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CHANGING TRENDS IN PENETRATING KERATOPLASTY INDICATIONS IN A HUNGARIAN AND A GERMAN CENTER BETWEEN 2006 AND 2018

Ph.D thesis

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Table of contents

1. Introduction 4

2. Objectives 8

3. Results 9

3.1 Changing trends in penetrating keratoplasty indications at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary between 2006 and 2017 9

3.2 Changing trends in penetrating keratoplasty indications, at the Department of Ophthalmology, Saarland University Medical Center in Homburg/Saar, Germany between 2011 and 2018 15

3.3 Introduction of posterior lamellar keratoplasty techniques at the Department of Ophthalmology of Semmelweis University; effect on number of keratoplasties and penetrating keratoplasties due to corneal decompensation between 2008 and 2017 22

4. Discussion 26

4.1 Changing trends in penetrating keratoplasty indications at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary between 2006 and 2017 26

4.2 Changing trends in penetrating keratoplasty indications, at the Department of Ophthalmology, Saarland University Medical Center in Homburg/Saar, Germany between 2011 and 2018 31

4.3 Introduction of posterior lamellar keratoplasty techniques at the Department of Ophthalmology of Semmelweis University; effect on number of keratoplasties and penetrating keratoplasties due to corneal decompensation between 2008 and 2017 35

5. Conclusions 38

6. Summary 39

7. References 40

8. Bibliography of the candidate's publications 47

9. Acknowledgements 49

DOI:10.14753/SE.2021.2517

List of abbreviations

ALK - Anterior Lamellar Keratoplasty

BK - Bullous Keratopathy

CHED - Congenital Hereditary Endothelial Dystrophy

DMEK - Descemet Membrane Endothelial Keratoplasty

DSAEK - Descemet-Stripping Automated Endothelial Keratoplasty

ECD - Endothelial Cell Density

FD - Fuchs' Dystrophy

GCD 1&2 – Granular Corneal Dystrophy

HSV – Herpes Simplex Virus

LCD 1&2 - Lattice Corneal Dystrophy

MCD - Macular Corneal Dystrophy

PKP - Penetrating Keratoplasty

PLK - Posterior Lamellar Keratoplasty

PPCD - Posterior Polymorphous Corneal Dystrophy

SCD - Schnyder Corneal Dystrophy

UT - DSAEK - Ultrathin Descemet-Stripping Automated Endothelial Keratoplasty

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1. Introduction

Penetrating keratoplasty (PKP) is one of the most widely practiced and the most successful form of tissue transplantation in humans worldwide [1]. The first anterior lamellar keratoplasty was performed by *Von Hippel* (**Figure 1.**) in 1886, however, due to technical challenges, lamellar transplants did not become widespread in the last century.

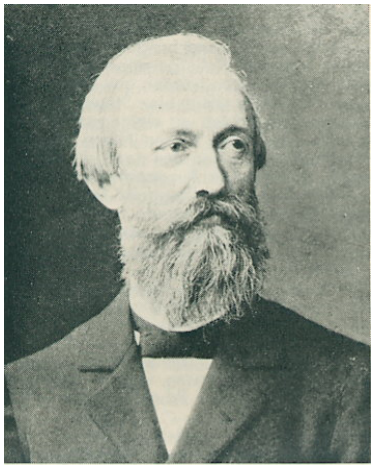

Figure 1. Arthur von Hippel (1841-1916).

Available from: https://en.wikipedia.org/wiki/Arthur_von_Hippel_(physician) Retrieved 10 April 2020

Eduard Zirm performed the first successful human full-thickness corneal transplantation in Olmütz in 1905 (**Figure 2.**) [2] and PKP remained a gold standard over the last century.

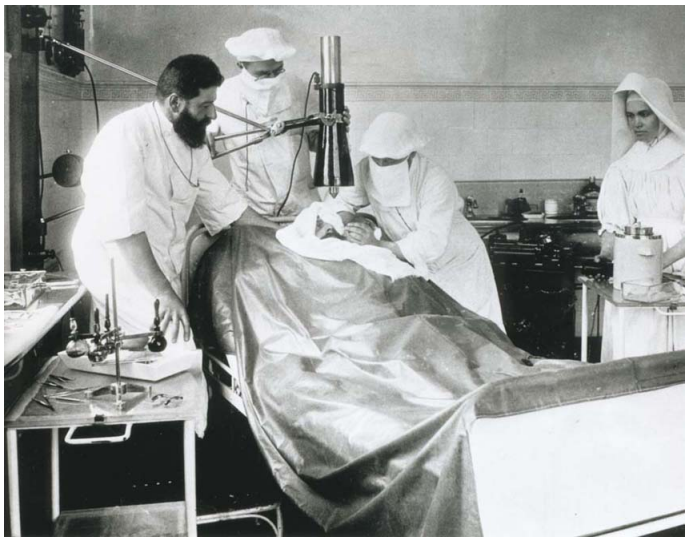

Figure 2. Eduard Zirm (1863-1944).

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Changes of corneal transplantation techniques and their instrumentation accelerated during the last decades. At the end of the 20st century, *Melles* introduced the modern lamellar keratoplasty techniques [3]. Anterior lamellar keratoplasty allows preservation of the patient's healthy endothelium. Consequently, the postoperative endothelial cell loss and the risk for graft rejection is significantly lower [4]. In case of posterior lamellar keratoplasty, *Melles* realised that it is unnecessary to secure the donor with sutures, but its positioning is satisfactory using an air bubble. During posterior lamellar keratoplasty, only the patient's endothelium and Descemet's membrane are removed, leaving other layers of the cornea intact [3].

Gorovoy modified the technique using an automated microkeratome to dissect donor lenticule and named the surgery "Descemet-Stripping Automated Endothelial Keratoplasty" (DSAEK) [5]. During surgery, the removed Descemet's membrane and endothelium were replaced by a thin stromal tissue with Descemet's membrane and endothelial cells. The next step was introduced also by *Gerrit Melles*, who described "Descemet Membrane Endothelial Keratoplasty" (DMEK) [6]. During this surgery, the removed Descemet's membrane and endothelium were replaced only by the donor Descemet's membrane and endothelium without stromal transplantation. Posterior lamellar keratoplasty techniques provide various benefits over the PKP, such as minimal invasiveness, quick visual improvement, minimal refractive shift and significantly lower risk of immune rejection [7].

Introduction of lamellar keratoplasty techniques decreased the proportion of PKPs all over the word. According to the German Keratoplasty Registry, *Flockerzi* et al [8] found, that among the corneal transplantations, the proportion of PKPs decreased from 96.0% in 2006 to 40.1% in 2016. In contrast, percentage of posterior lamellar keratoplasties increased from 14% in 2006 to 57% in 2016, and Descemet Membrane Endothelial Keratoplasty represented more than 90% of posterior lamellar keratoplasties [8].

In the USA, these trends were the same: percentage of PKPs decreased from 95.0% in 2005 to 46.0% in 2016 and percentage of posterior lamellar keratoplasties increased from 1.4% in 2005 to 58.4% in 2016 [9].

Matthaei et al. recently reviewed 34 years of changing indications of penetrating keratoplasty, globally. They have shown, that the main indications vary by geographic

regions. For example, in North America, the first or second main indications for PKP were pseudophakic or aphakic bullous keratopathy and regraft followed by keratoconus. In contrast, in the western part of Europe and Australia, the main PKP indication was keratoconus followed by pseudophakic or aphakic bullous keratopathy and keratitis. Instead, in Asia, the leading PKP indication was keratitis, followed by pseudophakic or aphakic bullous keratopathy and regraft [10].

In a previous study at the Department of Ophthalmology of Semmelweis University, Budapest, pseudophakic and aphakic bullous keratopathy was the first and regraft was the second most common PKP indication between 1993-2003 [11]. In a previous study at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar between 2001 and 2010 in Homburg/Saar, Germany, keratoconus was reported to be the major PKP indication, followed by Fuchs' dystrophy [12]. In North America, from 1980 to 2012, bullous keratopathy was the main clinical and histopathological diagnosis of PKPs [13-16]. Keratoconus was also the main PKP indication in the United Kingdom between 1999 and 2006 [17]. Nevertheless, with introduction and spreading of posterior lamellar keratoplasty techniques, PKP indications may change over all geographic regions.

In order to observe these changing trends, most studies use a classification based on histological diagnosis, although respecting the clinical diagnosis [12, 18, 19]. In case there is more than one histological diagnosis, the priority scheme suggested by Brady et al. is applied [13] and the following classification is used:

- pseudophakic or aphakic bullous keratopathy
- regraft
- corneal scar
- acute necrotizing and ulcerative keratitis
- keratoconus
- Fuchs' dystrophy
- corneal dystrophy other than Fuchs'
- other diagnoses.

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Analysing changing trends in PKP indications may help to evaluate the need of corneal grafts and to plan corneal banking procedures along these. Therefore, from time to time it is indispensable to observe these trends in different geographical regions.

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2. Objectives

The objective of our research was to analyse the changing trends in penetrating keratoplasty indications in a Hungarian and German center between 2006 and 2018. In order to achieve this objective, the aims of the present study were:

1. To analyse the changing trends in penetrating keratoplasty (PKP) indications between 2006 and 2017, at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary.

2. To analyse the changing trends in penetrating keratoplasty indications between January 2011 and December 2018, at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany.

3. To analyse the effect of the introduction of posterior lamellar keratoplasty techniques on total number of keratoplasties and number of penetrating keratoplasties (PKP) due to corneal decompensation at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary.

3. Results

3.1 Changing trends in penetrating keratoplasty indications at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary between 2006 and 2017

During the above-mentioned period, 1956 PKPs were performed and 1721 histological analyses of 1214 patients were available for review at the Department of Ophthalmology of Semmelweis University. Regarding the 1721 eyes, patient age at the time of surgery was 62.5±18.3 years, 805 (46.8%) were male and 915 (53.2%) females and 851 right (49.4%) and 870 left eyes (50.6%) were operated.

In the past 12 years, PKP indications were pseudophakic or aphakic bullous keratopathy in 487 (28.3%), regraft in 443 (25.7%), acute necrotizing and ulcerative keratitis in 313 (18.2%), corneal scar in 153 (8.9%), keratoconus in 140 (8.1%), Fuchs' dystrophy in 61 (3.5%), corneal dystrophy other than Fuchs' in 46 (2.7%), other diagnoses in 44 (2.6%) and failed posterior lamellar keratoplasty graft in 34 (2.0%) cases. Distribution of the diagnoses is summarized at **Figure 3** and **Table 1** [20].

