Optical Coherence Tomography

A Case Study in Medical Imaging Adoption

OCT technology has revolutionized ophthalmology. Cross-sectional scans of the eye and quantitative analysis are now critical for the diagnosis and monitoring of many ocular diseases. The adoption of OCT took time, however. In retrospect, ophthalmic OCT evolved through a series of "5-year" steps from invention to adoption and proliferation. Success came through close collaboration between researchers in academia, clinical users, and industry. The full potential of OCT in medical applications has yet to be achieved: there are opportunities for both further advances in ophthalmic imaging and adoption in new fields of medicine.

The diagnostic capabilities of optical coherence tomography have revolutionized ophthalmology. Every second, somewhere in the world, an ophthalmic OCT scan is performed. Widespread clinical adoption of this technology came from a convergence of technology, clinical applications, and needs of the medical community. More specifically, the success of OCT came from packaging clinical solutions into a medical device which provided demonstrable clinical benefits. This success has been achieved through collaboration of researchers, clinicians and industry.

In retrospect, OCT passed through several distinct phases. Creation of OCT in academic research led to a startup phase, establishing industrial partnerships in which the new technology was incorporated into prototypes and clinical applications were explored. Lessons from the prototype phase led to the first commercial generation of OCT, which can be characterized more as a "laboratory tool" used by clinical researchers. Knowledge gained in this phase was consolidated in the second generation, which became a clinical "workhorse." Expanding adoption drove further research, and implementation of even higher speed and resolution OCT technology led to today's third generation of technically advanced instruments which are now in widespread clinical use.

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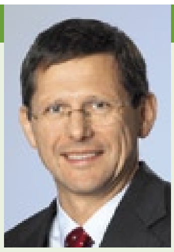

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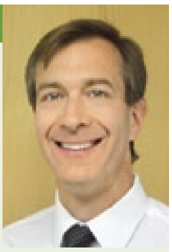

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Ophthalmic imaging with OCT

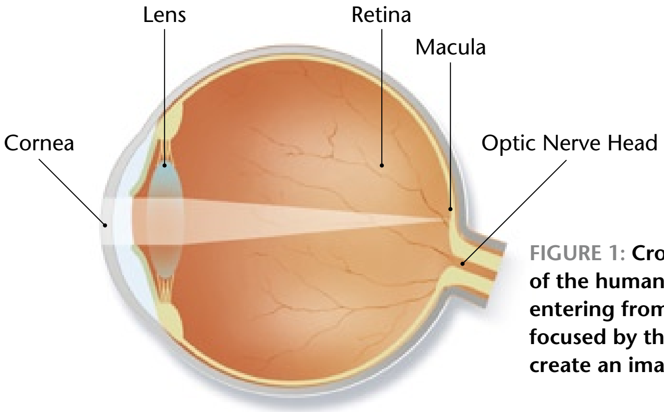


FIGURE 1: **Cross-sectional schematic of the human eye showing light entering from the left, and being focused by the cornea and lens to create an image on the retina.**

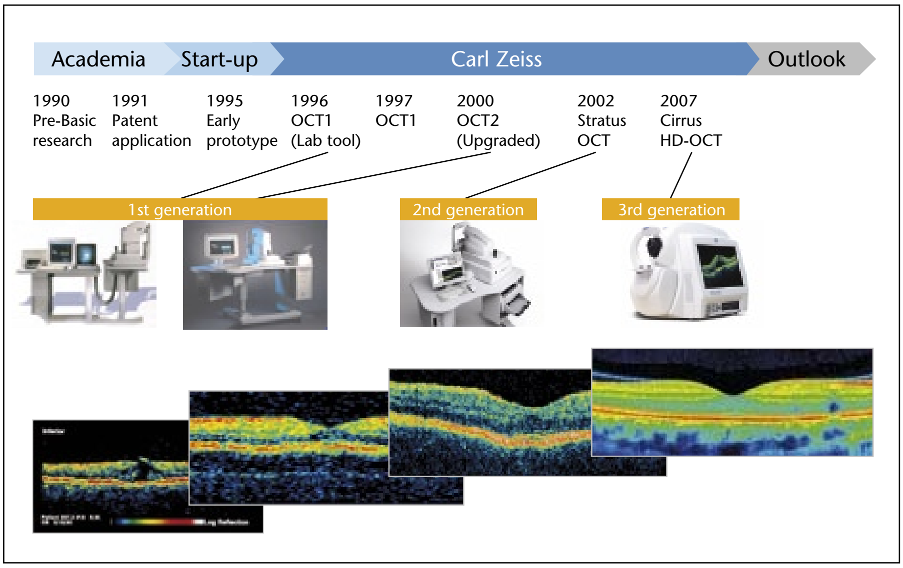


FIGURE 2: **Timeline showing development of various generations of OCT for ophthalmology.**

