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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Suitability Determination for Donors of Human Cellular and Tissue-Based Products,
[Docket No. 97N-484S]

Dear Sir/Madam:

The Eye Bank Association of America recently commissioned a committee to provide an independent report on the occurrence and transmissibility of Creutzfeldt-Jakob Disease (CJD) as it relates to cornea transplantation and to comment on the proposed rule concerning "Suitability Determination for Donors of Human Cellular and Tissue-Based Products." The committee includes members with expertise in prion disease, cornea transplantation, eye banking, neurology, and epidemiology. We have considered various approaches to minimize the risk of CJD development among cornea recipients and have reached the following conclusions:

1. Collection of information on signs and symptoms suggestive of CJD would not be a useful method of screening potential donors. At best, the possible reduction in risk of CJD transmission would likely be very small in relation to the associated costs, particularly due to decreased supply of useable tissue.
2. Current laboratory methods of testing for CJD are not adequate to screen potential donors within the short time before corneas must be used.
3. The death rates of CJD, though quite low, are highest in the older age groups. For purposes of minimizing the overall risk of CJD transmission, each Eye Bank should encourage policies and procedures that ensure maximum use of young donors even as the supply of older donors continues to expand.
4. The available medical information on potential donors should be reviewed for any evidence of a diagnosis or family history of CJD and for evidence that human pituitary-derived growth hormone had been received. Any with positive findings should be eliminated from further consideration for cornea donation. We are not aware of any Eye Bank in the United States that does not already adhere to this recommendation.

Collection of information on signs and symptoms suggestive of CJD: This issue was approached by evaluating epidemiological information on age-specific death rates of CJD, age-specific all cause death rates, the current age distribution of cornea donors, and estimates of the incubation period of CJD in humans. We estimated the levels of risk posed by potential donors who might have been symptomatic from CJD at the time of death (approximately 9% of total risk) as well as by those who might have been incubating CJD (assuming a 10-year incubation period) even though symptoms had not yet developed (approximately 91% of total risk). These estimates suggest that much of the potential risk could not be eliminated because donors with preclinical (not yet symptomatic) CJD could not be identified.

Among the annual total of approximately 45,000 cornea donors in the United States, we estimate that 1.3 donors might be expected to have either preclinical or symptomatic CJD. However, the

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risk of CJD occurring in a cornea recipient is much lower than the estimate of the likelihood of CJD occurring in a cornea donor. In the United States, a single case was reported in 1974, before guidelines were used to specifically exclude potential donors with known CJD. No additional cases of CJD have been reported among recipients of the more than 500,000 donor corneas that have been transplanted in the United States since that time. Because of the low frequency of CJD among potential donors, any screening program would need to have very high specificity (i.e., correctly identify those who do not have CJD) in order to avoid significant losses of useable tissue. Several factors would limit the specificity of questioning about symptoms of CJD including: 1) the symptoms of CJD overlap with common age-related findings among the elderly (e.g., mental deterioration); and 2) the information would be obtained by technicians with limited medical training from family members and others who may have considerable difficulty in judging and agreeing on whether a potential donor had a particular symptom.

Our estimates indicate that because of the combination of low occurrence of symptomatic CJD at the time of death of cornea donors (approximately 1 case every 8 years) and limited specificity of questioning about signs and symptoms, screening would likely result in many thousands of otherwise useable corneas being discarded in order to exclude even a single donor who had symptomatic CJD. For example, if the specificity of screening were as high as 90% and screening were applied only to donors 50 to 69 years of age (the group at highest risk), more than 15,000 donors (30,000 corneas) would be excluded during the same eight-year period. Although sufficient donor corneas are available to meet current demand in the United States, worldwide demand will far exceed supply for the foreseeable future. Consequently, restriction of the supply of donor corneas would have a direct impact on the number of patients who could have their vision restored by cornea transplantation.

Laboratory testing of potential cornea donors for CJD: Potential screening tests would be limited to immunohistopathological examination of either brain or retina. Neither test satisfies criteria necessary for testing to be performed on a routine basis. The criteria would include: 1) reasonable cost in relation to expected improvements in safety; 2) high sensitivity and specificity; 3) completion of testing within the short period of time before a donor cornea must be used; and 4) accessibility and availability of tissue for testing. Screening of blood for the presence of diagnostic prion protein might meet these criteria, but no sufficiently sensitive methodology has yet been discovered (several laboratories are currently working on the problem, and a blood test may become available within the next two years).

Encourage maximum use of young donors: The risk of CJD among donors less than 40 years of age at the time of death is approximately 40 times lower than the already low risk among older donors. This suggests that efforts to maximize the supply of young donors would help to keep the overall level of risk of CJD transmission as low as possible. However, exclusion of potential donors because of older age would not be an appropriate screening strategy because even among older donors the risk of CJD occurrence is quite low, more than half of all cornea donors are older than 60 years, and demand for donor corneas exceeds the available supply. If donors age 60 to 69 years were not selected, more than 19,000 donors (38,000 corneas) would be excluded for each case of preclinical or symptomatic CJD eliminated from the donor pool.

