The State of Descemet Membrane Endothelial Keratoplasty Tissue Processing: Current Practices and Challenges

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ABSTRACT

Purpose: To survey eye bank personnel regarding DMEK and gain insights about tissue processing and current practice standards, including tissue processing yields, preparation time, and technique.

Methods: In this cross-sectional survey-based study, 41 respondents completed the 17-question survey. Participants were recruited by email through the Eye Bank Association of America listserv and by chain referral sampling. Questions pertained to tissue processing, technician training, challenges, and efficiency. Main outcome measures included experience, volume, and frequency of DMEK preparation, time to train and time to process tissue, and estimated percent processing yield. Perceived tissue processing challenges, potential areas for improvement, and forecasted DMEK growth were evaluated.

Results: 46.3% of respondents had 1-3 years of experience preparing DMEK grafts, while 12.2% had less than one year and only 7.3% had more than 7 years of experience. 70.3% of participants reported involvement in DMEK preparation either frequently or every day, with 63.4% involved in 0-6 preparations per week. 56.1% estimated that greater than 95% of DMEK processing attempts are completed successfully at their eye bank, whereas 14.6% reported 50-90% processing yields. 58.4% reported peeling and 41.6% stated marking was “extremely difficult” or “somewhat difficult.” Improving tissue processing yields and efficiency/productivity were viewed as the most important areas for improvement.

Conclusions: Significant variation in DMEK processing exists among eye banks. The survey data suggest that further standardization among eye banks has the potential to reduce the difficulty and variability of existing tissue processing techniques, improving and de-skilling procedures to meet the evolving needs in endothelial keratoplasty.

Keywords: Corneal transplantation, DMEK, endothelial keratoplasty, SCUBA, eye banking

In 2018, over 85,000 corneal grafts were prepared in the United States for corneal transplantation.[1] Although full thickness penetrating keratoplasty was first accomplished over 100 years ago, by Dr. Eduard Zirm in 1905, the most significant advances in corneal transplantation have occurred over the last two decades, namely through partial thickness endothelial keratoplasty (EK).[2] Descemet stripping automated endothelial keratoplasty (DSAEK) is the most commonly performed EK procedure and involves transplantation of donor Descemet membrane (DM), endothelium, and stroma prepared using a microkeratome.[3,4] Descemet membrane endothelial keratoplasty (DMEK) is one of the newest EK techniques, involving a partial thickness corneal transplant where the host Descemet membrane (DM) and endothelium are replaced by donor DM and endothelium without accompanying stroma.[5]

There are a number of clinical indications for DMEK, including Fuchs’ endothelial dystrophy, post-cataract surgery edema, posterior polymorphous membrane dys-

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trophy, congenital hereditary endothelial dystrophy, bullous keratopathy, and iridocorneal endothelial (ICE) syndrome.[5] DMEK has been established as the most effective transplantation procedure for many of these indications, with multiple clinical studies since 2011 demonstrating faster recovery, higher patient satisfaction, better visual acuity, and reduced rejection rates.[6,7,8] A 2017 meta-analysis on postoperative outcome parameters comparing DMEK to DSAEK by Pavlovic, et al. concluded "the superiority in the visual outcome and patient satisfaction makes DMEK the preferred option for most patients."[9] However, there are higher rates of primary graft failure, graft detachment, and re-bubbling in DMEK compared to DSAEK, although there is a strong correlation between reduced graft detachment and increased surgeon experience.[7,10,11]

Despite superb clinical outcomes for its indications, DMEK was performed in only 8% of all corneal transplants in the United States in 2016.[1] Since the DM is an extremely delicate membrane, preparation of the donor graft and successful transplantation can be challenging for the trained eye bank technician and ophthalmic surgeon alike.[12] Moreover, because donor dissection can be automated using a microkeratome for DSAEK and DSAEK grafts are less technically challenging for surgeons to transplant, DSAEK is performed more than three times as often as DMEK.[1] As clinical evidence for DMEK efficacy builds, there is increasing pressure on surgeons to adopt DMEK in order to provide patients with the best possible outcomes. The number of annual EK procedures has increased steadily over the last decade, and continued growth is expected with increased surgeon demand.[1] The simultaneous emergence of new devices to implant DMEK grafts, including the CorneaGen EndoSerter, the Geuder Glass Cannula, and the Medicel Endoject, will likely reduce the difficulty of implantation and contribute to increased surgeon demand. In 2012, 184,576 corneal transplants were performed in 116 countries, of which more than 72,000 (39%) were indicated for Fuchs' dystrophy.[13] DMEK has demonstrated superior outcomes for Fuchs' dystrophy, thus, at least 72,000 cases in 2012 could have been optimally treated with DMEK.[7,8,13] Moving forward, it is likely that DMEK will become the preferred option for these 72,000 cases around the world, which will require access to appropriate amounts of eligible donor tissue and efficient, high yield processes for graft preparation.