Between 2006 and 2012 there were two Departments of Ophthalmology at Semmelweis University (1st and 2nd Departments of Ophthalmology) which were merged in January 2013. Therefore, two time-periods (2006-2012 and 2013-2017) underwent analysis and have been compared regarding PKP indications. We used the chi-square test for comparison of the corneal button numbers in every single group at both analysed time-periods. The number of the PKPs between 2006 and 2012 (6 years, n=1118) was a little bit less than double of those between 2013 and 2017 (5 years, n=603). The commonest first three PKP indications were the same in both time-periods (pseudophakic or aphakic bullous keratopathy, regraft, acute necrotizing and ulcerative keratitis). However, from the first to the second analysed time-period, incidence of acute necrotizing and ulcerative keratitis (from 16.7 to 20.9%; χ^2=4.57; p=0.032), corneal scar (from 7.1 to 12.3 %; χ^2=13.10 p<0.001) and Fuchs' dystrophy (from 2.7 to 5.1 %; χ^2=6.92; p=0.008) increased and incidence of keratoconus significantly decreased (from 9.3 to 6.0%; χ^2= 5.82; p=0.015) among PKP patients. The proportion of the pseudophakic or aphakic bullous keratopathy patients decreased slightly from 30.1% to

25.0% (χ^2=3.23; p=0.07), those of regrafts from 27.2% to 23.1% (χ^2=3.51; p=0.06) from first to second time-period, without statistically significant difference. PKP indications during two time-periods are shown at **Figure 4** [20]**.**

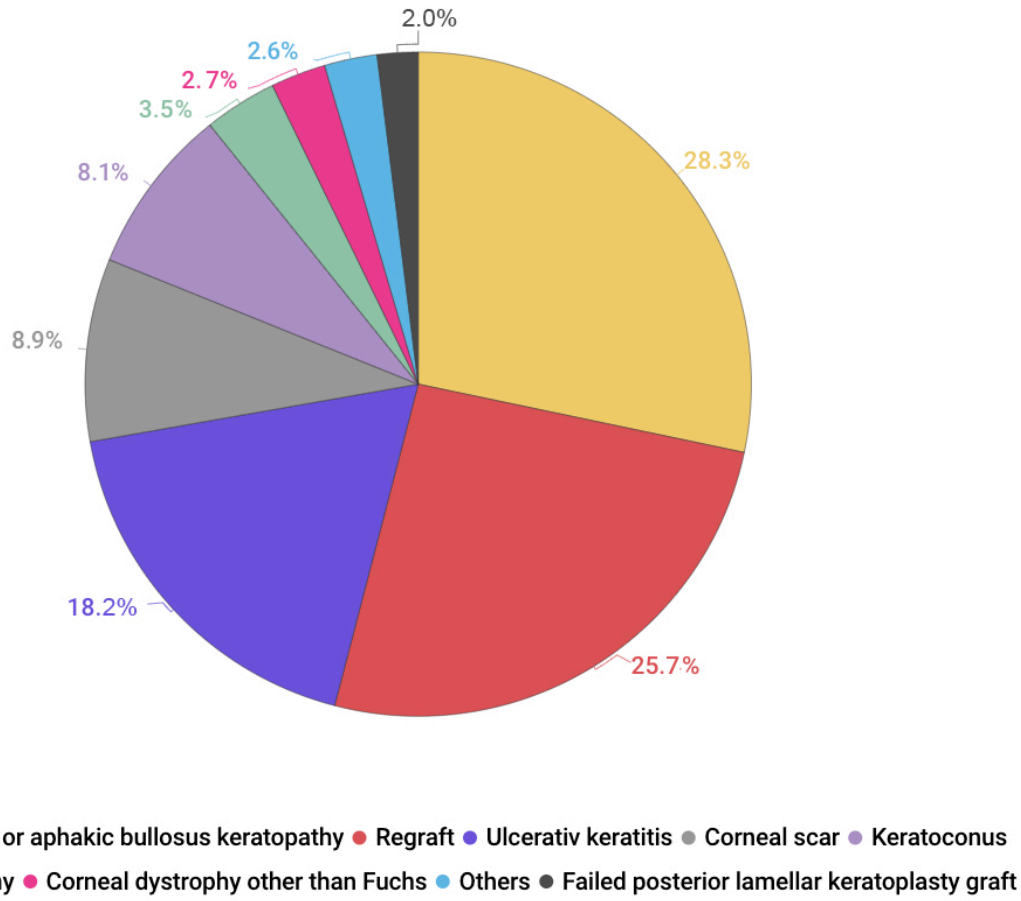

Figure 3. Penetrating keratoplasty indications between 2006 and 2017 (percentage), at the Department of Ophthalmology of Semmelweis University [20]

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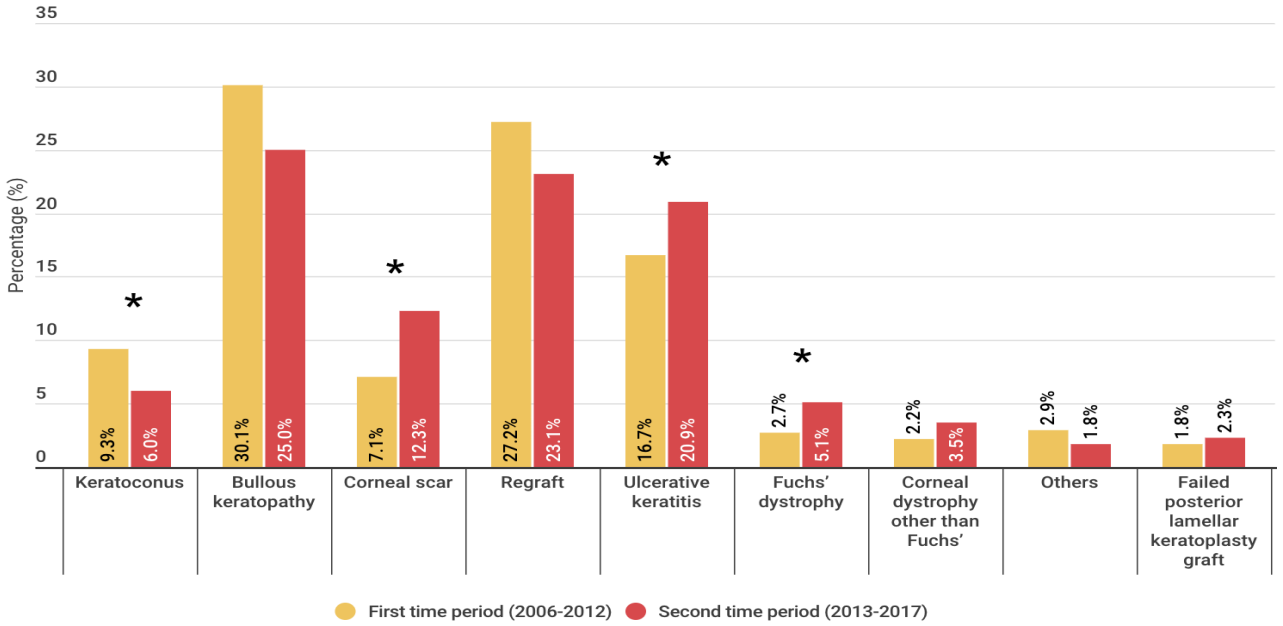

Figure 4. PKP indications in the first (2006-2012) and second (2013-2017) time-periods at the Department of Ophthalmology of Semmelweis University. Bullous keratopathy: pseudopkakic or aphakic bullous keratopathy; Keratitis: acute necrotizing and ulcerative keratitis

From the first to the second analysed time-period, incidence of acute necrotizing and ulcerative keratitis (from 16.7 to 20.9%; χ^2=4.57; p=0.032), corneal scar (from 7.1 to 12.3 %; χ^2=13.10 p<0.001) and Fuchs' dystrophy (from 2.7 to 5.1 %; χ^2=6.92; p=0.008) increased and incidence of keratoconus significantly decreased (from 9.3 to 6.0%; χ^2= 5.82; p=0.015) between PKP patients. The proportion of the pseudophakic or aphakic bullous keratopathy patients decreased slightly from 30.1% to 25.0% (χ^2=3.23; p=0.07), those of regrafts from 27.2% to 23.1% (χ^2=3.51; p=0.06) from first to second time-period, without statistically significant difference [20].

DOI:10.14753/SE.2021.2517

Table 1. Penetrating keratoplasty (PKP) indications annually between 2006 and 2017 (n, percentage). The most common PKP indications are in bold [20].

Indication	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
Pseudophakic or aphakic bullous keratopathy	**64 (32.3)**	**62 (36.5)**	**54 (31.4)**	58 (29.7)	**44 (26.7)**	37 (30.1)	17 (17.9)	20 (18.9)	**34 (29.1)**	31 (21.7)	**35 (28.5)**	31 (27.2)	**487 (28.3)**
Regraft	37 (18.7)	41 (24.1)	51 (29.7)	**60 (30.8)**	43 (26.1)	**44 (35.8)**	**28 (29.5)**	24 (22.6)	25 (21.4)	29 (20.3)	27 (22.0)	**34 (29.8)**	443 (25.7)
Acute necrotizing and ulcerative keratitis	43 (21.7)	26 (15.3)	26 (15.1)	27 (13.8)	35 (21.2)	13 (10.6)	17 (17.9)	**25 (23.6)**	20 (17.1)	**38 (26.6)**	17 (13.8)	26 (22.8)	313 (18.2)
Corneal scar	16 (8.1)	12 (7.1)	9 (5.2)	15 (7.7)	11 (6.7)	10 (8.1)	6 (6.3)	20 (18.9)	13 (11.1)	14 (9.8)	16 (13.0)	11 (9.6)	153 (8.9)
Keratoconus	21 (10.6)	18 (10.6)	12 (7.0)	11 (5.6)	18 (10.9)	12 (9.8)	12 (12.6)	9 (8.5)	8 (6.8)	10 (7.0)	8 (6.5)	1 (0.9)	140 (8.1)
Fuchs' dystrophy	6 (3.0)	1 (0.6)	7 (4.1)	4 (2.1)	6 (3.6)	0 (0)	6 (6.3)	3 (2.8)	3 (2.6)	10 (7.0)	9 (7.3)	6 (5.3)	61 (3.5)
Corneal dystrophy other than Fuchs’	3 (1.5)	5 (2.9)	5 (2.9)	6 (3.1)	3 (1.8)	2 (1.6)	1 (1.1)	0 (0)	8 (6.8)	9 (6.3)	2 (1.6)	2 (1.8)	46 (2.7)
Others	8 (4.0)	5 (2.9)	7 (4.1)	7 (3.6)	1 (0.6)	0 (0)	5 (5.3)	3 (2.8)	3 (2.6)	1 (0.7)	3 (2.4)	1 (0.9)	44 (2.6)
Failed posterior lamellar keratoplasty graft	0 (0)	0 (0)	1 (0.6)	7 (3.6)	4 (2.4)	5 (4.1)	3 (3.2)	2 (1.9)	3 (2.6)	1 (0.7)	6 (4.9)	2 (1.8)	34 (2.0)
Total	198 (100)	170 (100)	172 (100)	195 (100)	165 (100)	123 (100)	95 (100)	106 (100)	117 (100)	143 (100)	123 (100)	114 (100)	1721 (100)

Histological diagnosis in case of repeat grafts was endothelial dysfunction in 321 (72.5%), ulcerative keratitis in 90 (20.3%), donor necrosis and neovascularisation in 22 (5.0%) and graft rejection in 10 cases (2.3%) (**Table 2**).

In "acute necrotizing and ulcerative keratitis" patients, presence of microorganisms could be identified through histological diagnosis in 85 cases (27.1%). In 40 eyes (12.8%) viral, in 26 cases (8.3%) fungal, in 14 cases (4.4%) bacterial and in 5 cases (1.6%) acanthamoeba keratitis could be histologically described.