New variant CJD: Although no cases of new variant CJD have been identified in the United States, the possibility exists that new variant CJD could occur in the future. We believe that any screening or restriction of the supply of younger donors before a first case of new variant CJD has

been reported would not be beneficial because the risk of CJD is currently far lower (about 40 times lower) among donors less than 40 years of age than among older donors.

The risk of developing CJD following cornea transplantation is remarkably low with use of current practices for screening potential donors. Our analyses indicate that screening based on signs and symptoms suggestive of CJD would likely lead to minimal additional improvement in safety, but would reduce the supply of donor corneas and result in many patients not receiving needed treatment. Consequently, we would not recommend such screening. If you so desire, we would be pleased to discuss our analyses and recommendations in greater detail. Thank you for your consideration of this information.

Sincerely,



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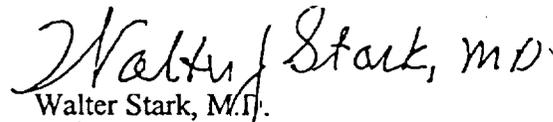
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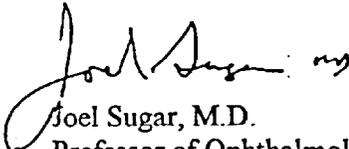
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Eye Banking and the Potential Impact of Increased Screening for Creutzfeldt-Jakob Disease

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ABSTRACT

Context: Emergence of new variant Creutzfeldt-Jakob disease (CJD) in the United Kingdom and other factors have raised concerns about the adequacy of current methods of screening tissue donors in the U.S. The Food and Drug Administration has issued a proposed rule that would require a "donor medical history interview" to identify possible indications of underlying disease.

Objective: To examine reported data on the occurrence of CJD, quantify the risk among cornea donors, and evaluate possible screening strategies.

Design and Setting: Reported information on deaths due to CJD, deaths from all causes, and total cornea donors was used to estimate the rate of CJD among cornea donors in the U.S. The impact of screening on risk of CJD and donor supply was estimated.

Main Outcome Measures: Numbers of donors with and without CJD that would be excluded by various screening approaches.

Results: Only 1.3 of the approximately 45,000 cornea donors in the U.S. each year might be expected to have CJD. Most of the estimated risk (91%) is due to preclinical (asymptomatic) disease, and therefore, could not be eliminated by screening for signs or symptoms. If only the highest risk age groups were screened and specificity were 90%, more than 21,000 otherwise acceptable donors would incorrectly be excluded for every potential donor with symptomatic CJD correctly excluded.

Conclusions: Currently, the risk of CJD transmission following cornea transplantation is remarkably low. Screening for symptoms of CJD would have minimal impact on safety, but would reduce the supply of donor corneas and result in many patients not receiving needed treatment.

It has been known since 1974 that Creutzfeldt-Jakob disease (CJD), a transmissible spongiform encephalopathy, can be transmitted from person to person through cornea transplantation. In the first reported case of transmission, the donor cornea was obtained from a 55 year-old man and transplanted before the characteristic findings of CJD were identified at autopsy.¹ The recipient, a 55 year-old woman, developed neurologic signs and symptoms approximately 18 months later and died shortly after that. The presence of CJD was confirmed by autopsy. Following that report, the Eye Bank Association of America established screening criteria to prevent those with a known diagnosis or family history of CJD from being selected as cornea donors.² Since then, more than 600,000 cornea transplants have been performed in the United States without any additional reported cases of transmission of CJD. Recently, however, several factors have raised concerns about the adequacy of current screening methods and have led to a re-examination of this issue by the Eye Bank Association of America, the Food and Drug Administration, and others.

In the United Kingdom, a new variant of CJD characterized by a relatively young age at onset has been identified and linked to the occurrence of "mad cow" disease (bovine spongiform encephalopathy).³⁻⁸ Because a large number of persons in the United Kingdom had likely been exposed to the causative agent (prion protein) from ingestion of affected beef during the 1980s and 1990s, the possibility could not be dismissed that CJD would occur with increasing frequency among potential cornea donors. Thus far, no cases of new variant CJD have been reported in the United States. Another factor that has focused attention on donor screening criteria has been the occurrence of two additional possible cases of transmission of CJD through cornea transplantation. One was reported from Japan in 1994 and the other from Germany in 1997.^{9,10} Also, two corneas and sclera were transplanted to three recipients in the United Kingdom from a woman who was found at autopsy to have had CJD.¹¹ Although she had exhibited characteristic neurological signs, the findings had been

attributed to central nervous system involvement from metastatic lung cancer. All three recipients underwent surgical removal of the donor tissue several months after placement, and none has yet developed CJD (approximately two years after removal).