Imaging the back of the eye presents unique challenges. The human pupil limits the aperture of the eye, and avoiding glare from reflections from the cornea and crystalline lens presents a significant challenge (see Fig. 1). Helmholtz is generally credited with invention of the first ophthalmoscope in 1850, permitting observation of the retina, and fundus cameras recording images on film followed. A major breakthrough in fundus imaging came in 1980 with introduction of the "Flying Spot TV Ophthalmoscope," a point scanning imager based on the principles of confocal scanning microscopes [1]. Several companies developed commercial versions of the scanning laser ophthalmoscope. These innovative instruments demonstrated the utility of retinal scanning. For laser scanners as well as confocal microscopes, the axial (depth) and transverse (lateral) resolutions depend strongly on the detector Numerical Aperture (NA):

$$\text{Axial resolution} \qquad \Delta z \; \alpha \; \frac{\lambda}{NA^2}$$

$$\text{Lateral resolution} \qquad \Delta x \; \alpha \; \frac{\lambda}{NA}$$

Confocal laboratory scanning microscopes, the fore-runner of the scanning laser ophthalmoscope, have excellent axial and transverse resolution because laboratory setups can have a large NA. Unfortunately, scanning laser ophthalmoscopes have limited depth (axial) resolution because the human eye has a relatively small pupil, and therefore, a small NA.

In the late eighties and early nineties, James Fujimoto's group at MIT Research Laboratory of Electronics overcame the limited depth resolution by decoupling axial resolution from NA [2]. Optical Coherence Domain Reflectometry (OCDR) is based on coherence gating, the principle that interference between broadband light from a sample and a reference will generate a signal only when the path lengths match. By varying the path length of the reference, the scattering intensity of the sample can be measured as a function of depth to create an A-scan. The axial resolution is limited by the bandwidth of the light source, $\Delta\lambda$, so the axial and transverse resolutions are decoupled [3]:

$$\text{Axial resolution OCT} \qquad \Delta z \; \alpha \; \frac{\lambda_0^2}{\Delta\lambda}$$

Low-coherence interferometry with short pulse lasers had previously been used for optical ranging (OCDR). At MIT, OCDR was adapted to tissue imaging by laterally scanning light from a superluminescent diode across tissue. Backscattered light was coupled into an interferometer to capture depth resolved scattering profiles, creating "B-scans" of the retina. This innovation sparked a series of engineering developments and clinical products, as shown in Figure 2.

Among the first OCT images published were cross-sectional images of the retina and optic disk in vitro, suggesting that OCT could provide a revolutionary method for visualizing the living retina. The healthy retina is a layered structure of photoreceptors and neural tissue with retinal vessels woven through it. Traditional fundus cameras provide a two-dimensional photo formed from light scattered by the retina, or from fluorescence generated by dyes injected into the patient's bloodstream. A typical photo from a healthy retina is shown in Figure 3. For many pathologies, traditional two-dimensional images are sufficient for characterizing the disease. In others, however, such as macular edema and macular holes, the tissue layers are disrupted. These changes are best viewed in cross-section, in views analogous to histological cross-section. OCT not only measures scattered light intensity, but it also resolves this scattering in the axial dimension. Measurement of scatter intensity vs. depth along a single line is referred to as an A-scan. Scanning across the retina to collect a series of A-scans generates a 2D image, referred to as a B-scan. The resulting B-scans thus create cross-sectional images of the living retina.

This first OCT setup was far from a practical clinical instrument, yet the inventors recognized the promise of this technology. OCT was patented in 1991, and transferred from MIT into Advanced Ophthalmic Devices, a company formed to further develop the technology in 1992. Humphrey Instruments (San Leandro, CA), now part of Carl Zeiss Meditec, purchased Advanced Ophthalmic Devices the next year to commercialize OCT.

