Gaucher Disease

Current Issues in Diagnosis and Treatment

NIH Technology Assessment Panel on Gaucher Disease

Objective.—To provide physicians with a responsible assessment of the diagnosis and treatment of Gaucher disease.

Participants.—A nonfederal, nonadvocate, 14-member panel representing the fields of pediatrics, obstetrics and gynecology, genetics, endocrinology, molecular biology, internal medicine, and biostatistics. In addition, 30 experts in genetics, pediatrics, neurology, obstetrics and gynecology, orthopedics, hematology, genetic counseling, clinical pathology, and epidemiology presented data to the panel and a conference audience of 230 during a 1½-day public session. Questions and statements from conference attendees were considered during the open session. Closed deliberations by the panel occurred during the remainder of the second day and the morning of the third.

Evidence.—The literature was searched through MEDLINE, and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process.—The panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and on the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference.

Conclusions.—Despite the success of enzyme therapy, treatment is limited by the cost of the agent. This makes it imperative to determine the lowest effective initial and maintenance doses, to define the appropriate clinical indications for treatment, and to establish uniform methods to optimize outcome assessment. The value of treatment for asymptomatic individuals has not been determined. General population screening for affected individuals and for carriers is not appropriate at this time. As a prototype for all rare diseases, the plight of patients with Gaucher disease raises difficult financial and ethical issues, which we as a society must address.

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GAUCHER DISEASE is a rare inherited enzyme deficiency, which researchers estimate may be present in 10 000 to 20 000 Americans. It is a panethnic disorder, with highest prevalence in the Ashkenazi Jewish population.

During the past decade, much progress has been made in understanding the molecular biology of the disease and in the ability to treat patients with the disorder. However, many issues regarding diagnosis, population screening, and therapy for patients with Gaucher disease are controversial.

Gaucher disease is characterized by a remarkable degree of variability in its clinical signs and symptoms, ranging from severely affected infants to asymptomatic adults. Many patients suffer from anemia, bone damage, and enlarged livers and spleens; a few develop severe central nervous system damage. Gaucher disease is a potentially lethal disorder. All patients with Gaucher disease have a genetic defect in the enzyme glucocerebrosidase, which results in the accumulation of the lipid glucocerebroside within intracellular structures known as lysosomes.

Patients with Gaucher disease have been classified into three major types on the basis of clinical signs and symptoms: type 1, nonneuronopathic (adult); type 2, acute neuronopathic (infantile); and type 3, subacute neuronopathic (juvenile). All types of Gaucher disease can be diagnosed by demonstrating a deficiency of glucocerebrosidase activity.

The most striking differences among the three types are the presence or absence of neurologic manifestations and the rate of their progression. However, people with the same type of the disorder may differ in their clinical presentation. For example, certain patients with type 1 Gaucher disease, which is by far the most common type, may display some combination of anemia, low blood

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platelet levels, massively enlarged livers and spleens, and extensive skeletal disease. In contrast, other type 1 patients may have no symptoms and can be identified only by screening or during evaluation for other diseases.

The gene for glucocerebrosidase, which is located on chromosome 1q21, has been characterized and sequenced. Many mutations in the glucocerebrosidase gene have been identified in DNA from different patients; several of these mutations are frequent. Although some patients with the same DNA mutations have similar clinical courses, other patients with the same mutations have very different clinical manifestations. It is still not clear to what extent a person's clinical features (phenotype) or prognosis can be accurately predicted through current mutation analysis. Furthermore, although the molecular techniques can be used for early prenatal diagnosis, detection of individuals carrying the disease gene, and population screening, the appropriate clinical application of these molecular techniques remains unresolved.

Gaucher disease has been traditionally managed by supportive therapy including total or partial removal of the spleen, blood transfusions, orthopedic procedures, and occasionally bone marrow transplantation. More recently, enzyme replacement therapy has become available and has proven effective in many patients. Enzyme replacement therapy has successfully reversed many of the manifestations of the disorder, including abnormal blood counts, increased liver and spleen size, and some skeletal abnormalities. The therapy is very costly, however, ranging from $100 000 to $400 000 annually for each patient.

