J. Eur. Opt. Society-Rapid Publ. 2023, **19**, 36
© The Author(s), published by EDP Sciences, 2023
https://doi.org/10.1051/jeos/2023032
Available online at: https://jeos.edpsciences.org

**Journal of the European Optical Society-Rapid Publications**

Advancing Society with Light, a special issue from general congress
ICO-25-OWLS-16-Dresden-Germany-2022

**Review Article** **Open Access**

# Medical femtosecond laser

Karsten König[1,2,*]

[1] Saarland University, Department of Biophotonics and Laser Technology, 66123 Saarbrücken, Germany
[2] JenLab GmbH, 12559 Berlin, Germany

Received 10 December 2022 / Accepted 29 May 2023

**Abstract.** Medical femtosecond laser devices are used in dermatology for non-linear high-resolution imaging to obtain non-invasive and label-free optical skin biopsies (multiphoton tomography) as well as in ophthalmology for refractive corneal surgery and cataract surgery. Applications of commercial certified multiphoton tomographs include early detection of skin cancer within minutes by two-photon autofluorescence imaging of coenzymes and melanin and second harmonic imaging of collagen as well as by testing the efficacy of pharmaceutical and cosmetical products. Goals are (i) to reduce the number of physically taken human skin biopsies in hospitals and research institutions, (ii) to optimize personalized medicine, and (iii) to reduce animal studies in pharmacy. Current diagnostic tools in dermatology include surface microscopy with a dermatoscope and ultrasound but have poor resolution. Optical coherence tomography and confocal reflectance microscopy have better resolution but provide limited information based on changes of the intratissue refractive index. Multiphoton tomography provides the best resolution of all clinical imaging methods and offer functional imaging such as optical metabolic imaging based on autofluorescence lifetime imaging. Goals of femtosecond laser eye treatment are (i) the replacement of mechanical microkeratomes for corneal flap generation, (ii) the replacement of the UV nanosecond excimer laser for stroma removal, and (iii) to replace, in part, the scalpel in the surgery of cataracts and other eye diseases. So far, millions of eye treatments have been conducted around the world. The major disadvantage of current certified medical femtosecond laser devices is the high price compared with the standard mechanical and optical medical devices.

**Keywords:** Laser medicine, Femtosecond laser, Multiphoton tomography, Laser refractive surgery, Cataract.

## 1 Introduction

Femtosecond laser radiation in the near-infrared (NIR) at transient light intensities of 100 MW/cm$^2$ up to TW/cm$^2$ is employed in CE/FDA-certified medical devices to generate multiphoton effects inside human tissue.

Non-resonant two-photon absorption was predicted by the PhD student *Maria Göppert* in Göttingen around 100 years ago. She got the Nobel Prize in physics in 1963. In 1961, her hypothesis was confirmed with the availability of the laser by *Kaiser and Garrett,* who demonstrated two-photon excited fluorescence, as well as *Franken et al.*, who demonstrated the generation of optical harmonics such as second harmonic generation (SHG) [1–3].

After the introduction of picosecond laser scanning microscopy in live sciences in 1989 by *Bugiel, König, and Wabnitz* [4], the two-photon scanning microscope was invented by *Denk, Strickler, and Webb* in 1990 using a sub-picosecond dye laser [5].

Later on, the femtosecond titanium:sapphire laser became the favorite light source for non-linear laser scanning microscopy of living cells and animal tissues [6].

*Stefan W. Hell* (Nobel Prize in Chemistry) employed the femtosecond Ti:sapphire laser to realize two-photon excitation stimulated-emission depletion (STED) microscopy/nanoscopy [7]. *James G. Fujimoto et al.* pioneered clinical optical coherence tomography (OCT) by using a NIR femtosecond laser for their early OCT work in 1991 [8]. Today's commercial medical-certified OCT devices used mainly in ophthalmology are based on non-femtosecond light sources such as superluminescent diodes or swept sources.

