Is early detection of keratoconus worthwhile? Systematic review based on the WHO criteria for screening.

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Promotors: Prof. Dr. I. Claerhout, Dr. E. Kreps

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Abbreviations

AC	Allergic Conjunctivitis
ARC	Anterior Radius of Curvature
ARMD	Age-Related Macular Degeneration
BAD-D	Belin/Ambrosio Enhanced Ectasia Total Derivation Value
BCVA	Best-Corrected Visual Acuity
BDVA	Best-Corrected Distance Visual Acuity
BSCVA	Best Spectacle-Corrected Visual Acuity
Can$	Canadian Dollars
CAT	Critical Appraisal Tool
CB	Chronic Blepharitis
CCT	Central Corneal Thickness
CL	Contact Lens(es)
CLEK	Collaborative Longitudinal Evaluation of Keratoconus
CSC	Cataract Surgical Coverage
CSR	Cataract Surgical Rate
CXL	Cross-linking
D	Diopter(s)
DALK	Deep Anterior Lamellar Keratoplasty
DM	Diabetes Mellitus
DRP	Diabetic Retinopathy
DUSKS	Dundee University Scottish Keratoconus Study
GDP	Gross Domestic Product
HDI	Human Development Index

HR	High Resolution
ICER	Incremental Cost-Effectiveness Ratio
ICRS	Intrastromal Corneal Ring Segments
ISV	Index of Surface Variance
IVA	Index of Vertical Asymmetry
JBI	Joanna Briggs Institute
KC	Keratoconus
KPI	Keratoconus Prediction Index
LASIK	Laser In Situ Keratomileusis
NEI-VFQ-25	National Eye Institute-Vision Function Questionnaire
NS	Not Specified
OSA	Obstructive Sleep Apnea
PK	Penetrating Keratoplasty
PRC	Posterior Radius of Curvature
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRK	Photorefractive Keratectomy
QALY	Quality-Adjusted Life Years
QoL	Quality of Life
RGP	Rigid Gas Permeable contact lenses
SE	Spherical Equivalent
t-PRK	Topography-guided Photorefractive Keratectomy
UCVA	Uncorrected Visual Acuity
UK	United Kingdom
USA	United States of America

US$	United States Dollar
UVA	Ultraviolet A
VA	Visual Acuity
VKC	Vernal Keractoconjunctivitis
WHO	World Health Organization

Abstract

Purpose: To research whether screening for keratoconus is worthwhile, based on the current evidence for early detection and treatment of keratoconus. The World Health Organization principles of screening are used as a guideline.

Methods: A systematic review of the Pubmed, Cochrane and Web of Science databases, according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Results: Recent reports suggest that the prevalence of keratoconus is substantially higher than previously thought. While keratoconus does not result in blindness, it does cause significant morbidity as it is a chronic eye disease affecting young, economically active patients, with a significant impact on the quality of life. The magnitude of the public health impact of keratoconus is disproportionate to its prevalence and clinical severity, and has an important impact on public health budget.

Corneal imaging techniques have greatly improved, enabling us to diagnose keratoconus in a subclinical stage. The ultimate goal of treating patients with keratoconus is to preserve or even improve their quality of life, and to improve their ability to perform visually related tasks. Even though no definite treatment is available, the introduction of corneal cross-linking in the early 2000s has revolutionized the care for keratoconus patients. Whereas in the past merely methods for optical correction were available, corneal cross-linking has proven to halt progression in keratoconus, thus reducing the need for corneal transplantation. Moreover, cross-linking has been proven to be cost-effective.

Conclusion: Early and reliable detection of keratoconus is required to fully utilize the benefits provided by stabilization of disease progression. Currently, insufficient data are available to estimate the possible effects and costs of a screening program. Further research - investigating the feasibility and (cost-)effectiveness of various screening strategies for keratoconus - is necessary to maximize the benefits of corneal cross-linking.

1. **Introduction**

1.a. Introduction on keratoconus

Keratoconus (KC) is a bilateral, yet asymmetrical chronic corneal disease, that affects patients in their puberty or early adulthood. The cornea becomes ectatic and assumes a conical shape, which is accompanied by stromal thinning. This leads to irregular astigmatism, myopia, and corneal protrusion. With progressing stromal thinning, this can evolve to a loss of correlation between the anterior and posterior corneal curvature. Clinical signs depend on the stage of disease and include conical protrusion, an iron deposition line surrounding the base of the cone (Fleischer ring), and fine vertical lines in the deep stroma and Descemet membrane (Vogt striae). In advanced stages, sudden breaks in Descemet membrane can lead to stromal imbibition of aqueous, a condition referred to as acute hydrops, and corneal scarring can occur. (1, 2) The progressive change in corneal shape prompts vision loss and can influence vision-related quality of life (QoL).(3)

The exact etiology of keratoconus remains unknown, yet it's widely accepted that it is a complex multifactorial disorder with environmental, biomechanical and genetic factors playing a role. Common risk factors are eye rubbing, atopic disease, family history of keratoconus, Down syndrome and connective tissue disorders.(4, 5)

The gold standard for the diagnosis of keratoconus is corneal topography (or tomography). An asymmetrical bowtie pattern (contrary to the symmetrical bowtie in regular astigmatism), high astigmatism or a conical shape should alert the examiner to the possible diagnosis of keratoconus. Different indices have been developed that differentiate keratoconic from normal corneas: commonly used indices are the central K value (calculated by averaging the dioptric power on rings 2-4 of the placido disc), inferior-superior (I-S) index (calculated by comparing the difference in dioptric power between points on the inferior cornea with corresponding points on the superior cornea), KISA% index (derived and calculated from 4 indices), and keratoconus prediction index (KPI, derived and calculated from 8 indices).(1, 6, 7) Frequently used diagnostic devices are based on slit-scanning elevation topography (e.g. Orbscan; Bausch and Lomb Surgical, USA), and Scheimpflug imaging techniques (e.g. Pentacam HR tomography; Oculus, Germany).(8, 9) With the Pentacam HR, combined factors and indices can be displayed as the Belin Ambrosio Enhanced Ectasia Display, or the Holladay 6 map display to facilitate quick and effective screening of ectatic disease.(1, 10)

Commonly used classification systems are the Amsler-Krumeich classification(1) (cfr. Table 1A), and the newer ABCD-grading system(11) (cfr Table 1B).

Table 1A: the Amsler-Krumeich classification

Stage	Findings
I	Eccentric steepening Myopia, induced astigmatism, or both <5.00 diopter (D) Mean central K readings <48 D
II	Myopia, induced astigmatism, or both from 5.00 to 8.00 D Mean central K readings <53.00 D Absence of scarring Corneal thickness >400 micron
III	Myopia, induced astigmatism, or both from 8.00 to 10.00 D Mean central K readings >53.00 D Absence of scarring Corneal thickness 300-400 micron
IV	Refraction not measurable Mean central K readings >55.00 D Central corneal scarring Corneal thickness < 200 micron

Table 1B: ABCD-grading system for keratoconus

	A (ARC) °	B (PRC) *	C (pachy) †	D (BDVA) °°	Scarring
Stage 0	>7.25 mm (<46.5D)	>5.90 mm (<57.25D)	>490	>20/20	-
Stage 1	>7.05 mm (<48.0D)	>5.70 mm (<59.25D)	>450	>20/20	-, +, ++
Stage 2	>6.35 mm (<53.0D)	>5.15 mm (<65.5D)	>400	<20/40	-, +, ++
Stage 3	>6.15 mm (<55.0D)	>4.95 mm (<68.5D)	>300	<20/100	-, +, ++
Stage 4	<6.15 mm (>55.0D)	<4.95 mm (>68.5D)	<300	<20/400	-, +, ++

*° ARC = anterior radius of curvature (3 mm zone), * PRC = posterior radius of curvature (3 mm zone), † Pachy = Thinnest pachy (μm), °° BDVA = best corrected distance visual acuity*

Treatment options for keratoconus include glasses in early disease and a variety of contact lenses (CL) in several stages of keratoconus (rigid gas-permeable lenses (RGP), Rose K, hybrid lenses, scleral lenses, etc.). Intrastromal corneal ring segments (ICRS) can be implanted to reduce the corneal curvature in patients who lack functional vision with glasses or contact

lenses. When the above treatment options fail to offer adequate visual acuity, i.e. in advanced keratoconus, corneal transplantation can be considered. Even though there is no definite cure for keratoconus, a method to stabilize disease progression is available since the early 2000s: corneal cross-linking (CXL). In this treatment riboflavin and ultraviolet A light are used to produce a photochemical reaction, resulting in an increase of corneal rigidity. Cross-linking has significantly altered the care for keratoconus patients.(12)

Prior to the cross-linking era, there was little incentive for early keratoconus diagnosis as there were no means to arrest the natural course of the disease other than advising patients against eye rubbing. Ideally, timely cross-linking would prevent progression from a mild to moderate or severe stage and thus allow for a reduction in lifelong contact lens dependency as well as further progression towards a corneal graft.

