# The Why and How of Cornea Donor Screening: A Review

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**ABSTRACT**:

Disease transmission from infections and communicable diseases, is always a concern for those screening, recovering or distributing allograft tissue for transplantation.

This review article covers a cross section of publications that elucidate the transmissibility concerns for bacteria, fungi, prions, and viruses, as well as communicable diseases.

Eye Bank professionals continue to be concerned with the potential of disease transmission by ocular transplant, although the actual transmission of communicable disease is extremely low.[1] This review paper, in addition to some historic disease perspective, primarily focuses on recent areas of concern over the last ten years, 2010 to 2020, for reactive serology, disease transmission, and medical social history as required by Food and Drug Administration, FDA, regulation 1271[2] in identifying and reducing risk of disease transmission. In a tutorial in 2015, Liabow et al discuss cornea donor eligibility and the steps that occur from the death of a registered donor to tissue transplantation.[3] Figure 1 reflects today's screening parameters and the steps to qualify or defer a donor or donor tissue. The goal of the guidance regarding relevant communicable disease provided by FDA 1271.50 (C) has not changed, but as new viral infections have occurred across the world, eye

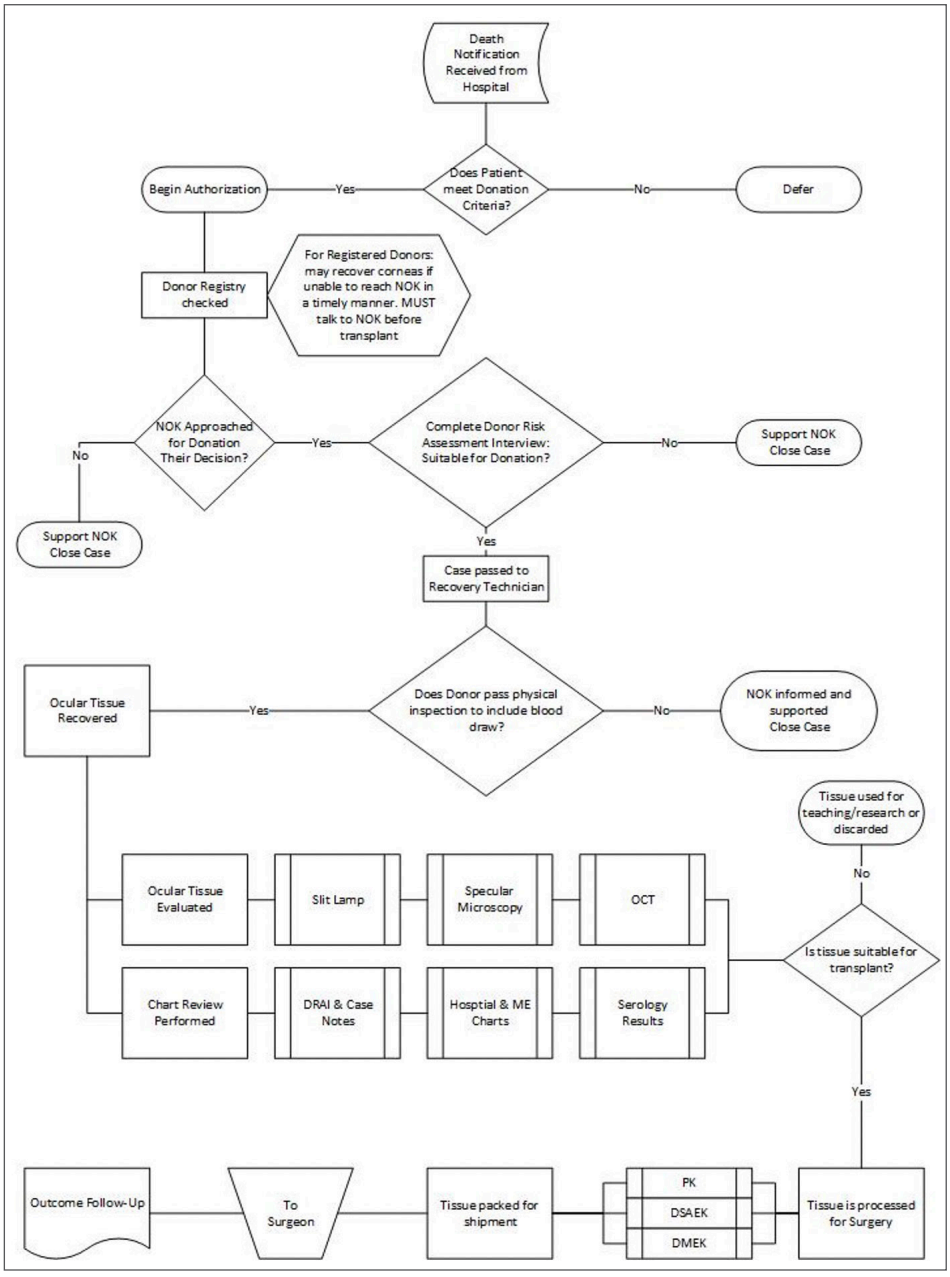


***Figure1:*** *Determination of Donor Eligibility from Death to Transplantation*

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banks have had to expand their screening criteria. Articles reviewed include those for vector transmitted, as well as blood and tissue transmitted agents. While donor designation has had a positive impact on transplantable allografts in the United States,[4] viral outbreaks, especially COVID-19, have resulted in hardships for eye banks both in tissue availability and in transplant demand nationally and internationally.[5,6] It is therefore important to continually evaluate the risk factors that affect physician and recipient services for transplantable allografts.

## METHODS

This review includes but was not limited to 32 referenced publications. These include concern where disease transmission, infection, and in some cases, death occurred related to the transmission of disease by corneal transplantation. Articles included in this review represent those that indicate the broad spectrum of potential agents; virus, bacteria, fungus, and prion, with potential for communicable disease transmission from corneal transplantation. It is impossible to list all contributions in this field and none are intentionally omitted, but space limitations affected these selections and readers are encouraged to look at references in the cited papers for additional articles of interest. This review calls attention to the variety of communicable risk factors that are associated with making donor tissues suitable for potential transplantation.