The purpose of this Technology Assessment Conference was to evaluate current concepts concerning diagnosis, screening, genetic counseling, and management of Gaucher disease. In this effort, the National Institute of Mental Health, together with the Office of Medical Applications of Research of the National Institutes of Health, convened a Technology Assessment Conference entitled "Gaucher Disease: Current Issues In Diagnosis and Treatment." The conference was cosponsored by the National Institute of Child Health and Human Development, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Diseases and Stroke, the National Center for Research Resources, the National Center for Human Genome Research, and the Office of Rare Disease Research.

Following 1½ days of presentations by experts in the relevant fields and discussions with the audience, an independent panel composed of specialists and generalists from the medical and other related scientific disciplines, as well as a public representative, considered the evidence and formulated a consensus statement in response to the following six previously stated questions:

1. What is the natural history of Gaucher disease, and what is the appropriate technology to assess the severity and to predict the progression of this disorder?
2. What are the roles of current molecular and enzymatic assays for ascertaining affected individuals and carriers in various populations?
3. What are the indications for treatment of patients with Gaucher disease, and what are the appropriate modes of therapy?
4. What are the goals for and consequences of treatment, and how can the therapeutic interventions be assessed?
5. Under what circumstances could genotype/phenotype correlations be used for patient care and counseling?
6. What are appropriate directions for future research and other relevant issues that should be pursued?

1. WHAT IS THE NATURAL HISTORY OF GAUCHER DISEASE, AND WHAT IS THE APPROPRIATE TECHNOLOGY TO ASSESS THE SEVERITY AND TO PREDICT THE PROGRESSION OF THIS DISORDER?

The natural history of Gaucher disease is incompletely documented. The progression and outcome are well understood only in type 2 disease (infantile form). Type 3 disease (juvenile form) has a more variable course. The type 1 (adult) form is most common, especially variable, and least well characterized. Furthermore, splenectomy, orthopedic intervention, and enzyme replacement therapy for type 1 Gaucher disease alter its course, natural progression, and outcome. Thus, it is important to standardize the reporting of the effects of these interventions.

Type 1 disease typically presents after infancy and often not until adult life. Indeed, some genotypically affected individuals may never come to medical attention, and their number is unknown. With DNA analysis of family members, many such individuals will be diagnosed. Current technologies may unmask and identify organ-specific manifestations in these asymptomatic individuals. Simple hematologic and biochemical assays and imaging techniques can be used to assess disease progression. Skeletal disease is especially difficult to assess. Mutation analysis provides precise diagnosis but may not give information concerning the severity or progression of the disease. In addition, there are considerable differences in the degree to which organ systems are affected. Furthermore, there are reports of intrafamilial variation. Differences in disease severity have been demonstrated even in identical twins. Thus, other genetic and nongenetic factors appear to be involved in the expression of the disease.

Prenatal diagnosis now affords an opportunity to assess the natural progression of the disease from before birth. Such information may be critical in choosing appropriate technologies for prognosis and therapy. Appropriate systematic and quantitative description of the disease is essential to understand its natural course. Patient characterization requires clarification of the terminology used to describe patients, which at this time is confused (eg, "asymptomatic" vs "asymptomatic but with physical signs and laboratory evidence of disease").

2. WHAT ARE THE ROLES OF CURRENT MOLECULAR AND ENZYMATIC ASSAYS FOR ASCERTAINING AFFECTED INDIVIDUALS AND CARRIERS IN VARIOUS POPULATIONS?

Enzyme analysis of leukocyte or fibroblast extracts is appropriate to confirm or exclude the diagnosis of Gaucher disease. Several methods for enzymatic diagnosis are currently available and are reliable in experienced hands. No consensus has yet been reached on a single most appropriate method, which makes it essential that each laboratory have rigid internal quality assurance and quality control of the method it uses.

The prognosis for patients with type 1 disease cannot be predicted from the residual enzyme activity measured in tissues. Enzymatic analysis cannot be used to detect carriers reliably.

Analysis of DNA for mutations by molecular methods (genotyping) is appropriate in all individuals with glucocerebrosidase deficiency. Genotyping of siblings and parents of affected individuals is important to ascertain other potentially affected individuals who may be asymptomatic and to identify carriers for genetic counseling. Enzyme analysis of parents of affected individuals is also valuable to exclude the possibility of asymptomatic glucocerebrosidase deficiency in a parent with two mutant alleles, only one of which was identified by genotyping. Although current genotype/phenotype correlations are imperfect, genotyping may indicate that neurologic complications are unlikely. It has less value in predicting the likelihood of other complications.