1.b. Purpose

This paper aims to research whether screening for keratoconus is worthwhile, based on the current evidence for early detection and treatment of keratoconus, and if so, which screening strategy could be implemented. By means of the World Health Organization (WHO) principles of screening, we will investigate whether early detection and treatment would result in reducing morbidity and costs. We will address critical areas where knowledge remains insufficient.

2. **Methods**

A systematic search according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines was performed, selecting studies on the topics of natural history of keratoconus, epidemiology, quality of life, cost of treatment, cost-effectiveness and cost of illness (Pubmed search: keratoconus AND (screening OR cost OR cost-effectiveness OR epidemiology OR natural course OR quality of life). Articles describing the mere diagnosis in refractive surgery candidates were excluded by adaptation of advanced search details. Studies were recovered from the Pubmed, Cochrane and Web of Science databases. All English language abstracts were evaluated for inclusion in this review, without limitation on publication date. The full PubMed search strategy and PRISMA flowchart can be found in Addendum 1.

Articles pertaining to the epidemiology of keratoconus, cost of illness, disease burden, screening strategies and cost-effectiveness of screening and treatment were identified. All articles were screened at title and abstract level.

The scientific quality of the remaining articles was assessed using the relevant Critical Appraisal Tool (CAT) issued by the Joanna Briggs Institute (JBI).(13-16) An example can be found in Addendum 2. Relevant references in the selected articles were additionally included and went through the same selection process. In total, 187 articles were included in the qualitative synthesis concerning keratoconus.

Next to this systematic search, articles discussing school-based vision screening were searched in PubMed. Articles that were found to be relevant to the discussion sections in this paper were manually selected.

3. <u>Results</u>

The classical screening criteria defined by Wilson and Jungner for the WHO in their 1968 statement '*Principles and practice of screening for disease*' (Table 2) will be used as a guideline. (17)

Table 2: Wilson and Jungner screening criteria

1	The condition sought should be an important health problem.
2	There should be an accepted treatment for patients with recognized disease.
3	Facilities for diagnosis and treatment should be available.
4	There should be a recognizable latent or early symptomatic stage.
5	There should be a suitable test or examination.
6	The test should be acceptable to the population.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8	There should be an agreed policy on whom to treat as patients.
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10	Case-finding should be a continuing process and not a "once and for all" project.

The original order of the above criteria will be adapted to create a logical and readable text structure. For the sake of clarity, results and discussion for every screening criterion will be discussed together.

3.a. The condition sought should be an important health problem

The importance of a health problem can be regarded from the point of view of both the individual and the community. It can be appraised in two ways: either by its degree of prevalence, or by the impact on quality of life of the individual.

3.a.1. Prevalence and incidence

Prevalence is calculated as the number of affected individuals at a given time divided by the number of individuals in the population, thus calculating the expected number of patients with a certain disease in the population. Incidence on the other hand, refers to new - rather than existing – cases that occur in the population over a specified period of time.(18)

Keratoconus has long been considered an uncommon disease based on the prevalence rate of 54.5 per 100,000 published by Kennedy et al in 1986.(19) A recent epidemiologic study in the Netherlands showed that the annual incidence and prevalence of keratoconus are five- to tenfold higher than previously reported. The annual incidence in white patients aged 10-40 was 1 in 7,500, while the prevalence in the general population was estimated to be 1 in 375.(20)

Findings of epidemiologic studies are listed in table 3A and 3B. The differences in denominators, study design (retrospective/prospective) and diagnostics (keratoscopy or corneal topography) hinder direct comparison of reported data from various regions. Advances in corneal imaging are presumably responsible for the increase in reported prevalence.

Table 3A: Retrospective/prospective studies

Country	Year	Duration (years)	Diagnostics	Incidence per 100,000	Prevalence per 100,000
USA(19)	1986	48	Irregular retinoscopic reflexes and irregular mires on keratometry	2	54.5
Finland(21)	1986	20	Hospital registration of diagnosis	1.5	28.8
UK(22)	2000	10	Hospital registration of diagnosis (age 10-44 y)	19.6 (Asians)° 4.5 (whites)°	229 (Asians) 57 (whites)
UK(23)	2004	6	Hospital registration of diagnosis	25 (Asians) 3.33 (whites)	NS
Saudi Arabia(24)	2005	1	Prospective registration of diagnosis (Irregular retinoscopic reflexes and irregular mires on keratometry)	20	NS
UK(25)	2005	4	Videokeratography	32.3 (Asians), 3.5 (whites)	NS
Denmark(26)	2007	11	Hospital registration of diagnosis	1.3	86
USA(27)	2009	4	Medicare expences, age > 65 y	NS	15.7-18.3
Iran(28)	2012	1	Clinical signs and Tomey TMS-4	22.3	NS
Lebanon(29)	2016	5	Hospital registration of diagnosis	530 (<14 y), 3,780 (>14 y)	NS
Netherlands(20)	2017	4	Registration of diagnosis for reimbursement	13.3*	265

° age-specific (10-44 years)/ age-specific (10-40 years), NS: not specified*

Table 3B: Screening studies

Country	Diagnostics	Sample size	Prevalence in cohort
New Zealand(30)	Medmont corneal topographer	441 secondary school students (age 13-18)	680 per 100,000
Iran(31)	Pentacam (Holladay criteria)	4,592 (age 40-64 y)	760 per 100,000
Iran(32)	Slit-lamp, Pentacam HR	2,703 (age > 10 y)	3,590 per 100,000
Iran(33)	Slit-lamp, Tomey TMS-4, Orbscan II	1,027 medical students	2,500 per 100,000
Israel(34)	Videokeratography	987 college students	2,340 per 100,000
Saudi Arabia(35)	Pentacam HR	522 patients (age 6-21 y)	4,790 per 100,000
India(36)	Mean SE $\geq$ 48D with non-automatic keratometer (no topographer available)	5,711 (age >30 y)	2,300 per 100,000

3.a.2. Quality of life

In healthcare economics, the concept of quality-adjusted life years (QALY) has been developed as a common impact measure of the burden of disease on both the quantity and quality of life. It takes into account the impact of a treatment on a patient's length of life, as well as the impact on their health-related quality of life. One QALY signifies one year in perfect health. The different health states individuals experience over time, are weighted according to the utility scores associated with them. These utility scores are the value that is attached to a certain health state, measured in terms of preference (desirability).(37, 38)

The National Eye Institute-Vision Function Questionnaire (NEI-VFQ-25) is a commonly used tool to asses vision-related quality of life: it measures different subscales and dimensions of self-reported vision targeted health status - such as general, near, distance and color vision, as well as dependency, social function and mental health.(39) The questionnaire has been validated in different studies, and is proven to be sensitive to the influence of several ophthalmologic diseases (e.g. age-related macular degeneration (ARMD), diabetic retinopathy (DRP), glaucomatous field loss, etc.).(40)

Keratoconus patients have significantly impaired vision-related quality of life similar to those with severe ARMD, to an extent disproportionate to visual acuity (VA) measures.(3, 41) They tend to score lower on all subscales of NEI-VFQ-25 compared to a control group of contact lens (CL) wearers, with significant lower scores in the subscales of general vision, ocular pain,

near vision, vision-specific mental health, vision-specific role difficulties, and peripheral vision.(40) Binocular entrance VA worse than 20/40 was associated with lower quality of life scores on all scales except general health and ocular pain in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) cohort. A steep keratometric reading (average of both eyes) >52 diopters (D) was associated with lower scores on the mental health, role difficulty, driving, dependency, and ocular pain scales.(3) Visual impairment (defined as entrance high contrast visual acuity <20/40 but >20/200) due to keratoconus in the baseline findings of the CLEK-study is 8.5% of all participants.(42) Even patients without visual decline show significantly lower vision-associated QoL as compared to a control group of CL wearers.(43) The impact on QoL also worsens with time.(41)

Health utility calculations based on the CLEK cohort have shown a significant association between reported health utility (based on SF-6D questionnaire) and best-corrected visual acuity (BCVA) of the better eye.(44) A recent study by Sahebjada et al. confirmed this finding.(45) Changes in the QoL scales are associated with changes in the asymmetry of VA and corneal curvature, yet with less impact than changes in the better eye.(46) This is a good reminder for clinicians not to ignore the better eye, as the clinical focus is often directed towards the worse eye. Whether the need for specialty CL in order to achieve adequate binocular vision (with poorer unaided vision) significantly influences QoL, remains unknown.