## RESULTS

Publications listed below include the organism reported, author and year of publication

## DISCUSSION:

While bacterial and fungal, primarily yeast, infections are of concern and referenced,[7] this literature review contains more references to the viral agents that could result in communicable disease in a transplant recipient. Other possible infectious complications will also be addressed where disease transmission might be possible but unestablished. This could include autopsy findings or blood culture results that were unavailable at the time of implantation of the donated

***Table 1:*** *Organism Reported, Author and Year of Publication*

| Disease/Infection | Type | Author | Publication Year |
|---|---|---|---|
| Bacteria & Fungal Infections | Review | Ellen L. Heck, Valerie Corder, Richard Jordan, Jill Urban, Dwight Cavanagh | 2019 |
| | Review | Thareja T, Kowalski R, Kamyar R, et al. | 2018 |
| | Lab Study | Brothers, Kimberly M., et al. | 2017 |
| | Review | Lambert, Nathan, and Winston Chamberlain | 2017 |
| | Lab Study | Nagaraja, Harsha, et al. | 2016 |
| | Clinical Study | Kitazawa, Koji, et al. | 2016 |
| | Clinical Study | Umang, et al. | 2015 |
| | Lab Study | Aldave AJ, DeMatteo J, Glasser DB, et al. | 2013 |
| West Nile Virus | Clinical Study | Blitvich BJ, Mullins RF, Greiner MA, et al. | 2016 |
| | Review | Lambert, Nathan, and Winston Chamberlain | 2017 |
| | Review | Dubord PJ, Evans GD, Macsai MS, et al. | 2013 |
| Zika | Lab Study | Ellen Heck., et al. | 2018 |
| | Clinical Study | Tsui I, Moreira MEL, Rossetto JD, et al | 2018 |
| | Lab Study | Heck E, Cavanagh HD, Robertson DM | 2017 |
| | Review | Lambert, Nathan, and Winston Chamberlain | 2017 |
| | Review | Marquezan MC, Ventura CV, Sheffield JS, et al. | 2017 |
| COVID-19 | Clinical Study | Ballouz, Dena, et al | 2021 |
| | Review | Gaussen A, Hornby L, Rockl G, et al. | 2021 |
| | Review | Salz, AnnaK, et al. | 2021 |
| | Review | Dockery, Dominique M., et al. | 2020 |
| | Lab Study | Miner JJ, Platt DJ, Ghaznavi CM, et al | 2020 |
| | Clinical Study | Villalba R, Santos S, Martinez MJ, et al. | 2020 |
| Rabies | Review | Lu X-X, Zhu W-Y, Wu G-Z. | 2018 |
| | Review | Lambert, Nathan, and Winston Chamberlain | 2017 |
| | Review | Houff SA, Burton RC, Wilson RW, et al. | 1979 |
| Hepititis B & C | Clinical Study | Zibbell JE, Asher AK, Patel RC, et al | 2018 |
| | Review | Lambert, Nathan, and Winston Chamberlain | 2017 |
| | Lab Study | Lee HM, Naor J, Alhindi R, et al. | 2001 |
| | Clinical Study | Hoft, Richard H., et al. | 1997 |
| Creutzfeldt-Jakob disease | Review | Maddox RA, Belay ED, Curns AT, et al. | 2008 |
| | Review | Lambert, Nathan, and Winston Chamberlain | 2017 |