Even though the risk of transmitting CJD through cornea transplantation is remarkably low, the question remains whether the benefits of implementing a more stringent screening process would outweigh the associated costs including decreased availability of donor corneas. An inadequate supply of donor tissue would have important public health consequences because of the generally favorable visual outcomes achieved with cornea transplantation and lack of satisfactory alternative therapies. In 1999, Hogan and associates¹¹ suggested that collection of additional information concerning previous neurologic findings among potential donors would reduce the risk of transmitting CJD. They did not estimate the costs associated with increased screening or the likely impact on individual eye banks and overall supply of donor corneas. Recently, the Food and Drug Administration has issued a proposed rule that would require a "donor medical history interview" to identify cognitive, behavioral, and other possible indications of underlying disease that would preclude tissue donation.¹² In response to those concerns and developments, the Eye Bank Association of America commissioned a committee to review available information on the occurrence and transmissibility of CJD as it relates to cornea transplantation. The committee's findings form the basis for this report.

METHODS

The frequency of occurrence of CJD among potential cornea donors in the United States was estimated from reported information on incidence and death rates of CJD,¹³ all cause death rates,¹⁴ and population figures by age.¹⁵ Holman and associates¹³ from the Centers for Disease Control and Prevention examined United States death records from 1979 through 1994, and calculated death rates of CJD by age, sex, and race. Because no statistically significant increase or decrease was identified over time, we used the average annual age-specific death rates to calculate expected numbers of deaths

due to CJD for the 1997 United States population (the most recent year for which final census estimates were available). The total numbers of deaths by age due to all causes were obtained from the National Vital Statistics Reports for 1997.¹⁴ Using those data, age-specific rates of CJD among all deceased individuals were calculated. The rates provide an indication of the level of risk of CJD by age among potential donors (all deceased individuals) if no screening criteria were used.

Since 1974, potential cornea donors with a known diagnosis or family history of CJD have been excluded. Also, the Eye Bank Association of America medical standards for documentation of cause of death require exclusion of tissue from potential donors who died of unknown causes or of unestablished neurologic disease.² Even with those safeguards, the possibility exists that a series of errors could potentially lead to transplantation of tissue from a donor who had the clinical diagnosis of CJD established before death. However, we believe this would be a very uncommon event; and we are not aware of it ever having occurred. An additional threat is posed by persons who die of CJD without ever having been diagnosed correctly. It is difficult to quantify how frequently this might occur, but it is probably uncommon, and any such potential donors could be excluded by other screening criteria (e.g., death of unknown cause). A consensus view of the authors is that no more than one percent of persons who die of CJD (approximately 2.6 cases per year) are not excluded by current screening criteria. This figure was used to estimate the frequency among cornea donors of CJD due to persons who had the diagnosis or died of the disease.

Separate estimates were made of the risk posed by potential donors who died of causes unrelated to CJD, but who had either preclinical disease (the phase before symptoms of CJD have developed) or symptomatic disease that had not yet been diagnosed. The numbers of potential donors by age with symptomatic (but not yet diagnosed) disease were calculated from age-specific death rates of CJD,¹³ the estimated duration of the interval from onset of symptoms to diagnosis, age-specific mortality rates based on all causes of death,¹⁴ and United States population estimates.¹⁵ Survival

following onset of CJD is generally no longer than a few months. In a recent review,¹¹ it was noted that the mean durations of disease before death reported from various case series were 7.0, 7.6, and 4.5 months. Consequently, there is a comparatively short period of time during which a person could potentially have symptomatic, undiagnosed disease but die of other causes and be selected as a cornea donor. We used a six-month interval to calculate the risk from this source. It was assumed that none of the potential donors that had symptomatic disease would be excluded by current screening criteria.

Given that the overall death rates of CJD have not changed significantly over time¹³ and that there is no evidence to suggest any change in mean duration of survival, the incidence rates of symptomatic disease are likely quite similar to the death rates. Therefore, the age-specific death rates and estimated mean duration of symptoms before diagnosis (6 months) were used to calculate age-specific prevalence rates of symptomatic disease. The prevalence rates were multiplied by the United States population figures and by age-specific death rates based on all causes of death to estimate the annual numbers of potential donors who had symptomatic (but not yet diagnosed) CJD.