3.a.3. Discussion

The question can be asked which criteria should be used to qualify a disease as an important health problem. Does this mainly refer to a high prevalence, or should the impact on quality of life be regarded? Or rather, should we focus on economic implications of the disease? The original paper by Wilson and Jungner outlining the principles of screening, states the following: *"To be considered an important problem, a disease need not necessarily have a high degree of prevalence, though that would be a usual requirement. […] Clearly the importance of the problem needs to be considered from the point of view both of the individual and of the community. Thus conditions with serious consequences to the individual and his or her family in general may warrant relatively uneconomic screening measures; while certain individually mild conditions, but having serious consequences for the community if not discovered early and treated, will justify screening on these grounds."*(17)

Despite the relatively low prevalence of keratoconus, the public health impact should not be underestimated as it affects young and economically active patients with a considerable effect on quality of life. Because clinical examination of people with keratoconus typically reveals

normal best-corrected VA as well as modest ocular comorbidity, the common clinical idea is to assume keratoconus to be a disease of modest consequence to its patient. However, considering the above results of self-reported impact on the QoL, keractoconus is highly significant from a patient's perspective, and QoL-scores worsen with time.(41)

As such, we can conclude that the existing evidence suggests that the magnitude of the public health impact of keratoconus is disproportionate to its prevalence and clinical severity. The impact on public health is greater than it may appear to be *prima facie*.(3) Nevertheless, most of this evidence is based on findings of the CLEK-study, which dates back to the era before cross-linking, and before the newer generation of contact lenses. All in all, little up-to-date evidence is available concerning the quality of life of keratoconus patients.

3.b. The natural history of the condition, including development from latent to declared disease, should be adequately understood

3.b.1. Demographics and natural progression

The mean age at the time of keratoconus diagnosis varies between different reports, but is most commonly in early adulthood and continues into earning and child-rearing years. This means mainly economically active patients are affected.(47) In younger patients with untreated keratoconus, the risk of progression (defined as an increase in Kmax) is significantly higher: those younger than 17 years old are likely to have more than 1.5 D of Kmax progression over a 12-month period.(48)

Higher rates of keratoconus are reported in the Middle East and Asia, but these data mainly originate from screening studies and no similar prospective studies have been performed in Caucasians. An ethnic variability may however exist, based on findings of increased relative risk in Asians compared to Caucasians in 2 UK-based retrospective reports.(22, 23) Black and Latino persons are reported to have approximately 50% higher odds of having keratoconus compared to white persons.(49) The higher prevalence rates in the Middle East from mainly Muslim communities may be correlated with the increased likelihood of consanguinity, which is shown to be a risk factor for keratoconus.(50) Moreover, untreated Middle-Eastern patients demonstrated significantly more progression (i.e. greater Kmax increase) than Europeans and East Asians in a recent meta-analysis by Ferdi et al.(48)

Large-scale longitudinal observational studies have documented the natural course of keratoconus in the pre-crosslinking era (cfr. Table 4). Keratoconus either self-limits at some point, presumably due to natural cross-linking, or evolves towards progressive corneal thinning

with apical scarring and risk of hydrops, requiring penetrating keratoplasty (PK). During the 8 years of follow-up, CLEK patients exhibited a gradual decrease in high- and low- contrast BCVA.(51) The study's five-year incidence of corneal scarring was 14% overall. Progression of disease in terms of changes in corneal curvature and VA resulted in continued decline in vision-related QoL as measured by the NEI-VFQ.(51) The Dundee University Scottish Keratoconus Study (DUSKS), a prospective observational longitudinal study, similarly followed 200 keratoconus subjects for 4 years. They also found a decrease in unaided vision (14%) and recorded best spectacle-corrected visual acuity (BSCVA) (24%) by one or more lines. During the study period, 4.5% of keratoconic eyes progressed to surgery.(52) A steeper Kmax at the time of diagnosis (certainly patients with greater than 55 D Kmax) is significantly associated with more progression.(48)

Table 4: CLEK vs DUSKS (Adapted from Weed et al.)(53)

	CLEK (16 clinics, n=1209)	**DUSKS (n=200)**
Age (years): enrolled	39.3+-10.9	30.9+-10.4
diagnosed	27.3+-9.5	24.05+-8.97
Male (%)	55.9	62.5
Family history (%)	13.5	5
Race (%)	African-American 19.9 White 68.5 Other 11.6	Asian 6.5 White 93 Afro-Caribbean 0.5
Eye rubbing (%)	50.5	48
Vogt striae (%)	45.5	(1) 67 (2) 68
Fleischer ring (%)	74.6	(1) 86 (2) 89
Scarring (%)	36.6	(1) 21 (2) 20
Corneal thickness (µm)	N/A	(1) 443 (2) 412
Contact lens (%)	73	(1) 80 (2) 76
Binocular VA (%)	77.9 6/12	(1) 93 6/9 (2) 90
Steep K (D)	50.8+-5.4	(1) 51.74+-5.36 (2) 50.76+-4.86
Flat K (D)	47.9+-5.4	(1) 46.66+-4.55 (2) 45.74+-4.09
Penetrating keratoplasty (%)	9.8	(1) 10.5 (2) 15
Atopy (%)	53	41.5

(1) and (2): review moments in DUSKS (spanning a 4 year-period)

3.b.2. Risk factors

Next to ethnicity, eye rubbing and a positive family history, multiple significant risk factors for keratoconus have been identified. Table 5 lists the evidence as found in the included articles.

Table 5: Significant risk factors for keratoconus

Risk factor	Result	Author, year published
Allergy	Odds ratio (OR) 4.22	Gordon-Shaag et al., 2013(50)
	OR 2.09	Naderan et al., 2015(54)
Asthma	OR 2.00	Merdler et al., 2015(55)
	OR 3.92	Naderan et al., 2015(54)
	OR 1.31	Woodward et al., 2016(49)
AC/CB/VKC°	OR 6.00	Merdler et al., 2015(55)
Consanguinity	OR 3.96 for 1st cousin and 2nd cousin	Gordon-Shaag et al., 2013(50)
	Higher mean inbreeding coefficient in KC	Jamali et al., 2018(56)
Diabetes	Higher prevalence of DM type 2 in KC	Kosker et al., 2014(57)
	No difference in prevalence of DM in KC patients vs control; having DM decreases odds of severe KC	Kuo et al., 2006(58)
	Protective effect of DM type 2 against KC	Naderan et al., 2014(59)
		Seiler et al., 2000(60)
	Lower odds of KC (uncomplicated DM: OR 0.80, complicated DM: OR 0.48)	Woodward et al., 2016(49)
Down syndrome	OR 6.22	Woodward et al., 2016(49)
Education	OR 4.79 (education >12 y)	Gordon-Shaag et al., 2013(50)
	Higher risk in lower education	Naderan et al., 2015(54)
Eye rubbing	OR 10.15	Gordon-Shaag et al., 2013(50)
	OR 3.37	Gordon-Shaag et al., 2015(61)
	OR 6.80	Jamali et al., 2018(56)
	OR 4.33	Naderan et al., 2015(54)
Family history of KC	OR 9.68	Gordon-Shaag et al., 2015(61)
	OR 8.40	Naderan et al., 2015(54)
Parents' education	OR 0.35 (fathers education)	Gordon-Shaag et al., 2015(61)
OSA†	Higher risk for OSA in KC	Naderan et al., 2015(62)
	Higher risk for OSA in KC (10-20 times higher than general population)	Pedrotti et al., 2018(63)
	OR 1.13	Woodward et al., 2016(49)
VKC*	OR 8.67	Naderan et al., 2015(54)

*° AC/CB/VKC = combination of allergic conjunctivitis, chronic blepharitis, and vernal keratoconjunctivitis, † Obstructive Sleep Apnea, * Vernal Keratoconjunctivitis*

Variations in odds ratios and statistical significance can be explained by differences in study design and number of patients examined, as well as by differences in population characteristics.

