



## City Research Online

### City, University of London Institutional Repository

---

**Citation:** Stanojcic, N., Hull, C. & O'Brart, D. P. S. (2019). Clinical and material degradations of intraocular lenses: A review. *European Journal of Ophthalmology*, 30(5), pp. 823-839. doi: 10.1177/1120672119867818

This is the accepted version of the paper.

This version of the publication may differ from the final published version.

---

**Permanent repository link:** <https://openaccess.city.ac.uk/id/eprint/23397/>

**Link to published version:** <https://doi.org/10.1177/1120672119867818>

**Copyright:** City Research Online aims to make research outputs of City, University of London available to a wider audience. Copyright and Moral Rights remain with the author(s) and/or copyright holders. URLs from City Research Online may be freely distributed and linked to.

**Reuse:** Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

---

---

---

City Research Online:

<http://openaccess.city.ac.uk/>

[publications@city.ac.uk](mailto:publications@city.ac.uk)

---

1 TITLE PAGE

2

3

4 **Clinical degradations of intraocular lens materials: A review of**  
5 **types, causes and related factors**

6

7 Nick Stanojcic<sup>1,2</sup> FRCOphth MCOptom, Christopher Hull <sup>3</sup>, David P.S. O’Brart<sup>1,2</sup>  
8 MD(Res) FRCS FRCOphth DO RefCert(RCOphth)

9

10

11 <sup>1</sup> Department of Ophthalmology, Guy’s and St. Thomas’ NHS Foundation Trust, Lambeth  
12 Palace Road, London SE1 7EH

13 <sup>2</sup> King’s College London

14 <sup>3</sup> School of Health Science, Division of Optometry and Visual Sciences, City University,  
15 Northampton Square, London EC1V 0HB

16

17 Corresponding author: Professor David O’Brart, Kings College London Frost Eye Research  
18 Unit, Department of Ophthalmology, St Thomas’ Hospital, London SE1 7EH.

19 Email: David.obrart@gstt.nhs.uk

20

21

22

23 **Key words: Glistenings, intraocular lens implants (IOLs)**

24

25

26

27 **Short title: IOL material degradations**

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

1 **Abstract**

2  
3 **Purpose:** To review the published scientific literature concerning clinical and material  
4 degradations of intraocular lenses (IOL) after implantation in cataract surgery.  
5

6 **Methods:** A search was undertaken using the following databases: CENTRAL (including  
7 Cochrane Eyes and Vision Trials Register; The Cochrane Library: Issue 2 of 12, February  
8 2019), Ovid Medline(R) without Revisions (1996 to February Week 2 2019), Ovid Medline(R)  
9 (1946 to February Week 2 2019), Ovid Medline(R) Daily Update Feb 19, 2019, Medline and  
10 Medline Non-Indexed Items, Embase (1980 to 2019 week 07), Embase (1974 to 2019  
11 February 19), Ovid Medline(R) and Epub Ahead of Print, in-Process & Other Non-Indexed  
12 Citations and Daily (1946 to February 19, 2019), Web of Science (all years), the *meta*Register  
13 of Controlled Trials (*mRCT*) ([www.controlled-trials.com](http://www.controlled-trials.com)), ClinicalTrials.gov  
14 ([www.clinicaltrial.gov](http://www.clinicaltrial.gov)) and the WHO International Clinical Trials Registry Platform (ICTRP)  
15 ([www.who.int/ictcp/search/en](http://www.who.int/ictcp/search/en)). Only published articles in English were selected. Search  
16 terms/keywords included 'IOL' or 'intraocular lens', combined with: 'opacification',  
17 degradation, glistenings, nanoglistenings, whitening, transmittance, light scatter,  
18 discolouration/discoloration, performance, quality, material, biocompatibility, calcification,  
19 explantation, ultraviolet/UV radiation. Relevant in-article references not returned in our  
20 searches were also considered.  
21

22 **Results:**

23 After review of the available articles, the authors included 126 publications in this review,  
24 based on the quality of their methodology and their originality. The studies included in this  
25 review were randomized controlled trials, cohort studies, case-controlled studies, case  
26 series, case reports, laboratory studies and review papers. Differing material degradations  
27 of IOLs have been described and their associated pathophysiology studied. Reported  
28 anomalies include photo-chemical alterations, water vacuoles, internal and surface calcific  
29 deposits, surface coatings and discolouration. The nature of such changes has been shown  
30 to depend on the type of IOL material used and/or manufacturing processes and storage  
31 conditions employed. Changes in the IOL can also be influenced by surgical technique, co-  
32 existing ocular pathologies and topical and systemic medications. The clinical significance of  
33 these degradations is variable, with some resulting in significant visual disturbance and the  
34 need for IOL explantation and others producing only minimal visual impairments. Failure to  
35 recognise the precise nature of the problem may lead to unnecessary laser capsulotomy  
36 procedures.  
37

38 **Conclusions:** Clinical degradations of IOLs are uncommon but have been reported following  
39 the implantation of IOLs made of differing biomaterials. Their correct identification and  
40 thorough investigation to determine the underlying cause is necessary for optimal patient  
41 management and the prevention of such problems. Choosing a lens made of a particular  
42 material may be important in patients with certain ocular conditions.  
43  
44  
45  
46  
47

## 1 Introduction

2

3 Cataract surgery is the commonest surgical intervention in the developed world, with more  
4 than a million such surgeries being conducted per annum in the US, 350,000 in the UK and  
5 20 million world-wide <sup>1</sup>. With modern surgical techniques, visual and refractive outcomes  
6 are excellent with almost 95% of eyes achieving 0.3LogMar corrected acuity or better. <sup>2</sup> As  
7 such, not only is it the most common surgical intervention but also one of the most  
8 successful, with increasingly high outcome expectations <sup>3</sup>.

9

10 Amongst the many innovations that have contributed to the superior outcomes of modern  
11 cataract surgery, the development of the intraocular lens (IOL) implant is of paramount  
12 importance. The concept of replacing the cataractous lens in cataract surgery with a  
13 prosthetic implant to improve unaided visual acuity and reduce dependence on spectacles,  
14 was first proposed by Sir Harold Ridley who implanted the IOL on the 8<sup>th</sup> February 1950 at  
15 our unit, St. Thomas' Hospital, in London <sup>4</sup>. These initial lenses were manufactured by  
16 Rayner Ltd (Worthing, UK) and made of Perspex CQ polymethylmethacrylate (PMMA). This  
17 material was apparently chosen as Sir Harold had noted that it was inert after seeing Royal  
18 Air Force personnel with pieces of intraocular Perspex from shattered canopies in World  
19 War II <sup>4</sup>.

20

21 Any IOL, implanted during cataract surgery needs to meet certain basic criteria such as being  
22 biocompatible, causing no inflammation or tissue reaction either in the short (months),  
23 medium (years) or long-term (decades), have excellent optical properties to restore vision  
24 and maintain its clarity and shape. Whilst clinical and material degradations of IOLs are  
25 uncommon, they have been reported and may cause significant visual impairment,  
26 necessitating lens explantation. Several types of degradations including photo-chemical  
27 material alterations, surface precipitations, depositions with the IOL material itself, water  
28 vacuolation (glistenings), surface coatings and discolouration have been described.  
29 Investigation of these changes show them to be typically related to the type of IOL material  
30 used and/or the manufacturing process to create such implants. Such conditions need to be  
31 recognized not only to avoid unnecessary laser capsulotomies, which may make any  
32 subsequent lens explantation problematic, but also to limit the future occurrence of such  
33 problems. The purpose of this review is to describe the clinically apparent material  
34 degradations that can occur in IOLs, how and why they have occurred and their typical  
35 clinical consequences and management.

36

37

## 38 Degradation/opacification/discolourations within the IOL

39

### 40 Photochemical material degradations of PMMA IOLs

41 The first IOLs were manufactured from PMMA. <sup>4</sup> This material appeared to be  
42 biocompatible and has been successfully used in cataract surgery for almost seven decades.  
43 Indeed, whilst in modern small-incision cataract surgery, rigid PMMA IOLs have been  
44 superseded by foldable silicone and acrylic polymers, they are still implanted as sulcus  
45 lenses and often routinely in the developing world, where phacoemulsification small-  
46 incision surgery may not be available.

1  
2 In 2002 Apple et al.<sup>5</sup> reported 25 cases in 18 patients of late-postoperative degeneration  
3 (typically over 10 years) of three-piece posterior chamber PMMA IOLs of which 10 were  
4 explanted due to visual loss. They documented spherical, white-brown crystalline  
5 opacifications within the optic of the IOL, composed of compressed, degenerated PMMA  
6 surrounded by an outer clearer area, which they described as “snowflake-like”. This  
7 condition occurred in lenses from more than one manufacturer but in some cases was  
8 restricted to certain lot numbers. Since this time other investigators have documented  
9 similar cases<sup>6-11</sup>. They also typically occurred several years after implantation, are present in  
10 the central and mid-peripheral zones of the optic with a clear zone around the optic edge,  
11 which is the portion covered by iris. The anomalies are usually focal with intervening areas  
12 of clarity, but occasionally can coalesce to form a confluent area of opacification. These  
13 opacities are not on the surface but within the anterior third of the substance of the optic  
14 and on X-ray spectroscopy the lesions are made of non-organic material<sup>5-7</sup>. They do not  
15 disappear when the lens is explanted and dried, which distinguishes them from glistenings  
16 (described later), which are typically small water filled vacuoles. However, while these  
17 snow-flake lesions are described as “dry”, water does collect within the affected area upon  
18 hydration, presumably from associated surface cracks and this can worsen the opacification  
19 <sup>7</sup>.

20  
21 Based on the findings described above, it has been postulated that the changes may be due  
22 to chronic light exposure causing material degradation of the PMMA. The exact nature of  
23 this material photo-chemical degradation is unknown and requires further investigation, but  
24 Werner et al.<sup>6</sup> have suggested that possible causes might have been insufficient post-  
25 annealing of the cured PMMA polymer, excessive thermal energy during curing causing  
26 voids in the polymer matrix, non-homogeneous distribution of the ultraviolet  
27 chromospheres and/or possible poor filtration of pre-cured monomeric components. It is  
28 unlikely that this degeneration will represent a significant problem in the future, as the  
29 majority of these lenses were implanted in the 1980s to early 1990s, so the majority of  
30 patients are now deceased. In addition, manufacturing processes have changed over the  
31 past three decades and modern PMMA lenses are mostly produced by lathing, which  
32 eliminates the possible causative steps postulated above.

33  
34

## 35 **Glistenings**

36  
37 Glistenings are small water-filled vacuoles within the IOL material (Figure 1). They are  
38 reported to be between 1 and 30 micrometers ( $\mu\text{m}$ ) in size and are thought to occur when  
39 water permeates micro-channels within the IOL material and forms small inclusions<sup>12-14</sup>.  
40 Due to the difference between the refractive index of the glistenings and the IOL material,  
41 they act as refractile particles that glisten on slit lamp examination. The first reports of  
42 glistenings date to 1984 and were described by Dr. Norman Ballin in a ‘Surgidev Leiske’ IOL  
43 with a hydrophobic poly (methyl methacrylate) optic<sup>15</sup>. He later acknowledged credit for  
44 the actual initial observations of glistenings to Dr John Pearce, who had observed them  
45 several years earlier (J. Pearce, MD, "Glistenings Observed in Injection-moulded Optics"  
46 [letter], Ocular Surgery News, October 15, 1985)<sup>15</sup>.

47

1 Whilst most reports of glistenings have been in hydrophobic acrylic lens materials <sup>16-19</sup>, they  
2 have also been reported in PMMA <sup>17, 20</sup> silicone <sup>17, 21</sup> and hydrophilic acrylic IOLs <sup>22</sup>. Tognetto  
3 et al. <sup>16</sup>, while investigating glistenings prospectively in a series of foldable IOLs, found them  
4 to be present in silicone (CeeOn Edge 911A, Pharmacia & Upjohn, NJ, Bridgewater, USA and  
5 SI-40NB; Allergan, Irvine, CA, USA), hydrophilic acrylic (ACR6D, Corneal®, Corneal  
6 Laboratories, Pringy, France, Hydroview H60M, Bausch and Lomb Surgical, Rochester, NY,  
7 USA and Stabibag, IOLTECH laboratories, Carl Zeiss Meditec Inc, Germany), and hydrophobic  
8 acrylic (AcrySof, Alcon Laboratories, Fort Worth, TX, USA and Sensar ,AMO, Santa Ana, CA,  
9 USA) IOLs. However, the hydrophobic acrylic 'AcrySof' group had a higher percentage and a  
10 greater density of glistenings than the other IOLs studied <sup>16</sup>. Similarly, Rønbeck, followed  
11 patients implanted with three different IOL materials for 12-years and found glistenings in  
12 all three IOLs but they were more prevalent in the hydrophilic acrylic lenses (AcrySof  
13 MA60BM), than in the silicone (SI-40NB, AMO) or heparin-surface-modified PMMA IOLs  
14 (8090C, Pharmacia & Upjohn) <sup>17</sup>.

