Honda Foundation Report No. 188
Commemorative Lecture at the 45th Honda Prize
Award Ceremony on the 18th November 2024

Optical Coherence Tomography: Development, Evolution and Future Prospects

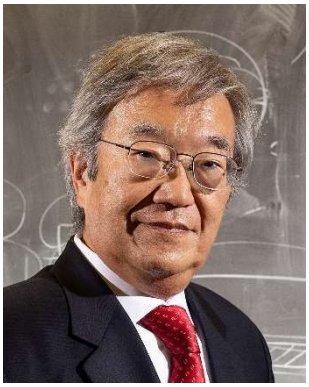
Dr. James G. Fujimoto

Elihu Thomson Professor,

Department of Electrical Engineering and Computer Science and
Research Laboratory of Electronics,

Massachusetts Institute of Technology (MIT)

HONDA FOUNDATION



Dr. James G. Fujimoto

Elihu Thomson Professor,
Department of Electrical Engineering and
Computer Science and Research Laboratory of Electronics,
Massachusetts Institute of Technology (MIT)

■Date of Birth

September 28, 1957, Illinois, U.S.A.

■Education

1979	Massachusetts Institute of Technology, SB
1981	Massachusetts Institute of Technology, SM, EE
1984	Massachusetts Institute of Technology, PhD

■Research and Professional Experiences

1985-1988	Assistant Professor, Department of Electrical Engineering and Computer Science, MIT
1985-1996	Consultant, Optical Communications Group, Lincoln Laboratory, MIT
1988-1994	Associate Professor, Department of Electrical Engineering and Computer Science, MIT
1992	Co-Founder of Advanced Ophthalmic Devices, startup developing ophthalmic OCT
1992-1995	Consultant, Humphrey Instruments
1994-present	Adjunct Professor of Ophthalmology, Tufts University
1994-present	Professor, Department of Electrical Engineering and Computer Science, MIT
1998	Co-Founder of LightLab Imaging, startup developing intravascular OCT
1998-2002	Consultant, LightLab Imaging
2010	Co-Founder of Idesta Quantum Electronics, startup developing ultrafast laser technology
2011-present	Elihu Thomson Professor of Electrical Engineering, MIT
2016-present	Adjunct Professor, Medical University of Vienna

■Professional Services

1996, 1998	Ultrafast Phenomena Conference: Program Co-Chair, General Co-Chair
2000-2023	Optical Coherence Tomography and Coherence Domain Methods in Biomedicine, Biomedical Optics Symposium, SPIE Photonics West
2001-2003	Optical Society of America: Board of Directors
2002, 2004	Conference on Lasers and Electro-Optics (CLEO): Program Co-Chair, General Co-Chair
2003-2017	Laser Microbeam and Medical Program (LAMMP), NIH Biomedical Technology Resource Center, University of California: Scientific Advisor
2003-2005	National Academy of Engineering, Japan-America Frontiers of Engineering Symposium: Co-Chair
2003, 2005	European Conferences on Biomedical Optics ECBO, Munich, Germany: Program Co-Chair
2007-present	International Society for Imaging in the Eye / Association for Research in Vision and Ophthalmology (ARVO) Imaging Conference: Co-Chair
2008-2019	SPIE Biomedical Optics Symposium: General Co-Chair
2008-2014	Multidisciplinary Optical Imaging Group of the Association for Research in Vision and Ophthalmology (ARVO): Co-Chair
2013-2018	SPIE, International Optics and Photonics Society: Board of Directors

■Awards

1990	National Academy of Sciences Baker Award for Initiatives in Research
1999	Discover Magazine Award for Technological Innovation
2001	National Academy of Engineering
2002	IEEE Lasers & Electro-Optics Society William Streifer Scientific Achievement Award
2002	Co-recipient of the Rank Prize in Optoelectronics
2002	American Academy of Arts and Sciences
2003	SPIE President's Award
2006	National Academy of Sciences
2011	Carl Zeiss Research Award
2012	Co-recipient of the António Champalimaud Vision Award
2015	Honorary Doctorate, Nicolaus Copernicus University, Torun, Poland
2015	Optical Society of America Ives Medal
2017	Co-recipient, European Inventor Award
2017	Beckman-Argyros Award in Vision Research
2017	Co-recipient, National Academy of Engineering, Fritz J. and Dolores H. Russ Prize
2018	Honorary Doctorate, Friedrich-Alexander-Universitat Erlangen-Nuremberg, Germany
2022	IEEE Medal for Innovations in Healthcare Technology
2023	National Medal of Technology and Innovation
2023	Lasker-DeBakey Clinical Medical Research Award
2024	Lawrence A. Yannuzzi Award, International Retinal Imaging Society

■Publications

- Journal Publications (568 Publications)
- Books (13 Books)
- Chapters in Books (44 Chapters in Books)

This report is the gist of the commemorative lecture at the 45th Honda Prize Award Ceremony at the Imperial Hotel, Tokyo on 18th November 2024.

Optical Coherence Tomography:
Development, Evolution and Future Prospects

Dr. James G. Fujimoto

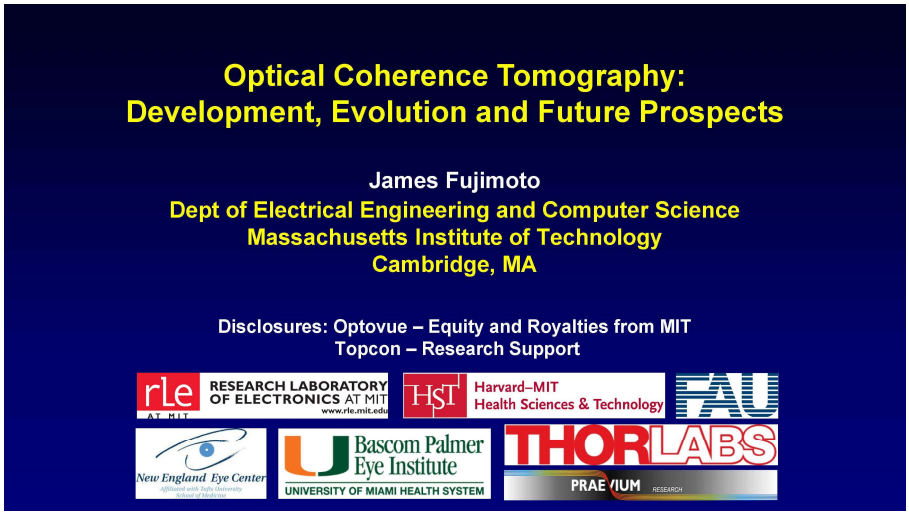


Fig. 1

〈Fig. 1〉 Thank you very much. It's really a great privilege to have the opportunity to speak to you this afternoon. The topic of this lecture is "Optical Coherence Tomography: Development, Evolution and Future Prospects", but before I begin, I wanted to express my sincere thanks to the Honda Foundation and the selection committee. As you know, the Honda Foundation emphasizes eco-technology and its impact on society, so I'm especially honored that the work that we've done, which is embodied by engineering and science in general, was nominated for the Honda Prize. We want to advance science and technology to make a positive impact on health and wellbeing, to create jobs, and to improve societal conditions in general.

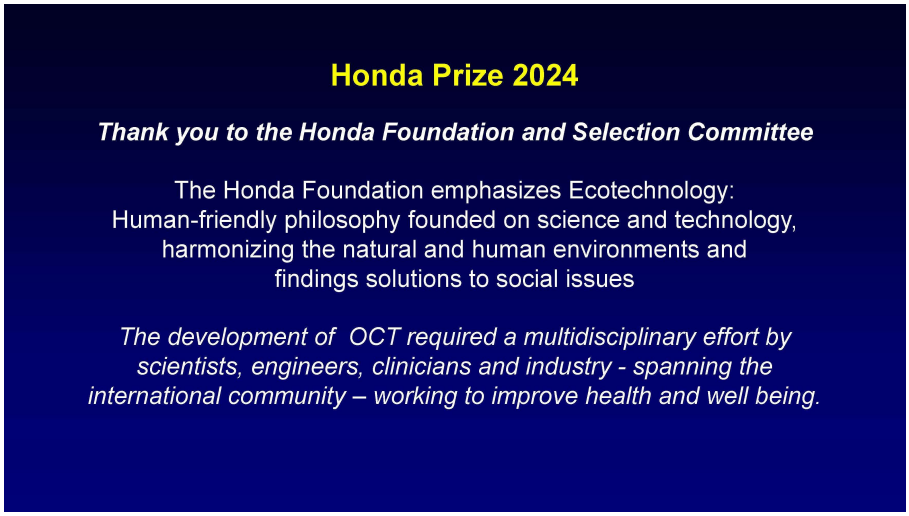


Fig 2

〈Fig. 2〉 The development of OCT is an especially interesting example, in the sense that it

is multi-disciplinary. It required a combination of science, engineering, clinical medicine, and industry commitment, spanning the international community, working together to improve health and well-being.



Fig. 3

〈Fig. 3〉 Before I begin, I also want to acknowledge our current and recent group members at MIT. We are also very fortunate to be able to work with clinical collaborators at the New England Eye Centre and multiple other institutions, with thought leaders in the field of ophthalmology and in other areas, as well as with industry; Thorlabs, Premium Research and with Topcon Corporation.

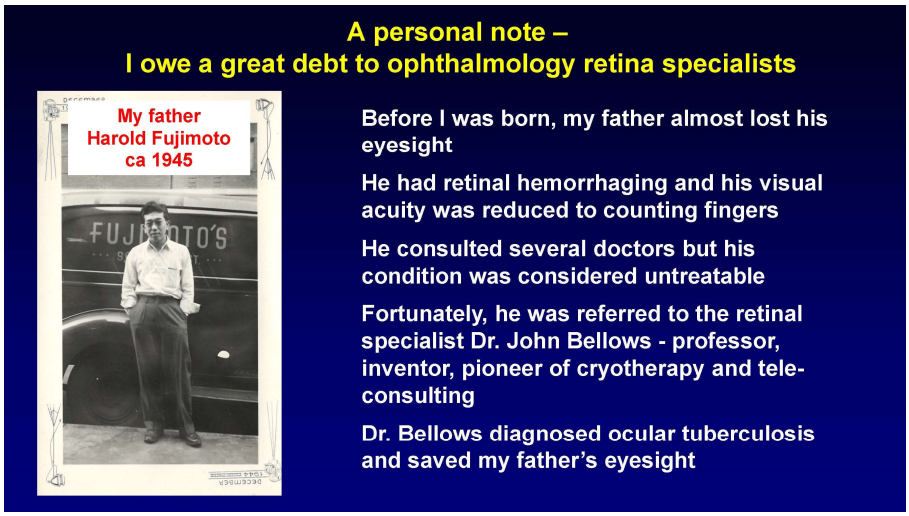


Fig. 4

〈Fig. 4〉 I also wanted to mention a personal note, because I know there are clinicians in the audience. I owe a great debt to ophthalmology retina specialists because my father almost lost his eyesight - this is his photo when he was younger. He had retinal hemorrhaging and his visual acuity was reduced to counting fingers. He saw several doctors, but his condition was difficult

to diagnose, and it was considered untreatable. But fortunately, he was referred to a retinal specialist, Dr. John Bellows. Dr. Bellows was a professor, a clinical thought leader, an inventor, a pioneer of cryotherapy, who also pioneered teleconsulting. He diagnosed my father with ocular tuberculosis, which is an uncommon disease and difficult to diagnose; he saved my father's eyesight. So, I have a great respect for clinical medicine and for retinal specialists in particular.

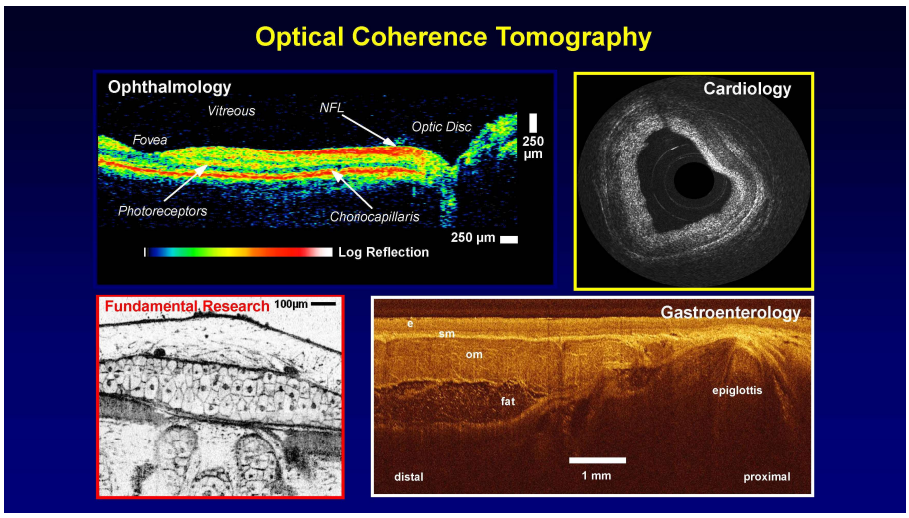


Fig. 5

〈Fig. 5〉 Optical coherence tomography (OCT) has had its largest application in the field of ophthalmology, but it's also used in cardiology and other areas, such as gastroenterology, as well as in fundamental research.

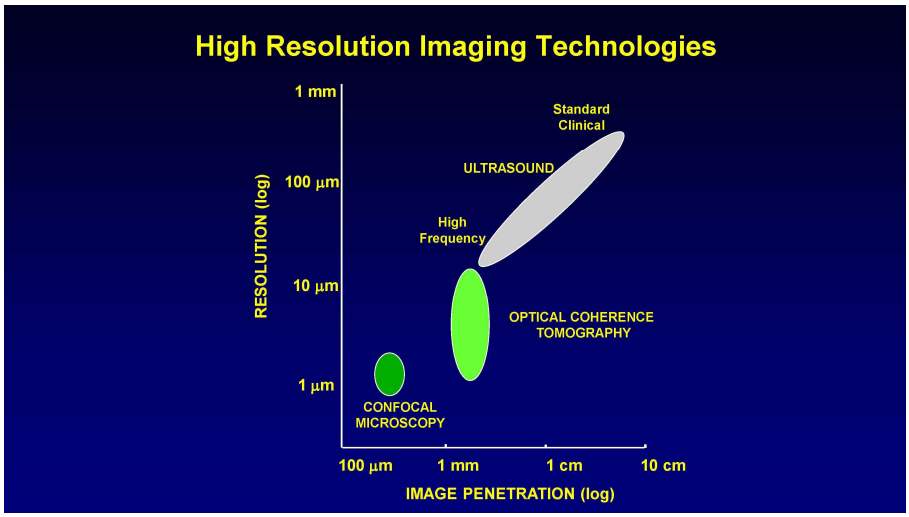


Fig. 6

〈Fig. 6〉 If we think about how OCT versus other imaging methods, here we have a comparison of resolution and image penetration; ultrasound is here, full body imaging, scaling the frequency to get higher resolution reduces penetration. The highest resolution imaging would be microscopy, and OCT fits between ultrasound and microscopy, micron scale resolution with a penetration depth a greater than microscopy, but less than ultrasound.

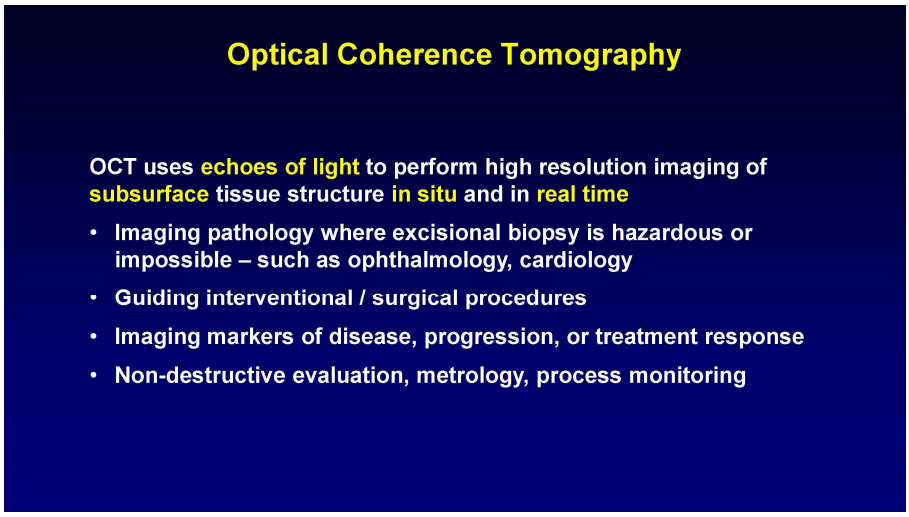


Fig. 7

〈Fig. 7〉 Optical coherence tomography is a technique that uses echoes of light to image internal or subsurface structure at high resolution, in situ without removing specimens and in real time.

There are multiple applications; imaging pathology where you could not do biopsy; the retina, in ophthalmology, would be an example, but also cardiology where the arteries are very rarely biopsied. It's possible to guide interventional or surgical procedures, and also to image markers of disease progression or treatment response, for diagnosis as well as pharmaceutical development. There are also applications for non-destructive evaluation, metrology and process monitoring.

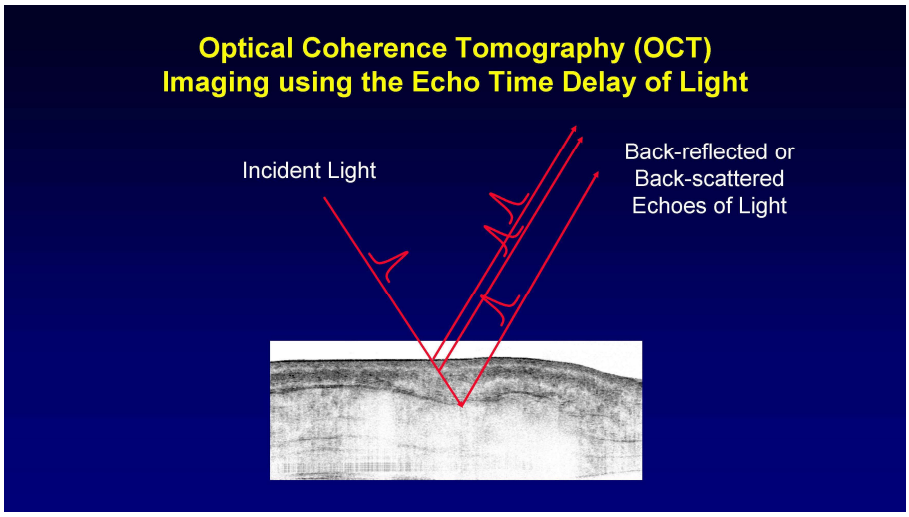


Fig. 8

〈Fig. 8〉 Essentially, OCT is the analogue of ultrasound; it uses echoes of light and by measuring the echo time delay and magnitude, it can construct information on subsurface structure.

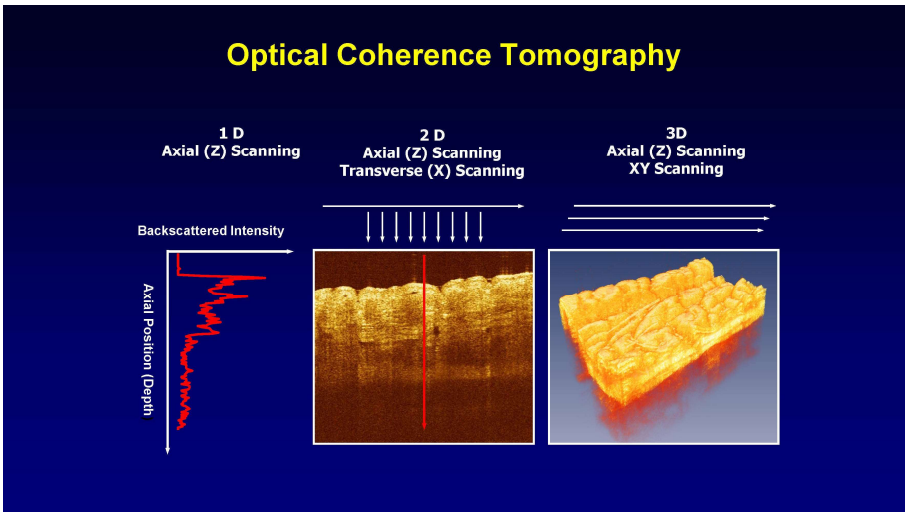


Fig. 9

〈Fig. 9〉 This can be done in one-dimension, axial scanning to measure depth; or by scanning the laser in two dimensions to generate a cross-sectional image; or in three dimensions to generate a volumetric image.

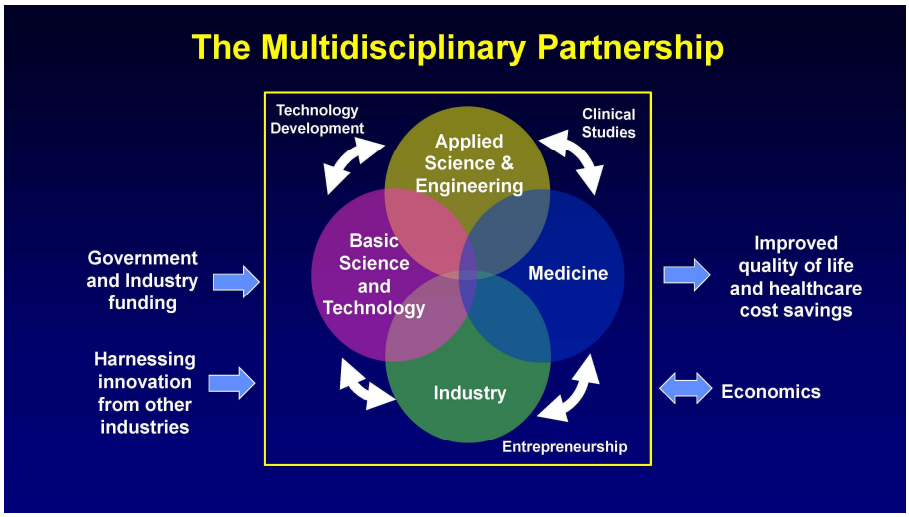


Fig. 10

〈Fig. 10〉 One of the interesting points about OCT is that is required a multi-disciplinary partnership; government and industry funding supports basic science and technology, but it's also important to have applied science and engineering to develop technology; studies by clinical thought leaders; and investment and development from industry. All of these are important and interact in order to bring new methods from the laboratory to clinical practice. The ultimate objective is to improve the quality of life and health care, as well as to have healthcare savings. In the case of OCT, it was possible to use innovations from other areas and other industries, and there also was an economic impact which we'll comment on later.



Fig. 11

〈Fig. 11〉 So let's start with basic science and technology.

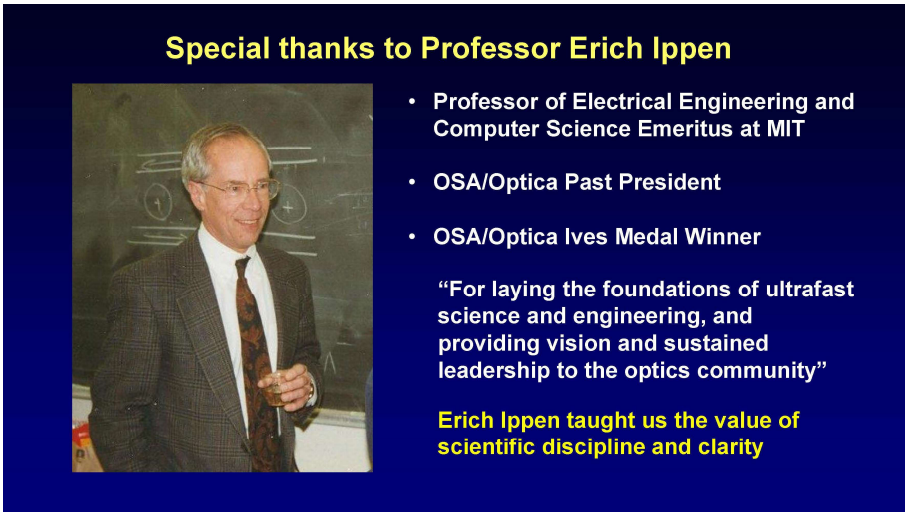


Fig. 12

〈Fig. 12〉 I especially wanted to acknowledge my mentor, my thesis advisor, Professor Erich Ippen. Professor Ippen was Professor of Electrical Engineering and Computer Science at MIT. He was the Past President for OSA/Optica, one of the large optical societies. He won the Ives Medal for laying the foundations of ultrafast science and engineering as well as for providing vision and sustained leadership to the optics community. Erich really had a profound impact on my scientific training. He taught us the value of scientific discipline and clarity of observation, which I think are important in many areas.

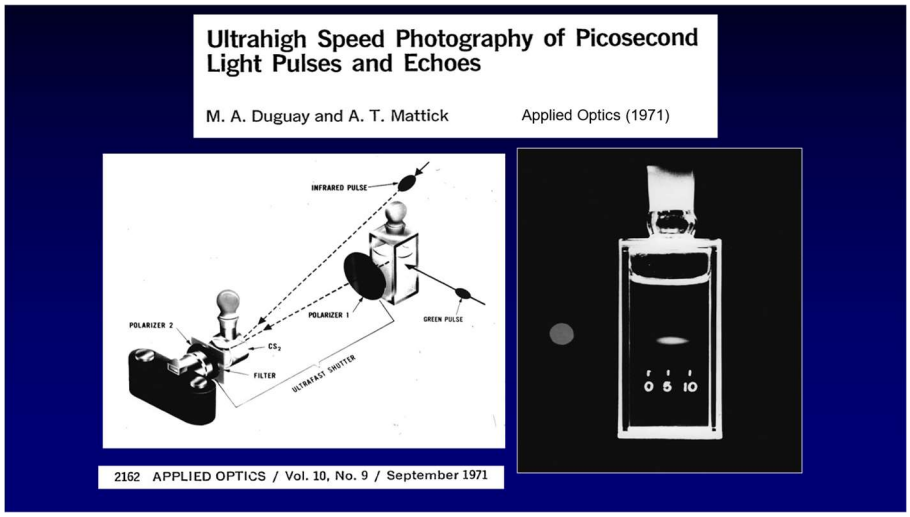


Fig. 13-1

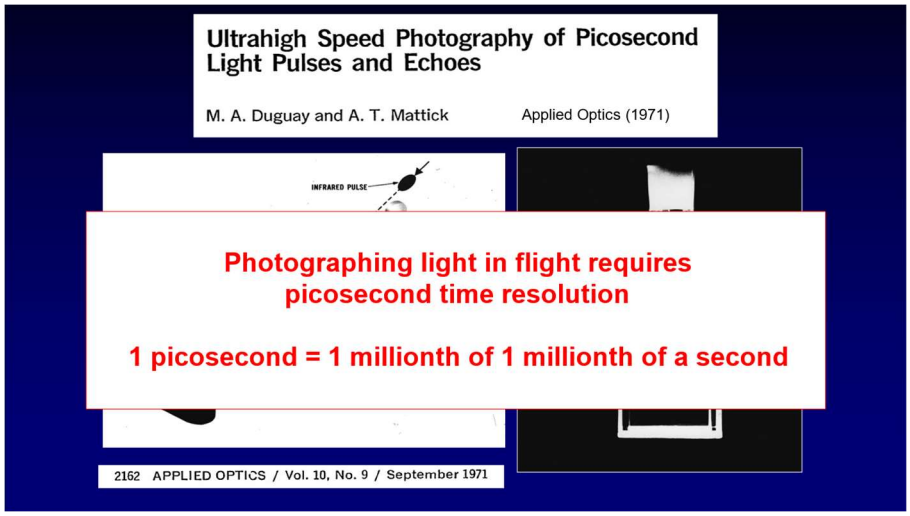


Fig. 13-2

〈Fig. 13〉 The original concepts for OCT imaging actually came from a study that was done at AT&T Bell Laboratories by Michel Duguay in 1971. He developed a method for high speed photography by using lasers, and he photographed a pulse of light in flight. This is a remarkably high-speed photograph requiring a picosecond time resolution; to put this in perspective, a picosecond is one millionth of one millionth of a second.