The NIR femtosecond laser is not only of high interest for high-resolution non-linear imaging in biomedicine. The other major biomedical application is micro- and nanoprocessing. *König* introduced and commercialized the femtosecond laser nanoprocessing microscope for femtosecond laser targeted transfection, optical reprogramming including the generation of induced pluripotent stem cells (iPS), and intraocular intrastromal femtosecond laser surgery with MHz nanojoule pulses in live rabbits [9–13]. A 10 femtosecond 80 MHz Ti:sapphire laser microscope based

---

[*] Corresponding author: `k.koenig@blt.uni-saarland.de`

on chirped mirror technology was used to realize low power nanosurgery (<10 mW) [14].

The Nobel Prize in Physics in 2018 was awarded to *Donna Strickland* (the third woman who got the Nobel Prize in Physics after *Marie Curie* and *Maria Goeppert-Mayer*) and *Gerard Mourou* for the development of powerful femtosecond lasers by chirped-pulse amplification for micro- and nanoprocessing that revolutionized ophthalmic refractive surgery.

The third applicant of the 2018 Nobel Prize was Arthur Ashkin for his development of optical traps, so-called laser tweezers, using continuous wave (cw) NIR laser microbeams. Such NIR laser tweezers have been used in medicine for *laser-assisted in-vitro fertilization*. Interestingly, these highly focused cw NIR laser beams can also induce two-photon effects that may influence the motility and viability of trapped sperm cells. Of course, the generation of two-photon effects with a cw laser is less efficient than the use of an ultrashort laser [15, 16].

Today's clinical femtosecond laser systems are CE/FDA-certified medical devices used in dermatology for multiphoton tomography (MPT) to get label-free and non-invasively high-resolution optical biopsies of suspicious skin lesions, as well as in ophthalmology for refractive corneal surgery and cataract surgery.

Advantages of femtosecond laser medicine are the rapid "on-line in vivo skin histology" with the best resolution compared to any other clinical imaging method and the high intratissue precision of the ultrashort multiphoton laser scalpel compared to mechanical or ultrasound devices. The major disadvantage is the high price of the medical laser device.

This paper provides a short review of these certified medical NIR multiphoton femtosecond laser devices.

## 2 Clinical femtosecond laser for nonlinear skin imaging

One decade after the invention of the two-photon femtosecond dye laser microscope by *Denk, Strickler, and Webb,* the German company *JenLab GmbH* translated the two-photon microscope into the first commercial clinical femtosecond laser device: the class IIa CE0118-marked multiphoton tomograph *DermaInspect*. The tomograph for high-resolution label-free non-linear skin imaging is based on an 80 MHz turn-key tunable Ti:sapphire laser [17].

In 2004, the very first two CE0118-marked multiphoton tomographs were employed (i) for early diagnosis of patients suffering from malignant melanoma and (ii) for the evaluation of anti-ageing cosmetics [18].

The multiphoton tomographs provide label-free and completely non-invasive optical skin biopsies with a superior submicron spatial resolution due to NA1.3 focusing optics and the inherent two-photon sectioning effect (0.3 μm lateral and 1–3 μm axial) better than conventional microscopes for histopathology with typically six micrometer thick stained sections and NA < 1 air objectives (Fig. 1). Furthermore, no other clinical skin imaging devices such as OCT systems, photoacoustic devices, and confocal reflectance microscopes possess such a high resolution.

A further advantage of multiphoton tomographs is multimodality. In fact, autofluorescence, SHG, and fluorescence lifetimes (FLIM: fluorescence lifetime imaging) can be measured. The *DermaInspect* can also be employed with a high numerical aperture (NA0.8) two-photon GRIN microendoscope. The first clinical two-photon FLIM [19] and the first two-photon microendoscopy in patients have been realized with the medical femtosecond laser device *DermaInspect* [18] (Fig. 2).