The distribution of corneal dystrophies other than Fuchs' is shown in **Figure 5**.

The age at the time of surgery in the different groups was 69.9±13.3 years in pseudophakic or aphakic bullous keratopathy (59.5% female and 40.5% male), 65.9±16.8 years in regraft (51.6% female and 48.4% male), 60.4±18.0 years in acute necrotizing and ulcerative keratitis (45.7% female and 54.3% male), 56.7±19.2 years in corneal scar (45.7% female and 54.3% male), 68.4±9.2 years in Fuchs' dystrophy (70.4% female and 29.6% male), 52.4±20.3 years in corneal dystrophy other than Fuchs' (54.3% female and 45.7 male), 52.9±17.3 years in other diagnoses (61.3% female and 38.7% male) and 70.1±11.5 years in failed posterior lamellar keratoplasty graft (76.4% female and 23.6% male) groups. The mean age of keratoconus patients at the time of surgery was 37.7±15.2 years and 34.2% were female and 65.8% were male.

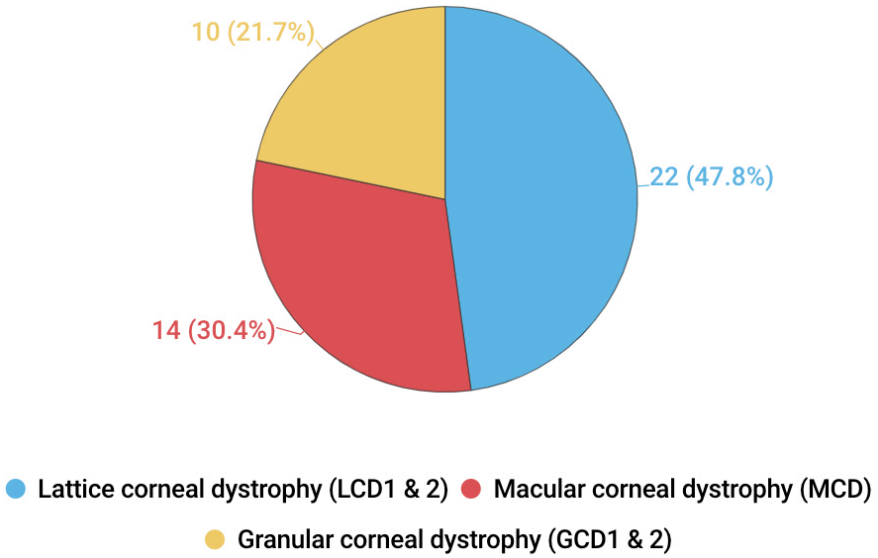

Figure 5. Histological diagnoses of corneal dystrophies other than Fuchs' between 2006 and 2017 (n, percentage), at the Department of Ophthalmology of Semmelweis University [20].

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Table 2. Histological diagnosis of repeat penetrating keratoplasties between 2006 and 2017 (n, percentage). The most common indications are in bold [20].

Indication	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
Endothelial dysfunction	**31 (83.8)**	**22 (53.6)**	**36 (70.6)**	**43 (71.7)**	**32 (74.4)**	**31 (70.4)**	**20 (71.4)**	**19 (79.2)**	**23 (92.0)**	**23 (79.3)**	**18 (66.7)**	**23 (67.7)**	**321 (72.5)**
Ulcerative keratitis	4 (10.8)	12 (29.3)	15 (29.4)	14 (23.3)	8 (18.6)	12 (27.3)	5 (17.9)	5 (20.8)	1 (4.0)	3 (10.4)	6 (22.2)	5 (14.7)	22 (5.0)
Donor necrosis and neovascularisation	1 (2.7)	4 (9.8)	0 (0)	2 (3.3)	2 (4.7)	0 (0)	2 (7.1)	0 (0)	1 (4.0)	2 (6.9)	2 (7.4)	6 (17.6)	10 (2.3)
Graft rejection	1 (2.7)	3 (7.3)	0 (0)	1 (1.7)	1 (2.3)	1 (2.3)	1 (3.6)	0 (0)	0 (0)	1 (3.4)	1 (3.7)	0 (0)	90 (20.3)
Total	37 (100)	41 (100)	51 (100)	60 (100)	43 (100)	44 (100)	28 (100)	24 (100)	25 (100)	29 (100)	27 (100)	34 (100)	443 (100)

3.2 Changing trends in penetrating keratoplasty indications, at the Department of Ophthalmology, Saarland University Medical Center in Homburg/Saar, Germany between 2011 and 2018

During the analysed time-period, 2232 PKPs were performed and 2123 histological analyses were available for evaluation. The 2123 PKPs were performed on 1993 eyes (1017 left eyes) and 56% were male, age of the patient at the time of surgery was 57.6±18.7 years.

Distribution of the histological diagnosis is summarized in **Table 3 and Figure 6** [21].

During the analysed 8 years, the histopathological diagnoses were keratoconus in 455 (21.5%), acute necrotizing and ulcerative keratitis in 384 (18.1%), regraft in 367 (17.3%), corneal scar in 350 (16.5%), pseudophakic or aphakic bullous keratopathy in 225 (10.6%), Fuchs' dystrophy in 194 (9.1%), other diagnoses in 64 (3.0%), corneal dystrophy other than Fuchs' in 52 (2.4%), and failed posterior lamellar keratoplasty graft in 32 (1.5%) cases [21].

Patient age at the time of surgery in the different groups was 41.6±15.5 years in keratoconus, 67.2±16.6 years in pseudophakic or aphakic bullous keratopathy, 60.7±15.9 in regraft, 61.9±19.5 in acute necrotizing and ulcerative keratitis, 56.5±18.8 in corneal scar, 70.1±10.4 in Fuchs' dystrophy, 49.5±20.9 in corneal dystrophy other than Fuchs', 57.1±17.8 in other diagnoses and 69.5±8.5 in failed posterior lamellar keratoplasty graft [21].

In "acute necrotizing and ulcerative keratitis" corneas, microorganisms could be identified through histological analysis in only 81 cases (21.0%). In 22 cases (5.7%) viral, in 26 cases (6.7%) mycotic, in 26 cases (6.7%) acanthamoeba and in 7 cases (1.8%) bacterial keratitis could be described histologically.

Histological diagnoses in case of repeat grafts were endothelial dysfunction in 159 (43.3%), ulcerative keratitis in 79 (21.5%), other diagnoses in 43 (11.7%), clinical diagnosis of high/irregular postkeratoplasty astigmatism in 34 (9.3%), graft rejection in 29 (7.9%) and corneal donor necrosis and neovascularisation in 23 (6.3%) cases (**table 4**) [21].

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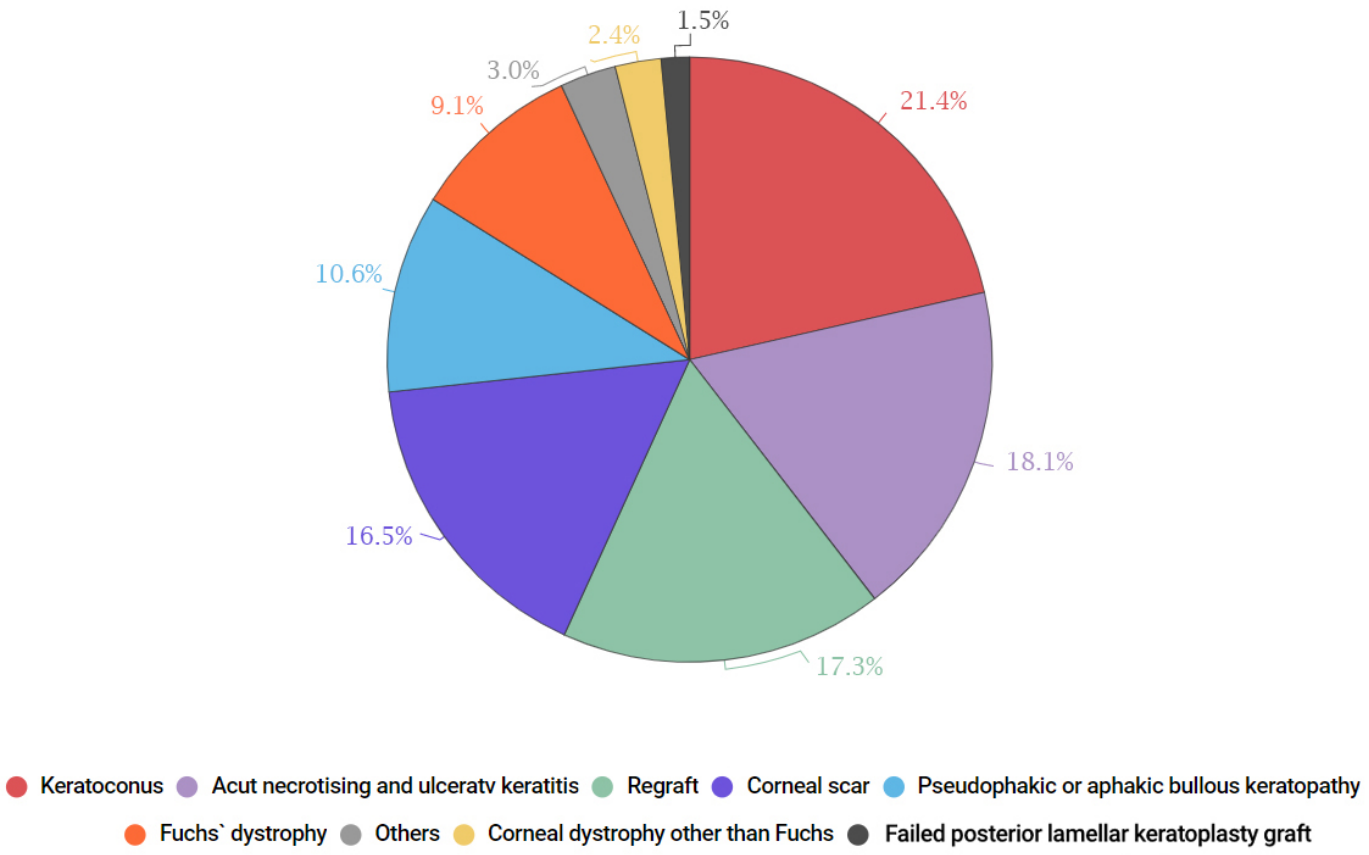

Figure 6. Penetrating keratoplasty indications between 2011 and 2018 (percentage), at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany [21].

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Table 3. Penetrating keratoplasty (PKP) indications at the Department of Ophthalmology of Saarland University Medical Center, Homburg/Saar, Germany in each year between 2011 and 2018 (n, percentage). The two main PKP indications are marked in bold [21].

