to define the clonal architecture for all samples, both because AML genomes harbor a compara-tively small number of mutations and because for 150 of 200 samples, only exome sequencing was performed. Nevertheless, we have used the data in Table S6 (available with the full text of our article at NEJM.org) to identify variants in significantly mutated genes that can be assigned with high confidence to either a founding clone or a subclone.

Mutations in some genes appear almost exclusively in founding clones, which suggests that they are disease initiators. These genes include *RUNX1* (9 of 9 mutations in founding clones), *NPM1* (3 of 3), *U2AF1* (5 of 5), *DNMT3A* (38 of 40), *IDH2* (13 of 14), *IDH1* (15 of 17), and *KIT* (5 of 6). In contrast, mutations in *NRAS* (1 of 12 in founding clones), *TET2* (13 of 18), *KRAS* (4 of 6), *CEBPA* (3 of 5), *WT1* (3 of 6), *PTPN11* (4 of 8), and *FLT3* (6 of 13), are often found in subclones, suggesting that they are often cooperating mutations. Many additional genomes will need to be tested to make these tentative assignments more definitive.

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Threshold Insulin-Pump Interruption to Reduce Hypoglycemia

TO THE EDITOR: Bergenstal et al. (July 18 issue)[1] report a reduction in nocturnal hypoglycemia with the use of the low-glucose (or threshold) suspend feature of an insulin pump combined with a continuous glucose monitor. Not only was the time patients spent in hypoglycemia reduced, but also the rate of nocturnal events was 31.8% lower in the intervention group. This finding is remarkable considering that the threshold-suspend feature starts to work only when hypoglycemia is encountered, not if it is imminent. Could it be that suspending insulin administration during a hypoglycemic event prevented subsequent events during that same night? If that is the case, then the number of nights with one or more nocturnal hypoglycemic events should be more or less similar in the two groups. Could the authors provide us with this additional information?

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