Eye Bank Association of Australia and New Zealand

Queensland Tissue Bank
Block 7, 39 Kessels Road
Coopers Plains
Qld 4108
+617 3121 2626

Lions Eye Bank of Western Australia
Lions Eye Institute
2 Verdun Street
Nedlands, WA 6009
+618 9381 0725

Lions Eye Donation Service Melbourne
Royal Victorian Eye and Ear Hospital
32 Gisbourne Street
East Melbourne, VIC 3002
+613 9929 8708

New South Wales Tissue Bank
Sydney Eye Hospital
Macquarie Street
Sydney NSW 2000
+612 9382 7855

Eye Bank of South Australia
Department of Ophthalmology
Flinders Medical Centre
Bedford Park SA 5042
+618 8204 4928

New Zealand National Eye Bank
Department of Ophthalmology
University of Aukland
Private Bag 92019
Aukland
+649 3737 599

09/07/2021

Response to Consultation: Remaking of standards and legislative instruments for human cell and tissue (HCT) products, blood and blood components

To whom it may concern,

Please find attached a joint submission from The Eye Bank Association of Australian and New Zealand (EBAANZ), endorsed by the EBAANZ Advisory Committee (MAC).

EBAANZ and the MAC represent the highest level of professional expertise in relation to eye donation, eye banking and corneal transplantation in Australia and New Zealand. The MAC is composed of senior ophthalmologists, members of the Royal Australian and New Zealand College of Ophthalmologists, senior eye banking professionals and a senior infectious disease clinician.

The attached document responds to questions 12 and 13 within the consultation document on the '*Remaking of standards and legislative instruments for human cell and tissue (HCT) products, blood and blood components consultation paper dated May 2021*'.

This proposal is of significant concern for the eye donation sector. It threatens the sustainability of Eye Banking in Australia, and will result in closure of eye banks, loss-of-benefit for the nation and unequitable access for corneal transplantation.

This submission updates the 2011 exemption response submission. This includes updated epidemiological data and clear evidence supporting the continuing exemption for 'cornea only' donors not requiring mandatory NAT testing as per TGO 88. We also demonstrate the ethical implications of the proposal.

We hope for a workable, rational, and efficient set of standards while still retaining the highest principles of safety and quality that are clinically significant to ocular tissue transplantation while ensuring that the Eye Banks can continue to uphold the ethical values of being given stewardship of the gift of donation.

Yours Sincerely,

Luke Weinel
EBAANZ Chair

Dr Con Petsoglou
EBAANZ Medical Advisory Committee Chair

Background

In 2011, an exemption for 'cornea only' donors was granted by the TGA. This exemption stipulated that 'cornea only' donors required serological testing for HIV, HBV and HCV to establish donor eligibility. This exemption was granted due to the comprehensive analysis of available data on the epidemiology of these blood borne viruses (BBV), in the Australian setting. This was in comparison to the TGAs proposal to mandate serological testing for HBV, HCV, HIV, HTLV-1 & 2, Syphilis and NAT testing for HIV, HBV and HCV.

We highlight that every new test not only has a financial cost, but a cost in false positives and tissue wastage. Decisions to implement mandatory NAT testing have been explored through 7 sections. They each provide sound scientific evidence with a clear understanding and explanation of the both the risks and benefits associated with such a decision.

EBAANZ SUMMARY RESPONSE FOR MANDATORY NAT TESTING:

- **NAT testing should NOT be mandated** for reasons discussed in this document
- Mandating NAT testing in the current Australian laboratory environment will result in:
  - Closure of eye banks
  - Loss-of-benefit for the nation
  - Unequitable access for corneal transplants
  - Pressure on a system that is already not meeting demand for corneal transplants nationally

Given the known prevalence of HIV, HBV and HCV in Australia, the probability of ocular only donors being in the window period (negative serology with a positive NAT) at the time of screening is incredibly negligible. These tests will not provide any real benefit in terms of risk-reduction to what serology donor testing alone provides.

- EBAANZ does however recognize the usefulness of NAT testing and we do not diminish its relevance in window periods.
- **EBAANZ would like to propose the following change to the proposal:**
  - To establish 'cornea only' donor eligibility, **mandatory tests** that **must** be conducted are **serological testing** for HIV, HCV and HBV.
  - **Where available**, it is **recommended** that NAT testing for HIV, HCV and HBV is performed.
- The above recommendation is in-line with international guidelines. Both the United States Food and Drug Administration and the Council of Europe.

EBAANZ SUMMARY RESPONSE FOR MANDATORY HTLV AND SYPHILIS TESTING:

- **HTLV serological testing should NOT be mandated.**
- **Syphilis serological testing should NOT be mandated.**

The responses to questions 12 and 13 have been divided into the following sections:

SECTION 1:
PREVALENCE, INCIDENCE AND RISK IN THE AUSTRALIAN EYE DONOR POPULATION

SECTION 2:
TRANSMISSION OF HIV 1 & 2, HEPATITIS B, HEPATITIS C, HTLV I & II AND SYPHILIS VIA TRANSPLANTATION OF OCULAR TISSUE (CORNEA AND SCLERA)

SECTION 3:
COMPARISON OF TGO88 AND THE PROPOSED TGO109 TO INTERNATIONAL REGULATORS

SECTION 4:
LOGISTICS OF NAT TESTING IN AUSTRALIA

SECTION 5:
FALSE POSITIVE RATE ASSOCIATED WITH NAT TESTING

SECTION 6:
LOSS OF BENEFIT ASSOCIATED WITH NAT TESTING IN AUSTRALIA

SECTION 7:
UN-EQUITABLE ACCESS ASSOCIATED WITH NAT TESTING IN AUSTRALIA

SECTION 1:

PREVALENCE, INCIDENCE AND RISK IN THE AUSTRALIAN EYE DONOR POPULATION

Prevalence, Incidence and Residual Risk in screening and testing regimes.

Key Points

- The prevalence rates estimated for Australian eye donors are likely to be an overestimate of the true prevalence in Australian eye donors.
- The incident rates and the residual risks calculated from this prevalence data must therefore be considered at the high end of estimates rather than a mean estimate figure.
  - This is due to several issues covered in the proceeding sections of this document.
- The Probability of an infected eye donor being missed per 100,000 using only serology testing is:
  - HIV - 1 in 166M
  - HBV - 1 in 555,555
  - HCV - 1 in 416,666
- The likelihood of an infected eye donor being missed per 100,000 using only serology testing, and that donor passing on a blood borne virus to which the recipient seroconverts is:
  - HIV: 1 in 55,555,555,555
  - HBV: 1 in 1,851,851 to 18,518,518
  - HCV: 1 in 25,252,525

Calculating Prevalence

For the six years 2015-2020 there were 8196 eye donors in Australia. In this time, unconfirmed reactive results reported were HIV - 30, HBV - 52 and HCV – 31 (these donors were all rejected on the basis of this first screening result).

During the period 2018-2020, EBAANZ data capture changes confirmed false positive results for:

- HIV – 100% (11 out of 11 confirmatory tests negative)
  - Proportion positive = 0
- HBV – 58% (11 out of 19 confirmatory tests negative)
  - Proportion positive = 0.42
- HCV – 63% (5 out of 8 confirmatory tests negative)
  - Proportion positive = 0.37

Zou's methodology of estimating the frequency of confirmed positive results among the unconfirmed reactive results (2) was used to produce estimated true positive rates for the Australian eye donor population (Table 1).