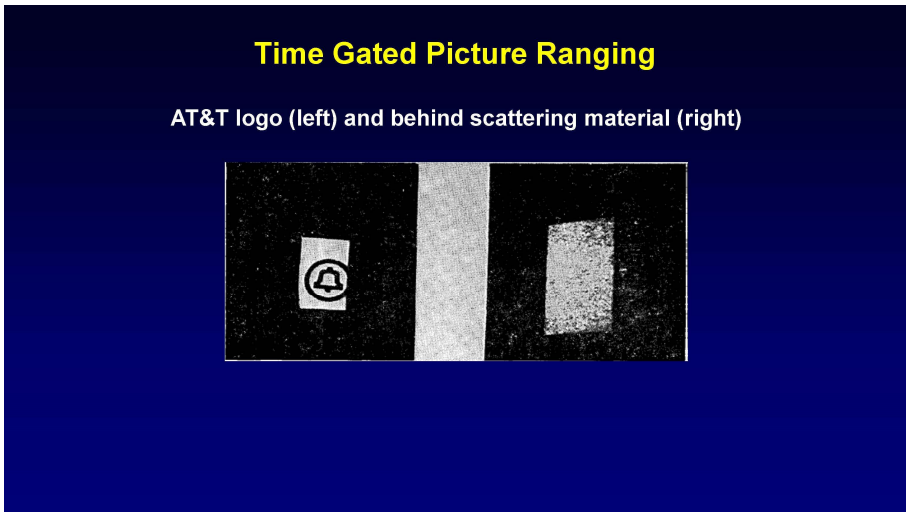


Fig. 14-1

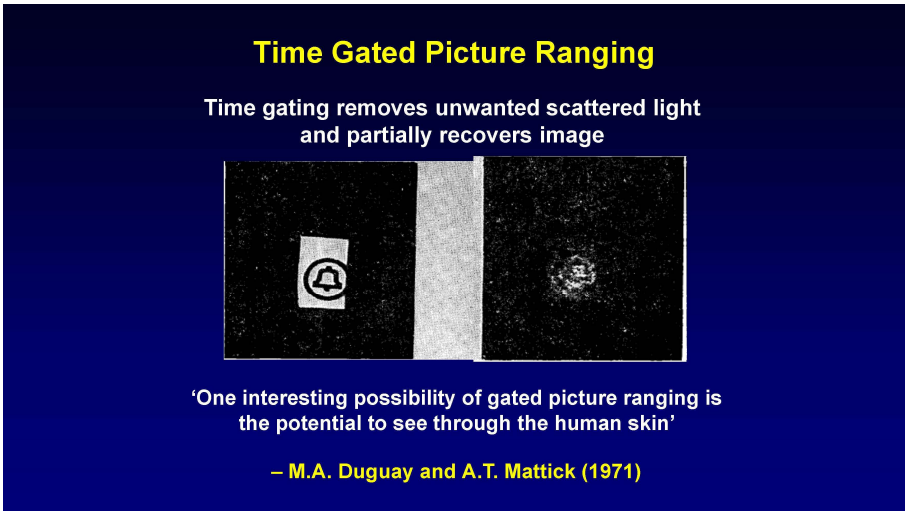


Fig. 14-2

〈Fig. 14〉 In his paper, he commented that you could take a photograph of an AT&T logo that is behind a scattering material and by gating out the unwanted scattered light you could partially recover the information that is essentially subsurface.

Duguay suggested the possibility of using this method to see inside the body, to see through human skin. I think this was one of the first proposals to use short-pulse technologies for biomedical imaging, back in 1971.

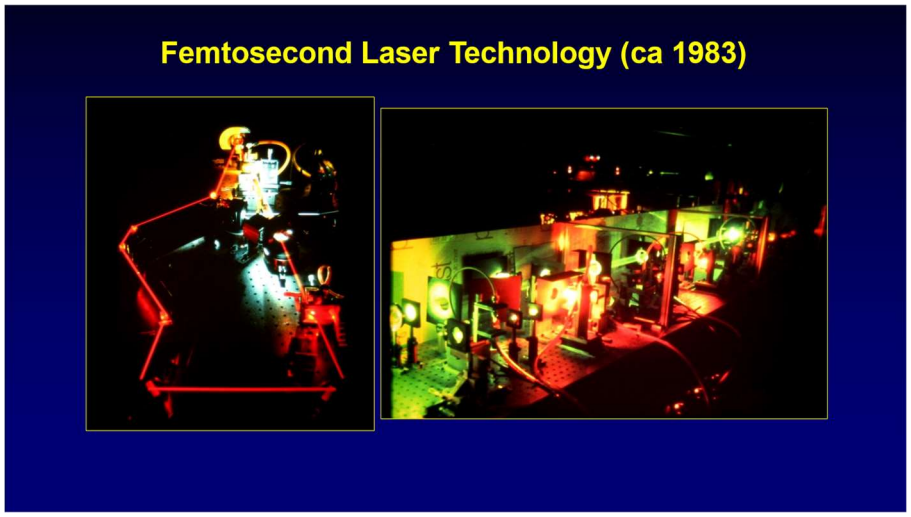


Fig. 15-1

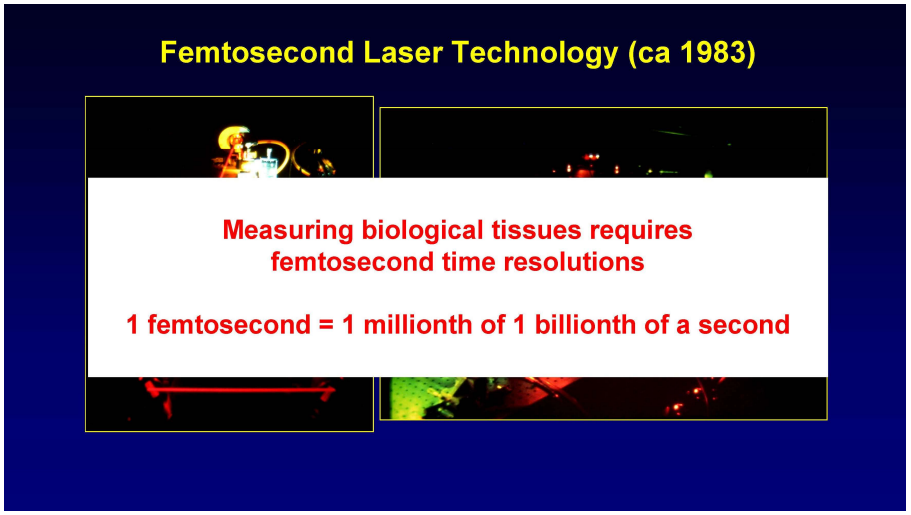


Fig. 15-2

〈Fig. 15〉 I was fortunate to work with Erich Ippen on femtosecond laser technologies. These are femtosecond lasers that you see here, 1983. To put this in perspective, if we want to measure biological tissues, we need essentially femtosecond time resolution. A femtosecond is one millionth of one billionth of a second, so it was faster even than picoseconds.

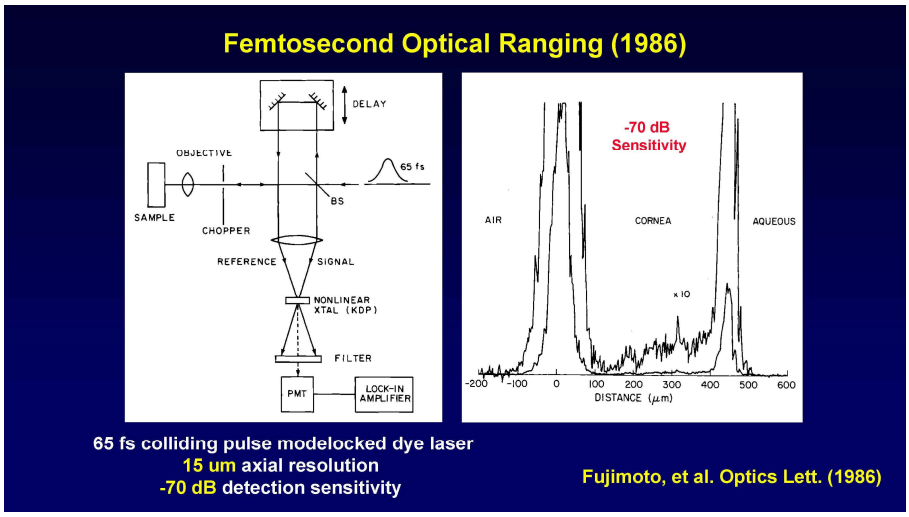


Fig. 16

〈Fig. 16〉 We became interested in applying this technology to measure biological specimens. This is a classic method in ultrafast science, a measurement comparing reflected or back-scattered light against a reference light. Using this, it was possible to measure the thickness of the cornea, the cornea-air interface, to see internal structure and it was also possible to image the skin. But the problem was, femtosecond lasers are expensive, and the sensitivity was limited.

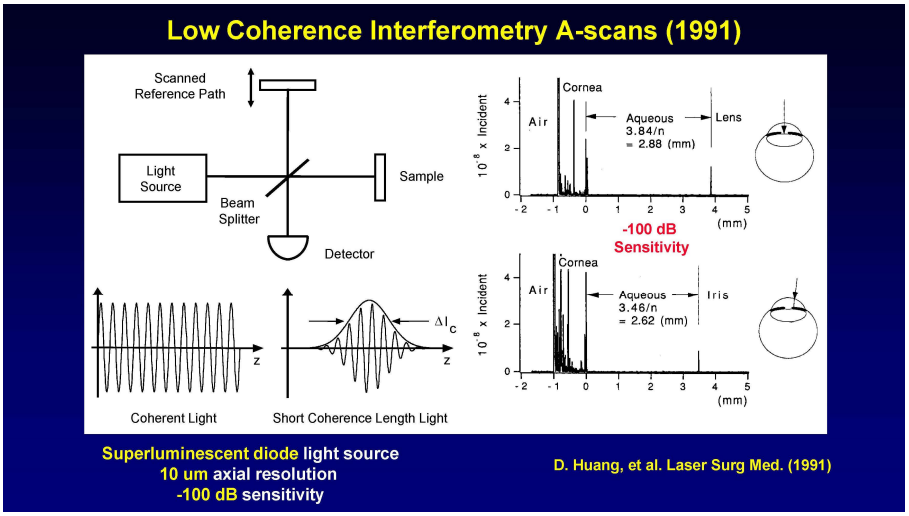


Fig. 17

〈Fig. 17〉 The solution was to use interferometry, a classic physics technique. The Michelson interferometer uses a light source and compares light from a sample to a reference path. By using low coherence light, it was possible to localize information or echoes of light from the sample. This shows an example measuring the air-to-cornea interface, the anterior chamber of the eye, aqueous to the lens, By displacing the beam, we can measure a different profile. Interferometry had the advantage of extremely high sensitivity and low cost.

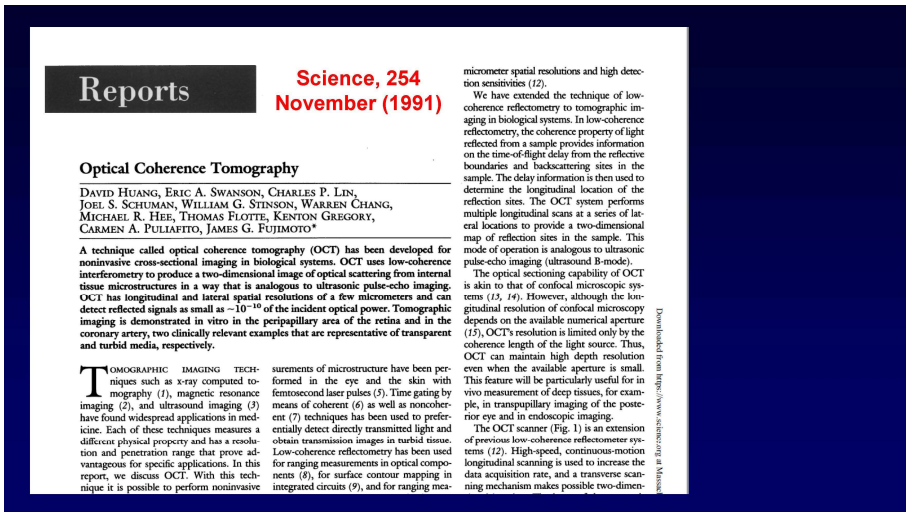


Fig. 18

〈Fig. 18〉 With this advance, it became possible to imagine performing imaging. Optical Coherence Topography was published in Science 1991, and I especially wanted to mention Dr. David Huang.



Fig. 19

〈Fig. 19〉 The person on the right is David as an MD, PhD student, This photo was taken at an optics conference with collaborators from Italy. David demonstrated the first OCT images in the retina and the coronary artery. He is now Professor of Ophthalmology and Bioengineering at the Oregon Health and Sciences University.



Fig. 20

〈Fig. 20〉 There were also people involved. Dr. Joel Schuman was a Glaucoma Fellow at the Massachusetts Eye and Ear Infirmary, Harvard Medical School, and did early studies imaging cow eyes, bovine eyes, as well as human cadaver eyes. Joel is now Professor of Ophthalmology, Vice-chair for Research and Innovation at the Wills Eye Hospital.

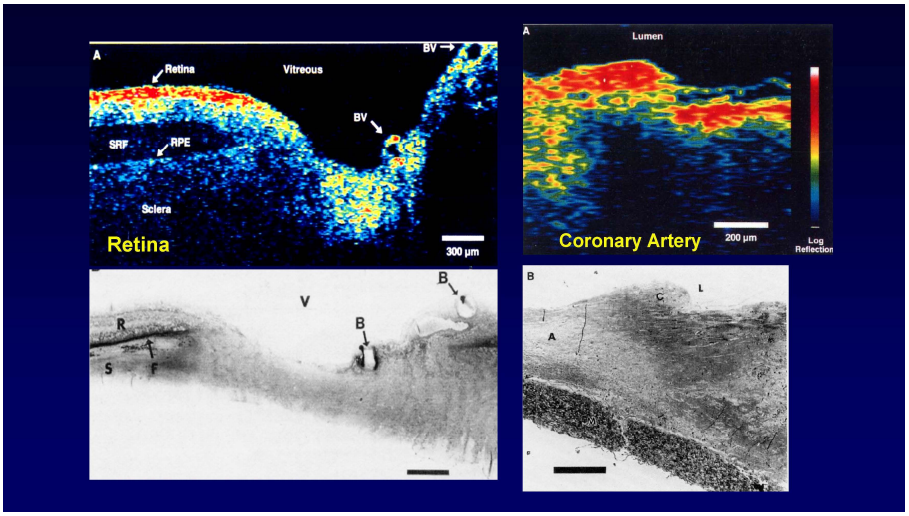


Fig. 21

〈Fig. 21〉 So, these are examples of the first OCT images in retina and also in the coronary artery. By coincidence these became the leading medical applications for this technology.

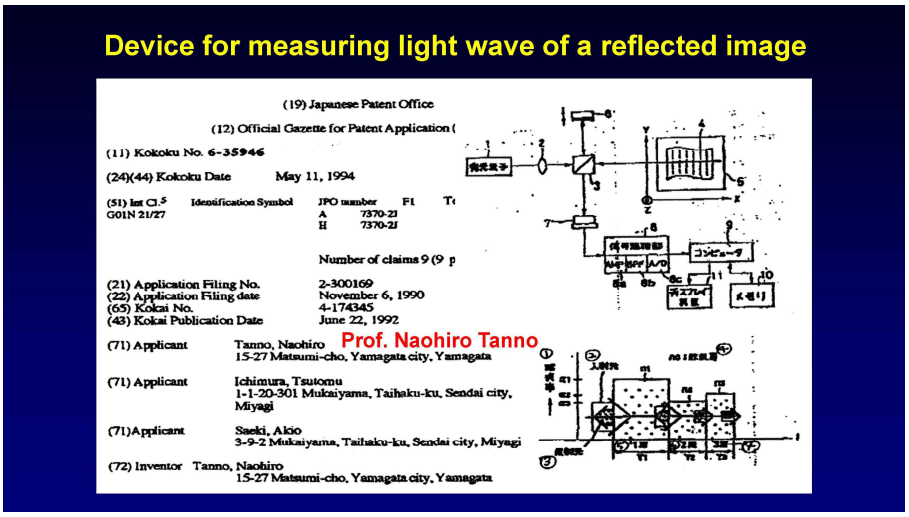


Fig. 22

〈Fig. 22〉 In parallel with this, there was work in Japan by Professor Naohiro Tanno. This shows a patent, “Device for measuring the light wave of a reflected image”. He also proposed the concept of using interferometry for precision measurement and for imaging.

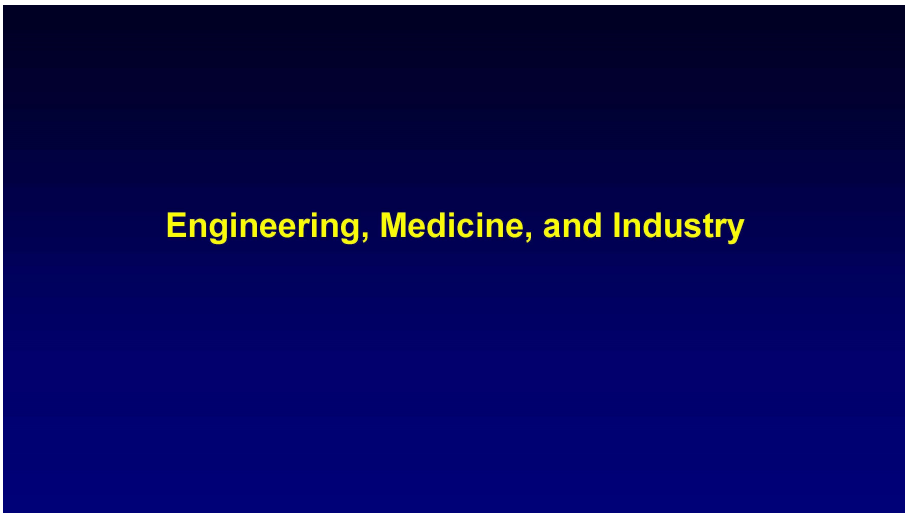


Fig. 23

〈Fig. 23〉 So, let’s consider how advances in engineering translated to medicine and industry.

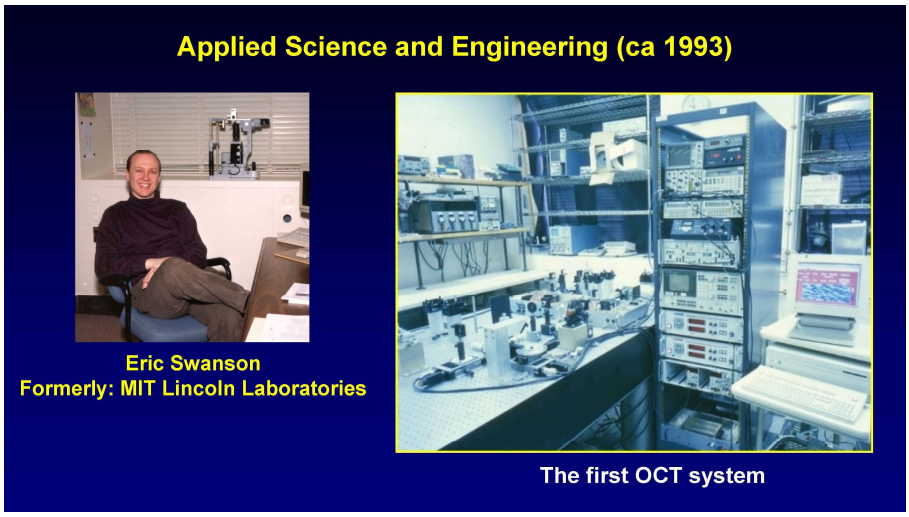


Fig. 24

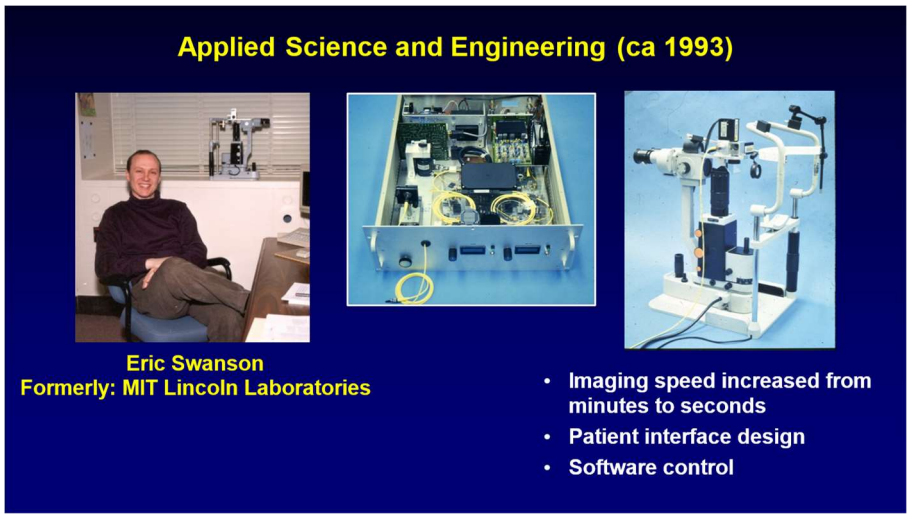


Fig. 25-1

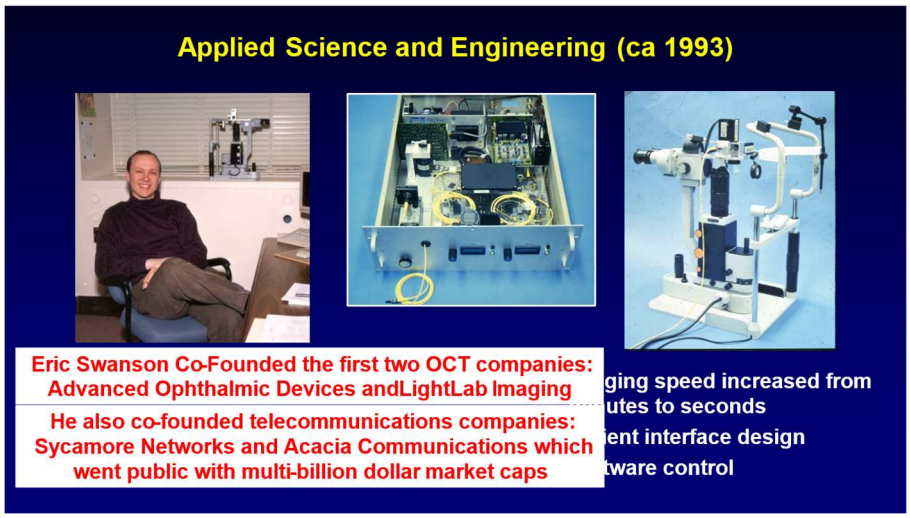


Fig. 25-2

〈Fig. 24 and 25〉 We were very fortunate to collaborate with Eric Swanson. Eric was a specialist

in optical communication and in particular satellite communication at MIT Lincoln Laboratories. This is his photo here. This is the first OCT system, which was quite large〈Fig. 24〉. Eric took this system, increased the imaging speed by a hundredfold, and developed a patient interface as well as software control. Eric was a co-founder of the first two OCT companies, Advanced Ophthalmic Devices and LightLab Imaging in ophthalmology and cardiology. But it's also interesting to note that he co-founded telecommunications companies, Sycamore Networks and Acacia Communications; these both went public with multi-billion-dollar market caps. I can't say that about OCT, telecom is certainly a much larger market.

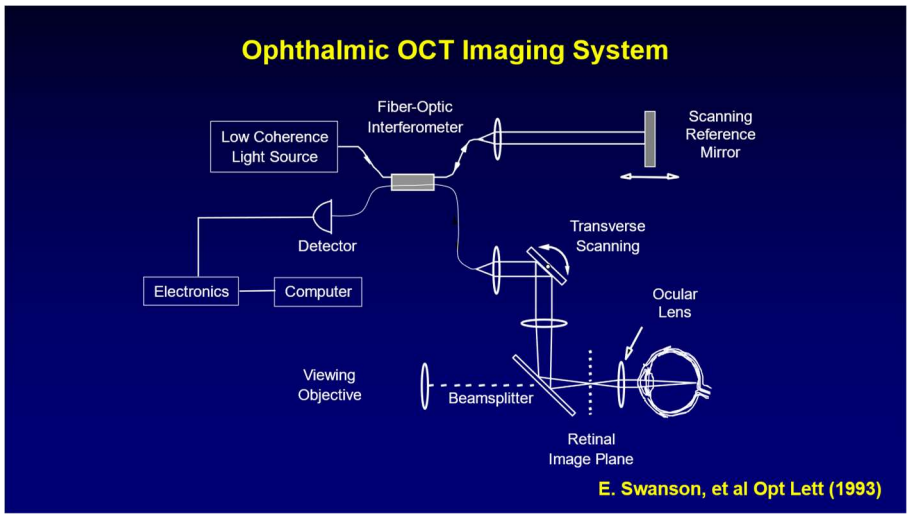


Fig. 26-1

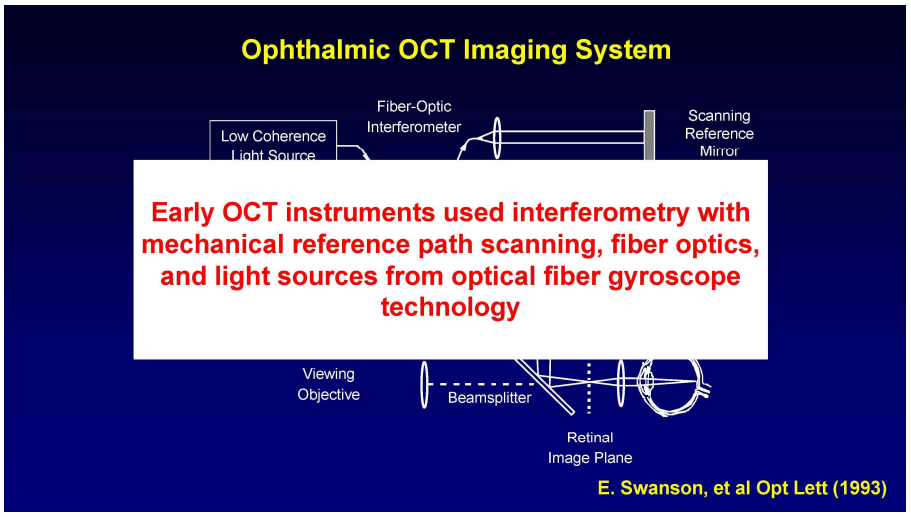


Fig. 26-2

〈Fig. 26〉 So, if we think about the technology, this is the system, a fiber-optic interferometer, shown schematically here. But one of the concepts is that this technology also used reference path scanning, mechanical beam scanning, fiber optics, and light sources from optical fiber gyroscope technology.