3.b.3. Development from latent to declared disease

A consensus paper regarding keratoconus definitions, diagnosis and management was published in 2015, based on expert panel discussions using the Delphi method. In this paper, it is proposed that keratoconus can be diagnosed when the following findings are present: (a) abnormal posterior ectasia, (b) abnormal corneal thickness distribution, and (c) clinical noninflammatory corneal thinning. It is stated that exact values for any parameter will vary based on the machine being used and, for elevation values, the reference surface. Consensus was that tomography (e.g., Scheimpflug or optical coherence tomography) is currently the best and most widely available test to diagnose early keratoconus, and that posterior corneal elevation abnormalities must be present to diagnose mild or subclinical keratoconus.(5) Progression of keratoconus is defined by a consistent change in at least 2 of the following parameters (and the magnitude of the change has to be above the normal noise of the testing system): (a) steepening of the anterior corneal surface, (b) steepening of the posterior corneal surface, and/or (c) thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point.(5) There is no consensus on more specific or quantitative data regarding diagnosis nor progression.

A recent meta-analysis by Ferdi et al. investigated the evolution and natural progression of untreated keratoconus. A significant increase in Kmax of 0.7 D at 12 months was demonstrated. Younger patients, patients with steeper Kmax at presentation, and Middle-eastern patients experienced more progression. No significant changes in visual acuity, refraction, or thinnest pachymetry were demonstrated. Although these last 3 parameters are undoubtedly important aspects of keratoconus progression, they may be less sensitive measures of progression compared to topography. In order to tailor progression predictions to individual patients, more data providing quantitative evidence of progression are needed.(48)

3.b.4. Discussion

The natural history of keratoconus is poorly understood because of lack of sufficient data. Nonetheless, this information is fundamental in making informed decisions on whether interventions - aiming to stabilize progression - have an advantageous benefit-risk-ratio.

To our knowledge, no formal definition for a latent stage of keratoconus, nor specific quantitative data concerning keratoconus progression from latent to declared disease are

available in literature. The natural course of keratoconus can be seen as a progressive continuum, in which it is difficult to identify a set point where it progresses from latent to declared disease.

Dependency on specialty contact lenses, a significant loss of visual acuity, acute hydrops, or the need for keratoplasty can be regarded as hard endpoints. As such, we could conclude that the diagnosis of keratoconus can be seen as the goal of screening, aiming to reduce the incidence of the above-mentioned hard endpoints.

3.c. There should be a recognizable latent or early symptomatic stage

The diagnosis of keratoconus can be seen as the goal of screening, whereas the early symptomatic stage might already be the moment when cross-linking is indicated (cfr. infra). Patients should thus be identified at an earlier, possibly pre-symptomatic, point in time. Advanced keratoconus stages show typical topographic patterns that are easy to recognize; however, the detection of the earliest, subclinical stage can be challenging. This is of particular importance in patients requesting refractive surgery (e.g. laser in situ keratomileusis (LASIK)), since subclinical KC in these patients could lead to iatrogenic keratectasia when undiagnosed.(64)

Various topographic metrics and indices to detect subclinical and definite keratoconus have been published. Tomographic systems add significantly more information, e.g. due to greater corneal coverage and by analyzing the posterior corneal surface.(65) Most published indices are based on a combination of keratometry and central corneal thickness (CCT) values. Jafarinasab et al. demonstrated that anterior and posterior corneal elevation data obtained by Orbscan II can discriminate between keratoconus and normal corneas, but that the reliability of their indices is lower in differentiating subclinical KC from normal cases.(66) Discriminant function values obtained from corneal Zernike coefficients from corneal anterior and posterior surfaces and from spatial-thickness profile data, have proven to detect subclinical keratoconus with reasonable accuracy.(64) Belin/Ambrosio enhanced ectasia total derivation value (BAD-D) as displayed by Pentacam was found to be a strong parameter to differentiate both keratoconus and subclinical keratoconus from normal corneas.(67) Hashemi et al. identified BAD-D, the index of vertical asymmetry (IVA), the index of surface variance (ISV), and 5th order vertical coma aberration as the best diagnostic criteria for the diagnosis of subclinical keratoconus with a sensitivity of 83.6% and specificity of 96.9% using Pentacam HR.(9) Unfortunately, no single descriptor has 100% sensitivity and specificity, indicating that topographic/tomographic indices should always be interpreted alongside other clinical data.

Efforts are being made to develop machine learning methods (artificial intelligence) for detecting keratoconus.(64, 68)

3.d. There should be a suitable test or examination

Even though definitions differ in terms of nomenclature, corneal topography is a sensitive tool in detecting keratoconus- or keratoconus suspect patients.(8, 10, 67, 69, 70)

Other examination options include corneal biomechanical measurement devices (e.g. Ocular Response Analyser, Reichert Ophthalmic Instruments, NY, USA), anterior segment OCT(71), scissoring reflex on retinoscopy(72), or even smartphone-based devices(73); however, these require clinical validation.

3.e. The test should be acceptable to the population

Corneal imaging devices are a non-invasive, painless, safe and simple imaging method and are generally easily accessible to opticians and local hospitals in developed countries. Corneal imaging also allows detection of subclinical keratoconus, which is of vital importance in screening refractive surgery candidates.(74)

3.f. There should be an agreed policy on whom to treat as patients

Disease progression, and the consequent deterioration of uncorrected visual acuity (UCVA) and BCVA, defines the need for treatment. As mentioned above, steepening of the anterior and/or posterior corneal surface, and/or thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point have been identified as criteria for keratoconus progression.(5) However, no consensus is reached on specific, quantitative criteria.

As a consequence, different studies describe their own parameters for progression (non-exhaustive list):

- A ten-letter loss of BCVA and a 3 D increase in corneal curvature, since these are associated with a significantly larger decline in QoL and should be avoided.(48)
- Any of the following criteria for a period of 24 months: (a) an increase of ≥ 1.0 D in the steepest keratometry measurement, (b) an increase of ≥ 1.0 D in manifest cylinder, or (c) an increase of ≥ 0.5 D in manifest refraction spherical equivalent.(43)
- Deterioration of ≥ 1 line in BCVA, increase of ≥ 1.0 D in refractive error, and topographically as an increase of ≥ 1.0 D in maximum keratometric reading (Kmax) on serial corneal topographs within the last 6 months.(75)

- Any of the following criteria over a period of 6 months: an increase in mean K or steep K (K2) of ≥ 0.75 D, an increase in cylinder of ≥ 1.0 D, an increase in sphere of ≥ 1.0 D, and a decrease of 2 lines of CDVA.(76)
- Any of the following criteria over a period of 12 months: increased simulated maximum keratometry (sim max K) of ≥ 1.0 D based on corneal topography, or ≥ 1.0 D increase in the curvature of the steep meridian based on keratometer measurements, or increased cylinder of ≥ 1.0 D based on the manifest refraction, or loss of ≥ 2 lines of BSCVA attributable solely to the progression of KC.(77)

These varying criteria for keratoconus progression demonstrate that the decision on whether or not to proceed with treatment to stabilize the disease, is often left to the discretion of the surgeon. In this decision process, important parameters associated with increased risk of topographic progression – such as young age, and steeper Kmax at presentation – should be taken into account. For these patients with higher risk, closer follow-up and a lower threshold for treatment should be minded.(48)

3.g. There should be an accepted treatment for patients with keratoconus

Historically, only glasses and lenses were available for refractive correction in keratoconus; progression to hydrops or corneal scarring could not be avoided, and could only be managed by keratoplasty. In the last decades, there has been a paradigm shift in the treatment of keratoconus due to the introduction of cross-linking, which has shown to slow or halt progression (cfr. infra). The treatment of choice for a particular patient depends on the stage of disease, and whether or not progression is documented.