The NIR laser beam with a typical mean power of 20 mW at the skin is focused with a piezo-driven NA1.3 objective and a working distance of 0.2 mm into the epidermis and the upper dermis. One horizontal optical section of 512 × 512 pixels is performed with galvoscanners within 1 s (high number of detected photons) to 6 s (low number of detected photons) without motion artefacts. The two photomultipliers simultaneously record signals based on two-photon excitation of endogenous fluorophores such as the coenzymes NADH and flavins, elastin, and the pigment melanin, as well as SHG of the extracellular matrix protein collagen. The autofluorescence is recorded by time-correlated single photon counting (TCSPC). From these data, 4D images can be realized with the false-color as a parameter of the mean fluorescence lifetime. König and his company JenLab GmbH also realized the first certified multimodal medical CARS (Coherent Anti-Stokes Raman Spectroscopy) device *DermaInspect-CARS* to image intratissue lipids [20].

The next generation of CE-certified medical tomographs was launched in 2010 and termed "MPT*flex*". This moveable tomograph was more flexible due to the use of an optical arm for femtosecond beam delivery in combination with a mechanical arm for fixation purposes, as well as the introduction of a 360° measurement head that contained up to four detectors (Fig. 3).

The MPT*flex* possesses a tunable femtosecond Ti:sapphire laser with a mean power of more than 1 W. This provides the possibility to realize a multimodal CARS system by splitting the beam into two beamlets and transmitting one of them through a photonic crystal fiber (PCF) for "white light generation" [21].

The latest multiphoton tomograph MPT*compact* (Fig. 4) is based on the use of a chiller-free and "optical-arm-free" ultracompact 50 MHz femtosecond fiber laser operating at 780 nm. The multimodal tomograph images autofluorescence, SHG, FLIM, and confocal reflectance. Five prototypes have been manufactured. Two of them were tested in a multicenter clinical study on 97 patients with suspicious pigmented lesions [22], and the third one is operating in the cosmetic industry in Japan. Currently, one multiphoton tomograph is in use at the *Wellman Labs* at *Massachusetts General Hospital/Havard University*. The certification process as a medical device by the Notified Body is ongoing.

So far, the multiphoton tomographs have been used on thousands of patients and volunteers in Australia, China, Japan, Russia, Singapore, the UK, the US, and within the *European Union*.

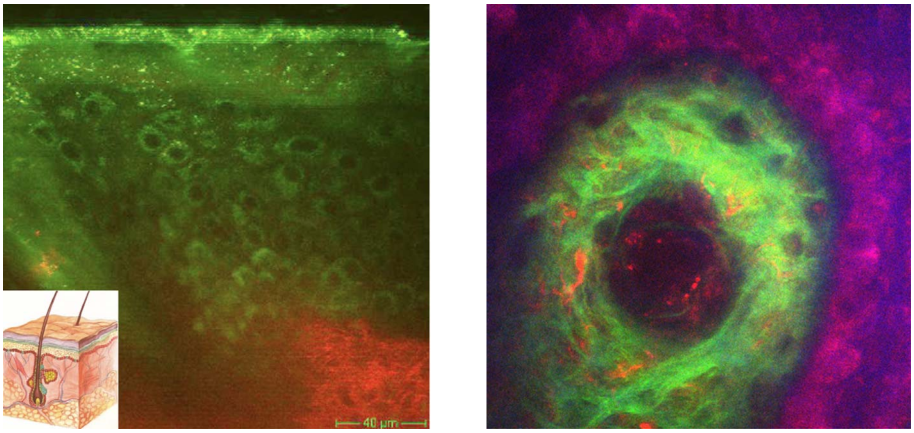

**Fig. 1.** Optical biopsies taken with the multimodal multiphoton tomograph. Left: vertical skin section. Right: horizontal 0.2x02.mm$^2$ overlay section (blue: confocal reflectance, red: two-photon excited autofluorescence, green: SHG of collagen) in a skin depth of 80 µm.