First generation

The first commercial instrument, OCT 1, was launched in 1996. This instrument gave researchers around the world the opportunity to investigate clinical applications of OCT. By today's standards, the performance of OCT 1 is modest, and there was a steep learning curve for interpreting images of retinal pathology. Nevertheless clinical researchers embraced the technology, in-

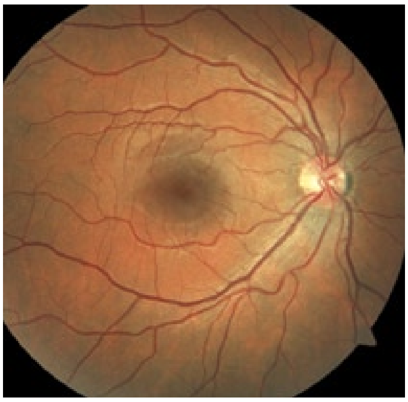
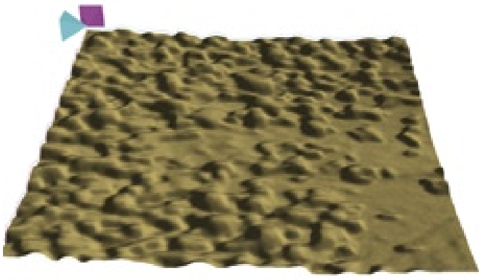
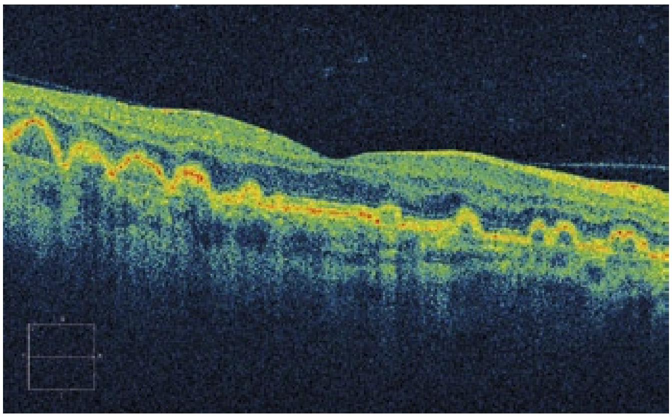


FIGURE 3: **Color fundus photograph of a healthy retina showing macula (center) and optic nerve head (right).**





◀▲ FIGURE 4: **Analysis of OCT data cubes reveals pathological drusen under the photoreceptor layers of the retina in early age-related macular degeneration.**

vestigating both a wide range of diseases and measurement methodologies.

With an expanding base of OCT instruments, analysis methods and manufacturing expertise quickly accumulated. Within a few years the instrument design was modified to take advantage of this knowledge. The instrument was consolidated into a single instrument table, the user interface was improved, and most importantly a quantitative glaucoma analysis package including a normative database was added.

Early users of OCT, mostly specialists in clinical research, not only guided OCT development, but also educated ophthalmologists in its use. OCT provided retinal specialists with dramatically new visualization capability and glaucoma specialists with new metrics for diagnosis. Clinicians involved in the creation of OCT educated the medical community, and many ophthalmologists, such as Carmen Puliafito, MD, Michael Hee, MD, and Joel Schuman, MD at the New England Eye Center, played pivotal roles in the retina and glaucoma specialist communities. During this time the first edition of Optical Coherence Tomography of Ocular Diseases, a textbook illustrating the use of OCT in ophthalmology, was published [4]. As researchers continued to gain access to OCT technology, the number of clinical publications mushroomed.

Second generation

Broader market demand required a new platform with better scanning technology and detection electronics, incorporating clinical know-how and engineered for routine clinical use. Successful clinical research had led to better understanding of clinical applications, but technology had advanced as well. James Fujimoto's group at MIT recognized that the phase delay techniques developed for laser pulse shaping could also provide a faster axial scan for OCT [5]. The light is spectrally separated and reflected from a mirror, the tilt of which creates a ramped phase delay across the spectrum. The resulting group delay can be substantial, allowing much faster scanning of the delay than possible by straightforward delay line designs. Refinements to the design of the rapid scanning optical delay line (RSOD) made it practical for instrument production. The RSOD was a key component of a complete redesign of the platform for widespread and routine clinical use. These design evolutions provided better technical performance, better ease-of-use, and a more compact platform, which would become a clinical workhorse.