3.g.1. Treatment options to improve visual acuity

a. Optical correction: glasses and contact lenses

Patients with very mild or early keratoconus can achieve adequate vision with glasses or soft contact lenses in the vast majority. Mild to moderate keratoconus, with higher degrees of (irregular) astigmatism can be treated with rigid gas permeable (RGP) or hybrid contact lenses, which create a new refractive surface in front of the conical cornea. The space between the corneal surface and rigid contact lens is filled with tears, thus masking the underlying irregular shape. Scleral lenses function likewise, but rest on the conjunctiva and vault over both the cornea and limbus, thus creating a more stable and better-centered fit. These are generally used for moderate to advanced keratoconus, decentered cones, or patients suffering from dry eye disease.(78, 79) Recent developments in lens material and design, such as hybrid or specialty soft contact lenses, allow for a combination of longer wearing time, more patient comfort, and

good visual performance.(12) The use of scleral lenses has even shown to reduce the need for corneal transplants in severe keratoconus (Kmax ≥ 70D).(79)

b. Intrastromal corneal ring segments (ICRS)

Intracorneal ring segments (e.g. Intacs (Addition Technologies, USA)) were originally designed for myopia correction. These are 0.25 - 0.35 mm thick segments made from inert material and are implanted in the corneal stroma. The ring segments should embrace the steepest keratoconus meridian, thus pursuing maximal flattening of the conus. The best candidates for ICRS are patients with mild to moderate keratoconus, low spherical equivalent and average keratometry readings of less than 53 D. Several studies show significant improvement in uncorrected visual acuity (UCVA), BSCVA, spherical equivalent, and a reduction of keratometry.(80, 81) However, study samples and duration of follow-up are limited, and several articles describe regression at longer follow-up periods, suggesting that implantation of ICRS does not significantly influence progressive keratoconus in patients with confirmed progression of the disease.(76, 82) Moreover, it should be noted that complication rates are high (up to 40%; with ring exposure secondary to corneal thinning over the implants as a major concern)(81), and that long-term results are unpredictable.(76, 82)

c. Keratoplasty

c.1. Penetrating keratoplasty (PK)

Historically, PK was the only treatment option available in the management of severe keratoconus. This technique involves replacing full-thickness corneal tissue of the patient (including healthy endothelium) with a donor cornea. The mean time to corneal grafting from diagnosis varies between reports, ranging from 3.2 to 8.8 years. However, these data refer to the time before the availability of CXL or the latest generation of specialty contact lenses. The time to grafting will presumably be longer now.(48)

Disadvantages of PK are that it is an 'open-sky' procedure, that there is a prolonged course of surgical wound healing necessitating tight suturing, the risk of suture-related infections and the persistent risk of wound dehiscence.(83) Long-term outcomes of PK in keratoconus show a relatively high risk of rejection (up to 48% at 20 years follow-up), as well as a risk of graft failure, and recurrence of keratoconus.(84) Notwithstanding these disadvantages, PK is still a frequently used and effective technique in the care for patients with advanced keratoconus.(83, 85, 86)

c. 2. Deep anterior lamellar keratoplasty (DALK)

Contrary to PK, DALK involves replacing the affected stroma with donor corneal tissue, in which the recipient retains his own endothelium. The advantages of DALK over PK include a lower prevalence of allograft rejection and faster visual rehabilitation. Due to these advantages, the relative contribution of lamellar techniques is increasing.(83, 86) Nevertheless, postoperative astigmatism, steroid induced ocular hypertension and persistent epithelial defects are reported in both DALK and PK with similar frequency. Complications during the DALK-procedure can necessitate a conversion to PK.(87)

A Cochrane review comparing outcomes of PK and DALK in keratoconus concluded that both techniques are successful in improving BCVA, SE and keratometric astigmatism at 12 months postoperatively. However, there was insufficient evidence to support a difference in outcomes with regards to BCVA at any of the time points analyzed, or that there is a difference in outcomes with regards to graft survival, final UCVA or keratometric outcomes. More randomized controlled trials are required to further assess which type of keratoplasty is preferable in treating keratoconus.(87) Henein et al. concluded in a systematic review that DALK is associated with better refractive astigmatism and reduced rejection episodes, yet visual outcomes are better with PK. There was no difference in SE and keratometric astigmatism.(88)

3.g.2. Treatment option to stabilize progression: Corneal cross-linking (CXL)

a. The procedure

Corneal cross-linking intends to strengthen the corneal stroma and stabilize its form. This is done by exposing corneal tissue treated with the photosensitizing riboflavin (vitamin B2) to 370nm ultraviolet light (UVA). The chemical reaction which is hence produced (e.g. production of free radicals) forms chemical bonds between collagen fibrils, thus strengthening the tissue.(89) It is only performed in patients with adequate visual potential, absence of corneal scarring, and central corneal thickness (CCT) of at least 400µm (to avoid irradiation damage to the corneal endothelium).(75) In more advanced stages of keratoconus, stromal thinning often leads to CCT of less than 400 micron, thus limiting the applicability of CXL in this group of patients.

Two established methods can be used: the transepithelial or the epithelium-off technique. Both can be performed as outpatient procedures under topical anesthesia. The transepithelial technique is performed by directly instilling a 0.1% riboflavin solution for a minimum of 16

drops over 30 minutes, after which irradiation with UVA (370 nm wavelength, irradiance of 3 mW/cm 2) is started. This second phase also lasts approximately 30 minutes, while 1 drop of riboflavin is continuously instilled every 5 minutes.(89, 90) Different methods have been developed to enhance the permeability of riboflavin, a hydrophilic molecule, through the hydrophobic corneal epithelium: the use of benzalkonium chloride, EDTA, gentamicin, iontophoresis, as well as minimal trauma (through epithelial poke marks) to the epithelium.(91) The epithelium-off technique consists of the same treatment protocol, preceded by abrasion of the corneal epithelium to facilitate penetration of riboflavin. Before the application of UV light, CCT is measured, and if less than 400 µm, hypotonic riboflavin can be applied until CCT is ≥ 400 µm.(75) A pressure patch is usually applied postoperatively. Both procedures are followed by postoperative topical antibiotics and anti-inflammatory drops.(89, 90)

b. Evidence for efficacy

Corneal cross-linking has been widely available for more than a decade and has demonstrated its efficacy in halting further progression and safety in numerous randomized controlled trials.(75, 89, 90, 92) Craig et al. published a meta-analysis of studies on epithelium-off cross-linking for the management of keratoconus and secondary ectasia in 2014. Statistically significant improvements were found in visual acuity, topography, refraction and astigmatism, and central corneal thickness at 12 month follow-up compared to baseline pre-procedure values. However, the authors noted that few well-conducted randomized controlled clinical trials (RCT) with long follow-up are available.(90) This concern was shared by the Cochrane reviewers, who concluded that evidence for the use of CXL in the treatment of keratoconus was limited due to the lack of properly conducted randomized clinical trials.(89)

More recent studies support the evidence that CXL is effective in improving the maximum keratometry value, BDVA, and UCVA in eyes with progressive keratoconus, and that it achieves long-term stabilization of the ectasia.(75, 92, 93) There are a few trials with longer-term follow-up (up to 10 years) indicating treatment success in the majority of patients; with reported stability after 10 years of follow-up in nearly 80% of the patients.(93, 94)

c. When to treat

General perception is that documentation of disease progression is warranted to perform cross-linking, but there is no international consensus on what exactly constitutes as documented progression. We are also unable to reliably predict the future rate of progression in early disease.

Treatment at the pre-symptomatic stage of disease without any documented progression would inevitably result in overtreatment; yet later stages of keratoconus often show significant corneal thinning, while a minimum CCT of 400µm is advised for CXL.