**Fig. 2.** The commercial multiphoton tomograph *DermaInspect* (laser class 1M) for high-resolution tissue imaging with a tunable near infrared 80 MHz femtosecond laser and time-resolved single photon counting (TCSPC) received the certificate of conformity as a class 2a medical device in 2004.

Applications include early detection of black skin cancer, testing anti-ageing effects of cosmetics, and measurement of the distribution of sunscreen nanoparticles and tattoo pigments, as well as skin modifications of astronauts after long-term space flights [23]. CE-certified multiphoton tomographs have also been employed in brain tumor imaging [24] and ophthalmology, such as for the quality check of human corneas prior to transplantation [25]. The sole manufacturer of multiphoton tomographs is the German company *JenLab GmbH*. The

**Fig. 3.** The second generation of multiphoton tomographs MPT*flex* is easy to move and possesses an optical arm with a 360° measurement head. The MPT*flex* received the certificate of conformity as a medical device in 2010. Left: "conventional" MPT*flex* with two PMT detectors. Right: Two-beam multiphoton tomograph MPT*flex*-CARS with four PMT detectors to measure simultaneously time-resolved autofluorescence, SHG, and Raman signals of lipids/water.

tomographs for non-linear skin imaging are used in large research hospitals, the cosmetic industry, the pharmaceutical industry, and at the *European Space Agency ESA*.

## 3 Clinical femtosecond laser for vision correction

The cornea is the outermost part of the eye and provides two-thirds of the total refractive power. Most refractive errors, such as myopia, can be corrected by shaping the cornea using ablation techniques. Refractive laser surgery started in 1988 by using an excimer laser to shape the human corneal stroma after mechanical removal of the corneal epithelium (*photorefractive keratectomy PRK*). The incorporation of the mechanical precision surgical instrument "microkeratome" for flap production to preserve the epithelium resulted in the laser treatment LASIK (*laser in situ keratomileusis*) [26, 27].

*Kurtz* and *Juhasz* performed pioneering work to introduce femtosecond lasers into refractive surgery. They conducted as cofounders of the US company *IntraLase* the first proof-of-concept clinical studies in Hungary and Italy in 1998 and 1999. In 2002, they reported on commercial applications of their femtosecond laser system in a clinical setting including 208 corneal procedures conducted from June to November 2000. The goal was, by using the femtosecond laser, to improve the precision of the flap production further and to replace the mechanical microkeratome [26, 27].

The NIR "femtosecond laser keratome" as a microsurgery tool based on photodisruptive effects due to multiphoton-induced plasma formation at transient laser intensities in the TW/cm$^2$ range received the FDA clearance in Dec 1999.

In 2002, 15 INTRALASE femtosecond laser systems were used by surgeons [26]. The two-laser method (NIR femtosecond laser for flap production and UV nanosecond laser for stromal ablation) was named "Femto-LASIK".

Certified medical laser devices based on a "photodisruptive" kHz/MHz femtosecond NIR laser in combination with the conventional photoablative nanosecond UV excimer laser have been used in the refractive surgery of hundreds

**Fig. 4.** The novel multimodal multiphoton tomograph MPT*compact*. The ultracompact fiber femtosecond laser is positioned inside the measurement head. A chiller and an optical arm are no longer required. The tomograph measures (i) 780 nm-excited autofluorescence of intratissue melanin, keratin, elastin, and the coenzymes NADH and flavins by time-correlated single photon counting, (ii) SHG at 390 nm from the collagen network, and (iii) confocal reflectance of the 780nm beam e.g., from the cell membranes. Furthermore, white-light images are provided for dermoscopy and laser beam location.

of millions of human eyes for cosmetic purposes. Ophthalmic femtosecond laser providers include, in alphabetic order, *Abbott Medical Optics Inc.* ("IntraLase" since 2001, Johnson & Johnson since 2016), *Alcon Laboratories Inc.* ("Wavelight FS200" since 2010), *Bausch + Lomb* ("Victus" since 2014), *Carl Zeiss Meditec AG* ("Visumax" since 2006), *SCHWIND* ("SCHWIND ATOS FS"), and *Ziemer Ophthalmic Systems* ("FEMTO LDV" since 2005).

