

# Fungal Infections in Endothelial Keratoplasty

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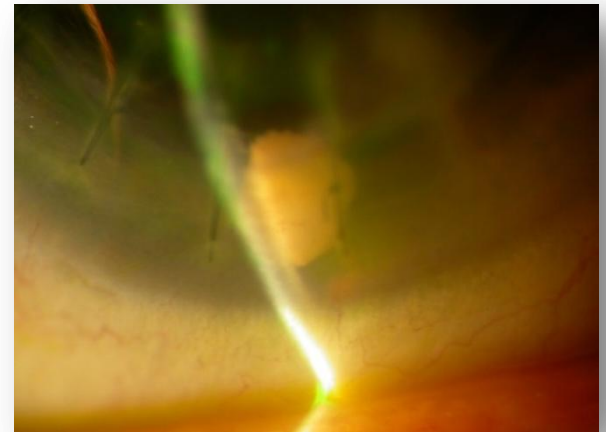
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# Disclosure Anthony J. Aldave, M.D.

- Consultant (ad hoc)
  - 5AM Ventures
  - Avellino Laboratories
  - W. L. Gore & Associates
  - Noveome Biotherapeutics (Stemnion)
  - Sun Ophthalmics
- Research Funding
  - National Eye Institute
- Speaker's Bureau
  - Avellino Laboratories

## Report of the Eye Bank Association of America Medical Advisory Board Subcommittee on Fungal Infection After Corneal Transplantation

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**Purpose:** To investigate the incidence of fungal infections after corneal transplantation to determine whether storage media supplementation with an antifungal should be considered.

**Methods:** Adverse reactions reported to the Eye Bank Association of America through the online adverse reaction reporting system between January 1, 2007, and December 31, 2010, were reviewed to identify cases of recipient fungal infection. Data were collected regarding the donor, the donor cornea, recovery and processing, and mate culture and clinical course of the recipients.

**Results:** Thirty-one cases of culture-proven fungal keratitis (n = 14) and endophthalmitis (n = 17) were reported out of 221,664 corneal transplants performed using corneal tissue distributed by domestic eye banks (1.4 cases per 10,000 transplants performed). Although the annual incidence of postkeratoplasty fungal infection has not increased significantly since 2005, a trend toward an increasing rate of fungal infection has been observed. Fungal infections were more commonly reported after endothelial keratoplasty procedures (0.022%) than penetrating keratoplasty procedures (0.012%), but the difference was not statistically significant ( $P = 0.076$ ). Additionally, no association was found between fungal infection after endothelial keratoplasty and whether the lamellar tissue cut was performed by the surgeon or the eye bank technician. Seventy-three percent (16 of 22) of the fungal cultures performed on the mate corneas were positive, with infection developing in 67% (10 of 15) of recipient eyes (endophthalmitis in 6 eyes and keratitis in 4 eyes).

**Conclusions:** Although a nonsignificant increasing trend in the rate of fungal infection has been observed over the past 6 years, it is not

sufficiently compelling to pursue antifungal supplementation of donor storage media.

**Key Words:** keratoplasty, fungal keratitis, fungal endophthalmitis, eye banking

(*Cornea* 2013;32:149–154)

Although fungal infection after corneal transplantation remains a rare event, the resultant visual morbidity has led to calls for antifungal supplementation of corneal preservation media.<sup>1–3</sup> At present, none of the commercially available preservation media in North America contain an antifungal agent, and the colorimetric indicators of microbial contamination do not consistently detect fungal contamination.<sup>4</sup> The inclusion of gentamicin and streptomycin in Optisol-GS (Bausch & Lomb, Rochester, NY) in the early 1990s is credited with a decreased incidence of postkeratoplasty bacterial endophthalmitis and has led to an increased interest in the feasibility of supplementing storage media with antifungal agents.<sup>2,3</sup> In the Optisol-GS era, the relative risk of fungal keratitis has been reported to be more than 3 times that of bacterial keratitis for corneas preserved for 4 or more days.<sup>2</sup> Therefore, corneas maintained in preservation media for even longer periods of time may be at increased risk of transmitting fungal infection to the recipient. Thus, even if the results of the recently initiated Cornea Preservation Time Study (funded by National Institutes of Health) demonstrate favorable clinical outcomes of using donor corneal tissue preserved for up to 12 days before endothelial keratoplasty (EK), corneal surgeons may be hesitant to accept donor tissue with a prolonged death to surgery interval given the concern about a greater risk of recipient fungal infection. Therefore, in October 2010, the Medical Advisory Board of the Eye Bank Association of America appointed a subcommittee to investigate the incidence of fungal keratitis and endophthalmitis after corneal transplantation and also to investigate the feasibility of supplementing preservation media with an antifungal agent.

### MATERIALS AND METHODS

All adverse reactions reported to the Eye Bank Association of America (EBAA) through the online adverse reaction reporting system (OARRS) for corneal transplants

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The authors have no funding or conflicts of interest to disclose. Reprints: Anthony J. Aldave, Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90095 (e-mail: aldave@jsei.ucla.edu). Copyright © 2012 by Lippincott Williams & Wilkins

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**TABLE 2.** Number of Cases of Bacterial and Fungal Endophthalmitis and Keratitis Per Year Since 2007

Year	2007	2008	2009	2010	Total
Endophthalmitis					
All cases*	5	6	7	9	27
Fungal cases	2	6	5	4	17 (63%)
Keratitis					
All cases*	3	4	11	4	22
Fungal cases	2	3	6	3	14 (64%)
All infections†					
All cases*	8	10	18	13	49
Fungal cases	4	9	11	7	31 (63%)
All procedures					
PK	34,806	32,524	23,269‡	21,970‡	112,569
Fungal cases	2	5	5	2	14 (0.012%)
EK	14,159	17,468	18,221‡	19,159‡	69,007
Fungal cases	2	4	5	4	15 (0.022%)
ALK	950	1072	774‡	1041‡	3837
Fungal cases	0	0	1	1	2 (0.052%)

\*All cases represent fungal plus bacterial infections.

†All infections represents endophthalmitis plus keratitis.

‡Numbers reflect corneal tissue distributed and used within the United States only. Information regarding the type of procedure performed was not collected for tissue distributed internationally in 2009 and 2010. Data for 2007 and 2008 include procedures performed both domestically and internationally.

Aldave AJ, Dematteo J, Glasser DB, et al. Report of the Eye Bank Association of America Medical Advisory Board Subcommittee on fungal Infection after corneal transplantation. *Cornea*. 2013; 32:149-54.

# Annual Incidence of Postkeratoplasty Fungal Infection

**TABLE 4.** Incidence of Fungal Infections (Keratitis and Endophthalmitis) Per Year Since 2005

Year	Infections (Fungal Cases)	Cornea Grafts (Total)*	Fungal Infection Rate (%)
2005	6	44,329	0.014
2006	2	45,035	0.004
2007	4	50,122	0.008
2008	9	52,487	0.017
2009	11	59,784	0.018
2010	7	59,271	0.012
Total	39	311,028	0.012 (mean)

\*All tissue distributed by US banks for domestic and international use.

