certain intracellular phosphorylation events representing functionally and clinically relevant signaling pathways in AML. The patient cells were analyzed under multiple perturbations to obtain a comprehensive picture of signaling dynamics specific to the patient and cell subtype. To distill the signaling status of each AML subpopulation into a matrix representing the response signature, the authors developed a new tool called statistical analysis of response amplitude (SARA).

Next, the authors used the healthy cohort to define signaling responses that were consistently associated with undifferentiated cells as defined by surface markers, assuming that these attributes were highly linked in normal hematopoietic cells. They defined a signaling classifier to calculate the percent of inferred functionally primitive cells (%IFPC) in each AML sample. This measure did not correlate well with the equivalent classification based on classic progenitor surface markers: only 64% of the subpopulations identified as IFPC were also labeled as primitive by surface markers. Importantly, when translated by deconvolution into an expression signature, the %IFPC, as a proxy for the incidence of leukemic stem cells, was more predictive of clinical prognosis than the predictor based on surface markers.

The main limitation of mass cytometry is the requirement to preselect a relatively small set of targets, which Levine *et al.*[1] accomplished through a preliminary analysis to choose the most highly informative markers for the heterogeneity of their cohort. In contrast, scRNA-seq eliminates the preselection requirement and the need for *in vitro* perturbation while providing high-resolution expression profiling of rare subpopulations[10,11]. This genomic approach relies on its own unique computational algorithms to enable study of the global regulation of individual cells, but is currently limited in throughput compared to mass cytometry. Combining these complementary technologies, along with novel analytical solutions, such as a modified version of the PhenoGraph algorithm, may represent the best of both worlds. As emerging fields, mass cytometry and scRNA-seq can be expected to undergo rapid improvements in robustness of measurements, sample throughput, signal sensitivity and cost, enabling truly exhaustive sampling of tissue heterogeneity in both health and disease.

With such advances, clinical treatments that are tailor-made for each patient are likely to follow. Levine *et al.*[1] did not expand on how the response signatures obtained from their set of signaling proteins could be used to design targeted therapies, but one can easily imagine new discoveries based on 'druggable' regulatory circuits emerging from this type of analysis. With an accurate assessment of tumor heterogeneity, it should be possible to go beyond prognosis to design therapeutic strategies that address the complexity and uniqueness of each tumor.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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