This can be done by calculating the expected rate of confirmed positive results by subtracting the number of false positive results (determined here based on confirmed false positive results from 2018-2020 in the Australian eye donor environment).

The corresponding prevalence rates for other donor sources are shown in Table 2.

Table 1. Australian Eye Donor Prevalence Rates (EBAANZ)

	Initial screening result – reported reactive	Estimated Positive†	Number of Donors	Prevalence per 100,000 persons
HIV	30*0	0	8196	0
HBV	52*0.42	21.84	8196	266.5
HCV	31*0.37	11.47	8196	140

Table 2. Prevalence Rates among different donor populations (2019)

PREVALENCE PER 100,000 PERSONS				
	Australian eye donors	Australian first -time blood donors†	Australian population†	United States population*
HIV	0	3.82	141	368
HBV	266.5	67.73	893	1524
HCV	140	63.91	507	731

† Transfusion-transmissible infections in Australia: 2020 Surveillance Report. Kirby Institute, UNSW Sydney, and Australian Red Cross Lifeblood; 2020
* United States Center for Disease Control

Calculating Estimated Incidence

Incidence rates are not available for eye donors because this type of donation is a single non-repeatable event (therefore no time-period can be assigned). To overcome this Zou and colleagues (2) extrapolated incidence rates from United States blood donors to assign estimated incidence rates among tissue donors. Yao and colleagues (3) made the same extrapolation between Australian musculoskeletal and Australian blood donors.

This calculation involves adjusting the rates to reflect the different prevalence rates among the tissue donors and the populations used for comparison (a prevalence ratio). The same prevalence ratio can be applied to the Australian eye donor population to estimate the incidence rates. The prevalence ratio and calculated incidence ratios for Australian eye donors are presented in Table 3.

Table 3: Incidence in Australian Eye Donors

	Prevalence ratio	Incidence rate in blood donors* (no./100,000 person-years)	Estimated Incidence rate in eye donors (no./100,000 person-years)
HIV	0:3.82 = 0	0.49	0
HBV	266.5:67.73 = 3.93	0.43	1.7
HCV	140:63.91 = 2.19	0.57	1.2

* Transfusion-transmissible infections in Australia: 2020 Surveillance Report. Kirby Institute, UNSW Sydney, and Australian Red Cross Lifeblood; 2020

^Calculated from the total number of eye donors tested (n=8196)

Calculation of residual risk

The estimated probability of viraemia at the time of donation can be calculated using the Incidence-window period Model B mathematical modelling equation described by Seed and colleagues (4).

This probability:

- Assumes that Window Period transmissions represent the major component of the residual risk.
- This probably holds true for HIV and HCV, but less so for HBV where chronic infection can be marked by transient HBsAg detection.
- $P = \lambda \times WP$ where
  P = probability donor gave infectious donation during window period
  λ = the incidence
  WP = window period (in days)

Results for Australian eye donors using serologic testing methods are presented in Table 4.

Table 4 – Residual risk after serologic testing in Australian Eye Donors

	Window period† (days)	Estimated Incidence rate in eye donors per 100 000 donors	Probability donor gave infectious donation during window period per 100 000 donors	Likelihood of an infected donor being missed per 100,000	Likelihood of infected eye donor in Australia (at 2000 donors/yr)
HIV	22	0.01*	22/365*0.01= 0.0006	100000/0.0006= 1 in 166M	166M/2000= 1 every 83,333 yrs
HBV	38	1.7	0.18	1 in 555,555	1 every 278 yrs
HCV	66	1.2	0.22	1 in 454,545	1 every 227 yrs

†Transfusion-transmissible infections in Australia: 2020 Surveillance Report. Kirby Institute, UNSW Sydney, and Australian Red Cross Lifeblood; 2020

* As no incidence could be calculated at '0', an incidence of 0.01 was used.

These results compare to the published:

- United States estimates for the Tissue donor population/100,000 donors of (2):
  - HIV 1.815 (1 in 55,096)
  - HBV 2.962 (1 in 33,760)
  - HCV 2.374 (1 in 42,122)
- Australian musculoskeletal donor population (2002-2004) (4):
  - HIV 0.78 (1 in 128,000)
  - HBV 0.53 (1 in 188,000)
  - HCV 1.82 (1 in 55,000)

Calculation of residual risk with Nucleic Acid Testing (NAT)

NAT testing for these viral markers reduces the estimated "window-period" and thus reduces the calculated theoretical residual risk (Table 5).

Table 5 – Residual risk after NAT testing in Australian Eye Donors

	Window period† (days)	**Estimated Incidence rate in eye donors per 100 000 donors**	**Estimated Incidence (no./100,000 person-years)**	**Likelihood of an infected donor being missed per 100,000**	**Likelihood of infected eye donor in Australia** (at 2000 donors/yr)
Anti-HIV	6	0.01*	0.00016	1 in 625,000,000	1 every 312,500 years
HBsAg	16	1.7	0.075	1 in 1,333,333	1 every 667 years
Anti-HCV	3	1.2	0.0099	1 in 10,101,010	1 every 5,050

* As no incidence could be calculated at '0', an incidence of 0.01 was used.

Calculation of Residual Risk of Transmission by Ocular Tissue Transplantation

There has never been a case of HIV or HCV transmission by corneal transplantation reported. And no cases of HBV transmission since the implementation of serological testing in 1986 (5) (see section 2).

Due to no data on transmission rates for BBV in corneal donation, the residual risk of transmission must therefore be based on theoretical rates of seroconversion, and these need to be based on published rates of seroconversion from similar inoculation scenarios.

For corneal transplantation (an avascular and bloodless transplant (6)) the likelihood of transmission is thought to be significantly less than that of percutaneous transmission (*See section 2)* with infected blood and is therefore more analogous to transmission through mucous membrane contact. For example, percutaneous transmission HCV is approximately 0.3% for HIV but 0.09% for mucous membrane transmission **Therefore, the following calculations are likely to represent an overestimation of residual risk of transmission by corneal tissue**.

Considering a transplant rate in Australia of approximately 1.6 corneal transplants per eye donor, and the residual risk calculations after serology testing one can calculate the residual risk of transmission from corneal transplantation (Table 6).

Table 6: Residual risk of transmission after *only serology* testing for Australian corneal transplants

	Probability donor having infectious donation during window period per 100 000 donors	**Theoretical rate of transmission in corneal transplantation** (% inoculated)	**Probability of transmission†** (no./100,000 eye donors)	**Likelihood of infected donor being missed and transmitting BBV per 100,000**	**Expected transmission in Australian eye donors** (@2000/yr)
HIV	0.0006/100= 0.000006	0.3	0.0000018	1 in 55,555,555,555	1 every 27,777,777 yrs
HBV	0.18/100= 0.0018	3 to 30	0.0054 to 0.054	1 in 1,851,851 to 18,518,518	1 every 925 to 9259 years
HCV	0.22/100= 0.0022	1.8	0.00396	1 in 25,252,525	1 every 12,626 yrs

† This takes into account approximately 1.6 corneal transplants from each Australian eye donor

Table 7: Residual risk of transmission after *only NAT* testing for Australian corneal transplants