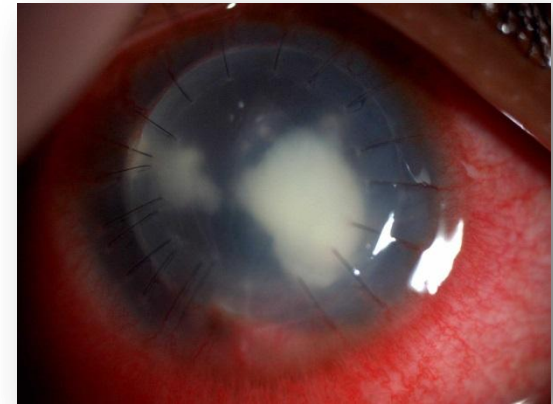
Aldave AJ, Dematteo J, Glasser DB, et al. Report of the Eye Bank Association of America Medical Advisory Board Subcommittee on fungal Infection after corneal transplantation. *Cornea*. 2013; 32:149-54.

# EBAA MAB Subcommittee Report on Fungal Infection Unanswered Questions

- Is the incidence of postkeratoplasty fungal infection increasing?
  - Is the risk really higher with EK than PK?
    - Is the risk associated with whether the cornea is prepared by the eye bank or the surgeon?
- What is the utility of performing donor corneal rim fungal cultures?
  - What percentage are positive?
  - What percentage of recipients of corneas with positive fungal rim cultures develop infection?


# EBAA MAB Subcommittee Report on Fungal Infection Purpose

- To determine the utility of performing fungal cultures of the donor corneal rim by determining
  - The percentage of donor corneal rim fungal cultures that are positive
  - The percentage of the corresponding corneal buttons that transmit infection to the recipient



Courtesy of Dr. Irv Raber

# EBAA MAB Subcommittee Report on Fungal Infection Methods

  
**GLOBAL SIGHT NETWORK**  
Facilitating Sight Across the World Through  
 International Eye Care Cooperation

**3-12 MONTH POST-OPERATIVE FOLLOW-UP REPORT**

Alabama Eye Bank is **Required** by the Eye Bank Association of American to obtain the following information  
**PLEASE PROVIDE ANY MISSING INFORMATION (FAX TO: 205-942-2129)**

Recipient Information			
Name		Date of Birth	Age
Unique ID Number (SSN, Driver's License, Hospital ID, Medical Record)			
Ocular Diagnosis			
Ocular Diagnosis: Operative Eye		Ocular Diagnosis: Non-operative Eye	
<input type="checkbox"/> Keratoconus		<input type="checkbox"/> Keratoconus	
<input type="checkbox"/> Glaucoma		<input type="checkbox"/> Glaucoma	
<input type="checkbox"/> Other: _____		<input type="checkbox"/> Other: _____	
Surgical Information			
Tissue ID Number		R.O. Number	
Surgeon Name		Surgical Facility	
Date of Surgery		Address	
Type of Surgery	City	State	Zip
<input type="checkbox"/> ALK <input type="checkbox"/> DALK <input type="checkbox"/> Tectonic <input type="checkbox"/> Trabeculectomy/shunt patch			
<input type="checkbox"/> OTHER: _____			
Alabama Eye Bank is <b>Required</b> by the Eye Bank Association of American to request the following information in regards to adverse reactions			
<b>Yes</b>	<b>No</b>	Did the patient experience a <b>Primary Graft Failure</b> associated with the surgery indicated above: If yes, what was the date of the diagnosis for the primary graft failure: _____	
<b>Yes</b>	<b>No</b>	Was any post-operative infection observed: If yes, Please describe the infection: _____ If yes, how many days after the surgery was the infection identified: _____ If yes, was the donor tissue the suspected source: <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, was donor culturing performed: <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, what was the cultures performed on: <input type="checkbox"/> Media only <input type="checkbox"/> Corneo-scleral rim <input type="checkbox"/> Both If yes, was the culture positive: <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, organism(s) identified: _____	
<b>Yes</b>	<b>No</b>	Did the recipient develop any systemic infectious disease following the transplant: If yes, was the donor tissue the suspected source: <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, what disease did the recipient develop: _____	
Any additional post-operative findings or comments: _____ _____ _____			

