The estimated average tumor purity in this study was 75%, which, although low by modern leukemia and lymphoma sequencing standards, is an improvement in signal-to-noise ratio for Hodgkin lymphoma given the incredible rarity of the Reed-Sternberg cell in its background nest of inflammatory infiltrate. Previous studies relying on laser capture microdissection could also increase the signal-to-noise ratio, but at the cost of time, effort, and still-low cell numbers.

This work raises additional questions. Variant allele frequencies range from 2% to 100% within single cases. Does this imply intratumoral heterogeneity? Do individual or multiple HRS cells exist as clones and subclones with different alterations and characteristics within the same lymphoma, and if so, what would that mean for molecularly targeted therapy?

Overall, this work is exciting for several reasons. It advances our knowledge of the genetic makeup of cHL but also demonstrates the feasibility of a new technique that could in the future be extended to provide additional information about transcription and potentially protein expression. The demonstration that restoration of B2M loss can reverse a characteristic phenotype is an important functional validation of a key finding and is timely and relevant because immune therapies are now being explored in Hodgkin lymphoma.10

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES
Predicting a positive response are low inhibitor level and a short interval between the appearance of the inhibitor and the start of therapy. FVIII level and inhibitor titer at diagnosis are not significantly associated with outcome. The likelihood of achieving CR was influenced by the presenting inhibitor titer and FVIII level.

The IST regimens are also variable in both the dosage and type of agents and with different outcome. There is no difference in inhibitor eradication or mortality between patients treated with steroids alone and combined therapy, and stable CR is more likely with steroids and cyclophosphamide than with steroids alone.

Different regimens have various incidences of AEs, but a higher proportion of patients treated with steroids and cyclophosphamide experienced AEs compared with steroids alone. The use of steroids, especially in relation to dosage and time of administration, could be revised in a population at high risk of AEs.

In the GTH study, FVIII ≥1 IU/dL and inhibitor level <20 BU/mL were independent predictors of overall survival and can define a subgroup of patients with better prognosis; this subgroup comprised about one-third of patients who may benefit from less aggressive treatment with a lower rate of AEs.

Future randomized studies are unlikely because of the rarity of the disease and the difficulty in collecting patients. This study is not a randomized study; nevertheless, it has been carried out with uniformity and therefore gives valuable information that can be followed in clinical practice.

Considering the high frequency of AEs, the future problem could be to identify the population of patients requiring less intensive therapy and how to carry out that therapy.

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**Engineering regulatory T cells against factor VIII inhibitors**

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In this issue of Blood, Kim et al show that engineered factor VIII (FVIII)-specific regulatory T cells inhibit immune responses to FVIII, suggesting the possibility of cellular therapy for FVIII inhibitors in hemophilia A.

Interactions between engineered Tregs and effector T cells (Teffs). A gene construct encoding for a T-cell receptor (TCR) specific for FVIII peptide is transduced into polyclonal Tregs, producing Tregs expressing that TCR. Tregs interact with antigen-presenting cells (APCs) via human major histocompatibility complex II (MHCII), as do Teffs. Tregs exert suppressive effects on Teffs, preventing immune responses to antigen and promoting tolerance. Kim et al demonstrate in vitro that such engineered Tregs can suppress the typically polyclonal responses to whole FVIII, despite expressing TCRRs specific for a single small FVIII peptide. Could this result in the off-target suppression of T-cell responses to non-FVIII antigens, such as antigens from pathogens or vaccines?
The problem of acquired hemophilia

Francesco Baudo and Francesco de Cataldo