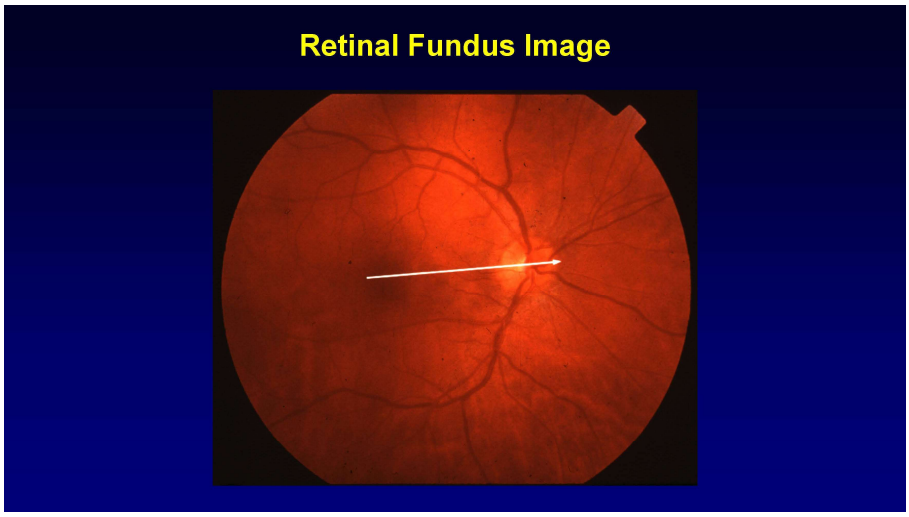


Fig. 27

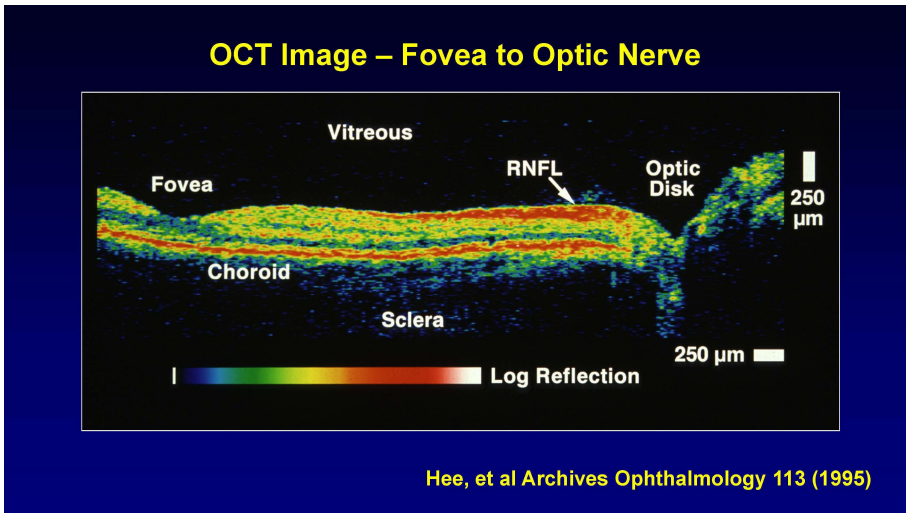


Fig. 28

〈Fig. 27 and 28〉 This is a view of the retina from the pupil of the eye that an ophthalmologist would typically see. We can scan the OCT beam from the fovea to the optic nerve head, 〈Fig. 27〉 and we can generate a cross-sectional image through the retina 〈Fig. 28〉 . We see the retinal fiber layer and there are various layers of the retina, into the subretinal space. This would be an example of an early OCT image.

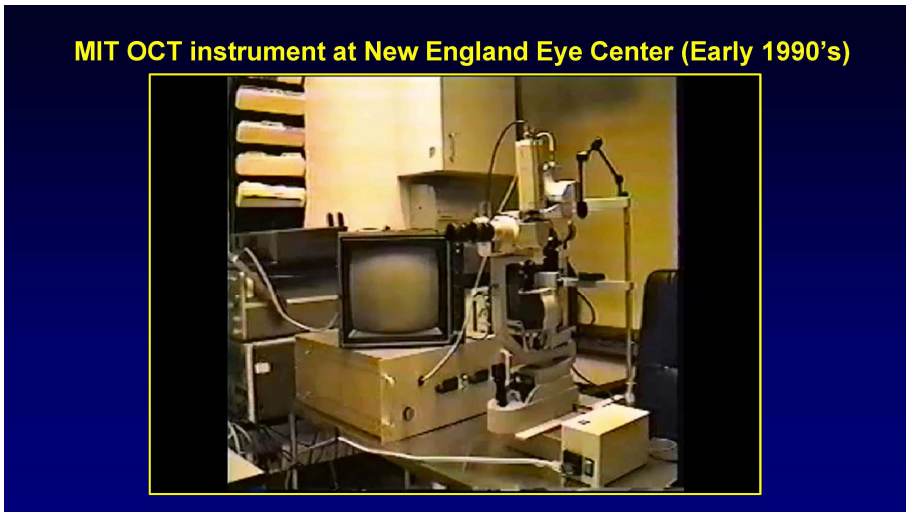


Fig. 29

〈Fig. 29〉 Here is a video of the instrument that was used at the New England Eye Center in the 1990s, scanning the beam on the retina, generating a cross-sectional image. This was controlled using a Macintosh, one of the early personal computers.

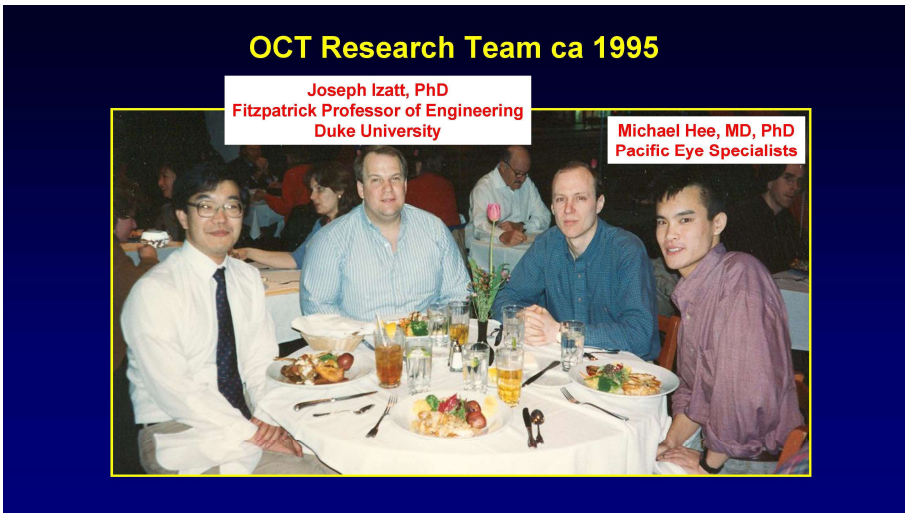


Fig. 30

〈Fig. 30〉 The research team at that time consisted of Joseph Izatt, who was a postdoctoral associate, he later went on to become Professor of Biomedical Engineering at Duke University; and Michael Hee, who was an MD PhD student who later went on to private practice. Working with our collaborators, this team did the first studies on patients.

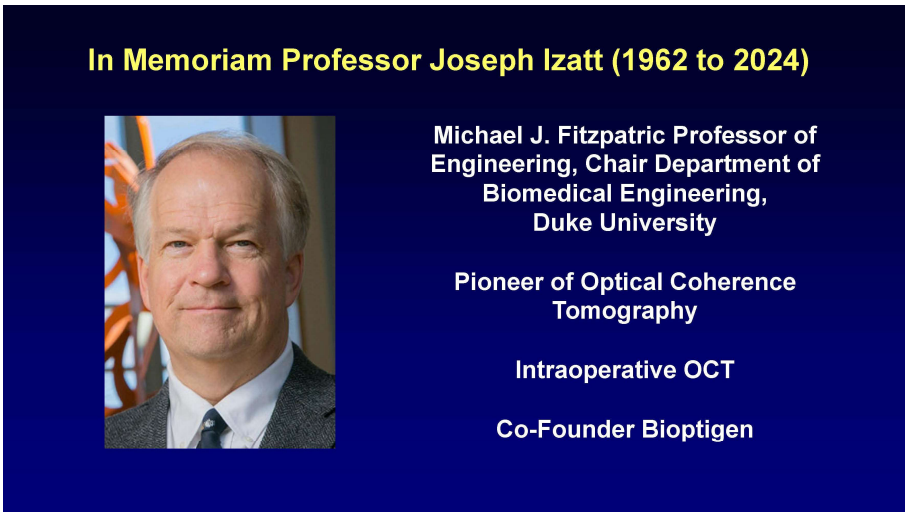


Fig. 31

〈Fig. 31〉 And I wanted to take a moment. We recently lost Joe Izatt. This I think was a tremendous loss to the field. Joe was Fitzpatrick Professor of Engineering, Chair of the Department of Biomedical Engineering at Duke University. He pioneered OCT, but also developed intraoperative techniques and many advances in the field. He was a co-founder of the company Bioptigen which was acquired by Leica. Bioptigen developed the first interoperative OCT.

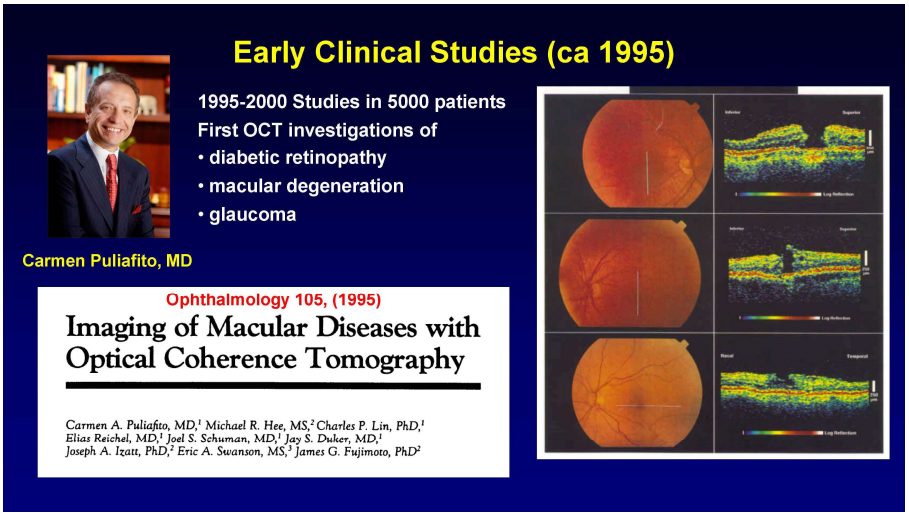


Fig. 32

〈Fig. 32〉 The early clinical OCT studies were led by Carmen Puliafito, a retina specialist. the first studies in over 5000 patients, you see examples here, macular diseases using OCT.

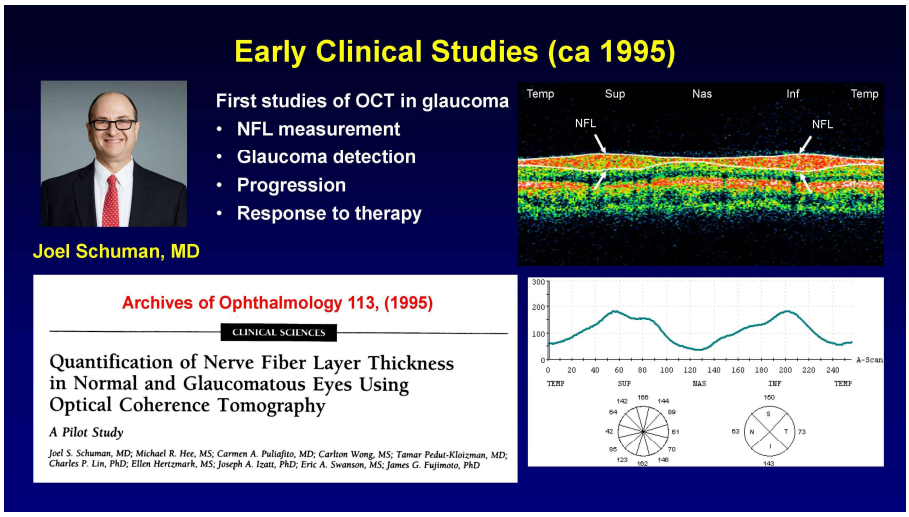


Fig. 33

〈Fig. 33〉 Glaucoma studies were led by Joel Schuman. These studies pointed out that one could measure the nerve fiber layer quantitatively and to assess the progression of glaucoma and the response to therapy.

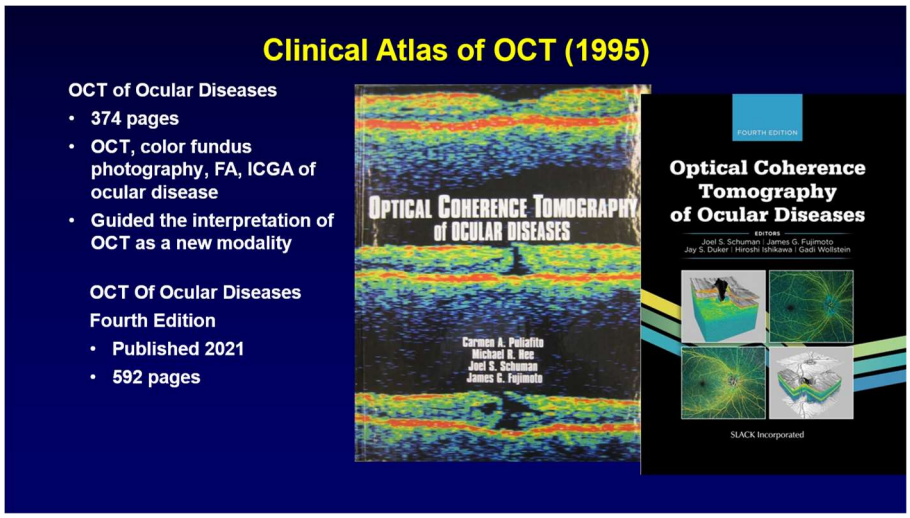


Fig. 34

〈Fig. 34〉 In order to have acceptance in the clinical community it was necessary to develop training, so the Clinical Atlas of OCT was created. This showed the correspondence between these images and standard ophthalmic diagnostics at that time, guiding the interpretation of OCT. This shows a later edition, the fourth edition, and it continues to be a reference for the clinical community today.

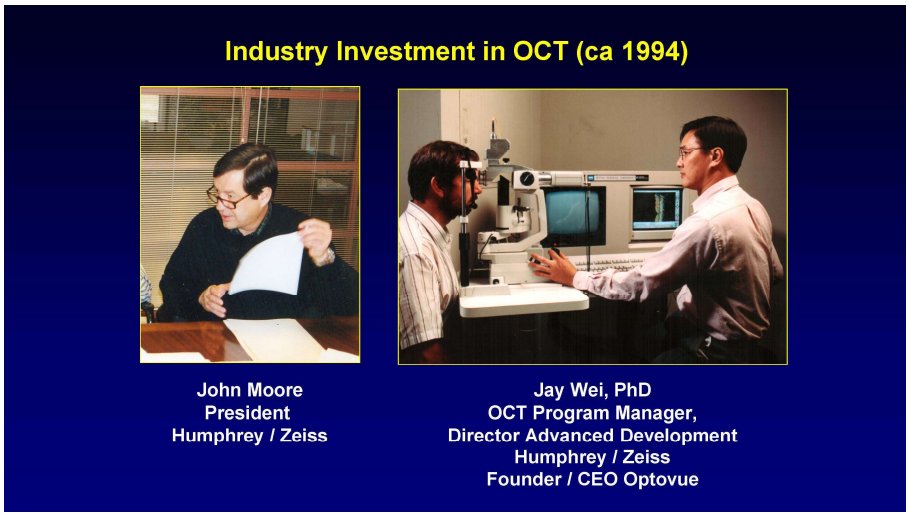


Fig. 35

〈Fig. 35〉 But I think one of the most important advances was industry investment. I especially wanted to mention John Moore, who was the president of Humphrey / Zeiss. I think Mr. Moore had tremendous courage and vision. He invested in this technology, although there was no precedent for its use in ophthalmology. The lead designer was Dr. Jay Wei; he was program manager and director of advanced development. He later went on to found an independent company, Optovue, which led many advances in ophthalmic OCT.

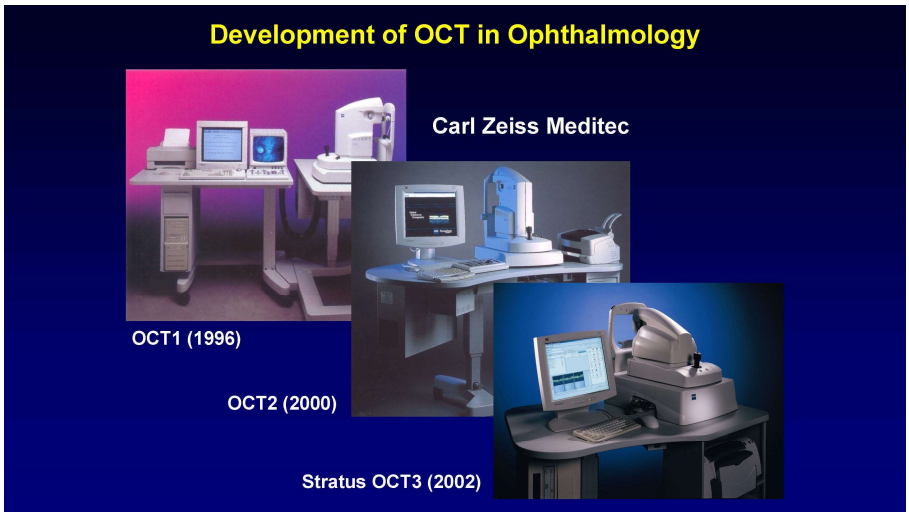


Fig. 36



Fig. 37

〈Fig. 36 and 37〉 Jay Wei led development of the first three instruments at Zeiss, OCT 1, 2 and 3. The Stratus OCT, was the third generation, in 2002. 〈Fig. 37〉 Here you see a video demonstrating the Stratus. showing alignment to the patient. One can perform multiple examination protocols as you see here, selection of the exam protocol, aligning through the pupil and then scanning to acquire data. This shows an acquisition protocol, different radially oriented cross-sections to measure retinal thickness.

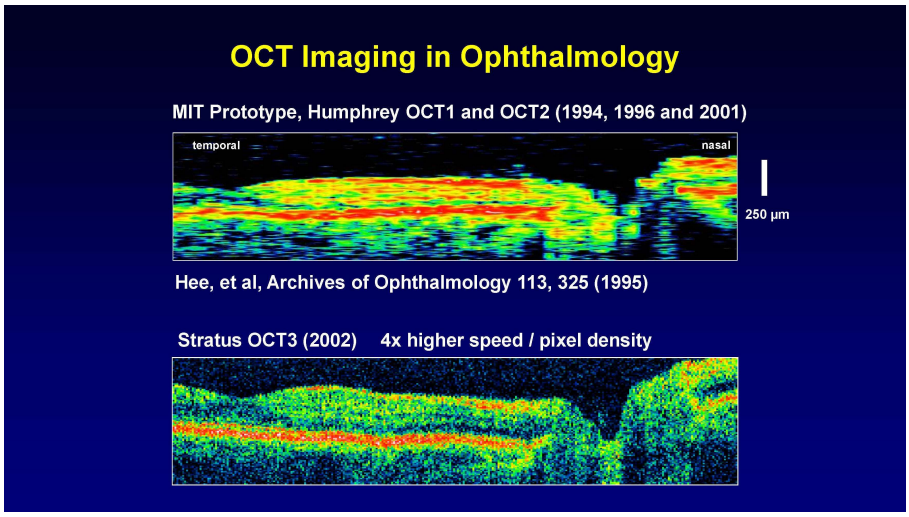


Fig. 38

〈Fig. 38〉 We can look at early images, this is the MIT prototype and the first two Humphrey / Zeiss instruments. The Stratus was higher speed, 4 times faster speed. This improved the image perception, although the resolution actually was the same. So higher pixel density improves image quality.

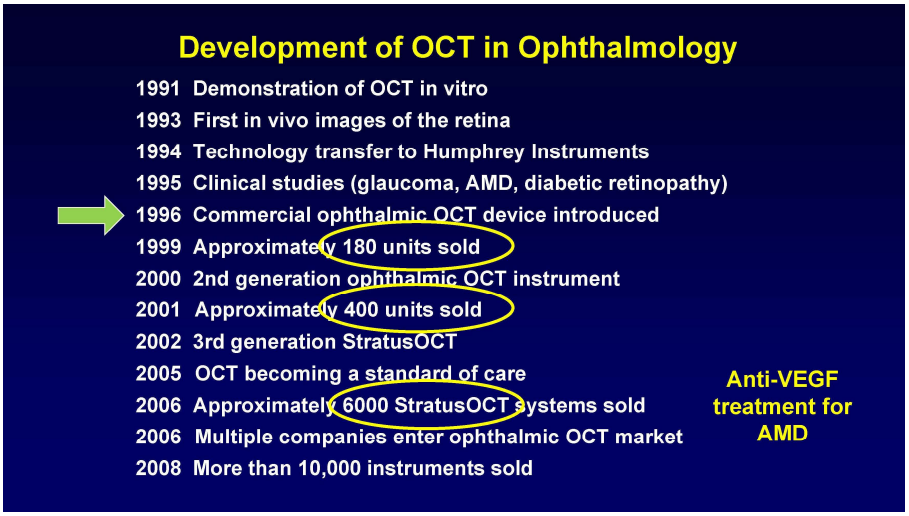


Fig. 39

〈Fig. 39〉 If we look the development of OCT in ophthalmology, the first demonstrations in vivo were 1991; it was actually commercialized very quickly, 1996. But if we look at the uptake, this is very disturbing. So, 180 units sold in 1999, 400 units in 2001, five years on the market. This is considered an extremely slow uptake. Only with the development of therapy, anti-VEGF, anti-vascular endothelial growth factor therapy for age-related macular degeneration; at that point we saw broad clinical acceptance.

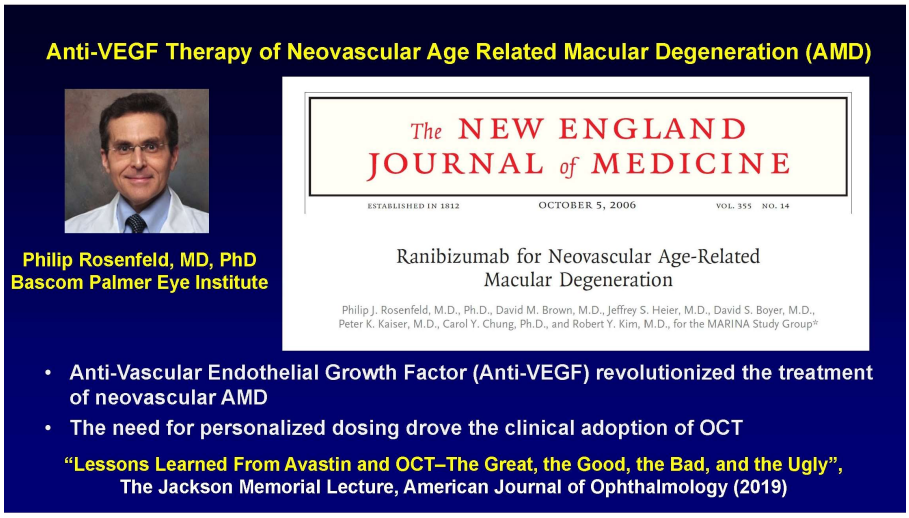


Fig. 40-1

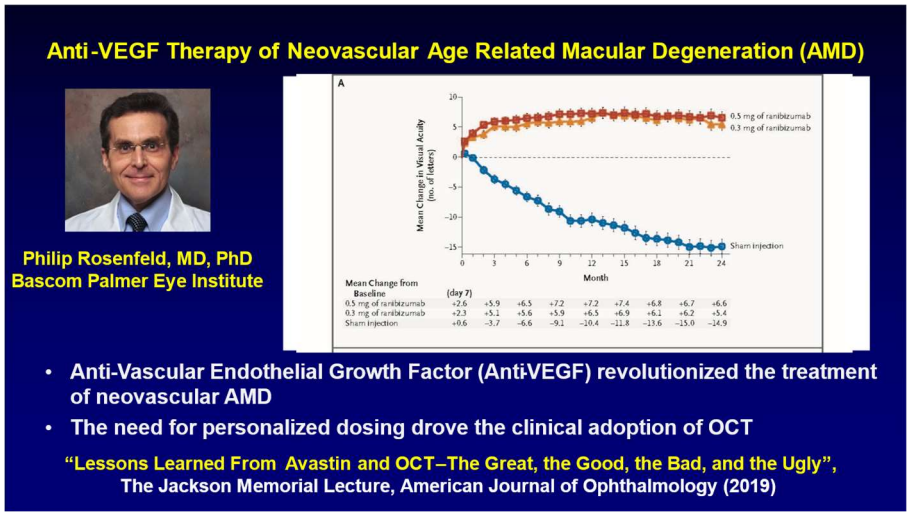


Fig. 40-2

〈Fig. 40〉 I especially wanted to acknowledge Dr. Philip Rosenfeld, who was a pioneer of anti-VEGF therapy for neovascular age-related macular degeneration. This was a profound advance, because before this, patients would rapidly lose vision. And at the same time, it drove the need for using OCT for personalizing the dosing. If we look at an example of acuity plotted here versus months, this was a randomized trial, treated patients preserved visual acuity and even recovered partial acuity, but patients that were treated with a placebo or sham, had a very rapid loss of vision.