15  
16 The incidence of glistenings varies between published studies. In AcrySof IOLs, Davison <sup>23</sup>  
17 reported an 11% incidence of glistenings in the AcrySof SA30AL and 0% in the AcrySof  
18 SA60AT model (Alcon Laboratories Inc, Fort Worth, TX, USA) albeit at only 3 months, while  
19 Waite and Faulkner <sup>24</sup> reported a 100% incidence in AcrySof SA60AT and SN60AT models  
20 and Leydolt et al.<sup>25</sup> a 97% incidence in AcrySof SN60WF IOLs at 3 years. Kahraman et al.<sup>26</sup>  
21 found that the presence of glistenings increased from 66% at 1 year to 86% at 3 years and  
22 was 100% at 5 years post-implantation of the AcrySof SA60AT IOL. This was similar to  
23 Tognetto et al.<sup>16</sup> who documented an increase in the incidence of glistenings in AcrySof IOLs  
24 with time, while interestingly they seemed to stabilize after 6 months in IOLs composed of  
25 other materials.

26  
27 This increase in glistening with time in AcrySof IOLs has been reported in several studies <sup>27-</sup>  
28 <sup>31</sup>. Dhaliwal et al. <sup>27</sup> identified that in a series of AcrySof IOLs, glistenings developed within  
29 weeks after implantation, but in some patients the number of glistenings reduced with time.  
30 Christiansen et al. <sup>13</sup> found no statistically significant increase in glistenings over a four-year  
31 follow-up period, although there was a positive trend. Colin et al.<sup>28</sup> in a retrospective study  
32 of AcrySof SN60AT, SN60WF, SA60AT IOLs found stabilisation of glistenings over time, with  
33 over 2 years follow up in many eyes. More recently, Johansson <sup>29</sup>, found that glistenings  
34 developed in AcrySof SN60WF IOLs, with an increase between 2 and 3 years after  
35 implantation, with as part of this randomized, controlled study, only a small number of  
36 glistenings seen in hydrophobic acrylic ZCB00 IOLs (AMO, Santa Ana, CA, USA) with no  
37 increase in their number in these lenses with follow-up. Similarly, Moreno-Montanes <sup>30</sup>  
38 reported that frequency and intensity of glistenings in AcrySof MA30BA IOLs increased with  
39 time up to 30 months after surgery and Behndig et al. <sup>31</sup>, with Scheimpflug photography,  
40 documented an increase in glistenings number with time with a mean follow-up time of  
41 105+/-33months (range 21 to 137 months).

42  
43 Two main theories concerning the development of glistenings in IOLs have been proposed<sup>32</sup>,  
44 namely: water absorption due to environmental temperature change<sup>12</sup>; and osmolarity  
45 change under isothermal conditions <sup>33</sup>. The first theory is based on the observation that the  
46 water absorption rate of polymers changes according to temperature. This theory proposes  
47 that glistenings are a result of IOL material water absorption due to environmental

1 temperature changes<sup>12</sup>. The second theory proposes that a change in the osmolality of the  
2 external environment within the eye can lead to an influx of water into the IOL material  
3 under isothermal conditions<sup>33</sup>. It is of note that the IOL material water content varies in  
4 differing materials. Hydrophobic acrylic polymers generally have a low water content (less  
5 than 0.5%)<sup>34</sup>, as do silicone IOL materials (less than 0.4%)<sup>34,35</sup> and PMMA IOLs (0.4-0.8%)<sup>34</sup>,  
6 while hydrophilic acrylic materials have higher water contents (up to 38% in some  
7 materials)<sup>34</sup>. However, the water content can vary in different environmental and aqueous  
8 solutions and how this may or may not relate to glistenings formation is unknown.

9  
10 AcrySof is composed of a cross-linked polymer network that can absorb significant amounts  
11 of water, which can be increased with temperature changes. Dhaliwal et al.<sup>27</sup>, showed that  
12 glistenings were related to hydration of the acrylic material and that they could be reversed  
13 by drying the IOL for 48 hours. Kato et al.<sup>12</sup> reported that even small changes in temperature  
14 (e.g. 37°C to 34°C) were enough to initiate glistenings formation and proposed that this  
15 occurrence may involve spinodal decomposition of the swollen polymer network, initiating  
16 the formation of microvacuoles consisting of water and loosely packed network chains. Kato  
17 et al.<sup>12</sup> showed that water content of the IOL material increases upon heating and that  
18 glistenings formation occurs upon their cooling, and the latter is also dependent on the rate  
19 of temperature change.

20  
21 Whilst, changes in temperature<sup>12, 27</sup>, equilibrium water content<sup>36</sup>, osmotic changes<sup>33</sup>,  
22 environmental factors<sup>36, 37</sup> and equilibrium water content<sup>14</sup> are important in the  
23 development of glistenings in IOLs, other factors are also relevant. Control of the  
24 polymerisation process, to make it as uniform as possible, appears to play a role<sup>32</sup>, with  
25 surface scattering and glistenings formation found to be more significant with IOLs  
26 manufactured by cast moulding than by lathe cutting<sup>32</sup>. In order to reduce the occurrence  
27 of glistenings in AcrySof IOLs, Alcon Inc. altered the manufacturing process in the early  
28 2010s, implementing tight environmental and process controls in the formulation, cast  
29 moulding and curing operations<sup>38-39</sup>. Subsequently, Miyata et al. found that surface light  
30 scattering due sub-surface nano-glistenings was significantly reduced<sup>38</sup> and Thomes and  
31 Callaghan found that the percentage of IOLs with glistenings, induced in the laboratory, with  
32 a density of >100 per mm<sup>2</sup> was 99% in the 2003 AcrySof IOL models and only 4.8% in  
33 AcrySof IOLs manufactured in 2012.<sup>39</sup>

34  
35 Breakdown of the blood aqueous barrier (BAB) and intraocular inflammatory factors may  
36 also be associated with the development of glistenings. Dick et al.<sup>40</sup> found that with AcrySof  
37 IOLs the incubation of these lenses in fluid containing serum increased vacuolation. They  
38 proposed that lipids within the serum can reach the cavitations in the acrylic material and  
39 become visible, as the space between the cross-linked molecule chains in the AcrySof  
40 polymer enhances the deposition of such hydrophobic substances. It is of note that an  
41 association between glistenings and diabetes mellitus, where there is often a breakdown of  
42 the BAB, has been documented<sup>32, 40</sup>. Werner et al., reported an incidence of glistenings in a  
43 group of diabetic patients of 76% compared to 47% in non-diabetic patients<sup>32</sup>. Indeed, they  
44 found that 21% of their so called higher-grade glistenings were in those patients with  
45 diabetes compared with 5.5% in non-diabetics<sup>32</sup>. Interestingly, Colin et al.<sup>28</sup> documented an  
46 association between the incidence of glistenings and glaucoma, which it has been  
47 postulated may be due to preservatives in topical anti-glaucoma medicines that can lead to

1 the breakdown of the BAB. In addition, uveitis<sup>41</sup> and post-operative inflammation<sup>37</sup>, which  
2 both result in BAB breakdown, have been linked with glistenings formation. Indeed,  
3 complex/prolonged surgery, which typically results in a higher degree of inflammation and  
4 BAB breakdown, has been found to be associated to glistenings occurrence<sup>37</sup>.

5  
6 Other suggested factors that might be associated with the development of glistenings  
7 include the 'tightness' of the capsular bag<sup>42</sup> and the presence and degree of anterior  
8 capsular opacification (ACO)<sup>29</sup>. This was postulated, as in a few randomized, controlled  
9 studies the ZCB00 IOL (AMO, Santa Ana, CA, USA), which is made of a hydrophobic acrylic  
10 polymer, appeared to have much less propensity to glistenings development than similar  
11 Alcon AcrySof IOLs, also manufactured from an acrylic polymer. As the ZCB00 IOL has an  
12 elevated anterior rim, which lifts the anterior capsule from the anterior optic surface,  
13 appearing to result in less anterior capsular fibrosis than that seen with the AcrySof lenses  
14 that are biconvex, it was then suggested that the occurrence of ACO and capsular bag  
15 'tightness' might be important in glistenings creation<sup>26,29</sup>.

16  
17 Finally, a positive correlation between higher IOL power and the presence of glistenings has  
18 been established<sup>37,43</sup>, although this relationship appears intuitive as higher-powered IOL  
19 are thicker with a larger volume of material, and therefore may have a greater chance of  
20 developing degradations.

21  
22 Clinical studies investigating the association between glistenings and visual performance  
23 have produced conflicting results. Whilst most have demonstrated no significant effect of  
24 glistenings on vision<sup>24,28,43-47</sup> a few have found that high numbers of such vacuoles within  
25 IOLs impair visual performance<sup>13,48</sup>, especially high spatial frequency contrast sensitivity<sup>27,</sup>  
26<sup>49,50,51</sup>. Waite et al.<sup>24</sup> in a longitudinal study of up to 3 years in AcrySof IOLs, found no  
27 correlation with corrected distance visual acuity (CDVA) and glare testing and glistening size  
28 or density, although they felt that the effects of glistenings on high spatial resolution  
29 contrast acuity required further investigation. Mönestam et al.,<sup>43</sup> in a series of 103 patients  
30 with 10-year follow-up, documented no significant impact between glistenings grade and  
31 vision, including low contrast visual acuity at 10% and 2.5%. Colin et al.<sup>28</sup> in a series of 157  
32 of 260 eyes with glistenings and up to 7 years follow-up in some eyes, found no association  
33 between glistenings and visual acuity. The same research group in a further study of yellow-  
34 tinted AcrySof IOL in 111 eyes of 74 patients<sup>44</sup>, reported that although there was a trend  
35 toward decreased visual acuities at higher glistening grades, there were no significant  
36 differences in CDVA between their glistening severity groups. Chang et al.<sup>45</sup> in 80 patients in  
37 a randomized, controlled trial at 5-7 years after surgery stated that glistenings were not  
38 correlated with CDVA and confirmed this in a follow up study of the patients at 9 years<sup>46</sup>.

39  
40 However, Christiansen et al.<sup>13</sup> in 42 eyes implanted with AcrySof IOLs found that Snellen  
41 acuity in eyes with severe glistenings grades was statistically less than those with mild  
42 glistenings. Xi et al.<sup>49</sup> in 120 eyes implanted with AcrySof IOLs at 2 years following surgery  
43 found that while there was no statistical correlation between glistening grades and unaided  
44 distance visual acuity (UDVA), CDVA and contrast sensitivity, sub-analysis did show more  
45 eyes with severe glistening grades had reduced contrast sensitivity at high spatial frequency.  
46 Henriksen et al.<sup>48</sup>, in 79 eyes with glistenings in AcrySof IOLs showed a correlation between  
47 glistening size and density and distance acuity and contrast acuity with glare. Gunenc et al.

1 <sup>50</sup> in 34 eyes with glistenings in a series of 94 eyes found no statistically significant difference  
2 in visual acuity and contrast sensitivity at low or medium spatial frequencies between eyes  
3 with glistenings and those without, although they did document a difference at high spatial  
4 frequency. Schweitzer et al. <sup>51</sup> in 67 pseudophakic eyes in 47 patients with co-existing  
5 glaucoma not only showed that a higher number of topical glaucoma medication were  
6 associated with a higher glistening severity grade (probably due to breakdown of the BAB as  
7 discussed above), but that higher grades of glistenings density had lower mean contrast  
8 sensitivity values at high spatial frequencies, although there was no difference in CDVA.

9  
10 It seems therefore that in most eyes glistenings are likely to have little effect on visual  
11 performance, except in some eyes with very high densities of glistenings, when high spatial  
12 contrast acuity is preferentially affected. It is of note, however, that most of these studies  
13 have used subjective glistening grading systems with the methods for using these scales  
14 often unclear <sup>13, 14, 27, 44,47, 50</sup>. Whilst the number of glistenings is likely to be important, size  
15 and distribution might also be expected to affect vision. Most reported glistenings grading  
16 systems have a 3-4-point ordinal scale, which might lack sensitivity depending on the grade  
17 boundaries and implementation. In addition, and importantly, published studies typically  
18 rely on subjective counting and grading of glistenings 'per field' of slit lamp <sup>13,52</sup> or 'in the slit  
19 lamp' <sup>28, 44</sup> without defining the regions of the IOL being studied or the illumination  
20 parameters used when viewing the glistenings. Clearly, such lack of standardization will  
21 introduce variability in glistenings assessment that could provide a partial explanation for  
22 the differences in the results of studies described above using subjective assessment. In  
23 addition, a further important variable will be differences in the visual tests employed in  
24 these studies and their sensitivities and the existence in some eyes of visually significant co-  
25 morbidities. To address such issues, in a recent study the authors<sup>47</sup> using a defined,  
26 reproducible, standardized 8-point ordinal scale of glistenings density and an array of  
27 computerized visual function tests, including contrast sensitivity and forward scatter,  
28 investigated the visual effects of glistenings in vivo in 34 eyes implanted with AcrySof IOLs  
29 (SA60AT; Alcon Laboratories Inc., Fort Worth, TX, USA) in patients with no other ocular or  
30 neurological morbidities. They found no association between glistening grades and visual  
31 function<sup>47</sup>.