Indication	2011	2012	2013	2014	2015	2016	2017	2018	Total
Keratoconus	**69 (30.7)**	**42 (21.0)**	**44 (19.0)**	**59 (24.7)**	**55 (19.2)**	**61 (20.7)**	**66 (19.9)**	59 (18.8)	**455 (21.5)**
Acute necrotizing and ulcerative keratitis	19 (8.4)	20 (10.0)	43 (18.5)	43 (18.0)	**51 (17.8)**	**62 (21.0)**	**86 (26.0)**	**60 (19.1)**	**384 (18.1)**
Regraft	26 (11.6)	**40 (20.0)**	31 (13.4)	36 (15.1)	**51 (17.8)**	58 (19.7)	59 (17.8)	66 (21.0)	367 (17.3)
Corneal scar	26 (11.6)	34 (17.0)	**44 (19.0)**	**48 (20.1)**	50 (17.4)	40 (13.6)	41 (12.4)	**67 (21.3)**	350 (16.5)
Pseudophakic or aphakic bullosus keratopathy	31 (13.8)	17 (8.5)	24 (10.3)	22 (9.2)	27 (9.4)	37 (12.5)	40 (12.1)	27 (8.6)	225 (10.6)
Fuchs' dystrophy	**40 (17.8)**	35 (17.5)	33 (14.2)	21 (8.8)	24 (8.4)	14 (4.7)	15 (4.5)	12 (3.8)	194 (9.1)
Corneal dystrophy other than Fuchs’	4 (1.8)	9 (4.5)	4 (1.7)	3 (1.3)	9 (3.1)	4 (1.4)	11 (3.3)	8 (2.5)	52 (2.4)
Others	8 (3.6)	2 (1.0)	8 (3.4)	5 (2.1)	11 (3.8)	16 (5.4)	5 (1.5)	9 (2.9)	64 (3.0)
Failed posterior lamellar keratoplasty graft	2 (0.9)	1 (0.5)	1 (0.4)	2 (0.8)	9 (3.1)	3 (1.0)	8 (2.4)	6 (1.9)	32 (1.5)
Total	225 (100)	200 (100)	232 (100)	239 (100)	287 (100)	295 (100)	331 (100)	314 (100)	2123 (100)

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Table 4. Histological diagnosis of repeat penetrating keratoplasties between 2011 and 2018 (n, percentage). The two main indications besides "other" are marked in bold [21].

Indication	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**Total**
Endothelial dysfunction	**15 (57.8)**	**22 (55.0)**	**15 (48.3)**	**19 (52.8)**	**19 (37.4)**	**26 (44.8)**	**19 (32.1)**	**24 (36.3)**	**159 (43.3)**
Ulcerative keratitis	2 (7.7)	2 (5.0)	3 (9.7)	**5 (13.9)**	**17 (33.3)**	**16 (27.6)**	**15 (25.4)**	**19 (28.8)**	**79 (21.5)**
Donor necrosis and neovascularisation	1 (3.8)	1 (2.5)	2 (6.5)	0 (0)	2 (3.9)	4 (6.9)	7 (11.9)	6 (9.1)	23 (6.3)
Graft rejection	3 (11.5)	**3 (7.5)**	3 (9.7)	3 (8.3)	2 (3.9)	4 (6.9)	5 (8.5)	6 (9.1)	29 (7.9)
High astigmatism	**4 (15.4)**	**3 (7.5)**	**5 (16.1)**	4 (11.1)	4 (7.8)	4 (6.9)	9 (15.3)	1 (1.5)	34 (9.3)
Other	1 (3.8)	9 (22.5)	3 (9.7)	5 (13.9)	7 (13.7)	4 (6.9)	4 (6.8)	10 (15.2)	43 (11.7)
Total	26 (100)	40 (100)	31 (100)	36 (100)	51 (100)	58 (100)	59 (100)	66 (100)	367 (100)

We found granular corneal dystrophy (GCD1&2) in 15 (30.6%), lattice corneal dystrophy (LCD1&2) in 13 (26.5%), macular corneal dystrophy (MCD) in 9 (18.4%), congenital hereditary endothelial dystrophy (CHED) in 5 (10.2%), Schnyder corneal dystrophy (SCD) in 4 (8.2%), Reis-Bücklers corneal dystrophy in 2 cases (4.1%) and posterior polymorphous corneal dystrophy (PPCD) in 1 case (2%) (**Figure 7.**) [21].

In order to observe the changing trends in PKP indications, two different time-periods (2011-2014 and 2015-2018) were also analysed and compared (using chi-square test), concerning PKP indications. The distribution of diagnosis in the two analysed time-periods is shown in **Figure 8.** Analysing the two different time-periods (2011-2014 and 2015-2018), the number of PKPs between 2011 and 2014 (4 years, n=896) was 1.37x less than between 2015 and 2018 (4 years, n=1227). Keratoconus was the main PKP indication between 2011 and 2014 and the second most common indication between 2015 and 2018. From the first to the second analysed time-period, percentage of PKPs for keratoconus changed from 23.9 to 19.6%, without statistical significant difference (χ^2=3.56; p=0.06). The acute necrotizing and ulcerative keratitis became the main indication in the second time-period and its incidence increased significantly (from 14.1 to 21.1% χ^2= 12.55; p<0.001). The percentage of PKPs for corneal scar (from 17.0 to 16.1 %; χ^2=0.18 p=0.67), pseudophakic or aphakic bullous keratopathy (from 10.5 to 10.7 %; χ^2=0.01; p=0.90), corneal dystrophy other than Fuchs' (from 2.2 to 2.6% χ^2=0.29; p=0.59) and other diagnoses (from 2.6 to 3.3%; χ^2=1.00; p=0.59) did not change significantly. The incidence of regraft (from 14.8 to 19.1%; χ^2= 4.56; p=0.03) increased significantly, and failed posterior lamellar keratoplasty graft did not change (from 0.7 to 2.1%; χ^2=7.12 p=0.07) comparing the two time-periods. In contrast, the percentage of PKPs for Fuchs' dystrophy (from 14.4 to 5.3 %; χ^2=100.20; p<0.001) decreased significantly [21].

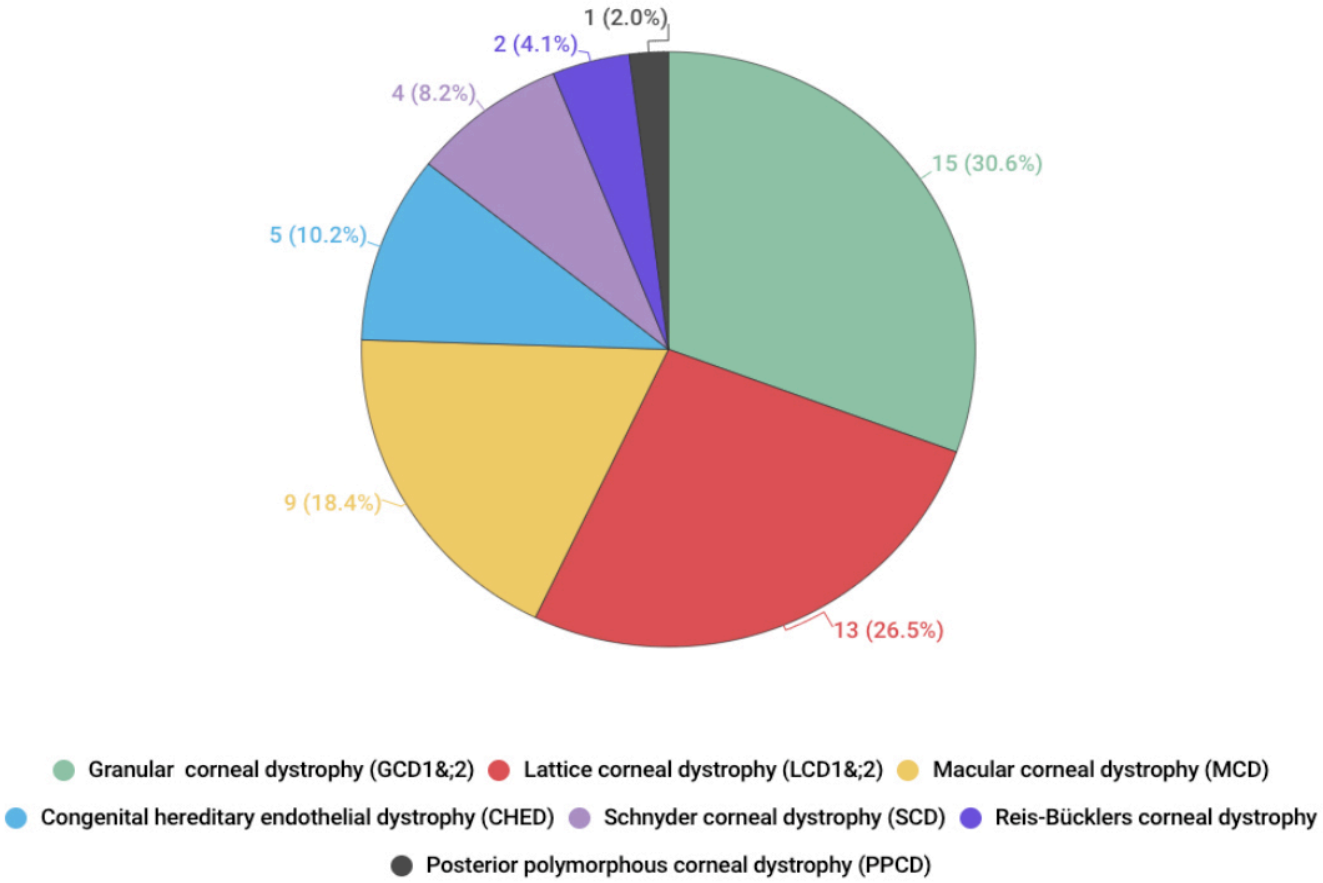

Figure 7. Histological diagnosis of corneal dystrophies (other than Fuchs') necessitating penetrating keratoplasty between 2011 and 2018 (n, percentage), at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany [21].