Treatment of patients at an early stage renders safety of the procedure of vital importance. Epithelium-off CXL is associated with a number of possible complications. Transient corneal haze occurs in virtually all eyes and resolves with time. Serious complications such as infections (0-3%), stromal scarring (0-6%) or sterile infiltrates (2-4%) have been reported in varying proportions, yet can be regarded as uncommon.(90, 91) Even though transepithelial CXL lacks many of the complications of epithelium-off CXL, the latter appears to be more efficient in stabilizing Kmax.(91)

We can thus summarize that multiple studies show the effectiveness of CXL in halting or slowing progression of keratoconus, and that it is a safe treatment. Whether or not re-treatment will be necessary in the long term (after 20 or 30 years) remains to be investigated.

d. Combined treatment

Cross-linking can be performed as a single procedure, or can be combined with refractive surgery (e.g. photorefractive keratectomy (PRK), LASIK, or ICRS) in order to improve visual acuity, known as *'CXL plus'*.(95, 96)

A review by Hashemi et al. showed that combined same-day ICRS and CXL might have an added value over each technique separately. The qualitative analysis of data from 17 trials showed that simultaneous surgery patients performed significantly better in terms of spherical refractive errors and flat-K compared to CXL-first, and significantly better in terms of steep-K compared to each technique separately. Uncorrected and best-corrected visual acuity did not show statistically significant differences between groups. The authors mention limitations concerning small sample size, short-term follow-up, a lack of high-quality study protocols and well reported outcomes.(95)

Labiris et al. performed a prospective, controlled trial comparing quality of life between a group of patients with keratoconus stage 1 (Amsler-Krumeich classification) and BSCVA of 20/20 in both eyes, who underwent either CXL or CXL combined with topography-guided PRK (t-PRK) (tCXL). The group that underwent CXL presented a significant improvement in the dependency subscale 1 year post-operatively; whereas tCXL group presented a significant improvement in the near activities, role limitations, dependency, and driving subscale scores.(43) At the three-year follow-up time point, additional significant improvement was detected in the driving

subscale in the CXL group, and in the distant activities in the tCXL group. These results indicate that even early CXL in patients with good BSCVA has a beneficial impact on self-reported QoL, and that CXL or tCXL should be delivered as soon as progression is established - even at the very early stages of the KC disease continuum.(97)

e. Cost-effectiveness of CXL

A Canadian cost-utility analysis based on simulated cohorts compared total costs and Quality-Adjusted Life Years (QALYs) of early cross-linking with conventional PK. In this study all relevant medical costs were assessed, but broader economic impact was not incorporated in the study design (e.g. absence from work due to consultations or surgery, driving ability etc.). Despite conservative assumptions, Leung et al. found that CXL is cost-effective compared with conventional PK at an Incremental Cost-Effectiveness Ratio (ICER) of Can$9,090/QALY (i.e. approx. €6,060/QALY). This is well below cited thresholds of Can$20,000 – 100,000/QALY for cost-effective interventions in Canada, or US$50,000/QALY as proposed in the United States.(98) Godefrooij et al. similarly used a Markov-model to calculate cost-effectiveness of CXL from a healthcare perspective (thus not taking into account costs incurred outside of the healthcare system). They found an ICER of €54,384 per QALY gained ($59,822/QALY), assuming a stabilizing effect of CXL of 10 years; decreasing to €10,149/QALY ($11,163/QALY) assuming a lifelong stabilizing effect of CXL.(99) A Markov-model developed by Salmon et al. showed that CXL is cost effective compared with standard management at an incremental cost of £3,174 per QALY (€3,629/QALY, or US$4,086/QALY[a]) over a 25-year time horizon. If CXL can only provide a one-off benefit of 5 years of halted progression, this value may rise to over £33,263 per QALY (€38,360/QALY, or US$43,192/QALY[b]).(100) The differences in the ICERs mentioned by the last two articles, can be explained by the different data used to base assumptions on regarding disease progression, as well as by the duration of the Markov model (25 years in the study by Salmon et al. versus the duration of the life of each patient in the model by Godefrooij et al), and by the choice of utility values (corneal curvature in the study by Salmon et al. versus VA in the model by Godefrooij et al.).

3.g.3. Discussion

Different treatment strategies for optical correction, including RGP contact lenses(101, 102) and ICRS(103) have proven to have a positive impact on the vision related quality of life.

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[a] Currency converted via xe.com on 22th of April 2019
[b] Currency converted via xe.com on 22th of April 2019

Various studies support the positive impact of CXL on self-reported quality of life.(43, 97) The CLEK-study showed significant improvements in quality of life scores after PK as well (104); yet it remains impaired, despite satisfactory results on visual outcome measures.(40, 102)

In the Netherlands, significantly fewer corneal transplants were performed for treating keratoconus following the introduction of cross-linking (reduction of 25% in the 3 years following introduction of cross-linking as compared to the 3 years before the introduction).(105) Sandvik et al. demonstrated a similar trend in Norway, where the frequency of keratoplasty for keratoconus has been more than halved.(106) Alongside the introduction of CXL, improvements in contact lens design might also partially explain the reduced need of corneal transplants.(79) If this trend would continue in other countries in the future, this could mean that costs and morbidity due to PK (e.g. rejection) would diminish.

In summary, different treatment options are available to improve visual acuity, while having a positive impact on vision-related quality of life. However, corneal cross-linking is the only treatment option available that has proven to stabilize progression, and leads to a reduction in the need for more invasive corneal transplants. Even early CXL in patients with good BSCVA has a beneficial impact on self-reported QoL; this emphasizes the need for early detection and treatment of keratoconus.

3.h. Facilities for diagnosis and treatment should be available

Facilities for diagnosis and treatment are available in most developed countries. This can be deducted from the places where clinical studies included in this systematic review took place. The earlier we want to detect keratoconus in its progressive continuum, the more specialized equipment is required for diagnosis and treatment. No specific data were found on the number of topography/tomography devices per clinic or per country, nor on the access to cross-linking or other treatment options.

Cataract surgical rate (CSR) and coverage (CSC) are used by the WHO as key indicators for the delivery of eye care, and for monitoring progress towards universal eye health coverage in different countries and regions. Strong associations are documented globally between CSR and socioeconomic indicators, such as gross domestic product (GDP) per capita and human development index (HDI). Countries with lower GDP per capita show a higher rate of cataract blindness, lower CSC, and fewer patients with good vision outcomes.(107) Even though this does not provide information on the care for keratoconus patients, it can be regarded as an important indicator for the quality of and access to eye care in different regions.

Availability of diagnostic tools and treatments options for keratoconus in developing countries may be restricted to larger hospitals, or is possibly not available at all. Consequently, patients will likely be diagnosed in a later stage, with restricted access to contact lenses or surgical options. If considering screening in these countries, it should presumably be organized in a different way (e.g. by retinoscopy(72)). No articles were found covering these subjects.

3.i. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole

Economic evaluations in healthcare can aid in allocating resources to prioritize these interventions with maximum benefit at the lowest possible cost, since healthcare resources remain scarce.(108) Costs of diagnosis and treatment can be assessed from either the societies' point of view or the patients' point of view, depending on patterns of reimbursement in different countries.

3.i.a. Societies' point of view

From a societies' point of view, one needs to take into account both the medical and non-medical costs. The unique epidemiology of keratoconus as a chronic eye disease affecting young, economically active patients entails that keratoconus may result in productivity loss. For instance, it is 'good clinical practice' to suspend rigid CL wear 3 weeks prior to corneal imaging in order to reliably assess progression. Provided patients do comply with this demand, it will inevitably impair their economic performances during this time. Other contact lens related complications (such as lens overwear, infectious keratitis, loss of a lens etc.) may also negatively impair the economic performance of this population. Saunier et al. examined 550 French keratoconus patients: in their case series almost 5% of participants reported having changed their job because of keratoconus, 7.8% received keratoconus-related disability, and 12.5% reported having difficulties with activities of daily living and are considered dependent.(109) To our knowledge, this aspect has not been assessed further in a keratoconus population.

The only article included in this systematic review that estimates the lifetime economic burden of keratoconus was published by Rebenitsch et al. They used a Markov-model to estimate the lifetime cost of keratoconus care when compared with the lifetime cost of myopia. This was estimated at $25,168, or equal to an annual cost of $653 per patient with keratoconus, over and above the cost of routine vision care. Even though these estimations were made with a high degree of uncertainty, this study shows that keratoconus represents a significant public health

concern.(47) However, as mentioned above, the non-medical costs (e.g. cost of productivity loss) are not included in this estimation; which would mean the annual cost of $653 per patient is an under-estimation.

Furthermore, health utilities – as used in cost effectiveness analyses – are typically based on the VA of the better-seeing eye, irrespective of the type of optical correction needed to achieve it. The impact of a patient's dependence upon visual aids (particularly specialty CL) on the quality of life in keratoconus patients remains to be investigated.

Lastly, we were unable to find studies that examine the cost-effectiveness of early detection programs for keratoconus. As described above, arresting keratoconus by means of CXL has proven to be cost-effective.(98-100) Whether a screening program would result in sufficient net benefit for the population to justify the program, will likely be country-dependent.