When Stratus OCT was launched in 2002, ophthalmic applications of OCT had advanced dramatically. The increasing number of clinicians using OCT demonstrated a growing understanding of how to interpret those images. Faster scanning speed and better axial resolution of Stratus OCT, based on the RSOD principle, gave even higher-quality images, thus accelerating this process. Quantitative analyses of the data improved as well with inclusion of normative data for both glaucoma and retinal analysis. As more ophthalmologists adopted OCT, evidence mounted for the use of OCT for common diseases like glaucoma, age-related macular degeneration, diabetic retinopathy, and retinal artery and

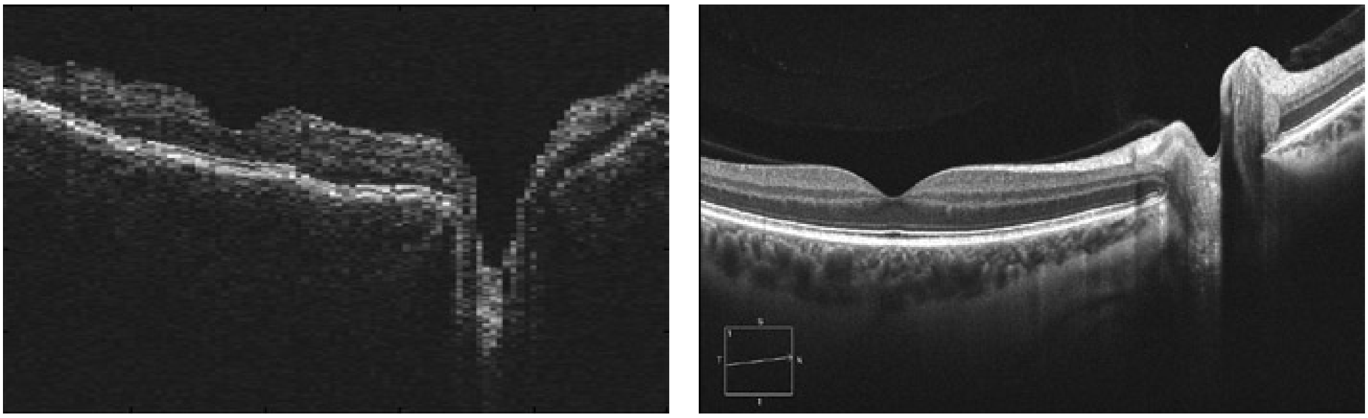


FIGURE 5: **Sample images from first generation (a) and third generation instruments (b), showing foveal depression (left) and optic nerve head (right).**

vein occlusions. Validation of Stratus OCT analysis tools was a key element of achieving clinical reimbursement for OCT scans, which was an important milestone in the commercial development of ophthalmic OCT.

Third generation

As clinical acceptance of OCT became widespread, technology research was continuing as well. Commercial development of OCT medical devices, both within and outside of ophthalmology, provided further incentive for funding agencies to support OCT research. A practical demonstration of spectral-domain OCT (SD-OCT) in an ophthalmic application was reported in 2003 [6]. Rather than detecting broadband light with a single-detector and scanning the interferometer's reference arm for axial resolution, SD-OCT dramatically increases efficiency by acquiring scattering information for all depths simultaneously. The backscattered light is collected and combined with the reference light. When the combined light is spectrally dispersed, the resulting spectrum is a combination of the broadband source spectrum and the "interference spectrum," fringes due to wavelength-dependent interference between scattered and reference light. The spectrum contains information about light scattering at all depths, so a Fourier-transform of the spectrum yields the scattering profile as a function of tissue depth. Although the concept of SD-OCT was widely known, the publication of experimental results in 2003 led other research groups to quickly follow with key publications on SD-OCT in ophthalmology [7, 8, 9].

Development of SD-OCT instruments has been fundamentally different from previous generations. Product development of first and second generation OCT occurred in an era of early adopters, but the current generation was developed after OCT 1 and Stratus OCT had firmly established the clinical importance of OCT. The existing user community covered broad ranges of medical specialization and of OCT expertise, with varying needs for data acquisition, imaging objectives, and data analysis. The large user base provided feedback on all aspects of the product needs, scientific, clinical, and operational.