32  
33 Additional evidence that supports the results of studies that demonstrate glistenings have  
34 little effect on vision comes from explantation rates. In 2013, 67 cases of IOL glistenings  
35 associated with visual impairment were reported to Canadian government, one of which  
36 was said to have been explanted <sup>53</sup>. Similarly, Raven et al. <sup>54</sup> reported a case where an  
37 AcrySof IOL required explantation due to intractable symptoms in bright light and when  
38 driving at night. Dogru et al. <sup>55</sup> also reported such a case, although it is of note that this  
39 patient developed glistenings several months after neodymium:YAG laser capsulotomy and  
40 this may have contributed to development of glistenings by disrupting the IOL material  
41 integrity. Similarly, Werner et al. <sup>56</sup> reported a case of explanted 3-piece AcrySof IOL  
42 because of glistenings that impaired fundus visualisation. Because of co-existent retinal  
43 disease, the effects of glistenings on visual function could not in this case be ascertained. It  
44 appears therefore that glistenings can, albeit very rarely, cause clinically significant changes  
45 in vision. Hopefully, however, with the improvement in AcrySof IOL manufacture,  
46 introduced in the early 2010s and the development of newer 'glistenings free' hydrophobic  
47 acrylic polymers such problems may be negated.

## Post-operative degradation/opacification of silicone IOLs

Werner et al.<sup>57</sup> reported on 6 cases of 3-piece Silicone IOLs (SI-40NB, Allergan, Westport, Ireland) which required explantation due to early (hours after surgery) opacification and associated visual loss. The lenses had been implanted in 4 different locations in Brazil and France, with the Brazilian lenses stored at the same location. The lenses underwent microscopy (including electron microscopy in one case) as well as gas chromatography/mass spectrometry (GC/MS) analysis and/or extraction by isopropyl alcohol or acetonitrile. All lenses had white optic opacification in the hydrated state, becoming transparent on drying. Unusual exogenous chemical compounds were identified, including terpenes and ketones, which are typically found in industrial cleaning agents and fumigants. It was postulated by the authors (although no clear history of chemical contamination could be identified) that spraying of the storage area with cleaning compounds and insecticides caused chemical contamination of the IOLs rendering the silicone material more hydrophilic so the influx of water into the IOL material was rapidly possible after implantation<sup>57</sup>. It is of note that many IOLs are enclosed in semipermeable packages to allow sterilization by ethylene oxide gas, while at the same time being impermeable to infective micro-organisms and contaminants. It is therefore feasible that during cleaning or disinfection of storage rooms, aerosolized solutions might introduce chemicals through the package and onto the IOLs.

Elgohary et al.<sup>58</sup> reported two similar cases of silicone (multifocal) IOLs, with opacification occurring within weeks of surgery. No obvious cause was apparent, and they suggested that possible causes might be the presence of low molecular weight silicone fractions that were not cross-linked during the curing process, large polymer impurities due to inadequate filtering leading to IOL hydration and interaction between silicone and intraoperative or postoperative medications. Tanaka et al.<sup>59</sup> also reported a similar case of a silicone SI-40NB (Allergan, Westport, Ireland) IOL which opacified with a brown haze within 24 hours of implantation, requiring explantation. Microscopic examination of the extracted IOL showed numerous spheroid structures, which the authors proposed may be due to water incorporation into the silicone IOL material.

Milauskas<sup>60</sup> in 1991 reported 15 cases of brownish discolouration of two silicone IOLs, manufactured by IOLAB Corp, Claremont, CA, USA and STAAR Surgical Co., Monrovia, CA, USA, which was documented 15 to 60 months after implantation. Visual acuity was 20/30 or better in all cases and no lenses were explanted. Two similar cases in the same lens type were reported by Koch and Heit in 1992<sup>61</sup>. No cause for this problem was identified, but it could be postulated that it may be due to ingress of water/water vapour into the lens due to anomalies in the manufacturing process. It is of note that the effects on visual performance appeared to be minimal and there have been no further reports in the literature possibly due to improvements in manufacturing techniques.

In 2007 Werner et al.<sup>62</sup> reported 12 cases of late (4 weeks to 2 years) opacification of silicone lenses in the USA. The opacification was generally less than they had observed in their series of early onset (weeks) opacification of silicone IOLs<sup>57</sup>. They undertook GC-MS analysis as in their previous study and found benzophenone in 7 of the 12 IOLs, which may

1 or may not have been implicated. Improvements in the manufacturing process since this  
2 problem was documented seems to have prevented the problem from recurring.

3  
4 Jones and Irwin<sup>63</sup> in 2002 reported a case of 'rose-colour' discolouration of a silicone IOL  
5 (model SI30NB; Allergan Inc., Irvine, CA, USA). This patient had undergone bilateral cataract  
6 surgery several years earlier. This patient had been on Rifabutin therapy for Mycobacterial  
7 infection for over 10 months, which was discontinued after the IOL discolouration was  
8 documented. Corrected visual acuity was 20/20 and there was no perceived visual acuity or  
9 colour discrimination problems by the patient, so the IOLs were not explanted. In a  
10 laboratory investigation<sup>63</sup>, the authors immersed IOLs from 4 different manufacturers  
11 representing 3 materials for 1 week in a concentrated Rifabutin solution. All lenses  
12 remained clear except for the silicone lenses which were discoloured rose, with the  
13 discolouration fully penetrating the lens.

14  
15 In 2007 Werner et al.<sup>64</sup> reported discolouration of a silicone IOL (SI40 NB; AMO, Irvine, CA,  
16 USA) in a patient who presented immediately post-operatively with corneal oedema and a  
17 blue IOL. A 'blue dye' had been used to enhance visualization during capsulorhexis. It was  
18 determined that methylene blue had been used instead of trypan blue in this case staining  
19 the IOL. The IOL was explanted and the corneal oedema resolved within 1 month.  
20 Microscopic analysis of the explanted IOL revealed that its surface and internal substance  
21 had been permanently stained blue. In a separate experiment, the authors immersed IOLs  
22 of differing materials (silicone, hydrophobic acrylic, hydrophilic acrylic, PMMA) in methylene  
23 blue at varying concentrations. All IOLs, except the PMMA lenses were permanently stained,  
24 with the hydrophilic acrylic lenses stained most intensely<sup>64</sup>. Methylene blue is not  
25 appropriate for intraocular usage, with Trypan blue being the appropriate dye for anterior  
26 capsule staining.

27  
28 Katai et al.<sup>65</sup> in 1999 reported a case of 'brown' discolouration of silicone IOLs (STAAR  
29 Surgical Co., Monrovia, CA, USA) in both eyes of the same patient. This patient had been  
30 treated with Amiodarone for 3 years. It was proposed that Amiodarone can cross BAB under  
31 certain conditions, and possibly after vitrectomy, which this patient also underwent in their  
32 left eye, and which resulted in unilateral worsening of discolouration. Contrast sensitivity  
33 and blue colour sensitivity were found to be impaired in this patient's right eye. The authors  
34 proposed that minute particles including water vapour that could not be removed by  
35 filtering may have also caused this brown discolouration.

36  
37 Sathyan et al.<sup>66</sup> reported a non-progressive green discolouration in a silicone IOL (Allergan  
38 SI-40NB, USA). This was documented 6 months after surgery in 2 patients. Contrast  
39 sensitivity without glare was slightly reduced but not the visual acuity and the patients were  
40 asymptomatic. No cause for discolouration has been elucidated. In 2008, Venkatesh et al.<sup>67</sup>  
41 reported a similar case of green IOL discolouration. There were no visual complaints and the  
42 patient had a best-corrected visual acuity of 20/20 with normal colour vision and contrast  
43 sensitivity. The explantation was required and no cause is yet established.

#### 44 45 46 **Opacification/discolourations of hydrophilic acrylic IOLs**

47

1 Werner et al.<sup>68</sup> in 2002 reported a blue discolouration of a hydrogel IOL 'Acqua' intraocular  
2 lens (IOL) (Mediphacos, Belo Horizonte, MG, Brazil). This patient underwent cataract surgery  
3 using Trypan blue 0.1% to stain anterior capsule and presented at 7 days with 'dark and  
4 double' vision, with CDVA of 20/60. After explantation two months later, CDVA improved to  
5 20/25. Microscopic analysis showed dark blue staining, denser in the optic, especially in its  
6 periphery, with the blue discoloration remaining even after 24 hours of immersion in  
7 balanced salt solution. Trypan blue should probably be avoided in cases where a high-water  
8 content IOL, such as hydrophilic acrylic IOLs, is to be implanted and/or complete anterior  
9 chamber irrigation undertaken before lens implantation.

10  
11 Goodal and Ghosh in 2004<sup>69</sup> reported 5 cases with 'total IOL' opacification a single-piece  
12 acrylic hydrophilic IOL (AquaSense IOL, Ophthalmic Innovations Inc., Ontario, CA, USA). In  
13 two cases opacification was mistaken for posterior capsule opacification (PCO) and in one  
14 case for a non-resolving diabetic vitreous haemorrhage. The patients in 5 of these cases had  
15 significant visual deterioration due to total opacification of the IOL more than a year after  
16 surgery and explantation was performed in most cases. After consultation with the  
17 manufacturer, it was suspected that opacification was due to an interaction between the  
18 silicone sleeve, used to hold the IOL in the vial, and the acrylic material of the IOL, which  
19 may have created negative charge resulting in opacification. These IOLs have been  
20 withdrawn.

## 21 **Opacification/dicolourations of hydrophobic acrylic IOLs**

22  
23  
24 Manuchechri et al.<sup>70</sup> described 'brown deposits' in IOLs in a series of pseudophakic, uveitis  
25 patients (54 patients; 71 eyes). These were said to be distinct from glistenings and difficult  
26 to image. The implantation of AcrySof MA60BM hydrophobic acrylic IOLs was strongly  
27 associated with these deposits. This lens is known to be associated with glistenings  
28 formation. One can therefore speculate that these deposits might have been a variation of  
29 glistenings. Albeit, rather than water vacuoles, the vacuoles within these IOLs may have  
30 contained different organic/inorganic material in association with the uveitis documented in  
31 these cases and perhaps topical medications used to treat this condition.

32  
33 More recently, a series of 14 brown discoloured AAB00, ZCB00 and ZMBOO IOLs (Abbott  
34 Medical Optics, USA) was recently reported by Wong et al.<sup>71</sup>. The browning of the IOLs was  
35 noted as early as day 1 post op and as late as 327 days. No patients had loss of lines of  
36 CDVA. However, desaturated Lanthony D15 Hue test was abnormal in 8 of 16 eyes. The  
37 authors were not able to find a clinical cause for the discolouration but suspected it was due  
38 to impurities in the IOL that occurred during the manufacturing process. No patient required  
39 IOL exchange.

40  
41 Twenty years after his first report of brown discolouration in silicone IOLs, Milauskas<sup>72</sup> in  
42 2012, reported brown discolouration of 2 AcrySof (no specific IOL model provided but  
43 author suggested a blue-light filtering IOL) hydrophobic acrylic IOLs and a yellow  
44 hydrophobic acrylic PY-60AD IOL (Hoya Surgical Optics GmbH). The implantation of these  
45 IOLs was between 6 months and 8 years. In some of these IOLs, glistenings co-existed with  
46 discolouration, and the author noted that discolouration occurred around glistenings. He  
47 also concluded that both Alcon and Hoya IOLs used the same blue-filtering agent, and that

1 glistenings may play a role in discolouration of IOLs. Assessment of visual function was  
2 difficult due to multiple patient comorbidities.

## 4 **Surface depositions/degradations/coatings of IOLs**

### 6 **Calcification**

8 The deposition of calcium within tissues, may be either physiological or pathological, and  
9 can also occur on any bio-prosthetic or biomaterial implant in the human body such as heart  
10 valves, blood pumps, intrauterine contraceptive devices, contact lenses, scleral buckles and  
11 IOLs <sup>73</sup>. Neuhann et al.<sup>73</sup> have proposed three possible routes for IOL calcification: primary  
12 calcification which is related to the IOL itself (e.g. the polymer, manufacturing or packaging  
13 process); secondary, that is not only dependent on the IOL but also associated with pre-  
14 existing disease, that may involve breakdown of BAB; and false positive calcification or  
15 pseudo-calcification that occurs due to misdiagnosis of tissue artefacts or incorrect use of  
16 special stains.

