THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

OSTEOPOROSIS is an increasing public health problem, and the costs related to hip fractures alone are expected to double in North America and Europe in the next 25 years. The disorder is characterized by enhanced bone fragility, resulting in an increased risk of fractures, and is usually defined according to the reduction in bone mineral density. Early diagnosis is now possible with the use of precise methods for measuring bone density. Optimal management consists of maximizing peak bone mass in early adulthood and preventing the rapid bone loss that occurs soon after the menopause in all women and again much later in some.[1] Treatment to restore bone strength in women with established disease may also reduce the risk of fractures.

In this issue of the *Journal*, Liberman et al.[2] report the results of a multicenter randomized, placebo-controlled trial of the effects of alendronate, a new bisphosphonate, in 994 postmenopausal women. Alendronate was given orally in a daily dose of 5 to 10 mg for three years or 20 mg for the first two years followed by 5 mg for the third year. All the women received 500 mg of calcium daily. The optimal regimen appeared to be 10 mg of alendronate daily, because the women receiving this dose had an increase of more than 8 percent in lumbar bone density at three years, as compared with a small decrease in the placebo group, with similar but less marked changes at other skeletal sites. The rate of vertebral fractures in the combined alendronate groups was approximately half that in the placebo group.

Internationally, the agents used most widely for the treatment of postmenopausal osteoporosis are calcium, estrogen, calcitonin, fluoride, calcitriol, and an early bisphosphonate, etidronate. In general, these agents can be divided into two categories according to whether they stimulate bone formation or inhibit bone resorption. Fluoride, the only one of these agents that stimulates bone formation, can increase bone density substantially. The effect of fluoride on the risk of fractures has been disappointing, although reanalysis of the data from one large trial showed a protective effect in women who had moderate increases in bone density,[3] and new, slow-release formulations offer promise. In contrast, the antiresorptive agents act primarily to prevent further bone loss; bone density usually increases somewhat for a year or two, then plateaus. The administration of calcium can slow bone loss in postmenopausal women and is relatively safe and inexpensive, but calcium generally does not increase bone mass at sites such as the lumbar spine.[4] Estrogen therapy can increase bone density at the lumbar spine in women with postmenopausal osteoporosis,[5] but side effects such as weight gain and breast tenderness decrease compliance among older women, and there is concern about an increased risk of breast cancer in women treated for many years. Calcitonin has a smaller effect on bone mass[6] and is relatively expensive. Unlike calcium, vitamin D analogues, such as calcitriol, can increase lumbar bone mass[7] and decrease the rate of vertebral fractures.[8]

Etidronate also increases lumbar bone mass in women with postmenopausal osteoporosis and appears to reduce the rate of vertebral fractures.[9] The agent must be given cyclically, however, to avoid adverse effects on bone mineralization. Alendronate is about 1000 times more potent, in terms of inhibiting bone resorption, than etidronate and therefore provides effective inhibition of bone resorption at doses that do not affect mineralization. Several other new bisphosphonates, including tiludronate and residronate, are being evaluated in clinical trials.

There are several intriguing aspects of the alendronate study reported by Liberman et al. Unlike most previous therapeutic trials in women with postmenopausal osteoporosis, which have been limited to women with at least one vertebral fracture at base line,[3,5-9] the alendronate study, in which osteoporosis was defined only on the basis of a reduction in bone density ($\geq$2.5 SD below the mean value in premenopausal white women), included women without vertebral fractures at base line, as well as those with fractures.

During the study, 3.2 percent of the women treated with alendronate had new vertebral fractures, as compared with 6.2 percent in the placebo group, and the effect appeared to be greatest in the women who were 65 or older or had previous vertebral fractures. There was also a trend toward a reduction in nonvertebral fractures in the alendronate group. Whether the rates of nonvertebral fractures will decrease significantly remains to be determined and is particularly important, because the overall incidence of nonvertebral osteoporotic fractures is higher than that of vertebral fractures.

The low incidence of adverse events suggests that alendronate has a favorable safety profile, but because bisphosphonates accumulate in the skeleton for prolonged periods, long-term safety remains an important question. Other questions, such as the long-term effect of the new bisphosphonates on bone turnover and mechanical strength, also remain to be answered.

