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In vitro reliability testing and *in vivo* lifespan estimation of wireless Pixium Vision PRIMA photovoltaic subretinal prostheses suggest prolonged durability and functionality in clinical practice

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¹ Author to whom any correspondence should be addressed.E-mail: mdeterre@pixium-vision.com**Keywords:** retinal prosthesis, implant corrosion, lifespan, reliability, subretinal

Abstract

Objective. Retinal implants have the potential to restore some sight in patients with retinal degeneration. The PRIMA implant's novel design features simpler insertion and no transscleral cabling or extraocular components. This *in vitro* study investigated PRIMA's durability under real time and accelerated conditions and estimated the device's lifespan *in vivo*. **Approach.** Two potential failure modes were examined: corrosion and overstimulation. Real-time aging was tested using implants immersed in balanced saline solution (BSS) at 37 °C, mimicking the intraocular environment. Accelerated aging was examined at 77 °C (Arrhenius theory). Confirmatory testing of acceleration factor was performed using different temperatures (37 °C–87 °C) and weakened implant coatings. The effect of repeated maximum stimulation was tested using a pulsed infrared laser (6x acceleration factor). Data were used to estimate device lifespan. **Main results.** 175 implants were tested for up to 33 months. No corrosion or water ingress was observed after approximately 20 accelerated years. A pixel failure rate of 0.15% was recorded after 10 accelerated years' stimulation. The derived lifespan estimation for the PRIMA implant was 27.0 years with a reliability of 90% (95% confidence interval). **Significance.** The PRIMA implant was found to be robust, with *in vitro* reliability of at least 10 years. The PRIMA implant shows durability and functionality for clinically relevant timespans under similar environmental conditions to the human eye. These results require *in vivo* confirmation.

1. Introduction

Patients affected by retinal degenerative conditions such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP) suffer from gradual photoreceptor loss [1, 2]. In AMD, patients develop a scotoma in their central vision and lose precision sight, whereas RP reduces their periphery field of view. Both conditions have similar pathophysiology: an inactivated yet functional inner retinal layer of bipolar and ganglion cells. Lost photoreceptor function can be partially replaced by electrical stimulation of these cells using retinal implants [3, 4].

Implants are typically placed in epiretinal, suprachoroidal, or subretinal locations. Epiretinal devices such as the Argus II[®] (Second Sight) [5] and IRIS II[®] (Pixium Vision) [6] target ganglion cells by means of electrodes placed on the retina surface. By

comparison, suprachoroidal implants share a similar design, but are positioned between the choroid and sclera [7]. The PRIMA (Pixium Vision) and Alpha IMS[®] and AMS[®] prostheses (Retina Implant AG), both classed as subretinal, are surgically inserted between the retinal pigment epithelium and the retinal cell layer. One of the main advantages of subretinal placements is their proximity to the target bipolar cells, which facilitates precise stimulation.

The PRIMA implant, developed and manufactured at Pixium Vision, is derived from the subretinal wireless implant invented at Stanford University [8]. Unlike its competitors, it lacks extraocular components, simplifying surgical placement and reducing the risk of adverse events. The positioning of the implant and absence of transscleral cabling significantly reduce mechanical stress due to eye movement. Additionally, other devices are typically centimetres