Formal HL380.L1 Effective Date: 07/15/2010

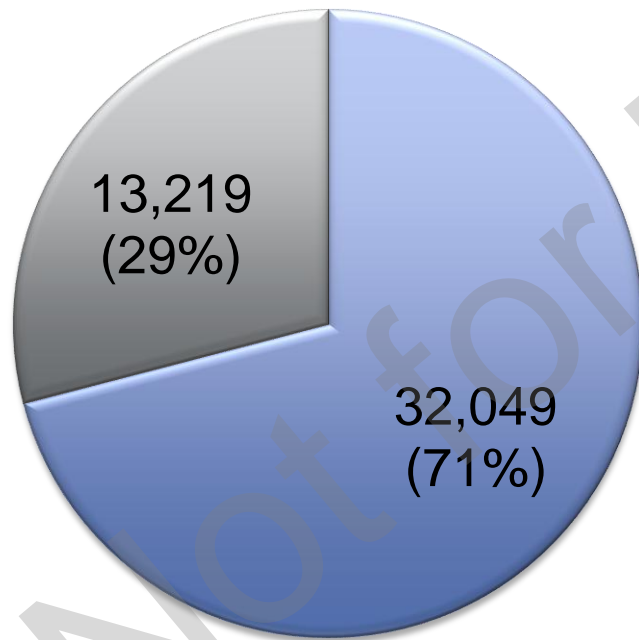


Courtesy of Tissue Banks International

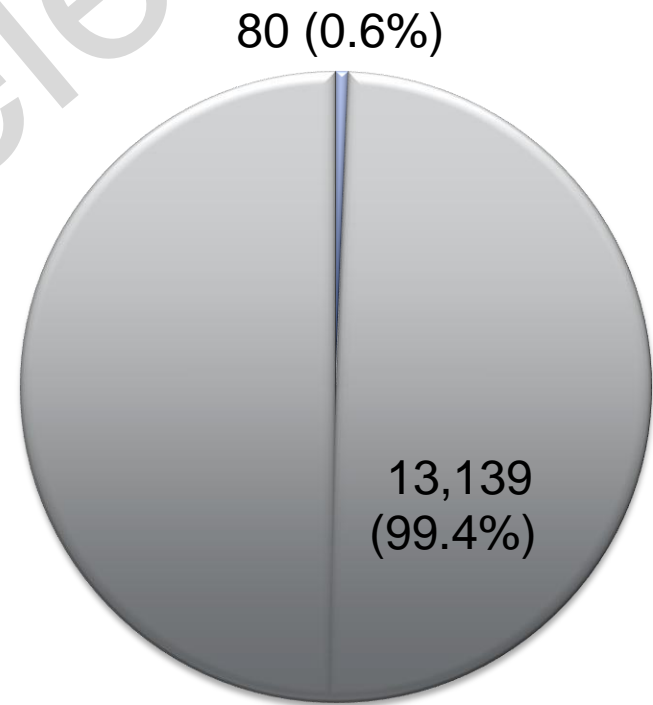


# EBAA MAB Subcommittee Report on Fungal Infection Results

- 61 eye banks reported number of donor rim fungal cultures performed



■ Not cultured   ■ Cultured

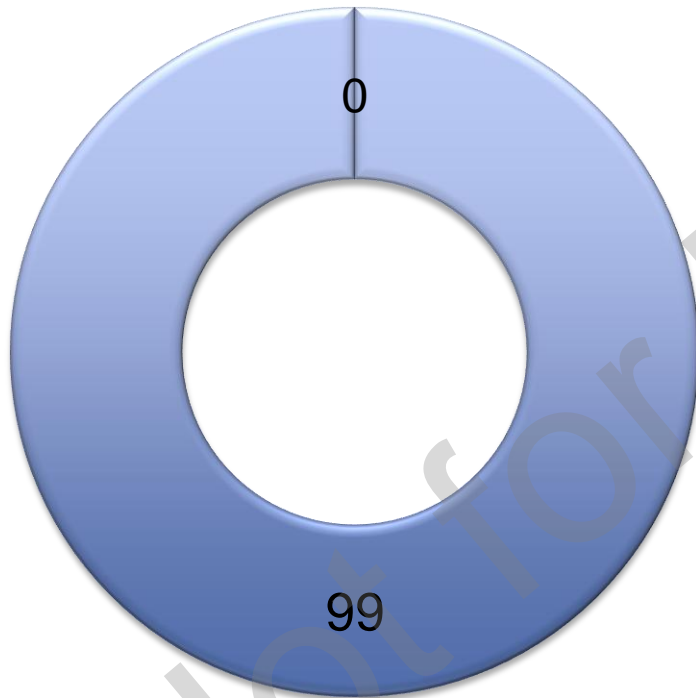


■ Culture Positive   ■ Culture Negative

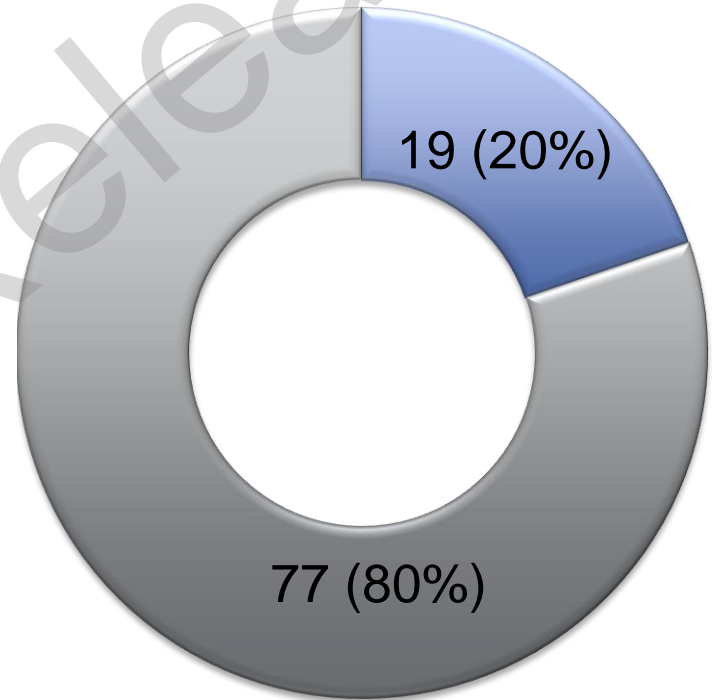
# EBAA MAB Subcommittee Report on Fungal Infection Results

- 61 eye banks reported number of donor rim fungal cultures performed
  - 80 positive fungal cultures
- 11 eye banks did not report number of donor rim fungal cultures performed
  - 19 positive fungal cultures

# EBAA MAB Subcommittee Report on Fungal Infection Results



■ Recipients of corneas from cx + donors

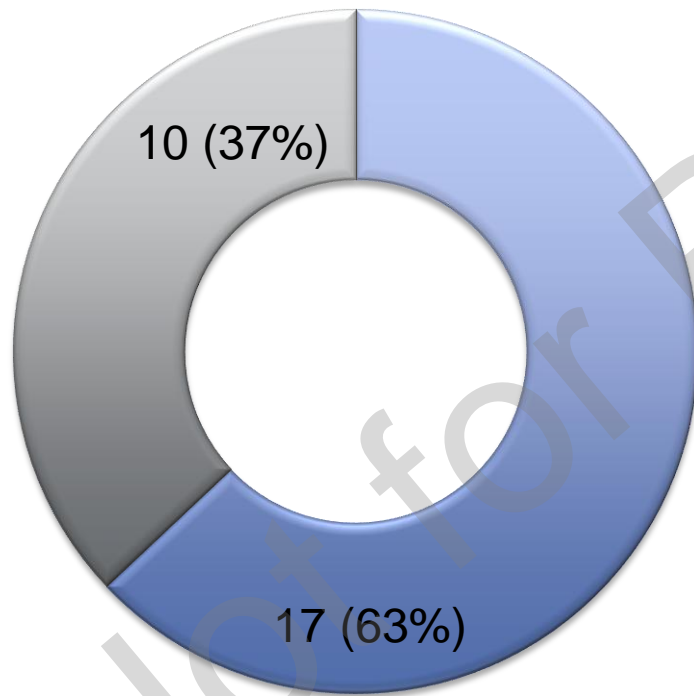


■ Postop Fungal Infection  
■ No Postop Infection

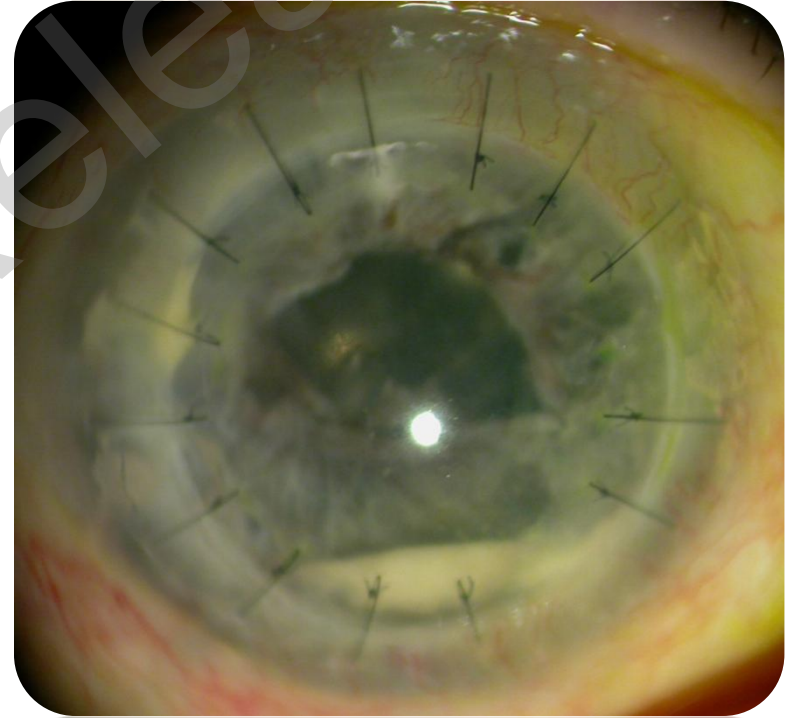
# EBAA MAB Subcommittee Report on Fungal Infection Postop Fungal Infxns