The key question may be whether bisphosphonates such as alendronate are superior to other antiresorptive agents used to treat women with postmenopausal osteoporosis. When treated women were compared with women receiving placebo, lumbar bone density was 5 percent higher after one year of treatment with estrogen and 2 percent and 6 percent higher after two years of treatment with calcitonin and calcitriol, respectively.[3,4,7] An initial increase in bone mass can be due to the filling of bone spaces that are undergoing remodeling, however, which makes the interpretation of short-term studies difficult.[10] In the study by Liberman et al., which provides data on three years of treatment, sus-

tained increases in bone density in the women receiving 10 mg of alendronate were evident in each year, including the third, which is surprising for an antiresorptive agent. This finding suggests that some reversal of osteoporosis may be possible in the long term with the 10-mg dose. Since the effect on bone density appeared to reach a plateau with the other doses (5 mg and 20 mg followed by 5 mg), continued treatment is likely to be necessary to maintain this benefit, and bone loss may well resume after the treatment has been stopped. To establish the superior efficacy of drugs such as alendronate in comparison with currently available treatments will require randomized clinical trials.

It has generally been considered more difficult to restore bone mass in women with established osteoporosis than to prevent its loss. Drugs such as alendronate that can not only prevent further bone loss but also increase bone mass should have a major effect on a disease that may reach epidemic proportions during the next several decades.

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SURGERY FOR EARLY BREAST CANCER — CAN LESS BE MORE?

THREE articles in this issue of the *Journal* advance our understanding of the treatment of early breast cancer. In one, the advance comes in the form of reassurance about the quality of a study whose results have already been reported. The results of a clinical trial (Protocol B-06) conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), reported in the *Journal* in 1985[1] and 1989,[2] had been interpreted as showing that lumpectomy followed by irradiation yielded results about as good as those of mastectomy. The results of this large randomized trial were in general agreement with those of other trials[3] and were widely accepted as being close to definitive. In 1991, however, staff members at the NSABP headquarters verified that fraudulent data had been submitted from St. Luc Hospital in Montreal, which had enrolled the largest number of patients in Protocol B-06. When this information became widely known in 1994, many physicians and patients were deeply troubled. Could they continue to rely on the findings of the trial? Among patients otherwise eligible for inclusion in the most recent update, fraudulent data were demonstrated for only 6 of the 322 patients from St. Luc Hospital, among a total of 1851 patients, but many additional fraudulent records were found at St. Luc Hospital for patients enrolled in other NSABP trials. Also, it was not clear whether fraud in Protocol B-06 might have been more widespread at St. Luc Hospital than was first suspected or might have occurred at other hospitals participating in the study.

In 1994 the National Cancer Institute (NCI) audited many of the original records at other participating hospitals to determine the scope of the problem. The results of the audit are reported by Christian et al.[4] in this issue of the *Journal* and are on the whole reassuring, though the audit suffers from some limitations. For example, the audit excluded 52 of the 89 participating hospitals, most because they had contributed fewer than 10 eligible patients, though one might expect rates of random (nondeliberate) error to be inversely correlated with the case volume because of less familiarity with protocol requirements. The audit was limited to reviewing patient eligibility and five other items; problems in additional items would escape detection. Quality control was surely compromised by the use of a very large number of auditors — 76 — in order to complete the work quickly. The auditors' training period was short, and there is no indication that any were experienced in the forensic examination of documents. The audit was separate from the audit of St. Luc Hospital, and the results may not be fully comparable. The audit was not blind to patient-specific information. It appears that only one auditor examined each case record; there is no mention that a sample was reaudited and no comment about the quality of the audits. Little information is given about the direction and effects of detected errors, and there is little comment about hospital-to-hospital variations in error rates. These limitations may have been appropriate to the limited purpose of validating

the results of Protocol B-06, but a rich opportunity to learn more about the conduct of clinical trials and to provide guidance for future audits, if any, has been lost.