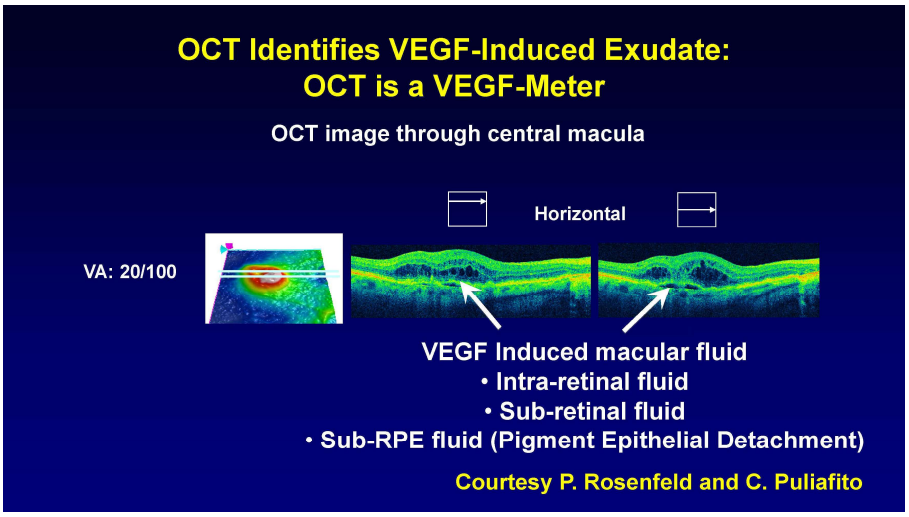


Fig. 41

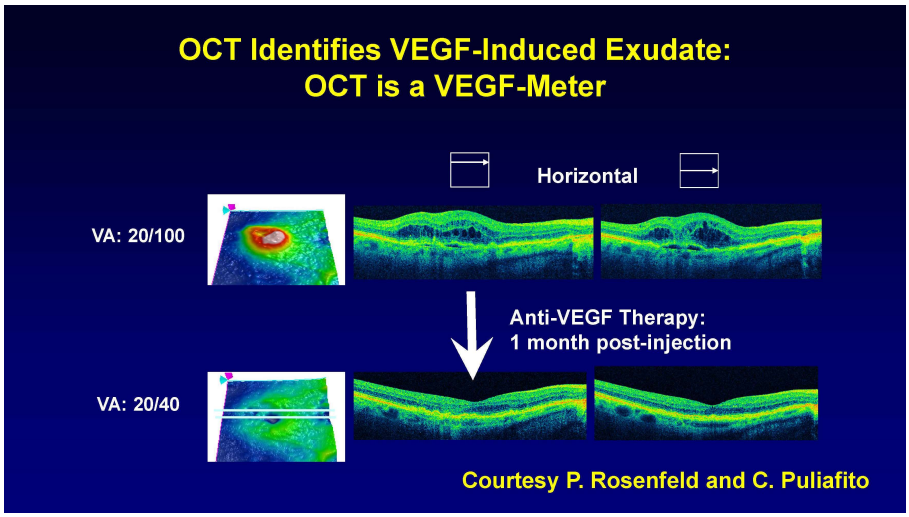


Fig. 42

〈Fig. 41 and 42〉 This was a profound advance 〈Fig. 41〉 and at the same time drove the adoption of OCT. If we look here, we can see visual acuity 20/100, this shows examples of exudative AMD with sub-retinal fluid, intra-retinal fluid, pigment epithelial detachment, which are all markers of exudative AMD. 〈Fig. 42〉 When the patient is treated with anti-VEGF injection, we see normalization of the retinal structure in the cross-sectional images. OCT shows treatment response and we also have recovery of visual acuity.



Fig. 43



Fig. 44

〈Fig. 43 and 44〉 With advances in treatment, we started to see wider-spread acceptance. In 2005, the American Academy of Ophthalmology chose OCT as its logo. 〈Fig. 44〉 And then in 2006 we saw multiple companies introducing OCT instruments in the ophthalmic market.

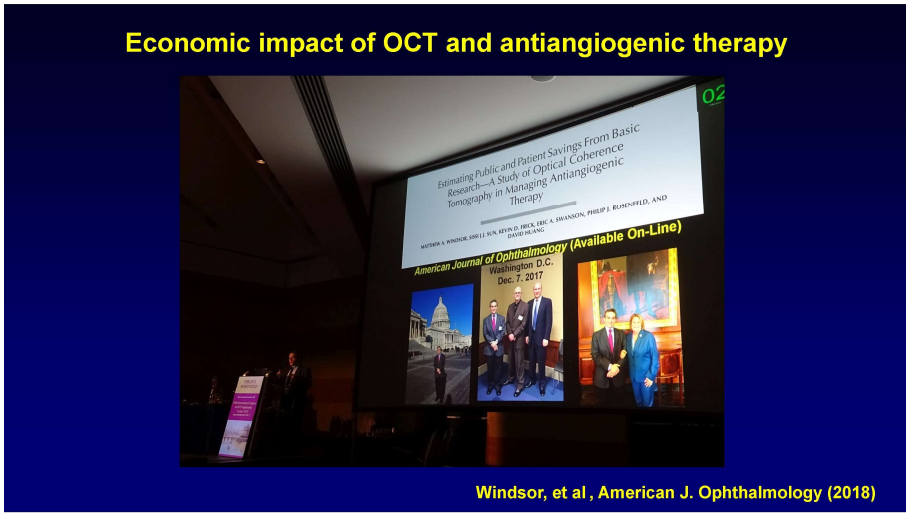


Fig. 45-1

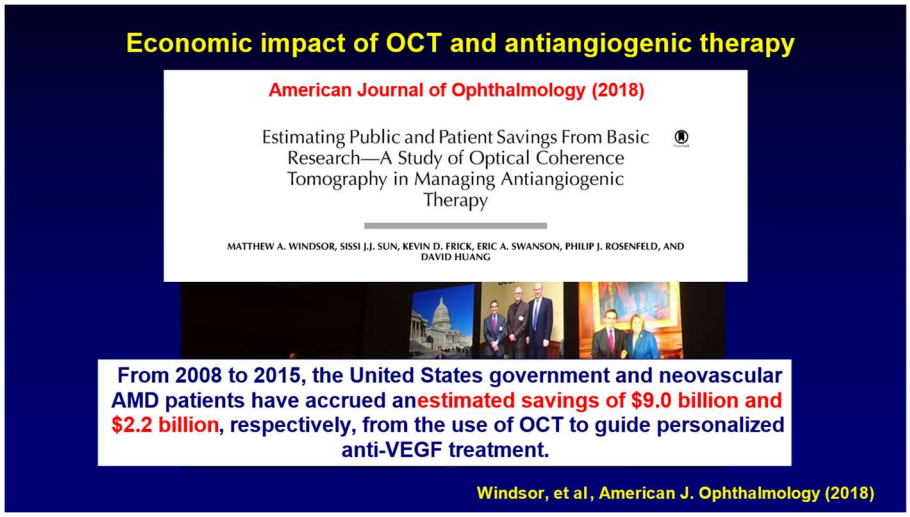


Fig. 45-2

〈Fig. 45〉 The economic impact of OCT was investigated in a study led by Matt Windsor and Phil Rosenfeld. Here you see Estimated Public and Patient Savings from Basic Research. Over a 7 year period of time, the US government saved an estimated $9 billion, patients saved $2.2 billion from the use of OCT to guide personalization of the treatment for AMD.

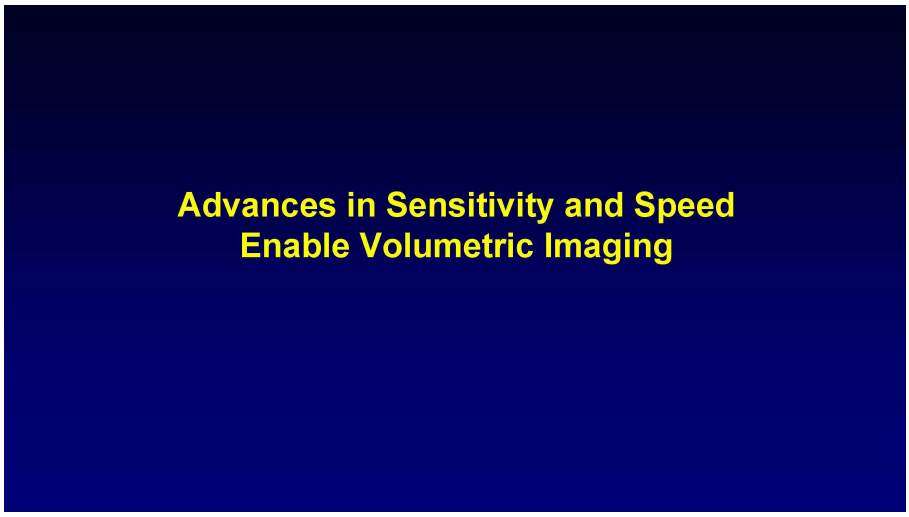


Fig. 46

〈Fig. 46〉 In parallel with these advances, we also saw technology improvements, advances in sensitivity and speed, which dramatically increased the amount of information that became available.

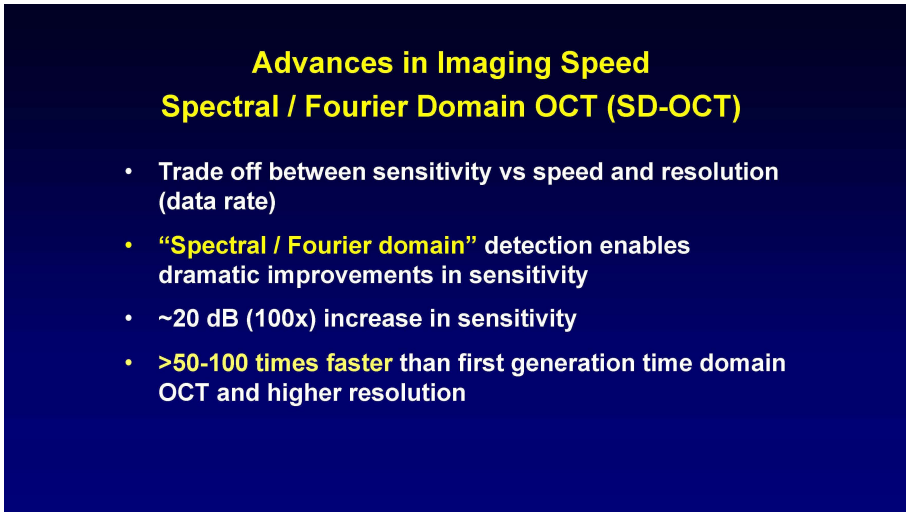


Fig. 47

〈Fig. 47〉 "Spectral or Fourier Domain" detection solved a trade-off in sensitivity, speed and resolution. This technology increased the sensitivity by 100 times, 20 dB, and in parallel it enabled a much faster imaging speed, 50 to 100 times faster, than the first-generation technology.

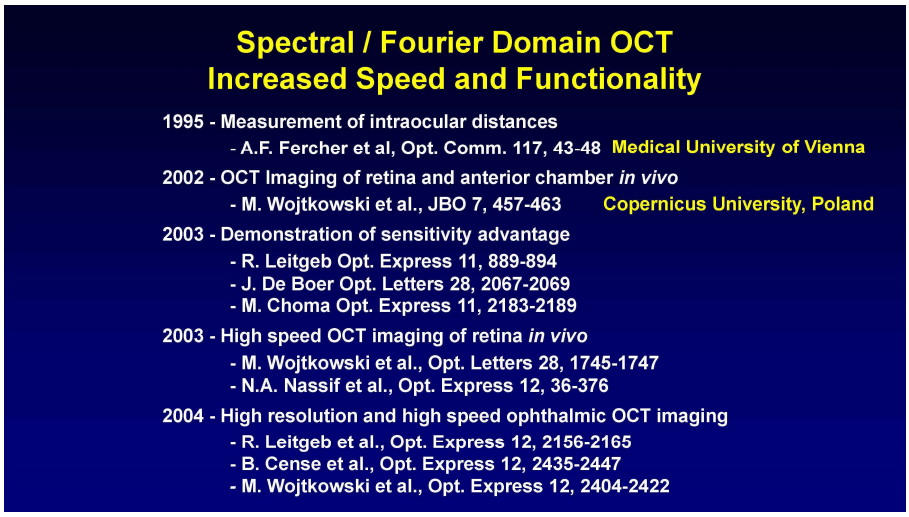


Fig. 48

〈Fig. 48〉 It's interesting that this technology also had a long history. In 1995, the group from the Medical University of Vienna proposed these concepts and then in 2002 the first demonstration was performed at the Copernicus University in Poland. After that, multiple groups demonstrated sensitivity and speed advantages, including our group.

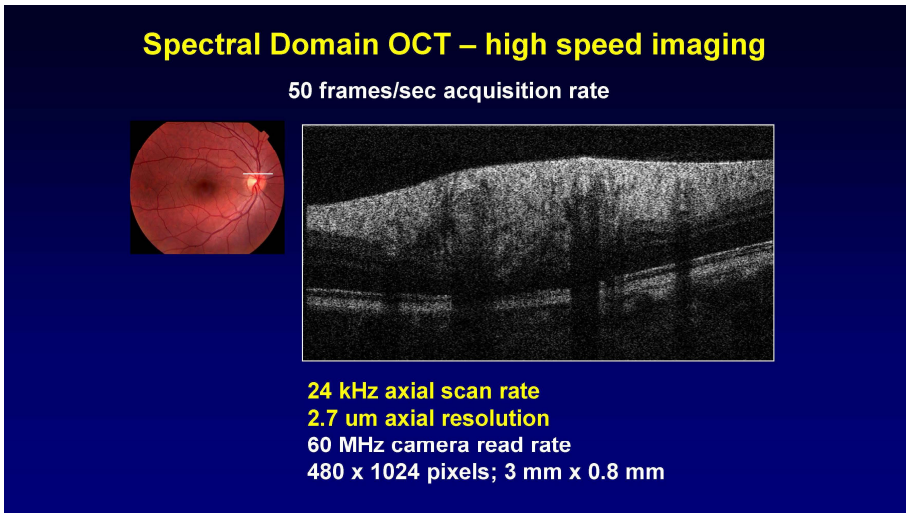


Fig. 49

〈Fig. 49〉 This video shows an example. If you compare this to the earlier examples, this is at a video rate of 50 frames per second, imaging repeatedly near the optic nerve head, retinal nerve fiber layer and the vasculature.

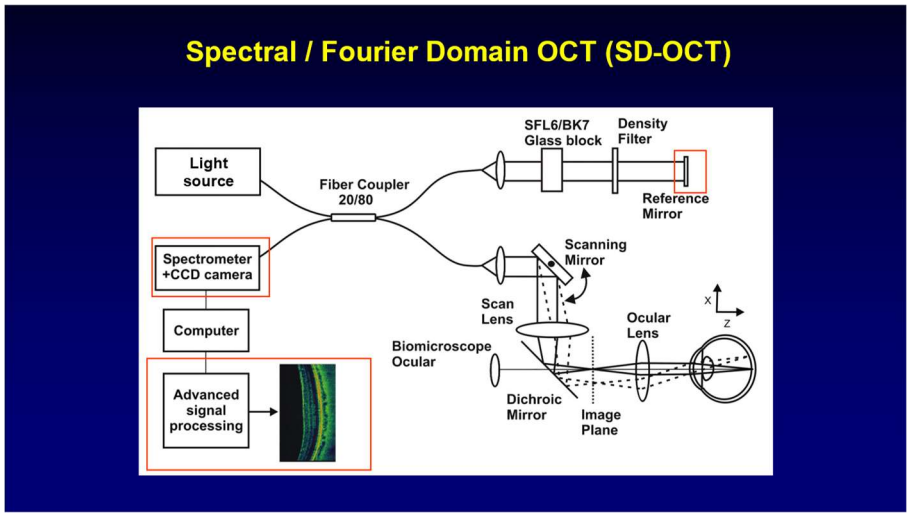


Fig. 50-1

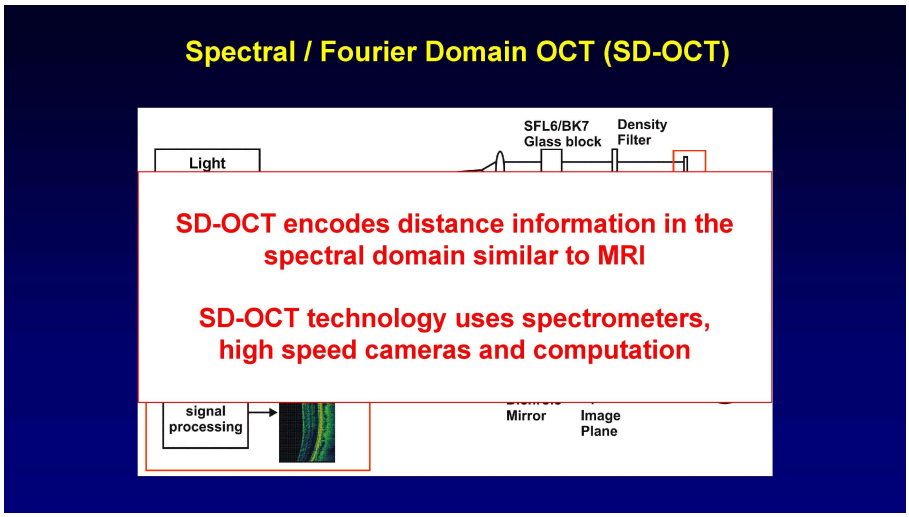


Fig. 50-2

〈Fig. 50〉 This shows the schematic of the system. A light source, spectrometer and camera, reference path, beam scanning in the patient interface and computation. Spectral domain essentially encodes the information on distance in a spectrum, similar to the way that magnetic resonance imaging works. The technology is based on spectrometers, high-speed detectors, cameras and computation.



Fig. 51

〈Fig. 51〉 This video shows an example of the Optovue instrument. You can see the extremely rapid image acquisition compared to the previous examples that we saw. It's possible to acquire a data volume by sequentially scanning cross-sections. You see this here.

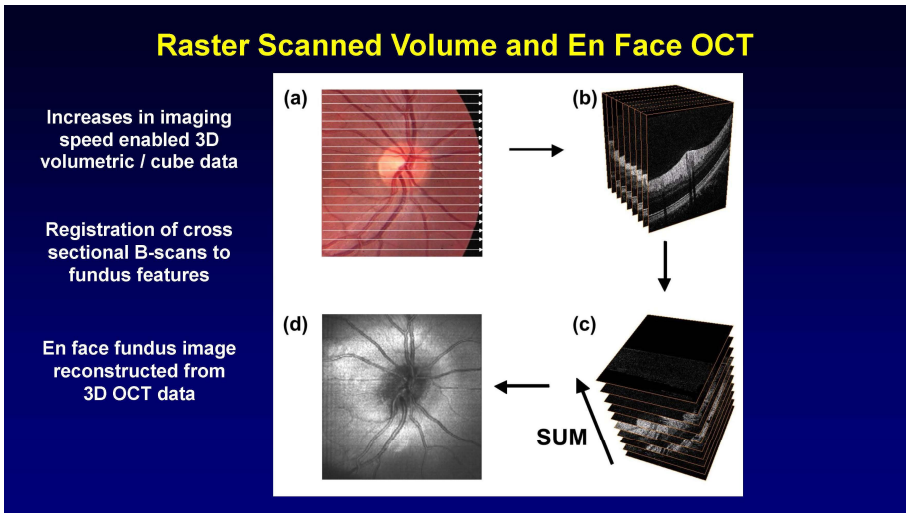


Fig. 52

〈Fig. 52〉 And then the data volume can be rendered or summed in the depth direction to generate an image that corresponds to the image of the retina that we would see ophthalmoscopically.

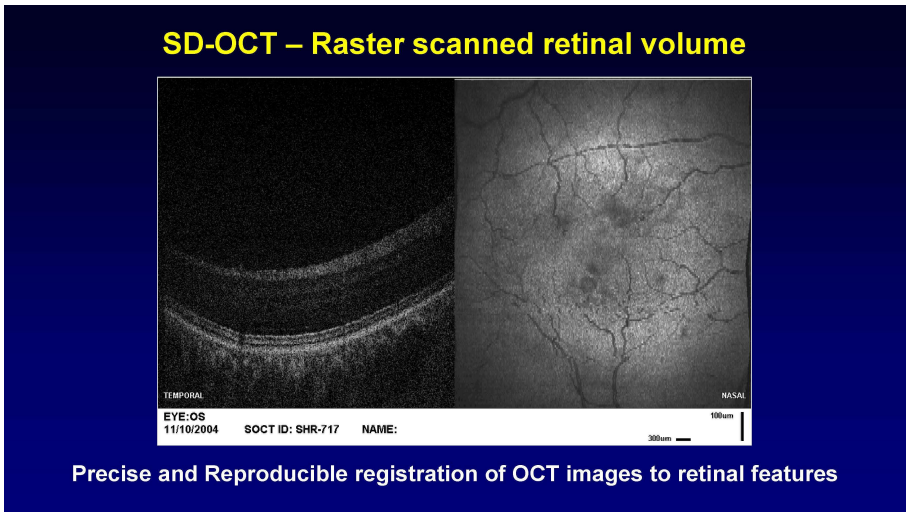


Fig. 53

〈Fig. 53〉 It's possible to extract cross-sections from this volume that are precisely registered to a location on the retina.

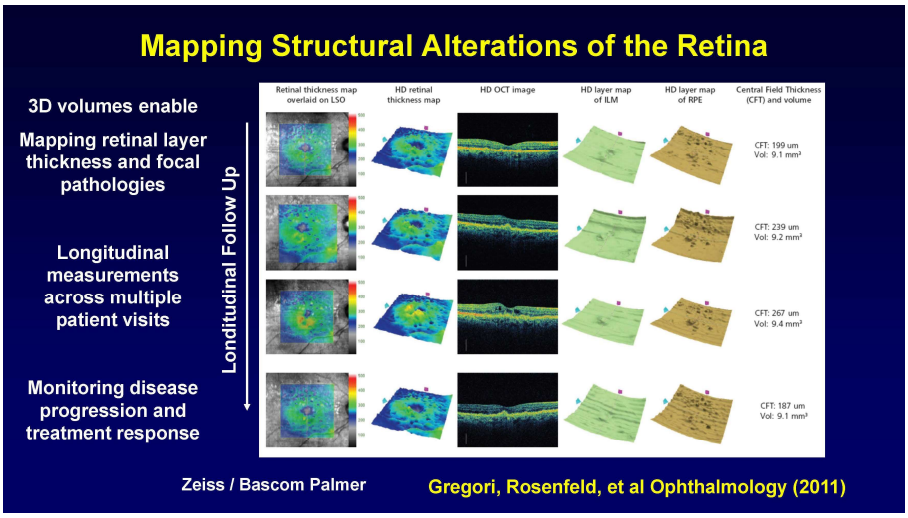


Fig. 54

〈Fig. 54〉 This is very powerful because it means that you can, over multiple patient visits, assess extremely small changes, and this can be done quantitatively. The ability to quantitate changes over time is extremely important for measuring progression of disease and treatment response as well as for pharmaceutical development.

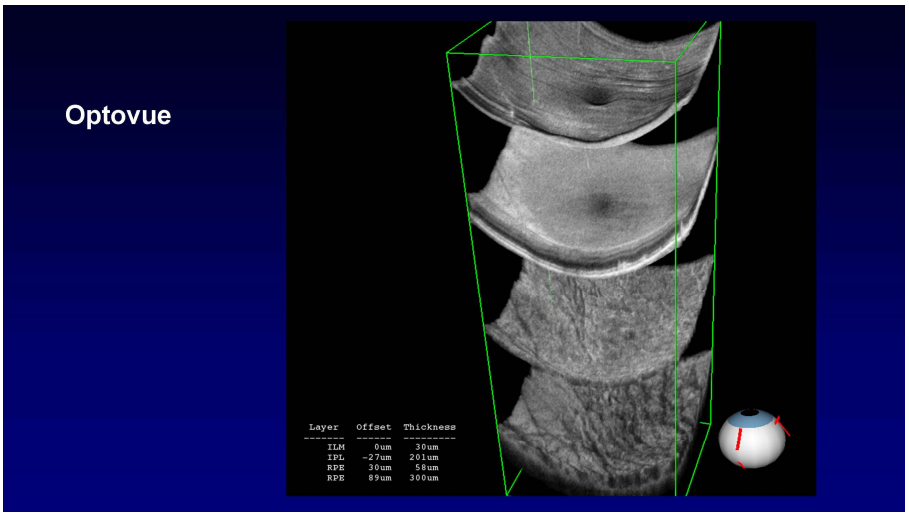


Fig. 55

〈Fig. 55〉 In this case we have a volume representation of the retina which can be separated into different layers. So we can see sub-surface below the retina, or separately see different layers in the transparent retina. This comes back exactly to what Michel Duguay proposed in 1971, that you could see subsurface image information.

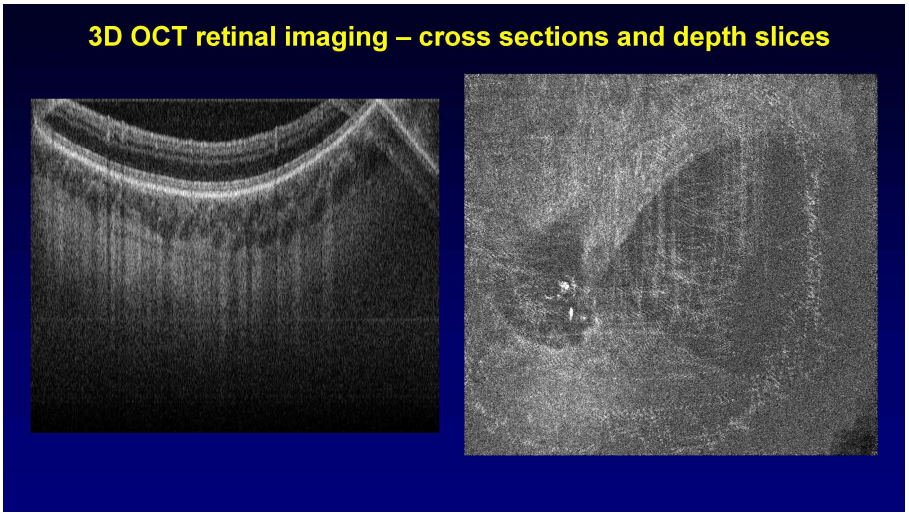


Fig. 56

〈Fig. 56〉 This video shows cross-sectional images and then sequential en face or flattened images of the retina, going from the retina into the subretinal space to see the vasculature below the retina.

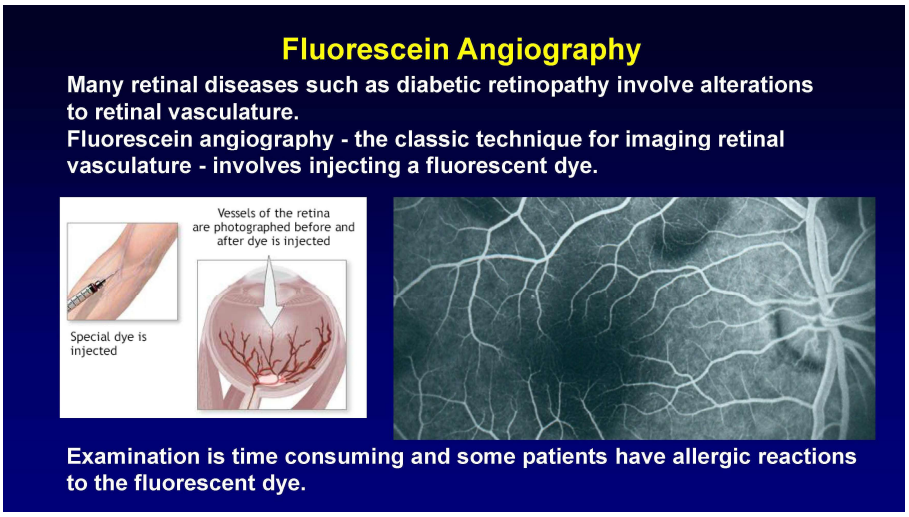


Fig. 57

〈Fig. 57〉 One of the other major advances was the ability to see blood vessels or vasculature. Many retinal diseases, such as diabetic retinopathy, change the retinal vasculature. The classic method to see vasculature is to inject dye and then acquire a florescence image of the retina, so-called fluorescein angiography. Here is an example of this type of image. The issue with fluorescein angiography is that it is a time-consuming exam and some patients have allergic reactions to the contrast agent.