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tissue.[8] Of particular concern in 2016 was West Nile Virus and in 2017 for Zika virus, which were definitely shown to have adverse effects on ocular tissue.[9,10] Concerns include the transmission of the virus as well as blindness caused by the virus.

With the devastating numbers of individuals contracting and dying from the COVID-19, new questions about transmissibility heightened concerns for donor screening. COVID-19 was found in conjunctiva[11] and in tears.[12] However, no case of actual transmission of COVID-19 via ocular transplantation have been reported.[13] There are documented cases of the transmission of rabies,[14] CJD (Creutzfeldt-Jakob Disease),[15] Hepatitis B[16] and possibly Hepatitis C.[17] Hoft et al, report on two cases of Hepatitis B associated with corneal transplantation.[16] Virus, prions and of course bacteria and fungus[18] can be found in and be transmitted by ocular tissue, thus making any viral outbreak a cause for specific scrutiny. In the case of these last two viral outbreaks, West Nile and Zika, no high risk behavior seems to be a factor. However, medical screening for evidence of clinical signs of infection, fever, leucocyte elevation, flulike symptoms and other manifestations as prescribed by FDA 1271, is an important part of tissue safety in any donor history review. In addition, concern for travel to certain endemic areas are included in the screening process and may result in a deferral.

The serologic testing and the reports of reactive serology and life style markers are demonstrated in recent studies.[19] Donor screening emphasizes the association of risk behaviors with communicable disease. These include but are not limited to male on male sex, multiple sex partners in exchange for money, drug use and incarceration. The relationship of toxicology and drug use, to reactive serology in 318 medical examiner cases demonstrated a significance with IV, intravenous drug administration. Correlation with non-intravenous drugs, incarceration and sexual activity was not established as significant, possibly due in part to the low numbers in the study. (Figure 2)

In examining the current concerns for fungal infections as referenced in the papers of Aldave AJ et al,[20] Kitazawa K, Wakimasu et al,[21] and Brothers KM, Shanks et al,[22] there appears to be a rise in fungal infections post EK , endothelial keratoplasty verses PK, penetrating keratoplasty. This increase is potentially related to additional warming during graft preparation. However, it has not been definitely established as to whether or not a procedural handling issue with multiple warming cycles is the only contributing factor. The use of an antifungal drug in the storage media is now an option that is being used in some practices but is not a standard of the Eye Bank Association of America, nor routinely added in commercially available storage media. The antibiotic addition to control bacteria in storage media thereby reducing the prevalence of these organisms may allow an increase in the yeast/fungus growth. However, the growth has not resulted in a clouding or pH change of the media as would be expected if the growth were occurring during storage. This might argue against addition of an anti-fungal to the media but rather to the patient as the growth occurs post-transplant and the anti-fungal in the media would likely be diluted or completely lost during the graft implantation. Fungal infection in cornea transplantation, although limited, can be devastating and more investigation, clinical studies and resulting treatment are needed to answer the questions of how and where the fungal infection arises.

| High Risk | Non-reactive | Reactive | Total |
|---|---|---|---|
| IVDA | 11 | 11 | 22 |
| Incarceration | 7 | 3 | 10 |
| Polysubstance abuse | 12 | 4 | 16 |
| Sexual High Risk | 4 | 2 | 6 |
| **Totals** | **34** | **20** | **54** |