Today, there is significant variability in DMEK graft preparation by eye banks. There are three predominant preparation methods, including submerged cornea using background away (SCUBA) method, the Muraine method, and the big bubble technique.[14,15,16,17,18,19,20] While the SCUBA method is the most widely used technique and is the basis for the majority of DM donor preparation used by eye bank technicians today, eye banks have varied protocols for preparing grafts using the SCUBA method, and the method itself suffers from a steep learning curve and a complex and laborious preparation process.[13] The preparation process is commonly divided into four steps: (1) scoring the corneal-scleral rim, which is demarcated by trypan blue staining, (2) carefully peeling or stripping the DM while submerged in balanced salt solution or corneal storage medium, (3) marking the posterior surface of the membrane to denote orientation using a skin marker and small metal stamp, and (4) evaluating the tissue graft through endothelial cell count. The Muraine method, published in 2013, involves scoring/trephination of the DM over 330 degrees and followed by peeling with Troutman forceps and hydrodissection.[15,16] The big bubble, pneumatic dissection, or "submerged hydro-separation (SubHyS) technique," has been published in various iterations since 2010 and involves injecting an air or liquid bubble in the posterior stroma to separate the DM.[16,17,19]

To date, differences in tissue processing yields, preparation time, and technique among eye banks have not been analyzed and reviewed. The purpose of this cross-sectional study is to survey eye bank personnel regarding DMEK and gain insights into tissue processing and current practice standards. We hypothesize that more standardization among eye banks is needed and existing techniques may be insufficient to meet future endothelial keratoplasty needs. We aim to better understand the changing corneal transplantation practice landscape, as well as the evolving needs of eye banks and ophthalmologists. In turn, the results of this study will help eye banks better understand the variety of current practices, their performance and methodology compared to others, and the opportunities for improvement to support increased surgeon demand.

MATERIALS & METHODS

To assess current opinions and techniques in DMEK processing and corneal transplantation, a 17-question survey was created. The survey consisted of 9 multiple choice, 4 Likert scale, and 4 free response questions (Table 1). The survey included questions about tissue processing, perspectives on challenges in the process, and questions related to eye bank and surgical volume. The survey was approved by the Johns Hopkins University Institutional Review Board and administered through professional online survey software (Qualtrics). The survey was sent to stakeholders (eye bank technicians, other eye bank personnel, ophthalmologists) via email. The Eye Bank Association of America (EBAA) emailed their Certified Eye Bank Tech-

Table 1: *List of the 17 Questions Included in the Survey.*

Survey Questions
What is your sex?
What is your age in years?
What is your job title?
In what US state do you work? If you do not work in the U.S., in what country do you primarily work?
How many employees are at the eye bank that you work in?
How frequently are you involved in DMEK processing?
Approximately how many years have you been involved in DMEK tissue processing?
How long does it take for the average technician at your skill level to process DMEK tissue?
In your opinion, how long does it take for an average technician to become proficient in processing DMEK tissue?
What technique does your eye bank use to process DMEK tissue?
How many DMEK processing procedures do you personally perform per week?
On average, what percentage of DMEK processing attempts are completed successfully at your eye bank?
In ten years, what percent of endothelial keratoplasties do you predict will be DMEK?
Please indicate the degree with which you agree or disagree with the following statement: "DMEK procedures will overtake DSAEK/DSEK procedures."
Please rate the following criteria in terms of importance for improving DMEK processing: Reduced Time to Process DMEK Tissue; Reduce Time to Train Technicians to Process DMEK Tissue; Improved Tissue Processing Yields; Improved Efficiency/ Productivity; Increased Cell Counts
What is the most difficult step in processing DMEK tissue? Please rate the following: Scoring; Peeling; Marking; Evaluation
Please rate the following in terms of time needed to complete each step: Scoring; Peeling; Marking; Evaluation

Table 2:Demographics of Participants

	Demographics (n=41)
Sex	
Males	23 (57.5%)
Females	17 (42.5%)
Mean Age	38.7 ± 9.5 years
Job Title	
Eye Bank Technician	14 (34.1%)
Upper Management (CEO, Director)	10 (24.4%)
Lab Manager, Technical Director	13 (31.7%)
Research	2 (4.9%)
Ophthalmologist	1 (2.4%)
Location	
Northeast	5 (12.2%)
Southeast	14 (34.1%)
Midwest	11 (26.8%)
Southwest	2 (4.9%)
West	3 (7.3%)
International	4 (9.7%)

nician listserv (538 members) on 2 separate occasions to recruit participants. Other stakeholders were recruited by chain-referral nonprobability sampling. Total number of complete responses and approximate response rate were recorded. Survey data was recorded and analyzed through Qualtrics, exported to Microsoft Excel, and analyzed using Stata 15. Results are reported as mean plus or minus standard deviation.