	Probability donor having infectious donation during window period per 100 000 donors	**Theoretical rate of transmission in corneal transplantation** (% inoculated)	**Probability of transmission†** (no./100,000 eye donors)	**Likelihood of infected donor being missed and transmitting BBV per 100,000**	**Expected transmission in Australian eye donors** (@2000/yr)
HIV	0.00016/100= 0.0000016	0.3	0.00000048	1 in 2,089,333,333,333	1 every 27,777,777 yrs
HBV	0.075/100= 0.00075	3 to 30	0.00225 to 0.0225	1 in 4,444,444 to 44,444,444	1 every 2,222 to 22,222 years
HCV	0.0099/100= 0.000099	1.8	0.000178	1 in 561,797,752	1 every 280,898 yrs

† This takes into account approximately 1.6 corneal transplants from each Australian eye donor

SECTION 3:

TRANSMISSION OF HIV 1 & 2, HEPATITIS B, HEPATITIS C, HTLV I & II AND SYPHILIS VIA TRANSPLANTATION OF OCULAR TISSUE (CORNEA AND SCLERA)

When assessing reports of disease transmission via ocular tissue transplantation it is necessary to be aware that:

- Corneal transplantation and whole eye donation (and release) was first described in 1905.
- It is the most common form of cadaveric donation and transplantation.
- World-wide numbers of accumulated corneal transplants are estimated at over 200,000 transplants per year for the past 25 years (7).
- Australian numbers of accumulated corneal transplants are estimated at over 38,000 transplants across the past 16 years, with the number of transplants increasing each year (8).
- Infectious disease transmission rates of populations outside of Australia cannot be used as surrogates for transmission figures within Australia, as the differences in geographical locations reflect the variability of disease distribution based on individual populations (9).
- The essential basis for reducing the risk of virus transmission includes a detailed medical and social history of the tissue donor and the exclusion of persons with "high-risk behavior," as well as clinical and biological testing procedures as described in this detection (10).

HIV 1 and 2

HIV has never been reported to be transmitted via transplantation of corneas, sclera or any other ocular tissue.

- HIV 1 has been documented to be in tears (11) and some corneal buttons (12-14).
- Only a small percentage of donors with antibody HIV have detectable genome in the cornea (12).

The cornea is avascular tissue.

- The potential for transmission of HIV via corneal transplantation is considered to be lower than that of percutaneous transmission and is likely to be more analogous to transmission through mucous membrane contact.
- The incidence of seroconversion after exposure to HIV-positive blood is 0.3% after a percutaneous exposure (e.g. needle-stick injury) and 0.09% after mucous membrane exposure (15-17).
- The risk of seroconversion after exposure to other tissues or fluids, while not quantified, is felt to be considerably lower (17). In comparison, transmission approaches 100% through blood transfusion (18).

HIV has never been transmitted via corneal transplantation.

- There are three reports in the literature detailing nine patients who have received corneas from HIV-positive donors.

- None of the corneal recipients seroconverted or became ill, although all other organ and tissue recipients from these donors seroconverted (19-22).

Hepatitis C

Hepatitis C virus (HCV) has never been reported to be transmitted via transplantation of cornea, sclera or any other ocular tissue.

- There are reports in the literature detailing six patients who received corneas from three HCV seropositive donors, at least two of whom had viral RNA in their serum).
    - **None of the corneal recipients seroconverted after transplantation (23).**

- The risk of contracting hepatitis C after exposure to HCV-positive blood is 1.8% after a percutaneous exposure (e.g. needle-stick injury) and is considered rare after a mucous membrane exposure (17).

- Polymerase chain reaction assays indicate that only 20-26% of seropositive cornea donors have viral RNA in their serum, and initial attempts to detect viral RNA in the cornea were unsuccessful (24, 25).
    - More recently there was one report of HCV RNA detection in 24% of corneas obtained from seropositive donors (26), one of 77% (27) and one of 0% (28).
    - However, the potential for transmission of HCV via corneal transplantation is considered to be lower than that of percutaneous transmission and, like HIV, is likely to be more analogous to transmission through mucous membrane contact (17).
    - The potential for transmission of HCV via the surgical use of sclera is thought to be similar to percutaneous transmission (17).

Hepatitis B

Since serologic screening for HBV was introduced (in the late 1980's) there have been no cases of transmission via transplantation of cornea, sclera or any other ocular tissue.

- Prior to serological screening for HBV, transmission of hepatitis B virus (HBV) has been documented in two corneal recipients from two separate donors (29).
    - These cases occurred in 1984 and 1985, before screening for HBV was required.
    - Recipients of one cornea from each donor developed clinical and serological evidence of HBV infection 2 months and 14 weeks after penetrating keratoplasty. The recipient of the fellow cornea from one donor died from a CVA 4 months after surgery without undergoing serologic testing. The recipient of the fellow cornea from the other donor never developed clinical characteristics of hepatitis but tested positive for prior exposure to HBV 2 years after penetrating Keratoplasty (29).
    - **The risk of HBV transmission through corneas is significantly lower due to the low amount of blood components in the processed tissue** (10).

- **Since serologic screening for HBsAg was introduced (in the late 1980's) there have been no reported cases of transmission.**

- Less than 10% of HBsAg-seropositive donors have detectable HBsAg in their corneas (30), and in a similar study no viral genome was detected (28). The chance of a cornea being infectious prior to the appearance of surface Ag in the blood is considered to be very small. (28).

- It has been demonstrated that HBsAg-positive donors can demonstrate HBV DNA negative NAT tests. In such situations, these donors may be considered to have a false positive HBsAg (31). However, this would be incorrect with the HBV DNA NAT test instead being a false negative.

- Although occult HBV (OBI) can be detected by serology HBsAg-negative and NAT HBV-positive testing, the existing negligible risk of the likelihood of an infected donor of HBV being missed per 100,000 being 1 in 555,555, would be even more negligible if re-calculated for OBI. This is due to the prevalence of OBI being less than non-OBI HBV. For example, in a high-risk Australian patient cohort it was reported that out of 1,451 high-risk liver clinic patients, 0.69% were classified as having OBI (32). Also, the ARCBS detected 90 of 1.49 million blood donors in 2019 as having HBV. Of which 29 were classified as occult HBV (33). The actual risk of transmission would therefore be substantially less than for non-OBI HBV. HBV NAT has also been demonstrated to produce conflicting results (10).

HTLV I & II

HTLV-I or HTLV-II has never been reported to be transmitted via transplantation of cornea, sclera or any other ocular tissue.

- The prevalence of HTLV in the Australian blood donor population has been reported to be 0.3 per 100 000 donations between the 2010-2019 period (33), which is far less than that of HIV, HBV or HCV.

- The FDA requires HTLV testing only for relevant 'viable, leukocyte-rich cells and tissues.' The FDA does NOT consider corneas to be a viable leukocyte-rich tissue (34).

- In testing donors for the presence of HTLV, it has been demonstrated that tissue allografts should be assessed regarding the presence and number of leukocytes. This has been deemed as the most prominent and relevant factor to accurately assess the risk of HTLV in tissue transplantation. Corneas have been identified as not being leukocyte-rich, containing few to no leukocytes, as well as being avascular (35).

- Repeat donors donating plasma for fractionation only no longer require testing for HTLV (33).

- There is one report in the literature detailing transplantation of a HTLV-I positive organ and tissue donor. None of the corneal transplant recipients seroconverted (36).

SYPHILIS

Syphilis has never been reported to be transmitted via transplantation of cornea, sclera or any other ocular tissue.