A major problem, and one that could have serious implications for studies with predictably high rates of refusal by patients to participate, was the failure of the physicians enrolling patients in Protocol B-06 to be meticulous about informed consent. Although consent status was not audited as vigorously as other items, it appears that of the 1554 records reviewed, only in 1098 — about two thirds — was documented signed informed consent obtained before surgery. In another 210, documented informed consent was obtained after surgery, and in 137 cases the consent forms were not dated. Informed-consent status could not be determined for 38 patients and was simply not verified for 71. This incompleteness is unjustifiable, contrary to protocol, and one may fear, scarcely limited to Protocol B-06 or the NSABP. Informed consent is critically important to the protection of patients' rights, to the individual patient–doctor relationship, and to public acceptance of research on human subjects. Even with the best will, investigators have problems aplenty in obtaining consent that is both free and informed. To find that large numbers of investigators treat consent so casually is disheartening. Patients, if not investigators, take their autonomy seriously, as is documented by the 36 patients in Protocol B-06 who agreed to participate but later apparently withdrew their consent. There is no evidence here that these lapses affected the outcome of Protocol B-06, but that does not excuse the laxity apparent in this critical aspect of patient participation.

A separate issue is the timing of the request for consent called for by the protocol. When the trial began in 1976, the protocol conventionally called for consent to precede randomization. In mid-trial, when faced with seriously low accrual rates, the investigators reversed the order and began to randomize before requesting consent (prerandomization). This meant that patients were told how they would be treated at the time their consent was requested. The rate of enrollment increased sixfold. Although this change in timing affects the attitudes of both physicians and patients, the increase itself is strong evidence that some patients who would have refused to participate in a more usual kind of trial were induced to provide consent after they were already enrolled. The ethical issues raised by this approach, with specific reference to Protocol B-06, were discussed in the *Journal* in 1984.[5-7]

Despite the limitations, I take the basic data of Protocol B-06, excluding those from St. Luc Hospital, to be largely confirmed by the NCI audit and of a quality quite adequate to bear the considerable weight of interpretation placed on them. Physicians and patients can be reassured that their faith in the results, with the exclusion of the data from St. Luc Hospital, was not misplaced.

In a second paper on breast cancer in this issue of the *Journal,* Fisher et al.[8] use the data from the audited patient base, supplemented with additional follow-up, to reexamine the original question. Again, physicians and patients can be reassured. After 12 years, no significant differences in survival could be demonstrated among the groups treated by total mastectomy, lumpectomy alone, or lumpectomy followed by irradiation, when all patients also had surgical clearance of the lower axilla. This was true for both the original cohort (excluding the six patients from St. Luc Hospital whose data were known to be fraudulent) and the cohort that excluded all patients from St. Luc Hospital. It is not surprising that these two analyses led to nearly identical findings, because the revised cohort of 1529 patients made up 83 percent of the 1851 patients included in the most recent update.

Troubling questions remain, however, about the propriety of using any of the data from St. Luc Hospital. I am also troubled that Fisher et al. do not present the findings from St. Luc Hospital separately. I firmly disagree with their reasons for this omission. Internal evidence suggests that these results may differ markedly from the rest of the results. For example, Table 2 of their article shows that the odds of survival for patients assigned to lumpectomy and irradiation, as compared with total mastectomy, were 1.07 with the inclusion of all patients and 1.18 with the exclusion of all patients from St. Luc Hospital. For the exclusion of 17 percent of patients to make a difference of this size, that 17 percent must have had an odds ratio far below the 1.18 for the remainder. Careful, skeptical, and much broader analysis of the entire St. Luc cohort alone is still needed. Pending a report of such work, I recommend the complete exclusion of all data from St. Luc Hospital from interpretations of the main study question in Protocol B-06. I do not mean for this criticism to detract from the substantial accomplishments of the NSABP and Protocol B-06. Even with the St. Luc data excluded, the remaining data are quite sufficient to support the initial, critically important, interpretation for at least the first 12 years of follow-up.

In a third paper on breast cancer in this week's issue, the Early Breast Cancer Trialists' Collaborative Group[9] reports a meta-analysis of randomized trials of radiotherapy and surgery for early breast cancer. Among the 64 trials whose results are summarized are 3 by the NSABP, including Protocol B-06. Serious problems in the performance of meta-analyses are becoming widely recognized.[10,11] These include egregious carelessness by untrained and inexperienced analysts, insufficient understanding of the substantive issues to be resolved when experts in these matters are not deeply involved, failure to consider relevant variables, gross heterogeneity in studies (so that there is no common effect to be estimated), and even serious bias in the interpretation of pooled data. Although these problems may be reparable, the technique of meta-analysis

is currently widely abused, even by well-known practitioners.