- 8 cases of post-keratoplasty fungal infections in recipients of corneas from eye banks that did not report the number of positive donor rim fungal cultures
  - 1 from donor with positive donor rim fungal culture
  - 7 from donors with no donor rim fungal culture

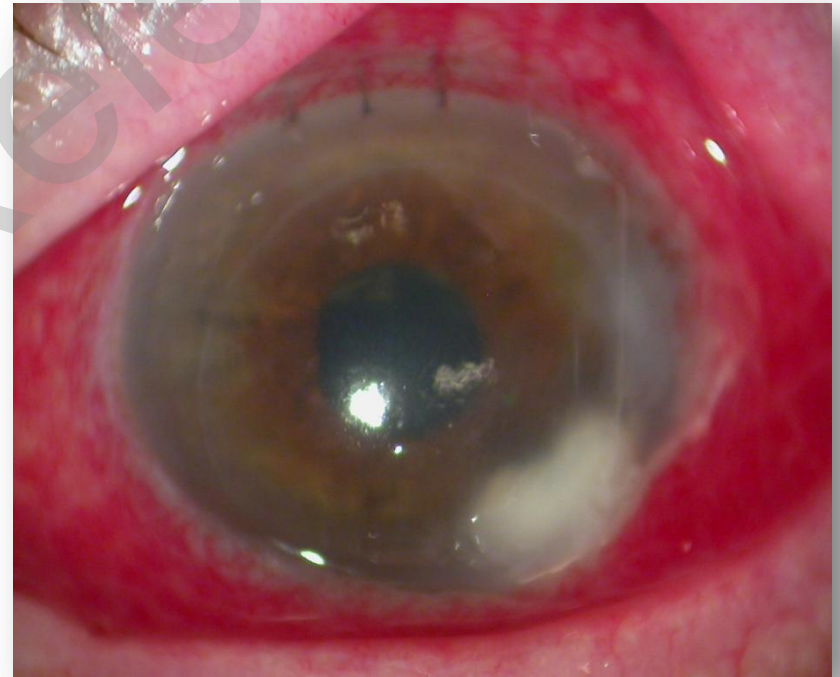
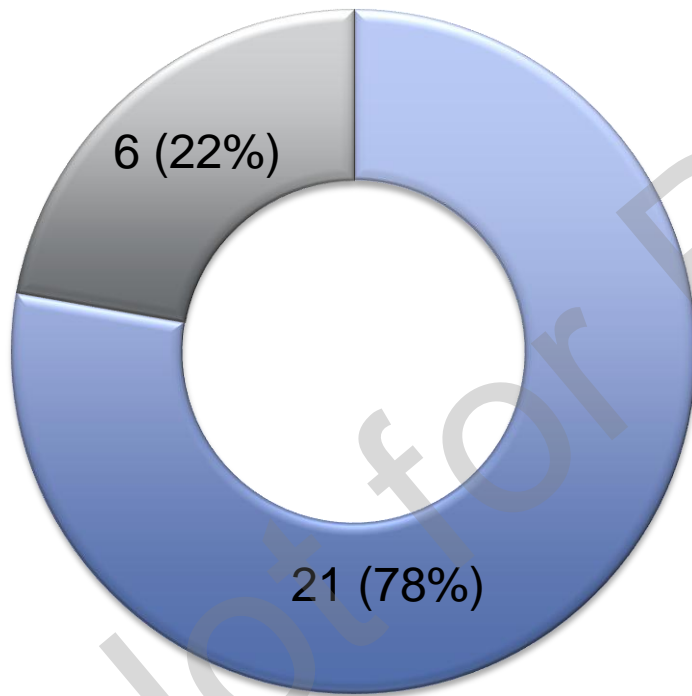
# EBAA MAB Subcommittee Report on Fungal Infection Postop Fungal Infxns



■ Endophthalmitis   ■ Keratitis

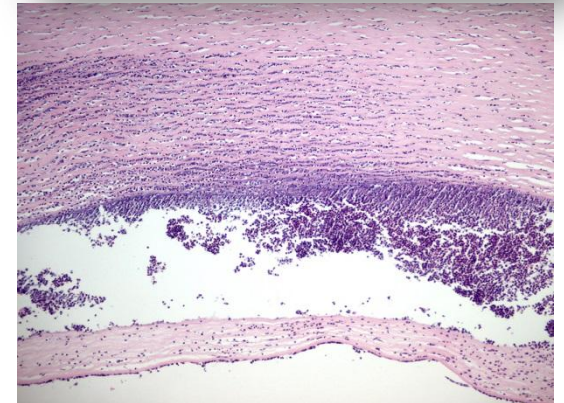
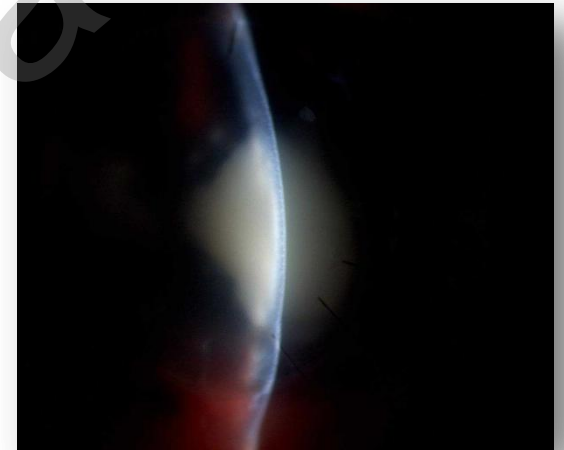
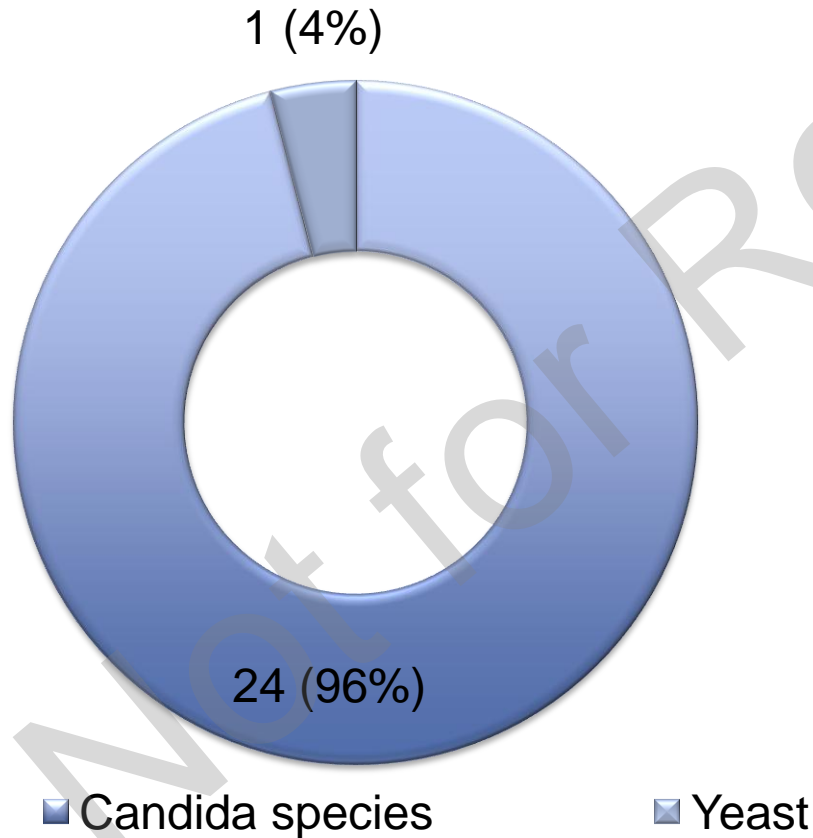