Historically, the reason for donor syphilis testing came from a suggested correlation between syphilis and HIV seropositivity. The hypothesis then being that a positive syphilis serology may identify recent HIV infection for a donor not yet converted to HIV seropositivity (5).

- A recent study in 2021 found that out of 291 seropositive HIV patients, none (0%) were seropositive for syphilis (9).
- This has also been shown more historically in 1995(37).
- Such studies **recommended re-evaluation of the decision of screening of potential cornea donors for syphilis** (9, 37).

- In animal experiments, transmission of syphilis by corneal transplantation has not been demonstrated (38).

- Other experiments with donor corneas from rabbits infected with *Treponema Pallidum* showed that rabbit corneal tissue contains few, if any, *T.Pallidum* organisms under corneal preservation conditions (cold storage in OptiSol), and expert opinion concluded that it is highly unlikely that any treponemes present in human corneas would survive to cause infection in recipients (39).

Syphilis testing is not conducted for plasmapheresis donations in Australia. The below are excerpts from the 2020 Kirby and Lifeblood Report (33) which can also be applied to all ocular tissue donation types (Cornea and Sclera).

"For the purpose of this report the term TTI refers to infections for which there is mandatory blood donation testing. Mandatory tests differ between donations for fresh blood components (i.e. HIV, HBV, HCV, HTLV, syphilis) and plasmapheresis donations, which are exclusively sent for fractionation (i.e. HIV, HCV and HBV only).

"Potentially infectious syphilis (PIS) is a blood safety definition designed to capture donors that have a theoretical risk of transmitting syphilis by transfusion. ***Importantly, the risk of syphilis transfusion transmission is quite distinct from the viral TTIs.***

"A published Lifeblood analysis concluded that the residual risk of syphilis transmission is currently negligible (1 in 49.5 million per unit transfused)","The risk of syphilis transmission can be considered 'theoretical', given the absence of cases of transfusion transmission."

SECTION 4:

COMPARRISON OF TGO88 AND THE PROPOSED TGO109 TO INTERNATIONAL REGULATORS

SECTION 4 SUMMARY:

1. TGO 88 is aligned with international regulators (FDA & CoE).
2. TGO 109 mandating NAT will not be in-line with international regulators (FDA & CoE).
3. TGO 109 mandating NAT contrasts with TGAs proposal comment of TGO88 not being 'world's best practice' for international harmonization.
4. Table 1 summarizes international regulatory body donor testing requirements.
5. The FDA only recommends, it does NOT mandate NAT testing
6. The CoE only recommends, it does NOT mandate NAT testing

Associations have not been included in for regulatory comparisons, as they are not regulatory bodies.

FEDERAL DRUGS ADMINISTRATION:

The FDA has both a code and guidance document for donor testing:

- '*Title 21 Code of Federal Regulations, part 1271' (40)*
- *'Guidance for Industry. Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (34)'*

The **FDA 'code'** although mandates donor testing for HIV, HBV, HCV and Syphilis, **the FDA does not mandate how such testing should be performed** (Table 8). For example, whether by serology, NAT, or both.

The **FDA guidance** does not establish legally enforceable responsibilities, but purely **describes only the FDA's current thinking and recommendations**, unless specific regulatory or statutory requirements are cited. This is clearly demonstrated in the guide which states the following:

'This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. ***You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.****'*

AND

'FDA's guidance documents, including this guidance, ***do not establish legally enforceable responsibilities****. Instead, guidance's describe the FDA's current thinking on a topic and should be* ***viewed only as recommendations****, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA's guidances means that something is suggested or recommended, but not required.'*

The FDA also stipulates that testing for a transmissible disease is only relevant if it is one for which an '*appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA* ***and is available***' (34). **This identifies a key approach by the FDA in acknowledging limitations that exist in availability of some testing platforms.**

COUNCIL OF EUROPE:

The CoE '*Commission Directive 2006/17/EC*' has a set of minimum standards which includes donor testing for the below antibody and antigen serology tests. **The CoE does not mandate NAT testing** (table 8) and considers that demonstrating sero-negativity is achieved sufficiently through these tests alone.

- HIV 1/2 Antibody
- HBsAg
- HBcAb
- HCV Ab
- Syphilis
- HTLV-1 Ab (only for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas).

The CoE guidance document is via the '*EDQM guide to the safety and quality of tissues and cells for human application'* also does not suggest mandating NAT testing. What is expressed is that consideration may also be given to performing NAT tests.

INDIA:

The Directorate General of Health Services, Standards of Eye Banking in India **does not mandate NAT testing**, and states that the decision to conduct NAT testing is acted upon by the Medical Director (41).

- HIV 1/2 Antibody
- HBsAg
- HCV Ab
- Syphilis

Table 8: Comparison of the current TGO 88, Council of Europe (CoE) and the United States Food and Drug Drug Administration (FDA) regulations for conducting infectious disease testing for deceased and ocular only donors.

		FDA (34) (40)		CoE (42)		TGO 88 (43)	
Donor Group		Deceased donors	Ocular only donor	Deceased donors	Ocular only donor	Deceased donors	Ocular only donor
Testing Requirement							
Serology test Initial sample	Anti HIV-1 Anti HIV-2	✓	✓	✓	✓	✓	✓
	Anti-HCV	✓	✓	✓	✓	✓	✓
	HBsAg	✓	✓	✓	✓	✓	✓
	HTLV-1/2 (antibodies	Not required for non-lymphocyte rich	**NOT mandated**	Risk based **NOT mandated**		✓	**NOT mandated**
	Syphilis	✓	✓	✓	✓	✓	**NOT mandated**
_		AND		AND		AND	
NAT initial sample	HIV	Recommended **NOT mandated**	Recommended **NOT mandated**	Recommended **NOT mandated**	Recommended **NOT mandated**	✓	**NOT mandated**
	HCV					✓	
	HBV					✓	

SECTION 5:

LOGISTICS OF NAT TESTING IN AUSTRALIA

IMPACT SUMMARY FOR THE LOGISTICS OF NAT TESTING:

In Australia, access to NAT testing within the timeframes required for transplantation would reduce the number of safe and viable corneas available for transplant in Australia and increase rather than reduce overall risk to the recipient.

In summary, the requirement for NAT testing will:

1. Increase the risk of poorer surgical outcomes from tissue that has been stored for a longer period of time.
2. Reduce access to quality optimal surgical grade tissue.
3. Compromise corneal quality and viability, jeopardizing the efficacy of the transplant and safety of the recipient.
4. Decrease access to eye tissue for waiting Australian recipients – particularly those in lower populated regions.
5. Increase wait time for Australian recipients.
6. Increase wait lists for Australian recipients.
7. Waste eligible donations.
8. Increase costs for the eye banks, and subsequent reimbursement bodies (being Medicare or the recipient's health insurance company); and
9. Potentially close eye donation and eye bank services in lower populated regions of Australia.

Logistics of NAT testing relate to:

a. Availability
b. Sample & testing requirements
c. Turn-around times
d. Testing requirements
e. Sample volume

A. AVAILABILITY

Within Australia, TGA approved NAT testing services/facilities for both living and cadaveric sample management are not routinely and readily available. There are no clinical testing facilities outside of the eastern states of Australia. The average turn-around times (not including transport time) for these services are 7-11 days. This contrasts with current serologic testing of HIV, HBV, and HCV, which routinely has a less than 24-hour turnaround time across Australia.