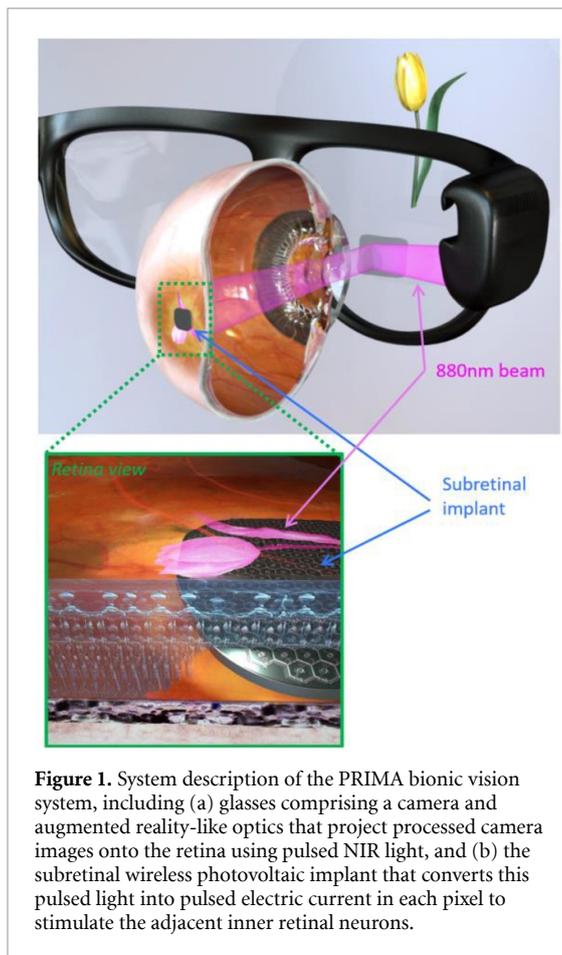


Figure 1. System description of the PRIMA bionic vision system, including (a) glasses comprising a camera and augmented reality-like optics that project processed camera images onto the retina using pulsed NIR light, and (b) the subretinal wireless photovoltaic implant that converts this pulsed light into pulsed electric current in each pixel to stimulate the adjacent inner retinal neurons.

in length and millimetres in thickness, whereas the less invasive PRIMA microchip is an order of magnitude smaller with a thickness of $30\ \mu\text{m}$.

Each implant consists of hundreds of independent pixels (378 in the clinical device) that convert infrared (IR) light into localized electrical stimulation. The PRIMA system includes glasses with an inbuilt camera-projector that projects a patterned IR laser beam through the pupil to the implant at the back of the retina similarly to an augmented reality device (figure 1). The electrical stimulus produced by the pixels is intended to generate the same visual pattern as normally functioning photoreceptors.

One of the main challenges facing retinal implants is their post-implant lifespan. The eye environment is corrosive, and long-term stimulation of the implant can cause irreversible electrochemical damage. Accelerated *in vitro* testing is necessary to understand the likely device lifetime *in vivo*. As many prostheses are still in acute testing or development, lifespan data are limited. The Argus II® implant, which consists of a 60-electrode array linked to an extraocular housing by a foil substrate [5], is reported to have a lifetime of five years *in vivo* [9] and 10 years *in vitro* with accelerated testing [10]. Both the Alpha IMS® and AMS® have *in vitro* and expected *in vivo* lifespans of < 1 year and < 5 years, respectively [11]. For Prima, *in*

in vivo data from pre-clinical study [12] demonstrate an implant lifetime of at least 2 years in two non-human primates and 3 years in a third one, while current data from ongoing clinical trial show full implant functionality in all five patients after 12 months implantation [13].

This study aimed to test the durability of the PRIMA implant *in vitro*. The primary objective was to evaluate resistance to corrosion and/or water ingress and repeated stimulation at the highest parameters under accelerated conditions. These data were used to estimate implant lifespan *in vivo*.

2. Device description

Five different designs of the PRIMA implant were tested, varying in size and pixel count (table 1). These designs included a version currently being tested in clinical trials (implant design D). All pixel sizes are equivalent as they scale in design (electrodes and photodiodes) and are therefore subjected to the same voltage and current density.

Each pixel consists of an electronic circuit comprising two photodiodes connected to a shunt resistor, a central active electrode and a local return electrode at the pixel perimeter (figure 2). The return electrodes are all connected, creating an implant-wide return grid. The photodiodes (p–n junctions) are wired in series to optimize the stimulation voltage and maximize charge injection levels [14]. These p–n junctions convert the incoming infrared laser into electrical pulses between electrodes. The pulses are anodic first and biphasic through capacitive discharge of the electrodes in the cathodic phase which is optimized by the shunt resistor [14, 15].

Compared with monopolar designs, local return electrodes reduce the spatial spread of electrical stimulation, thereby optimising separation of stimuli from neighboring pixels and enhancing implant spatial resolution. However, stronger stimulation levels may be needed to reach and excite the target neurons [16].

Using a near-infrared wavelength (880 nm) away from the visible spectrum helps avoid the photophobic and phototoxic effects of bright illumination [8], as well as any interference with residual vision AMD patients have in their peripheral field of view.

The implant is fully encapsulated in nontoxic, corrosion-resistant sub-micron hermetic coatings. The front side is protected by a ceramic transparent layer and the edges and back sides are protected with an opaque layer. Coatings thicknesses, in the sub-micrometer range, are optimized for maximum light absorption in the silicon. The design is intended to be biocompatible even in case of a coating breach. The electrodes are formed of iridium oxide due to its high charge density properties and resistance to electrochemical degradation.