3.i.b. Patients' point of view

Multiple studies have shown an improvement in quality of life for keratoconus patients treated with contact lenses or CXL (cfr. supra). From the patients' point of view, the cost of diagnosis and treatment, and whether these are reimbursed by public health systems or private insurance, can be an important factor in the decision to proceed with treatment. In Brazil, for example, CXL is available to all citizens or residents; hoping to prevent at least 90% of the keratoplasties in keratoconus patients, and thus saving the Brazilian public health system over US$ 1,5 million per year.(110) The total cost per cross-linking treatment in the Netherlands, including preoperative assessment and follow-up during 1 year, was calculated by Godefrooij et al. at €1,754.06 (± 177.23) or US$1,929.47 (± 194.95).(111)

In Belgium, CXL is not reimbursed by public health insurance to date. It would by all means be unethical to screen for KC in order to halt progression by performing CXL early in the disease continuum, without reimbursing this treatment.

3.i.c. Discussion

Due to insufficient economic data and studies, incorporating both medical and non-medical costs in the care for keratoconus patients, it is not possible to calculate or estimate the cost-effectiveness of (early) detection programs. Since cross-linking in itself is cost-effective, it would be interesting to further research possible screening strategies. The cost of case-finding will greatly vary depending on the screening strategy used (e.g. screening based on VA and automated refraction versus topographic/tomographic screening). Countries that would

consider keratoconus screening programs in the future, should consider incorporating cross-linking and other treatment options in their national public health insurance system.

3.j. Case-finding should be a continuing process and not a "once and for all" project

Paediatric vision screening programs are well-established in most European countries, with coverage up to > 95% in Austria, Czech Republic, Denmark, Finland, Flanders, Germany, Hungary, Iceland, Luxembourg, the Netherlands, Norway, Serbia, Slovenia, Sweden, and parts of the UK. Since these programs are designed to screen for and treat amblyopia, screening starts early in life (first measurement from 3-7 years old).(112) Considering keratoconus manifests in early adulthood, these programs could not be used as an existing framework to identify KC patients.

Recent reports show an epidemic of myopia in East and Southeast Asia, with a prevalence of myopia around 80-90% in children completing secondary schooling at the age of 17-18.(113) A similar trend, though to a lesser extent, has been reported in Nordic European countries: among 14- to 15-year-old school children in Finland, myopia doubled during the twentieth century to about 21%.(114)

Ideally, vision screening at late adolescent age would target both uncorrected refractive errors and allow detection of early keratoconus. Various screening strategies can be proposed: school-based screening programs at the end of secondary school, screening of candidates undertaking a driving test in order to obtain their driver's license, screening of individuals with certain risk factors (e.g. first-degree family members of KC patients, patients with VKC, patients with connective tissue disorders), etc. The method of screening can vary as well: from visual acuity testing or automated refraction, retinoscopy to look for a scissoring reflex, to topographic or tomographic screening – possibly with smartphone applications or artificial intelligence to reduce costs. Costs will also be determined by the person or organization carrying out the screening examination (ophthalmologist, optometrist, nurse, etc.). A stepped approach - for example by screening all adolescents at the end of secondary school with retinoscopy, and referring those with a positive or suspicious scissoring reflex for topographic corneal imaging – can be considered as well.(72)

Whether a certain screening program will be feasible, effective and cost-effective will be determined by the above choices, and by the prevalence of keratoconus in that region.

To conclude, a quick and very simplified calculation considering keratoconus care in Belgium provides some food for thought. There are 1,298,448 people between the ages of 15 - 25 in Belgium (reference date: 01/01/2018).(115) Using the prevalence data published by Godefrooij et al. (265 KC patients per 100,000 (20)), this would mean there are 3,441 KC patients in Belgium between 15 and 25 years old. Assuming they could all be screened at the price of the honorarium of corneal topography (€ 11.22, as stated by the Belgian national institute for health insurance, RIZIV(116)), and that this would identify each and every one of them, it would cost the Belgian public health care system €14,568,586. Using the cost of CXL as published by Godefrooij et al. (€1,754.06 per patient, for the procedure and 1 year of follow-up), it would cost € 6,035,720.46 to cross-link all Belgian keratoconus patients between 15 and 25 years old. Adding the cost for screening, this sums up to €20,604,306. Even though this calculation is oversimplified; it can provoke a useful discussion concerning the possibility of keratoconus screening.

4. **Final discussion**

The principles of screening as defined by Wilson and Jungner can be applied to keratoconus (screening), as elaborated in table 6.

Table 6: Wilson and Jungner screening criteria, applied to keratoconus

1	The magnitude of the public health impact of keratoconus is disproportionate to its prevalence and clinical severity, and is greater than it may appear to be *prima facie*.
2	There is an accepted treatment for patients with recognized disease.
3	Facilities for diagnosis and treatment are available in developed countries, but may be restricted in developing countries.
4	There is a recognizable subclinical and early symptomatic stage.
5	There is a suitable test or examination, namely topography or tomography.
6	Topography/tomography is a safe and non-invasive diagnostic tool.
7	The natural history of keratoconus is roughly known, yet sufficient and up-to-date details on the evolution of disease are lacking.
8	Disease progression defines the need for treatment, but there is no consensus on specific, quantitative criteria that define progression.
9	The cost of case-finding is currently unknown; however, it should be emphasized that cross-linking in itself has been proven to be cost-effective.
10	No existing screening programs, nor research regarding such programs were identified through this systematic review.

The introduction of corneal cross-linking has revolutionized the care for keratoconus patients, since it is the first and only treatment that has proven to stop disease progression. Screening for subclinical keratoconus - in order to treat these patients as soon as possible - could prevent vision loss and associated loss of vision-related quality of life. This, in turn, could reduce healthcare costs in the long term (e.g. by reducing the number of corneal transplantations). Whether a screening program would result in sufficient net benefit for the population to justify the program, will likely be country-dependent. Further research regarding the feasibility and cost-effectiveness of keratoconus screening programs is needed.

Dutch summary

Doelstelling: Onderzoeken of screenen naar keratoconus aangewezen en nodig is, rekening houdend met de huidige evidentie omtrent vroege detectie en behandeling. De criteria voor verantwoorde screening, zoals opgesteld door Wilson en Jungner voor de Wereldgezondheidsorganisatie, worden hiervoor als leidraad gebruikt.

Methode: Een systematische review van de *Pubmed*, *Cochrane* en *Web of Science* databanken.

Resultaten: Recente artikels tonen aan dat de prevalentie van keratoconus aanzienlijk hoger is dan voorheen werd gedacht. Hoewel keratoconus niet leidt tot blindheid, heeft het wel een belangrijke impact op de levenskwaliteit van veelal jonge en economisch actieve patiënten. De impact van keratoconus op het leven van patiënten is groter dan in eerste instantie gedacht wordt, wanneer men louter zou afgaan op de prevalentie en klinische ernst. Zodoende heeft keratoconus een niet te onderschatten financiële en economische impact, zowel binnen als buiten de gezondheidszorg.

Methodes voor corneale beeldvorming, waaronder topografie, zijn de laatste decennia geoptimaliseerd; en zijn in staat keratoconus te diagnosticeren in een subklinisch stadium. Het ultieme behandeldoel is de visus van keratoconuspatiënten zolang als mogelijk te vrijwaren of zelfs te verbeteren, en als dusdanig de impact op hun levenskwaliteit zo beperkt mogelijk te houden. Hoewel er tot heden geen definitieve behandeling mogelijk is, betekende de ontwikkeling van corneale cross-linking een ware revolutie in de zorg voor keratoconuspatiënten. In het verleden waren enkel behandelopties voorhanden om het zicht van keratoconuspatiënten te verbeteren (zoals brillen, contactlenzen, of hoornvliestransplantaties), maar dankzij cross-linking kan de progressie van keratoconus nu afgeremd of zelfs gestopt worden. Studies tonen aan dat cross-linking inderdaad leidt tot een vermindering van het aantal hoornvliestransplantaties, en dat het bovendien een kosteneffectieve behandeling is.

Conclusie: Vroege detectie van keratoconus is primordiaal; opdat de voordelen van stabilisatie van progressieve ziekte (dankzij cross-linking) optimaal benut kunnen worden. Programma's ter screening naar keratoconus zijn op heden niet geïmplementeerd, en onderzoek naar dergelijke programma's is schaars. Er zijn onvoldoende gegevens beschikbaar om in te schatten of screening naar keratoconus een gunstige kosten-batenanalyse zou hebben. Verder

onderzoek in dit gebied is dan ook aangewezen teneinde het gebruik van cross-linking te optimaliseren.