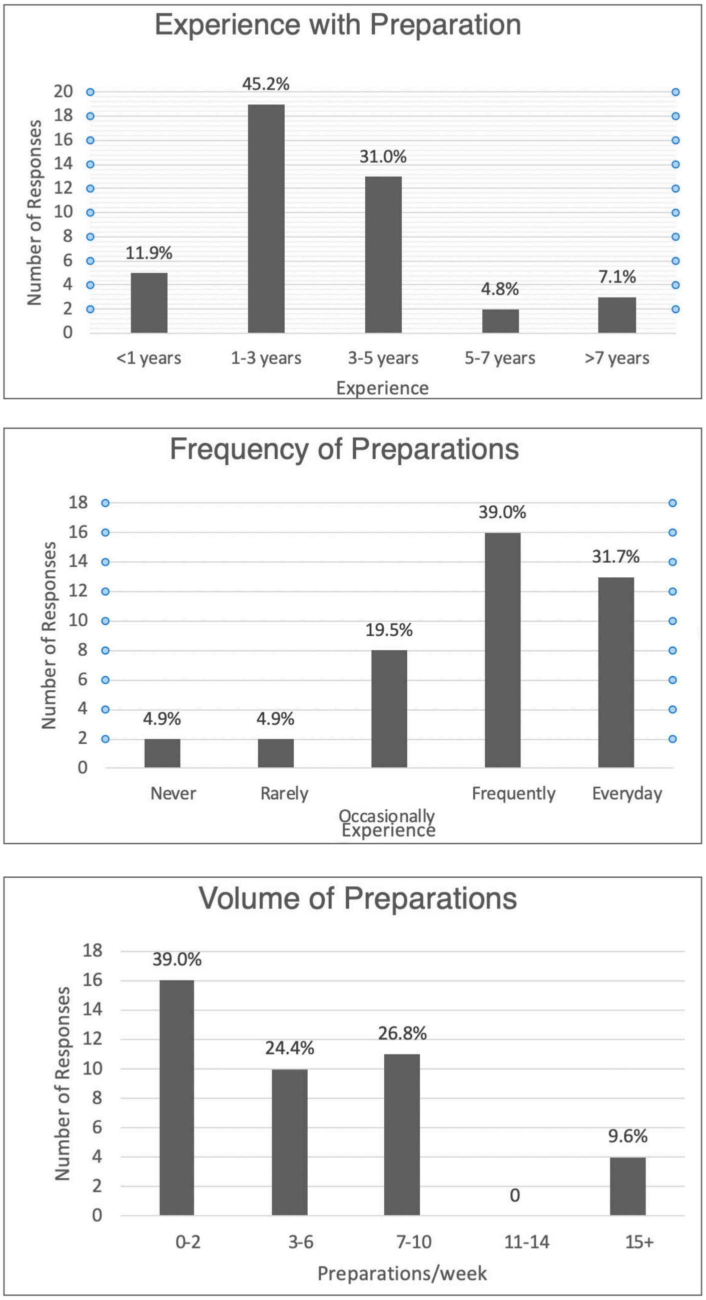
RESULTS

41 respondents participated in our survey. The mean age of participants was 38.7 ± 9.5 years. Response rate was approximately 6%. Eye bank technicians (34.1%) were the most common respondents, but eye bank managers and lab directors were also common. One ophthalmologist also participated, as this survey was primarily directed at personnel within the eye bank environment, rather than the clinical environment. Participants were from a wide range of geographies, with most from the Southeast (24.1%) or Midwest (26.8%). While eye bank affiliation was not requested to preserve confidentiality, all U.S. regions were represented, with North Carolina the most common location of participants (15.9% of respondents). A complete summary of demographics can be found in Table 2.

Participant experience processing DMEK tissue grafts was assessed using three separate questions, including years involved in DMEK processing, frequency of DMEK preparation, and weekly volume of DMEK preparation. 19 (45.2%) respondents had 1-3 years of experience with DMEK, while 5 (11.9%) had less than one year of experience, 15 (35.8%) had 3-7 years of experience, and only 3 (7.1%) had more than 7 years of experience. 29 (70.3%) participants reported involvement in DMEK preparation either frequently or every day. The majority of participants (63.4%) are involved in 0-6 preparations per week, with 4 (9.6%) reporting more than 15 preparations per week. Figure 1 summarizes participant experience processing DMEK tissue grafts. Figure 2 characterizes the eye banks at which survey participants were employed. While there was a wide range of eye bank sizes reported, most have 10-25 (34.1%) or 26-75 (26.6%) employees. Only 5% of eye banks reported more than 150 employees. The vast majority use either the SCUBA (31.7%) or modified SCUBA (29.2%) technique to prepare DMEK tissue grafts.