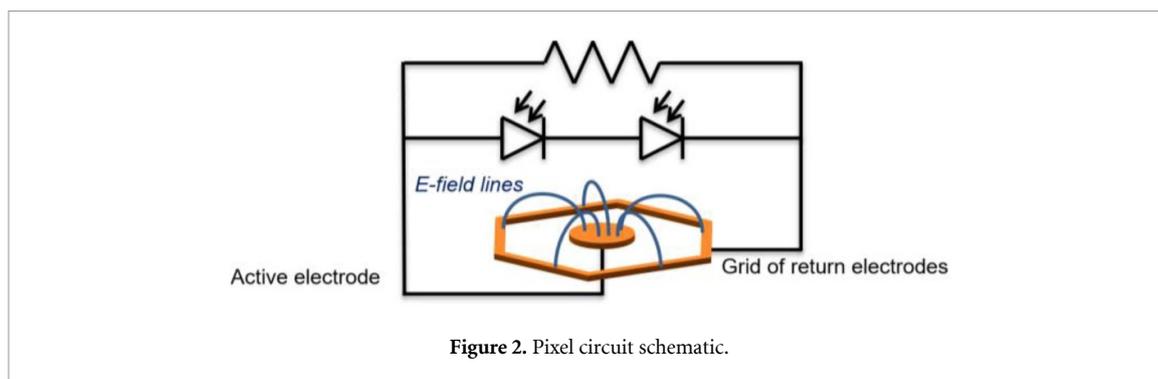


Figure 2. Pixel circuit schematic.

Table 1. Characteristics of PRIMA implant designs.

| Implant design | Implant size (mm) | Pixel pitch (μm) | No. of pixels |
|----------------|-------------------|-------------------------------|---------------|
| A | 1.5 | 140 | 100 |
| B | 2 | 140 | 182 |
| C | 1.5 | 100 | 205 |
| D | 2 | 100 | 378 |
| E | 2 | 75 | 686 |

3. Method

3.1. Failure modes

To examine the reliability and lifespan of the PRIMA implant *in vitro*, two tests were carried out to simulate conditions *in vivo*. First, the implant's resilience to corrosion and water ingress (corrosion testing) was assessed. Second, electrodes and circuitry were inspected for damage caused by repetitive electrical pulses (stimulation testing). Due to the location of the implant and the absence of movable or flexible parts, eye movements do not cause mechanical strain and testing for damage caused by mechanical stress was considered irrelevant and not conducted.

3.2. Corrosion testing

Corrosion testing was performed by soaking the implant in balanced saline solution (BSS, Alcon Laboratories), a medium similar in corrosiveness to the eye's medium. To ensure maximum corrosivity, the solution was not diluted. The submerged implant was then placed in a sealed glass bottle and kept in a temperature-regulated oven.

Implants underwent either real-time aging or accelerated aging. For real-time testing, temperature was maintained at 37 °C, approximating average human body temperature. To accelerate aging, implants were soaked at 77 °C. According to the Arrhenius equation with a typical $Q_{10} = 2.0$ [17], it is assumed that a 10 °C temperature increase will accelerate aging by a factor of two. Therefore, a rise in temperature from 37 °C to 77 °C theoretically represents a 16-fold increase in aging.

To more accurately determine the aging acceleration coefficient, implants with weaker coatings

(same material and thickness with on-purpose pinholes induced by a minor process variation) expected to display corrosion/water ingress were manufactured and tested. The chips were soaked at a range of temperatures: 37 °C, 57 °C, 67 °C, 77 °C, and 87 °C. Matching the extent of corrosion to the test temperature allowed us to develop a specific temperature-driven law of accelerated aging, which could then be compared with that obtained using the theoretical Arrhenius equation.

3.3. Stimulation testing

To assess the impact of long-term use, implants were activated with a pulsed infrared laser at maximum stimulation parameters (several mW mm^{-2} irradiance, pulse duration up to 10 ms, frequency of 30 Hz). Implants were kept in a specially designed holder that exposed their electrodes, photodiodes, and external coatings, enabling all pixels to be stimulated. Irradiance was verified biweekly at each implant location on the holder using a calibrated power meter and photodiode having an implant-size pinhole.

The implants were stimulated continuously (24 h per day), representing an illumination exposure six times longer per day than estimated under typical clinical conditions. To mimic the situation *in vivo*, implants were kept at 37 °C in BSS diluted with demineralized water. This medium dilution ensured a solution resistivity of 1000 $\Omega\cdot\text{cm}$ to match the electrical resistivity of the human retina [15, 18]. To some extent, this testing also permits to detect if there is any impact of the stimulation on real-time corrosion effects, although these are likely to be not impactful as no DC voltage should be built-up on the electrodes that discharge after the pulses.