18 The pathogenesis of IOL calcification is not fully understood <sup>74</sup>. Two possible mechanisms  
19 have been proposed for calcification of biomaterials: intrinsic (material-dependent) and  
20 extrinsic (host- and cell-dependent) <sup>73</sup>. Extrinsic calcification may be due to foreign body  
21 reaction to the biomaterial and it has been suggested that blood cells, devitalized cells,  
22 bacterial, inflammatory cells or lipids may provide an initial nidus for calcification <sup>73</sup>.

24 IOL calcification has most commonly been associated with surface deposition on hydrophilic  
25 acrylic IOLs <sup>73-74</sup>, but also has been reported in silicone IOLs in the presence of asteroid  
26 hyalosis <sup>75-76</sup>. Wackernagel et al. <sup>75</sup> and Foot et al. <sup>76</sup> in the early 2000s reported opacification  
27 of plate haptic IOLs occurring a few years after cataract surgery in the presence of unilateral  
28 asteroid hyalosis. These lenses were explanted, and white deposits were documented on  
29 the posterior lens surface only. Light microscopy, scanning electron microscopy and  
30 dispersive x-ray spectrometry showed the deposits consisted of calcium and phosphate,  
31 presumably hydroxyapatite. It was hypothesized that this deposited material might be  
32 derived from the asteroid bodies within the vitreous themselves or due to the process that  
33 is responsible for this condition. Werner et al. <sup>77</sup> described a similar case in one eye  
34 implanted with a 3-piece silicone IOL SI30 NB (AMO, Irvine, CA, USA) in a patient with  
35 bilateral asteroid hyalosis. The IOL was explanted, while the other eye in which an acrylic  
36 IOL was implanted did not develop opacities with 6 years of follow-up. More recently,  
37 Stringham et al.<sup>78</sup> (16 eyes) and Espandar et al. <sup>79</sup> (3 eyes) have also described cases with  
38 posterior surface calcification on silicone IOLs in the presence of asteroid hyalosis. In the last  
39 report laser capsulotomy was documented to make IOL explantation/exchange problematic  
40 <sup>77</sup>. While such cases are rare considering the vast numbers of silicone IOLs that have been  
41 implanted, the use of such lenses in the presence of pre-existing asteroid hyalosis needs to  
42 be carefully considered and the selection of an IOL with another material may be prudent.

44 As discussed above IOL surface calcification has most commonly been on hydrophilic acrylic  
45 IOLs <sup>74-75</sup>. Apple et al. <sup>80</sup> and Werner et al.<sup>81</sup> in 2000 were the first to describe calcification in  
46 foldable hydrogel 'Hydroview' IOLs (Bausch and Lomb Surgical, Rochester, NY, USA). Surface  
47 staining of explanted IOLs with Alizarin red, suggested that the deposits on the lens surface,

1 both anterior and posterior, were composed of calcium and phosphates. According to this  
2 group at this time in 2000, there had been 76 cases in 9 centres worldwide with the same  
3 anomaly and in 17 of these cases the IOLs were explanted.

4  
5 There have since been multiple reports in several different hydrophilic acrylic IOL models  
6 from different manufacturers both in the USA and Europe <sup>6, 73, 82-86</sup>. Within the US during the  
7 early 2000s, four major designs of IOLs seem to have had problems with deposits on the  
8 optic surface made up largely of calcium and phosphate: 'Hydroview' (Bausch & Lomb  
9 Surgical, Rochester, NY, USA), 'Memory Lens' (Ciba Vision Duluth, GA, USA), 'SC60B-OUV'  
10 (Medical Developmental Research, Clearwater, FL,) and 'Aqua-Sense' IOLs (Ophthalmic  
11 Innovations International, Claremont, CA, USA) <sup>6, 73, 82-86</sup>. Time to explantation of these IOLs  
12 was approximately 2 years with microscopic analysis, as well as x-ray spectroscopy of  
13 explanted IOLs confirming the presence of calcium and phosphate within the deposits on  
14 the IOL hydrophilic acrylic surfaces <sup>81-86</sup>.

15  
16 The precise patho-physiology of the factors involved in the calcification of these IOLs is yet  
17 undetermined. Dorey et al. <sup>84</sup> using energy dispersion x-ray spectrometry showed that  
18 many of the deposits were composed of calcium and phosphate in an electron-dense  
19 periphery with silicone in the electron-lucent centre. They proposed that the silicone gasket  
20 in the 'Surefold' packaging system, manufactured specifically for the 'Hydroview' IOL, might  
21 be responsible, contaminating the lens with silicone particles on the IOL surface, which then  
22 act as a nidus for calcium deposition <sup>84</sup>. It was of note that the IOLs in packaging prior to  
23 introduction of the silicone gasket did not appear to opacify and that the manufacturer  
24 (Bausch and Lomb) changed packaging to one sealed with a gasket made from a  
25 perfluoroelastomer rather than silicone to negate this problem. Guan et al. <sup>87</sup> and Wu et  
26 al.<sup>88</sup> examined the role of silicone compounds in the calcification of hydrophilic acrylic IOLs,  
27 examining their interaction with long saturated fatty acids. They showed that IOL surfaces  
28 treated with fatty acids, such as behenic acid, present in aqueous humour, calcify in vitro.  
29 They suggested that hydrophobic cyclic silicones adsorbed on the IOL surfaces can interact  
30 with hydrophobic hydrocarbon chains of the fatty acids to create a layer of amphiphiles  
31 which may act as sites of calcification <sup>87</sup>. Werner et al. <sup>86</sup> also demonstrated the presence of  
32 silicone compounds on the 'Memory Lens' IOL and on and within SC60B-OUV and Aqua-  
33 Sense IOLs, suggesting their importance in the development of calcification of these  
34 hydrophilic acrylic lenses as well. Ophthalmic Innovations International ('Aqua-Sense' IOL)  
35 subsequently excluded siloxane silicone elastomers from their IOL packaging components to  
36 address possible contamination problems. In addition to manufacturers removing silicone  
37 compounds from their acrylic hydrophilic IOL packaging, Ciba vision changed its polishing  
38 process of its 'Memory Lens' IOL with which it correlated the opacification problem <sup>82</sup>.  
39 Hunter et al. <sup>89</sup> reported a single case of calcification in a 'Memory Lens' IOL manufactured  
40 after this time, although this was attributed an intrinsic defect in the optic itself and not the  
41 mechanism described above.

42  
43 Gartaganis et al. <sup>90</sup> examined explanted opacified hydrophilic acrylic IOLs, from the 4 types  
44 described above, chemically analysed aqueous humour from eyes in which the IOLs had  
45 been explanted and conducted in vitro experiments. They concluded that the opacification  
46 is due to the deposition of calcium phosphate crystallites, with hydroxyapatite  
47 predominating and the surface hydroxyl groups of the polyacrylic material polymer

1 facilitating surface nucleation and calcific crystalline growth<sup>90</sup>. They also suggested that the  
2 calcium and phosphate may be derived from residual cataractous material and surgical  
3 technique such as cortical clean-up may be of importance, explaining the occurrence of  
4 unilateral cases in patients implanted with the same lens type in both eyes.  
5

6 Since these initial case series and studies and despite changes in manufacturing and  
7 packaging, there have been multiple reports of calcification of other hydrophilic acrylic IOLs  
8 in the past decade, both in cataract surgery and other surgical situations. Werner et al.<sup>91</sup>  
9 published in 2015 a series of 7 hydrophilic acrylic IOLs, 6 designs from 5 manufacturers that  
10 required explantation due to granular calcific surface deposits within the margins of the  
11 capsulorhexis or the pupil on the anterior IOL surface/sub-surface that caused decreased  
12 visual acuity. These deposits had developed in these eyes after the patients underwent  
13 Descemet's stripping endothelial keratoplasty (DSEK) (Figure 2). The authors proposed three  
14 possible causes for this calcification including: direct contact between the intra-cameral air  
15 and hydrophilic acrylic IOLs material; intra-cameral metabolic changes because of the  
16 presence of exogenous substances injected during surgery; and exacerbated inflammatory  
17 reaction with breakdown of the BAB due to the surgical procedure itself<sup>91</sup>. They suggested  
18 that surgeons should be aware of this phenomenon following DSEK and Descemet's  
19 stripping automated endothelial keratoplasty (DSAEK) procedures in pseudophakic patients  
20 with hydrophilic acrylic IOLs and counsel patients accordingly<sup>91</sup>. Similarly, Giers et al.<sup>92</sup>,  
21 reported the occurrence of opacification of 13 hydrophilic IOLs, months to years after  
22 DSAEK and Descemet's membrane endothelial keratoplasty (DMEK), identifying a thin layer  
23 of calcium-phosphate deposition just beneath the central, anterior IOL surface. These lenses  
24 typically required explantation<sup>92</sup>. Such reports suggest that surgeons might be advised to  
25 avoid using hydrophilic acrylic IOLs in patients who are likely to require corneal endothelial  
26 lamellar surgery, such as in eyes with (e.g. Fuchs' endothelial and other corneal endothelial  
27 dystrophies.  
28

29 In addition to the injection of air/gas into the anterior chamber during DMEK/DSAEK  
30 procedure, similar changes have been reported after pars plana vitrectomy (PPV) and  
31 intravitreal gas injection. Recently, Marcovich et al.<sup>93</sup>, reported 11 cases of hydrophilic IOL  
32 opacification, 1 month to 6 years after PPV with gas injection, with calcium and phosphate  
33 deposition on the anterior, central IOL surface in explanted IOLs<sup>93</sup>. They suggested that a  
34 hydrophobic IOL may be preferred when a simultaneous phacoemulsification and  
35 vitrectomy with intravitreal gas being considered. It is of note, however, that there have  
36 been recent case reports of calcification of hydrophobic acrylic IOLs (AcrySof SA60AT; Alcon  
37 Laboratories Inc., Fort Worth, TX, USA) associated with intravitreal gas injection and  
38 retained perfluorocarbon liquid following vitreoretinal surgery, so that this problem is not  
39 entirely related to hydrophilic Acrylic polymers<sup>94</sup>.

40 Aside from air/gas injections, recombinant tissue plasminogen activator (rtPA) has also been  
41 recently reported to cause IOL opacification secondary to calcification in hydrophilic acrylic  
42 IOLs (Rayner C-Flex 570C and Rayner Superflex 620H; Rayner, Worthing, UK). Fung et al.<sup>95</sup> in  
43 a case series of 7 eyes of 7 patients reported IOL anterior surface/subsurface opacification,  
44 which stained positive for calcium salts, within 12 months of the use of rtPA to treat  
45 inflammatory membranes that formed after cataract surgery. They proposed that the rtPA  
46 may have released sequestered calcium from the fibrinous inflammatory membranes and

1 introduced phosphate ions contained in its buffer solution, potentiating calcium  
2 deposition<sup>95</sup>.

3  
4 Other reports of IOL calcification include those by, Tandogan et al.<sup>96</sup> who documented in  
5 2015 a series of explanted opacified 'Euromaxx ALI313Y' and 'ALI313' IOLs (Argonoptics,  
6 Germany) hydrophilic acrylic IOLs. X-ray spectroscopy revealed fine granular surface  
7 deposits made of calcium and phosphate. These IOLs were explanted due to reduced visual  
8 acuity, the reasons for the calcification in these eyes was not elucidated. Similarly,  
9 Zuberbuhler and Carifi<sup>97</sup> in 2012 reported a series of 5 patients with glittering deposits on  
10 the surface of hydrophilic acrylic IOLs (3 C-flex 970C IOLs, Rayner, Worthing, UK, and 2 with  
11 Akreos AO, Bausch and Lomb Surgical, Rochester, USA). Disposable forceps were found to  
12 be the cause of these during injector loading process. None of the patients experienced  
13 visual symptoms. The IOLs did not undergo staining to see if these deposits were calcific<sup>97</sup>.

14  
15 In addition, there have been a number of recent reports concerning calcification in hybrid  
16 hydrophilic acrylic IOLs with hydrophobic surfaces manufactured by Oculentis GmbH, Berlin,  
17 Germany<sup>98-99</sup> (Figures 3a and 3b). Gartaganis et al.<sup>98</sup> reported 6 cases with the Lentis LS-  
18 502-1 IOL, 2 of which had undergone vitreo-retinal procedures. Analysis confirmed the  
19 presence of subsurface formation of calcium phosphate crystalline deposits. Gurabardhi et  
20 al.<sup>99</sup> in 2018 reported the largest series so far (71 eyes, 63 patients) of these calcified acrylic  
21 hydrophilic IOLs with hydrophobic surfaces (LS-502-1, LS-402-1Y, LS 312-1Y, LS-313-1Y, L-  
22 402, L-312). Light microscopy revealed numerous granules within opacified areas (optic  
23 and/or haptic), close to the surface or on the surface of the IOLs, which were positive for  
24 alizarin red 1% suggesting calcium deposition. The lenses were implanted between 2009 and  
25 2012 and explantation was performed 4 years  $\pm$  1.2 (SD) after initial phacoemulsification.  
26 Ocular and systemic comorbidities were found without statistical correlation, with the most  
27 frequent being diabetes, uveitis, and glaucoma. A definitive cause was not identified but it  
28 was suggested by the authors that a manufacturing issue might be the reason<sup>99</sup>. This has  
29 been supported by a voluntary recall of lenses, implemented by Oculentis first in December  
30 2014 who stated at that time that "analysis suggests a possible interaction between  
31 phosphate crystals originating from the hydration process of the IOL material and the  
32 fluctuating, batch related presence of silicone residues on some IOLs". According to relevant  
33 literature, such residues may potentially change the IOL surface properties, making it under  
34 certain medical conditions more prone to deposition of calcium phosphate from the  
35 aqueous humour in predisposed patients. These deposits may compromise the optical  
36 transparency of the IOL, potentially leading to a reduction in the patient's visual acuity." In  
37 September 2017 Oculentis issued a further 'Field Safety Notice', applying to all Lentis  
38 foldable IOLs with model numbers starting with L-, LU- and LS- and having an expiry date  
39 between January 2017 and May 2020. Within this notice they reported that they have  
40 identified the source of calcific opacification as phosphate-containing cleaning agent used in  
41 their production process, which they apparently changed in June 2015.