However, the analyses reported by the Early Breast Cancer Trialists appear to be carefully done. The authors were able to collect data on individual patients from the original investigators and analyze them patient by patient, so that they avoided many of the problems that stem from differences in approach among the original papers. Their findings thus have some of the additional strength of those from a multicenter trial. The authors found that the addition of radiotherapy to surgery reduced the rates of local recurrence by a factor of 3. However, survival at 10 years was not demonstrably affected by radiotherapy, though it may have induced a small shift in the cause of death from breast cancer to other causes. The authors also found no effect on survival of the removal of more as compared with less breast tissue or of surgical as compared with radiotherapy-induced clearing of the axilla. This analysis adds much weight to similar conclusions drawn from many of these trials individually.

The evidence is now persuasive that reducing the scope of surgical intervention for early breast cancer, within the limits carefully defined in these papers, has little or no effect on survival, at least in the short and midterm. Substantial additional follow-up will be needed to determine whether the reduction in the rates of local recurrence associated with radiotherapy has long-term implications for survival or the quality of life. Limited surgery can hardly be more effective than mastectomy, as measured by survival, but it does not seem to be much less effective either, and the other advantages of more sparing removal of tissue can be very important to patients.

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SOUNDING BOARD

XENOTRANSPLANTATION AND XENOGENEIC INFECTIONS

THE ongoing shortage of human organs and tissues for transplantation, coupled with scientific and biotechnological advances, has catalyzed new attempts to use animal tissues in humans — a field known as xenotransplantation. Pigs and nonhuman primates have been used as sources of organs, with limited success.[1,2] Recently, the transplantation of baboon bone marrow to attempt to reconstitute the immune system in patients with AIDS was proposed,[3] and fetal-pig mesencephalon cells are being studied for the treatment of patients with refractory parkinsonism.

The use of xenogeneic tissues in transplantation has raised concern about potential infection with both recognized zoonotic pathogens and unknown xenogeneic agents. Some authorities have cogently argued that the use of nonhuman primates as sources of tissue for humans presents unacceptable risks.[4] Often, in the public debate, these reasoned arguments are either quickly discounted or unreasonably exaggerated. It is useful to examine them in the light of the experience with viral zoonotic infections.

IS THERE A RISK FOR TRANSPLANT RECIPIENTS?

The transmission of pathogens through human-to-human organ transplantation has been well documented[5,6] and has caused serious complications in immunosuppressed transplant recipients.[7] The terms "xenosis" and "xenozoonosis" have been proposed to describe infectious illnesses introduced into humans through procedures involving xenogeneic tissue.[8,9] In contrast, "zoonosis" refers to a disease mediated by an animal pathogen and transmitted to humans under natural conditions. Zoonoses serve as logical models when one is considering the risk of transplant-associated xenogeneic infections.

Mechanisms of evolutionary adaptation are inherent in both pathogens and their natural hosts. The disease-producing potential of an infection is a function of the relation between the host and the infecting agent; the biologic features of both are contributory.[10] Thus, the pathogenic potential of an infection can change in an unpredictable fashion when the infecting microbe is transmitted from its natural host into a new species. For

example, each of five hantaviruses recognized as causing zoonotic disease in humans is associated with a distinct rodent host. The phylogenetic relation among the viruses mirrors that among their rodent hosts, indicating that they have evolved together.[11,12] In the rodent hosts, the hantaviruses produce no detectable morbidity or mortality. However, when the viruses cross species lines into humans, they cause disease with mortality rates as high as 50 percent.[13]

The unpredictability of the pathogenic potential of a microbe in humans does not diminish with less phylogenetic distance between the host species and humans. For example, in the macaque monkey, its natural host, cercopithecine herpesvirus 1 (B virus) has a clinical profile very similar to that of herpes simplex infection in humans. However, B virus infections in humans or other primates that are not macaques result in an encephalitis for which the mortality rate is about 70 percent.[14] Conversely, the infection of rhesus monkeys with measles results in mild disease similar to that in humans, but in marmosets such infection produces severe, frequently fatal disease.[15]

Is There a Potential Threat to the Public Health?