A similar method was used to estimate the level of risk posed by potential donors who had preclinical disease (incubating CJD but not yet symptomatic). There is little reported information concerning the intervals from onset of preclinical disease to development of symptoms of CJD. In a report on 278 patients with CJD,¹⁶ most (234 patients) had sporadic disease (no known family history or exposure to other affected persons), 36 had familial disease, and 8 had iatrogenic disease (contracted from use of contaminated intracerebral electroencephalogram electrodes, treatment with cadaveric human growth hormone, or cornea transplantation). Among those with iatrogenic disease, the intervals from exposure to onset of CJD ranged from 16 months to 17 years. For estimation of the risk associated with preclinical disease, we used 10 years as the interval from onset of preclinical disease to onset of symptoms. The age-specific death rates of CJD,¹³ estimated duration of preclinical disease (10 years), and United States population figures¹⁵ were used to calculate age-specific expected numbers of

persons with preclinical disease. Those numbers were multiplied by age-specific death rates based on all causes of death¹⁴ to estimate the annual numbers of potential donors who had preclinical CJD. It was assumed that none of those potential donors would be excluded by current screening criteria.

The Eye Bank Association of America conducts an annual survey of eye banks in the United States to collect data concerning total numbers of cornea donors, demographic characteristics, and uses of donated tissue. The age distribution data for 1998 (the most recent data available) were used to estimate the proportions of all deceased individuals (potential donors) by age that meet the selection criteria and become donors.¹⁷ Those proportions (cornea donor fractions) were multiplied by the estimated numbers of deceased individuals who either died of CJD and were not excluded by the screening criteria or who had preclinical or symptomatic disease. This provided estimates of the annual numbers of donors by age that could potentially transmit CJD to cornea recipients. Data from the Eye Bank Association of America were also used to estimate the total number of donor corneas that have been transplanted in the United States from 1974 through 1999. Information concerning the age distribution of donors obtained through legislative consent was obtained from the Florida Lions Eye Bank, the Lions Eye Bank of Texas, and Tissue Banks International.

RESULTS

The average annual age-specific death rates of CJD based on a study of United States death records from 1979 through 1994 are shown in Table 1.¹⁵ During that 16-year period, CJD was reported as a cause of 3,642 deaths. Approximately 98% of deaths occurred among persons 45 years of age or older and 80% among those aged 60 years or older. The average annual age-specific rates peaked at 5.75 deaths per 1,000,000 population among the 70 to 74 year age group. The overall annual age-adjusted death rates remained quite stable during the study period, varying from 0.78 to 1.11 (average annual rate of 0.95 deaths per 1,000,000 population).

The expected numbers of deaths due to CJD based on the 1997 United States population are greatest in the 70 to 74 year age group (Table 1). By comparison, total deaths due to all causes continue to rise with increasing age, and are greatest among those 85 years of age or older. For this reason, the age-specific numbers of deaths due to CJD per 1,000,000 deaths due to all causes peak in the 60 to 64 year age group at 266.7 and decline substantially among older groups. Those rates provide an indication of the risk that a deceased person of any particular age would have had a diagnosis of CJD. To account for the impact of current cornea donor screening practices, estimates of the numbers of those who had the diagnosis or died of CJD and, for whatever reason, remain undetected in the pool of potential donors were based on one percent of expected deaths due to the disease.

The numbers of persons by age who at any given time would be expected to be symptomatic but not diagnosed as having CJD are shown in Table 2. Death rates based on all causes of death were used to calculate the numbers of such persons who would be expected to die each year. Also, the expected numbers of potential donors with preclinical disease (incubating CJD) were calculated. Because of the much longer assumed duration of the incubation period (10 years) than the symptomatic period (6 months), the estimated frequencies of preclinical disease are much greater.

The numbers of cornea donors were divided by total deaths to yield the proportions of all deceased individuals that become cornea donors within each age group (Table 3). Although the Eye Bank Association of America does not provide the data on age by 5-year intervals, the estimated proportions of cornea donors are quite similar over the age range of 21 to 70 years. The age-specific proportions of cornea donors were used to estimate the annual numbers of cornea donors that might be expected to have had preclinical or symptomatic disease or to have had the diagnosis or died of CJD (Table 4). Among the annual total of approximately 45,000 cornea donors in the United States, the estimates indicate that 1.3 donors might be expected to have had preclinical or symptomatic disease or

to have died of CJD. Most of the estimated risk (approximately 91% of total risk) is due to preclinical disease. The age-specific rates of CJD were 1.1 per 1,000,000 cornea donors aged 21 to 40 years, 20.2 among those 41 to 60 years, 52.1 in the 61 to 70 year group, and 31.1 among those older than 70 years.

DISCUSSION

Currently, there is no laboratory test that meets all criteria necessary to be used for widespread screening of potential cornea donors for CJD. The criteria would include reasonable cost in relation to expected improvements in safety, high sensitivity and specificity, completion of testing within the short period of time before a donor cornea must be used, and accessibility and availability of tissue for testing. Consequently, it is not possible at the present time to identify and exclude individual potential donors that had preclinical disease. Screening of blood for the presence of diagnostic prion protein (the etiologic agent of CJD) might eventually be useful, but no sufficiently sensitive methodology has yet been discovered.