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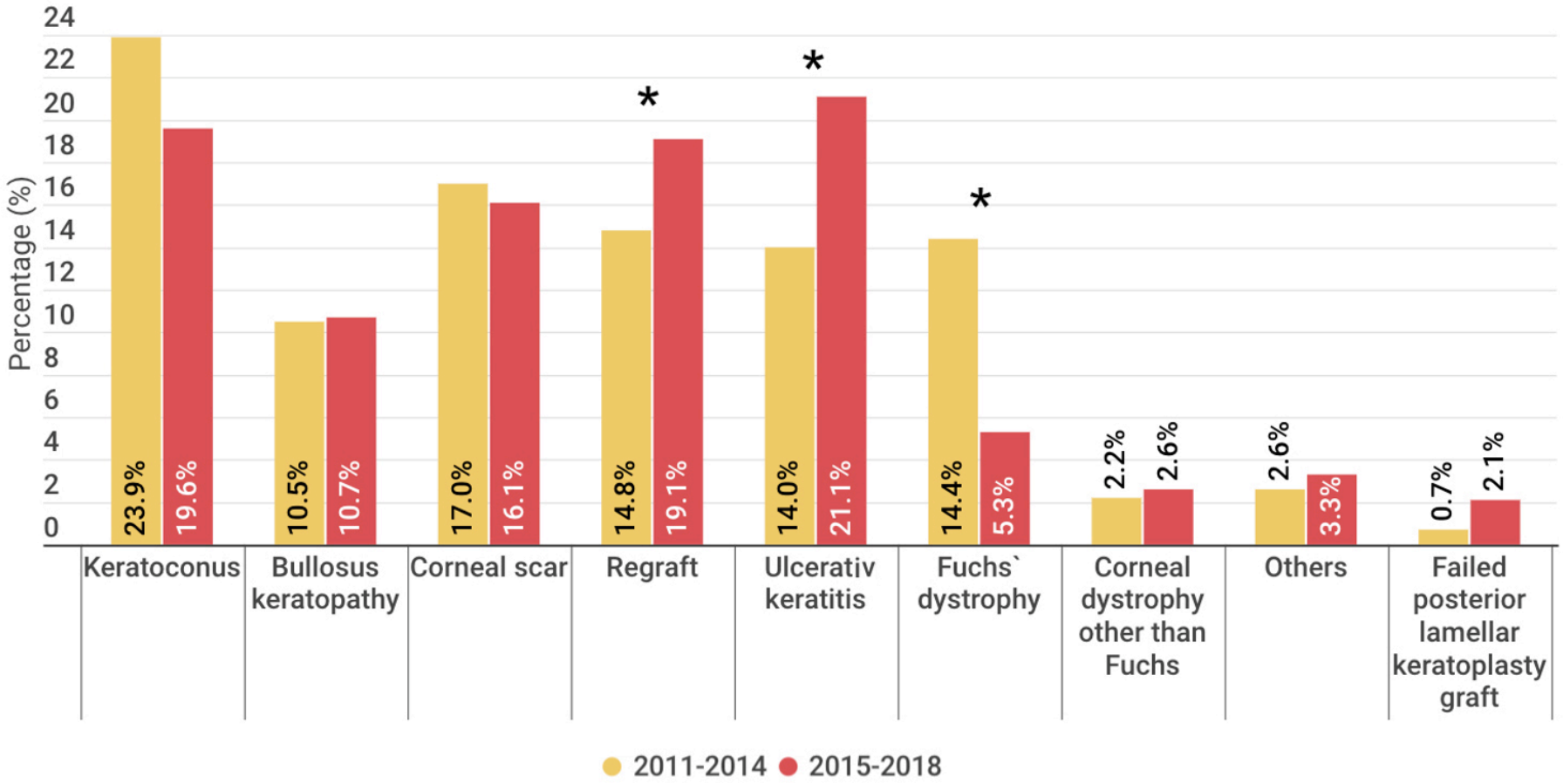

Figure 8. Penetrating keratoplasty indications between 2011-2014 and 2015-2018 (percentage), at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany. Significant differences between both time-periods in the percentage of PKPs with a certain diagnosis are marked with "*" [21].

3.3 Introduction of posterior lamellar keratoplasty techniques at the Department of Ophthalmology of Semmelweis University; effect on number of keratoplasties and penetrating keratoplasties due to corneal decompensation between 2008 and 2017

During the analysed 10 years, 1715 eyes of 1237 patients underwent corneal transplantation. Age of the patients at the time of the surgery was 61.4±16.5 years.

Anterior lamellar keratoplasty have been performed in 53 eyes of 48 patients (29 (60.4%) males) (3.1% of all keratoplasties). Patient age at the time of surgery was 55.5±20.6 years for this group.

Penetrating keratoplasty have been performed in 1474 eyes of 1040 patients (85.9% of all keratoplasties). In this group, the mean age at the time of surgery was 63.6 ± 17.9 years, with 699 (47.4%) male patients.

PKP have been performed due to pseudophakic or aphakic bullous keratopathy in 361 (21.5%) cases (age 71.6 ± 17.1 years, 164 (44.6%) males) and due to Fuchs' dystrophy in 54 (3.2%) cases (mean age 68.5 ± 16.2 years, 19 (33.9%) males). Both indications have been verified by histological diagnosis.

Primary posterior lamellar keratoplasty have been performed in 169 eyes of 152 patients (9.6% of all keratoplasties), patients age at the time of the surgery was 72.1±17.8 years.

The total number of corneal transplantations and the number of PKPs decreased with 30-40% during the analysed time-period. Following introduction of posterior lamellar keratoplasty techniques, the number of PKPs due to pseudophakic or aphakic bullous keratopathy and Fuchs' dystrophy was approximately 40% less every year [22]. Distribution of patients' data is summarised in **Table 5.** and **Figure 9-11** [22]**.**

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Table 5. Anterior lamellar keratoplasty (ALK), primary posterior lamellar keratoplasties (PLK), primary PKPs due to pseudophakic or aphakic bullous keratopathy (BK), primary PKPs due to Fuchs' dystrophy and the total number of the keratoplasties between 2008 and 2017 at the Department of Ophthalmology of Semmelweis University (n, percentage) [22] .

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
ALK	6 (2.9)	7 (2.8)	3 (1.4)	10 (6.9)	3 (2.4)	5 (3.5)	6 (3.8)	3 (1.7)	4 (2.6)	6 (4,1)	53 (3.1)
Primary PLK	1 (0.5)	16 (6.3)	18 (8.6)	7 (4.9)	11 (8.9)	13 (9.0)	26 (16.6)	30 (16.6)	24 (15.7)	23 (15,9)	169 (9.6)
BK - PKP	54 (26.2)	58 (22.9)	44 (21.0)	37 (25.7)	17 (13.8)	20 (13.9)	34 (21.6)	31 (17.1)	35 (22.9)	31 (21,4)	361 (21.0)
Fuchs' dystrophy – PKP	7 (3.4)	4 (1.6)	6 (2.9)	0 (0)	6 (4.9)	3 (2.1)	3 (2.5)	10 (5.5)	9 (5.9)	6 (4,1)	54 (3.1)
All PKPs	199 (96.6)	230 (90.9)	187 (89.5)	125 (86.8)	107 (87.0)	125 (86.8)	120 (76.4)	144 (79.6)	123 (80.4)	114 (78,6)	1474 (85.9)
All keratoplasties	206 (100)	253 (100)	209 (100)	144 (100)	123 (100)	144 (100)	157 (100)	181 (100)	153 (100)	145 (100)	1715 (100)

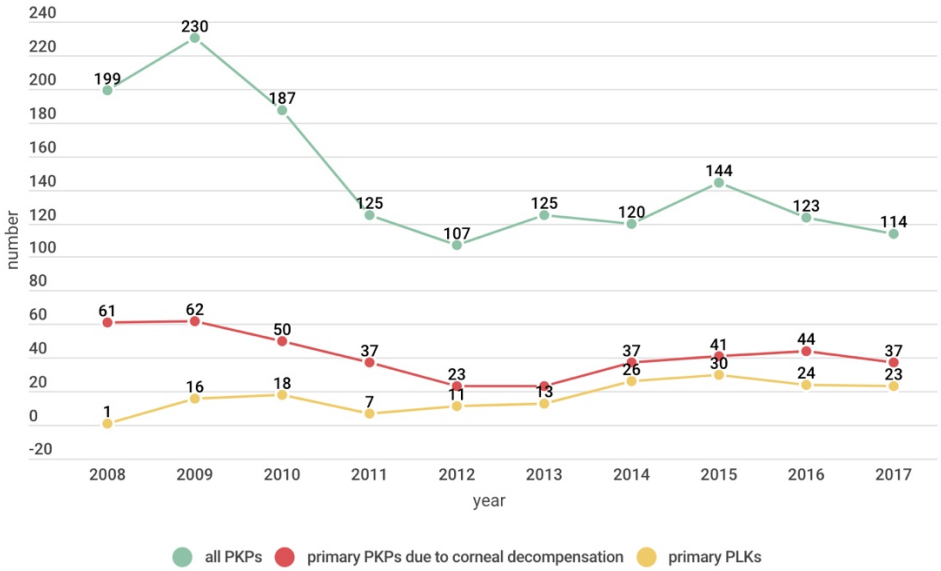

Figure 9. Number of penetrating keratoplasties (PKP), primary penetrating keratoplasties due to corneal decompensation (pseudophakic or aphakic bullous keratopathy and Fuchs' dystrophy) and primary posterior lamellar keratoplasties between 2008 and 2017 at the Department of Ophthalmology of Semmelweis University [22].

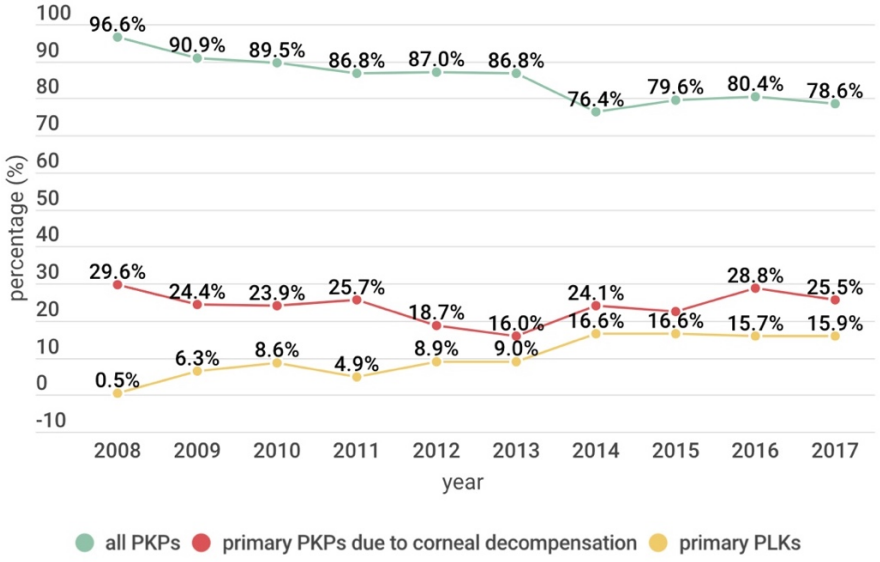

Figure 10. The proportion of penetrating keratoplasties (PKP), primary penetrating keratoplasties due to corneal decompensation (pseudophakic or aphakic bullous keratopathy and Fuchs' dystrophy) and primary posterior lamellar keratoplasties between 2008 and 2017 at the Department of Ophthalmology of Semmelweis University [22].