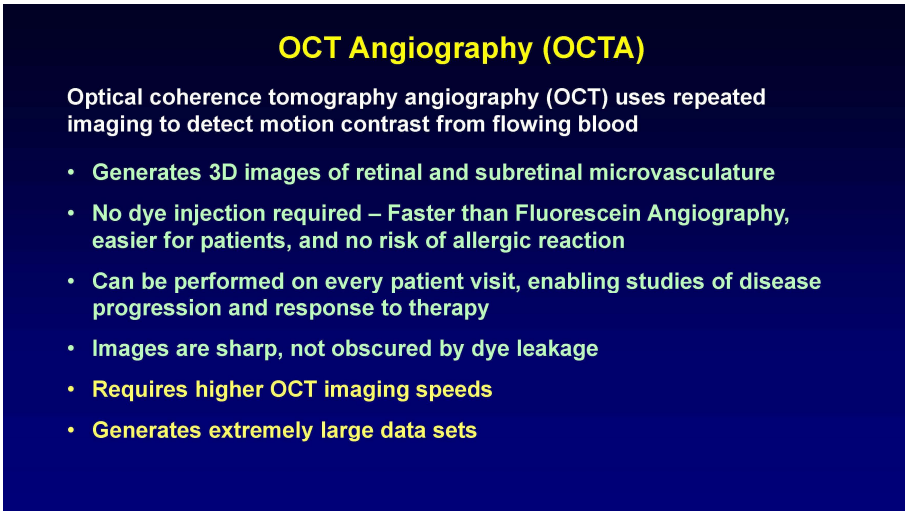


Fig. 58

〈Fig. 58〉 OCT can image vasculature by detecting motion contrast from the moving blood cells. OCT Angiography generates volumetric images which are depth resolved and does not require dye injection. Therefore, it can be performed on every patient visit, where we would normally not have this information available. The images are sharp and they are not obscured by dye leakage. But OCTA requires extremely high imaging speeds and the amount of data that it generates becomes larger and larger.

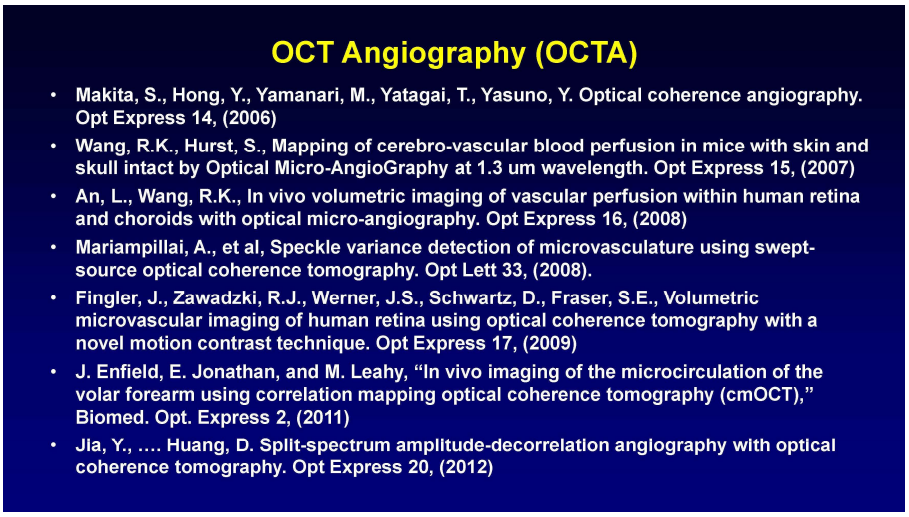


Fig. 59

〈Fig. 59〉 This advance also has a long history. Some of the earliest work was done here in Japan by Professor Yasuno's group, and multiple international groups worked on this. Then around 2012 we started to see adoption of this technique.

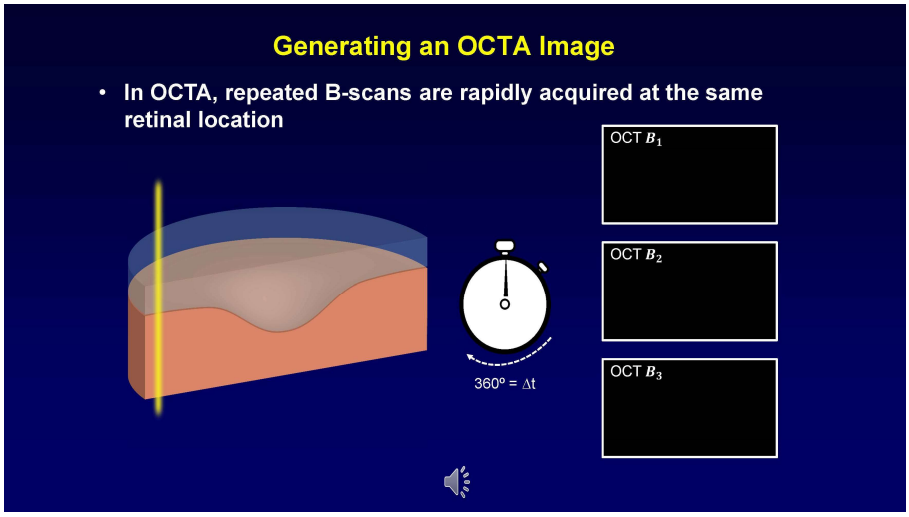


Fig. 60

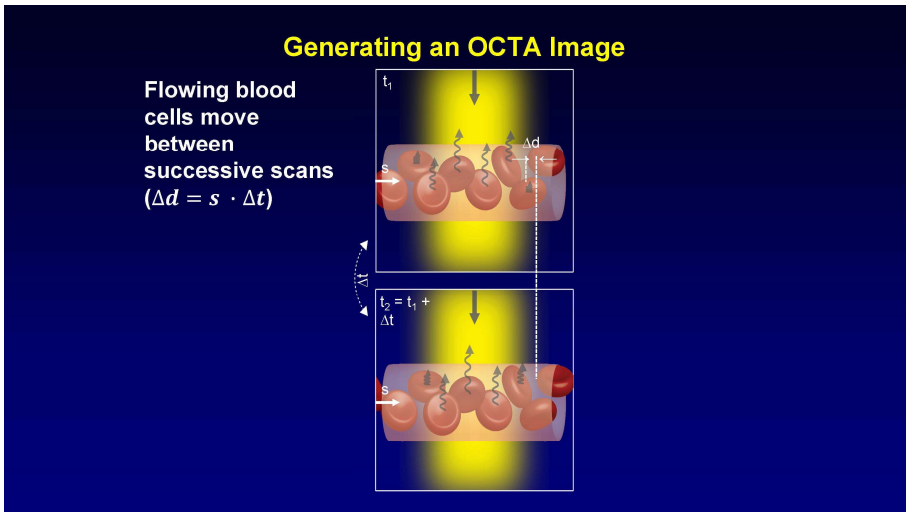


Fig. 61

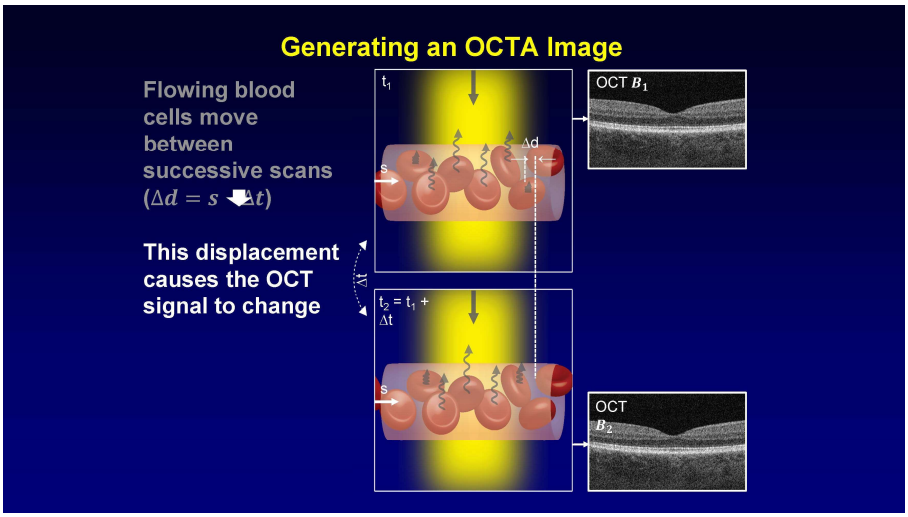


Fig. 62

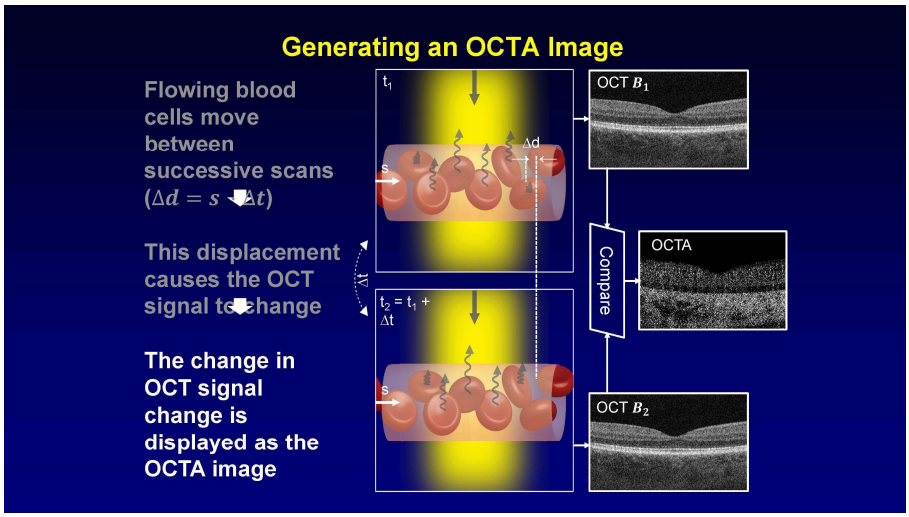


Fig. 63

〈Fig. 60－63〉 Essentially what's happening is, multiple cross sectio nal images are acquired,

separated by time Fig. 60. If there are moving blood cells〈Fig. 61〉we can detect them as differences between these images.〈Fig. 62〉So at one particular time if we look later the blood cells have displaced and we can see a change in the OCT image, by taking a difference or decorrelation〈Fig. 63〉. This will highlight the moving blood cells.

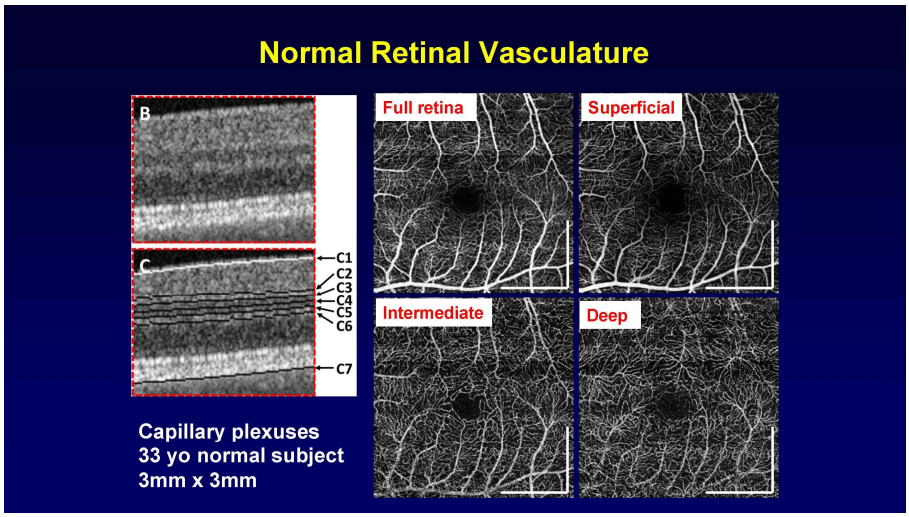


Fig. 64

〈Fig. 64〉We can separate the normal retinal vasculature into the different layers or plexuses, the superficial, intermediate and deep capillary plexuses.

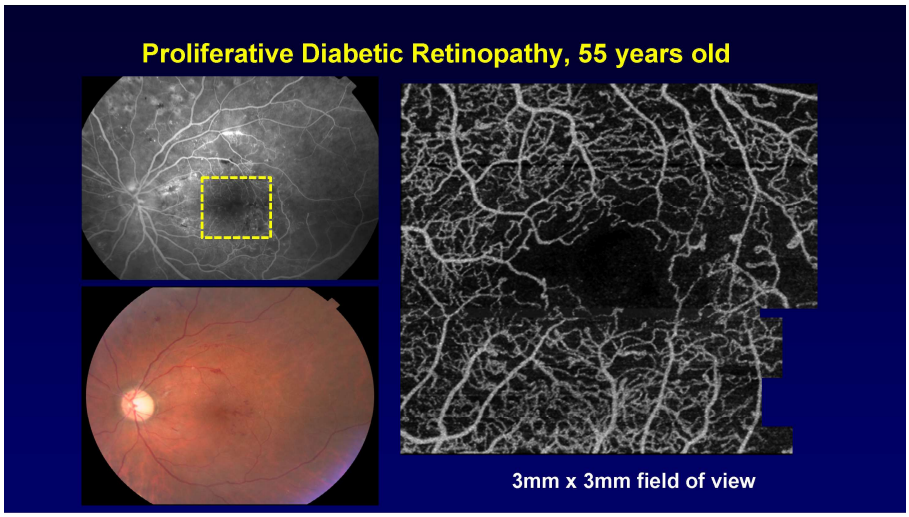


Fig. 65-1

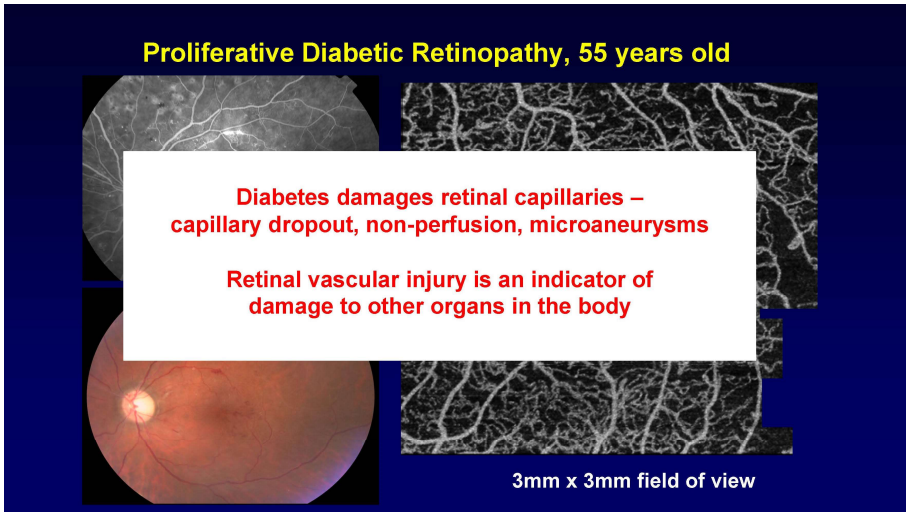


Fig. 65-2

〈Fig. 65〉 If we look at patients with diabetic retinopathy, we see pronounced changes of the vasculature, which you can see here in this image. Diabetes damages the capillaries, causing capillary drop-out, non-perfusion, microaneurysms; and the retina is an indicator of the damage vasculature that is occurring in all organs of the body.

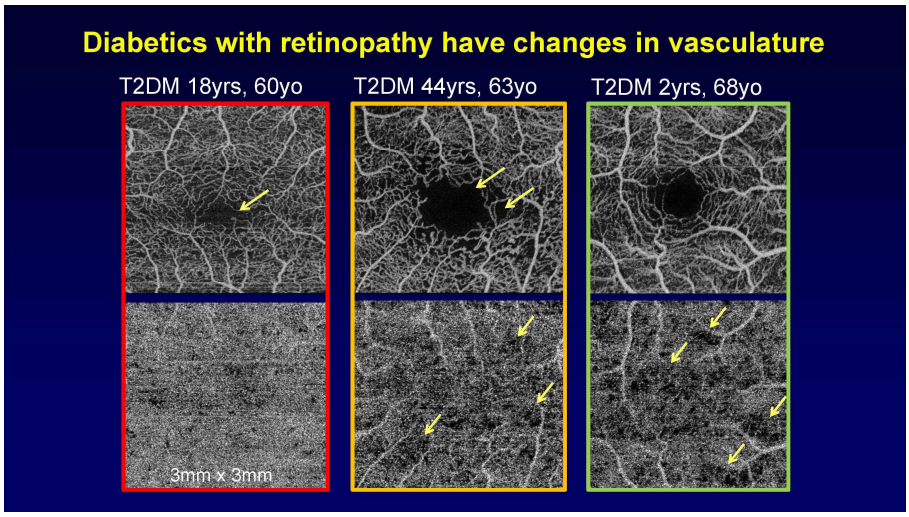


Fig. 66

〈Fig. 66〉 This provides a way to assess progression of diabetic injury. Even in patients with diabetes without retinopathy we see these changes, loss of retinal vasculature, subretinal vasculature as well. So this says diabetes is a progressive disease with progressive injury to the vasculature.

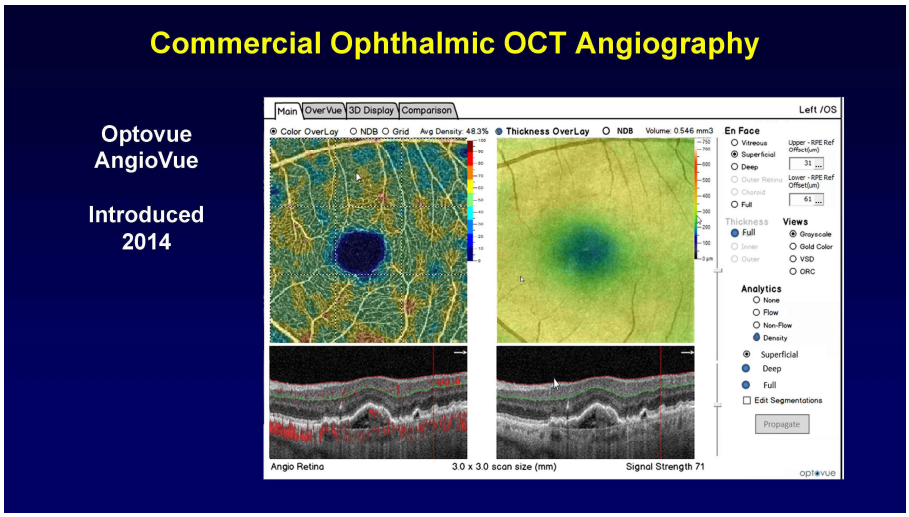


Fig. 67

〈Fig. 67〉 Octovue commercialized OCT angiography, introduced in 2014. This shows an example of their examination report. I'll show a video of their instrument.

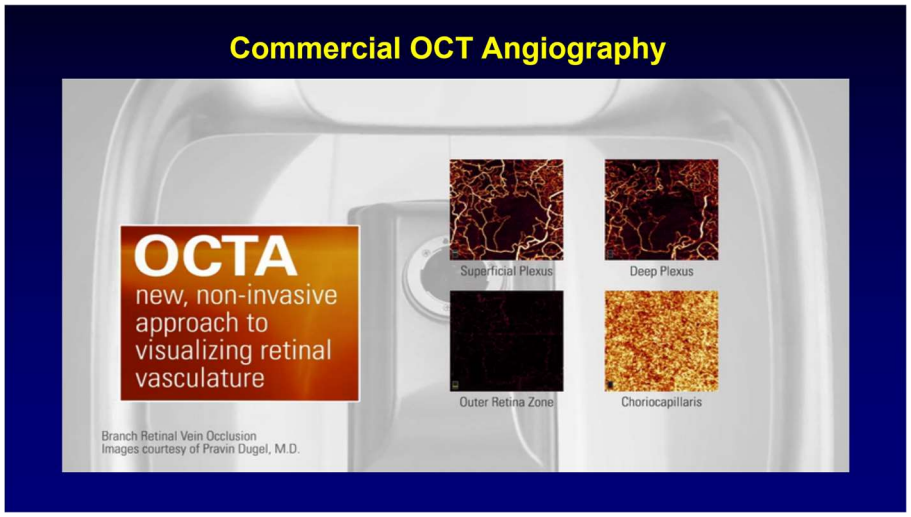


Fig. 68

〈Fig. 68〉 "At Optovue our vision is to offer advanced eye care technology to patients around the world by expanding the frontiers of OCT innovation. Optical Coherence Tomography Angiography, or OCTA, is a new non-invasive approach to visualizing retinal vasculature that is transforming the way physicians see the vessels of the retina and cornea. With the collaboration of industry-leading ophthalmic specialists, Optovue pioneered the technology that makes OCTA a clinical reality today." I apologize for showing commercial videos, but I think it conveys very nicely the concepts and the advance it enabled for the clinical community.

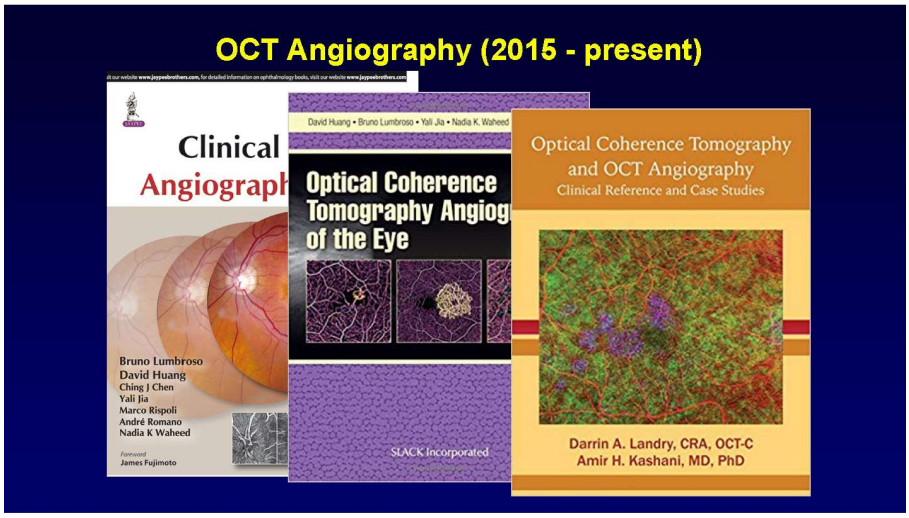


Fig. 69-1

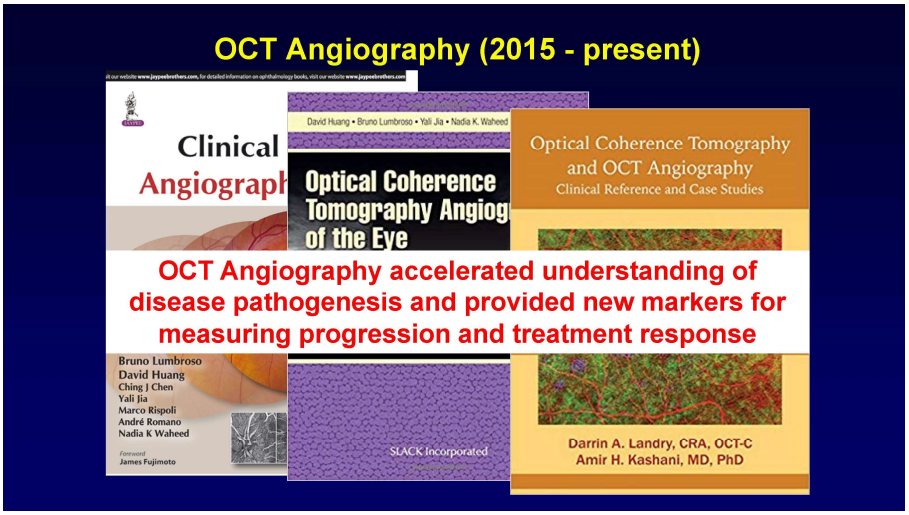


Fig. 69-2

〈Fig. 69〉 The development of OCT Angiography advanced the fundamental understanding of disease, because it provided information that was not previously possible. Here you see multiple editions of atlases on OCT Angiography. This contributed to the understanding of pathogenesis, and provided new markers for progression and treatment response.

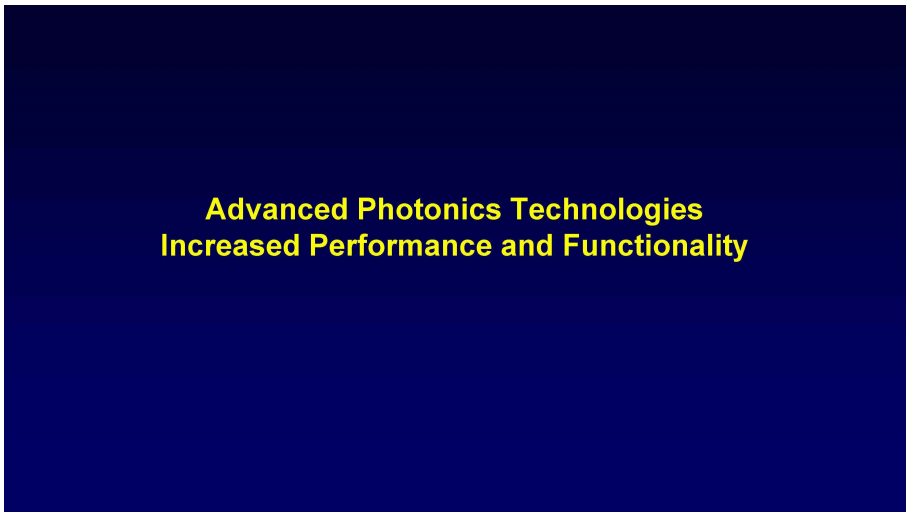


Fig. 70

〈Fig. 70〉 There are additional advances from photonic technology that improved performance and functionality.

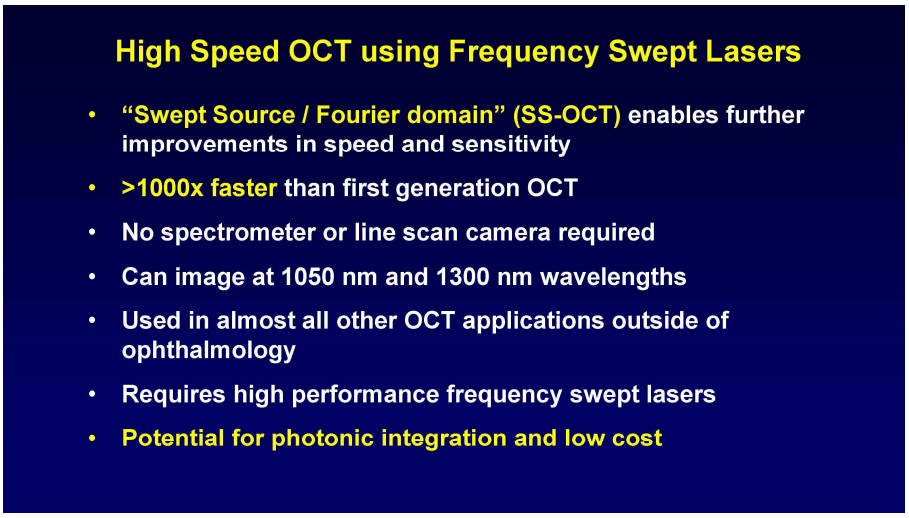


Fig. 71

〈Fig. 71〉 There is an even faster method, called Swept Source OCT, which is a thousand times faster than the first generation technology. This technology is actually used in all other applications outside of ophthalmology, and it has the interesting feature that it could potentially be built using photonic integration to make very low-cost, high performance instruments.