42  
43 Such cases clearly high-light the need for vigilance on behalf of both surgeons and  
44 manufacturers alike to be aware of such problems, strongly consider analysis of any  
45 explanted IOL in a specialist centre to provide a definitive diagnosis, as well as feedback to  
46 the manufacturer and regulatory medical device agency. This requirement for increased

1 post-market surveillance of medical devices is stated in the latest Medical Devices  
2 Regulation, issued by the European Union in April 2017<sup>A</sup>.

### 5 **Sub-surface whitening/nano-glistenings**

7 Surface light scattering was first reported in hydrophobic acrylic IOLs by Nishihara et al. in  
8 2003<sup>100</sup>. They described 'surface whitening' of 40 patients implanted with AcrySof  
9 Hydrophobic acrylic IOLs (Alcon Laboratories Inc., Fort Worth, TX, USA). They could only  
10 examine 5 eyes in 4 patients in vivo with a slit lamp and could therefore not elucidate the  
11 cause, as the lenses in these eyes were not explanted. They felt the problem was on the  
12 surface/sub-surface and was not due to glistenings (discussed above) as these are normally  
13 within the substance of the IOL, not on its surface. The authors postulated that the structure  
14 of the IOL polymer might have changed over time with reorganization of the surface or near  
15 the surface to produce such changes.

17 Further reports of such phenomena in AcrySof IOLs have attempted to elucidate the nature  
18 of these problems<sup>101-102</sup>. Matsushima et al.<sup>101</sup> examined 4 explanted IOLs (due to  
19 dislocation) and found that light transmission in the visible range was only 4% less than that  
20 of unused IOLs, that x-ray analysis showed no calcium phosphate deposits, Fourier-  
21 transform infrared spectrophotometry showed no evidence of hydrolysis and that the  
22 opacification disappeared after drying of the IOLs but reappeared with immersion in  
23 physiologic saline. They postulated that it was likely that the 'whitening' of the hydrophobic  
24 acrylic IOLs was due to trace water molecules infiltrating sub-surface of the lens optic and  
25 that within the 3-dimensional network of the acrylic lens polymer, water molecules were  
26 able to form aggregates of sufficient size to scatter visible light, causing opacification or so  
27 called 'whitening'<sup>101</sup> (Figure 4).

29 Ong et al.<sup>103</sup> described a similar phenomenon to 'whitening', in AcrySof IOLs following  
30 explantations in 5 eyes and from human cadavers in 8 eyes, with non-implanted IOLs as  
31 controls. They found no inorganic/organic deposits on the IOL surfaces, but the hydration  
32 state of the IOLs significantly contributed to the intensity of surface light scattering and that  
33 clinically explanted and cadaver-eye explanted IOLs (but not control IOLs) exhibited minimal  
34 scatter when dry, intermediate scatter when wetted, and maximum scatter when hydrated.  
35 They documented on scanning electron microscopy sub-surface 'nano-glistenings', with  
36 diameters of less than one micrometre (between 140 and 185 nanometres) and within  
37 120µm of the IOL surface, as the source of the hydration-related surface light scattering.

39 Miyata et al.<sup>104</sup> investigated this IOL surface light scattering phenomenon and found it was  
40 greater in 'AcrySof MA60BM' and 'AcrySof SA60AT' IOLs (Alcon Laboratories Inc., Fort  
41 Worth, TX, USA) than that of 'AR60' and 'ClariFlex' IOLs (AMO, Santa Ana, California, USA),  
42 although of note was that contrast sensitivity under photopic conditions was not statistically  
43 different amongst the four groups of IOLs at any spatial frequency. They reported that this  
44 scattering was due to uniform, membrane-like whitening of the IOL surface and was distinct  
45 from glistenings, concluding that glistenings and surface scattering differed in both location  
46 and appearance and probably in origin<sup>104</sup>. In a follow-up study, Miyata et al.<sup>105</sup> evaluated  
47 the surface light scatter using a Scheimpflug camera in a cross-sectional study of 466 eyes,

1 implanted with either AcrySof 3-piece (MA30BA, MA60AC and MA60BM) or 1-piece  
2 (SA60BM) IOLs and showed that surface light scattering continued to increase up to 15 years  
3 post-operatively in all the AcrySof IOLs (Alcon Inc.)<sup>105</sup>. Unfortunately, they did not assess  
4 contrast sensitivity or assess for the presence of glistenings in the IOLs in this study, which  
5 could have influenced the results. Takahashi et al.<sup>106</sup> performed an optical simulation using  
6 ray-tracing software to evaluate visual effects of subsurface nano-glistenings (SNG) in IOLs.  
7 They found that increased size and volume ratio of SNGs increased forward light scatter but  
8 that the modulation transfer function (MTF) was not affected. They also found that peak  
9 retinal irradiance reduced with increased SNG volume ratios. The limitation of this study  
10 was that the SNGs in this simulation were evenly distributed which is not the case in real life  
11<sup>106</sup>. The authors discussed an interesting observation, where visual function improved in  
12 patients with retinal diseases when IOLs with SNGs were replaced. Research has shown  
13 dissociation of Snellen acuity and contrast sensitivity, indicating that contrast sensitivity can  
14 be used as an early index of changes in the retina not demonstrated by measurements of  
15 visual acuity<sup>107</sup>. The finding of no effect of SNGs on MTF by Takahashi et al.<sup>105</sup> is in line with  
16 findings by Werner et al.<sup>108</sup> who investigated light scatter and straylight in 17 AcrySof IOLs  
17 with SNGs removed from cadavers (11 SN60WF and 6 SA60AT; Alcon Inc.). In addition to  
18 MTF, these authors examined Badal images obtained with the explanted IOLs through  
19 different size pupils and found no significant difference to controls (non-implanted IOLs).  
20 There was similar light transmission but increased light scatter in the explanted IOLs  
21 compared to control IOLs. However, the reported values were well below the value of  
22 straylight hindrance and the authors concluded that the light scatter caused by the SNGs  
23 would be unlikely to cause noticeable visual impairments<sup>104</sup>. Beheregaray et al.<sup>105</sup> also  
24 investigated the impact on visual function of SNGs in 42 eyes implanted with AcrySof IOLs  
25 (models SA60AT, SN60AT, MA60AC, MA60BM) and found that eyes with SNGs had increased  
26 forward light scatter but the CDVA was unaffected compared to 17 eyes implanted with  
27 hydrophobic acrylic iSert 251 or iSert 255 IOLs (Hoya Corp., Shinjuku, Tokyo, Japan) used as  
28 controls. The authors excluded subjects with ocular co-morbidities. They documented that  
29 forward light scatter correlated with reductions in VA and contrast sensitivity, but the values  
30 were within the normal age range.

31  
32 It appears therefore that in most eyes, SNGs while increasing light scatter do so at a level  
33 unlikely to be visually symptomatic. However, this is not always the case. In a recent case  
34 report, subjective visual impairment due to SNGs occurred in a single-piece AcrySof IOL  
35 SA60AT (Alcon Inc.) 5 years after IOL implantation with starbursts, flare/glare and cloudy  
36 vision<sup>106</sup>. Explantation was not performed, as the other eye was amblyopic. It will be of  
37 interest to note if acrylic IOLs manufactured after 2010 will show less propensity to the  
38 development of SNGs and if so-called 'glistenings-free' hydrophobic acrylic polymers IOL will  
39 not have this problem.

40  
41  
42  
43  
44  
45  
46  
47

## Coatings of silicone IOLs

## 1 **Silicone Oil**

2  
3 Late opacification of silicone IOLs due to interaction with silicone oil was reported by Apple  
4 et al.<sup>107</sup> in 1996 in 3 eyes. It generally is not seen by the implanting cataract surgeon but  
5 usually later if the patient undergoes vitreo-retinal surgery necessitating the use of silicone  
6 oil. In 2 of the 3 reported eyes the IOLs were explanted, with the silicone oil coating  
7 manifest as a thick droplet-like glaze that was tenaciously adherent to the lens surface and  
8 could not apparently be dislodged by instruments or injection of viscoelastics<sup>107</sup>. In a further  
9 study, Apple et al.<sup>108</sup> performed an *in-vitro* experimental study to investigate silicone oil  
10 adhesion to various IOLs of different biomaterials, including fluorine-treated, heparin-  
11 surface-modified, PMMA, acrylic and silicone IOLs. The oil coverage of dry silicone IOLs was  
12 100% and 82.5% silicone IOLs were immersed in normal saline. The least coverage was on  
13 the heparin-surface-modified lenses (mean score 9.4%). Yaman et al.<sup>109</sup> looked at the effects  
14 of heavy silicone oil and found it to be akin to normal silicone oil. The mean heavy silicone  
15 oil coverage was 7.05% +/- 7.88% on PMMA IOLs, 100% on silicone IOLs, 12.17% +/- 11.43%  
16 on hydrophobic acrylic IOLs, and 34.64% +/- 13.28% on hydrophilic acrylic IOLs. Oner et  
17 al.<sup>114</sup> also evaluated the interaction between various IOLs, including: hydrophilic acrylic IOLs  
18 (Morcher, type 92s; Morcher GmbH, Germany); hydrophobic acrylic IOLs (AcrySof-SA60AT,  
19 Alcon Inc.); PMMA IOLs (Intraocular Optical International-IOI-65130) and silicone optic IOLs  
20 (CeeOn Edge 911A, Pharmacia UpJohn). Silicone IOLs once again had the highest percentage  
21 (79.9%) coverage whereas hydrophilic acrylic IOLs were the least (7.8%). They found no  
22 effect with varying concentration of the silicone oil. All these studies, show that when  
23 performing small-incision cataract surgery in patients who may be at risk of requiring vitreo-  
24 retinal surgery with silicone oil injection e.g. family history of retinal detachment, extreme  
25 myopia, congenital cataract, proliferative diabetic retinopathy, etc., hydrophilic acrylic or  
26 hydrophobic acrylic lenses should be preferred over silicone lenses and that it is best to  
27 avoid, if possible, the use of silicone oil in eyes with pre-existing silicone IOLs.  
28

## 29 **Toxic anterior segment syndrome due to ophthalmic ointments and IOL** 30 **materials**

31  
32 Werner et al.<sup>111</sup> reported 8 cases of toxic anterior segment syndrome (TASS) related to an  
33 oily substance in the anterior chamber of patients following cataract surgery, with an oily  
34 coating of the IOL in some cases. All cases were performed by the same surgeon using clear  
35 corneal incisions, with implantation of the same type of 3-piece silicone IOL. Immediately  
36 post-operatively antibiotic/steroid ointment and pilocarpine gel was administered and the  
37 eyes firmly patched. On the first day, some patients presented with corneal oedema, raised  
38 intraocular pressure, and an oily film-like material within the anterior chamber coating the  
39 endothelium, while others had an oily bubble floating in the aqueous, which later coated  
40 the IOL. Some of these eyes required additional surgical procedures such as keratoplasty,  
41 IOL explantation, and trabeculectomy. Six explanted IOLs were analysed by microscopy in 4  
42 cases by gas chromatography-mass spectrometry (GC-MS), which confirmed the presence of  
43 an oily substance coating large areas of the anterior and posterior IOL optic surfaces with a  
44 mixed chain hydrocarbon compound seen on GC-MS, akin to that found in the ointment  
45 used post-operatively. Chew et al.<sup>112</sup> reported a case, where a patient required lens  
46 repositioning 11 and 13 months after initial apparently uncomplicated surgery and then at

1 18 months developed a greasy film over a 3-piece silicone IOL. The lens was explanted, with  
2 GC-MS identifying the presence of hydrocarbons, including docosane, tricosane, and  
3 tetracosane (often found in ophthalmic ointments), on the IOL surface, which matched that  
4 found in one of the ointments used after IOL re-positioning. Chen et al.<sup>113</sup> reported a similar  
5 case, where 'Garamycin' (gentamicin; Schering-Plough, USA) ophthalmic ointment, applied  
6 immediately post-operatively, was identified on the surface of an explanted IOL, removed at  
7 3 years due to reduced vision and an oily-like lump on the anterior surface of the IOL.