The capability of this current generation of OCT to visualize the retina in three dimensions and to provide automated analysis of complex retinal pathologies is clear. Figure 4 demonstrates the value of automated layer detection to facilitate clinical decision-making. Rather than reviewing an entire 3D data set, the clinician quickly reviews disruptions of the retina photoreceptors with a single rendering. Figure 5 compares B-scans from OCT 1 to the current generation of SD-OCT. Improved axial resolution and higher scanning speed show new detail in the photoreceptors, a tissue layer compromised by age-related macular degeneration. Finally, Figure 6 demonstrates the extension of second generation glaucoma analysis to a third generation data cube. The retinal nerve fibers, which transmit visual signals from the retina to the brain, are slowly destroyed by glaucoma. The cube is automatically analyzed to measure the thickness of the vulnerable retinal nerve fiber layer, and the usual cross-section analysis is performed by extracting a virtual circle scan from the data. A more traditional glaucoma exam is based on evaluating the appearance of the optic nerve head, and this figure shows how the traditional cup-to-disc analysis is improved by detection of the cup and rim boundaries around the optic nerve head.

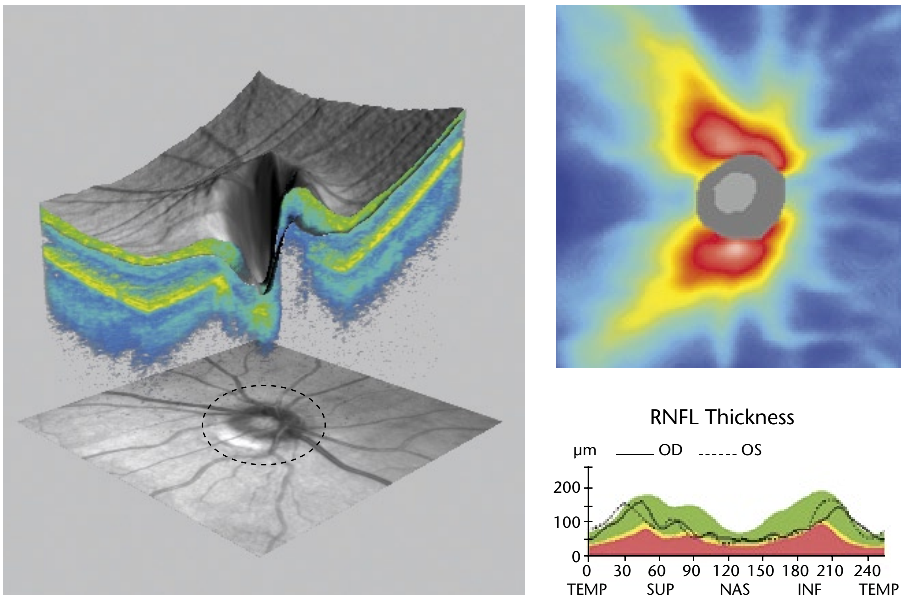


FIGURE 6: **Extension of glaucoma analysis from second to third generation. Image at left shows data cube, and annulus selected for retinal nerve fiber layer (RNFL) thickness plot. RNFL thickness map with cup and disc of optic nerve head (top right). RNFL thickness plot (lower right).**

THE COMPANY

Carl Zeiss Meditec

Carl Zeiss Meditec AG is one of the world's leading medical technology companies. The company supplies innovative technologies and application-oriented solutions designed to help doctors improve the quality of life of their patients. It provides complete packages of solutions for the diagnosis and treatment of eye diseases – including implants and consumable materials. The company creates innovative visualisation solutions in the field of microsurgery. Carl Zeiss Meditec's medical technology portfolio is rounded off by promising future technologies such as intraoperative radiation therapy.