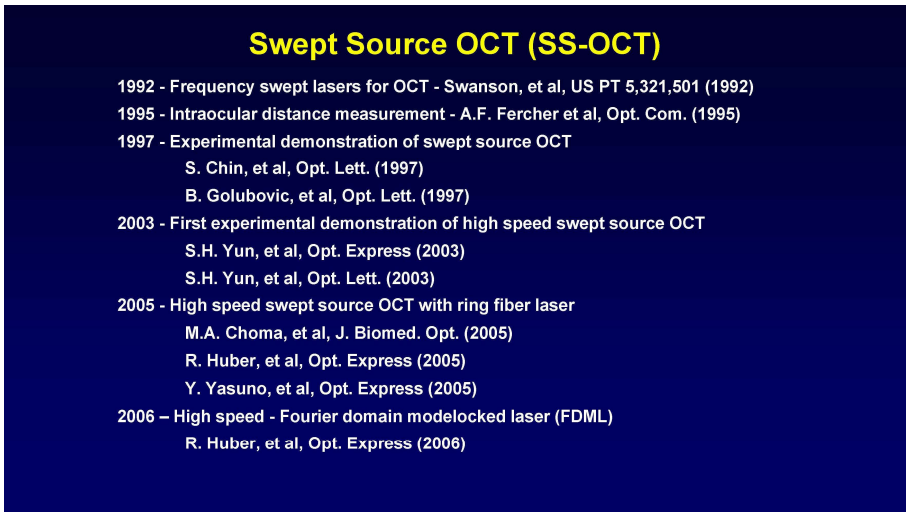


Fig. 72

〈Fig. 72〉 Again, this has a long history, starting in 1992 and then resulting in demonstrations of high-speed imaging more than a decade later.

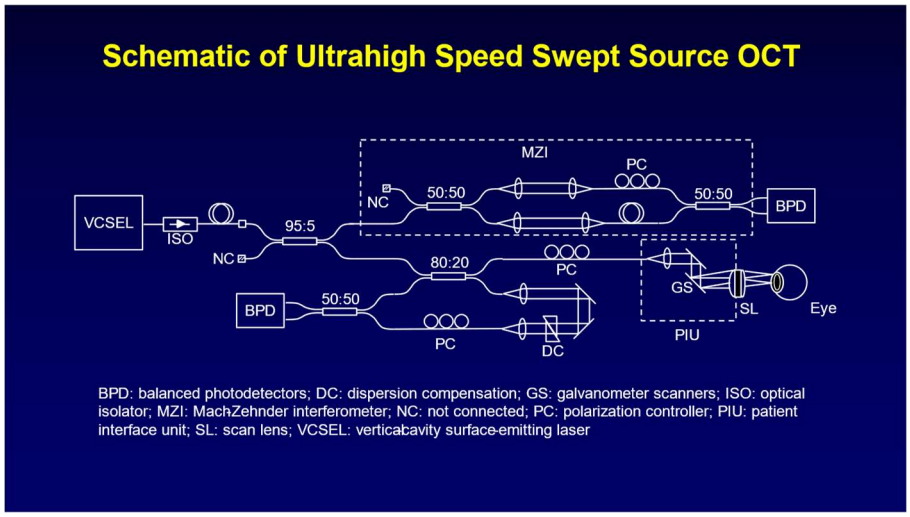


Fig. 73-1

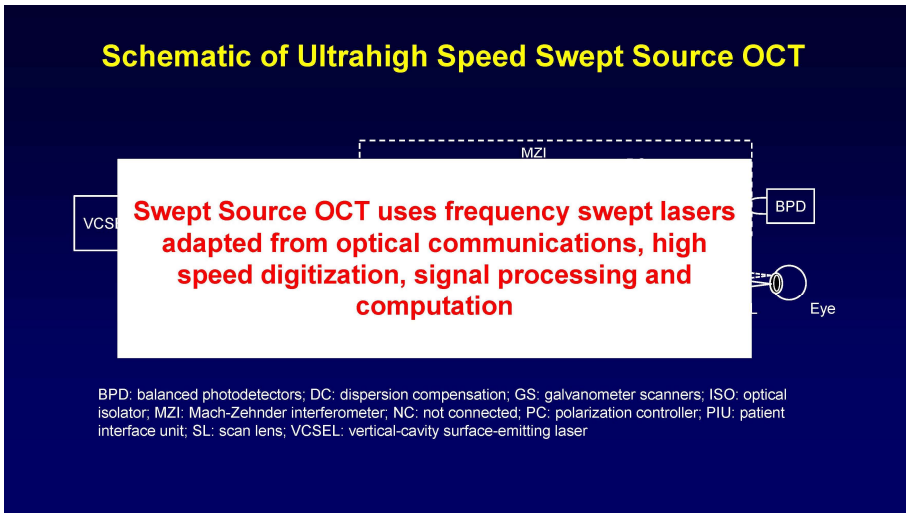


Fig. 73-2

〈Fig. 73〉 If we look at the systems, these are becoming progressively more and more complicated, with multiple interferometers, high speed detectors and so forth. This technology is using frequency swept lasers which are adapted from optical communications, high-speed digitization, signal processing and increasing computational power.

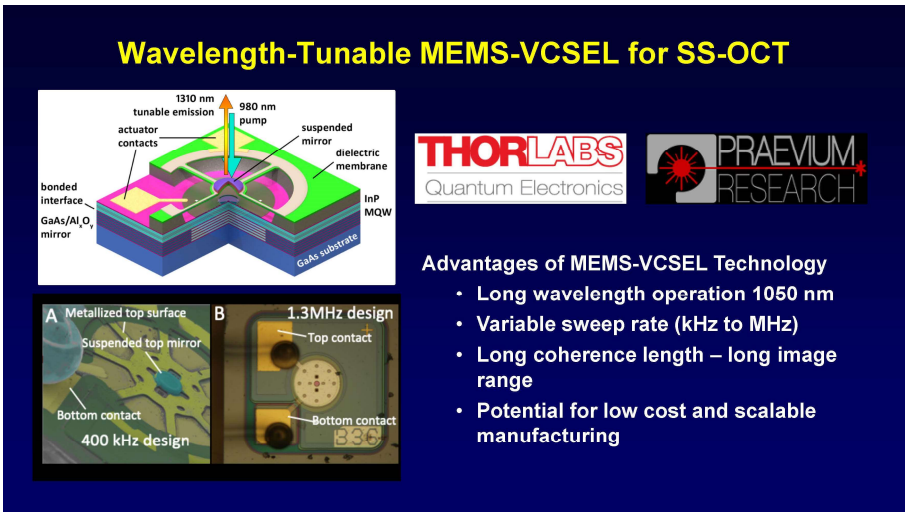


Fig. 74

〈Fig. 74〉 This is an example of a light source that was developed for OCT, but it's based on a telecommunications light source, called the vertical cavity surface-emitting laser. This has the potential for lower cost and scalable manufacturing and it achieves extremely high performance.

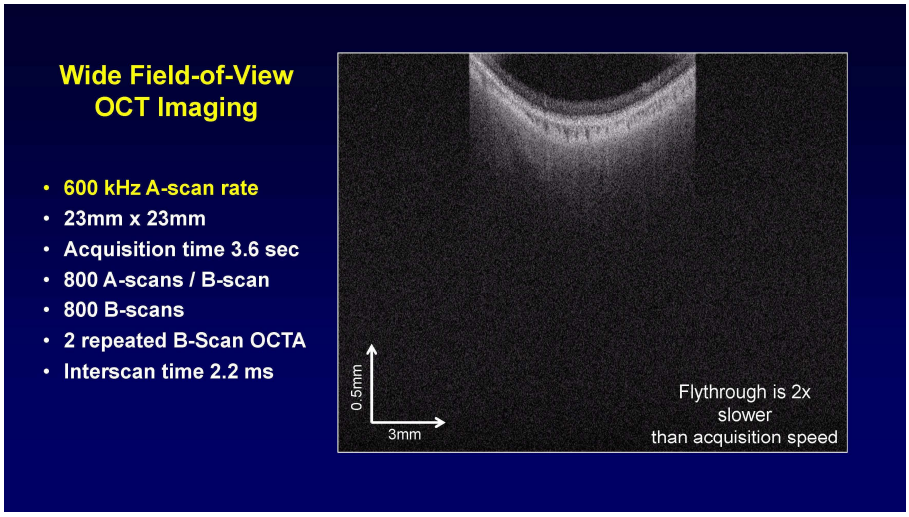


Fig. 75

〈Fig. 75〉 Here you see an example. Wide field-of-view retinal imaging, which can generate detailed cross-sectional images. More and more information is acquired rapidly, this video is actually slowed-down by a factor of 2.

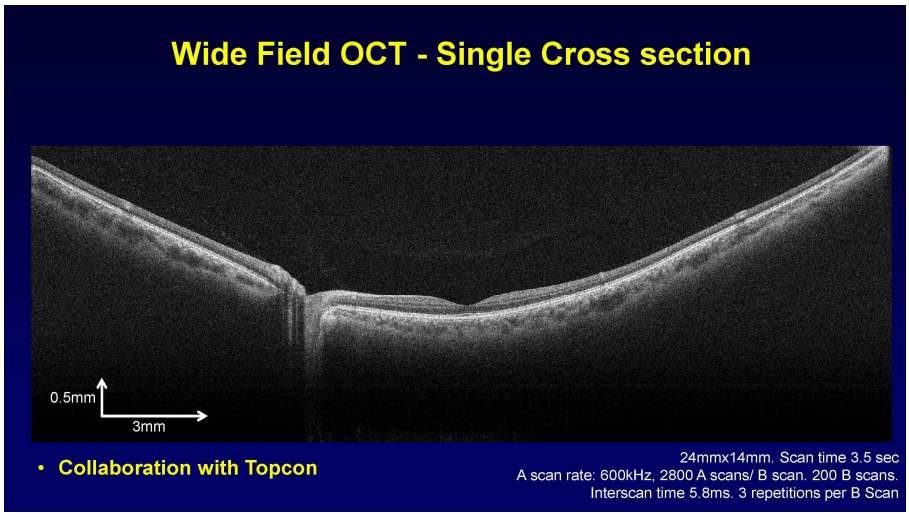


Fig. 76

〈Fig. 76〉 We can generate extremely detailed cross-sectional images of the retina.

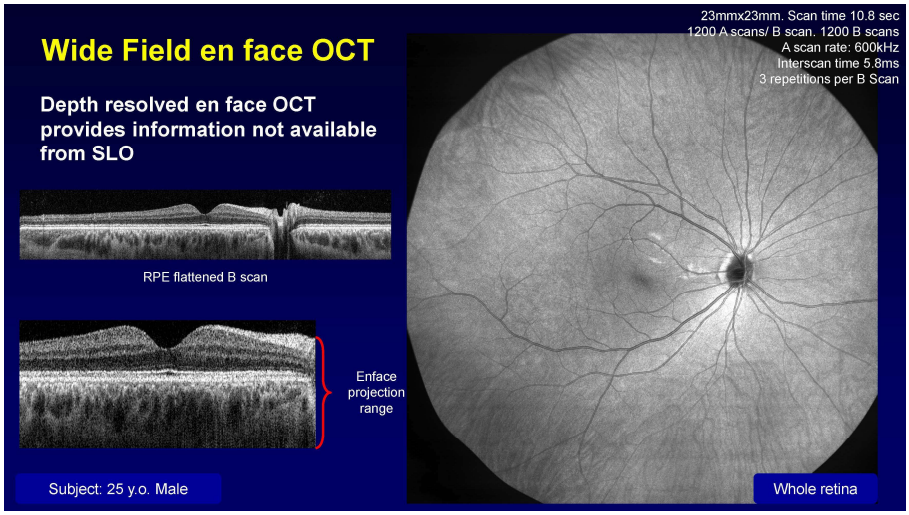


Fig. 77

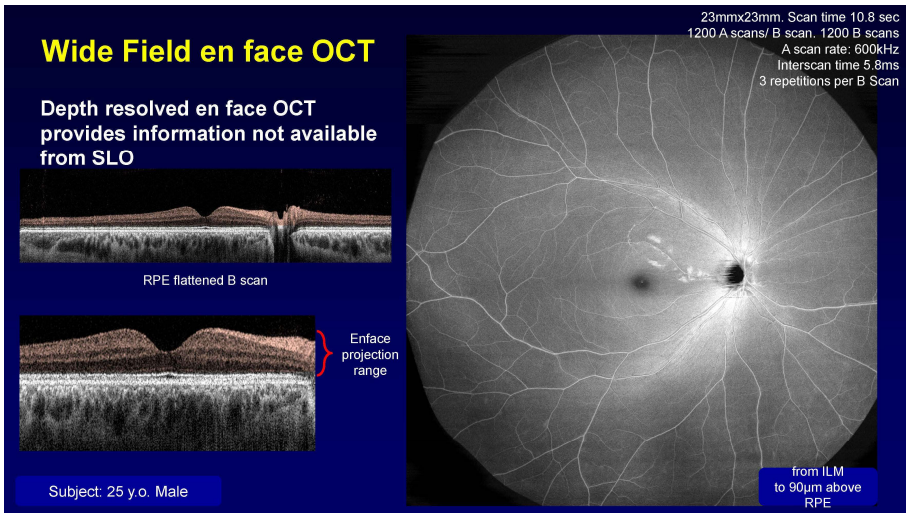


Fig. 78

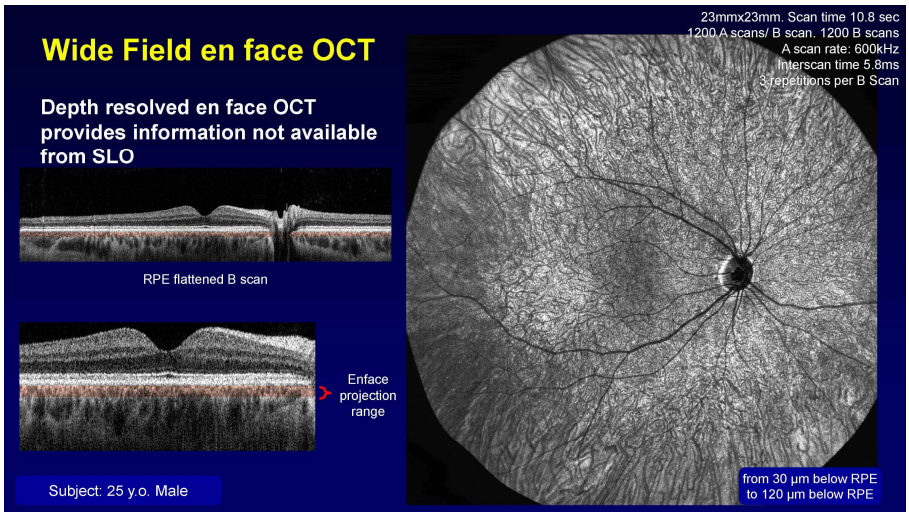


Fig. 79

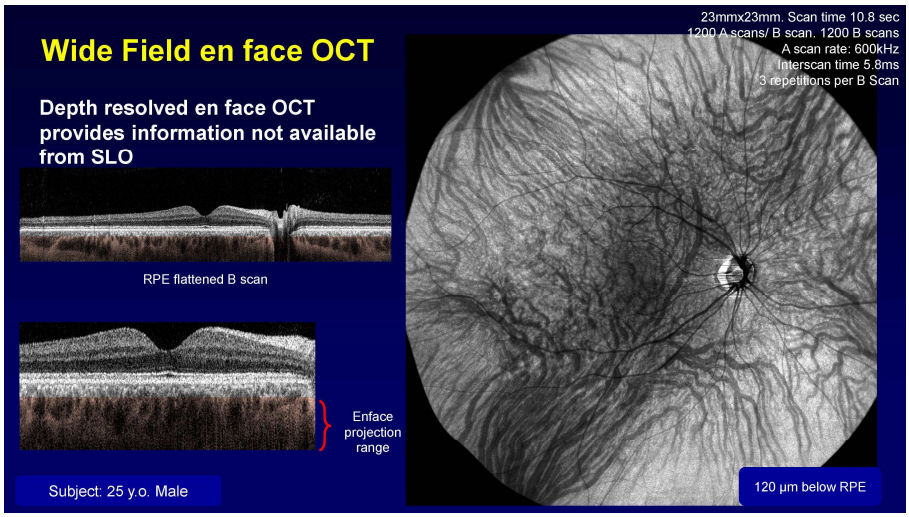


Fig. 80

〈Fig. 77－80〉 We can render a volume, this is the entire volume, shown here〈Fig. 77〉 and then different layers in the retina.〈Fig. 78〉 You can see the subretinal space and〈Fig. 79〉 then even deeper you see the vasculature〈Fig. 80〉 which is normally hidden by the pigment epithelium below the retina.

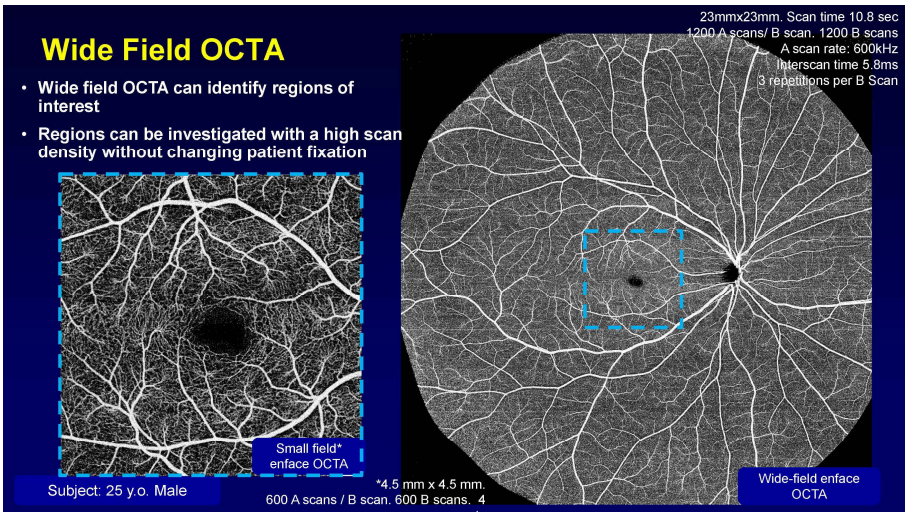


Fig. 81

〈Fig. 81〉 And we can also perform wide-field OCT angiography, and then by zooming in on particular regions we can see detailed vascular structure. All of this becomes possible if we have faster and faster acquisition speeds with more data.

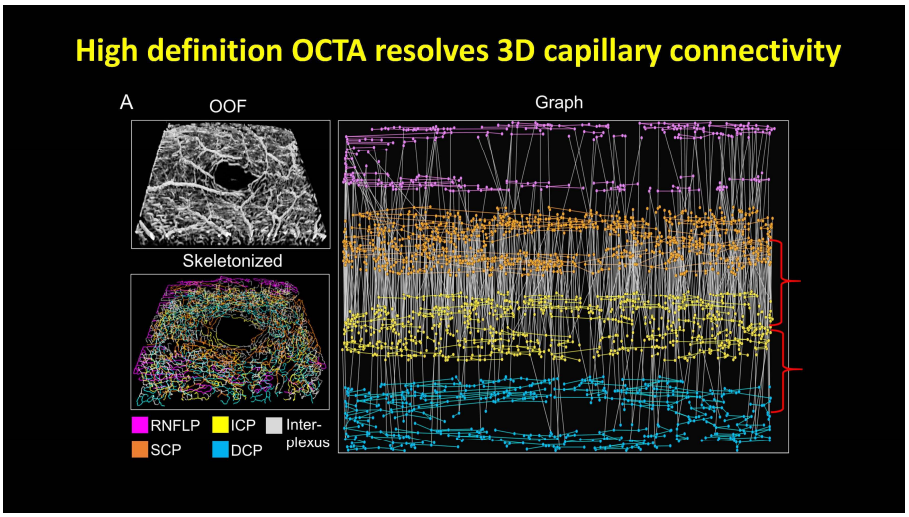


Fig. 82

〈Fig. 82〉 We can resolve the connectivity of the capillaries from the different layers; these represent the connections of vascular flow between the plexuses.

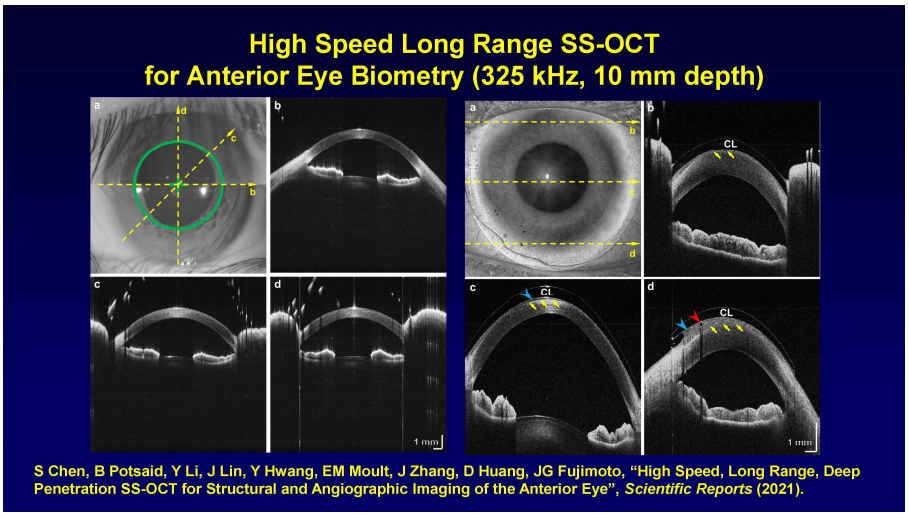


Fig. 83

〈Fig. 83〉 We can do long-range imaging, imaging the anterior of the eye, from cornea to the lens.

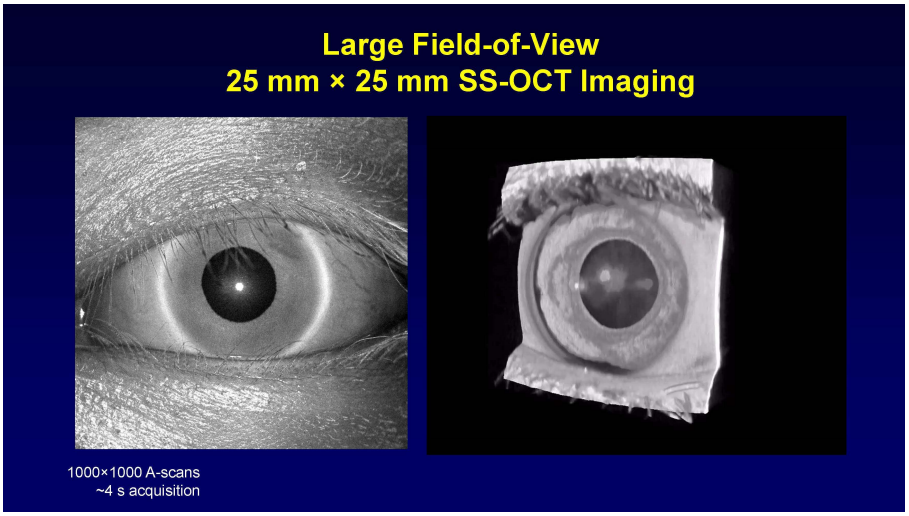


Fig. 84

〈Fig. 84〉 And you can do volumetric imaging like this three-dimensional volume. This is relevant if you're performing cataract surgery. You need precise measurement for calculation of the intraocular lens power for cataract surgery.



Fig. 85

〈Fig. 85〉 If we think about applications in the future, there's the potential for an impact on public health.

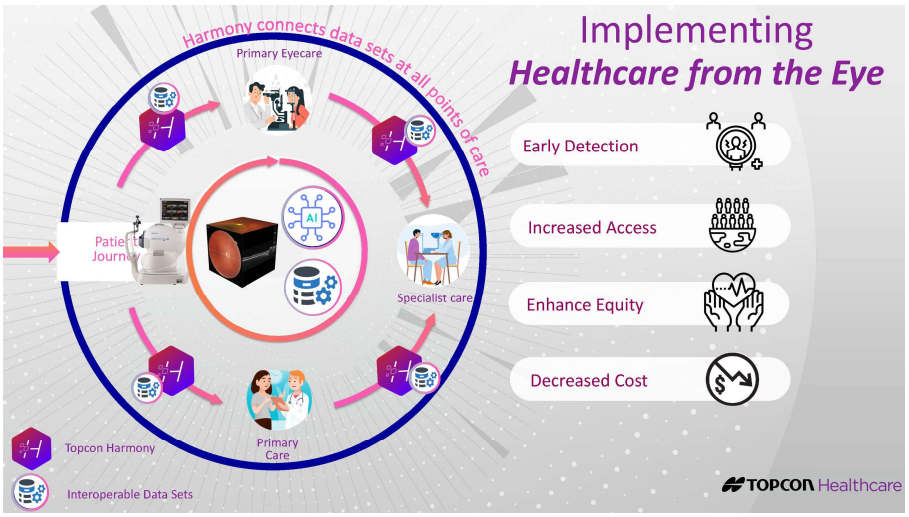


Fig. 86

〈Fig. 86〉 I'll describe an effort by Topcon, "Healthcare from the Eye". The concept is that one can use imaging and develop a comprehensive database which essentially links multiple parties, primary care, specialist care and so forth, to enable early detection of disease, to improve outcomes and decrease healthcare cost.

I want to show a short segment from a promotional video that demonstrates the potential impact.



Fig. 87

〈Fig. 87〉 "Your health. At Topcon Healthcare, we are revolutionizing the delivery of healthcare with Healthcare from the Eye. We see the eye as a window to the body; a way to transform management of health and detection of human diseases with a simple scan. Harmony, powered by Microsoft Azure, intelligently connects data and leverages AI for a real-time clinical decision support, empowering delivery and scalability."

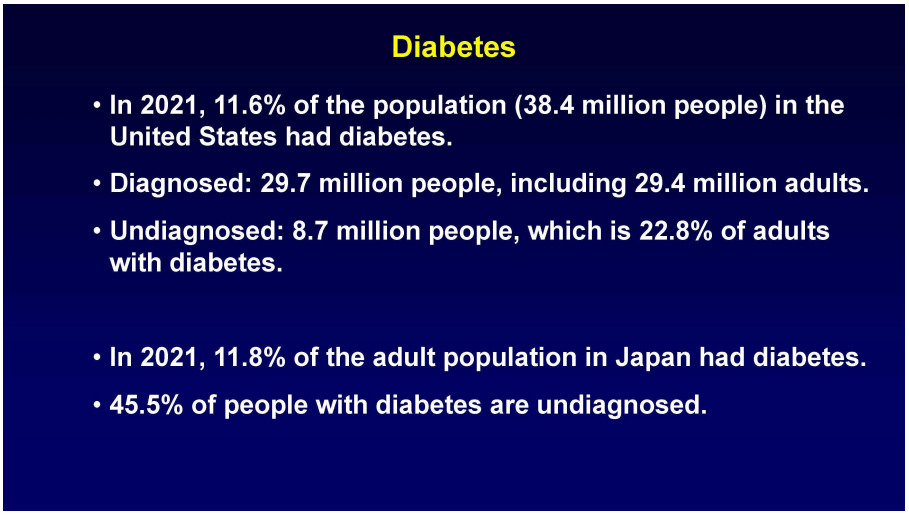


Fig. 88

〈Fig. 88〉 One of the themes is health screening becomes possible because one can link different interested parties and also do AI assessment of information.