3.4. Inspection method

PRIMA implants undergoing both corrosion and stimulation testing were checked biweekly to monthly for structural and functional changes. Visual inspections were conducted on each pixel using an optical microscope at 1000x magnification. All the implants were examined for signs of deterioration, corrosion, coating/electrode damage, or delamination. Implants were then all functionally tested.

Functional testing involved implants being immersed in diluted BSS with several pixels being illuminated by a homogeneous 880 nm laser irradiance through an upright microscope at typical stimulation parameters that a patient might experience (4 ms pulses, 30 Hz). The amplitude of the electrical response was verified using a tungsten glass coated micro electrode (Alpha Omega, Cat#366-0502-11), placed 20 μm above the surface of the active pixel, and connected to an amplifier and its head stage (AMS 3000, AM Systems) having a total amplifying gain of x50. Measurement were made against a Ag/AgCl reference electrode in the solution. As shown in figure 3 in the results section, typical recorded voltage amplitudes are in the 100 mV range (after division of the raw signal by the x50 gain)—far above any measurement noise. For each design, a functionality threshold of this order of magnitude was determined. The setup was calibrated and validated to rule out test artefacts and false positives. Per device, a minimum of five pixels evenly distributed on the implant surface, on top of any pixel that showed visible alteration during visual inspection, were functionally characterized. Full functionality of the pixels without visual alteration at 1000X optical inspection was validated on thousands of samples (11 457 pixels in total), allowing to speed up the inspection and assess the functionality of all tested pixels. All inspection methods were performed according to Pixium Vision ISO 13 485 certified quality system.

3.5. Implant lifetime estimation

Data from the tests were used to estimate the lifetime of the PRIMA implant. Weibull analysis for pixel reliability at a 95% confidence interval (CI) was performed using Weibull ++ software (ReliaSoft Corporation), where t = given time, η = scale of distribution, and β = shape of the distribution (1).

$$R_{\text{pixel}}(t) = e^{-\left(\frac{t}{\eta}\right)^\beta} \quad (1)$$

As an implant is comprised of independent pixels, the functionality of a full device can be derived by multiplying the reliability of each pixel [19]. The reliability of an implant was defined as 75% of pixels operating normally as this level was deemed sufficient for proper operation. The equation for implant reliability can be found below, where n = total pixels and k = total failed pixels.

$$R_{\text{implant}}(t) = \sum_{k \leq 0.75 * n} \binom{n}{k} (1 - R_{\text{pixel}}(t))^k R_{\text{pixel}}(t)^{n-k} \quad (2)$$

The absolute reliability of the implant is defined as the product of the implant reliabilities to the various failure modes. Implant design D (378 electrodes, table 1) was selected for lifetime estimation due to its ongoing use in clinical trials.

4. Results

4.1. Determination of the corrosion aging acceleration coefficient

The intentionally weakened implants were used to more accurately calculate the acceleration coefficient of the corrosion testing. All implants showed water ingress within several weeks of immersion, confirmed by optical inspection. As expected, ingress was exponentially accelerated by temperature, up to 87 °C. Due to a correlation factor, R^2 , of 0.976, it was determined that the speed of ingress was multiplied by a factor of $Q_{10} = 1.93$ for each 10 °C increase. Therefore, the acceleration factor between 37 °C and 77 °C was calculated to be 14.

4.2. Corrosion testing

A total of 68 implants comprising four designs underwent corrosive testing; 35 at 37 °C (real-time aging) and 33 at 77 °C (accelerated aging). As described in table 2, all implants except for the design E which is still ongoing, exceeded two and 20 years, for real-time and accelerated aging, respectively. Regardless of aging, implant functionality remained at 100% in all units until study completion (table 2), i.e. none of the tested pixels failed. An example of functional response before and after testing is shown in figure 3. The voltage baseline is arbitrary as it depends from the open-circuit potentials of the electrodes. The exact shape of the waveforms can also vary depending on the low pass filter settings of the noise cancelling electronics.

No visual defects nor pixel failures due to corrosion or water ingress have been observed. In particular, 1000X magnification optical inspections revealed no damage, breaches nor change in coatings texture or color (figure 4). The latter also indicates an absence of thinning of the front side transparent coating which thickness is in the order of the visible wavelength. In absence of sign of material degradation, further potential material release analyses were not performed. Occasionally, impact marks or scratches induced by the repeated and numerous manipulations with implant picking tools appeared, typically on the implant edges, but did not cause pixel failure nor further implant degradation.

An additional challenge during this study was the degradation of the plastic caps used to seal the BSS bottles blackening the surface of some components. Once discovered, the plastic caps were replaced. Implant performance was not affected.