Molecular methods can provide accurate carrier detection, particularly in defined populations. For example, in the Ashkenazi Jewish population, screening for five mutations allows detection of approximately 95% of heterozygous individuals. The greater variety of mutations in non-Jewish populations makes carrier detection in these populations more challenging with currently available technology. Analysis of some mutations by DNA amplification can be complicated by the presence of a highly homologous pseudogene that is located nearby. Quality control of the molecular techniques is important, as is awareness of the complexities in interpreting data produced by these amplification methods.

Widespread application of genetic screening to detect either presymptomatic patients with Gaucher disease or heterozygous carriers is not appropriate at this time. The medical value of presymptomatic diagnosis of patients with Gaucher disease and carrier testing has not been established. For this reason, pilot studies examining the potential benefits and/or harms of such screening programs should be encouraged. Ideally, the target community should be involved in the implementation and evaluation of such pilot studies.

3. WHAT ARE THE INDICATIONS FOR TREATMENT OF PATIENTS WITH GAUCHER DISEASE, AND WHAT ARE THE APPROPRIATE MODES OF THERAPY?

The clinical features of type 1 glucocerebrosidase deficiency are highly variable, ranging from serious multisystem involvement to the absence of signs or symptoms. In addition, the age of onset of clinical features in those who develop symptoms is variable. This degree of variability raises several important issues that must be considered before initiating treatment. First, the characteristic signs of the disorder, which include anemia, thrombocytopenia without bleeding, hepatosplenomegaly without pain or discomfort, and radiologic changes without evidence of fractures or bone pain, must be differentiated from the symptoms of the disorder, such as bleeding, somatic pain, bone crises, and fractures. Second, knowledge is inadequate on the effect of treatment for patients who display signs but no symptoms of the disease. There is a reasonable consensus to treat those who exhibit symptoms; however, no agreement exists on the clinical criteria for initiating treatment. No consistent guidelines are available at this time because of the lack of sufficient information about the natural history of the disease.

In addition, a group of individuals of unknown number have the enzyme deficiency but have not developed signs or symptoms. Because we cannot predict whether these individuals will ever become symptomatic, the appropriateness of prophylactic therapy has not been determined.

A systematic evaluation of enzyme-deficient individuals to define the natural history of the disease is lacking. For symptomatic patients, there should be sufficient extant data given the number of patients who have already been identified, treated, and extensively followed. For asymptomatic individuals, it is necessary to develop protocols for longitudinal evaluation.

Conservative therapy has a role in Gaucher disease, such as hydration, analgesics, and narcotics for pain in bone crises and orthopedic surgical intervention for fractures. The use of vitamin D, calcium, and bisphosphonate in bone crises and for bone growth requires further study.

Although bone marrow transplantation is an effective form of therapy, the risk of mortality and morbidity makes this mode of treatment less desirable.

In type 1 disease, there is good evidence that enzyme replacement therapy with mannose-terminated placental or recombinant glucocerebrosidase is beneficial in reducing hepatosplenomegaly, improving hematologic parameters, and, to a lesser extent, in alleviating bone disease. Enzyme therapy appears to obviate the need for splenectomy in most cases.

Several patients with type 2 disease are reported to have been treated with enzyme replacement therapy, and there was no substantial improvement in their neurologic problems. With current technology, enzyme replacement therapy is unlikely to prove efficacious for patients with type 2 disease. The efficacy of enzyme replacement for neurologic abnormalities in type 3 disease remains to be established.

For individuals with type 1 disease, controversies continue over aspects of enzyme replacement therapy, such as dosage, methods and frequency of administration of the enzyme, and cost. The most contentious issue, and potentially the most difficult for patients and their physicians, is enzyme dosage. Clinical successes have been observed with both the high- and low-dosage regimens (described as the amount of enzyme administered during a 4-week interval for purposes of comparison, independent of dosage schedule): 120 U/kg for 4 weeks and 30 U/kg for 4 weeks, respectively. Inadequate clinical responses were also reported for all dosage regimens tested. The debate about dosage is complicated by the failure to compare data adequately and by the diversity of protocols. Review of the data indicates two salient points. First, patients vary considerably and unpredictably in their responses. Second, many patients do well on lower-dosage regimens. The use of low-dose regimens for such patients would markedly reduce costs. Debates focusing on minimal differences in degrees and rate of improvement have detracted from the appreciation of the treatment's value.