The flap production with the femtosecond laser typically occurs within 5 s. Parameters of the modern class 4 excimer refractive laser *MEL90* from ZEISS are 193 nm laser wavelength, 4–7 ns pulse width, <2 mJ pulse energy,

**Fig. 5.** The commercial medical device *VISUMAX VM800* (laser class 3B) for refractive SMILE surgery and conventional "Femto-LASIK" in combination with the laser class 4 excimer laser *MEL90*. Source: ZEISS.

**Fig. 6.** Corneal refractive surgery with the *VISUMAX VM800*. Source: ZEISS.

and 500 Hz rep rate. A fast laser ablation speed of 1.3 s to correct for one diopter can be achieved. Today, more than 10 million "Femto-LASIK" procedures have been performed.

Nowadays, femtosecond NIR lasers are also employed without the combination with the excimer laser. This "flap-free" "all-femtolaser-based" technique is called SMILE (small incision lenticule extraction). The first SMILE proce-

**Fig. 7.** The ophthalmic femtosecond laser platform FEMTO LDV Z8 *for Femto-LASIK and* Corneal Lenticue Extraction for Advanced Refractive Correction (CLEAR), source: ZIEMER.

dures in the human cornea started in 2006 [27]. ZEISS received the European conformity approval for the SMILE procedure in 2011 and the FDA approval in 2016.

The minimally invasive laser vision correction with a small incision of 2 mm is performed with a focused NIR laser beam typically at 1043 nm laser wavelength, 200–600 fs pulse width, 2 MHz repetition rate, and 0.1 µJ pulse energy (760 mW) in 6–10 s laser time. SMILE has been performed with the laser class 3B medical device *VisuMax FS* from Carl Zeiss Meditec AG since 2007. The latest commercial ZEISS system VISUMAX VM800 (European conformity approval in 2022) is shown in Figures 5 and 6. The femtosecond laser is also employed for the precise shaping/cutting of donated corneas for transplantation.

In April 2020, the company *Ziemer Ophthalmic Systems AG* (Switzerland) with the femtosecond laser *FEMTO LDV Z8* platform got the European conformity approval for its laser-assisted lenticule extraction method *CLEAR* (Corneal Lenticule Extraction for Advanced Refractive Correction). Interestingly, the laser system operates at low nanojoule pulse energy with a high repetition rate up to 20 MHz under intraoperative OCT guidance [27] (Fig. 7).

The German company SCHWIND with the medical device *SCHWIND ATOS FS* (up to 4 MHz, 75–135 nJ) received the European conformity approval for its *SmartSight* application to extract lenticules in July 2020 [28, 29] (Fig. 8).

## 4 Clinical femtosecond laser for cataract surgery

Cataracts are the major course of blindness. Cataract surgery means the removal of the natural “cloudy” lens and its replacement by an artificial intraocular lens (IOL). Typically, the surgery is performed by minimal invasive phacoemulsification including 2–3 mm corneal cuts in a surgical center under local anesthesia with very low complication rate.

In order to improve the surgical outcome, the additional use of a NIR photodisruptive femtosecond laser beam as in LASIK has been suggested. The laser procedure is named “femtosecond laser assisted cataract surgery (FLACS)”, FALCS femtosecond-assisted laser cataract surgery (FALCS), and (refractive laser-assisted cataract surgery (ReLACS). First clinical femtosecond laser cataract surgeries were performed in Budapest and published in 2009 by Nagy et al. [30].