4.3. Stimulation testing

A total of 107 implants representing all device types were subject to pulsed testing. In real time, the study duration ranged from 91 to 615 d, which reflected approximately 1.5 to 10 years of equivalent electrical activity.

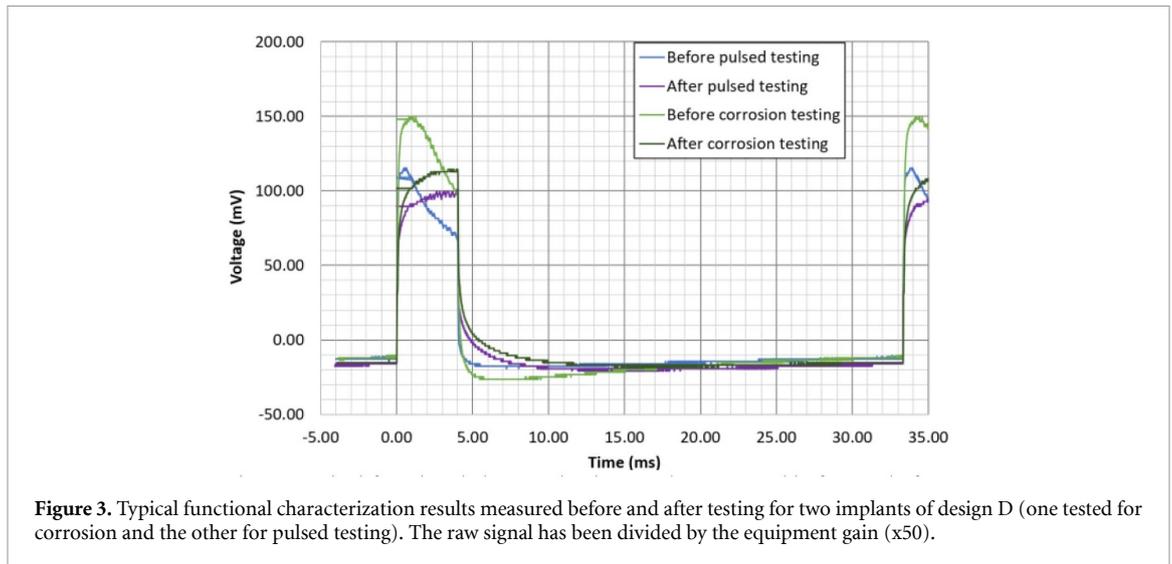
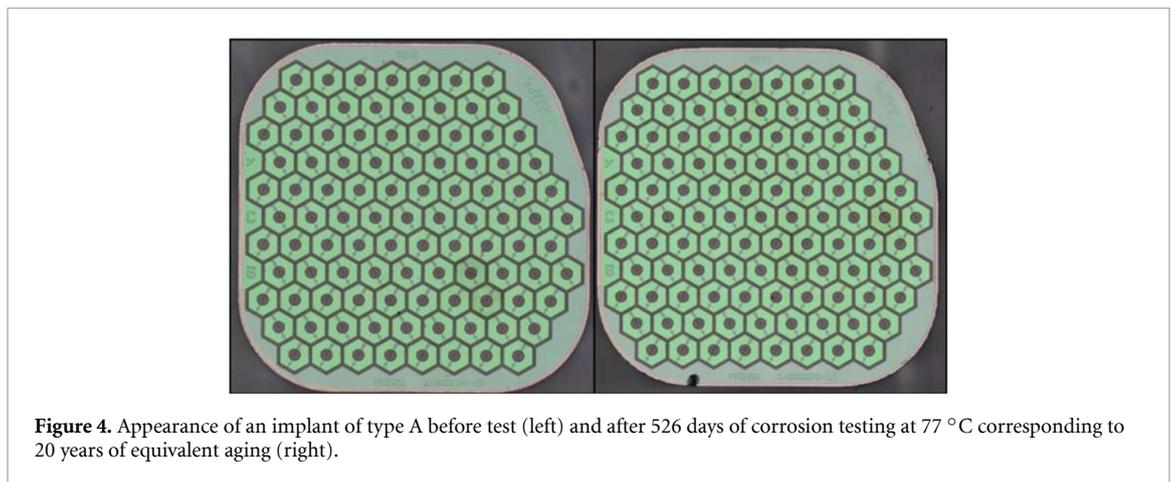


Table 2. Summary of implant functionality after real-time or accelerated corrosion testing.