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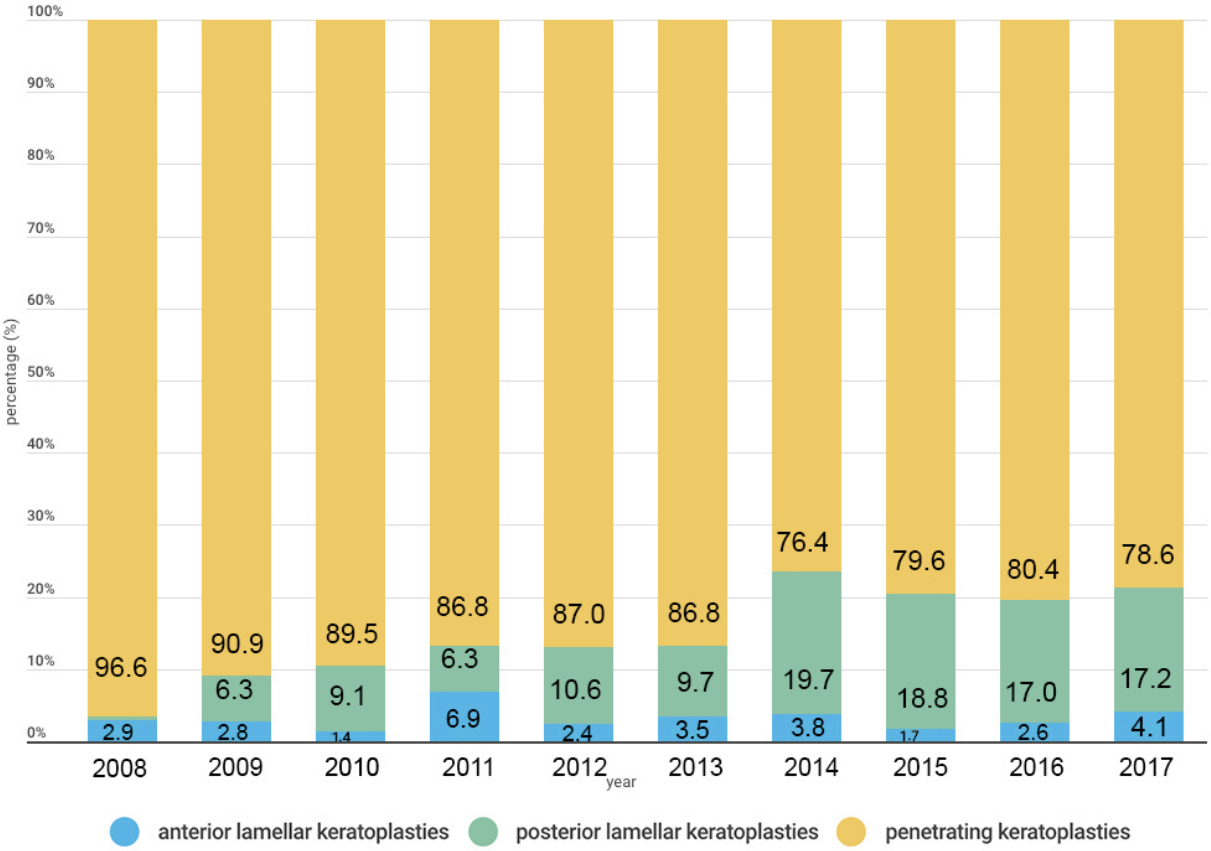

Figure 11. Proportion of anterior lamellar keratoplasties, posterior lamellar keratoplasties and penetrating keratoplasties between 2008 and 2017 at the Department of Ophthalmology of Semmelweis University [22].

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4. Discussion

4.1 Changing trends in penetrating keratoplasty indications at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary between 2006 and 2017

In our study, we summarize diagnoses - based on histopathological analysis - of 1721 keratoplasties from the Department of Ophthalmology of Semmelweis University, Budapest over 12 years, between January 2006 and December 2017. In the previous study from our clinic, Szentmáry et al. found, that between 1992 and 2003, the major indication for PKP was pseudophakic or aphakic bullous keratopathy (43.4%), followed by regraft (14.2%), acute necrotizing an ulcerative keratitis (14.2%), keratoconus (9.4), corneal scar (8.8%), Fuchs' dystrophy (5.7%), corneal dystrophy other than Fuchs' (2.0%) and others (1.9%). [11] Comparing the previous study (11 years) with our current data from the last 12 years, the order of the main PKP indications did not change, except the diagnoses of keratoconus and corneal scar which have reversed their order. The percentages of the main PKP indications in different corneal centres in Hungary in the past, and in the present study are shown in **Figure 12**.

In our Department, pseudophakic or aphakic bullous keratopathy (28.3%)(confirmed by histological diagnosis) was the leading indication for PKP during the analysed 12 years, which is in accordance with studies from North America; the United States between 1982 and 1996 [15] and Canada from 1995 to 2005 [16]. These studies showed a decreasing trend of PKPs due to pseudophakic or aphakic bullous keratopathy recently. [11] In the developed countries, bullous keratopathy is no longer the main indication for PKP. First, with the improvement of viscoelastic materials [23] and intraocular lens technology and cataract surgery technics [24], its incidence decreases. Second, with the development of posterior lamellar keratoplasty techniques (Descemet-stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) fewer subjects undergo a penetrating keratoplasty for endothelial decompensation [25, 26].

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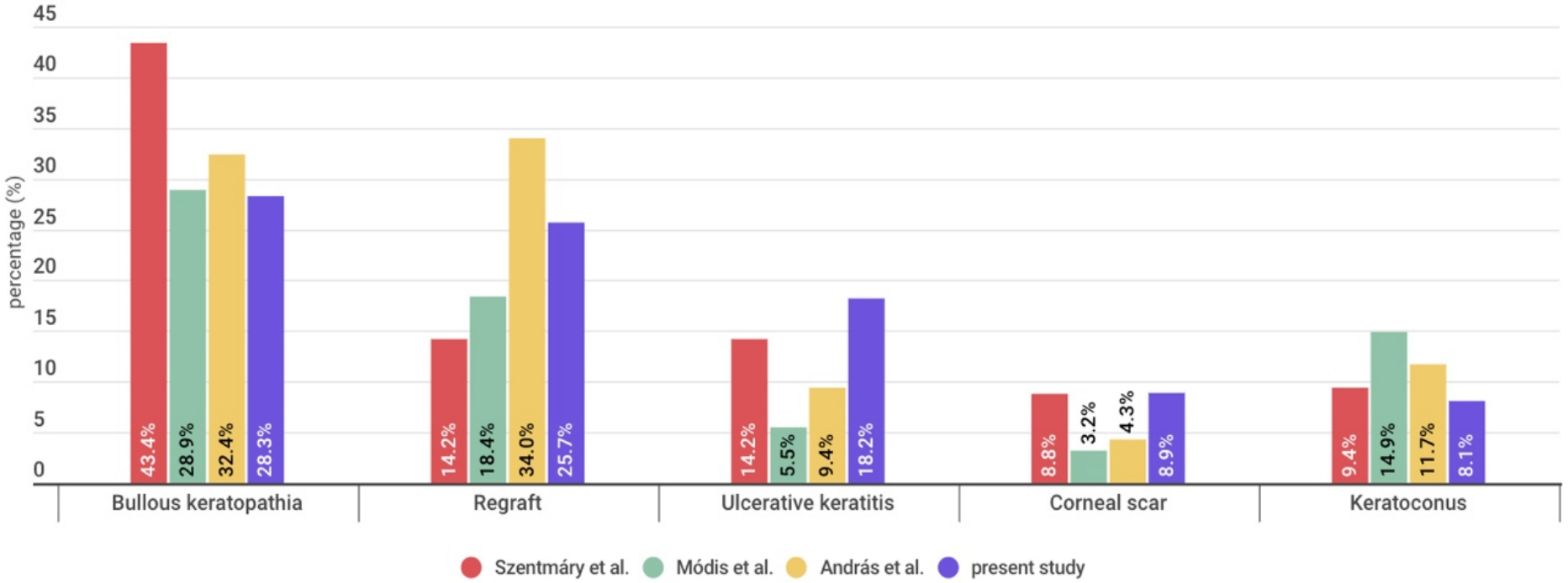

Figure 12. Percentages of the main PKP indications at the 1st Department of Ophthalmology, Semmelweis University, Budapest, Hungary between 1992-2003 (Szentmáry et al. [11]), at the Department of Ophthalmology, University of Debrecen, Debrecen, Hungary between 2006-2009 (Módis et al. [27]) and at Bajcsy-Zsilinszky Hospital, Budapest, Hungary between 2005-2017 (András et al.[28]).

Due to this reason, in Germany, the proportion of posterior lamellar keratoplasties have been increasing from 1.4% to 57% between 2006 and 2016 and the proportion of PKPs decreased from 96% to 40.1% during the same period. [8]

At the Department of Ophthalmology of Semmelweis University, posterior lamellar keratoplasty technique has been introduced in 2008 with DSAEK and in 2017 with DMEK. The percentage of posterior lamellar keratoplasty grafts have been increasing to 10-20% of all corneal transplantations over the last few years (data not shown) and with this relative low percentage, a significant decrease of PKP patients with bullous keratopathy could not be observed over the years in our series. In our patient population, there was only a slight decreasing trend in the percentage of PKPs performed due to pseudophakic or aphakic bullous keratopathy from 2006 to 2017. Most interestingly, we could not see the same trend for Fuchs' dystrophy, its incidence increased significantly among PKP patients from the first to the second time-period. This could be explained through the fact that Fuchs' dystrophy patients are referred relative late (with significant stromal scarring) to corneal surgery centres in Hungary.

The second most common PKP indication in Budapest was regraft (25.7%), similar to Scotland (19.2%) [29], the United States (22.0%) [30] and India (11.5%) [31]. Concerning other European countries, for example Germany, it was only the sixth most common indication (7.0%) [12], and in Greece the third (11.9%) [32].

In a report from the United Kingdom [33], endothelial dysfunction (41.8%) and graft rejection (16.5%) were also lower than in our study. Analysing percentage of regrafts though endothelial dysfunction (72.5% in our series), the source and quality of donor material have to be addressed. About 80% of our donor tissues were delivered through a cornea bank, using cold storage (Optisol GS, endothelial cell density (ECD) above 2000 cell/mm^2 at one single measurement). Another ca. 20% originated from multiorgan donors (also cold storage), nevertheless, ECD was not determined before the use of donor tissue. In our opinion, lack of repeat ECD measurements in both cases could have been one reason for the relatively high percentage of regrafts due to endothelial dysfunction in our series. Nevertheless, lack of patient cooperation may also have increased these numbers.

The third most common indication for PKP was acute necrotizing and ulcerative keratitis (18.2%) in our study. This is similar to other European countries like Greece

(13.1%) [32], but differs from the USA (7.2%) [30]. There are many studies from Asia which have shown keratitis as the leading indication for PKP [31, 34, 35].

In our study in 13% cases viral, 8.3% fungal, 4.4% bacterial and 1.6% cases *Acanthamoeba* keratitis could be verified histologically. The proportion of the different keratitis entities was lower than in a study from Poland between 2010 and 2017 with 26% bacterial, 14% fungal and 4.25% *Acanthamoeba* keratitis diagnosis [36]. However, they did not report on incidence of herpetic keratitis. The percentage of the successful histologically diagnosed keratitis was lower in Hungary than in Poland. In contrast, in Vietnam, the commonest infectious keratitis was fungal between 2002 and 2012, with an incidence of 53.1%. There were 33.3% bacterial, 8.4% viral and 2.2% *Acanthamoeba* keratitis in Vietnam [37], which are explained mainly with the climatic differences between these countries.

Corneal scarring (8.9%) was the fourth most common PKP indication in the current study. In India and China, one of the leading indications of corneal transplantation is keratitis. These studies have shown that the most common causes of corneal scarring were healed infectious keratitis and traumatic corneal scars [31, 35]. According to our study, the proportion of keratoplasties for corneal scarring (8.9%) has been reported to be lower than in those countries (28.1-38.0%), similar to the lower incidence of infectious keratitis in our country. [31, 38, 39].

Keratoconus (8.1%) was the fifth most common PKP indication in Budapest, 65.7% of the patients were male. Incidence of keratoconus among PKP patients is in agreement with studies from Canada (12.0%) [40] and developing countries, such as China (13.0%) [35] and India (2.37%) [31] [41], where keratoconus is still a rare indication for PKP. Nevertheless, keratoconus is reported to be the first most common PKP indication in other European countries such as Germany [12] and Great Britain [29]. In our opinion, as prevalence of keratoconus is also reported to be lower in some developed countries, such as the United States (54.5 cases per 100.000 people) [42] and e.g. the Netherlands (265 cases per 100.000 people) [43], the low percentage of PKPs in keratoconus may be related to the lower incidence of keratoconus disease in Hungary. Nevertheless, population-based studies still have not been performed in Middle-Europe.