Due to the turn-around time required for NAT testing, results will often not be available prior to product release in several circumstances. This will result in a reduction in the ability of eye banks to release ocular tissue for transplantation outside of exceptional releases, and result in

older and less optimal grade tissue for Australian recipients awaiting routine surgery. This places Australian recipients in a compromised position in terms of the possible post-operative outcomes. Recipients requiring emergency tissue, where the turn-around time of the tissue is less than 24 hours would have to be provided as Exceptional Release tissue.

Additionally, NAT testing to be nationally mandated, with all Australian eye banks seeking services from the same few NAT testing providers, turnaround times may expand beyond 11 days due to the increased volume and demand. This will exacerbate access issues resulting in a further reduction of access to surgical grade tissue for recipients.

B. SAMPLE AND TESTING REQUIREMENTS

Sample collection restrictions, storage, transport conditions, and the volume required (*see section 5c*) for NAT testing creates significant problems for both pre-mortem and cadaveric eye donation blood samples.

- *Cadaveric samples must be collected within 15 hours of death if the donor has not been refrigerated within 12 hours and 24 hours after death otherwise.*

  Particularly for cases under coronial jurisdiction, where consent to proceed with donation (and blood sampling) can be delayed for extended periods, these time frames will increasingly preclude donation because the blood sample will not be valid for NAT testing.

- *Cadaveric whole blood must be tested within 72 hours.*

  This has significant logistical and cost implications for donations "remote" from a testing laboratory and especially if interstate transport is required.

- *If 72 hours cannot be accommodated, whole blood must be centrifuged and plasma separated into a transport tube, frozen <-18°C and shipped on dry ice to the laboratory to test for HVC, HIV and HBV NAT.*

  Eye banks do not have centrifuges within their facility as this is laboratory equipment is not required for eye bank operations. In order to centrifuge whole blood, the sample needs to be taken to a willing pathology laboratory in order for them to carry out centrifugation and separation of the plasma. Such laboratories willing to assist in such activities are limited. Therefore, this requirement is not able to be met by a number of eye banks.

  In addition, given the time-frame required in shipping samples interstate for eye banks without a local TGA approved NAT testing facility, the distances and times involved would mean that compliance to these timeframes is not always possible. This will result in a significant loss of ocular donors.

- *Pre-mortem samples (often required if cadaveric sampling cannot be performed or obtained, or if plasma dilution has occurred) must be tested within 72 hours of*

collection. If this is not possible plasma frozen at collection and stored <-20°C must be provided.

This is a significant impost and precludes donation for the majority of patients where post-mortem blood cannot be obtained or is invalid due to plasma dilution. Frozen pre-mortem samples of plasma are rarely held by pathology laboratories, especially in the volumes required (*refer to 1c of this submission*). The alternative of fresh refrigerated plasma restricts the samples to within 2 days prior to death (at a minimum) thus restricting the availability of plasma in the volumes required, and for plasma diluted donors restricts the availability to those donors who have only been plasma diluted in the day preceding their death.

- *Samples for NAT testing are required in an EDTA or Plasma preparation tube.*

  Restricting blood samples to an EDTA/PPT tube further restricts access to pre-mortem samples if they are required.

- *Numerous laboratories do not provide both validated pre-mortem and/or cadaveric serology and NAT testing.*

  Therefore at least two separate samples would be required to be sent to two separate laboratories. Again, this is significant regarding cost and, more importantly, sample volume and validity issues (*refer to following points in section 5c*).

- *NAT testing facilities commonly preclude pre-mortem blood samples.*

  Hospital collected blood samples have previously been aliquoted and used for clinical tests, increasing the potential for contamination, and increased false positives.

C. SAMPLE VOLUME

- *The volume of blood typically obtained at cadaveric collection, or that which is available pre-mortem from laboratories is extremely limited.*

  The volume of sample required for NAT testing, serology testing and testing for HTLV-I and syphilis exceeds the serum volume requirements for what is typically available.

  Most laboratories indicate the need for up to 5-10mls of whole blood to perform the three NAT tests. The ability to obtain such a large amount of whole blood from a cadaver is rare, and even so the ability to obtain an adequate sample volume without hemolysis of the sample is limiting (44).

  These requirements are in addition to the volumes required to complete serology testing. These samples, which are often required to be split between two laboratories to satisfy TGA approved testing and accreditation (*see section 5b*) is required to complete all serology, NAT, HTLV-1 and syphilis testing. **For most eye donors this is not obtainable.**

- *Amount of serum available is often not known until received by the testing laboratory.*

  If required to be sent interstate and there is not enough sample volume for testing, eye banks will be unable to obtain more sample due to the turnaround time and the 'time out' of the period to collect cadaveric blood (24 hours post-mortem).

D. TURNAROUND TIMES

Unlike all other TGA Class 2 biologicals, donated corneas (released as corneoscleral discs or whole eyes) are extremely time-sensitive, much like whole organs.

Rapid, routine turnaround times are available for serologic testing of HIV, HBV and HCV across Australia, but not for NAT testing. For example, the National Reference Laboratory (NRL) can only provide turn-around times of 3 days for urgent, or 10 days for non-urgent.

This does not include any transport components (which is especially restrictive for eye bank and eye care services in South and Western Australia). Therefore, for Western Australia this would equate to 5 days for urgent and 12 days for non-urgent. For South Australia, this would equate to 4 days for urgent and 11 days for non-urgent. Based on standard shipping timeframes.

Table 9 shows data supplied by the Australian Corneal Graft Registry for the period of 2001-2020 (20 years) regarding storage to transplant time frames. In regards to this data:

- Optisol:
  - **Hypothermic storage of corneas is the most widely used form of corneal preservation in the world. It is safe, effective and efficient and provides good time for the implementation of significant risk reduction strategies that are routinely available to eye banks. To change a storage system that might allow longer times frames, solely because of the time required to perform tests that don't result in significant risk reduction cannot be justified.**
  - Is used by all Australian states when tissue is required at short notice due to the limitations of organ culture storage and microbiological testing requirements of media.
  - **Is solely used by one eye bank which services an entire Australian State. Implementation of organ culture storage is not feasible for this eye bank due to both cost and operations.**
  - For Optisol stored corneas, increased storage times affects surgical handling, extends the post-operative period for the recipient, and transplant outcomes are less successful (45-47).
  - Loss of Optisol stored corneas would:
    - Result in the closure of an Eye Bank (*see sections 6, 7 and 8 for analysis of the implications of this*)
    - Corneal transplantation involving hypothermic preservation requires the flexibility to transplant corneas within 24 hours after donor death. This is due to emergency requirements, the current pool of eligible donors and transportation.

- Due to turn-around times for NAT testing within the time frame for emergency cornea requests, mandatory NAT testing would prohibit the availability of emergency corneal grafts.

- Organ culture storage allows corneas to store for up to 30 days before transplantation.

Table 9: Percentage of corneal grafts performed each day post storage of donor cornea

Day	Optisol	Organ Culture	Total
0-2	24.5%	0.2%	3.6%
0-5	68.4%	0.6%	40.5%
0-7	92.9%	1.6%	55.3%
7-14 days	15.3%%	26.5%	20%

SECTION 6:

FALSE POSITIVE RATE ASSOCIATED WITH NAT TESTING

IMPACT STATEMENT:

Increase false positives rates associated with NAT testing and cadaveric sera will add to donors being excluded where in fact they may be are eligible for donation. As testing occurring after retrieval, this would also result in cost implications for the eye bank and surgery cancellation (*see also sections 5 & 7*).