Possible strategies to improve safety could be based on exclusion of potential donors in the age groups at highest risk or on more intensive efforts to identify the estimated small number of donors with a known diagnosis or symptoms of CJD that are missed by current screening methods. Hogan and associates¹¹ previously suggested the latter approach, and a requirement for a “donor medical history interview” to identify cognitive, behavioral, and other possible indicators of underlying disease is included in a recently proposed rule drafted by the Food and Drug Administration.¹² In order for any such program to be beneficial, it would need to have the capability of preventing the highly infrequent occurrence of cornea procurement from a donor that had a known diagnosis or symptoms of CJD. We estimate that approximately one such case would occur every 8.1 years (0.123 cases per year) at current annual volumes of cornea donation (Table 4). This would represent approximately one case among every 368,000 donors.

Even if a screening approach were available that could identify all potential donors with a known diagnosis or symptoms of CJD (sensitivity of 100%), it might not be practical to use it unless the specificity (proportion of those without disease that are correctly identified) were sufficiently high. In general, screening for an uncommon disease requires very high specificity to avoid misclassification of large numbers of subjects who do not have the disease. A critical question, therefore, is whether screening interviews to identify symptoms suggestive of CJD would have high enough specificity to avoid unacceptably large losses of otherwise suitable cornea donors.

Frequent clinical features of CJD include cognitive impairment (personality and behavioral changes, disorientation, and memory loss), myoclonus, cerebellar dysfunction, speech abnormalities, and visual impairment.^{11,16} Because of the overlap of symptoms with other neurologic disorders, histologic verification of CJD at autopsy is required to establish a definitive diagnosis. This overlap with common age-related findings among the elderly (e.g., mental deterioration) would tend to limit the specificity of screening based on symptoms suggestive of CJD. Also, the information would not generally be collected by neurologists or other physicians, but by technicians with limited medical training. Another factor is that family members and other respondents might have considerable difficulty in judging and agreeing whether a potential donor had a particular symptom.

The numbers of otherwise suitable donors that might incorrectly be excluded in order to correctly exclude a single donor with symptomatic or diagnosed disease (that without screening based on symptoms would remain in the donor pool) were calculated for various levels of specificity (Table 5). If only the highest risk age groups (60 to 69 years) were screened and specificity were as high as 90%, tissue from approximately 21,580 donors would incorrectly be discarded over a period of 17.5 years to exclude one donor with symptomatic or diagnosed disease. The numbers of otherwise suitable donors not selected (per donor with disease appropriately excluded) would be much greater if screening were applied to a broader age range of donors or if the sensitivity of screening were less than

100%. Screening based on age alone would not be an attractive strategy either. If donors age 60 to 69 years were not selected, more than 19,000 donors (38,000 corneas) would be excluded for each additional case of symptomatic, diagnosed, or preclinical CJD eliminated from the donor pool. However, because the risk of disease among donors less than 40 years of age at the time of death is approximately 40 times lower than among older donors, efforts to maximize use of young donors would help to keep the overall level of risk of CJD transmission as low as possible.

There are sufficient donor corneas to meet current demand in the United States, but worldwide demand will far exceed supply for the foreseeable future. Consequently, loss of donor corneas due to more intensive screening would have a direct impact on the number of persons who could have their vision restored by cornea transplantation, and for others would likely lengthen the waiting time for surgical treatment. This view is supported by the recent initiation of a study sponsored by the National Eye Institute to evaluate outcomes following use of tissue from older cornea donors.¹⁸ If the results are favorable, the goal will be to increase the supply and acceptance of tissue from older donors. Also, concerns have been expressed that growth in the volume of refractive surgical procedures may constrain future availability of donor corneas. It is important, therefore, that consideration of new screening requirements take into account the likely impact on supply of donor corneas and that the supply not be limited unnecessarily.

In some states, the law allows for procurement of donor corneas by the medical examiner or coroner through a legislative consent process that does not require communication with the next of kin. Although current federal regulations require a “donor medical history interview,” there is an exception for corneas obtained through legislative consent. The recently proposed rule drafted by the Food and Drug Administration would eliminate this exception.¹² If the donor’s next of kin, acquaintances, or primary treating physician must be interviewed about symptoms suggestive of CJD, the number of donors obtained through legislative consent will be substantially reduced (possibly by as much as 90%)

because of the difficulty in locating appropriate individuals to interview during the short time available for procurement following the frequently sudden, unexpected, and traumatic deaths that are evaluated by medical examiners and coroners. At present, approximately 10% of all cornea donors in the United States are obtained through legislative consent. Data concerning the age distribution of those donors were collected from the Florida Lions Eye Bank, the Lions Eye Bank of Texas, and Tissue Banks International. It shows that in 1998 approximately 50% were age 40 years or less (as compared to 15% among all donors). Based on those data, we estimate that the overall risk of preclinical, symptomatic, and diagnosed CJD in this subgroup is about 40% less than the estimated preclinical risk alone among all other donors. This should more than compensate for any potential increase in risk due to less complete ascertainment of information concerning family medical history because only about 13% of patients with CJD have a family history of the disease.¹⁶ Consequently, the data support the view that more intensive screening of donors obtained through legislative consent might actually reduce the level of safety rather than enhance it because of the loss of a large proportion of those donors. It should be noted that ethical concerns have been expressed about the process of obtaining legislative consent, but those concerns do not center on the issue of risk due to CJD.