Nowadays, certified medical femtosecond laser devices, also used in Femto-LASIK, are employed in cataract surgery to perform the required corneal incisions, the capsulotomy, and to support the cataract nucleus fragmentation. Advantages are e.g. the very precise incisional astigmatism management and the reduction of the required phacoemulsification energy due to prior laser-induced lens fragmentation. Disadvantage is the higher price of the laser treatment compared with the standard procedure. So far, it has not been shown yet that femtosecond laser devices have a significant benefit over manual low-cost phacoemulsification [31–35].

## 5 Conclusions

So far, only two types of CE/FDA-marked commercial medical devices based on femtosecond laser technology exist: The multiphoton tomograph to generate optical tissue biopsies of high resolution based on two-photon imaging of autofluorescence/SHG and CARS as well as the micromachining refractive laser device for vision correction and cataract surgery based on photodisruptive effects due to multiphoton ionization and plasma formation.

The major disadvantage of current certified medical femtosecond laser devices is the high price compared with the standard mechanical (e.g. microkeratome) and optical medical devices (e.g. dermoscopy devices, confocal reflectance microscope, excimer laser). However, in near future, the price will drop due to technical improvement and mass production of the femtosecond laser (e.g. directly laser diode pumped ultrashort laser).

The introduction of the new *Medical Device Regulation* within the European Union combined with a significant increase of bureaucracy is considered to become a major

**Fig. 8.** The medical femtosecond laser system SCHWIND ATOS FS can be employed for the *SmartSight lenticule extraction*, source: SCHWIND eye-tech-solutions.

problem for innovative small and medium medical device enterprises.

Current medical multiphoton skin imaging devices have a limited working distance of (0.2–0.3) mm and a field of view of 0.3 × 0.3 $mm^2$ due to the use of conventional NA1.3 microscope objectives. New developments in focusing optics including adoptive optics, endoscopes, and tomograph-skin-interfaces may result in deeper and large-field imaging.

Applications of multiphoton tomographs include the early detection of skin cancer by two-photon autofluorescence imaging of intracellular coenzymes and of melanin in melanocytes, in particular in the case of malignant melanoma. Interestingly, tumor cells can be seen within minutes on the screen compared to standard procedure of taking biopsies, slicing, staining and microscopic evaluation that typical takes up to one week. In near future, also femtosecond laser guided tumor resection becomes feasible. Furthermore, cosmetic and pharmaceutical agents can be evaluated directly in the natural human intratissue microenvironment. For example, the biosynthesis of collagen by anti-ageing components can be studied over long-term periods (e.g. three months) as well as the interaction of topically administered pharmaceutics with human intratissue cells. This helps also to reduce animal studies.

Future MPT applications include the study of effects of air pollution in cities (particulate matter/dust) on our immune system including allergic skin reactions and the effect of climate changes to the skin including UV exposure response, sweat gland production, and “dry skin” effects such as impaired barrier function. Also the effect of long-term space flights on thickness, metabolism, and skin ageing can be studied with multiphoton tomographs.

However, the major application of medical femtosecond laser systems is their use as “optical scalpel”. Millions short-sighted persons have conducted a “femtosecond LASIK” treatment to get rid of their glasses or contact lenses.

Commercial femtosecond laser eye treatment devices replaced already mechanical microkeratomes for corneal flap generation in many hospitals. Interestingly, due to the new “all-in-one” femtosecond laser systems, the generation of flaps for corneal surgery is no longer required. The refractive surgery can now completely be done with an infrared femtosecond laser without the additional use of a nanosecond ultraviolet excimer laser.

There is the realistic hope, that, once the femtosecond laser device is already in place, it will be used more often in the surgery of cataracts and other eye diseases.

## Conflict of interest

The author is co-founder and CEO of the company JenLab GmbH.

## References

1 Goeppert-Mayer M. (1931) Über Elementarakte mit zwei Quantensprüngen (Göttinger Dissertation), *Ann. Phys.* **401**, 273.

2 Franken P.A., Hill A.E., Peter C.W., Weinrich G. (1961) Generation of optical harmonics, *Phys. Rev. Lett.* **7**, 118.