8  
9 It appears from these cases that ophthalmic ointments for topical use only can gain access  
10 to the anterior chamber, and as well as causing damage to other internal ocular structures  
11 can coat the surface of silicone IOLs. Such cases high-light the importance of good wound  
12 construction and post-operative wound integrity and the risks of tight eye patching  
13 following placement of topical ointment. Certainly, there have been several previous  
14 reports of ointment applied externally after reaching the anterior chamber, which has  
15 occurred both after cataract surgery and other anterior segment procedures<sup>113-116</sup>, so care  
16 need to be taken with its immediate post-operative usage with any penetrating ocular  
17 surgical wound.

## 20 **Other types of IOL surface degradation: inter-lenticular opacification**

21  
22 While not a cause of opacification of the IOL itself, inter-lenticular opacification, can result  
23 in significant visual loss necessitating IOL explantation. Gayton et al.<sup>117</sup> in 2000 presented  
24 two pairs of piggyback AcrySof hydrophobic acrylic IOLs, placed in the capsular bag, which  
25 were explanted because of opacification between the lens optics. There appeared to be a  
26 membrane-like, white material between the lenses, which on histopathological examination  
27 identified retained/proliferative lens epithelial cells mixed with lens cortical material<sup>117</sup>.  
28 Werner et al.<sup>118</sup> further examined the nature of the inter-lenticular material and  
29 documented that Elschnig pearls, which could be surgically aspirated, were observed in the  
30 peripheral interface between the lenses but the central interface between the lenses was  
31 occupied by an amorphous material, which could not be removed and was acellular on  
32 histological examination. In a follow-up paper, Werner et al.<sup>118</sup> reported on the  
33 histopathologic and ultrastructural features of three cases of inter-lenticular opacification  
34 and found the material opacifying the inter-lenticular space was composed mostly of  
35 retained/regenerative cortical material. They concluded that the pathogenesis was akin to  
36 that of posterior capsule opacification and that very careful removal of lens epithelial cells  
37 and cortical material is necessary in cases where piggyback implantation is being considered  
38<sup>119</sup>. Such findings were confirmed by Eleftheriadis et al.<sup>120</sup> who published 2 pairs of in-the-  
39 capsular-bag piggyback AcrySof IOL implantation with bilateral intra-lenticular opacification  
40 in one patient. They documented a central contact zone between the two IOLs, surrounded  
41 by a homogenous paracentral opacity, which in turn were surrounded by Elschnig pearls.

42  
43 Werner et al.<sup>121</sup> in an in vivo rabbit study, compared dual-optic silicone IOLs to piggyback in-  
44 the-bag IOL implantation with silicone and with hydrophobic acrylic IOLs. They confirmed  
45 that intra-lenticular opacification was significantly associated with pairs of hydrophobic  
46 acrylic lenses implanted in the bag and not silicone IOLs. Finally, Jackson and Koch<sup>122</sup>  
47 documented a case where in an eye with piggyback implantation, whilst the posterior IOL

1 was placed completely within the capsule, one of the haptics of the anterior IOL was  
2 inadvertently placed in the ciliary sulcus and the other in the capsule. They noted that inter-  
3 lenticular opacification was localized to the area adjacent to the anterior lens haptic placed  
4 within the capsule but absent from the area near the anterior lens haptic in the ciliary  
5 sulcus. They concluded that sulcus placement of the anterior IOL may help to prevent inter-  
6 lenticular opacification.

7  
8 Whilst rare, it appears that intra-lenticular opacification is related to paired in-the-capsular-  
9 bag hydrophobic acrylic IOLs <sup>117-122</sup>. It has been proposed that if such acrylic lenses are being  
10 inserted in the fashion, then meticulous removal of the lens epithelial cells and cortical  
11 material is mandatory. However, silicone lenses seem less susceptible to this complication  
12 and insertion of the anterior IOL into the ciliary sulcus (with an appropriate sulcus lens to  
13 avoid iris trauma and pigment dispersion) and not the capsule, together with correct  
14 placement of the posterior IOL into the capsular bag with complete coverage of the optic  
15 edge by the capsulorhexis, should negate this problem.

## 16 17 **Conclusions**

18  
19 Over the past decades several differing degenerations, opacifications and discolourations of  
20 IOLs implanted after cataract surgery have been described. Reported anomalies have  
21 included photo-chemical degenerations, water vacuolation, internal and surface calcific  
22 deposits, surface coatings and discoloration. Investigations of the patho-physiology of these  
23 changes depend on the type of IOL material used and/or manufacturing processes and IOL  
24 storage conditions employed and can also be influenced by surgical technique, co-existing  
25 ocular pathologies and topical and systemic medications. The clinical significance of these  
26 degradations is variable, with some resulting in significant visual disturbance and the need  
27 for IOL explantation and others in only minimal optical impairments. Failure to recognise the  
28 precise nature of the problem may lead to unnecessary laser capsulotomy procedures. The  
29 correct identification and thorough investigation to determine the underlying cause is  
30 mandatory both for optimal patient management and the prevention of such problems.  
31 Indeed, there is a paucity of published research investigating the effects of material  
32 degradations of IOL, especially with time, on their optical properties, which needs to be  
33 addressed.

## 34 35 **Disclosures**

36 Financial support: The author(s) received no financial support for the research, authorship,  
37 and/or publication of this article.

38 Conflict of interest declaration: Professor O'Brart and Professor Hull have held non-  
39 commercial research grants from Alcon Inc.

## 40 41 **References**

- 42  
43 1. Kuopam S. The Global Intraocular Lens Market is Forecast to Reach \$3.1 Billion ASD  
44 Reports". [www.asdreports.com](http://www.asdreports.com). Retrieved 2015-09-14.
- 45 2. Day AC, Donachie PH, Sparrow JM, Johnston RL2 Royal College of Ophthalmologists'  
46 National Ophthalmology Database. The Royal College of Ophthalmologists' National

- 1 Ophthalmology Database study of cataract surgery: report 1, visual outcomes and  
2 complications. *Eye (Lond)* 2015;29(4):552-60.
- 3 3. Pager CK. Expectations and outcomes in cataract surgery: a prospective test of 2  
4 models of satisfaction. *Arch Ophthalmol* 2004;122(12):1788-92.
- 5 4. Williams H. Sir Harold Ridley's Vision. *Br J Ophthalmol* 2001;85:1022-1023
- 6 5. Apple DJ, Peng Q, Arthur SN, Werner L, Merritt JH, Vargas LG, et al. Snowflake  
7 Degeneration of Polymethyl Methacrylate Posterior Chamber Intraocular.  
8 *Ophthalmology* 2002;6420(2):1666-75.
- 9 6. Werner L. Causes of intraocular lens opacification or discoloration. *J Cataract Refract*  
10 *Surg* 2007;33:713-26.
- 11 7. Dahle, N., Werner L, Fry L, & Mamalis N Localized, central optic snowflake  
12 degeneration of a polymethyl methacrylate intraocular lens: Clinical report with  
13 pathological correlation. *Arch of Ophthalmol* 2006;124(9): 1350-1353.
- 14 8. Patel H, Chaleff A, Patel N, Shah A, Patel CK, Ferguson DJP. Snowflake degeneration  
15 of a poly(methyl methacrylate) intraocular lens. *JCRS Online Case Reports*  
16 2017;5(1):9-11.
- 17 9. Garrott H, O'Day J. Snowflake degeneration of an intraocular lens. *Clin Exp*  
18 *Ophthalmol* 2004;32(5):534-5.
- 19 10. Tan LT, Shuttleworth GN. Asymptomatic snowflake degeneration in a polymethyl  
20 methacrylate (PMMA) intraocular lens implant. *Ann Ophthalmol (Skokie)* 2008 Fall-  
21 Winter;40(3-4):173-4.
- 22 11. Maia OO Jr, Nakashima AF, Barbosa EP, Primiano Júnior HP, Nakashima Y. Late  
23 opacification of a polymethylmethacrylate (PMMA) intraocular lens: case report. *Arq*  
24 *Bras Oftalmol* 2005 Sep-Oct;68(5):683-5. Epub 2005 Nov 28.
- 25 12. Kato K, Nishida M, Yamane H, Nakamae K, Tagami Y, Tetsumoto K. Glistening  
26 formation in an AcrySof lens initiated by spinodal decomposition of the polymer  
27 network by temperature change. *J Cataract Refract Surg* 2001 Sep;27(9):1493-8.
- 28 13. Christiansen G, Durcan FJ, Olson RJ, Christiansen K. Glistenings in the AcrySof  
29 intraocular lens: Pilot study. *J Cataract Refract Surg* 2001;27:728-33.
- 30 14. Henriksen BS, Kinard K, Olson RJ. Effect of intraocular lens glistening size on visual  
31 quality. *J Cataract Refract Surg* 2015;41:1190-8.
- 32 15. Balin N. Glistenings in injection-moulded lens (letter). *Am Intra-Ocular Implant Soc J*  
33 1984;10:473.
- 34 16. Tognetto D, Toto L, Sanguinetti G, Ravalico G. Glistenings in foldable intraocular  
35 lenses. *J Cataract Refract Surg* 2002; Jul;28(7):1211-6.
- 36 17. Rønbeck M, Behndig A, Taube M, Koivula A, Kugelberg M. Comparison of glistenings  
37 in intraocular lenses with three different materials: 12-year follow-up. *Acta*  
38 *Ophthalmol* 2013; Feb;91(1):66-70.
- 39 18. Hayashi K, Hirata A, Yoshida M, Yoshimura K, Hayashi H. Long-term effect of surface  
40 light scattering and glistenings of intraocular lenses on visual function. *Am J*  
41 *Ophthalmol* 2012;154:240-51.
- 42 19. Gregori NZ, Spencer TS, Mamalis N, Olson RJ. In vitro comparison of glistening  
43 formation among hydrophobic acrylic intraocular lenses. *J Cataract Refract Surg.*  
44 2002;28:1262-8.
- 45 20. Wilkins E, Olson RJ. Glistenings with long-term follow-up of the surgidev B20/20  
46 polymethylmethacrylate intraocular lens. *Am J Ophthalmol.* 2001; 132(5):783-5.

- 1 21. Cisneros-Lanuza A, Hurtado-Sarrió M, Duch-Samper A, Gallego-Pinazo R, Menezo-  
2 Rozalén JL. Glistenings in the Artiflex phakic intraocular lens. *J Cataract Refract Surg*  
3 2007;33(8):1405–8.
- 4 22. Chang A, Kugelberg M. Glistenings 9 years after phacoemulsification in hydrophobic  
5 and hydrophilic acrylic intraocular lenses. *J Cataract Refract Surg* 2015;41(6):1199–  
6 204.
- 7 23. Davison JA. Clinical performance of Alcon SA30AL and SA60AT single-piece acrylic  
8 intraocular lenses. *J Cataract Refract Surg* 2002; 28(7):1112–23.
- 9 24. Waite A, Faulkner N, Olson RJ. Glistenings in the Single-Piece, Hydrophobic, Acrylic  
10 Intraocular Lenses. *Am J Ophthalmol* 2007;144:143–4.
- 11 25. Leydolt C, Schriefl S, Stifter E, Haszcs A, Menapace R. Posterior capsule opacification  
12 with the iMics1 NY-60 and AcrySof SN60WF 1-piece hydrophobic acrylic intraocular  
13 lenses: 3-year results of a randomized trial. *Am J Ophthalmol* [Internet]. Elsevier Inc.;  
14 2013;156(2):375–81. Available from: <http://dx.doi.org/10.1016/j.ajo.2013.04.007>
- 15 26. Kahraman G, Ferdinano C, Wetzel B, Bernhart C, Prager F, Amon M. Intraindividual  
16 comparison of capsule behavior of 2 hydrophobic acrylic intraocular lenses during a  
17 5-year follow-up. *J Cataract Refract Surg* 2017;43(2):228–33.
- 18 27. Dhaliwal DK, Mamalis N, Olson RJ, Crandall AS, Zimmerman P, Alldredge OC, et al.  
19 Visual significance of glistenings seen in the AcrySof intraocular lens. *J Cataract*  
20 *Refract Surg* 1996;22(4):452–7.
- 21 28. Colin J, Orignac I, Touboul D. Glistenings in a large series of hydrophobic acrylic  
22 intraocular lenses. *J Cataract Refract Surg* 2009;35:2121–5.
- 23 29. Johansson B. Glistenings, anterior/posterior capsular opacification and incidence of  
24 Nd:YAG laser treatments with two aspheric hydrophobic acrylic intraocular lenses - a  
25 long-term intra-individual study. *Acta Ophthalmol* 2017;30:1–7.
- 26 30. Behndig A, Mönestam E. Quantification of glistenings in intraocular lenses using  
27 Scheimpflug photography. *J Cataract Refract Surg* 2009 Jan;35(1):14–7.
- 28 31. Werner L. Glistenings and surface light scattering in intraocular lenses. *J Cataract*  
29 *Refract Surg* 2010;36:1398–420.
- 30 32. Saylor DM, Coleman Richardson D, Dair BJ, Pollack SK. Osmotic cavitation of  
31 elastomeric intraocular lenses. *Acta Biomater* 2010;6(3):1090–8.
- 32 33. Tetz M, Jorgensen MR. New Hydrophobic IOL Materials and Understanding the  
33 Science of Glistenings, *Current Eye Research*, 2015; 40:10, 969-981.
- 34 34. Blume I, Schwering PJF, Mulder MHV, Smolders CA. Vapour sorption and permeation  
35 properties of poly(dimethylsiloxane) films. *J Memb Sci* 1991;61:85–97.
- 36 35. Miyata A, Yaguchi S. Equilibrium water content and glistenings in acrylic intraocular  
37 lenses. *J Cataract Refract Surg* 2004 Aug;30(8):1768-72.
- 38 36. Moreno-Montañés J, Alvarez A, Rodríguez-Conde R, Fernández-Hortelano A. Clinical  
39 factors related to the frequency and intensity of glistenings in AcrySof intraocular  
40 lenses. *J Cataract Refract Surg* 2003;29:1980–4.
- 41 37. Miyata K, Ogata M, Honbo M, Mori Y, Minami K. Suppression of surface light  
42 scattering in intraocular lenses manufactured with improved production process. *J*  
43 *Cataract Refract Surg* 2016;42(12):1716–20.
- 44 38. Thomes BE, Callaghan TA. Evaluation of in vitro glistening formation in hydrophobic  
45 acrylic intraocular lenses. *Clin Ophthalmol* 2013;7:1529–34.