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Observations

A remarkable technology like OCT is not immediately embraced by the medical community on its own merits. Adoption into daily ophthalmic care required several other key elements. Close partnerships between researchers and industry transferred the technology from the university lab and generated a cycle of technology improvements followed by technology deployments and further innovation. These partnerships developed and demonstrated tangible medical advantages: depth-resolved imaging of the retina complemented traditional fundus imaging, and quantitative diagnostics facilitated clinical decision-making. Close partnerships were also critical in providing this technology in an approved medical device, reducing doctor's workloads and expanding their diagnostic abilities. Patients also benefit from this technology because exams are noninvasive, noncontact, and fast. Compared to traditional fundus imaging, OCT generates excellent retinal images with near infrared light. This allows doctors to achieve comprehensive retinal imaging without patient discomfort from

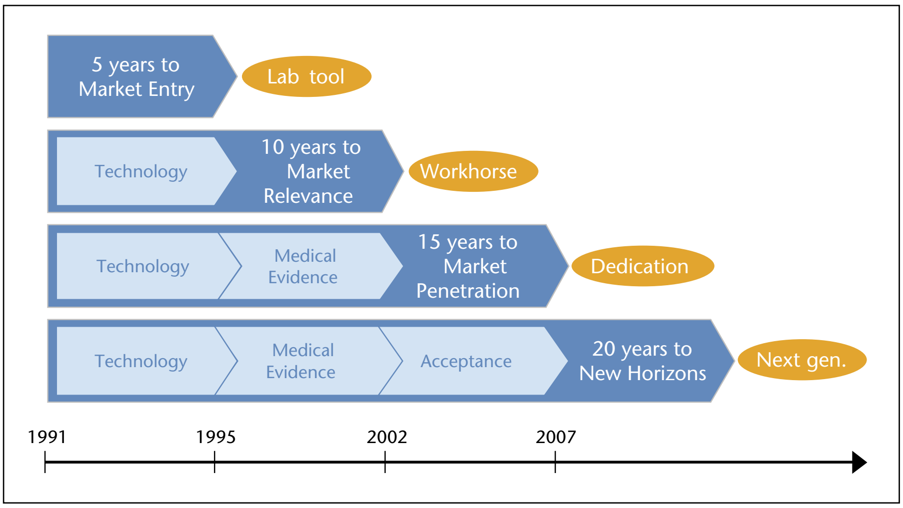

FIGURE 7: **Development and adoption of OCT in ophthalmology came in five year increments (“five year rule”) [11].**

bright light. Implementation of OCT created entirely new exam types and results, and appropriate educational resources were made possible by cooperation between industry, advisors, and professional societies. Perhaps most important was the vision of the inventors to recognize the potential of this technology and to actively pursue it.

Success did not come immediately, and a decade passed between the first investments and market success. In retrospect, the adoption of OCT in ophthalmology has gone through distinct phases spaced about five years apart. In the startup phase, the potential of OCT was recognized and the technology transferred from the research lab to industry. The first generation OCT was a laboratory tool employed largely by researchers. OCT 1 laid the groundwork for the market breakthrough by the second generation, which became a clinical workhorse. After this market success came today’s third-generation in which radical technology improvements were applied to established clinical applications.

The long adoption period of OCT is not unique among medical technologies. We propose a “five year rule” to describe this technology development and adoption process, as shown in Figure 7. A review of refractive laser development reveals a similar pattern [12]. The initial IP (Trokel, Srinivasan) was created in 1983, followed in 1987 by the first proof-of-concept PRK, analogous to the OCT lab tool. The first LASIK by Pallikaris was in 1991, followed by commercialization of flying spot lasers in 1998 and customized ablation in the early 2000’s. These successive generations of excimer lasers are now being followed by a new technology leap, the use of femtosecond all-in-one procedures without excimer lasers, such as the VISUMAX All-In-One.

Outlook beyond third generation of OCT

Generalizing from the current OCT landscape and other medical imaging modalities, the fourth generation may be one of technology “proliferation” as development appears to be following dual paths. Adoption of OCT in ophthalmology will be followed by adoption in more invasive applications with longer regulatory and development cycles, with systems increasingly specialized for endoscopy, cardiology, and other fields [10]. In ophthalmology, remarkable images will not be enough. Technology developments will be accompanied by fuller integration into medical practices with other, established technologies, such as automation, data management, image fusion, and communications platforms. Efforts to include OCT in interventional procedures and to combine OCT with other imaging modalities will continue. Of course new components and techniques will expand the performance envelope of axial resolution, scan speed, data analysis, and optical sampling mechanisms like endoscopes. Exciting technology development lies ahead for ophthalmology and the expansion of imaging capabilities into other medical disciplines.

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