Reichardt's COS cell system, Q188R-GALT retains ~10% residual activity (Reichardt et al. 1991), and S135L-GALT is "a polymorphism because it encodes normal GALT specific activity" (Reichardt et al. 1992*b*, p. 5432). Hemolysates from seven Q188R homozygotes (Elsas et al. 1994) and lymphoblast extracts from three unrelated Q188R homozygotes (Fridovich-Keil and Jinks-Robertson 1993) have all demonstrated a complete absence of GALT activity, and both hemolysates and lymphoblast extracts from patients (or carriers) with the S135L mutation have demonstrated extremely low, if any, GALT activity attributable to the S135L allele (Fridovich-Keil et al. 1995).

With regard to Dr. Reichardt's concern over the current lack of published data illustrating detection of human GALT protein (not just activity) in yeast; these data were alluded to in an abstract published in the *Journal* in 1994 (Fridovich-Keil et al. 1994), and some of these data are also included in a manuscript currently under review (J. L. Fridovich-Keil, B. B. Quimby, L. Wells, L. A. Mazur, and J. P. Elsevier, unpublished data).

3. Dr. Reichardt is correct that "no reports on expression of the common N314D mutation in yeast have been published." These data are, however, included in the manuscript under review. Dr. Elsas referred to these data when he stated that "N314D in yeast encodes near normal activity" (see letter above). Similarly, Reichardt and Woo (1991, p. 2636) have reported from their COS cell work that "the aspartate-314 polymorphism actually increases the specific activity of the GALT enzyme."

I would like to stress, however, that regardless of how many times the yeast system may "give the right answer" in terms of modeling human biochemical phenotypes, it, as with any other model system, including one that uses mammalian cells, is still a model, and must always be interpreted with caution as such.

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Defining "Proband"

To the Editor:

Bennett et al. (1995) presented recommendations of the Pedigree Standardization Task Force of the National Society of Genetic Counselors. As the authors clearly state, the importance of standardized nomenclature is without question for reducing the chances of incorrect interpretation of patient and family information and for facillitating communication between researchers and clinicians involved in genetic family studies.

Most of the recommendations are appropriate and allow recording of the complex situations that can result from today's reproductive and diagnostic technologies. However, there is a problem with the definition presented for "proband" (Bennett et al. 1995, fig. 1, p. 746), i.e., the "first affected family member coming to medical attention".

This definition illustrates the dichotomy that seems to have developed in the use of the term "proband" by clinicians versus researchers. The Bennett et al. (1995) definition is the one that clinicians seem to have evolved

(see, e.g., Thompson et al. 1991, pp. 58, 438). Researchers, on the other hand, rely on the original use of the word "proband" (Weinberg 1927; Morton 1959) as an affected person who is necessary and sufficient to ascertain a family for study. Depending on the comprehensiveness of the sampling frame, there may be more than one proband per family. The first proband in a family is sometimes termed the "propositus" or "index case." Additional nonproband affected individuals in a family are termed "secondary cases" (Morton 1982). Careful delineation of probands and nonprobands in families is extremely important in correcting for ascertainment biases in the statistical genetic analysis of patterns of inheritance (although even then problems may arise; see, e.g., Vieland and Hodge 1995).

The Bennett et al. (1995) definition implies that there would be only one "proband" indicated per family, which could seriously bias analysis efforts of family structures recorded following the recommendations. I submit that the definition of "proband" used by Bennett et al. (1995) and other clinicians (e.g., Thompson et al. 1991) is more properly the definition of "index case" and that "proband" be reserved for the above more general definition of an affected person who is ascertained for study via a particular sampling scheme.

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Standardized Pedigree Nomenclature

To the Editor:

Although an attempt to standardize the representation of genetic and social relationships using pedigree diagrams is welcome, there are problems with the present recommendations (Bennett et al. 1995) that should be addressed. Essentially, I would describe these problems as arising from a reliance on topographic rather than topological conventions to represent relationships between individuals. As an example of what I mean, it seems perfectly sensible to use solid lines for biological relationships and dotted lines for adoptive relationships, but it seems problematic to use a vertical line to indicate a gestational relationship and a diagonal line for gamete donation. The use of shorter lines for pregnancies that do not go to term may also be problematic.

In practice, it can be extremely difficult, perhaps impossible, to produce a diagram in which symbols need to occupy certain positions with respect to each other. This is especially the case if clarity is valued. Although the example pedigree diagram presented by the authors of the recommendations appears complicated, in fact only minor differences in the pedigree structure would make it impractical to represent it according to their guidelines. For example, reversing the birth order of any of the main sibships would produce a bewildering tangle of connecting lines, and similar difficulties would result if the second pair of twins in the first generation had produced offspring or if the second twin in the next generation had remarried. If subjects must appear in birth order, how are we to represent the situation where one pair of sibs marries another pair, with the older of one pair marrying the younger of the other?

The problems posed by the new recommendations become even more severe if we consider it desirable that computer programs should be able to produce pedigree diagrams automatically. My experience of writing such a program (Curtis 1990) leads me to believe that it is feasible to construct quite complicated diagrams automatically if one needs to be concerned primarily with the types of connections (relationships) between subjects and only secondarily with their relative positions. I do not know whether it would be possible to devise an algorithm that could comply with the new recommendations. Although the authors say that such computer programs would be useful, and although they have consulted widely among genetic professionals, there is no evidence that they have sought the opinions of the people who would actually have to write the software, and it is discouraging that the example symbols and pedigrees were produced with a desktop publishing package.