# EBAA MAB Subcommittee Report on Fungal Infection Postop Fungal Infxns



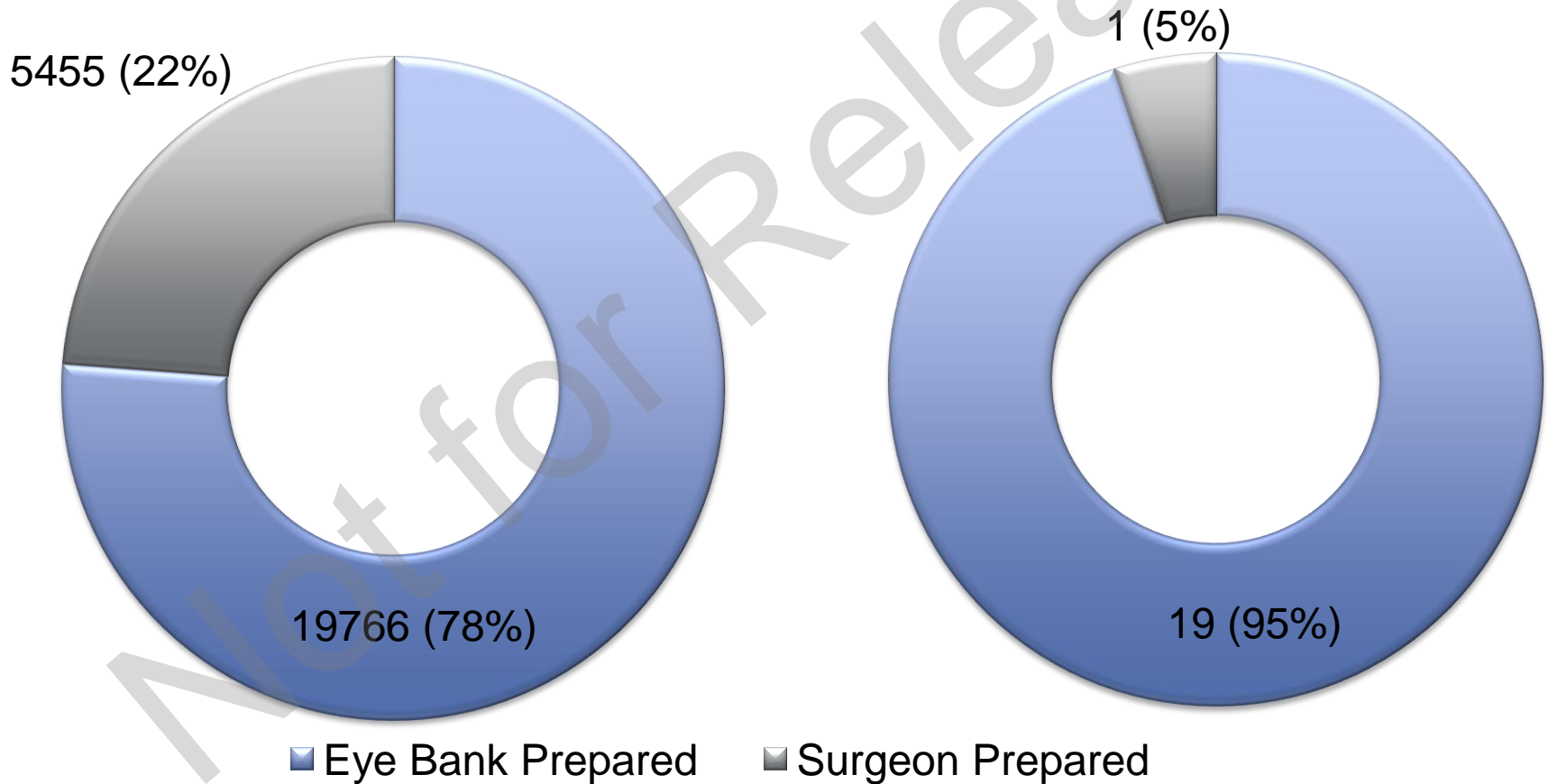
- Endothelial keratoplasty
- Penetrating keratoplasty