In our study the proportion of PKPs for keratoconus decreased from 2006 to 2017. This may be related to the fact that some adjacent eye centres started with PKPs and

increased their yearly PKP quote over the years in Budapest, at the same period. This is also displayed in the decreasing trend of the total number of corneal transplantations at the Department of Ophthalmology of Semmelweis University.

In our study Fuchs' endothelial dystrophy (3.5%) was the sixth most common PKP indication. The reported rate of Fuchs' dystrophy is highly variable between different countries. According to a report from Germany (21.2%) [12] and from the USA (23.2) [15], Fuchs' dystrophy was the second most common PKP indication**.** Other studies ranked Fuchs' dystrophy from the USA (10.8%) [30] as fourth and from Asia (4.5%) [39] as fifth most common PKP indication. In Europe, in Great Britain (13.5%) [29] it was reported as the third most common PKP indication.

The gender distribution of the Fuchs' dystrophy group showed a female preponderance (70.4%), and the mean patient age (68.4±11.6 years) was higher in this group than in other groups, which is in agreement with studies from North America [15, 40].

The seventh most common diagnosis was corneal dystrophy other than Fuchs' in 46 cases (2.7%). We found lattice corneal dystrophy (LCD1&2) in 22 (47.83%), macular corneal dystrophy (MCD) in 14 (30.43%) and granular corneal dystrophy (GCD1&2) in 10 (21.74%) cases (**figure 3**). Most interestingly, the incidence of lattice corneal dystrophy was the highest between these dystrophy types in our country.

Through introduction of DSAEK and DMEK, the percentage of failed endothelial grafts did not increase significantly between the two analysed time-periods in our Institution, which probably shows the success of the introduced surgical techniques.

The major limitation of our study is the retrospective design. As the study was limited by the available histopathological results, there was a possibility for bias, resulting in an over- or underestimation of observed trends.

In conclusion, pseudophakic or aphakic bullous keratopathy is the leading indication for PKP at our Institution, followed by regraft and acute necrotizing and ulcerative keratitis. Introduction of posterior lamellar keratoplasty techniques in 2009 did not change this order. Advancement in corneal banking and a better referral system of patients to corneal subspeciality centers should change this order the next decades in Hungary.

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4.2 Changing trends in penetrating keratoplasty indications, at the Department of Ophthalmology, Saarland University Medical Center in Homburg/Saar, Germany between 2011 and 2018

In our study, we report diagnoses of 2123 keratoplasties from the Department of Ophthalmology of Saarland University, over 8 years, between January 2011 and December 2018.

In 2011, posterior lamellar keratoplasty has been introduced at Saarland University. From that time-point, an increasing number of posterior lamellar keratoplasties could be observed (data not shown). Nevertheless, the number of PKPs also slightly increased, which may refer to the generally increasing number of all types of keratoplasties in Homburg/Saar (60 in 2006 and more than 500 in 2018) **(Figure 13.)**.

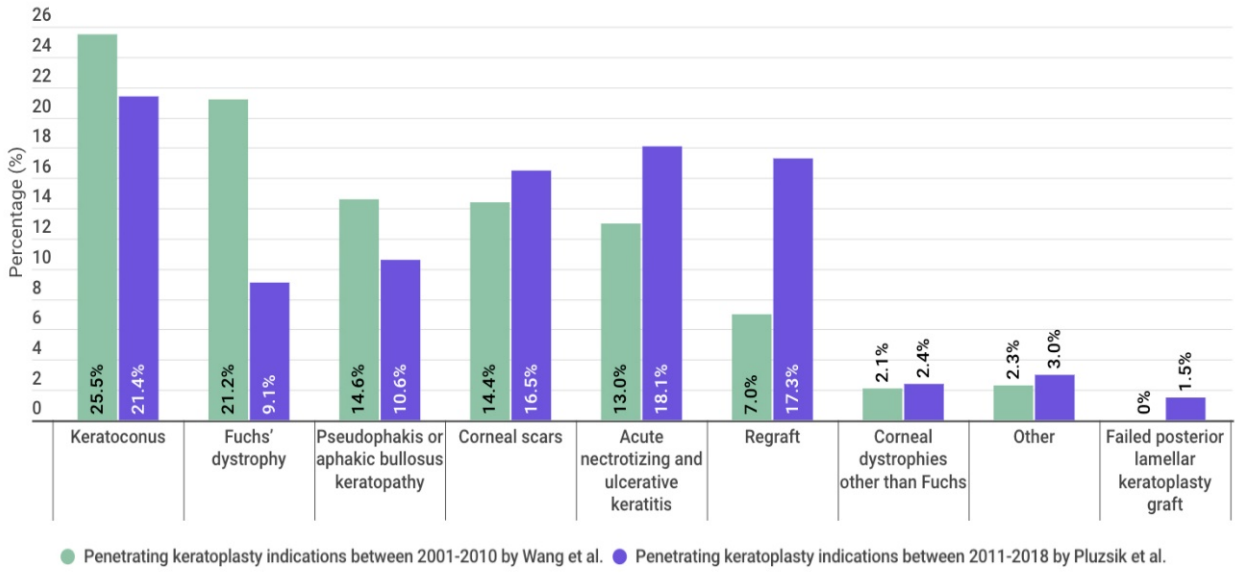

Figure 13. Penetrating keratoplasty indications at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany between 2001-2010 (Wang et al. [12]) and 2011-2018 (percentage) [21].

In Saarland University, keratoconus (21.5%) was the main PKP indication. This is in agreement with a previous study at the same institution (25.5%) [12] and other

European countries such as Great Britain [29] and Italy [44] [45]. However, in Greece (26.0%) [32], keratoconus was the second and in Hungary (18.6%) [27] only the third most frequent PKP indication. In other centres in Germany, keratoconus was the first (20.8%, 34.0%) [18, 46-48] or second (23.0%) [49, 50] most common PKP indications. In developing countries, such as China (5.7%-11.2%) [35, 51, 52] and India (1.96-2.7%) [31] [38], keratoconus is still a rare PKP indication. In Homburg/Saar the proportion of PKPs for keratoconus did not change significantly between the two time-periods, which may be related to the foundation of the "Homburg Keratoconus Center" in 2011 and the fact that PKPs for keratoconus are exclusively performed using excimer laser assisted trephination with well demonstrated advantages [53].

The second most frequent indication for PKP was acute necrotizing and ulcerative keratitis (18.1%) in our study. In Europe, keratitis was the third (13.2%), in North America only the fifth most common PKP indication (13.2%) [10]. Studies from the Asian continent, e.g. from India (43%) [54] and China (24.1-37.1%) [34, 52], showed keratitis as the leading PKP indication. Most interestingly, the proportion of PKPs with the diagnosis of keratitis showed a statistically increasing trend from the first to the second time-period of our study and ulcerative and necrotizing keratitis even became the main indication in the second time-period. This may be related to population movements from developing countries to Germany, but also to environmental climate changes with increasing temperatures. In addition, over the last decades, the reputation of the University of Saarland as a referral centre for complex infectious keratitis (e.g. *Acanthamoeba, fungi, HSV*) has increased.

Keratitis as PKP indication has reached its peak in 2017 with 26.2% (n=86). In 81 keratitis cases (21.0%) microorganisms could be verified histologically: in 22 cases viral, in 26 cases fungal, in 26 cases *Acanthamoeba* and in 7 cases bacterial keratitis could be identified. The proportion of the different keratitis entities differed from a study in Vietnam, where the main infectious keratitis types was mycotic between 2002 and 2012, with 53.1%. In 33.3% bacterial, in 8.4% viral and in 2.2% *Acanthamoeba* keratitis could be identified in Vietnam [37], which may mainly be explained through the climatic differences between these countries.

The third most common PKP indication in Homburg/Saar was regraft (17.3%), similar to other European countries, such as Hungary (14.2%) [11] and Greece (11.9%) [32]. In contrast, in Great Britain (19.2%), regraft was the second most common PKP indication. In North America it was also the second most common indication with 16.3% [10]. In Asia, India (12.7%) [38] and in China (6.75%) [52] regraft was also the second most common PKP indication. The incidence of regraft has increased significantly from the first to the second time-period, as with the increasing reputation of the University of Saarland as a referral center for corneal diseases, an increasing number of patients came to our Department with failed grafts, which had been operated previously in other hospitals in Germany.

Corneal scarring (16.5%) was the fourth most common PKP indication in the present study, similar to our previous report (14.4%) [12] and its incidence did not change between the two time-periods. In Europe (4.5%) and in North America (8.5%), corneal scarring was one of the least common indications, in contrast to Asia and Middle East (19.5%), where this was the second most common indication [10]. In the group of corneal scars, there have mainly been patients with healed keratitis and following corneal injury through trauma at Saarland University. In the developing countries, such as India [31] and China [35], the main reason for corneal scarring was also healed infectious keratitis and trauma.

Pseudophakic or aphakic bullous keratopathy (10.6%) was the fifth most common PKP indication in Saarland and its absolute number did not change significantly between the two time-periods. However, it was the third most common indication (14.6%) in the previous report from the same Department [12]. In the last decade, in the developed countries, bullous keratopathy is no longer the main PKP indication, due to improvement of cataract surgery techniques (viscoelastic materials, intraocular lenses, skills of microsurgeon) [55] and the development of endothelial keratoplasty techniques for decompensated corneas after phacoemulsification. Therefore, less subjects undergo penetrating keratoplasty for endothelial decompensation [25, 26]. In our patient population there was also a decreasing trend in the percentage of PKPs performed due to pseudophakic or aphakic bullous keratopathy from 2011 to 2018. At the same time, the percentage of posterior lamellar keratoplasties increased.

In our study, Fuchs' endothelial dystrophy (9.1%) was the sixth most common PKP indication and its incidence decreased to the second time-period. In contrast, in our previous report, the second most common PKP indication was Fuchs' dystrophy [12]. The decreasing incidence of Fuchs' dystrophy between PKP patients in a previous [12] and the current study are shown in **Figure 14.** This fact may mostly be related to introduction of posterior lamellar keratoplasty techniques in Homburg but even more so in other leading keratoplasty centres in Germany (such as Erlangen, Cologne and Freiburg). In the USA (23.2%) [15] it was the second, in West of Scotland (13.5%) [29] the third most common PKP indication. In Asia (4.5%) [39], it was reported as the fifth most common PKP indication.