Current studies are evaluating regimens with dosages even lower than 30 U/kg for 4 weeks. The patients in these studies may respond well, but some respond more slowly. Initial and maintenance therapy should be directed at achieving sustained benefit with the lowest possible dosage. The choice of dosage and frequency of enzyme administration will have to be adjusted individually while each patient's progress is monitored. Response may be slow regardless of dosage.

Given the limited number of patients, the treatment strategies, including criteria for intake, dosage, and periodic reevaluation, should be standardized to ensure that data from multiple centers can be pooled to evaluate the proposed treatment regimens. The resolution of these treatment issues can be addressed best through carefully designed, cooperative clinical trials. The questions to be answered by such trials will be refined if existing data sets are pooled and analyzed without preconceived constraints. In addition, further studies should include the development of more efficient cellular targeting and uptake of the enzyme. The clinical and ethical ramifications of enzyme therapy and the funding of clinical trials must be considered.

Studies to evaluate alternative forms of enzyme replacement therapy and alternative approaches, such as the use of inhibitors of sphingolipid biosynthesis, should be encouraged. Moreover, Gaucher disease is an excellent candidate for gene therapy, and continued research on this modality, including the use of animal models, is therefore indicated.

4. WHAT ARE THE GOALS FOR AND CONSEQUENCES OF TREATMENT, AND HOW CAN THE THERAPEUTIC INTERVENTIONS BE ASSESSED?

The goals of treatment are the amelioration of the manifestations of Gaucher disease and the overall improvement of the health and quality of life of patients.

Although enzyme replacement therapy (alglucerase) has been shown to amelio-

rate many of the manifestations of type 1 Gaucher disease, the major current concerns are the proper indications to begin treatment, the most appropriate treatment regimens, and cost. Answering the many questions concerning the management of Gaucher disease will require a cooperative effort of considerable scale. For this cooperative effort to have its intended impact, the organizer of the cooperative effort must be free of real or perceived bias. The National Institutes of Health should take the initiative and foster the establishment of a cooperative group of investigators involved in the diagnosis and treatment of patients with Gaucher disease. Three phases in the operation of the proposed group are (1) establishment of a patient registry, (2) analysis of the existing data on natural history and response to therapy, and (3) design and conduct of clinical trials to address unanswered questions.

It would be advantageous to enter all patients with Gaucher disease into a registry. Such a registry would provide a valuable resource for increasing our knowledge of the natural history of the disease, help to identify predictors of response, and facilitate clinical trials to answer specific questions about therapy.

Clinical trials will be most informative if recruitment numbers are adequate to answer the questions addressed, if individuals are stratified for the most relevant variables (eg, genotypes or baseline enzyme levels) to ensure comparability of the various subject groups, and if patients are randomized to treatment arms where appropriate.

A high priority for an early clinical trial is comparison of the dosage and frequency of enzyme administration to symptomatic patients. Outcomes to be assessed should include not only hemoglobin concentration, platelet count, spleen and liver size, and bone integrity, but also the patient's functional state, convenience, satisfaction, quality of life, impact on the family, and cost.

A second priority for a clinical trial is to assess the need for enzymatic treatment of asymptomatic patients. Such a trial might initially be confined to high-risk, asymptomatic patients to increase the likelihood of observing a preventive effect of treatment.

5. UNDER WHAT CIRCUMSTANCES COULD GENOTYPE/PHENOTYPE CORRELATIONS BE USED FOR PATIENT CARE AND COUNSELING?

More than 50 mutations of the glucocerebrosidase gene have been identified. Investigators are using disparate nomenclature for mutations with reference to genomic DNA, cDNA, the exon involved, and the amino acid alteration in the enzyme. For consistency and ease of communication, mutations should be described using both the amino acid sequence and cDNA, when appropriate.