Addendum 1: Search strategy

Pubmed search last updated on 23/02/2019: English, keratoconus AND (screening OR cost OR cost-effectiveness OR epidemiology OR natural course OR quality of life), excluding articles on diagnosis only by adaptation of advanced search details to: ("keratoconus"[MeSH Terms] OR "keratoconus"[All Fields]) AND (("screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "screening"[All Fields] OR ("early"[All Fields] AND "detection"[All Fields]) OR "early detection"[All Fields]) OR ("economics"[Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR ("cost-benefit analysis"[MeSH Terms] OR ("cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR ("cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost effectiveness"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms]) OR (natural[All Fields] AND course[All Fields]) OR ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]))
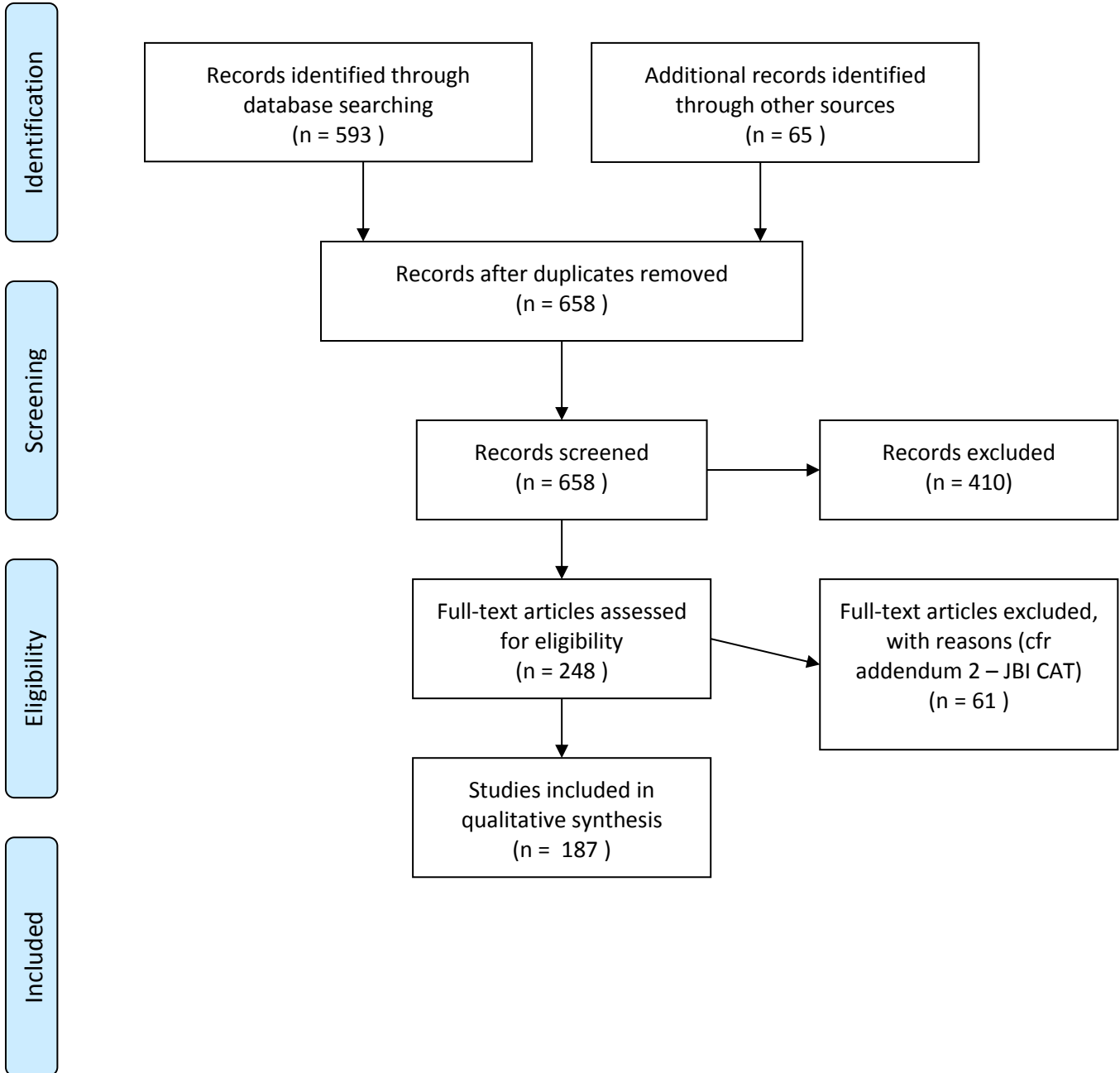
PRISMA 2009 Flow Diagram

Addendum 2: JBI Critical Appraisal Tool for Quality assessment of articles

Example of JBI appraisal tool, applied for prevalence/incidence studies

Using JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. *Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data*. Int J Evid Based Healthc. 2015;13(3):147–153.

Author	Title	Journal	Year	Remarks	Include	Q1: Was the	Q2: Were	Q3: Was the	Q4: Were t	Q5: Was t	Q6: Were	Q7: Was t	Q8: Was the resp…)	Q9: Was t
ak-Nielsen, S., Re	A nationwide population-b	Acta ophthalmologica	2018		Y	Y	Y	Y	Y	Y	U/NA	U/NA	Y	U/NA
Assiri, A. A., Yous	Incidence and severity of ke	The British journal of o	2005		Y	Y	N	U/NA	N	Y	N	U/NA	Y	U/NA
Cozma, I., Atherl	Influence of ethnic origin o	Eye (London, England)	2005		Y	Y	N	U/NA	N	Y	U/NA	U/NA	Y	U/NA
El-Khoury, S., Abt	Pediatric Keratoconus in a T	Journal of refractive su	2016		Y	Y	N	Y	Y	Y	Y	U/NA	Y	U/NA
Georgiou, T., Fun	Influence of ethnic origin o	Eye (London, England)	2004		Y	Y	Y	U/NA	Y	Y	U/NA	U/NA	Y	Y
Godefrooij, D. A.,	Age-specific Incidence and	American journal of op	2017		Y	Y	Y	Y	Y	Y	U/NA	U/NA	Y	Y
Gokhale, N. S.	Epidemiology of keratocon	Indian journal of ophth	2013	Short review	N	U/NA	U/NA	U/NA	U/NA	U/NA	U/NA	U/NA	U/NA	U/NA
Hashemi, H., Beir	Prevalence of keratoconus	Cornea	2013		Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Hashemi, H., Hey	High prevalence and familii	Ophthalmic & physiolo	2018		Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Hashemi, H., Kha	Topographic Keratoconus is	Ophthalmic epidemiol	2013	No FT available	N									
Hashemi, H., Kha	The prevalence of keratoco	Ophthalmic & physiolo	2014		Y	Y	N	Y	Y	Y	Y	U/NA	Y	Y
Jonas, J. B., Nang	Prevalence and association:	American journal of op	2009	No topography!	Y	Y	Y	Y	Y	Y	N	N	Y	Y
Kennedy, R. H., B	A 48-year clinical and epide	American journal of op	1986		Y	Y	N	U/NA	Y	Y	Y	U/NA	Y	Y
Millodot, M., Shn	Prevalence and associated I	Ophthalmic epidemiol	2011	No VA reported	Y	Y	Y	N	Y	Y	Y	Y	Y	U/NA
Nielsen, K., Hjort	Incidence and prevalence o	Acta ophthalmologica S	2007	Estimation based	Y	Y	U/NA	Y	Y	Y	U/NA	U/NA	N	U/NA
Owens, H. and Gc	A profile of keratoconus in	Cornea	2003		Y	Y	Y	N	Y	Y	Y	Y	Y	U/NA
Pearson, A. R., So	Does ethnic origin influenc	Eye (London, England)	2000		Y	Y	N	U/NA	Y	Y	U/NA	U/Na	Y	U/NA
Reeves, S. W., Ell	Keratoconus in the Medica	Cornea	2009		Y	Y	Y	Y	N	Y	U/NA	U/NA	Y	U/NA
Rivera, L. and Me	Keratoconus in Puerto Rico	Boletin de la Asociacio	2004	No FT available	N									
Torres Netto, E. A	Prevalence of keratoconus	The British journal of o	2018	No clinical exami	Y	Y	Y	Y	Y	Y	N	Y	Y	U/NA
Ziaei, H., Jafarina	Epidemiology of keratocon	Cornea	2012		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

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