***Figure2:*** *Reactive Serology vs High Risk*

Because the limited time periods for post retrieval transplantation and optimal tissue function do not permit the weeks and months of storage seen with other tissue transplants such as bone, autopsy and blood culture finding are often not available at the time of tissue placement. In examining 1350 medical examiner donor cases, Heck, Cavanagh et al[8] found 26 cases of myocarditis identified by histology and not suggested in prior medical history screening. Myocarditis of a viral origin could represent a possibility of transmission to a graft recipient and because of the often occult nature of such infection, never be recognized as associated with a prior transplant. In addition, blood culture growth of Enterococcus and Candida albicans was reported, which history did not suggest as a donor risk. While pre-mortem blood cultures might indicate growth within the first 48 hours of collection, the identification and reporting might be several days later depending on the amount of growth and the ease of identification. Even in the cases of solid organ transplantation the findings of donor positive bacterial blood cultures has not been shown to be a frequent finding in post-transplant recipients.[23,24]These studies would suggest it would be less likely to affect ocular transplant recipients, as these grafts are much less vascular.

Screening for West Nile Virus and Zika Virus was implemented in response to the out breaks of both of these viral diseases. Both of these viruses are commonly vector transmitted via mosquitos, but the possibility of


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human-to-human transmission is considered. Zika has been reported to be transmitted congenitally with significant ocular abnormalities. It also has been documented to be transmitted by blood transfusions, sexually and by organ transplantation by Marquezan, May et al.[25] Zika virus was found in the vitreous RNA in a polymerase chain reaction assay,[26,27] but has not been reported to have been transmitted by ocular transplantation. West Nile virus, also a flavivirus with ocular manifestations that include intra-retinal hemorrhage and choroiditis, has not been reported to be transmitted by corneal transplantation.[9]

Although to date, documented transmission of COVID-19, Sars-CoV2, by corneal transplant has not been reported, the pandemic nature of this viral spread and the deaths associated with it worldwide make it of paramount concern. This respiratory virus has been documented by reverse transcription polymerase chain reaction to be present in tears and conjunctiva.[28] Viral load in tissue from these individuals with the COVID-19 virus is possible as eyes may be a portal of entry for respiratory virus. These infected individuals may have symptoms ranging in severity from "common" cold or flu like responses to death, and therefore screening for the virus must currently be on going.

The lack of documented transmission of the virus and bacteria included above may lead eye bankers and ophthalmologists to feel a false sense of security about the risk level for corneal transplantation. Transmission of the rabies virus[29] and prion disease CJD[19] shows the cornea can indeed transmit disease, however infrequently. Increases in Hepatitis C infections due to increased opioid use is currently being reported[30] and although testing has been significantly improved with NAT (nucleic acid testing), continuing diligence is required. Additionally, with the current treatments of Hepatitis C, that reports state cures the host disease and only a reactive antibody test remains, changes may need to occur in the use of ocular tissue from these individuals. If the possibility of transmission is removed by the drug treatment, FDA could change their recommendation for these potential donors. Such a change however has not yet been proposed. Both old and new infective possibilities challenge the eye banks tissue delivery of safe and effective ocular allografts.

## CONCLUSION

The corneal transplant recipient follow-up is a semi-passive process, dependent on physician recognition and association of the infection post-transplant with the transplanted tissue and then reporting to the eye bank.[31] The current process has been acceptable for the identification of graft function, primary graft failure and in a few cases post-operative infections. However, it may not be active or aggressive enough for the future in identifying viral related complications. Sentinel monitoring on a worldwide and national scale has been suggested for years, but has yet to achieve universal acceptance.[32] With increasing viral infections that may cause a varied range of symptoms and even outcomes, disease transmission by corneal transplantation may not be considered or recognized. In an unusual transmission, such as rabies, where health departments and the media would likely be investigating the source, the current outcome system might be involved. In cases where the symptoms are more commonplace and easily associated with other disease processes like the "flu", the current monitoring would likely not be triggered. Due to the increasing and varied virus, ophthalmologists and eye banking professionals will likely need to add an infective disease outcome component to a more active monitoring program. While this may not be the reality or outcome we desire, it is one that which we must consider and look to implement.

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