Most investigators have categorized their study populations into Ashkenazi Jewish and non-Jewish cohorts. Four mutations are reported to account for 90% of type 1 Gaucher alleles in the Ashkenazi Jewish population and 61% of type 1 Gaucher alleles in non-Jewish populations. However, these studies do not provide an unbiased estimate of the allele frequencies. Therefore, accurate calculations of the number of individuals who carry the disease genotype are not possible.

Concordance between the genotype and phenotype in Gaucher disease is imperfect. Families with multiple affected members having different clinical presentations and families with discordant identical twins further demonstrate the imprecision of genotype/phenotype correlation. However, the following general conclusions can be drawn based on current data:

1. Homozygosity for N370S (1226G) precludes neuronopathic involvement; that is, it produces type 1 disease only. Nevertheless, this genotype is present in individuals with considerable variability in expression, ranging from absence of signs and symptoms, to mild to moderate disease, to, less commonly, severe type 1 Gaucher disease.

2. Compound heterozygotes with one N370S (1226G) allele have nonneuronopathic Gaucher disease (the one exception a child with oculomotor involvement). These individuals generally have more severe type 1 disease than do N370S (1226G) homozygotes.

3. Homozygotes for L444P (1448C) in the Swedish Norrbottnian population generally present with neuronopathic type 3 disease of variable severity. This same genotype in the Japanese population is associated with nonneuronopathic disease, indicating that genotype/phenotype correlations, to the extent that they exist, may vary with genetic background.

The lack of predictability of phenotype from genotype suggests other genetic and/or nongenetic effects on the phenotype. The opportunity exists to study ethnic isolates, such as the Swedish Norrbottnian and Israeli Jenin Arab populations, each with a single Gaucher genotype and variable expression, to determine the nature of these other genetic and nongenetic factors.

This imperfect agreement between genotype and phenotype limits the ability to establish the prognosis for individual patients and also restricts the usefulness of genotyping for population screening and prenatal diagnosis. The failure of genotype to predict phenotype complicates genetic counseling for newly diagnosed patients and their families, and for prenatal diagnosis.

Testing has been conducted for affected individuals, for carriers, and for prenatal diagnosis. Another reason for genotyping is to estimate carrier and affected frequencies in various populations. Genotyping of anonymous unselected populations is recommended to determine allele frequencies.

The benefits of general population screening for affected individuals are not clear, because treatment of individuals with glucocerebrosidase deficiency who do not have signs or symptoms has not yet been demonstrated to be necessary or efficacious. In addition, the genotype offers limited prognostic information for the individual. Extensive education of health care providers about Gaucher disease should be initiated to ensure accurate and early diagnosis of symptomatic patients.

Carrier screening has most commonly been conducted to provide reproductive counseling and options to couples. This requires (1) a simple, accurate, and relatively inexpensive test to identify most of the carriers (>95% sensitivity) with few false positives (high specificity); (2) a disorder of significant clinical severity; (3) a defined population for screening; (4) a test that allows accurate prediction of the clinical course of the disease; (5) a public and professional education program; and (6) informed consent for screening. Although genotyping for Gaucher disease meets the test criteria, genetic counseling can provide only a risk assessment of passing on the gene but not a specific prognosis for future affected children. The uncertainty of disease severity in each affected individual and the lack of public and professional awareness of Gaucher disease argue against carrier screening in the general population at this time. Cultural mores within specific communities should be considered and may justify carrier screening. Carrier testing for family members of affected individuals is appropriate. In addition, peer-reviewed pilot studies of carrier screening programs may be of value.

Prenatal diagnosis for Gaucher disease is possible and allows couples at risk to make informed reproductive decisions. Because of the considerable variability in disease severity, personal experience with Gaucher disease in a family member will influence the genetic counseling process and ultimate decision. Genetic counseling is confounded by the inability to predict clinical prognosis uniformly, by the heightened anxiety en-

gendered by facing probabilistic information, and by the availability of an encouraging but extremely expensive enzyme replacement therapy. The description of the illness, its manifestations, and its potential response to therapy all influence the decisions made by couples, individuals, and families.

6. WHAT ARE APPROPRIATE DIRECTIONS FOR FUTURE RESEARCH AND OTHER RELEVANT ISSUES THATS SHOULD BE PURSUED?

Nomenclature must be standardized throughout the field, from the clinical setting to the molecular genetic laboratory. For example, a term as basic as "asymptomatic" is used by workers in the field in very different ways. It is recommended that the term asymptomatic be reserved for individuals who are truly without symptoms. The mutation designation also needs to be standardized for improved ease of communication.