For several reasons, our estimate of the annual number of cornea donors with CJD (Table 4) is greater than the number of cornea recipients who might be expected to develop the disease. Data from the Eye Bank Association of America indicate that more than one third of donated tissue is either not suitable for transplant or is used for research or training purposes.¹⁷ Also, various biologic factors may influence the likelihood of transmission even if a recipient were to receive tissue from an affected donor. For example, genetic homozygosity for methionine at codon 129 (present in approximately 50% of the general population) is over-represented (80%) in patients with iatrogenic CJD.^{19, 20} Additionally, attempts to transmit disease to experimental animals fail for 10% of patients with the most common form of CJD (sporadic disease).¹⁶

In the United States, more than 600,000 donor corneas have been transplanted without any additional reports of CJD transmission since 1974. This would require at least 300,000 donors (two corneas per donor). Using our overall estimated rate of CJD among donors, it can be calculated that 8.6 of those donors (99% CI, 8.3 – 9.0) would be expected to have had preclinical, symptomatic, or diagnosed CJD. Biologic and other factors probably account for the lower than expected rate of disease among recipients. For this reason, we believe the estimates of otherwise suitable donors that would be excluded by screening (Table 5) understate the numbers that would be excluded per case of CJD transmission prevented among cornea recipients.

In summary, the risk of disease transmission following cornea transplantation is remarkably low with use of current practices for excluding potential donors with a known diagnosis or family history of CJD. Our analyses indicate that screening based on signs and symptoms would likely lead to minimal additional improvement in safety, but would reduce the supply of suitable cornea donors, particularly young donors obtained through legislative consent, and result in many patients not receiving needed treatment in a timely manner. Consequently, we would not recommend such screening. It is possible that new variant CJD could be identified in the United States in the future and pose a new threat to cornea recipients. However, pre-emptive screening or restriction of the supply of young donors before the occurrence of sufficient cases to document a growing risk would likely not be beneficial because the incidence rate of disease is currently much lower among donors less than 40 years of age than among older donors.

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REFERENCES

1. Duffy P, Wolf J, Collins G, DeVoe AG, Streeten B, Cowen D. Possible person-to-person transmission of Creutzfeldt-Jakob disease. *N Engl J Med* 1974; 290:692-3.
2. Eye Bank Association of America, Medical Standards 1994:9.
3. Wilesmith JW, Wells GAH. Bovine spongiform encephalopathy. *Curr Topics Microbiol Immunol* 1991; 172:21-38.
4. Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996; 347:921-5.
5. Collinge J, Sidle KCL, Heads J, et al. Molecular analysis of prion strain variation and the aetiology of "new variant" CJD. *Nature* 1996; 383:685-90.
6. Hill AF, Desbruslais M, Joiner S, et al. The same prion strain causes vCJD and BSE. *Nature* 1997; 389:448-50.
7. Brown P. The risk of bovine spongiform encephalopathy ("mad cow disease") to human health. *JAMA* 1997; 278:1008-11.
8. Pocchiari M. Early identification of variant Creutzfeldt-Jakob disease. [Editorial]. *Br Med J* 1998; 316:563-4.
9. Uchiyama K, Ishida C, Yago S, Kuramaya H, Kitmoto T. An autopsy case of Creutzfeldt-Jakob disease associated with corneal transplantation. *Dementia* 1994; 8:466-73.
10. Heckmann JG, Lang CJG, Petruch F, et al. Transmission of Creutzfeldt-Jakob disease via a corneal transplant. *J Neurol Neurosurg Psychiatry* 1997; 63:388-90.
11. Hogan RN, Brown P, Heck E, Cavanagh HD. Risk of prion disease transmission from ocular donor tissue transplantation. *Cornea* 1999; 18:2-11.
12. The Food and Drug Administration, Suitability Determination for Donors of Human Cellular and Tissue-Based Products, [Docket No. 97N-484S], 1999.