It is important to avoid false-positive virological results to ensure that corneas which carry no viral risk are not needlessly discarded.

- *Cadaveric blood (sera) can yield false positive results.*

  Cadaveric sera are commonly macroscopically abnormal being hemolyzed, turbid and lipemic. These factors can result in increased false positive rates (44, 48) through weakened sensitivity due to the presence of inhibitors such as hemolysis, heparin, bilirubin and dextrans. This can result in unnecessary discarding of donor corneas (49).

- *NAT HBV testing and false positive or negative rates.*

  Within the blood donor pool, the widespread implementation of screening by NAT has demonstrated challenges with non-discriminatory results related to HBV. It has been reported that a non-discriminate result in the absence of serological reactivity, although may represent acute infections in the serological window period with low levels of virus, most are in fact false positive results (50).

SECTION 7:

FINANCIAL COSTS ASSOCIATED WITH NAT TESTING IN AUSTRALIA

IMPACT STATEMENT:

The costs associated with NAT testing where local TGA approved platforms are not accessible or available will result in loss of donors due to the turn-over time and the time from donor cornea storage to surgery release (*see also section 5d*).

An analysis of the costs and reduced theoretical risks in undertaking NAT testing of Australian eye donors is presented in Table 9. These figures have increased since the 2011 submission with testing costs now quoted by the National Reference Laboratory at $106 per sample for non-urgent batched testing of donor plasma. This is compared to the ARCBS cost in 2009 of $45 per sample for non-urgent batched testing of donor plasma. The average price across laboratories for a single NAT test is $50.

This does not consider the additional expenses of transport from donor site to testing laboratory, or the additional costs involved in providing "at-call" testing of donor serum or the cost of serology (ELISA) testing that must be performed in conjunction with NAT testing.

The figures also assume that the residual risk after NAT testing is zero (the actual calculated residual risks are listed in Table 5-6) – thus the calculated costs are the *additional* costs of detecting one donor (and one transmission) by NAT testing that would not have been detected by serology testing. This was calculated by:

- (Likelihood of an infected donor being missed per 100,000) * (cost of NAT test)
  = Cost of detecting one infected donor per 100,000
- (Likelihood of infected donor being missed and transmitting BBV)*(cost of NAT test)
  = Cost of preventing one case of transmission

Table 5 – Residual risk after NAT testing in Australian Eye Donors

	Window period† (days)	**Estimated Incidence rate in eye donors per 100 000 donors**	**Estimated Incidence (no./100,000 person-years)**	**Likelihood of an infected donor being missed per 100,000**	**Likelihood of infected eye donor in Australia** (at 2000 donors/yr)
Anti-HIV	6	0.01*	0.00016	1 in 625,000,000	1 every 312,500 years
HBsAg	16	1.7	0.075	1 in 1,333,333	1 every 667 years
Anti-HCV	3	1.2	0.0099	1 in 10,101,010	1 every 5,050

Table 7: Residual risk of transmission after *only NAT* testing for Australian corneal transplants

	Probability donor having infectious donation during window period per 100 000 donors	**Theoretical rate of transmission in corneal transplantation** (% inoculated)	**Probability of transmission†** (no./100,000 eye donors)	**Likelihood of infected donor being missed and transmitting BBV per 100,000**	**Expected transmission in Australian eye donors** (@2000/yr)
HIV	0.00016/100= 0.0000016	0.3	0.00000048	1 in 2,089,333,333,333	1 every 27,777,777 yrs
HBV	0.075/100= 0.00075	3 to 30	0.00225 to 0.0225	1 in 4,444,444 to 44,444,444	1 every 2,222 to 22,222 years
HCV	0.0099/100= 0.000099	1.8	0.000178	1 in 561,797,752	1 every 280,898 yrs

† This takes into account approximately 1.6 corneal transplants from each Australian eye donor

Table 10: Additional costs of NAT testing in Australia

	Cost per test	**Cost of detecting one infected donor**	**Cost of preventing one transmission**
Individual			
Anti-HIV	$50	625000000*50= $31 bill	208 bill*50= $10 trillion
HBsAg	$50	1333333*50= $66 mill	4,444,444*50= $222 mill to 44,444,444*50= $2 billion
Anti-HCV	$50	101010103*50= $416 mill	561,797,752*50= $28 bill
Total	**$150**	**$31 bill & 482 mil**	**$10 trill & 30 bill**

†Assumes 30% transmission rate.

Due to the turn-around time of NAT testing (*see section 5d*), one state has calculated the cost of retrieving tissue, but not being able to release that tissue for transplantation (outside of exceptional release) due to NAT testing results not being available. This was calculated with the urgent turn-around time of NAT testing for this state being 4 days. **The cost lost would be between more than what is cost recovered per year for this Eye Bank. This eye bank would cease operations in response.**

- *Additional testing and costs per donor also have a greater relative effect on eye donation and transplantation than on any other forms of tissue donation.*

  Most donors in Australia are eye-only donors (due to age and medical contraindications precluding other forms of donation), with two possible transplants (corneas) and two possible grafts (sclera) arising

- *It does not take into consideration that this cost is transferred to Medicare and the recipient's health insurance company.*

  Most donors in Australia are eye-only donors (due to age and medical contraindications precluding other forms of donation), with two possible transplants (corneas) and two possible grafts (sclera) arising from one donor. Therefore, reimbursement of the costs involved in the donation can only be divided between four possible service fees.

Most donors in Australia are eye-only donors (due to age and medical contraindications precluding other forms of donation), with two possible transplants (corneas) and two possible grafts (sclera) arising from one donor. Therefore, reimbursement of the costs involved in the donation can only be divided between four possible service fees.

  In comparison, long storage and quarantine times for other tissue types such as skin, musculoskeletal and cardiovascular also mean it is possible to pool samples for testing, avoiding high on-call costs of testing (or re-testing of false positive or equivocal samples). Thus, the additional testing costs involved with one donor can be amortized over several types of donations. By consequence, the additional cost impost to the patient, health system and manufacturer is substantially less than for eye donation.

SECTION 8:

LOSS OF BENEFIT ASSOCIATED WITH NAT TESTING IN AUSTRALIA

IMPACT STATEMENT:

Mandating NAT testing results in a critical loss of benefit and increased risk for the Australian Population and Healthcare System as well as eye banks ceasing operation.

- *At the time a corneal transplant is required, treating clinicians have concluded there is no suitable equivalent or alternative treatment available to the recipient, to alleviate, restore or improve their visual status.*

- *Mandatory NAT testing will result in a reduction of eye donors (see previous sections), the availability of ocular tissue for transplantation, increase wait lists and wait time, and the demand for corneas for transplantation will not be met.*

- *Several eye banks will not be able to continue operation operate due to the sections highlighted in this application. This is especially so for eye banks that would be most affected, i.e., those using solely hypothermic corneal storage media.*

- ***The loss of benefit*** *for the Australian population will be critical.*

Australia will no longer be self-sufficient in meeting eye transplantation demand, due to the increasing number of corneal transplants required and Australia currently only just meeting demand (8, 51).