# EBAA MAB Subcommittee Report on Fungal Infection Organisms



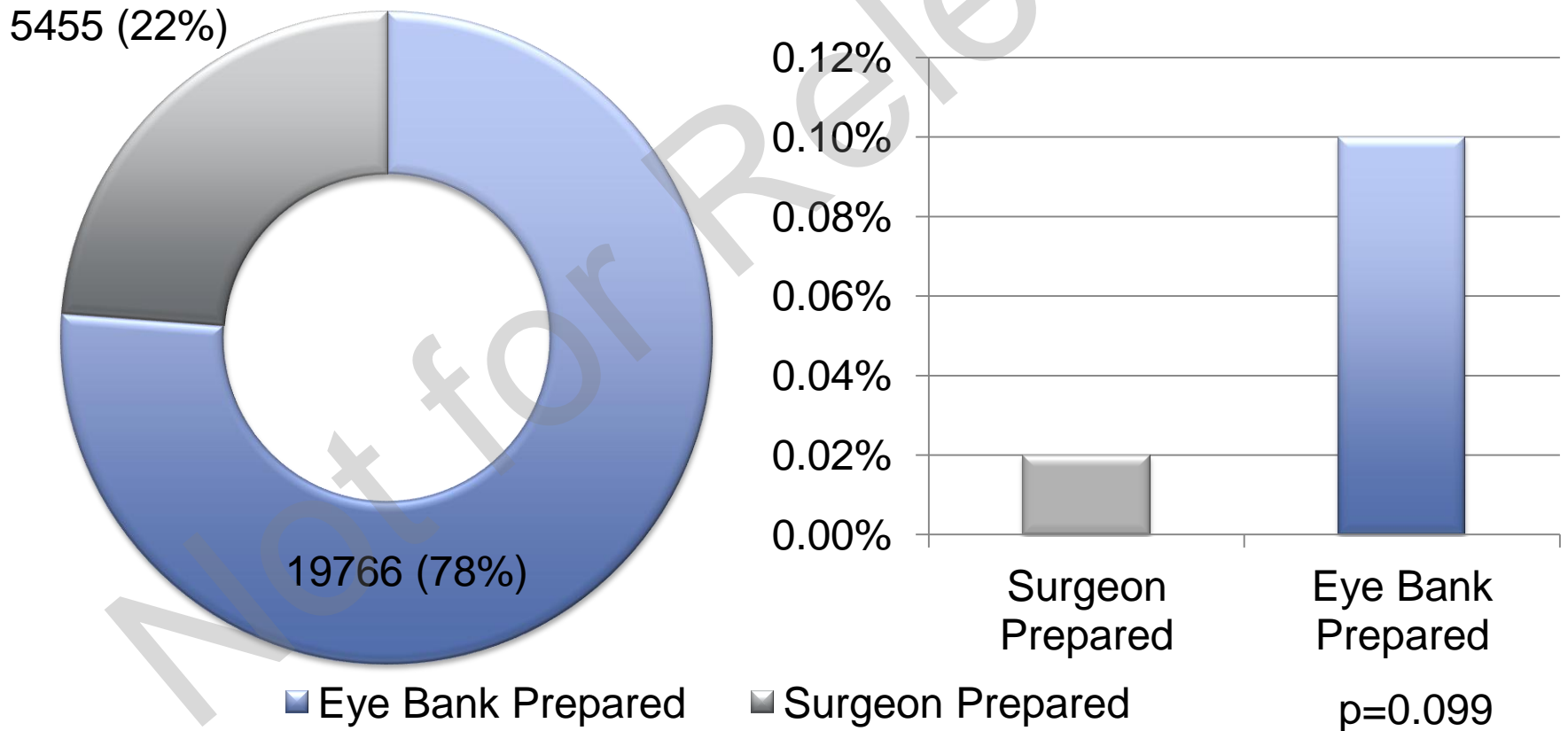
Images courtesy of Dr. Irv Raber

# EBAA MAB Subcommittee Report on Fungal Infection