A uniform clinical severity score for type 1 Gaucher disease must be developed and formally validated to permit effective communication regarding the efficacy of treatment. This clinical rating scale should be sensitive to both the signs and the symptoms of the disorder.

A nationwide clinical database should be established that is independent of any corporate entity, particularly those involved in the screening, diagnosis, management, or treatment of Gaucher disease. This will facilitate research to elucidate the natural history of the disease, identify key prognostic factors for disease progression, and determine the influence of various therapies. The database should accumulate existing information and collect missing data on previously diagnosed patients to permit evaluation of enzyme targeting, uptake efficiency, optimal dosage and schedule, and clinical outcome. In the event of prenatal diagnosis, the neonatal, childhood, adolescent, and adult course of the disease should be carefully documented. Molecular genetic data should be determined and correlated with the clinical information to refine the limits of genotype/phenotype correlations. Such a database will permit the use of mathematical modeling to investigate these questions. The information in the database should be made available to investigators after formal review of their research proposals. Within the database, it should be recognized that multiplex families and identical twins represent unique groups for the study of other factors influencing phenotype.

Nationwide, cooperative, controlled clinical trials should be conducted to establish optimal regimens and to determine their efficacy for asymptomatic individuals with minimal clinical signs. These clinical trials should be free of influence from any commercial entity.

The available technology is not yet appropriate for large-scale, population-based screening for Gaucher disease. However, we recommend that additional pilot projects be supported, independent of corporate influence, to identify carriers and affected individuals. Examples of potential projects include estimation of the true prevalence of the various mutant alleles in defined or mixed populations by anonymous testing; further evaluation of educational needs within screened populations; and elucidation of the value of enzyme delivery to asymptomatic, enzyme-deficient individuals with varying clinical signs. Laboratories providing screening or diagnostic testing should participate in national quality assurance and quality control programs.

Studies to better understand the basic biochemistry and cell biology of the enzyme are needed. Identifying and developing animal models should be encouraged. They provide opportunities to improve the understanding of the pathogenesis and to test experimental strategies including gene therapy.

Enzyme replacement therapy clearly has improved the health and quality of life of individuals with Gaucher disease. This treatment has been made possible through the efforts of investigators at the National Institutes of Health and other researchers nationally and internationally. The cooperative efforts of government and industry have also proven effective. The contributions of the patients and their families, who have participated so willingly in many therapeutic trials, have been especially important.

The experience with enzyme replacement therapy to date has led to new understanding about the disease and its treatment. At the same time, this experience has raised concerns about the development of costly therapies for disorders of very low prevalence. These concerns include the following:

- Should the rights to exclusive marketing of an orphan drug be coupled to federal approval of the price charged for the drug, and should uniform accounting practices be required?
- Can such price regulation of orphan drugs be imposed without deterring the development of effective drugs for uncommon diseases?
- How can it be ensured that the price patients pay for a drug reflects the federal contribution to its development?
- Should society be informed of corporate and other relationships between entities engaged in screening and the manufacturers of therapeutic agents?
- Should pharmaceutical companies and their representatives have direct access to patients?
- Given the potentially extraordinary costs of treatment, how should the benefits to affected individuals and their families be balanced with the other health care needs of society?
- Regarding costly treatments such as alglucerase, what are the implications for the future health care of patients and their families when insurance becomes exhausted and/or when coverage is provided by managed care systems employing fixed capitation limits?

CONCLUSIONS

The success of enzyme replacement therapy for Gaucher disease is a credit to the investigators, the National Institutes of Health, the pharmaceutical manufacturer, and the many patients and their families. Evidence presented at this Technology Assessment Conference leads to the following conclusions:

- Despite the success of enzyme therapy, treatment is limited by the cost of the agent.
- The cost of the treatment makes it imperative to determine the lowest effective initial and maintenance dosages and the most cost-effective dosage for clinical response, to define the appropriate clinical indications for treatment, and to establish uniform methods to optimize outcome assessment.
- The value of treatment for asymptomatic individuals has not been determined.
- General population screening for affected individuals and for carriers is not appropriate at this time.