Why is this important? If we think about diseases, such as diabetes, in the United States about 11% of the population has diabetes, and a surprising number of people are undiagnosed; 22% of adults with diabetes are not diagnosed. There's a similar percentage in Japan, and an even higher percentage of people with diabetes are not diagnosed. So, without careful management you have progressive injury to multiple organ systems in the body.

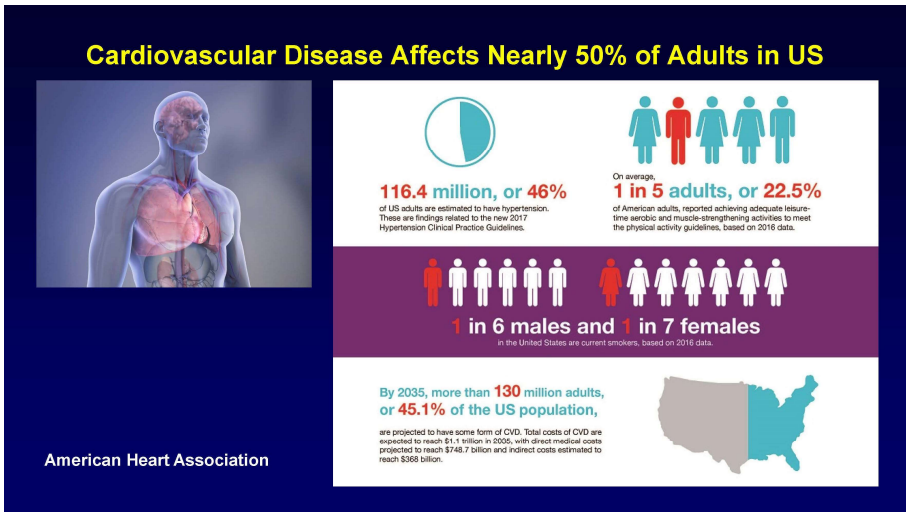


Fig. 89

〈Fig. 89〉 Another application is cardio-vascular disease. In the US this affects early half of the adults, a hundred and sixteen million people. And it's largely because people are not getting enough exercise, they're smoking and so forth.

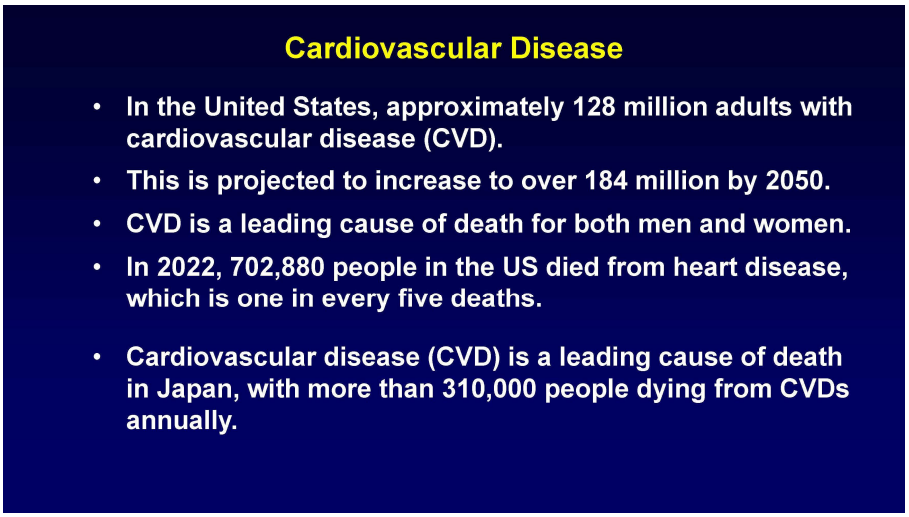


Fig. 90

〈Fig. 90〉 If we look at the aging population, this will become an increasingly important problem. 184 million projected cases of cardiovascular disease by 2050. This is a leading cause of mortality and it's accounting for one in every five deaths in the US. In Japan, this is also a leading cause of mortality.

Imagine if it was possible to predict risk of heart attack before you had a heart attack, or if it was possible to predict a risk of stroke and then intervene to reduce the risk.



Fig. 91

〈Fig. 91〉 The other major application of OCT is intravascular imaging in cardiology.

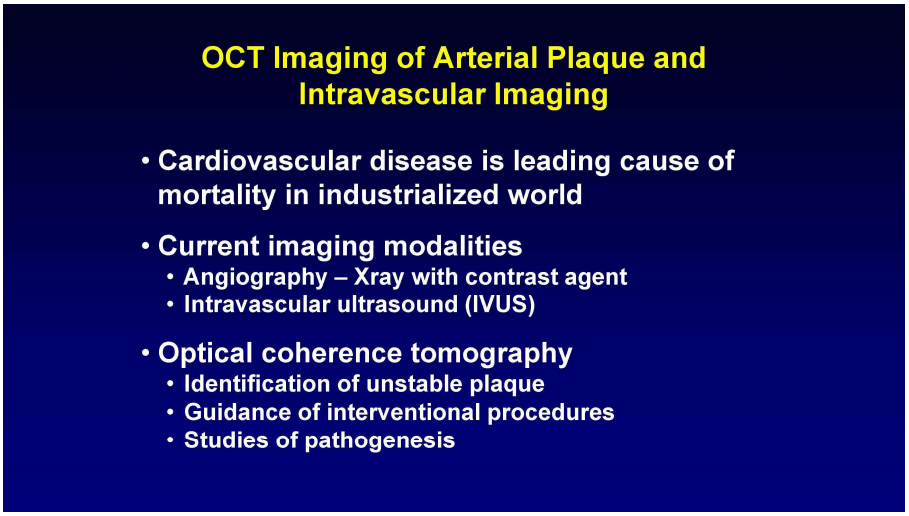


Fig. 92

〈Fig. 92〉 As we said, cardiovascular disease is a major cause of mortality. Imaging methods like angiography or ultrasound are currently used, but OCT has the advantage of much higher resolution, so it can identify the structure of the coronary arteries.

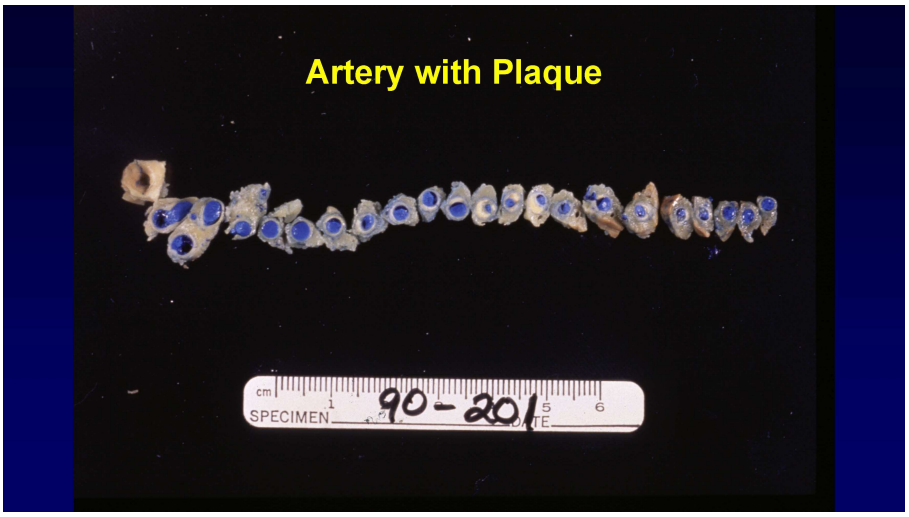


Fig. 93

〈Fig. 93〉 The presence of plaque in the arteries, which we see here - this is ex vivo and there is a dye injected - you can see the extent of occlusion of the artery, of stenosis, which restricts the perfusion.



Fig. 94

〈Fig. 94〉 If we have blockage of prefusion or ischemia, then death of the heart muscle and a heart attack occurs. Depending on where this is, it can disrupt the conduction pathway of the heart and cause sudden death.

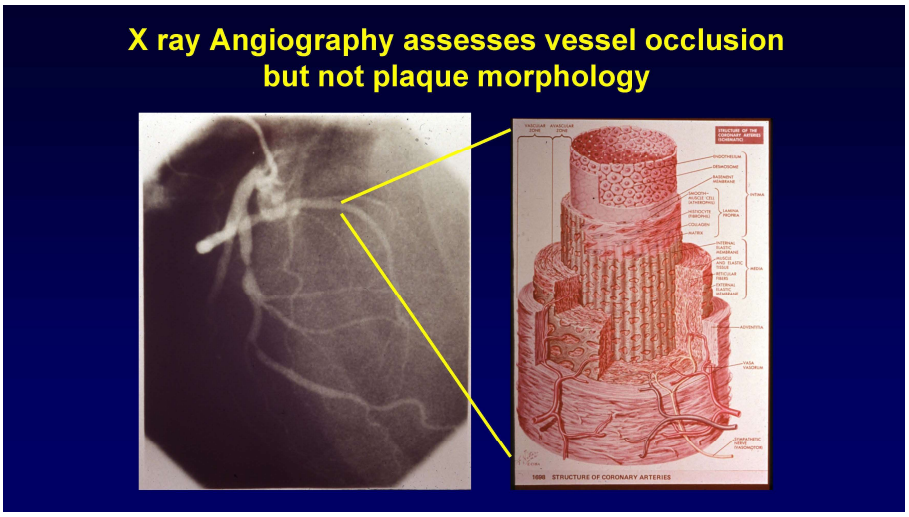


Fig. 95

〈Fig. 95〉 X ray angiography can see occlusions, but cannot see the structure of the coronary artery.

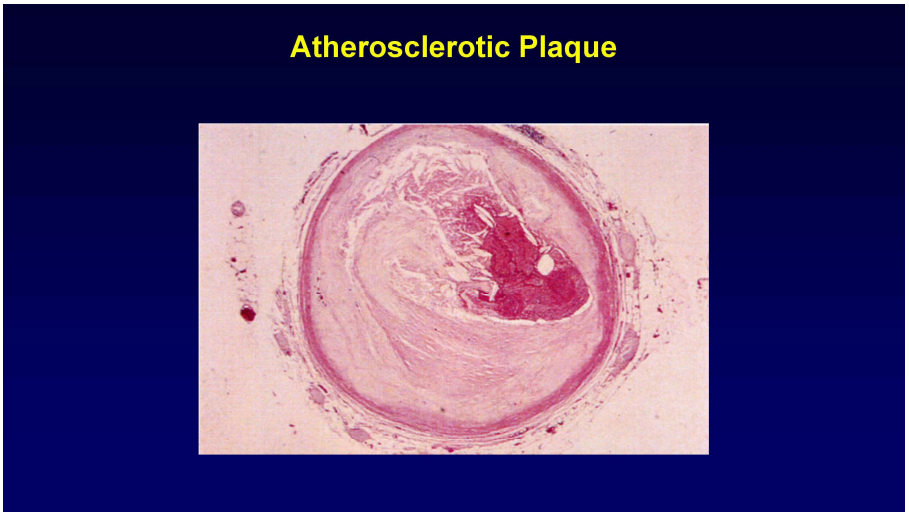


Fig. 96

〈Fig. 96〉 This is an example of plaque and a thrombus, a blood clot that causes sudden blockage of the artery.

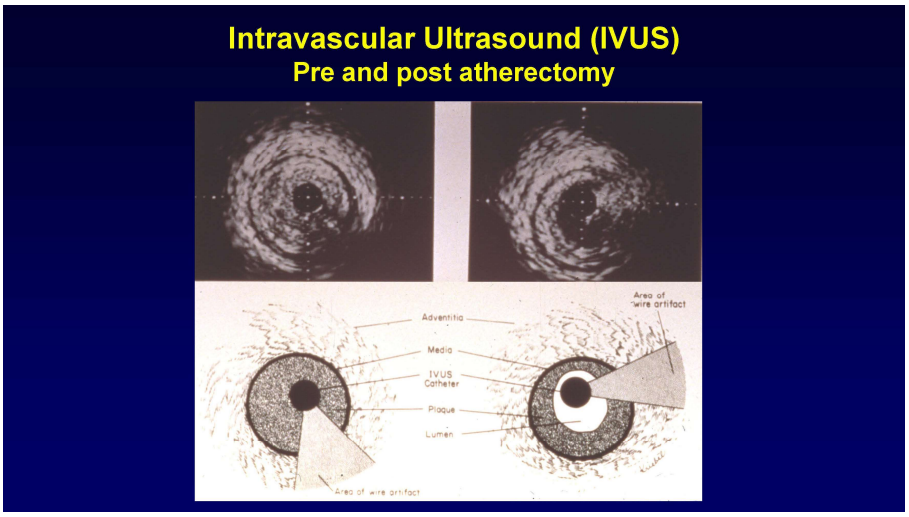


Fig. 97

〈Fig. 97〉 If we use ultrasound, it's possible to have deep image penetration, but it's difficult to resolve the morphology of the plaque.

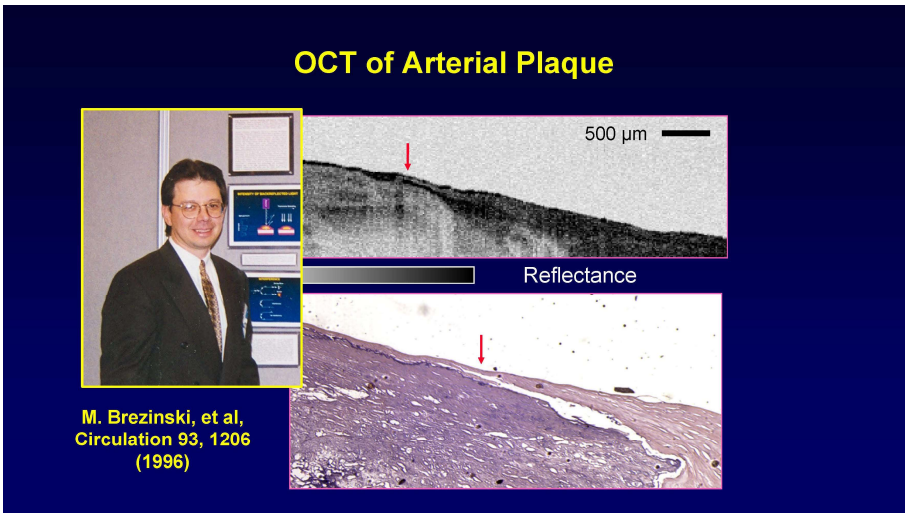


Fig. 98

〈Fig. 98〉 OCT has the advantage that it has high resolution. If we look ex vivo, this shows a plaque with a thin cap, called a thin cap fibroatheroma. This is an unstable plaque and it has been attributed to sudden coronary death. I want to especially acknowledge Dr. Mark Brezinski, MD, PhD from the Harvard Medical School. He proposed the use of OCT in cardiology and the idea that OCT could see and treat unstable plaque. Dr. Brezinski led many of the first studies in this area.

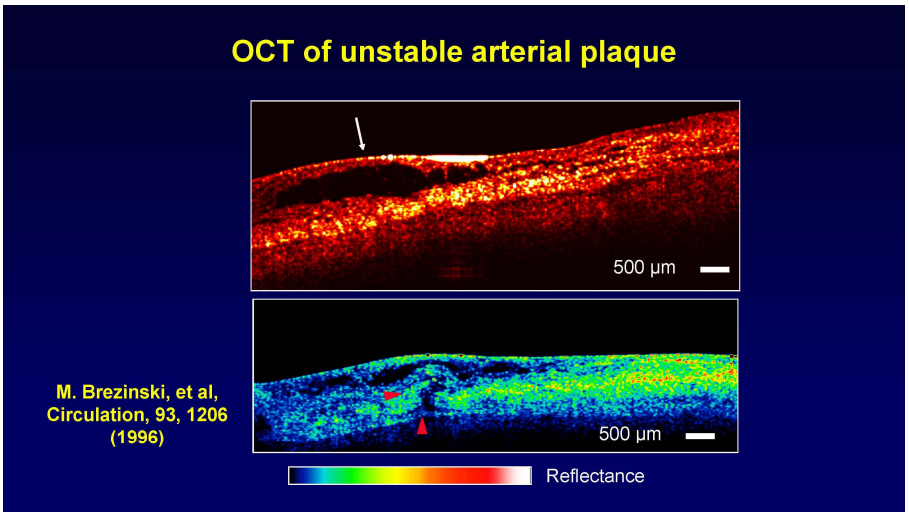


Fig. 99

〈Fig. 99〉 This is another example of unstable plaque. There's a lipid layer and a thin cap here which is prone to rupture and could rapidly block the artery.

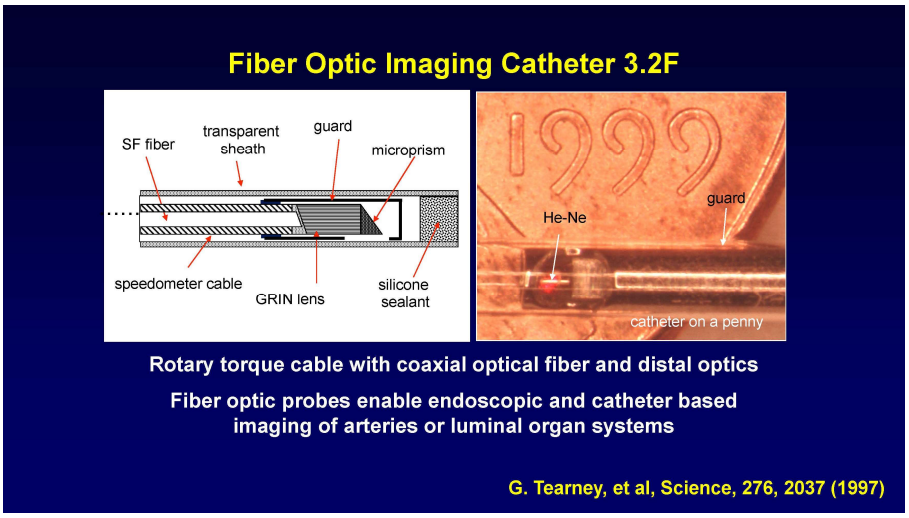


Fig. 100

〈Fig. 100〉 It's possible to image arteries by designing fiber optic devices, shown schematically and on a United States penny. This is a millimeter in diameter, and with this it's possible to image inside the body;

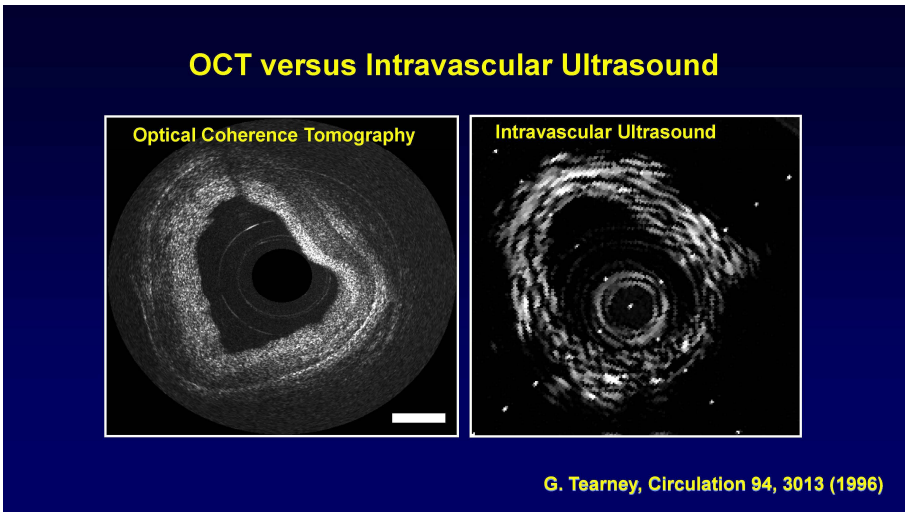


Fig. 101

〈Fig. 101〉 This is an example intravascular OCT image. This is ex vivo, but it compares OCT to ultrasound and shows the improvement in resolution.

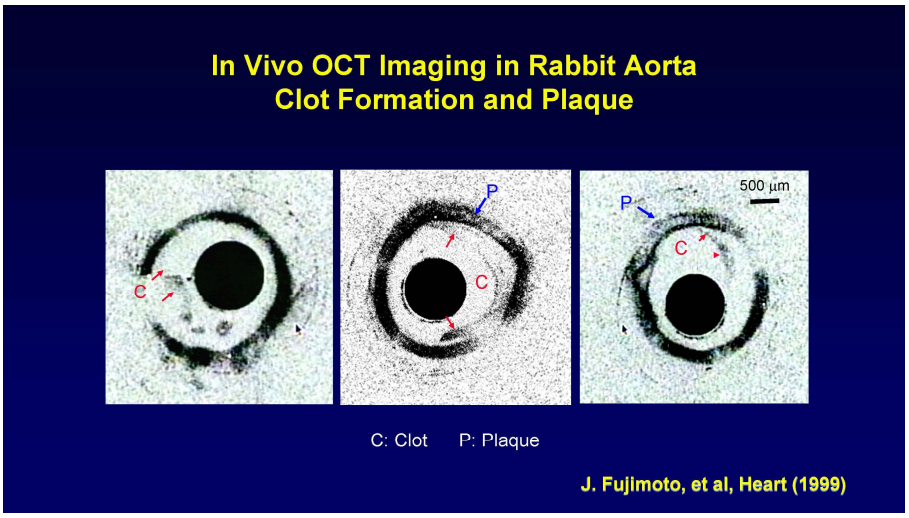


Fig. 102

〈Fig. 102〉 The next step was animal studies. This shows a rabbit aorta. You can see the imaging of the aorta in cross-section.

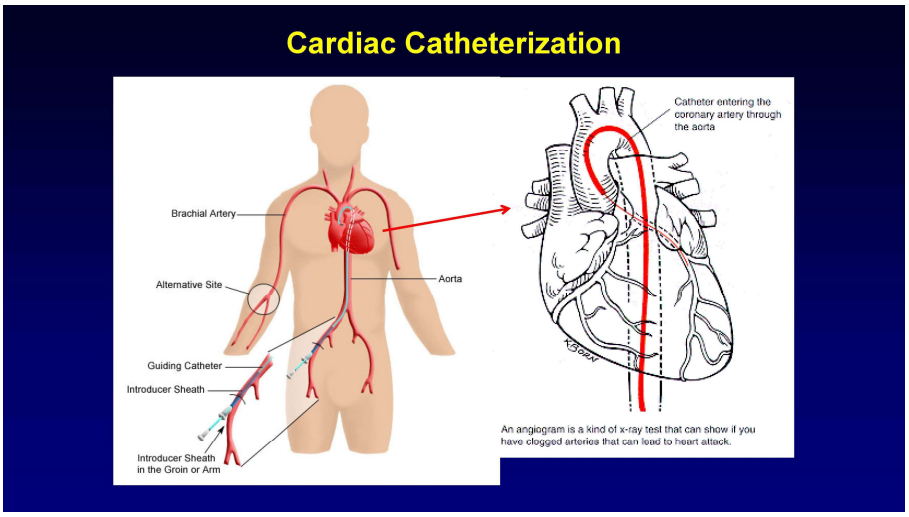


Fig. 103

〈Fig. 103〉 To put this in a larger perspective, this is a procedure where the catheter is advanced into the coronary artery.

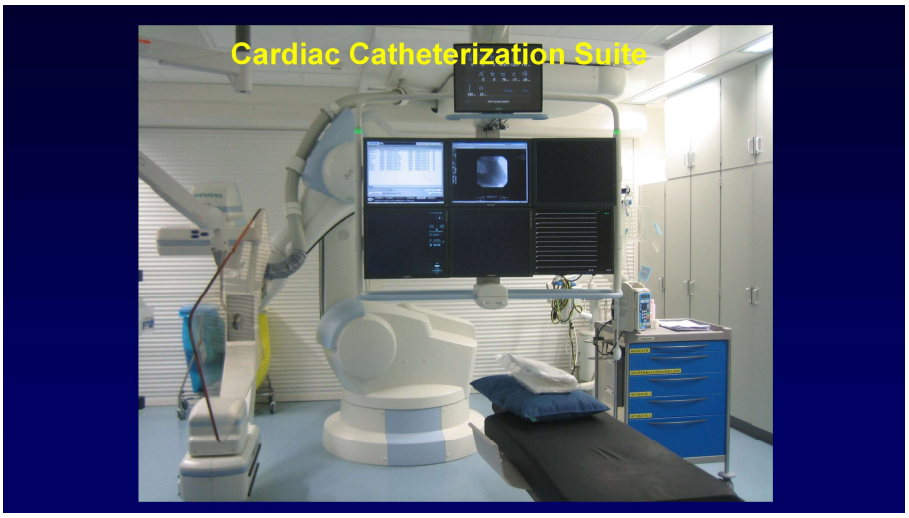


Fig. 104

〈Fig. 104〉 These procedures are done in a catheterization suite.

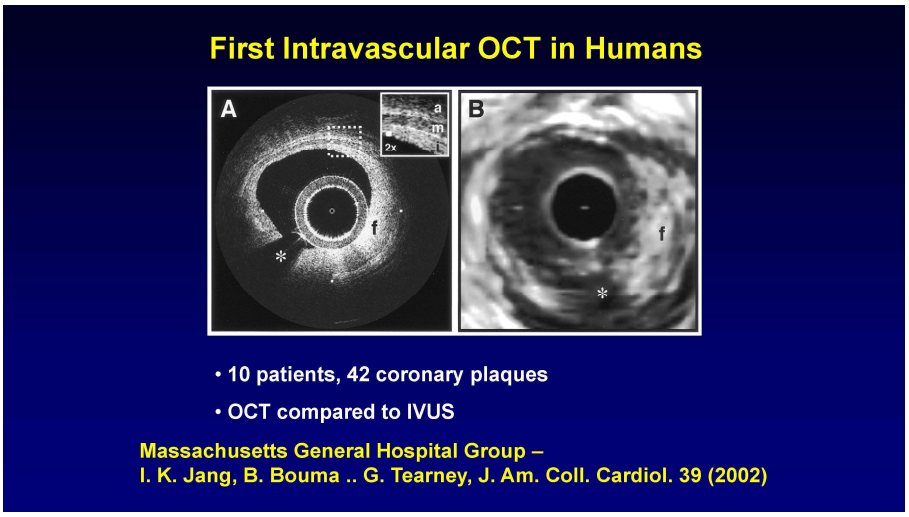


Fig. 105

〈Fig. 105〉 I especially wanted to acknowledge the group at the Massachusetts General Hospital. I think they did a monumental experiment. The first intravascular OCT imaging in humans was performed in South Korea by I.K. Jang. The study had ten patients, comparing OCT imaging to intravascular ultrasound.