Location of Preparation

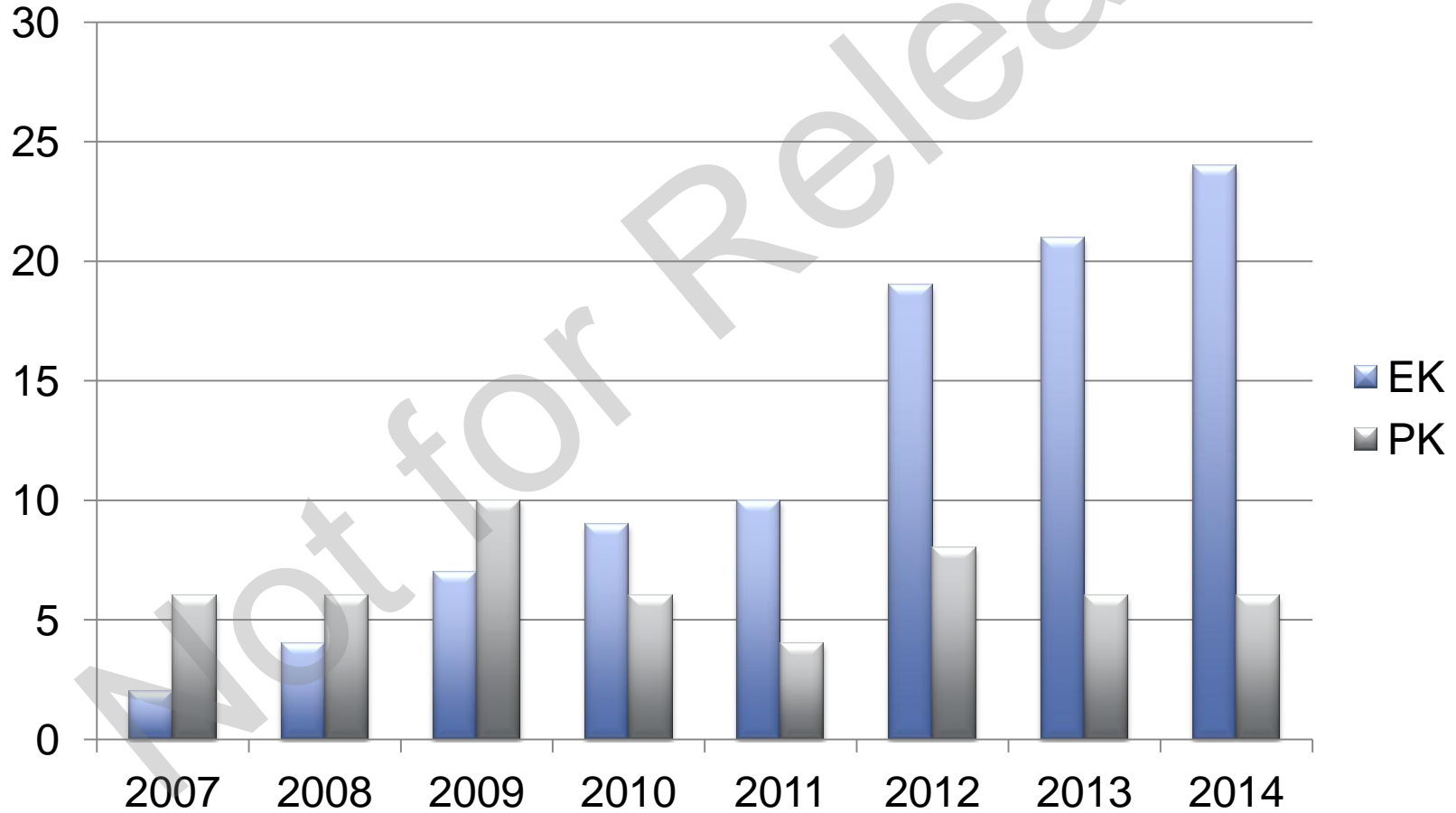




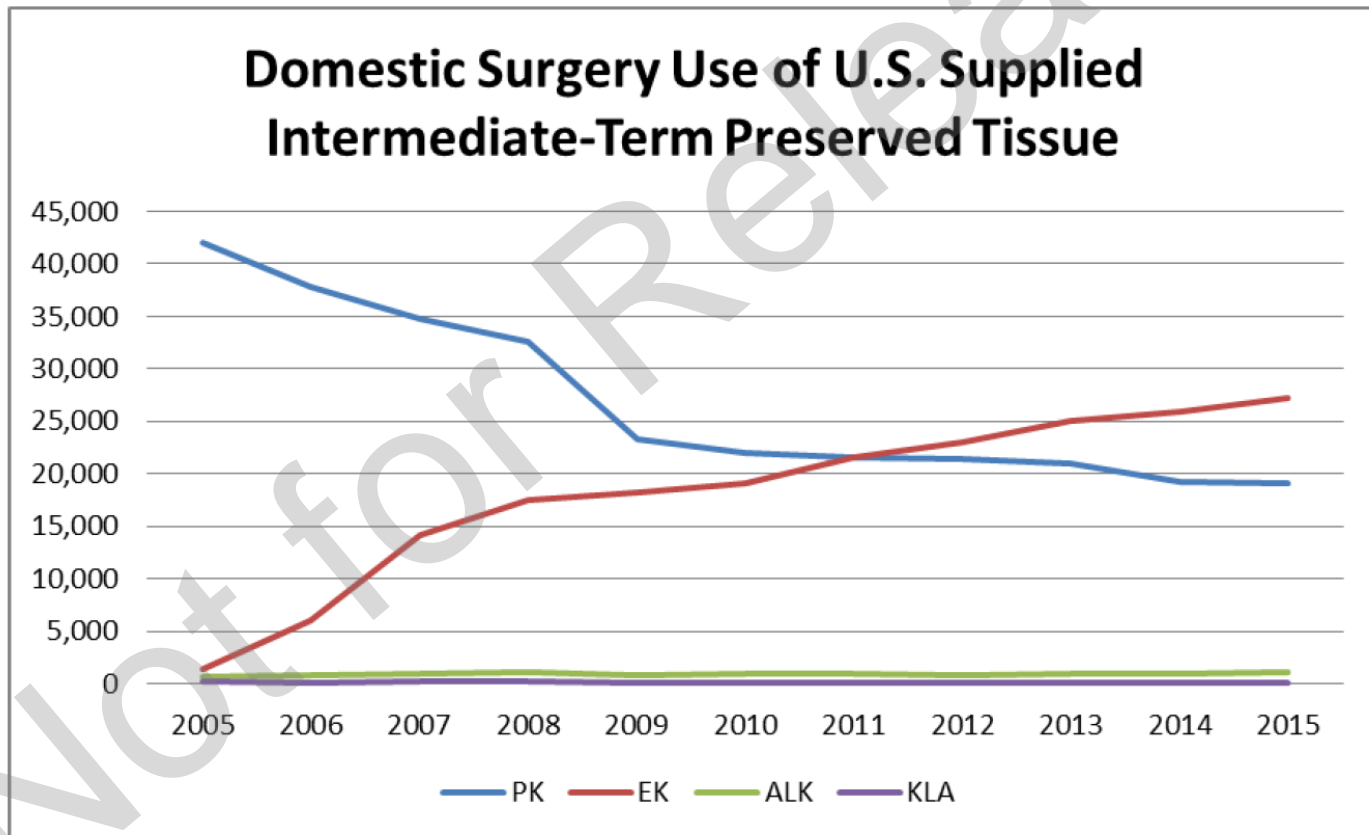
# EBAA MAB Subcommittee Report on Fungal Infection Location of Preparation