3 Kaiser W. (2018) The long journey to the laser and its use for nonlinear optics, in: König K. (eds.), *Multiphoton microscopy and fluorescence lifetime imaging*, De Gruyter, Berlin/Boston, 17 p.

4 Bugiel I., König K., Wabnitz H. (1989) Investigation of cells by fluorescence laser scanning microscopy with subnanosecond time resolution, *Lasers Life Sci.* **3**, 1.

5 Denk W., Strickler J.H., Webb W.W. (1990) Two-photon laser scanning microscopy, *Science* **248**, 4951.

6 Krueger A. (2018) Ultrafast lasers biophotonics, in: König K. (ed.), *Multiphoton microscopy and fluorescence lifetime imaging*, De Gruyter, Berlin/Boston, 53 p.

7 Moneron G., Hell S.W. (2009) Two-photon excitation STED microscopy, *Opt. Express* **17**, 14567.

8 Huang D., Swanson E.A., Lin C.P., Schuman J.S., Stinson W.G., Chang W., Hee M.R., Flotte T., Gregory K., Puliafito C.A., Fujimoto J.G. (1991) Optical coherence tomography, *Science* **254**, 1178.

9 König K. (1999) Intracellular nanosurgery with near infrared femtosecond laser pulses, *Cell. Mol. Biol.* **45**, 195.

10 Tirlapur U., König K. (2002) Targeted transfection of cells by femtosecond near-infrared laser pulses, *Nature* **418**, 290.

11 Uchugonova A., Breunig H.G., Batista A., König K. (2015) Optical reprogramming of human somatic cells using ultrashort Bessel-shaped near-infrared femtosecond laser pulses, *J. Biomed. Opt.* **20**, 11.

12 König K. Verfahren zur nicht-invasiven optischen Bearbeitung von Geweben des Auges sowie zu dessen Diagnose und Vorrichtung zur Durchführung dieser Verfahren. DE10115751 and DE 10148783B4, filed on 27.03.2001 and 28.09.2001. Device for the treatment of tissues of the eye and for diagnosis thereof. EP1372552B1, filed on 26.03.2002. Licensed to Wavelight.

13 König K. (2003) High-resolution multiphoton imaging and nanosurgery of the cornea using femtosecond laser pulses, in: Fankhauser F., Kwasniewska S. (eds.), *Lasers in ophthalmology. Basics, diagnostic and surgical aspects*, Kugler Publications, Amsterdam, Netherlands, pp. 79–89.

14 König K., Uchugonova A., Straub M., Zhang H., Licht M., Afshar M., Feili D., Seidel H. (2012) Sub-100 nm material processing and imaging with a sub-15 femtosecond laser scanning microscope, *J. Laser Appl.* **24**, 042009-1.

15 König K., Liang H., Berns M.W., Tromberg B.J. (1995) Cell damage by near-IR microbeams, *Nature* **377**, 20.

16 König K. (2018) Laser tweezers are sources of two-photon effects, in: König K. (ed.), *Multiphoton microscopy and fluorescence lifetime imaging*, De Gruyter, Berlin/Boston, 177 p.

17 König K., Riemann I. (2003) High-resolution multiphoton tomography of human skin with subcellular spatial resolution and picosecond time resolution, *J. Biomed. Opt.* **8**, 432.

18 König K. (2023) Invited paper: History of clinical multiphoton tomography, in: Periasamy, König, So (eds.), Proceedings vol. 12384 Multiphoton Microscopy in the Biomedical Sciences XXIII of the SPIE Conference Photonics West, San Francisco, 2023, p. 12384-40.

19 König K. (2020) Review: Clinical in vivo multiphoton FLIM tomography, *Methods Appl. Fluoresc.* **8**, 034002.

20 König K., Breunig H.G., Bückle R., Kellner-Höfer M., Weinigel M., Büttner E., Sterry W., Lademann J. (2011) Optical skin biopsies by clinical CARS and multiphoton fluorescence/SHG tomography, *Laser Phys. Lett.* **8**, 1.