- 1 39. Dick HB, Olson RJ, Augustin AJ, Schwenn O, Magdowski G, Pfeiffer N. Vacuoles in the  
2 Acrysof™ intraocular lens as factor of the presence of serum in aqueous humor.  
3 *Ophthalmic Res* 2001;33(2):61–7.
- 4 40. Manuchehri K, Mohamed S, Cheung D, Saeed T, Murray PI. Brown deposits in the  
5 optic of foldable intraocular lenses in patients with uveitis. *Eye (Lond)*  
6 2004;18(1):54–8.
- 7 41. Arshinoff FRCSC S. letters Does a Tight Capsular Bag Cause Glistenings? *J Cataract*  
8 *Refract Surg* 1998;24:6.
- 9 42. Monestam E, Behndig A. Impact on visual function from light scattering and  
10 glistenings in intraocular lenses, a long-term study. *Acta Ophthalmol* 2011;89:724–8.
- 11 43. Colin J, Praud D, Touboul D, Schweitzer C. Incidence of glistenings with the latest  
12 generation of yellow-tinted hydrophobic acrylic intraocular lenses. *J Cataract Refract*  
13 *Surg* 2012;38:1140–6.
- 14 44. Chang A, Behndig A, Rønbeck M, Kugelberg M. Comparison of posterior capsule  
15 opacification and glistenings with 2 hydrophobic acrylic intraocular lenses: 5- to 7-  
16 year follow-up. *J Cataract Refract Surg* 2013;39(5):694–8.
- 17 45. Stanojcic N, O’Brart DPS, Maycock N, Hull CC. Effects of intraocular lens glistenings  
18 on visual function: a prospective study and presentation of a new glistenings grading  
19 methodology. *BMJ Open Ophthalmol* 2019;4:e000266. Doi:10.1136/bmjophth-2018-  
20 000266.
- 21 46. Xi L, Liu Y, Zhao F, Chen C, Cheng B. Analysis of glistenings in hydrophobic acrylic  
22 intraocular lenses on visual performance. *Int J Ophthalmol* 2014;7(3):446–51.
- 23 47. Gunenc U, Oner FH, Tongal S, Ferliel M. Effects on visual function of glistenings and  
24 folding marks in AcrySof intraocular lenses. *J Cataract Refract Surg* 2001  
25 *Oct*;27(10):1611-4.
- 26 48. Schweitzer C, Orignac I, Praud D, Chatoux O, Colin J. Glistening in glaucomatous eyes:  
27 visual performances and risk factors. *Acta Ophthalmol* 2014 Sep;92(6):529-34.
- 28 49. Biber H, Schuber E, Honig M, Spratte B, Baumeister M, Kohnen T. Objective  
29 classification of glistenings in implanted intraocular lenses using Scheimpflug  
30 tomography. *J Cataract Refract Surg* 2015;41:2644–51.
- 31 50. Djelouah, Ihemme; Al-Khalili E. Intraocular lenses and the development of  
32 glistenings. *Can Advers React Newsl* 2013;23(2).
- 33 51. Raven ML, Burris CKH, Nehls SM. Glistening Intraocular Lens. *Ophthalmology*  
34 2016;123(7):1483.
- 35 52. Dogru M, Tetsumoto K, Tagami Y, Kato K, Nakamae K. Optical and atomic force  
36 microscopy of an explanted AcrySof intraocular lens with glistenings. *J Cataract*  
37 *Refract Surg* 2000;26(4):571-5.
- 38 53. Werner L, Storsberg J, Mauger O, Brasse K, Gerl R, Müller M, et al. Unusual pattern  
39 of glistening formation on a 3-piece hydrophobic acrylic intraocular lens. *J Cataract*  
40 *Refract Surg* 2008 Sep;34(9):1604-9.
- 41 54. Werner L, Dornelles F, Hilgert CR, Botelho F, Conte PF, Rozot P, Andrenyak DM,  
42 Mamalis N, Olson RJ. Early opacification of silicone intraocular lenses: Laboratory  
43 analyses of 6 explants. *J Cataract Refract Surg* 2006 Mar;32(3):499-509.
- 44 55. Elgohary M, Zaheer A, Werner L, Ionides A, Sheldrick J, Ahmed N. Opacification of  
45 Array SA40N silicone multifocal intraocular lens. *J Cataract Refract Surg* 2007  
46 *Feb*;33(2):342-7.

- 1 56. Tanaka T, Saika S, Hashizume N, Ohnishi Y. Brown haze in an Allergan SI-40NB  
2 silicone intraocular lens. *J Cataract Refract Surg* 2004 Jan;30(1):250-2.
- 3 57. Milauskas AT. Silicone Intraocular Lens Implant Discoloration in Humans. *Arch*  
4 *Ophthalmol* 1991;109(7):913
- 5 58. Koch DD, Heit LE. Discoloration of silicone intraocular lenses. *Arch Ophthalmol* 1992  
6 Mar;110(3):319-20.
- 7 59. Werner L, Mamalis N, Olson RJ. Postoperative optic opacification of silicone IOLs:  
8 Analyses of 20 explants. Free Papers, Cataract Session, American Academy of  
9 Ophthalmology Annual Meeting, New Orleans, LA USA, November 11, 2007.
- 10 60. Daniel Fuller Jones AEI. Discoloration of Intraocular Lens Subsequent to Rifabutin  
11 Use. *Arch Ophthalmol* 2000;118(June):281–92.
- 12 61. Stevens S, Werner L, Mamalis N. Corneal edema and permanent blue discoloration  
13 of a silicone intraocular lens by methylene blue. *Ophthalmic Surg Lasers Imaging.*  
14 2007 Mar-Apr;38(2):136-41.
- 15 62. Katai N, Yokoyama R, Yoshimura N. Progressive brown discoloration of silicone  
16 intraocular lenses after vitrectomy in a patient on amiodarone. *J Cataract Refract*  
17 *Surg* 1999;25(3):451–2.
- 18 63. Sathyan P, Myint K, Singh G, Mon S, Sathyan P, Dhillon B. Late green discoloration of  
19 Allergan SI-40NB silicone intraocular lens. *J Cataract Refract Surg* 2006;32(9):1584–5.
- 20 64. Venkatesh R, Kumar TT, Ravindran RD. Greenish discoloration of silicone intraocular  
21 lens. *Indian J Ophthalmol* 2008;24(3):614–614.
- 22 65. Werner L, Apple DJ, Crema AS, Izak AM, Pandey SK, Trivedi RH, et al. Permanent blue  
23 discoloration of a hydrogel intraocular lens by intraoperative trypan blue. *J Cataract*  
24 *Refract Surg* 2002;28(7):1279–86.
- 25 66. Goodall KL, Ghos YK. Total Opacification of Intraocular Lens Implant After  
26 Uncomplicated Cataract Surgery: A Case Series. *Arch Ophthalmol*  
27 2004;122(May):782–5.
- 28 67. Wong MHY, Su DHW, Chee SP. Brown discoloration of acrylic hydrophobic  
29 intraocular lens. *Can J Ophthalmol* 2016;51(4):277–81.
- 30 68. Milauskas AT. Brown discoloration of acrylic multifocal, monofocal, and blue light-  
31 filtering IOLs. *J Cataract Refract Surg* 2012;38(1):176–7.
- 32 69. Neuhann IM, Kleinmann G, Apple DJ. A New Classification of Calcification of  
33 Intraocular Lenses. *Ophthalmology* 2008;115(1):73–9.
- 34 70. Barra D, Werner L, Pacini Costa JL, Morris C, Ribeiro T, Ventura BV, et al. Light  
35 scattering and light transmittance in a series of calcified single-piece hydrophilic  
36 acrylic intraocular lenses of the same design. *J Cataract Refract Surg* 2014;40(1):121–  
37 8.
- 38 71. Wackernagel W, Ettinger K, Weitgasser U, Bakir BG, Schmut O, Goessler W,  
39 Faschinger C. Opacification of a silicone intraocular lens caused by calcium deposits  
40 on the optic. *J Cataract Refract Surg* 2004 Feb;30(2):517-20.
- 41 72. Foot L, Werner L, Gills JP, Shoemaker DW, Phillips PS, Mamalis N, Olson RJ, Apple DJ.  
42 Surface calcification of silicone plate intraocular lenses in patients with asteroid  
43 hyalosis. *Am J Ophthalmol* 2004 Jun;137(6):979-87.
- 44 73. Werner L, Kollarits CR, Mamalis N, Olson RJ. Surface calcification of a 3-piece silicone  
45 intraocular lens in a patient with asteroid hyalosis: a clinicopathologic case report.  
46 *Ophthalmology* 2005 Mar;112(3):447-52.

- 1 74. Stringham J, Werner L, Monson B, Theodosios R, Mamalis N. Calcification of different  
2 designs of silicone intraocular lenses in eyes with asteroid hyalosis. *Ophthalmology*  
3 2010 Aug;117(8):1486-92.
- 4 75. Espandar L, Mukherjee N, Werner L, Mamalis N, Kim T. Diagnosis and management  
5 of opacified silicone intraocular lenses in patients with asteroid hyalosis. *J Cataract*  
6 *Refract Surg* 2015 Jan;41(1):222-5.
- 7 76. Apple, David J, Lilianna Werner, MD P, Marcela Escobar-Gomez, MD Suresh K. Pandey  
8 M. Deposits on the Optical Surfaces of Hydroview Intraocular Lenses. *J Cataract*  
9 *Refract Surg* 2000;26(6):796.
- 10 77. Werner L, Apple DJ, Escobar-Gomez M, Ohrström A, Crayford BB, Bianchi R, Pandey  
11 SK. Postoperative deposition of calcium on the surfaces of a hydrogel intraocular  
12 lens. *Ophthalmology* 2000 Dec;107(12):2179-85.
- 13 78. Neuhann IM, Werner L, Izak AM, Pandey SK, Kleinmann G, Mamalis N, Neuhann TF,  
14 Apple DJ. Late postoperative opacification of a hydrophilic acrylic (hydrogel)  
15 intraocular lens: a clinicopathological analysis of 106 explants. *Ophthalmology* 2004  
16 Nov;111(11):2094-101.
- 17 79. Werner L, Apple DJ, Kaskaloglu M, Pandey SK. Dense opacification of the optical  
18 component of a hydrophilic acrylic intraocular lens: a clinicopathological analysis of 9  
19 explanted lenses. *J Cataract Refract Surg* 2001 Sep;27(9):1485-92.
- 20 80. Dorey MW, Brownstein S, Hill VE, Mathew B, Botton G, Kertes PJ, El-Defrawy S.  
21 Proposed pathogenesis for the delayed postoperative opacification of the hydroview  
22 hydrogel intraocular lens. *Am J Ophthalmol* 2003 May;135(5):591-8.
- 23 81. Haymore J, Zaidman G, Werner L, Mamalis N, Hamilton S, Cook J, Gillette T.  
24 Misdiagnosis of hydrophilic acrylic intraocular lens optic opacification: report of 8  
25 cases with the MemoryLens. *Ophthalmology* 2007 Sep;114(9):1689-95.
- 26 82. Werner L, Hunter B, Stevens S, Chew JJ, Mamalis N. Role of silicon contamination on  
27 calcification of hydrophilic acrylic intraocular lenses. *Am J Ophthalmol* 2006  
28 Jan;141(1):35-43.
- 29 83. Guan X, Tang R, Nancollas GH. The potential calcification of octacalcium phosphate  
30 on intraocular lens surfaces. *J Biomed Mater Res A* 2004 Dec 1;71(3):488-96.
- 31 84. Wu W, Guan X, Tang R, Hook D, Yan W, Grobe G, Nancollas GH. Calcification of  
32 intraocular implant lens surfaces. *Langmuir* 2004 Feb 17;20(4):1356-61.
- 33 85. Hunter B, Werner L, Memmen JE, Mamalis N. Postoperative localized opacification of  
34 the new MemoryLens design: analyses of an explant. *J Cataract Refract Surg* 2005  
35 Sep;31(9):1836-40.
- 36 86. Gartaganis SP, Kanellopoulou DG, Mela EK, Panteli VS, Koutsoukos PG. Opacification  
37 of hydrophilic acrylic intraocular lens attributable to calcification: investigation on  
38 mechanism. *Am J Ophthalmol* 2008 Sep;146(3):395-403.
- 39 87. Werner L, Wilbanks G, Nieuwendaal CP, Dhital A, Waite A, Schmidinger G, et al.  
40 Localized opacification of hydrophilic acrylic intraocular lenses after procedures  
41 using intracameral injection of air or gas. *J Cataract Refract Surg* 2015;41(1):199–  
42 207.
- 43 88. Giers BC, Tandogan T, Auffarth GU, Choi CY, Auerbach FN, Sel S, Mayer C, Khoramnia  
44 R. Hydrophilic intraocular lens opacification after posterior lamellar keratoplasty - a  
45 material analysis with special reference to optical quality assessment. *BMC*  
46 *Ophthalmol* 2017;17(1):150.