The cost to the healthcare system for vision loss in the Australian healthcare landscape was estimated at $16.6 billion in 2009, an increase from $9.8 billion in 2006. In response to the aging population and inflation over time, this number will continue to increase (52). The consequence of not being able to meet ocular tissue transplant demands in Australia would negatively contribute to this and place further burden on the healthcare system. This would also place greater burden on the under resourced low vision services (e.g. services that support those with vision impairment with their daily activities).

In addition, there is supporting evidence that visual impairment is associated with a higher hazard of mortality (53) (arguing that ocular tissue transplants are indeed a potentially "life-saving" treatment).

As there is a significant wait list in Australia for corneal transplants this would be critically concerning for waiting recipients (51). While it may be assumed that Australia could simply import to meet the shortfall caused by the implementation of mandatory NAT testing, unfortunately there are not enough corneal tissue globally (1 cornea available for every 70 needed), to supply to Australia (54).

This in turn would impact the waiting recipient, and there is a wealth of information produced by the eye care sector on the economic impact of vision impairment on those with vision

impairment and the community they live in, most recently the WHO World Report on Vision (55).

The implementation of the NAT HIV mandatory step does not support positive efforts to improve access to eye care services, it is anti-economic (56) and it does not comply with the United Nation's Sustainable Development Goals – in particular Goal 3, to improve access to health services, and to improve quality of life (55, 57, 58). Finally, when surgical intervention is delayed, recipient conditions will deteriorate. In these instances, surgical treatment will need to be altered to treat advanced conditions. This may impact the surgical technique, and limit surgical treatment options for the waiting recipient. This has flow-on consequences for the wider eye care field. For example, this encroaches on the already stretched low-vision services.

If the demand for corneal transplantation cannot be met, the Australian eye transplant sector will be forced to import eye tissue from overseas under special purpose access schemes. They will be reliant on ad hoc non-routine importation services which will not prioritize Australians (as the export provider will prioritize their own population). There are only a few exporters that would meet the regulatory, ethical, and psycho-social expectations of the Australian public and eye care sector. This would render Australia reliant and 'hand-tied' to those few providers. Finally, as there is a global shortage of corneas for transplantation as already highlighted, Australia would not be able to receive an adequate supply from elsewhere to meet the domestic shortfall. Access therefore would be based on ability to pay, rather than need – which is anti-equitable access.

SECTION 9:

UN-EQUITABLE ACCESS ASSOCIATED WITH NAT TESTING IN AUSTRALIA

IMPACT STATEMENT

Mandating NAT testing results in un-equitable access to eye transplantation within Australia and poorer patient outcomes. This contrasts with Australia's commitment to the World Health Organization Vision 2020 via Vision 2020 Australia's goal 2 to 'Influence policy changes to **enable equitable access to eye health and vision care**'

- *The result of the cost impact of mandatory NAT testing (see section 7) is that the Public Health Insurance (PHI) cost of ocular tissue for transplantation will be increased.*

- *The access to, and cost of ocular tissue for transplantation will be un-equitable across Australia.*

  As the cost of NAT testing varies between Australian states based on location, logistics and requirements, this will result in each eye bank within each state having a different cost associated with providing ocular tissue for transplant.

  The result is disparity across Australia for the cost of the provision of ocular tissue for transplantation. Such an occurrence will result in patients travelling between states to where ocular tissue transplants may be cheaper, driven solely by the cost of the ocular tissue.

- *Increased transportation of ocular tissue across Australia results in poorer patient outcomes.*

  Surgeons may be forced to import tissue from states with the lowest cost or from overseas. It has been demonstrated that in the Australian landscape, corneas that are moved between states for transplant have poorer transplant outcomes than locally acquired and transplanted corneas (59). Again, this adds to patients not having equitable access to the best healthcare treatment and outcome possible.

REFERENCES:

1. Australia V. Vision 2020 Australia 2017-2020 Strategic Plan. 2018.
2. Zou S, Dodd RY, Stramer SL, Strong DM, Tissue Safety Study G. Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States. N Engl J Med. 2004;351(8):751-9.
3. Yao F, Seed C, Farrugia A, Morgan D, Cordner S, Wood D, et al. The risk of HIV, HBV, HCV and HTLV infection among musculoskeletal tissue donors in Australia. Am J Transplant. 2007;7(12):2723-6.
4. Seed CR, Kiely P, Keller AJ. Residual risk of transfusion transmitted human immunodeficiency virus, hepatitis B virus, hepatitis C virus and human T lymphotrophic virus. Intern Med J. 2005;35(10):592-8.
5. Patel MH PA, , Shah AM. Seroprevalence of HIV, HBV, HCV & RPR among cornea donor in the regional institute of ophthalmology. Journal of Integrated Health Sciences. 2017;5(1):39-43.
6. Simonds RJ. HIV transmission by organ and tissue transplantation. AIDS. 1993;7 Suppl 2:S35-8.
7. Research GV. Corneal Implants Market Size, Share & Trends Analysis Report. 2020.
8. KA Williams MK, NE Coffey, VJ Jones, RAD Mills and DJ Coster. The Australian Corneal Graft Registry 2018 Report. 2018.
9. Roy A, Das S, Fernandes M, Mohamed A, Chaurasia S. Seropositivity of blood samples of 31,355 cornea donors from a tertiary care network of eye banks. Int Ophthalmol. 2021;41(5):1743-51.
10. Pruss A, Chandrasekar A, Sanchez-Ibanez J, Lucas-Samuel S, Kalus U, Rabenau HF. Algorithms for the Testing of Tissue Donors for Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus. Transfus Med Hemother. 2021;48(1):12-22.
11. Qian Y, Wu Z, Chen C, Du K, Wei W. Detection of HIV-1 viral load in tears of HIV/AIDS patients. Infection. 2020;48(6):929-33.
12. Qavi HB, Green MT, SeGall GK, Hollinger FB, Lewis DE. The incidence of HIV-1 and HHV-6 in corneal buttons. Curr Eye Res. 1991;10 Suppl:97-103.
13. Cantrill HL, Henry K, Jackson B, Erice A, Ussery FM, Balfour HH, Jr. Recovery of human immunodeficiency virus from ocular tissues in patients with acquired immune deficiency syndrome. Ophthalmology. 1988;95(10):1458-62.
14. Heck E, Petty C, Palestine A, Luckenbach M, Salahuddin SZ, Nussenblatt R, et al. ELISA HIV testing and viral culture in the screening of corneal tissue for transplant from medical examiner cases. Cornea. 1989;8(2):77-80.
15. Rapiti E Pr-ÜA, Hutin Y. Sharps injuries. Assessing the burden from sharps injuries to health-care workers at national and local levels. Geneva: World Health Organization; 2005.
16. Coppola N, De Pascalis S, Onorato L, Calo F, Sagnelli C, Sagnelli E. Hepatitis B virus and hepatitis C virus infection in healthcare workers. World J Hepatol. 2016;8(5):273-81.
17. Prevention CfDCa. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. 2001. Contract No.: RR-11.
18. Scott SR WZ. Risks and challenges of HIV infection transmitted via blood transfusion. Biosafety and Health. 2019;1(3):124-8.
19. Pepose JS, MacRae S, Quinn TC, Ward JW. Serologic markers after the transplantation of corneas from donors infected with human immunodeficiency virus. Am J Ophthalmol. 1987;103(6):798-801.