21 König K., Breunig H.G., Batista A., Schindele A., Zieger M., Kaatz M. (2020) Translation of two-photon microscopy to the clinic: Multimodal multiphoton CARS tomography of in vivo human skin, *J. Biomed. Opt.* **25**, 014515.

22 König K., Pankin D., Paudel A., Hänßle H., Winkler J.K., Zieger M., Kaatz M. (2021) Invited Paper: Skin cancer detection with a compact multimodal fiber laser multiphoton FLIM tomograph, in: Periasamy, König, So (eds.), Proceedings vol. 11648 Multiphoton Microscopy in the Biomedical Sciences XXI of the SPIE Conference Photonics West, San Francisco, p. 116480A.

23 König K., Weinigel M., Pietruszka A., Bückle R., Gerlach N., Heinrich U (2015) Invited paper. Multiphoton tomography of astronauts, in: Periasamy, König, So (eds.), Proceedings vol. 93290 Multiphoton Microscopy in the Biomedical Sciences of the SPIE Conference Photonics West, San Francisco, p. 93290Q.

24 Kantelhardt S.R. (2018) Multiphoton microscopy and fluorescence lifetime imaging for resection guidance in malignant glioma surgery, in: König K. (ed.), *Multiphoton microscopy and fluorescence lifetime imaging*, De Gruyter, Berlin/Boston, p. 395.

25 Batista A., Breunig H.G., Donitzky C., König K. (2018) Two-photon microscopy and fluorescence lifetime imaging of the cornea, in: König K. (ed.), *Multiphoton microscopy and fluorescence lifetime imaging*, De Gruyter, Berlin/Boston, p. 303.

26 Kurtz R. (2002) The story of IntraLase, *Cataract Refract. Surg. Today.*

27 Juhasz T., Kurtz R.M., Horvath C., Suarez C.G., Nordan L., Slade S. (2002) Femtosecond laser eye surgery: The first clinical experience, *SPIE Proceed.* **4633**, 461363.

28 Fuest M., Mehta J.S. (2021) Advances in refractive corneal lenticule extraction, *Taiwan J. Ophthalmol.* **24**, 113.

29 Bohac M., Derhartunian V., Pradhan K.R., Gabric I. (2022) *ATOS and SmartSight: Current Trends and Procedural Volume*, CRST Europe.

30 Nagy Z., Takacs A., Filkorn T., Sarayba M. (2009) Initial clinical evaluation of an intraocular femtosecond laser in cataract surgery, *J. Refract. Surg.* **25**, 1053.

31 Roberts T.V., Lawless M., Bali S.J., Hodge C., Sutton G. (2013) Surgical outcomes and safety of femtosecond laser cataract surgery: A prospective study of 1500 consecutive cases, *Ophthalmology* **120**, 227.

32 Alió J.L., Abdou A.A., Puente A.A., Zato M.A., Nagy Z. (2014) Femtosecond laser cataract surgery: Updates on technologies and outcomes, *J. Refract. Surg.* **30**, 420.

33 Popovic M., Campos-Möller X., Schlenker M.B., Ahmed I.I. (October 2016) Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: A meta-analysis of 14 567 eyes, *Ophthalmology* **123**, 10, 2113–2126.

34 Moshirfar M., Milner D., Patel B.C. (June 21, 2022) *Cataract surgery*. https://www.ncbi.nlm.nih.gov. National Center for Biotechnology Information. PMID 32644679. Retrieved March 10, 2023.

35 Xu J., Li W., Xu Z., Zhao B., Zhong Y., Wang K., Liu X., Song X., Yu Y., Zhu Y., Tang Q. (2023) Comparative visual outcomes of EDOF intraocular lens with FLACS vs. conventional phacoemulsification, *J. Cataract Refract. Surg.* **49**, 55.