# EBAA MAB Subcommittee Report on Fungal Infection Infections Per Year

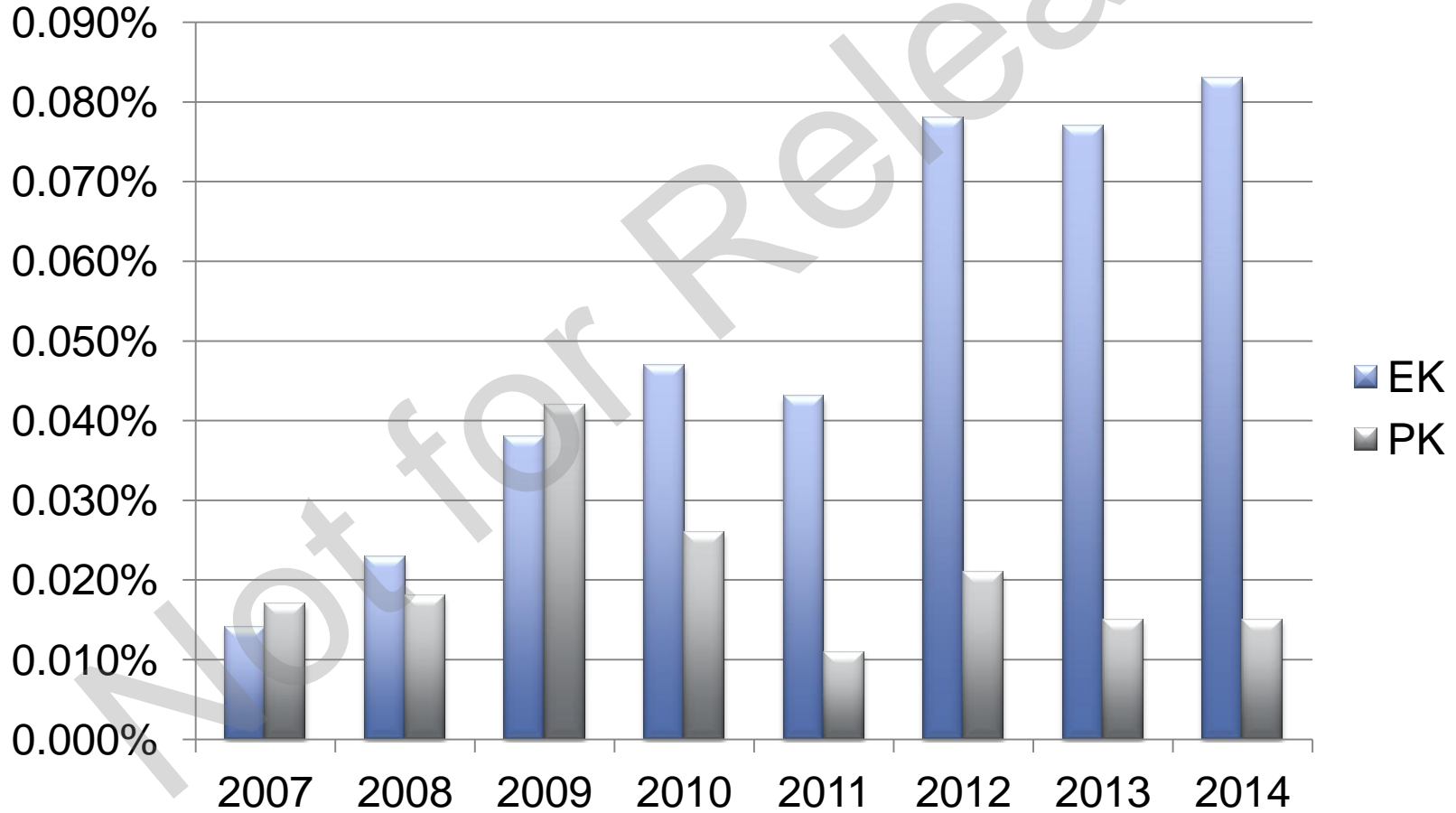


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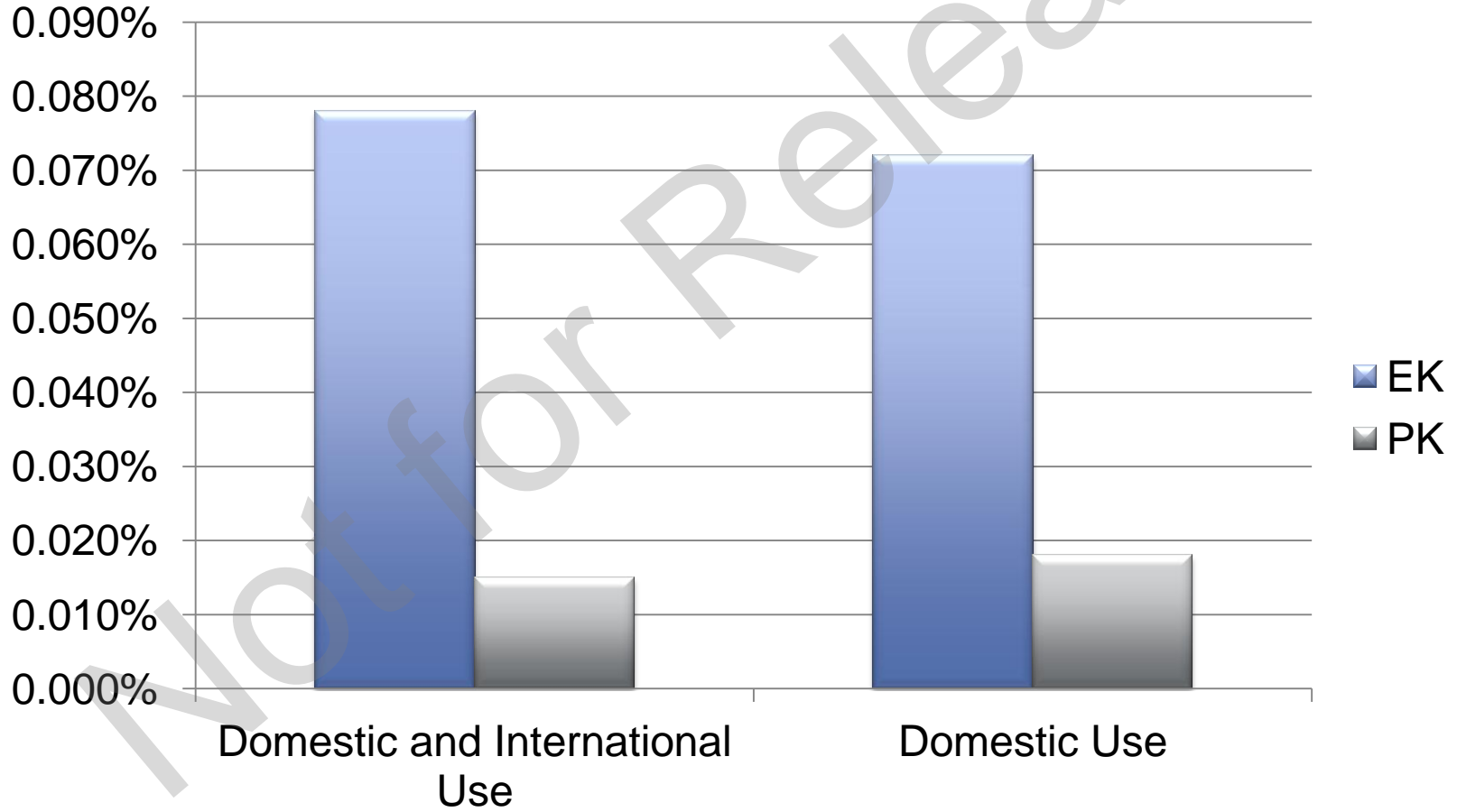


2015 EBAA Statistical Report

# EBAA MAB Subcommittee Report on Fungal Infection Incidence Per Year

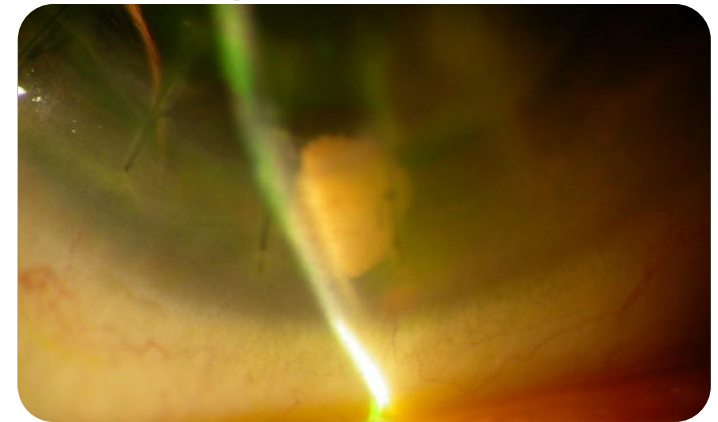


# EBAA MAB Subcommittee Report on Fungal Infection 2013



# EBAA MAB Subcommittee Report on Fungal Infection Unanswered Questions

- What is the utility of performing donor rim fungal cultures?
  - What percentage are positive?
    - 0.6%
  - What percentage of recipients of corneas with positive donor rim fungal cultures develop infection?
    - 19.8%

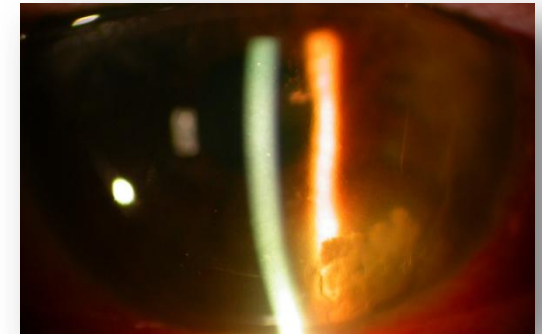


# EBAA MAB Subcommittee Report on Fungal Infection Unanswered Questions

- Is the incidence of postkeratoplasty fungal infection increasing?

- 2006-2008            19 cases
- 2009-2011           46 cases
- 2012-2014           84 cases

- Cochran-Armitage trend test  $p < .0001$



- Is the risk really higher with EK than PK?

- DSEK                    0.078%
- PK                        0.015%

- P value < 0.001

# EBAA MAB Subcommittee Report on Fungal Infection Unanswered Questions

- Is the risk associated with whether the cornea is prepared by the eye bank or the surgeon?
  - Eye bank preparation 0.10%
  - Surgeon preparation 0.02%
  - P value = 0.099





# EBAA MAB Subcommittee Report on Fungal Infection Recommendations

- If a donor corneal rim fungal culture is positive, the surgeon should report the result to the distributing and/or source eye bank
- Funding should be provided to support additional studies to:
  - Confirm preliminary studies on the relationship between temperature fluctuations and the proliferation of *Candida* species associated with post-keratoplasty fungal infection
  - Determine the safety and efficacy of antifungal supplementation of donor storage media

# MAB Subcommittee on Fungal Infection Following Corneal Transplantation

- Jennifer DeMatteo
- David Glasser
- Craig Fowler
- Stephen Kaufman
- Marian Macsai
- Jackie Malling
- Elmer Tu



**EYE BANK  
ASSOCIATION  
OF AMERICA**

# Thank You!

- Questions
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