13. Holman RC, Khan AS, Belay ED, Schonberger LB. Creutzfeldt-Jakob disease in the United States, 1979-1994: using national mortality data to assess the possible occurrence of variant cases. *Emerg Infect Dis* 1996; 2:333-7.
14. National Vital Statistics Reports, Deaths: Final Data for 1997, Vol. 47, June 30, 1999.
15. US Census Bureau. Population estimates for the US, regions, divisions, and states by 5-year age groups and sex, 1990-1998. Washington, DC, 1999.
16. Brown P, Gibbs CJ, Rodgers-Johnson P, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. *Ann Neurol* 1994; 35:513-29.
17. *1998 Eye Banking Statistical Report*. Washington, DC: Eye Bank Association of America, 1998.
18. Cornea Donor Study, Sponsored by the National Eye Institute, 1999.
19. Brown P, Cervenakova L, Goldfarb LG, et al. Iatrogenic Creutzfeldt-Jakob disease: an example of the interplay between ancient genes and modern medicine. *Neurology* 1994; 44:291-3.
20. Brown P, Preece M, Brandel JP, et al. Iatrogenic Creutzfeldt-Jakob disease at the Millennium. *Neurology* (in press).

Table 1 -- Creutzfeldt-Jakob Disease Deaths and Death Rates, and Deaths Due to All Causes in the United States, 1997

Age (years)	CJD Death Rate *	Expected CJD Deaths	All Cause Deaths **	CJD Deaths Per 1,000,000 All Cause Deaths
0-4	<0.01	0.2	33,546	6.0
5-9	0	0	3,645	0
10-14	0	0	4,416	0
15-19	0	0	14,272	0
20-24	<0.01	0.2	17,272	11.6
25-29	<0.01	0.2	19,272	10.4
30-34	0.04	0.8	26,266	30.5
35-39	0.08	1.8	38,172	47.2
40-44	0.16	3.4	51,236	66.4
45-49	0.45	8.3	65,090	127.5
50-54	0.99	15.0	79,792	188.0
55-59	2.14	25.2	98,130	256.8
60-64	3.55	35.7	133,863	266.7
65-69	5.03	49.2	194,776	252.6
70-74	5.75	50.3	269,498	186.6
75-79	5.60	39.7	325,799	121.9
80-84	3.94	18.4	344,731	53.4
>85	<u>2.42</u>	<u>9.5</u>	<u>594,068</u>	<u>16.0</u>
Total	-	257.9	2,314,245	111.4

Table 1 (cont) - - Creutzfeldt-Jakob Disease Deaths and Death Rates, and Deaths Due to All Causes
in the United States, 1997

* Average annual deaths per 1,000,000 population, 1979 – 1994. Source: Holman RC, Khan AS, Belay ED, Schonberger LB: Creutzfeldt-Jakob disease in the United States, 1979 – 1994: using national mortality data to assess the possible occurrence of variant cases. *Emerg Infect Dis* 1996; 2:333-7.

** Source: National Vital Statistics Reports, Deaths: Final Data for 1997, Vol. 47, June 30, 1999.

Table 2 - - Expected Annual Deaths Among Patients with Preclinical or Symptomatic Creutzfeldt-Jakob Disease in the United States

Age (years)	All Cause Death Rate *	Living	Living	<u>Expected Deaths</u>	
		Preclinical Patients **	Symptomatic Patients +	Preclinical Patients	Symptomatic Patients
0-4	358	1.0	0.1	0	0
5-9	185	0	0	0	0
10-14	232	0.6	0	0	0
15-19	748	1.6	0	0	0
20-24	986	3.8	0.1	0	0
25-29	1,021	9.8	0.1	0	0
30-34	1,266	20.8	0.4	0	0
35-39	1,687	45.5	0.9	0.1	0
40-44	2,397	93.3	1.7	0.2	0
45-49	3,524	167.2	4.2	0.6	0
50-54	5,262	263.1	7.5	1.4	0
55-59	8,346	376.5	12.6	3.1	0.1
60-64	13,312	468.3	17.9	6.2	0.2
65-69	19,951	469.0	24.6	9.4	0.5
70-74	30,849	354.3	25.2	10.9	0.8
75-79	46,125	199.9	19.9	9.2	0.9
80-84	74,259	112.8	9.2	8.4	0.7
≥85	<u>153,452</u>	<u>95.0</u>	<u>4.8</u>	<u>14.6</u>	<u>0.7</u>
Total	-	2,682.5	129.2	64.1	3.9

Table 2 (cont) - - Expected Annual Deaths Among Patients with Preclinical or Symptomatic

Creutzfeldt-Jakob Disease in the United States

- * Deaths per 1,000,000 population, 1997. Source: National Vital Statistics Reports, Deaths: Final Data for 1997, Vol. 47, June 30, 1999.
- ** Estimated numbers of living preclinical patients at any point in time were derived from age-specific death rates of Creutzfeldt-Jakob disease, estimated duration of preclinical disease (10 years), and United States population estimates.
- + Estimated numbers of living symptomatic patients at any point in time were derived from age-specific death rates of Creutzfeldt-Jakob disease, estimated duration of the interval from onset of symptoms to diagnosis (6 months), and United States population estimates.