| Implant design | No. of tested implants | Test temperature (°C) | Test duration (days) | Equivalent lifetime duration (years) | Implant functionality (%) |
|----------------|------------------------|-----------------------|--------------------------|--------------------------------------|---------------------------|
| A | 18 | 37 | [915; 1002] ^a | 2.5 | 100 |
| | 18 | 77 | [522; 549] ^a | 20.0 | 100 |
| C | 6 | 37 | 821 | 2.2 | 100 |
| | 3 | 77 | 523 | 20.0 | 100 |
| D | 6 | 37 | 817 | 2.2 | 100 |
| | 6 | 77 | [522; 523] ^a | 20.0 | 100 |
| E | 5 | 37 | 329 | 0.9 | 100 |
| | 6 | 77 | 329 | 12.6 | 100 |

^aSeveral implants with similar test durations have been grouped for conciseness.



Overall, visual inspection of the implants showed no global change, and 99.85% of the tested pixels (30 427 out of 30 472) were functional. It should be noted that salt crystals originating from the test medium are typically observed during testing (figure 5). These salt residues do not diminish the level of laser irradiance during testing as implants have unchanged functional response to IR stimulation after the apparition of salt crystals (figure 3). Inspection at maximum level allows to monitor the electrode color below the residues, and those

residues can be removed by gentle wiping of the implant to ensure the coatings below have not been degraded.

Approximately 0.85% (258) of the electrodes presented a strong color or aspect change, which resulted in a pixel failure rate of 0.15% (45). The malfunctioning pixels appeared to be randomly distributed and no pixel fault was observed on electrodes without visual change. The failure modes of the Prima pixels can therefore be attributed to sole electrode degradation. Further, no corrosion and/or

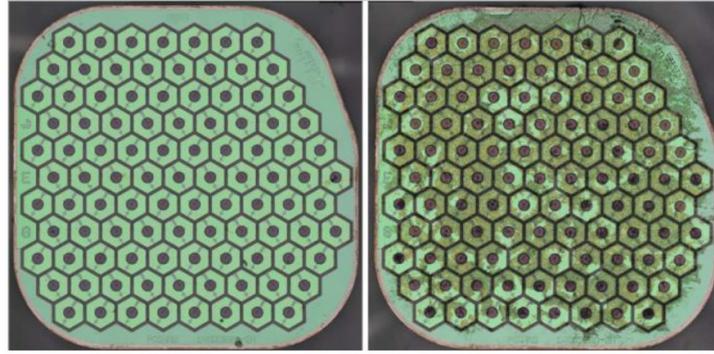


Figure 5. Implant of design A before test (left) and after 609 days of pulsed testing corresponding to 10 years of equivalent lifetime (right).

water ingress was observed, indicating that repeated electric activity does not reduce durability. For 71% of implants (38 out of 53), functionality remained at 100% after an equivalent lifetime of 10 years. In the worst case, performance dropped to 95.6%. Six implants were broken during the experiment due to handler error (figure 6).

4.4. Implant lifetime estimation

As the pixels have not failed corrosion testing so far in up to 20 years of equivalent lifetime, their reliability to corrosion is deemed to be 100%. Therefore, absolute pixel reliability is equal to pixel reliability to stimulation testing.

The pixel failures were plotted on a Weibull reliability diagram and the pixel reliability function was determined (figure 7). The nominal reliability function (1) was calculated with $\beta = 3.52$ and $\eta = 52.4$ according to the following equation, where t is expressed in years and plotted in blue (3).

$$R_{\text{pixel}}(t) = e^{-\left(\frac{t}{52.4}\right)^{3.52}} \quad (3)$$

Additionally, the pixel reliability for a 95% lower-bound one-sided CI was derived by the following equation (with $\beta = 4.39$ and $\eta = 37.0$) and plotted in red in figures 6 and 8 (4).

$$R_{\text{pixel}, 95\% \text{ confidence}}(t) = e^{-\left(\frac{t}{37.0}\right)^{4.39}} \quad (4)$$

Pixel reliability was calculated as 99.6% at 10 years with a median lifetime of 34.0 years, both with a 95% lower-bound one-sided CI.

Using the pixel reliability coefficient for PRIMA implant design D, there is 100% probability that the implant would be functional (*i.e.* more than 75% of functional pixels) at 10 years. As presented in figure 8, although the reliability of a pixel can be relatively spread out (red plot), the implant reliability (blue plot) is much steeper as it pools an important number of pixel samples. Therefore, the implant reliability is crossing the 75% level very close to the 75% level of

the pixel reliability function (4). The median implant lifetime was estimated at 27.9 years with a 95% lower-bound one-sided CI (figure 8) and 27.0 years at a 95% CI with 90% reliability. When using a CI of 75%, prosthesis lifetime increased to 32.7 years.