Variation in DMEK preparation was illustrated through questions concerning time to train, time to prepare, and estimated percent processing yield. Participants reported a wide range of training times when asked "How long does it take for an average technician to become proficient in processing DMEK tissue?" Time to prepare DMEK tissue grafts was most commonly reported as 26-40 minutes (47.5%) or 10-25 minutes (37.5%). The majority of respondents (56.1%) estimated that greater than 95% of DMEK processing attempts are completed successfully at their eye bank. However, 14.6% reported 50-90% processing yields. The complete results are found in Figure 3.

In order to better understand the pace of each step in DMEK processing, participants were asked to estimate time required to complete different preparation steps, including scoring, peeling, marking, and evaluation. The



**Experience was tabulated using the question "Approximately how many years have you been involved in DMEK tissue processing?"*

Fig. 1: *Participant Experience with DMEK Preparation*

majority felt that each step took less than 5 minutes on average (48.8-78.0%). Peeling/stripping was reported as the most time-consuming step, followed by marking. No step was reported by any participant to require more than 30 minutes on average. Complete data is available in Figure 4. In the same vein, participants were also asked which steps were perceived as most difficult in the DMEK preparation process (Figure 5). Scoring was rated as the easiest step, with 70.9% reporting scoring to be "extremely easy"

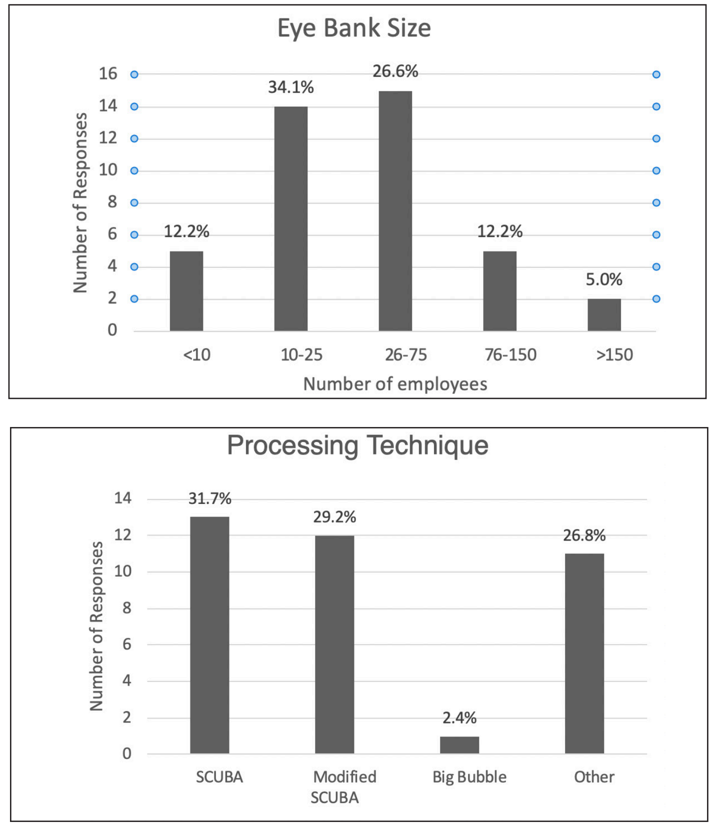


Fig. 2: *Eye Bank Characteristics*

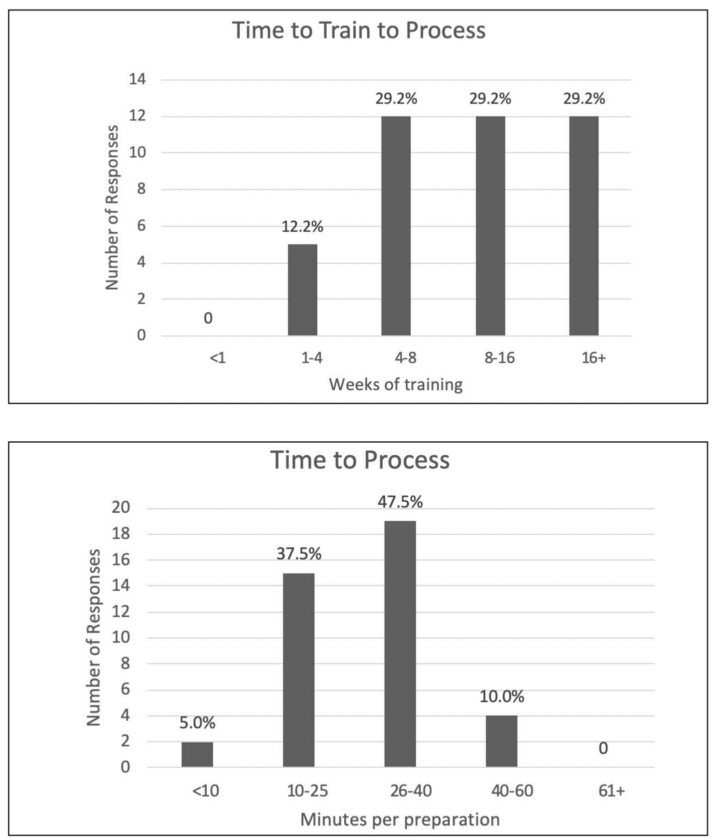


Fig. 3: *DMEK Processing Details*

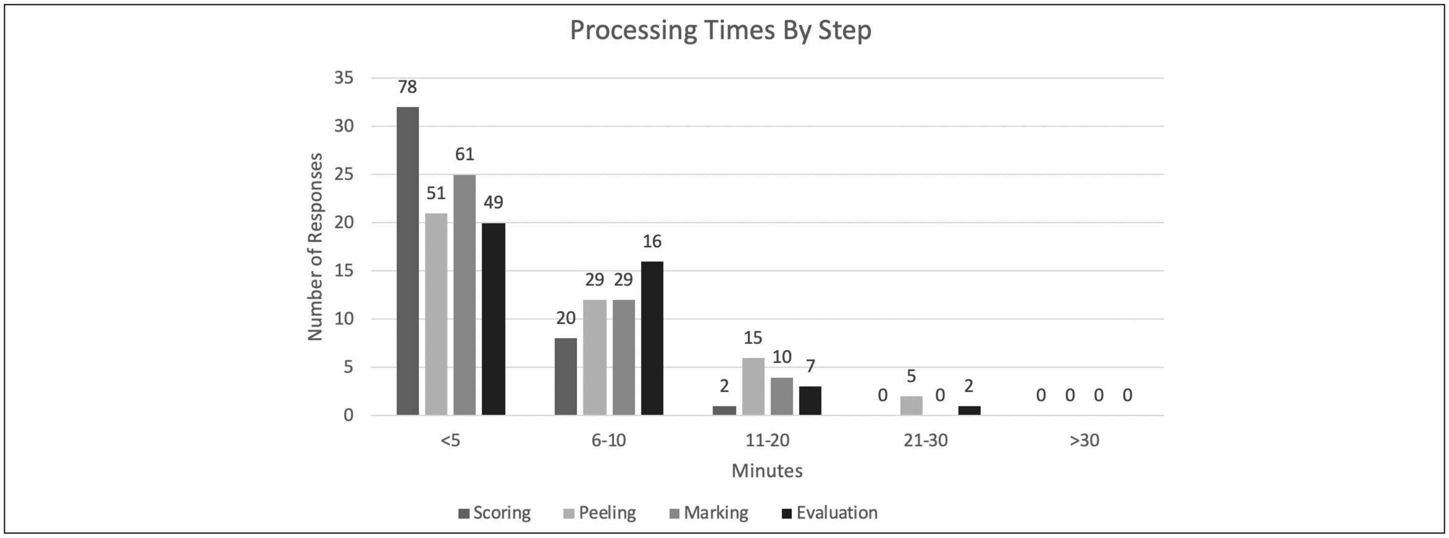


Fig. 4: Processing Times by Step