- 1 89. Marcovich AL, Tandogan T, Bareket M, Eting E, Kaplan-Ashiri I, Bukelman A, Auffarth  
2 GU, Khoramnia R. Opacification of hydrophilic intraocular lenses associated with  
3 vitrectomy and injection of intraocular gas. *BMJ Open Ophthalmol* 2018;3(1):  
4 e000157. Doi: 10.1136/bmjophth-2018-000157.
- 5 90. Ma ST, Yang CM, Hou YC. Postoperative intraocular lens opacification. *Taiwan J*  
6 *Ophthalmol.* 2018;8(1):49–51. doi:10.4103/tjo.tjo\_78\_17
- 7 91. Fung SS, Sykakis E, Islam NM, et al. Intraocular Lens Opacification following  
8 Intracameral Injection of Recombinant Tissue Plasminogen Activator to Treat  
9 Inflammatory Membranes after Cataract Surgery. *J Ophthalmol.* 2015;2015:975075  
10 doi:10.1155/2015/975075.
- 11 92. Tandogan T, Khoramnia R, Choi CY, Scheuerle A, Wenzel M, Hugger P, et al. Optical  
12 and material analysis of opacified hydrophilic intraocular lenses after explantation: a  
13 laboratory study. *BMC Ophthalmology.* 2015;15(1):170.
- 14 93. Zuberbuhler B, Carifi G. Pigment deposits on hydrophilic intraocular lenses after  
15 phacoemulsification cataract surgery. *Saudi J Ophthalmol.* 2012;26(1):109–11.
- 16 94. Gartaganis SP, Prahs P, Lazari ED, Gartaganis PS, Helbig H, Koutsoukos PG.  
17 Calcification of Hydrophilic Acrylic Intraocular Lenses with a Hydrophobic Surface:  
18 Laboratory Analysis of 6 Cases. *Am J Ophthalmol* 2016;168:68–77.
- 19 95. Gurabardhi M, Häberle H, Aurich H, Werner L, Pham DT. Serial intraocular lens  
20 opacifications of different designs from the same manufacturer: Clinical and light  
21 microscopic results of 71 explant cases. *J Cataract Refract Surg* 2018;44(11):1326–32.
- 22 96. Nishihara H, Yaguchi S, Onishi T, Chida M, Ayaki M. Surface scattering in implanted  
23 hydrophobic intraocular lenses. *J Cataract Refract Surg* 2003;29(7):1385–8.
- 24 97. Matsushima H, Mukai K, Nagata M, Gotoh N, Matsui E, Senoo T. Analysis of surface  
25 whitening of extracted hydrophobic acrylic intraocular lenses. *J Cataract Refract Surg*  
26 2009;35(11):1927–34.
- 27 98. Nagata M, Matsushima H, Mukai K, Terauchi W, Senoo T, Wada H, et al. Clinical  
28 evaluation of the transparency of hydrophobic acrylic intraocular lens optics. *J*  
29 *Cataract Refract Surg* 2010;36(12):2056–60.
- 30 99. Ong MD, Callaghan TA, Pei R, Karakelle M. Etiology of surface light scattering on  
31 hydrophobic acrylic intraocular lenses. *J Cataract Refract Surg* 2012;38(10):1833–44.
- 32 100. Miyata K, Otani S, Nejima R, Miyai T, Samejima T, Honbo M, et al. Comparison  
33 of postoperative surface light scattering of different intraocular lenses. *Br J*  
34 *Ophthalmol* 2009;93:684–7.
- 35 101. Miyata K, Honbo M, Otani S, Nejima R, Minami K. Effect on visual acuity of  
36 increased surface light scattering in intraocular lenses. *J Cataract Refract Surg*  
37 2012;38(2):221–6.
- 38 102. Takahashi Y, Kawamorita T, Mita N, Hatsusaka N, Shibata S, Shibata N, et al.  
39 Optical simulation for subsurface nanoglistening. *J Cataract Refract Surg*  
40 2015;41(1):193–8
- 41 103. Sokol S, Moskowitz A, Skarf B, Evans R, Molitch M, Senior B. Contrast Sensitivity in  
42 Diabetics with and Without Background Retinopathy. *Arch Ophthalmol* 1985;103(1):51–  
43 4.
- 44 104. Werner L, Stover JC, Schwiegerling J, Das KK. Light scattering, straylight, and optical  
45 quality in hydrophobic acrylic intraocular lenses with subsurface nanoglistenings. *J*  
46 *Cataract Refract Surg* 2016;42(1):148–56.

- 1 105. Beheregaray S, Yamamoto T, Hiraoka T, Oshika T. Influence on visual function of  
2 forward light scattering associated with subsurface nanoglistenings in intraocular lenses.  
3 J Cataract Refract Surg 2014;40(7):1147–54.
- 4 106. Rullo J, Lloyd JC. Clinically significant deterioration in the quality of vision as a result  
5 of subsurface nanoglistenings in a hydrophobic acrylic intraocular lens. J Cataract Refract  
6 Surg 2014;40(2):336–7.
- 7 107. Apple DJ, Federman JL, Krolicki TJ, Sims JC, Kent DG, Hamburger HA, Smiddy WE,  
8 Cox MS Jr, Hassan TS, Compton SM, Thomas SG. Irreversible silicone oil adhesion to  
9 silicone intraocular lenses. A clinicopathologic analysis. Ophthalmology 1996  
10 Oct;103(10):1555-61.
- 11 108. Apple DJ, Isaacs RT, Kent DG, Martinez LM, Kim S, Thomas SG, Basti S, Barker D,  
12 Peng Q. Silicone oil adhesion to intraocular lenses: an experimental study comparing  
13 various biomaterials. J Cataract Refract Surg 1997 May;23(4):536-44.
- 14 109. Yaman A, Saatci AO, Sarioğlu S, Oner FH, Durak I. Interaction with intraocular lens  
15 materials: does heavy silicone oil act like silicone oil? J Cataract Refract Surg 2007  
16 Jan;33(1):127-9.
- 17 110. Oner FH, Saatci OA, Sarioğlu S, Durak I, Kaynak S, Cabuk M. Interaction of  
18 intraocular lenses with various concentrations of silicone oil: an experimental study.  
19 Ophthalmologica 2003 Mar-Apr;217(2):124-8.
- 20 111. Werner L, Sher JH, Taylor JR, Mamalis N, Nash WA, Csordas JE, Green G, Maziarz EP,  
21 Liu XM. Toxic anterior segment syndrome and possible association with ointment in the  
22 anterior chamber following cataract surgery. J Cataract Refract Surg 2006 Feb;32(2):227-  
23 35.
- 24 112. Chew JJ, Werner L, Mackman G, Mamalis N. Late opacification of a silicone  
25 intraocular lens caused by ophthalmic ointment. J Cataract Refract Surg 2006  
26 Feb;32(2):341-6.
- 27 113. Chen KH, Lin SY, Li MJ, Cheng WT. Retained antibiotic ophthalmic ointment on an  
28 intraocular lens 34 months after sutureless cataract surgery. Am J Ophthalmol 2005  
29 Apr;139(4):743-5.
- 30 114. Fraunfelder FT, Hanna C. Ophthalmic ointment. Trans Am Acad Ophthalmol  
31 Otolaryngol 1973 Jul-Aug;77(4):OP467-75.
- 32 115. Garzosi HJ, Muallem MS, Harris A. Recurrent anterior uveitis and glaucoma  
33 associated with inadvertent entry of ointment into the anterior chamber after radial  
34 keratotomy. J Cataract Refract Surg 1999 Dec;25(12):1685-7.
- 35 116. Aralikatti AK, Needham AD, Lee MW, Prasad S. Entry of antibiotic ointment into the  
36 anterior chamber after uneventful phacoemulsification. J Cataract Refract Surg 2003  
37 Mar;29(3):595-7.
- 38 117. Gayton JL, Apple DJ, Peng Q, Visessook N, Sanders V, Werner L, Pandey SK, Escobar-  
39 Gomez M, Hoddinott DS, Van Der Karr M. Interlenticular opacification:  
40 clinicopathological correlation of a complication of posterior chamber piggyback  
41 intraocular lenses. J Cataract Refract Surg 2000 Mar;26(3):330-6.
- 42 118. Werner L, Shugar JK, Apple DJ, Pandey SK, Escobar-Gomez M, Visessook N, Evans  
43 BB. Opacification of piggyback IOLs associated with an amorphous material attached to  
44 interlenticular surfaces. J Cataract Refract Surg 2000 Nov;26(11):1612-9.
- 45 119. Werner L, Apple DJ, Pandey SK, Solomon KD, Snyder ME, Brint SF, Gayton JL, Shugar  
46 JK, Trivedi RH, Izak AM. Analysis of elements of interlenticular opacification. Am J  
47 Ophthalmol 2002 Mar;133(3):320-6.

1 120. Eleftheriadis H, Marcantonio J, Duncan G, Liu C. Interlenticular opacification in  
2 piggyback AcrySof intraocular lenses: explantation technique and laboratory  
3 investigations. Br J Ophthalmol 2001 Jul;85(7):830-6.

4 121. Werner L, Mamalis N, Stevens S, Hunter B, Chew JJ, Vargas LG. Interlenticular  
5 opacification: dual-optic versus piggyback intraocular lenses. J Cataract Refract Surg  
6 2006 Apr;32(4):655-61.

7 122. Jackson DW, Koch DD. Interlenticular opacification associated with asymmetric  
8 haptic fixation of the anterior intraocular lens. Am J Ophthalmol 2003 Jan;135(1):106-8.

9  
10 A) Regulation (EU) 2017/745 of The European Parliament and of The Council of 5 April 2017  
11 on Medical Devices. Available at: [https://eur-lex.europa.eu/legal-](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&fromZEN)  
12 [content/EN/TXT/PDF/?uri=CELEX:32017R0745&fromZEN](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&fromZEN)

13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26 **Figure 1:** Slit-lamp photograph of glistenings within an AcrySof IOL appearing as multiple  
27 small refractile bodies within the bulk of intraocular lens optic.

28  
29 **Figure 2.** A hydrophilic acrylic IOL opacified following DSEK (courtesy of Mr. M Nanavaty,  
30 Sussex Eye Hospital, Brighton, UK)

31  
32 **Figure 3.** (a) Slit lamp image of a calcified Lentis (Oculentis, GmbH, Berlin, Germany)  
33 intraocular lens (Courtesy of Mr. M Rajan, Addenbrookes Hospital, Cambridge, UK); (b)  
34 Electron microscopy (x5000 magnification) of a cross-section of a calcified LentisM30  
35 (Oculentis, GmbH, Berlin, Germany) intraocular lens showing calcium deposits extending 20  
36  $\mu\text{m}$  from the lens surface (Courtesy of Mr J. Stevens, Moorfields Eye Hospital, London, UK)

37  
38 **Figure 4.** Subsurface whitening or nanoglistenings seen as intense light scattering or  
39 whitening on anterior and posterior IOL surfaces. In addition, glistenings can be seen in the  
40 bulk of the IOL optic of an AcrySof SA60AT; Alcon, inc, USA.