20. Schwarz A, Hoffmann F, L'Age-Stehr J, Tegzess AM, Offermann G. Human immunodeficiency virus transmission by organ donation. Outcome in cornea and kidney recipients. Transplantation. 1987;44(1):21-4.
21. Caron MJ, Wilson R. Review of the risk of HIV infection through corneal transplantation in the United States. J Am Optom Assoc. 1994;65(3):173-8.
22. Simonds RJ, Holmberg SD, Hurwitz RL, Coleman TR, Bottenfield S, Conley LJ, et al. Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. N Engl J Med. 1992;326(11):726-32.
23. Pereira BJ, Milford EL, Kirkman RL, Levey AS, Tomford WW, Leibowitz H, et al. Low risk of liver disease after tissue transplantation from donors with HCV. Lancet. 1993;341(8849):903-4.
24. Badenoch PR. Corneal transplantation and infectious hepatitis. Br J Ophthalmol. 1995;79(1):2.
25. Laycock KA, Essary LR, Delaney S, Kuhns MC, Pepose JS. A critical evaluation of hepatitis C testing of cadaveric corneal donors. Cornea. 1997;16(2):146-50.
26. Lee HM, Naor J, Alhindi R, Chinfook T, Krajden M, Mazzulli T, et al. Detection of hepatitis C virus in the corneas of seropositive donors. Cornea. 2001;20(1):37-40.
27. Heck E, Dingrando A, Proctor C, Cavanagh HD. Viral HCV RNA reactivity of corneal cells in plasma HCV nucleic acid-positive eye donors. Cornea. 2013;32(4):506-7.
28. Sengler U, Reinhard T, Adams O, Gerlich W, Sundmacher R. Testing of corneoscleral discs and their culture media of seropositive donors for hepatitis B and C virus genomes. Graefes Arch Clin Exp Ophthalmol. 2001;239(10):783-7.
29. Hoft RH, Pflugfelder SC, Forster RK, Ullman S, Polack FM, Schiff ER. Clinical evidence for hepatitis B transmission resulting from corneal transplantation. Cornea. 1997;16(2):132-7.
30. Khalil A, Ayoub M, el-Din Abdel-Wahab KS, el-Salakawy A. Assessment of the infectivity of corneal buttons taken from hepatitis B surface antigen seropositive donors. Br J Ophthalmol. 1995;79(1):6-9.
31. Kuhns MC, Kleinman SH, McNamara AL, Rawal B, Glynn S, Busch MP, et al. Lack of correlation between HBsAg and HBV DNA levels in blood donors who test positive for HBsAg and anti-HBc: implications for future HBV screening policy. Transfusion. 2004;44(9):1332-9.
32. Martinez MC, Kok CC, Baleriola C, Robertson P, Rawlinson WD. Investigation of occult hepatitis B virus infection in anti-hbc positive patients from a liver clinic. PLoS One. 2015;10(3):e0117275.
33. Kirby Institute US, and Australian Red Cross Lifeblood. Transfusion-transmissible infections in Australia: 2020 Surveillance Report. . 2020.
34. Research FDACfBEa. Guidance for Industry. Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products. 2007.
35. Podzemny CE, Brenton MD, Brubaker SA, Marians RC. A quantitative polymerase chain reaction test to enumerate leukocytes in allograft tissue and the implications for donor eligibility testing. Cells Tissues Organs. 2013;198(3):221-6.
36. Zarranz Imirizaldu JJ, Gomez Esteban JC, Rouco Axpe I, Perez Concha T, Velasco Juanes F, Allue Susaeta I, et al. Post-transplantation HTLV-1 myelopathy in three recipients from a single donor. J Neurol Neurosurg Psychiatry. 2003;74(8):1080-4.
37. Goldberg MA, Laycock KA, Kinard S, Wang H, Pepose JS. Poor correlation between reactive syphilis serology and human immunodeficiency virus testing among potential cornea donors. Am J Ophthalmol. 1995;119(1):1-6.
38. Randolph ME. An experimental study of the possibility of transmitting syphilis by a corneal graft. Am J Ophthalmol. 1952;35(3):352-7.

39. Macsai MS, Norris SJ. OptiSol corneal storage medium and transmission of Treponema pallidum. Cornea. 1995;14(6):595-600.
40. Administration FD. CFR 1271. Human Cells, Tissues, and Cellular and Tissue-Based Productsrev. 16/6/2021.
41. Impairment NPFCoBV. Standards of eye banking in india. New Delhi: Directorate General of Health Services; 2020.
42. Communities CotE. Commission Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. Official Journal of the European Union. 2006.
43. Australian Goverment DoHaA, Therapeutic Goods Administration. Therapeutic Goods Order No. 88 - Standards for donor selection, testing, and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products. 2013.
44. Raj A, Mittal G, Bahadur H. Factors affecting the serological testing of cadaveric donor cornea. Indian J Ophthalmol. 2018;66(1):61-5.
45. Simon M, Fellner P, El-Shabrawi Y, Ardjomand N. Influence of donor storage time on corneal allograft survival. Ophthalmology. 2004;111(8):1534-8.
46. Thuret G, Chiquet C, Bernal F, Acquart S, Romanet JP, Mouillon M, et al. Prospective, randomized clinical and endothelial evaluation of 2 storage times for cornea donor tissue in organ culture at 31 degrees C. Arch Ophthalmol. 2003;121(4):442-50.
47. Wagoner MD, Gonnah el S. Corneal graft survival after prolonged storage in Optisol-GS. Cornea. 2005;24(8):976-9.
48. Miedouge M, Chatelut M, Mansuy JM, Rostaing L, Malecaze F, Sandres-Saune K, et al. Screening of blood from potential organ and cornea donors for viruses. J Med Virol. 2002;66(4):571-5.
49. Rock T, Beck R, Jurgens S, Bartz-Schmidt KU, Bramkamp M, Thaler S, et al. Factors influencing the virological testing of cornea donors. Medicine (Baltimore). 2017;96(47):e8561.
50. Kiely P, Hoad VC, Wood EM. False positive viral marker results in blood donors and their unintended consequences. Vox Sang. 2018.
51. Machin H, Buckland L, Georges P, Ghabcha M, Golding-Holbrook T, Leighton C, et al. Supply and Demand of Domestic Corneal Tissue and Its Implications on Export Potential-Using Australia as an Example. Cornea. 2020.
52. Economics A. Clear Focus. The Economic Impact of Vision Loss in Australia in 2009.; 2009.
53. Ehrlich JR, Ramke J, Macleod D, Burn H, Lee CN, Zhang JH, et al. Association between vision impairment and mortality: a systematic review and meta-analysis. Lancet Glob Health. 2021;9(4):e418-e30.
54. Gain P, Jullienne R, He Z, Aldossary M, Acquart S, Cognasse F, et al. Global Survey of Corneal Transplantation and Eye Banking. JAMA Ophthalmol. 2016;134(2):167-73.
55. Organization GWH. World report on vision. 2019.
56. Machin HP, B. Ross, C. Sutton, G. Baird, P. Part Two: Defining Surplus and Waste in the Pre- and Post-COVID-19 Era Via Australian and USA Examples. International Journal of Eye Banking. 2020;8(3).
57. Development. OfEC-oa. 2020. Health policy study: waiting times for health Services – next in line.
58. Nations U. Transforming our World: The 2030 Agenda for Sustainable Development. 2016.

59. Keane MC, Lowe MT, Coster DJ, Pollock GA, Williams KA. The influence of Australian eye banking practices on corneal graft survival. Med J Aust. 2013;199(4):275-9.