As a prototype for all rare diseases, the plight of the patients with Gaucher disease raises difficult financial and ethical issues that we as a society must address.

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Speakers: Johannes M. F. G. Aerts, PhD, "Enzymatic Diagnosis and Biochemical Detection of Disease Manifestation"; John A. Barranger, MD, PhD, "Gene Therapy for Gaucher Disease"; Norman W. Barton, MD, PhD, "Introduction to Enzyme Replacement Therapy"; Ernest Beutler, MD, "North American Patients With Gaucher Disease," "Binding, Internalization, and Degradation of Glucocerebrosidase by Macrophages," and "Enzyme Replacement Therapy"; Roscoe O. Brady, MD, "Overview and Introduction to Gaucher Disease"; Ian J. Cohen, MD, ChB, "Use of Enzyme Replacement Therapy and Bisphosphonate in Severely Affected Children in Gaucher Disease"; Timothy M. Cox, MD, "In Vivo Distribution of Mannose-Terminated Human Glucocerebrosidase in Patients With Gaucher Disease"; Rabbi Josef Ekstein, "Premarital and Anonymous Screening for Recessive Genetic Diseases: Recent Experience With Gaucher Disease"; Christine M. Eng, MD, "Genetic Screening in the Ashkenazi Jewish Population: Experience With a Pilot Program for the Simultaneous Screening of Three Genetic Diseases"; Anders Erikson, MD, PhD, "Norrbottnian Patients With Gaucher Disease"; Deborah M. Findling, MS, "Demographic Study From a National Gaucher Screening Program"; Alan M. Garber, MD, PhD, "Economic Considerations in Alglucerase Therapy of Gaucher Disease"; Edward I. Ginns, MD, PhD, "Animal Models of Gaucher Disease" and "Development of Alternative Therapies for Gaucher Disease"; Gregory A. Grabowski, MD, "Genotype-Phenotype Correlations in Gaucher Disease" and "Enzyme Therapy in Gaucher Disease"; Suvimol C. Hill, MD, "Radiographic Assessments of Gaucher Disease"; Carla E. M. Hollak, MD, "Individualized Low-Dose Alglucerase Therapy for Type 1 Gaucher Disease"; Michael M. Kaback, MD, "Type 1 Gaucher Disease: Heterozygote Screening in the Ashkenazi Jewish Population—An Alternative Perspective"; Robert E. Lee, MD, "The Natural History and Pathology of Gaucher Disease"; Henry J. Mankin, MD, "Bone Disease in Patients With Gaucher Disease: Evolution, Assessment, and Therapy"; Pramod K. Mistry, PhD, MRCP, "In Vivo Distribution of Mannose-Terminated Human Glucocerebrosidase in Patients With Gaucher Disease"; Richard A. Moscicki, MD, "Adverse Reactions and Development of Antibodies During Enzyme Replacement Therapy"; Gary J. Murray, PhD, "In Vivo and In Vitro Studies on Targeting and Receptor-Mediated Uptake of Glucocerebrosidase"; Marvin Natowicz, MD, PhD, "Ethical, Legal, Social, and Insurance Aspects of Screening for Genetic Diseases"; Gregory M. Pastores, MD, "Enzyme Replacement Therapy for Gaucher Type 1 Disease: The Mount Sinai Experience"; M. Clara Sá Miranda, PhD, "Phenotypic and Genotypic Characterization of Different Gaucher Populations: European/Asian Patients With Gaucher Disease"; Ellen Sidransky, MD, "DNA Mutational Analysis of Phenotypically Diverse Populations of Gaucher Patients"; John E. Ware, Jr, PhD, "Estimating the Health Burden of Gaucher Disease and the Health Benefit of Enzyme Replacement Therapy: A Psychometric Approach"; Rob Willemsen, "Visualization of Alglucerase Targeting: An Immunocytochemical Study on Mouse Liver"; Rina Zaizov, MD, "Use of Enzyme Replacement Therapy and Bisphosphonate in Severely Affected Children in Gaucher Disease"; Ari Zimran, MD, "Phenotype Correlation in Israeli Patients With Gaucher Disease" and "Results of Splenectomy, Partial Splenectomy, and Enzyme Replacement Therapy in Israel."

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