caused the phenotypic changes in the patients or was simply a neutral polymorphism. Therefore, there has been a continuing debate as to whether the disorders should be classified by their clinical presentations or by the causative genes. As an illustration of the problems, mutations in 437 genes have been found associated with the 461 defined disorders of the skeleton. The latest nosology for the disorders remains “hybrid” in nature in the sense that the classification is not always based on the same criteria. Some diseases are grouped based on the causal gene, others are listed together, because they share common radiographic features, and still others are brought together because of a similar clinical course (lethality) or involvement of similar parts of the skeleton. A simpler system of classification proved feasible for one rare heritable disorder of skin, epidermolysis bullosa. The disorder was first defined clinically into subtypes based on the layers of the skin that were cleaved in friction-induced blisters. Most patients in each subtype were subsequently shown to have mutations in genes expressed in the corresponding layer of skin. Even with these patients, the strength of the genotype-phenotype correlation varies and mutations have not yet been found in every patient.

The best pathway through this maze of information is probably to begin by matching the signs and symptoms in a patient with the presentations that define each clinical classification. A major focus should be on the most common disorders, recognizing that the signs and symptoms may vary among different individuals and family members with the same diagnosis. Then, attempt to reach a decision, in consultation with the patient, parents, and specialist, as to whether a DNA analysis for the probable mutation is indicated. Among the considerations are the cost, the rigor with which the clinical classification has been linked to mutated genes, the reassurance the diagnosis can bring to patients and their families, the use of the information for prenatal diagnosis, and the possibility that mutation-specific therapies may be developed in the future. For patients with the most severe forms, it is probably best to consult a specialist in the disease to determine a multidisciplinary program for management and therapy. Patient support groups have formed for many of the diseases and are an important source of information.