If the risk of xenotransplant-associated infections is restricted to the recipient, it simply constitutes one more factor affecting the risks and benefits of transplantation. However, there may be wider implications for the human community. Once introduced into humans, zoonotic viruses that are not particularly pathogenic in their host species have produced noteworthy outbreaks of disease. For example, the importation into Germany in 1967 of vervet monkeys infected with the Marburg filovirus resulted in two generations of human-to-human transmission, involving 31 persons, with a case fatality rate of 23 percent.[16] The admission to the hospital of patients infected with Ebola, another zoonotic filovirus, resulted in large nosocomial outbreaks in Sudan in 1976 and Zaire in 1976, 1979, and 1995,[17] with multiple generations of human-to-human transmission and case fatality rates of 80 to 90 percent. In Pakistan in 1976, a shepherd with gastrointestinal bleeding due to unrecognized infection with Crimean–Congo hemorrhagic fever virus, a zoonotic bunyavirus, underwent an exploratory laparotomy. Two generations of human-to-human transmission ensued, involving 17 persons and producing a case fatality rate of 24 percent.[18] In such outbreaks the virus is initially transmitted from the patient to medical-staff and family members and then the wider community.[19,20] Thus, the global experience with zoonotic viruses provides substantial evidence of the potential for epidemic infection in humans due to transplant-associated xenogeneic infections.

The suddenness and severity of a zoonotic outbreak may predict how much attention it will receive but not its eventual importance to the public health. Indeed, the public health consequences of xenogeneic infections may be most profound when the immediate pathogenicity is least evident. The infection of humans with filoviruses and bunyaviruses results in acute clinical illness followed by recovery or death. The human host, with no evolutionary adaptation to these viruses, cannot sustain viral amplification for more than a short time, limiting its effectiveness as a source of transmission among humans. Thus, the public health consequences of such outbreaks are limited. They contrast sharply with the quiet but pandemic spread of the human immunodeficiency virus (HIV).

Compelling arguments suggest that the epidemics of HIV types 1 and 2 (HIV-1 and HIV-2) resulted from the adaptation of simian retroviruses introduced across species lines into humans. When mixed populations of captive nonhuman primates are housed together, transmission of retroviruses across species lines occurs with relative ease. Although infected members of the primary host species generally remain healthy, cross-species transmission is usually followed by increases in both the diversity of viral phenotypes and the virulence of the virus in the new host species.[21,22] Comparisons of genetic sequences reveal close relations between HIV-1, HIV-2, and the simian immunodeficiency viruses (SIV).[23,24] Although the pathogenic potential and the transmissibility of SIV among humans remain undefined, active infection has been confirmed in a person who works with nonhuman primates.[25] A serologic survey of 472 workers who had been in contact with such primates identified antibodies to SIV in 3.[26] HIV-2 is more closely related to a strain of SIV that is endemic in sooty mangabey monkeys than to HIV-1.[23,27] Furthermore, the geographic distribution of HIV-2 infection in humans in West Africa parallels the natural habitat of the sooty mangabey.

These data suggest that the HIV-2 epidemic in West Africa began with the transmission of SIV from a sooty mangabey into a human, with subsequent transmission among humans. In Central Africa, the cross-species transmission of SIV from a different species of primate, probably the chimpanzee, appears to have resulted in the HIV-1 pandemic.[28,29] Initial infections of humans before 1970 resulted in more than a decade of insidious human-to-human transmission before AIDS was first identified as a public health problem in the early 1980s. Besides SIV, an expanding number of exogenous retroviruses are recognized as infecting nonhuman primates.[22,30-35] Standardized diagnostic tests are not available for most of these retroviruses.

Endogenous retroviruses, widely present in mammalian species, presumably originated as exogenous viruses that became permanently integrated into the host germ line; they are transmitted from mother to child.[36] The endogenous retroviruses cause even more uncertainty than the exogenous retroviruses. In the host species they are benign. However, endogenous viruses are

frequently xenotropic; although the original host is refractory to infection, the viruses can infect related species. For example, the proviral DNA of the baboon endogenous retrovirus can be detected in the tissues of all baboon species, as well as those of many monkeys. This xenotropic virus can be readily isolated by cultivating baboon tissue with human cells, although the direct risk of infection it presents in humans is unknown.[37] Phenotypic mixing of baboon endogenous retrovirus with other primate viruses occurs under appropriate experimental conditions, which suggests that endogenous retroviruses may recombine in humans after xenotransplantation.[38] Viral mixing could create a hybrid better adapted to survival, replication, and pathogenicity in the human host.