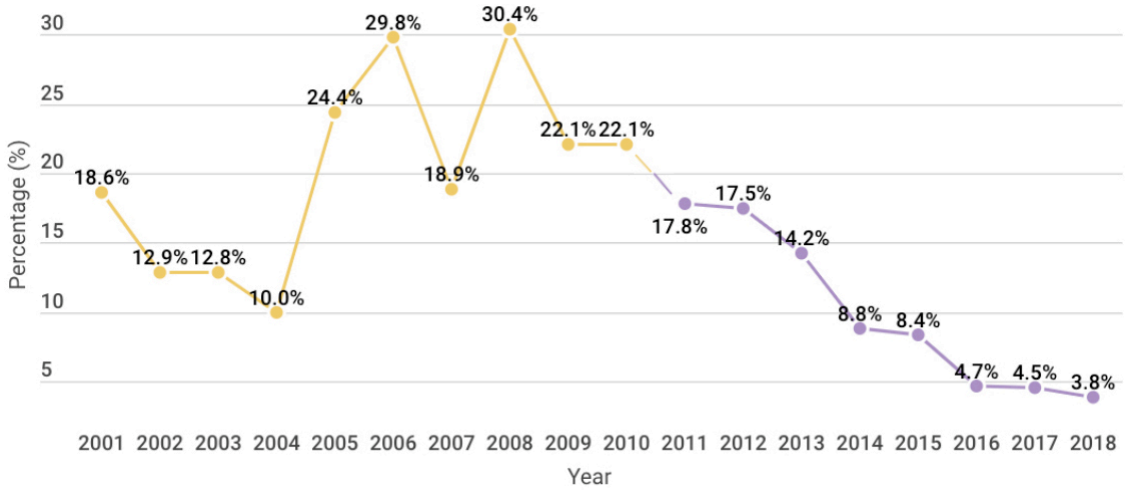

Figure 14. Percentage of the diagnosis of Fuchs' dystrophy between penetrating keratoplasty patients at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany between 2001-2010 (Wang et al.[12], yellow) and 2011-2018 (purple) (percentage) [21].

The seventh common PKP indication in Homburg/Saar was corneal dystrophy other than Fuchs' (2.4%). There were no relevant differences to our report between 2001-2011 (2.1%) and there were no changes in its incidence over the years of the present study.

The major limitation of our study is the retrospective design. As the study was somewhat limited by the available histopathological results, there was a little chance for bias, resulting in an over- or underestimation of observed trends. However, the numbers

of analysed corneal excisions (n=2123) compare well with those of other studies (n=921 [29], n=875 [52], n=1300 [37], n=1200 [12].)

In conclusion, with introduction of posterior lamellar keratoplasty, keratoconus remains the leading PKP indication in Saarland University with excimer laser-trephination on a routine basis. A trend towards increasing numbers can be observed regarding acute necrotizing and ulcerative keratitis patients and regrafts. However, the incidence of Fuchs' dystrophy decreased dramatically within PKP patients, with the introduction of posterior lamellar keratoplasty.

4.3 Introduction of posterior lamellar keratoplasty techniques at the Department of Ophthalmology of Semmelweis University; effect on number of keratoplasties and penetrating keratoplasties due to corneal decompensation between 2008 and 2017

In endothelial decompensation, endothelial keratoplasty (DSAEK and DMEK) may substitute PKP, with its several advantages over full-thickness corneal transplantation. While in Germany the number of DMEKs is more than ten times higher than those of DSAEKs [8], in the United States, DSAEK is the most often performed endothelial keratoplasty form [9].

Several advantages/disadvantages of DSAEK over DMEK are known. Surgery may be more feasible using DSAEK due to easier manipulation of the slightly thicker donor tissue. Nevertheless, best corrected visual acuity is worse after DSAEK than following DMEK. According to literature data, the mean best corrected postoperative visual acuity is expected to be 0.6 after DSAEK and 0.9-1.0 following DMEK [56-58]. This difference may be explained through interface irregularities and incongruence between donor and recipient in DSAEK, which is not the case for DMEK [59].

The thinner the transplanted tissue in DSAEK, the more favourable visual acuity is expected. In case of "ultrathin DSAEK" (donor thickness <100μm), the expected postoperative best corrected visual acuity approaches or even reaches the value provided by DMEK [60, 61].

DMEK is technically more difficult due to the fragility of the thin donor tissue. However, the smaller volume of the transplanted tissue reduces the risk of rejection

reaction [62]. According to Anshu et al., the incidence of rejection reaction was 9.0% after DSAEK and 0.7% following DMEK over a 2-year follow-up period. In contrast, the incidence of a rejection reaction for PKPs reaches 17.0% in a 2-year follow-up period [63, 64].

Nevertheless, endothelial keratoplasty does not provide sufficient visual improvement in case of stromal scarring, when it is better to decide for a full-thickness corneal transplantation. Therefore, in case of corneal decompensation, endothelial keratoplasty should be performed in time, before stromal scarring occurs. In Western European countries even patients with a best corrected visual acuity of 0.6-0.8 undergo endothelial keratoplasty on a routine basis and therefore, the annual number of corneal transplantations constantly increases [65].

This trend was not observable in the data set from Semmelweis University. Here, in addition to the decrease in the total number of corneal transplantations, the number and proportion of primary PKPs performed due to endothelial decompensation decreased between 2008 (61, 30.7%) and 2017 (37, 25.5%). In contrast, the number and proportion of endothelial keratoplasties performed due to corneal decompensation first increased and then remained stable between 2008 (1; 0.5%) and 2017 (23; 15.9%) (**Figures 9 - 10**).

The decrease in number of PKPs was much more obvious in the United States [9] and the United Kingdom, where the proportion of PKPs, performed due to corneal decompensation decreased from 98.3% to 46.6% between 1999 and 2009, while percentage of endothelial keratoplasties increased from 3% to 51.2% [66].

In our study at Semmelweis University, pseudophakic or aphakic bullous keratopathy (24.5%) was the leading indication for PKP among diseases resulting in endothelial decompensation. Studies from North-America show similar results in the 90’s and 00’s [15, 16]. In other developed countries, such as Germany and the United Kingdom, bullous keratopathy is not among the most common PKP indications nowadays [12, 29]. This is in part due to the improvement of the surgical techniques [24, 67] and in part thanks to the common use of the endothelial keratoplasty techniques [8, 9]. The proportion of PKPs performed due to bullous keratopathy also decreased at Semmelweis University between 2008 and 2017, which can be explained by the

introduction of endothelial keratoplasty technic. However, the decreasing trend was much slower than in West European countries [8, 9].

Fuchs' dystrophy (3.7%) was the sixth most common PKP indication between 2008 and 2017 at the Department of Ophthalmology of Semmelweis University. Internationally, its incidence is highly variable, as in European and North American centres it was the second [12, 15], in Asia only the fifth most common indication [39]. Although the incidence of PKPs due to Fuchs' dystrophy shows annual differences at our Institution, it has not changed considerably during the study period. This could be explained by the fact that patients are generally referred to our institution at the relative late stage of the disease (with significant stromal scarring) and therefore, rather a PKP is performed.

Overall, the number of endothelial keratoplasties remained stable after an initial increase, and the number of PKPs decreased. The decrease of the total number of keratoplasties may be explained by reduced availability of donors.

In conclusion, with introduction of posterior lamellar keratoplasty techniques, the annual number of PKPs due to bullous keratopathy decreased at the Department of Ophthalmology of Semmelweis University, similar to other countries. However, the total number of corneal transplantations also decreased. Introduction of posterior lamellar keratoplasties may also result in increasing number of corneal transplantations in Hungary, in case of development in corneal banking.

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5. Conclusions

Our studies aimed to analyse changing trends in penetrating keratoplasty indications at a Hungarian and a German center between 2006 and 2018.

5.1 Pseudophakic or aphakic bullous keratopathy is the leading PKP indication at the Department of Ophthalmology of Semmelweis University, followed by regraft and acute necrotizing and ulcerative keratitis. Introduction of posterior lamellar keratoplasty techniques in 2009 did not change this order. Advancement in corneal banking and a better referral system of patients to corneal subspeciality centers should change this order in the next decades in Hungary.

5.2 With introduction of posterior lamellar keratoplasty, keratoconus remains the leading PKP indication at the Department of Ophthalmology, Saarland University Medical Center, with excimer laser-trephination on a routine basis. A trend towards increasing numbers can be observed regarding acute necrotizing and ulcerative keratitis patients and regrafts. However, the incidence of Fuchs' dystrophy decreased dramatically within PKP patients, with the introduction of posterior lamellar keratoplasty.

5.3 With introduction of posterior lamellar keratoplasty techniques, the annual number of PKPs due to bullous keratopathy decreased at the Department of Ophthalmology of Semmelweis University, similarly to other countries. However, the total number of corneal transplantations also decreased. Introduction of posterior lamellar keratoplasties may also result in increasing number of corneal transplantations in Hungary, in case of development in corneal banking.

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6. Summary

This retrospective study included all patients who underwent PKP between 2006 and 2017 at the Department of Ophthalmology, Semmelweis University and Saarland University Medical Center. We also analysed the effect of increasing numbers of lamellar keratoplasties on PKP numbers between 2008 and 2017 at Semmelweis University.

At Semmelweis University, PKP indications were pseudophakic or aphakic bullous keratopathy in 487 (28.3%), regraft in 443 (25.7%), acute necrotizing and ulcerative keratitis in 313 (18.2%), corneal scar in 153 (8.9%), keratoconus in 140 (8.1%), Fuchs' dystrophy in 61 (3.5%), corneal dystrophy other than Fuchs' in 46 (2.7%), other diagnoses in 44 (2.6%) and failed endothelial keratoplasty graft in 34 (2.0%) cases.

Keratoconus was the leading indication for PKP in 455 (21.5%) cases at the Saarland University, followed by acute necrotizing and ulcerative keratitis in 384 (18.1%), regraft in 367 (17.3%), corneal scar in 350 (16.5%), pseudophakic or aphakic bullous keratopathy in 225 (10.6%), Fuchs' dystrophy in 194 (9.1%), other diagnoses in 64 (3.0%), corneal dystrophy other than Fuchs' in 52 (2.4%) and failed endothelial keratoplasty graft in 32 (1.5%) cases.

Pseudophakic or aphakic bullous keratopathy is the leading indication for PKP at Semmelweis University, followed by regraft and acute necrotizing and ulcerative keratitis. This order did not change through introduction of lamellar keratoplasty in 2009. Advancement in corneal banking and a better referral system of patients to corneal subspeciality centers should change this order in the next decades in Hungary.

With introduction of posterior lamellar keratoplasty, keratoconus remains the leading PKP indication at Saarland University Medical Center, with excimer laser-trephination on a routine basis. A trend towards increasing numbers can be observed regarding acute necrotizing and ulcerative keratitis patients and regrafts. However, the incidence of Fuchs' dystrophy decreased dramatically within PKP patients, with the introduction of posterior lamellar keratoplasty.

With introduction of posterior lamellar keratoplasty techniques, the annual number of PKPs due to bullous keratopathy decreased at Semmelweis University, similar to other countries. However, the total number of corneal transplantations also decreased.

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8. Bibliography of the candidate's publications

Thesis related publications

1. Pluzsik MT, Seitz B, Flockerzi FA, Langenbucher A, Tóth G, Bohle RM, Szentmáry N. (2020) Changing trends in penetrating keratoplasty indications between 2011 and 2018 - Histopathology of 2123 corneal buttons in a single center in Germany. Curr Eye Res, 13:1-6. Online ahead of print. **IF: 1.754**
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1. Pluzsik MT, Schneider M. (2014) [Bilateral idiopathic choroidal folds]. Orvosi Hetilap, 155: 1083-1086.
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