

ASHG STATEMENT Statement on Gene Therapy, April 2000

Board of Directors of the American Society of Human Genetics

The American Society of Human Genetics (ASHG), founded in 1948, is a society of researchers and professionals in human genetics and represents more than 6,700 scientists, physicians, nurses, genetic counselors, and students who are actively engaged in the genetic discovery, teaching, and application of knowledge of human genetics and the human genome.

The membership has a keen interest in gene therapy, its scientific basis, and its translation into clinical practice, and members are frequently called upon to provide advice to families confronted with the opportunity to participate in experimental gene therapy. If, in the future, gene therapy becomes available as a routine treatment option, many ASHG members will be involved in both the application of gene therapy and the decision-making process that families will undergo to determine whether gene therapy is suitable for them or their loved ones.

As representatives of one of the few organizations whose members share broad expertise and interest in matters related to human genetics and in the application of genetic knowledge to the well-being of people everywhere, the ASHG Board of Directors has prepared this statement.

The Need for More Rigorous Research

At this time, gene therapy is a highly experimental area of research, and both researchers and the public would agree that, to date, demonstrable progress has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. Even the safety of gene therapy procedures has now been called into question by recent events involving a patient death. Both the lack of progress and the safety issues are related to a poorly developed scientific base when experimentation began and to an initial lack of appreciation for the extensive experimental work in gene delivery and gene expression that would be required prior to clinical studies. Unrealistic expectations have also resulted from overzealous pronouncements by some gene therapy enthusiasts who

have underestimated the complexity of the problem. Since the appearance, in 1995, of a highly critical National Institutes of Health (NIH) review of gene therapy, the field has begun to mature, the scientific base has grown considerably, and expectations—for the most part—appear to be more firmly based in reality. Much more, however, remains to be done.

The ASHG recognizes that gene therapy holds much promise. However, this promise will only be achieved through continued rigorous research on the most-fundamental mechanisms underlying gene delivery and gene expression in animals. Clinical trials should be undertaken only after solid evidence of both safety and efficacy has been obtained in an appropriate animal model, when these are available for the disease under investigation. When clinical trials are undertaken, they must be subjected to the same rigorous and critical evaluation.

Who Looks After the Interests of the Patient?

In any gene therapy trial, the greatest responsibility for patient safety lies with the investigators, who, more than anyone, should know the potential risks and benefits of the proposed trial. The investigators also have access to all data accumulated during a trial and are able to assess risk factors continuously throughout the trial, allowing them to make adjustments as the trial proceeds.

The local institutional review board (IRB) has a mandate to evaluate each protocol adequately prior to approving any clinical trial. The IRB also has a responsibility to require that all relevant information generated during the trial be made available so that the estimated risk/benefit ratio can be continuously updated. It must also require investigators to monitor developments in the field and to report them to the IRB so that the trial may be stopped or revised if a significant new development makes the current protocol inferior in terms of either risk or efficacy.

Issues related to potential conflict of interest must also be continually monitored by the IRB, to ensure that decisions regarding clinical trials are made on the basis of sound scientific and medical judgment, with primary regard for the patient's well-being, and are unclouded by motivations related to personal gain or publicity. Indeed, many would argue that financial interest in a commercial venture should preclude direct participation

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in a clinical trial supported by that commercial enterprise.

All scientists and clinicians with relevant expertise, regardless of whether they are involved in clinical trials, have a responsibility to speak up if a gene therapy protocol seems inadequate or dangerous on the basis of the evidence at hand. Such individuals, many of whom are ASHG members, have an opportunity to evaluate data pertaining to the efficacy or safety of an experimental protocol, through review of the scientific literature, attendance at scientific meetings, or participation in review panels. They are therefore in a position to serve as watchdogs at the most fundamental level of clinical investigation, and they have a responsibility commensurate with this privileged position.

In the United States, the Food and Drug Administration (FDA) is the only independent agency that has responsibility for all the proposals and that has the expertise necessary to evaluate them. The FDA's regulatory role in establishing standards for gene therapy trials is critical. Similarly, the Recombinant DNA Advisory Committee (RAC), which has responsibility for recombinant DNA technology (one of the building blocks of gene therapy), must ensure that the technology is safe and adequate for the task of gene therapy research. Further oversight is provided by the NIH, for those institutions that receive NIH funding.

For all of these groups, the problem is in determining when a new procedure is ready for a clinical trial and who should be enrolled in the trial. With regard to the latter problem, the ASHG Board of Directors suggests a "litmus test" for its members: if you or your family were in this circumstance, would you enroll yourself or

your loved one in this trial? Only if the answer is "yes" is it appropriate to seek patients for enrollment or to support a family's decision to enter a clinical trial.

The ASHG suggests that most patients and their families cannot apply the litmus test to themselves. They usually do not know enough about the science that determines the potential risks and benefits of the procedure, and their emotional involvement makes it difficult to make independent decisions. They therefore require assistance and unbiased information when making the decision to participate (or not to participate) in a clinical trial—the very basis of "informed" consent. The process of obtaining informed consent can be assisted and/or monitored by the FDA, the local IRB, and the geneticists or other physicians who know the families; all should apply the litmus test when making their judgments. However, it is fundamentally the obligation of the investigator to apply this litmus test and to proceed only if it is clear that "yes" is the appropriate and unequivocal response.

As stewards of the field of human genetics, elected by the membership of the Society, the ASHG Board of Directors affirms that the development and future application of gene therapy require the same commitment to scientific integrity and social responsibility that has served our field well for the past 50 years. The considerable promise of gene therapy must not be lost in the wake of premature claims and tragic consequences in some clinical trials. The appropriate course is to proceed with a greater commitment to rigorous critical evaluation and a heightened sense of responsibility to the patients who entrust their life and health to us.