The general presumption that the greater phylogenetic distance between humans and swine (as compared with nonhuman primates) makes swine safer donors has not been completely explored. The biologic and pathogenic features of a type C retrovirus identified in the blood of leukemic or irradiated swine have not been completely characterized.[39,40] The short life expectancy of the average pig minimizes the opportunity to observe the clinical manifestations of infections with agents that have long periods of clinical latency, such as retroviruses or prions.[41] We do not know what the potential is for endogenous retroviruses in transplanted porcine tissue to infect immunosuppressed human recipients, convert replication-defective viruses to viruses capable of replicating, or recombine with latent human viruses to create pathogenic hybrids. The development of techniques of encapsulation intended for the immunologic isolation of xenogeneic tissue and the creation of transgenic animals whose organs are intended to survive immune surveillance after transplantation may increase the potential for viral recombination or reassortment.[2] It has been suggested that the periodic emergence of new pandemic strains of influenza occurs by such a process of reassortment between influenza viruses from humans and animals (including swine).[42]

Like retroviruses, prion encephalopathies have protracted clinical latency.[43] No diagnostic tests are available. Transmission has been documented both between species and through transplanted tissue.[43,44] The transmission of prions has no epidemic potential, however.

How Can the Public Health Risks Be Minimized?

The lessons learned from zoonotic disease argue that there are enough risks of infection inherent in xenotransplantation to justify a reasonable degree of public concern. There are public health guidelines intended to minimize the risk of transmitting known pathogens through human-to-human transplantation, and similar guidelines addressing xenotransplantation are under development. In the interest of patients, medical staffs, and the public, planning for these risks should be incorporated into any clinical strategy involving the use of xenographic tissue in humans.

Infections with recognized zoonotic pathogens should be relatively preventable and identifiable. The risk of infecting a recipient can be decreased by controlling the quality of the source of animals, screening and quarantining those animals, and procuring tissue with aseptic techniques. For some purposes, the use of special pathogen-free or gnotobiotic animals may be warranted.[45] Bacterial and parasitic infections of donor animals can be readily identified and treated before tissue is collected.[46] However, in patients with xenotransplants the diagnosis and management of familiar zoonoses may be complicated by immunologic manipulations that alter the clinical presentation of illness, the reliability of antibody testing, and the response to therapy. Infusions of bone marrow from the animal and other new strategies proposed for manipulating the immune response of the host undergoing xenotransplantation may also raise the risk of infectious disease. The intense immunosuppression of patients undergoing xenotransplantation may facilitate both the amplification and the epidemic potential of pathogens. The effect xenogeneic tissue will have on antigen presentation and the targeting of effective immune responses to new pathogens is not known. The evaluation of disease may require diagnostic tests based on the detection of nucleic acids, methods of cell culture, or other nonstandard techniques.

It will be essential to monitor the individual recipients of xenogeneic tissue for the occurrence of unexplained illnesses and populations of recipients for clustering of events. Once there is a problem in the general population, public health measures can decrease but rarely eliminate the risk. For this reason, we need surveillance that can detect new xenogeneic infections in recipients before they spread to the general population, plus a mechanism for the prompt suspension of protocols involving the same species or tissue. The development of a national registry of exposure to xenogeneic tissue would greatly facilitate such surveillance.

Judgments always differ about the extent to which the potential for medical progress justifies the acceptance of associated risks. Therefore, before proceeding further with xenotransplantation, we need a multidisciplinary consensus to facilitate the development of measures designed to protect the safety of all, to indicate the directions of further research, and to advance well-designed clinical trials as the use of xenogeneic tissue makes the transition from animal models to medical practice. Clinicians and policy makers alike must recognize that although xenotransplantation promises benefits for specific patients, that promise is accompanied by an unquantifiable but undeniable potential for harm to the wider community. Thus, in this new field the determination of what constitutes an acceptable risk in the balance between caution and progress is a matter

of public concern, not merely a private matter for individual scientists, physicians, and patients to decide.

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