5. Discussion

The results from this *in vitro* study show that the PRIMA implant is resistant to corrosion, water ingress, and repeated stimulation for over 10 years using accelerated measures. A pixel failure rate of 0.15% was observed under these conditions, resulting in an estimated prosthesis life span of 27 years. A lack of corrosion and water ingress after accelerated testing suggests that the implant is hermetic and well adapted to an aggressive medium similar to that of the human eye for up to 20 years. Further, the electrode design successfully survived the effects of maximum stimulation by billions of IR pulses. Improper charge balancing would have caused rapid irreversible electrochemical damage resulting in electrode failure.

An important feature unique to the PRIMA design is the independent nature of each pixel. Pixel failure does not cause implant malfunction, but rather reduces functionality by only a fraction of a percent. This design nature is very robust, although it limits the implant ability to be locally tuned or provide feedback. Neither does the prosthesis require transscleral cabling, as is the case in retinal devices such as the Argus II® [5] or the Alpha IMS/AMS® [11]. This greatly reduces the risk of implant malfunction due to eye movements and mechanical stress. Furthermore, Prima circuit design features voltage levels within the electrode water window and no persistent DC voltage, minimizing the probability of electrode irreversible degradation.

In some patients, AMD can be diagnosed as early as 50 years of age [1], whereas RP can begin in adolescence [2]. It is important that retinal implants have a suitable clinical life to avoid the need for

