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


THE AUTHORS REPLY: Focosi points out several appropriate alternatives to the methods depicted in our video of bone marrow aspiration and biopsy. Our experience does not suggest that the degree of pain associated with the procedure is lower when the biopsy is performed first, and the sequence probably does not matter in the sedated patient.

We agree that a frail biopsy specimen may be damaged by collection onto gauze; however, immediate inspection of the biopsy specimen is critical and requires placement onto gauze or a glass slide. It is not uncommon for an extracted biopsy specimen to contain exclusively cortical bone without marrow, which is an inadequate sample for evaluation. Immediate placement into formalin precludes the ability to inspect the specimen appropriately. In addition, a touch preparation may provide useful information.

Although collecting aspirate into anticoagulated vacuum tubes may be feasible, in certain conditions, marrow can be difficult to aspirate and requires substantial suction. There is no ability to modify the force or pull when using vacuum tubes. In regard to the preparation of slides, we agree that a slide should be appropriately anchored to create an evaluable aspirate smear.

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

Lack of Population Diversity in Commonly Used Human Embryonic Stem-Cell Lines

TO THE EDITOR: Human embryonic stem-cell research may lead to new methods of drug discovery, insights into mechanisms of disease, and eventually, cellular therapies. The potential benefit to patient populations may depend partially on the diversity of the stem-cell lines that are available for research and clinical use. However, investigators have been unable to target their research to diverse subgroups of existing lines or to ensure the inclusion of lines from the human populations most relevant to their diseases of interest, because almost no information has been available on the human population origin of existing stem-cell lines.

Therefore, with the approval of the University of Michigan’s Human Pluripotent Stem Cell Research Oversight Committee, we determined the genetic ancestry of a large collection of stem-cell lines, including the most commonly used lines that were approved for federally funded research under the Bush administration’s policy, other lines derived in the United States that have been widely distributed, and additional lines derived in other countries (for details, see the table in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Using the Illumina 660W genotyping platform, we genotyped genomewide single-nucleotide polymorphisms (SNPs) in each stem-cell line. Control experiments showed that the presence of mouse embryonic feeder cells did not affect the SNP genotypes (>99.99% identity of SNP genotypes between stem-cell lines that were grown with or without feeder cells) or the inferred ancestry (data not shown). Genotypes of the stem-cell lines were compared with previously obtained genotypes on a reference set of 2001 subjects from the HapMap Project and the Human Genome Diversity Project, comprising 63 populations with worldwide representation. We analyzed 483,304 high-quality SNPs that had been genotyped in all sets of samples.

A cluster analysis of combined stem-cell and worldwide reference genotypes showed that nearly all the stem-cell lines clustered exclusively with reference subjects of known European and Middle Eastern origin (Fig. 1). Two stem-cell lines clustered with East Asians. Using a European and Middle Eastern subgroup of the reference data, we found that most lines clustered primarily with subjects of northern and western European an-
The clustering of human embryonic stem-cell lines with subjects of known origin, including 2001 worldwide subjects (Panel A). Shown are the clustering of human embryonic stem-cell lines with this population was not observed. CIPF denotes Prince Felipe Research Center, C. & S. Asia Central and South Asia, WA14. The Mozabite population from North Africa is included as part of the “Middle East” reference sample, but close clustering of

Figure 1. Cluster Analysis of Combined Stem-Cell and Worldwide Reference Genotypes. Shown are the clustering of human embryonic stem-cell lines with subjects of known origin, including 2001 worldwide subjects (Panel A) and 458 European and Middle Eastern subjects (Panel B). In both plots, classic metric multidimensional scaling analysis was performed on pairwise individual genetic distance matrices that were computed with the use of identity-by-state allele sharing. Each sample (stem-cell lines and reference subjects) is depicted as a point so that proximate placement reflects genetic similarity. Each stem-cell line has been given a distinct numeric label. Reference subjects appear as either colored symbols (for subjects from the Human Genome Diversity Project) or letters (for subjects from the HapMap Project). Inferred sets of stem-cell lines that derive from the same of some of these lines from embryos with likely origins in Israel and Spain. Interestingly, an analysis of genotype sharing identified several sets of

cesty. The remaining lines clustered with Middle Eastern and southern European populations, a finding that was compatible with the derivation...
lines for which all lines in a given set had the same
gamete donors (Fig. 1).

We have found that widely distributed stem-
cell lines lack population diversity and that none
of these lines derive from populations with recent
African ancestry. Other existing lines that we did
not analyze probably derive from populations that
were not represented in our study, but most pub-
lished stem-cell studies have used the lines that
we investigated.5

Efforts to derive and disseminate new stem-
cell lines should now emphasize underrepresented
populations, to allow researchers to assess the
extent to which the ancestry of stem-cell lines in-
fluences disease models, cellular therapies, and
drug screening with the use of stem cells. Avail-
ability of more diverse lines will reduce the risk
that the potential benefits of stem-cell research
will be limited to patients with certain ancestries.

Another promising approach to increasing the di-
versity of pluripotent human cell lines is to derive
induced pluripotent stem-cell lines from diverse
donors. It is not yet clear, however, whether certain
types of studies and therapies will be more readi-
ly performed with human embryonic stem cells.

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