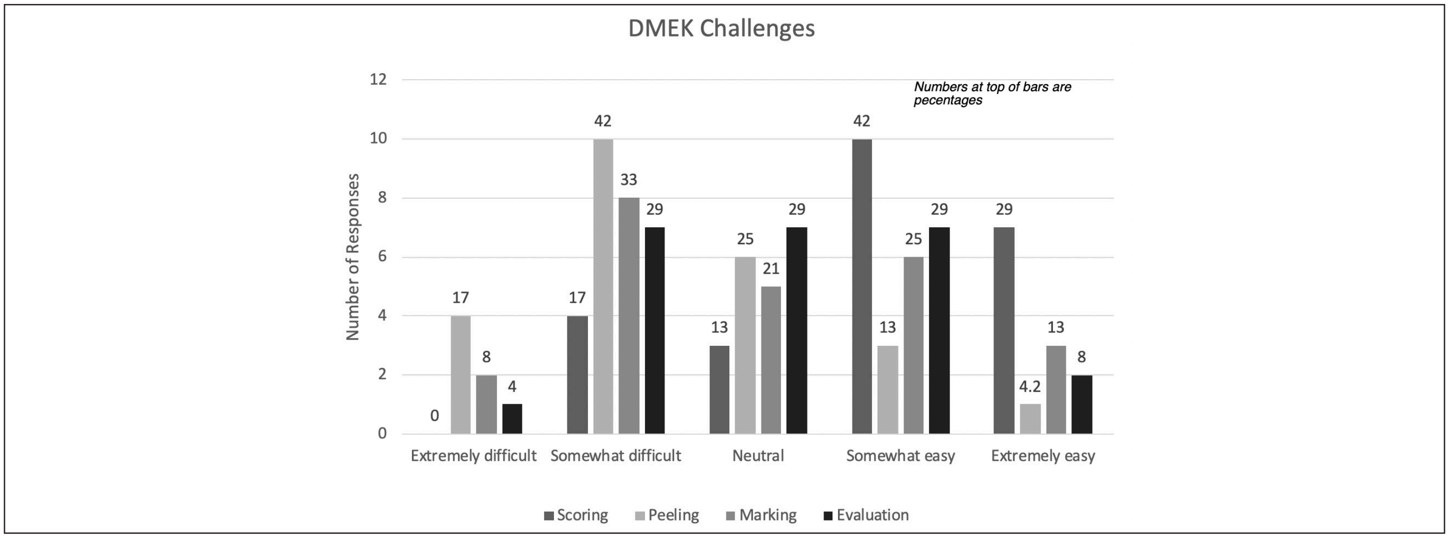


Fig. 5: DMEK Challenges

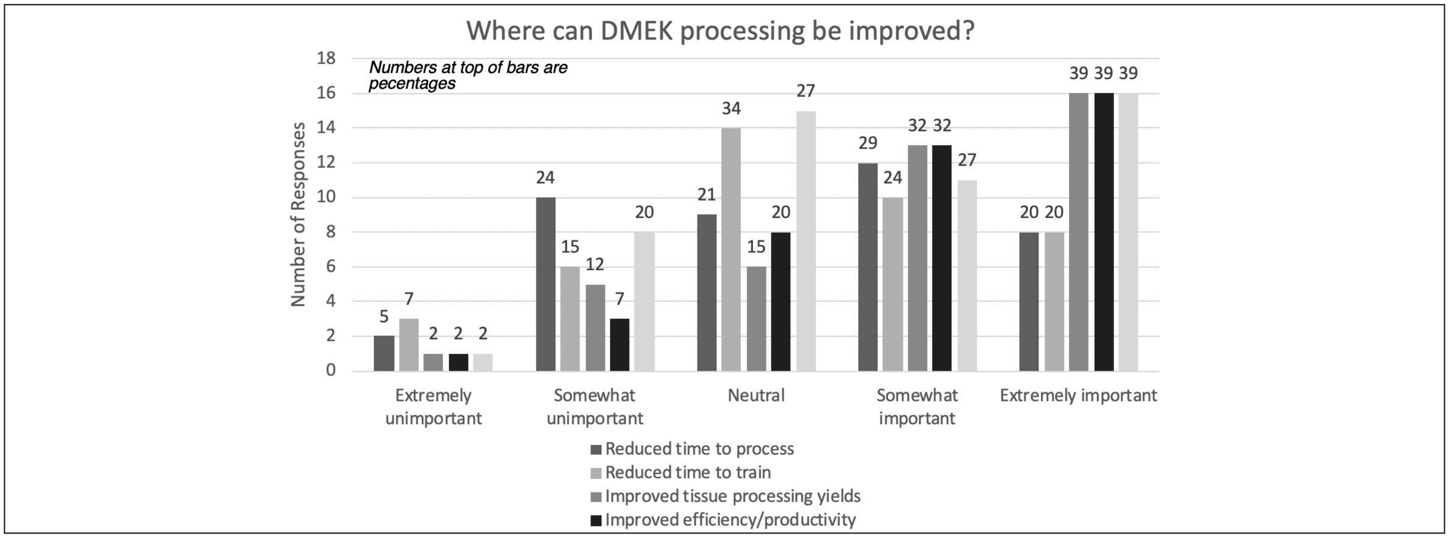


Fig. 6: Where can DMEK processing be improved?

or “somewhat easy.” The majority (58.4%) reported that peeling was “extremely difficult” or “somewhat difficult.” Marking was also perceived as “extremely difficult” or “somewhat difficult” by 41.6% of respondents.

Opportunities for improving DMEK processing and relative importance of different points of intervention were assessed next. Improving tissue processing yields and improving efficiency/productivity were reported as the most important areas for improvement, with 39% stating these metrics were “extremely important” and 31.7% stating “somewhat important.” Improved cell viability (higher endothelial cell count post-preparation) was also thought to be “extremely important” by 39% of participants. Complete data can be found in Figure 6.