Table 3 - - Estimated Proportions of All Deaths that Yield Donor Corneas

Age (years)	Cornea Donors *	All Cause Deaths **	Cornea Donor Fraction +
0-10	635	37,191	0.017
11-20	1,890	18,688	0.101
21-40	4,390	100,982	0.044
41-60	13,095	294,248	0.045
61-70	12,234	328,639	0.037
>70	12,813	1,534,096	0.008
Unknown	<u>245</u>	<u>401</u>	<u>-</u>
Total	45,302	2,314,245	-

* Source: 1998 *Eye Banking Statistical Report*. Washington, DC: Eye Bank Association of America, 1998. The age groupings are those used by the Eye Bank Association of America.

** Source: National Vital Statistics Reports, Deaths: Final Data for 1997, Vol. 47, June 30, 1999. The age groupings used for this column are: 0-9, 10-19, 20-39, 40-59, 60-69, and ≥ 70 .

+ Calculated by dividing the numbers of cornea donors by the numbers of all cause deaths.

Table 4 - - Estimated Annual Numbers of Cornea Donors Who Died of Creutzfeldt-Jakob Disease or Who had Preclinical or Symptomatic Disease at the Time of Death *

Age (years)	Preclinical Disease	Symptomatic Disease	Died of CJD	Total
0-4	0	0	0	0
5-9	0	0	0	0
10-14	0	0	0	0
15-19	0	0	0	0
20-24	0	0	0	0
25-29	0	0	0	0
30-34	0.001	0	0	0.001
35-39	0.003	0	0.001	0.004
40-44	0.010	0	0.002	0.012
45-49	0.026	0	0.004	0.030
50-54	0.061	0	0.007	0.068
55-59	0.140	0.004	0.011	0.155
60-64	0.232	0.007	0.013	0.252
65-69	0.348	0.019	0.018	0.385
70-74	0.092	0.007	0.004	0.103
75-79	0.077	0.008	0.003	0.088
80-84	0.070	0.006	0.002	0.078
≥85	<u>0.122</u>	<u>0.006</u>	<u>0.001</u>	<u>0.129</u>
Total	1.182	0.057	0.066	1.305

Table 4 (cont) - - Estimated Annual Numbers of Cornea Donors Who Died of Creutzfeldt-Jakob Disease or Who had Preclinical or Symptomatic Disease at the Time of Death*

* The estimates were derived by multiplying the expected numbers of preclinical and symptomatic deaths shown in Table 2 by the cornea donor fractions for the corresponding age groups from Table 3. Because most patients who die of Creutzfeldt-Jakob disease are excluded from becoming cornea donors by current donor screening criteria, one percent of the expected deaths from the disease in each age category shown in Table 1 were multiplied by the cornea donor fractions. Slight differences in the values shown in Table 4 from those derived by multiplying the numbers shown in Tables 1-3 are due to rounding in the underlying calculations.

Table 5 - - Estimated Numbers of Otherwise Suitable Donors Incorrectly Excluded by Screening for Symptoms Suggestive of Creutzfeldt-Jakob Disease Per Donor with Disease Correctly Excluded *

Age Range Screened	Proportion of All Donors Screened (%)	No. of Years Screening Required to Exclude One Case of CJD **	Donors Incorrectly Excluded By Specificity of Screening		
			95%	90%	80%
All	100	8.1	18,415	36,831	73,662
>50 years	72	8.6	13,976	27,952	55,904
60-69 years	27	17.5	10,790	21,580	43,160

* Donors with Creutzfeldt-Jakob disease correctly excluded by screening are defined as those that without screening based on symptoms would remain in the donor pool. The estimated annual numbers of such donors are shown in the “symptomatic disease” and “died of CJD” columns in Table 4. For these calculations, it is assumed that the sensitivity of screening would be 100% (i.e., all donors with “symptomatic disease” or “died of CJD” as estimated in Table 4 would be excluded by the screening process). The calculations are based on the volume and age distribution of cornea donors in the United States as reported by the Eye Bank Association of America for 1998.¹⁷

Table 5 (cont) - - Estimated Numbers of Otherwise Suitable Donors Incorrectly Excluded by
Screening for Symptoms suggestive of Creutzfeldt-Jakob Disease Per Donor with
Disease Correctly Excluded*

** The number of years of screening required to correctly exclude one donor with disease is the inverse of the sum of the estimated numbers of such donors as shown in the “symptomatic disease” and “died of CJD” columns in Table 4 for the age categories being screened. The numbers of years of screening were multiplied by the annual numbers of donors in the corresponding age categories. The indicated levels of specificity were applied to these figures to calculate the numbers of otherwise suitable donors that might incorrectly be excluded.