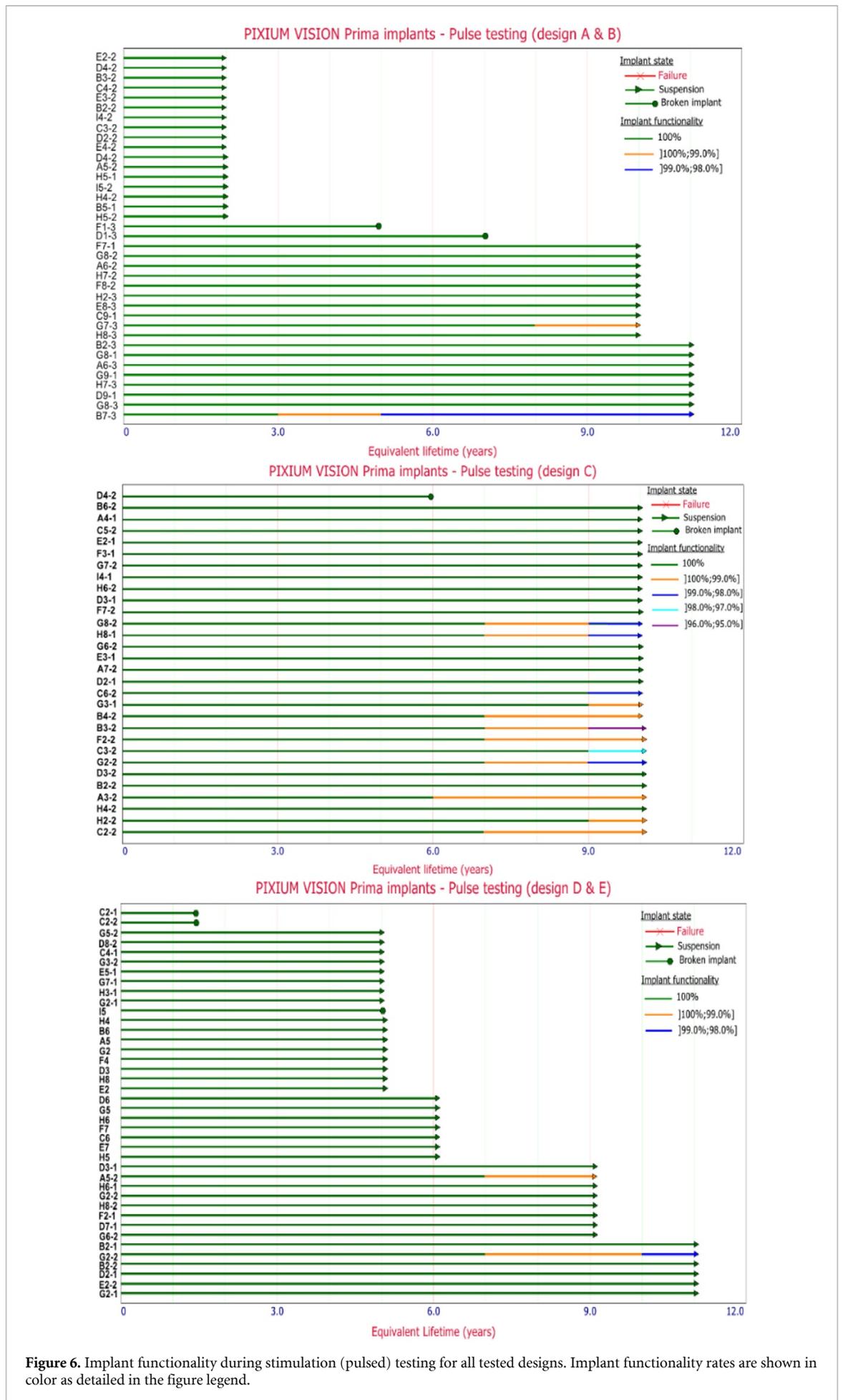


Figure 6. Implant functionality during stimulation (pulsed) testing for all tested designs. Implant functionality rates are shown in color as detailed in the figure legend.

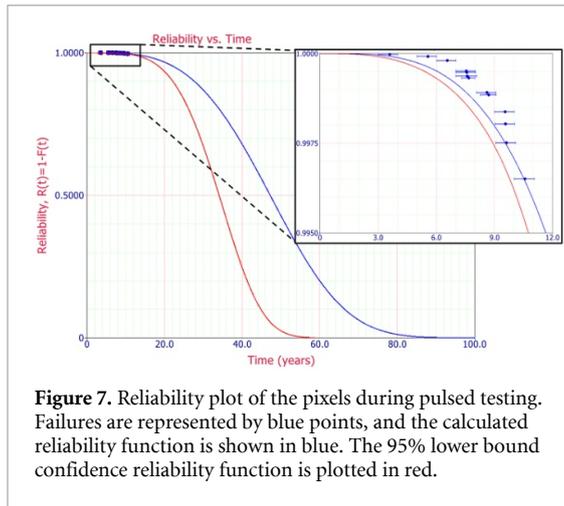


Figure 7. Reliability plot of the pixels during pulsed testing. Failures are represented by blue points, and the calculated reliability function is shown in blue. The 95% lower bound confidence reliability function is plotted in red.

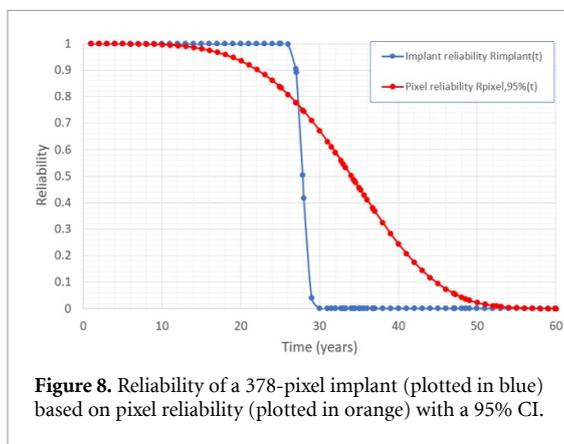


Figure 8. Reliability of a 378-pixel implant (plotted in blue) based on pixel reliability (plotted in orange) with a 95% CI.

multiple operations. These *in vitro* data are at least comparable to those provided for the Argus II® implant, for which a ten year lifespan is claimed [10]. Further, PRIMA lifespan estimations were superior to the Alpha IMS® and AMS® retinal chips' by over 28 years at a 75% CI [11]. This considerably greater durability can be explained by PRIMA's robust coatings, independently functioning pixels, and lack of mechanical stress due to transscleral components.

Care must be taken in interpreting these data, and the generation of *in vivo* lifetime estimations from *in vitro* data remains speculative. Many physiological, electrical, and mechanical aspects of the human eye are unreproducible in a laboratory and accelerating their effect would be impossible. It is important that *in vivo* studies are conducted to confirm these lifespan approximations. Currently, *in vivo* data with intermittent implant activation from pre-clinical study have shown no failure after 3 years in one animal and after 2 years for two others [12], while current data from ongoing clinical trial show full implant functionality in all five patients after 12 months implantation [13]. These results are so far consistent with the presented *in vitro* results.

6. Conclusion

The PRIMA implant can withstand corrosive and electrical stimulation pressures in conditions similar to those of human eye for at least a decade. The pixel failure rate was negligible, and no implants malfunctioned. Statistical reliability analysis estimates a PRIMA median lifespan of over 27 years. Future studies should attempt to confirm these results *in vivo*.

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