Finally, respondents were asked to forecast DMEK growth and offer opinions about the future growth and landscape of DMEK (Table 3). Zero participants felt that DMEK would account for less than 35% of EKs in ten years. In fact, nearly half (48.8%) estimated that DMEK would account for greater than 66% of EKs, and 17.1% felt that greater than 81% of EKs will be DMEK in 10 years. The vast majority also reported they “strongly agree” or “somewhat agree” that DMEK procedures will overtake DSEK/DSAEK procedures.”

Table 3: *How is the DMEK landscape perceived? Report on Forecasted DMEK Growth*

DMEK Predictions	
In ten years, what percent of endothelial keratoplasties do you predict will be DMEK?	
<35%	0
35-50%	6 (14.6%)
51-65%	15 (36.6%)
66-80%	13 (31.7%)
>81%	7 (17.1%)
DMEK procedures will overtake DSAEK/DESK procedures	
Strongly disagree	2 (4.9%)
Somewhat disagree	3 (7.3%)
Neither agree nor disagree	6 (14.6%)
Somewhat agree	18 (43.9%)
Strongly agree	12 (29.3%)

DISCUSSION

In this study, eye bank personnel including technicians, lab managers, and upper management were surveyed about the current practices and challenges of DMEK. Our survey sought to understand the changing endothelial keratoplasty practice landscape and the evolving needs of eye banks and ophthalmologists. Techniques, standards, and preferences in corneal transplantation are continually and rapidly changing, and in the context of the more than 12.7 million patients awaiting corneal transplant, understanding current trends and future directions is absolutely critical.[13,21] Overall, the survey data suggest that standardization among eye banks is lacking and existing processing techniques are insufficient to meet the evolving needs in endothelial keratoplasty.

Standardization has been demonstrated to substantially improve quality and efficiency in the surgical setting as well as the aviation industry. Among eye banks, there is an opportunity to increase standardization, which could lead to improvements in processing efficiency and donor graft quality.22,23 While 60.9% of survey respondents reported using the SCUBA or modified SCUBA technique to process donor corneas, 26.8% described other vague or incomplete techniques (Figure 2). It is likely that many in the “Other” category use a technique based on the SCUBA method. The EBAA mandates that standardized protocols for graft preparations are established at certified eye banks. Even so, most technicians have their own individual modifications to the technique, such that preparation can be varied across both eye banks and even between individual technicians. Technicians have the choice of stripping the DM with a central corneoscleral button or peripheral hinge using a variety of diverse and specialized instruments such as strippers, forceps, and hooks.[24,25] After stripping, the DM graft can be marked using a single peripheral triangular mark, the 2-dot technique, the S-stamp, or other methods.[26,27,28] The stripped tissue can be stored in an artificial anterior chamber, with endothelium-in or endothelium-out, or placed in an injector cartridge.[29,30] Although no single tissue preparation procedure has been shown to be significantly superior to other preparation procedures, standardizing and streamlining techniques and reducing preparation difficulty could help shorten training, improve processing efficiency, and increase processing volumes. A Lean Six Sigma approach to process improvement has been demonstrated to improve performance and efficiency and reduce waste across a range of sectors, including healthcare.[31,32]

Furthermore, there is substantial variation in key DMEK processing metrics (Figure 3). For example, 29.2% reported that training takes on average 1-2 months, 29.2% stated 2-4 months, and 29.2% stated greater than 4 months for new technicians to gain adequate proficiency to process DMEK grafts. The same variation is seen in tissue processing times. While 47.5% said donor preparation takes

26-40 minutes, 10% reported processing times from 40-60 minutes. Estimated percent processing yields, an important parameter for quantifying tissue waste as well as eye bank efficiency, varies widely. While 56.1% of respondents claimed greater than 95% yields (in other words, less than 5% of eligible donor corneas are destroyed or discarded due to processing difficulties), 14.6% reported yields below 90%. Of the 14.6% of eye banks with below average yields, 83.3% had less than 25 employees, revealing an important trend that smaller eye banks may perform worse on key corneal graft preparation parameters. For these lower performing eye banks, improved training, higher processing volumes, detailed analysis of preparation practices, and systematic quality assurance strategies should be established in an effort to bring this metric higher. It is still unclear what accounts for this variation, whether eye bank size, resources, technician skill, or another unidentified factor. Regardless, despite individual differences in aptitude for preparing tissue, eye banks with longer training times, longer processing times, and lower yields have an opportunity to improve on their current methodologies.

We also examined whether existing processing techniques are sufficient to meet the evolving needs of eye banks and surgeons. In 2018, only 35.5% of endothelial keratoplasties were DMEK or DMAEK procedures.[1] Yet nearly half (48.8%) of the respondents in our sample estimated that DMEK will account for greater than 66% of EKs, and 17.1% felt that greater than 81% of EKs will be DMEK in 10 years. 73.2% also reported they "strongly agree" or "somewhat agree" that DMEK procedures will overtake DSEK/DSAEK procedures" (Table 3). If these predictions are realized, eye banks may struggle to meet demand for DMEK tissue grafts for a variety of reasons, from inadequate efficiency to dearth of viable tissue donations.[21] Moving forward, it is likely that DMEK will become the preferred option for the 72,000 eyes with Fuchs' dystrophy around the world, which will require access to appropriate amounts of eligible donor tissue and efficient, high yield processes for graft preparation.[13]

Of note, 58.5% of participants had less than 3 years of experience preparing tissue. Although DMEK is still a relatively new procedure, one would expect there to be a higher percentage of more experienced technicians processing tissue. It is possible that demand is only now beginning to drive an increase in the number of technicians who regularly process DMEK grafts. Additionally, there may be turnover of eye bank technicians who move on to other roles or careers. Participants also revealed that it was most common (39.0%) for technicians to process two or less DMEK grafts per week. Yet in ophthalmic surgery and similar highly manual, technical tasks, it is well established that experience is a significant predictor of success.[10,33] If surgeon demand for DMEK does indeed increase, technicians will have higher graft preparation volumes, but demand could outpace supply. To put this in perspective, DMEK procedures increased by 14-fold over only a six-year span from 2012 to 2018.[1]

Given that the sum total of technician experience in processing DMEK tissues is relatively low and demand has the potential to continue to grow rapidly, understanding the current challenges throughout the corneal transplantation process is invaluable. Challenges to widespread use and acceptance of DMEK can be divided into two broad categories: donor cornea tissue preparation and surgical technique. DMEK tissue is more challenging to prepare and position in the recipient eye, and the difficulty of the surgical technique has driven many surgeons to prefer DSAEK despite the faster recovery, better visual acuity, and reduced rejection rates offered through DMEK.[34,35] On the other hand, tissue preparation has moved largely to the purview of eye banks, which reduces time requirements and risk of tissue damage for surgeons who previously stripped the DM themselves. At eye banks, DMEK preparation remains a highly technical, challenging, and time-consuming process.

The primary tissue processing challenges identified by respondents were peeling/stripping and marking. 58.4% stated that peeling was "extremely difficult" or "somewhat difficult," while 41.6% stated that marking was "extremely difficult" or "somewhat difficult" (Figure 4). This correlates well with the average time required to complete each step. Peeling was reported as the most time-consuming step, followed by marking, and the majority felt that each step took less than 5 minutes on average. In terms of opportunities to improve DMEK processing and innovation priorities, increasing tissue processing yields and improving efficiency/productivity were reported as the most important areas for improvement, with improved cell viability the next most important metric (Figure 6). Even with many eye banks only processing a few DMEK grafts per week and demand not yet outstripping supply, productivity and efficiency are key priorities. Tissue processing yields are also very important, likely because honoring donor gifts involves reducing non-transplantable corneas to a minimum. Future efforts to improve DMEK processing should be directed with these insights in mind.

It is important to note that there are several potential limitations to this study. In this rapidly evolving clinical space, DMEK may not be broadly utilized in five to ten years which could render potential DMEK tissue processing improvements obsolete. Researchers and industry have demonstrated keen interest in the promise of endothelial cell culture to transform corneal transplantation.[36,37] Using this concept, human corneal endothelial cells are cultivated in vitro and then injected into the recipient eye to restore endothelial cell function. While promising, it is unclear how long it will take for this technology to surmount scientific, technological, and regulatory hurdles to translate into clinical practice. Limited sample size in a small industry precluded statistically significant subgroup analysis. In terms of sampling methodology, the survey was emailed to contacts and to an EBAA Certified Eye Bank Technician listserv. Survey response rate was poor. Response bias, with only specific types of respondents taking the time and effort to complete the survey, could potentially skew the data. However, based on the geographic distribution of survey participants by state, we believe the majority of participants were from distinct eye banks, and that at least one-third of all U.S. eye banks were represented.

In the future, we hope to continue to build on this understanding of eye bank practices and challenges through larger surveys and more extensive statistical analyses. Investigation in training processes and methods are another area of interest. It would be beneficial to better understand why variations in yields, training time, and processing time occur. Does technician experience, volume, frequency, eye bank size, or geography play any role? How do leaders in eye banking perceive endothelial cell culture and other prospective innovations in the pipeline? Continued innovation in eye banking is vital to improving quality and efficiency, reducing waste, and meeting the changing demands of ophthalmologists and patients. Ultimately, these advances will benefit the eyesight and the lives of patients.

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