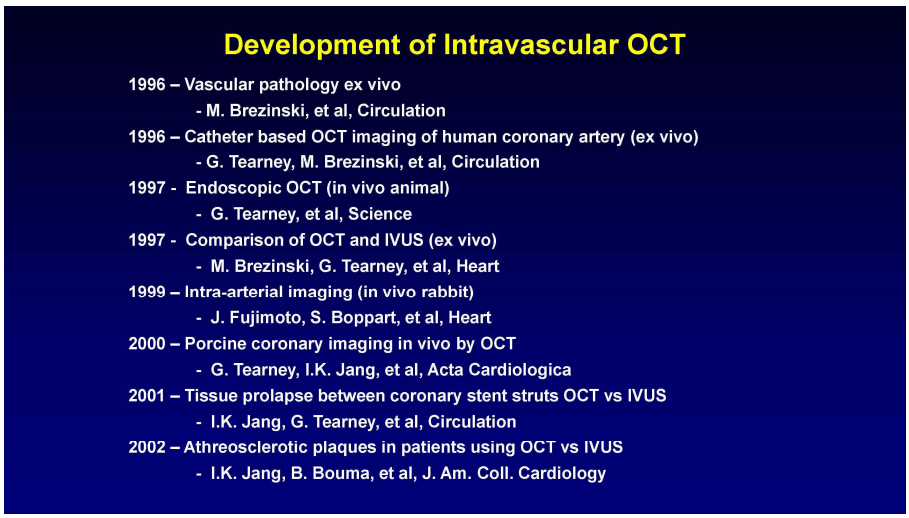


Fig. 106

〈Fig. 106〉 If we look at the development, there are multiple milestones for intravascular OCT.



Fig. 107

〈Fig. 107〉 We took the approach of developing this technology in a start-up company rather than in academics. LightLabs Imaging was founded in a joint venture with Carl Zeiss.

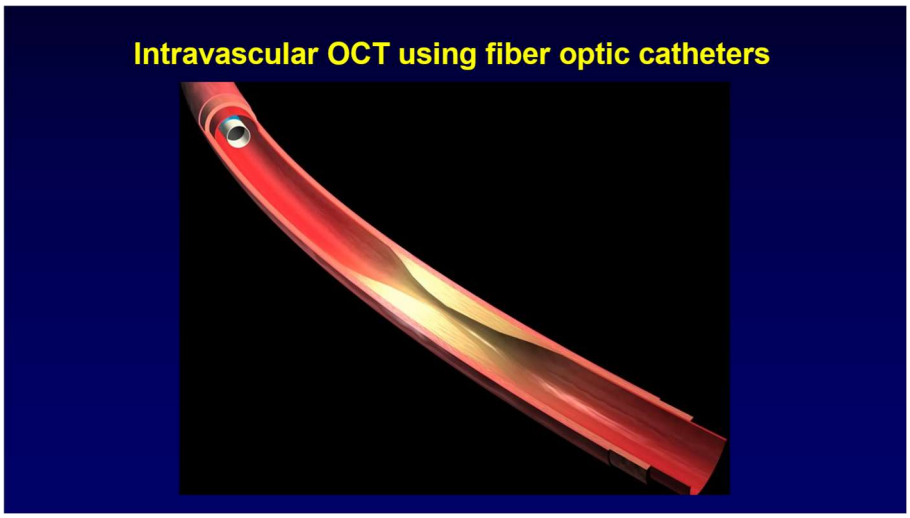


Fig. 108

〈Fig. 108〉 In this example, the catheter is advanced over a guidewire which you see here, and then there is rapid imaging retracting the catheter and imaging plane, generating a volumetric image over a region of the artery.

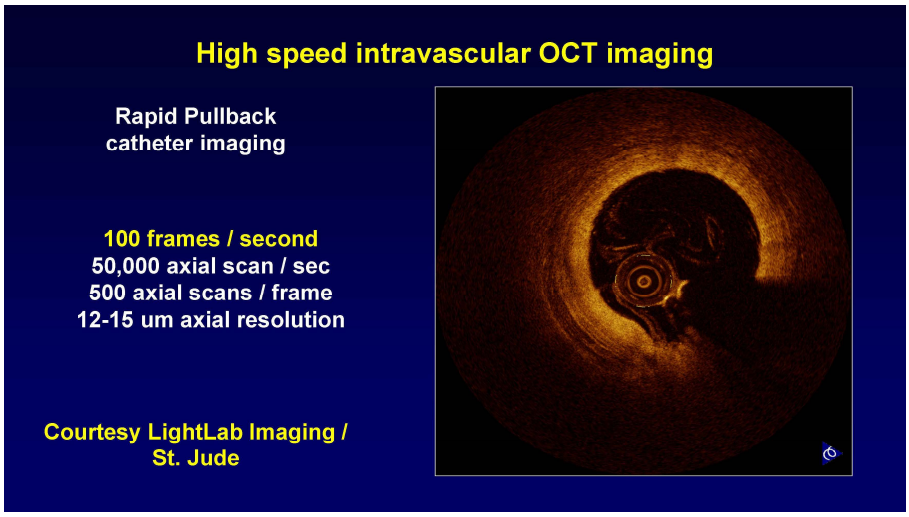


Fig. 109

〈Fig. 109〉 This video shows the imaging speed which is possible.

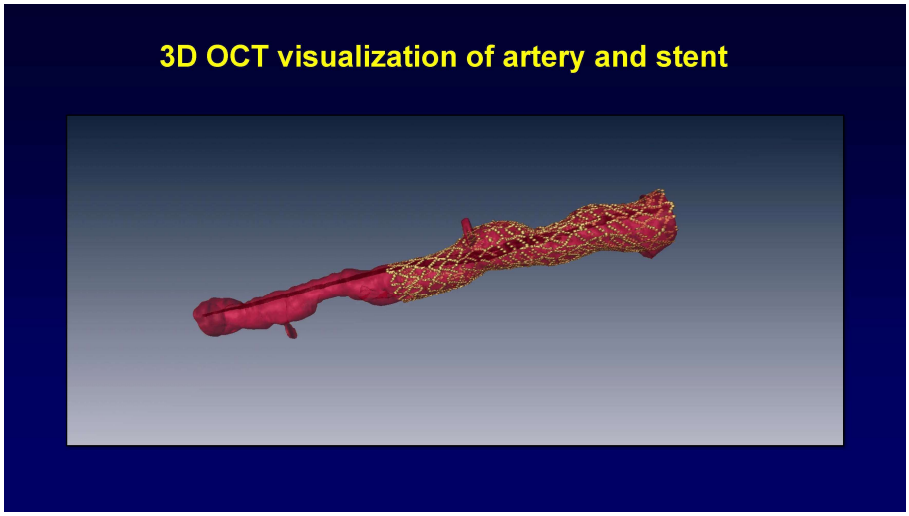


Fig. 110

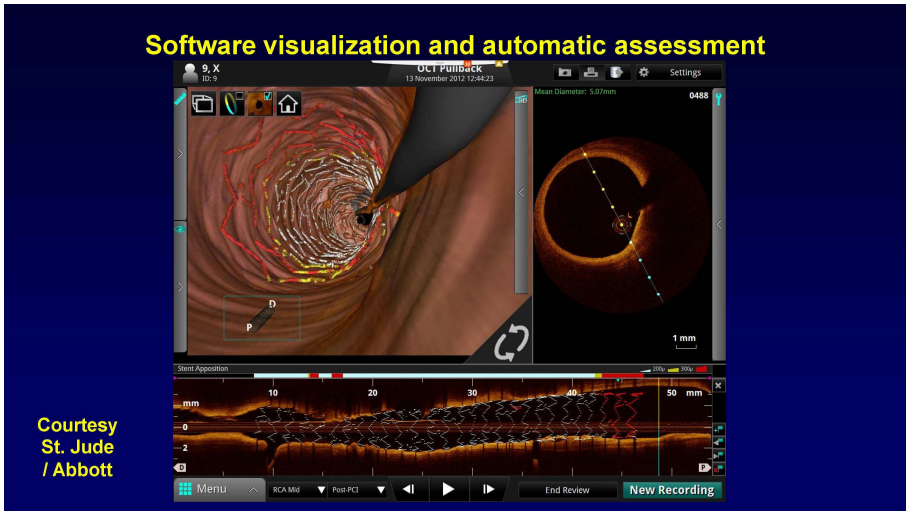


Fig. 111

〈Fig. 110 and 111〉 Imaging over a region of the artery 〈Fig. 110〉 the data can be rendered.

This shows the stent which is used to reopen the artery. 〈Fig. 111〉 We can use computational methods to extract information on the stent and structure in general.

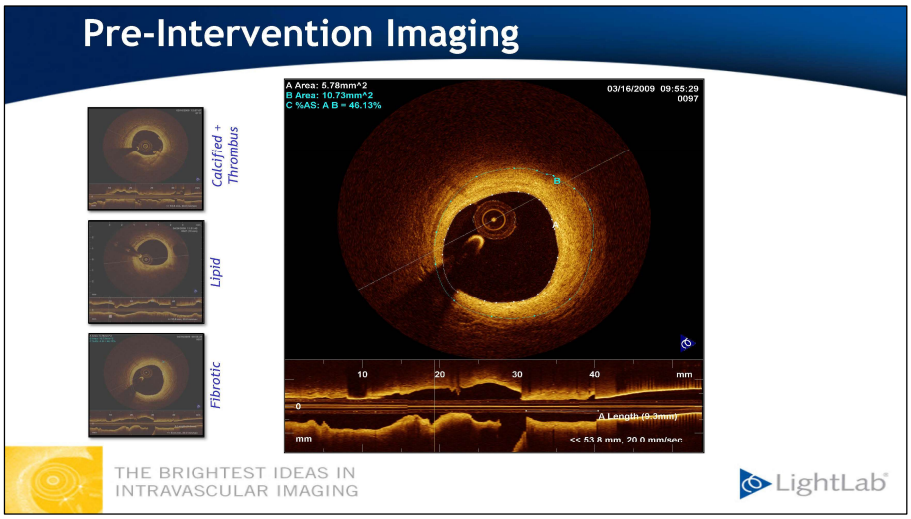


Fig. 112

〈Fig. 112〉 As an example, this shows assessing pathology and then guiding the intervention. This is a cross-section of the artery and here we see a thrombus. In another example which shows plaque, it's possible to measure the thickness of the plaque. You can see measurements here.

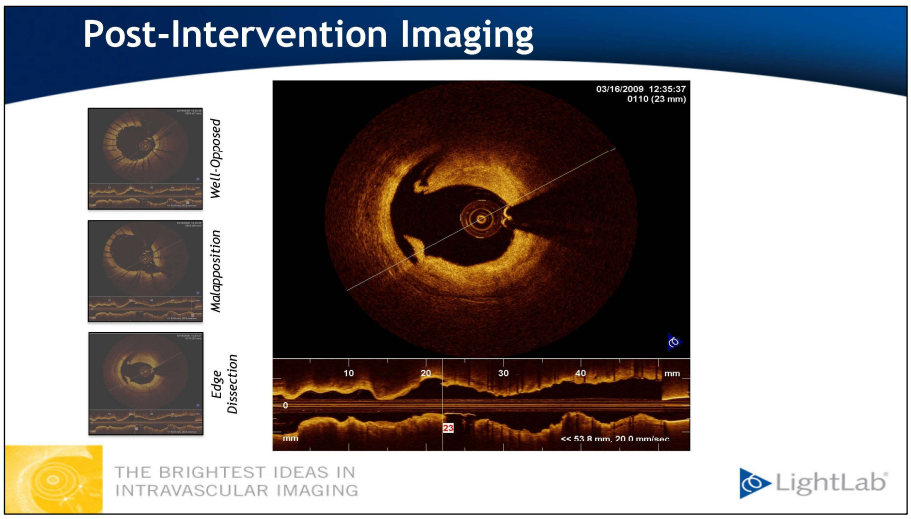


Fig. 113

〈Fig. 113〉 If we look after intervention, this is a stent that has been placed to reopen the artery, so these are the wires, the shadowing of the stent is here, and we can see the stent should be close to the artery wall, well-apposed; versus malapposed. There is separation here which can regenerate a thrombus. These are examples of planning and guiding interventional treatment.

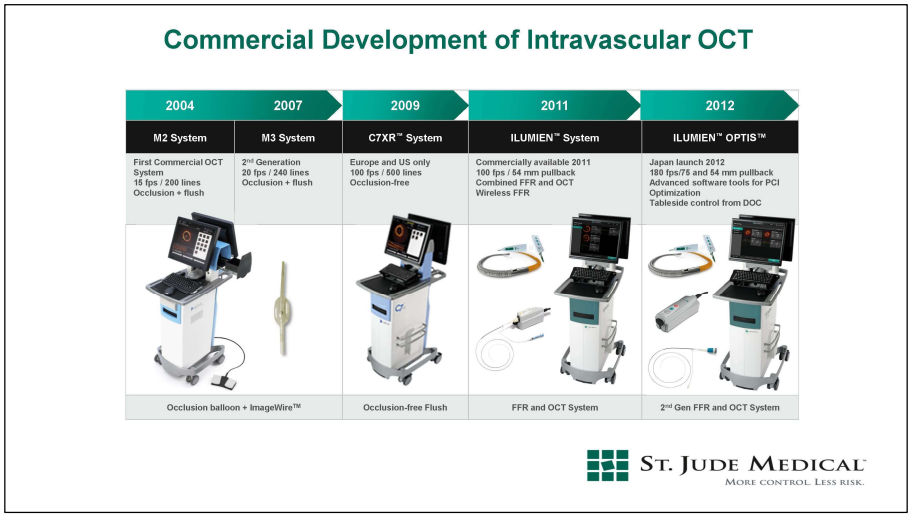


Fig. 114

〈Fig. 114〉 If we look at commercialization, this involved multiple instruments going through multiple iterations, with progressively higher performance and higher speed.

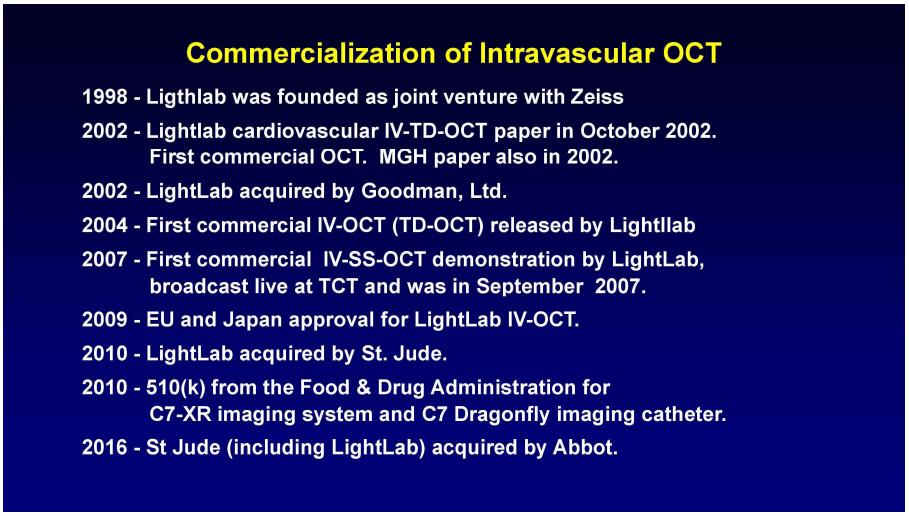


Fig. 115

〈Fig. 115〉 And here we show a timetable; 1998 was the founding of Lightlab as a joint venture with Carl Zeiss, and next the milestones; FDA approval and so forth. And ultimately, I think one of the messages is, this was a slow process.

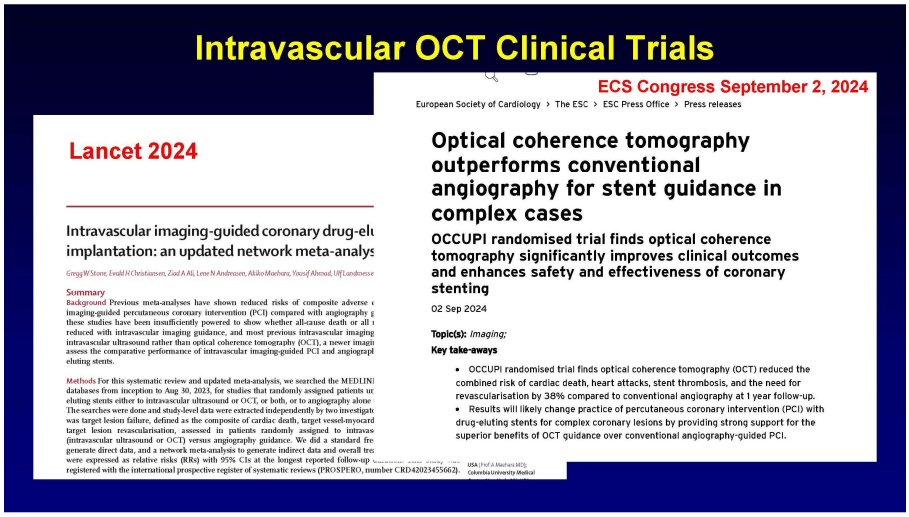


Fig. 116-1

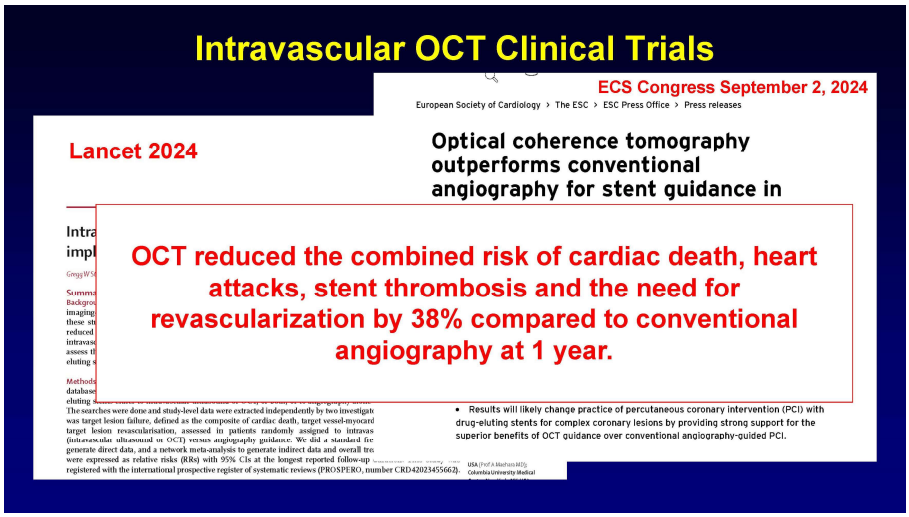


Fig. 116-2

〈Fig. 116〉 If we look at recent trials, Lancet 2024 had a metanalysis of OCT and other guidance. Then this ECS report in September, I think is an impressive result, “OCT outperforms conventional angiography for stent guidance in complex cases”, the OCCUPI randomized clinical trial. This showed that OCT reduced the combined risk of cardiac death, heart attacks, stent thrombosis and need for retreatment by 38% compared to angiography at a one-year time point. This I think is a very powerful advance, but achieved relatively late after the development and commercial introduction of this technology. Again, it shows that the timeline is quite slow for new medical technologies.



Fig. 117

〈Fig. 117〉 As an example of an application outside of medicine, I'll show art conservation and metrology.

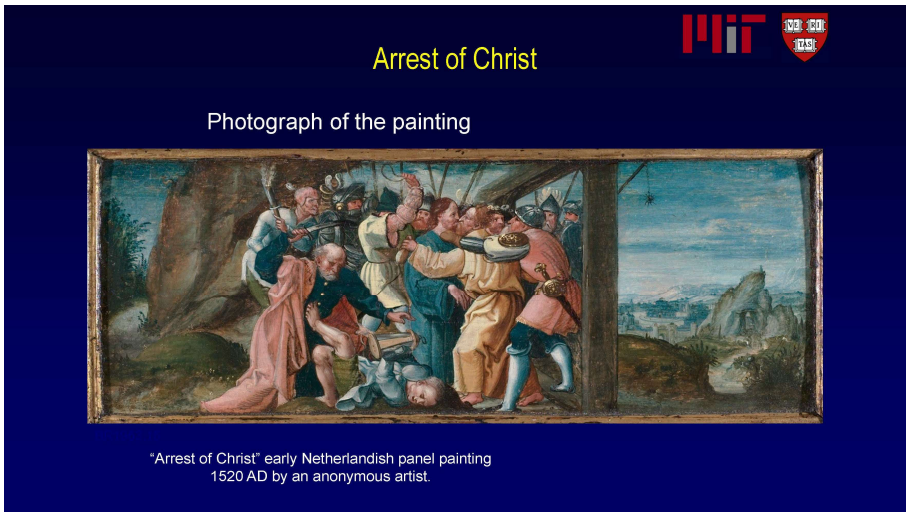


Fig. 118



Fig. 119

〈Fig. 118〉 This was a study done with the Harvard Art Museum. A photograph of the painting - The Arrest of Christ, 1520. This is the painting and then you can do infrared photography 〈Fig. 119〉 which will see below the surface, partially anyways, of the painting.

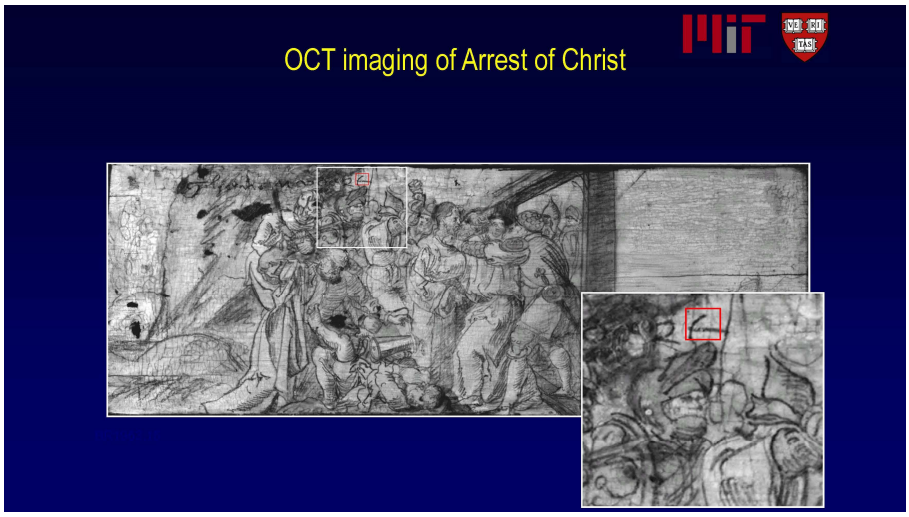


Fig. 120

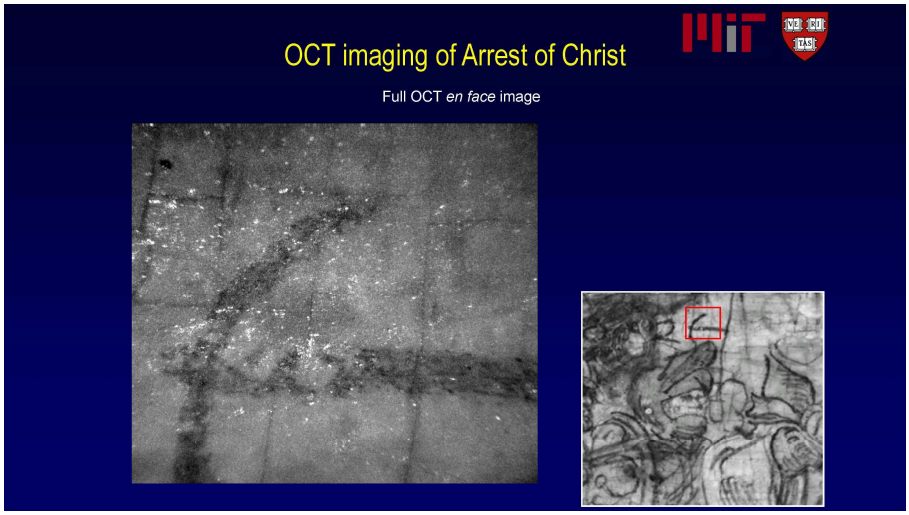


Fig. 121

〈Fig. 120 and 121〉 We can look here at a small region 〈Fig. 121〉 and do an OCT image. This is a full projection OCT image over all depths.



Fig. 122

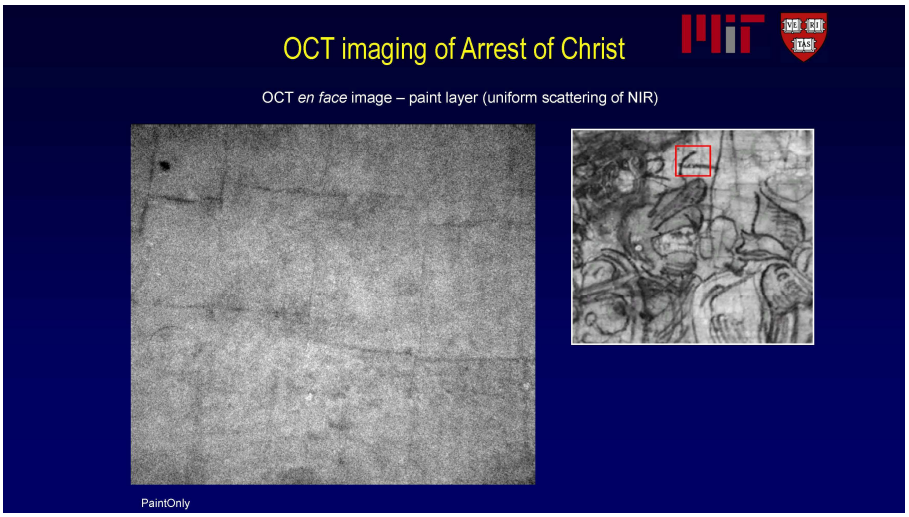


Fig. 123

〈Fig. 122 and 123〉 We can look at the surface which shows the varnish on top of the painting 〈Fig. 122〉 and we can progressively section down as if we're cutting deeper into this painting, of course you can't cut it, but this is optically sectioning. 〈Fig. 123〉 We see the layer of paint here and then there's fracturing in the paint.



Fig. 124

〈Fig. 124〉 And finally go to the planning or under-drawing which we can see below the painted surface. And this again comes back to the concept that Michel Duguay showed, that you can see below the surface of the paint or scattering tissues.

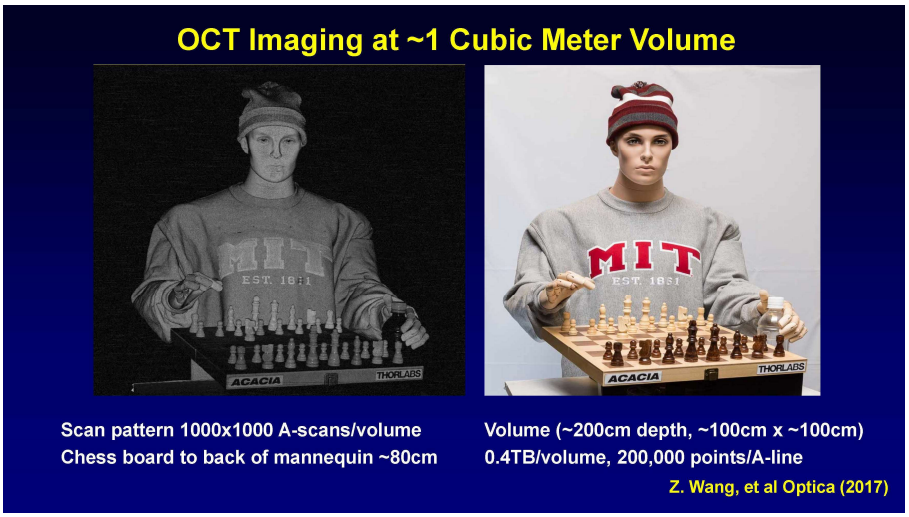


Fig. 125

〈Fig. 125〉 It's also possible to image very long distances. This shows a mannequin, life-size, and with OCT imaging over a one-meter scale.



Fig. 126

〈Fig. 126〉 Here we see a three-dimensional image. By rotating it virtually we can appreciate the depth contour.

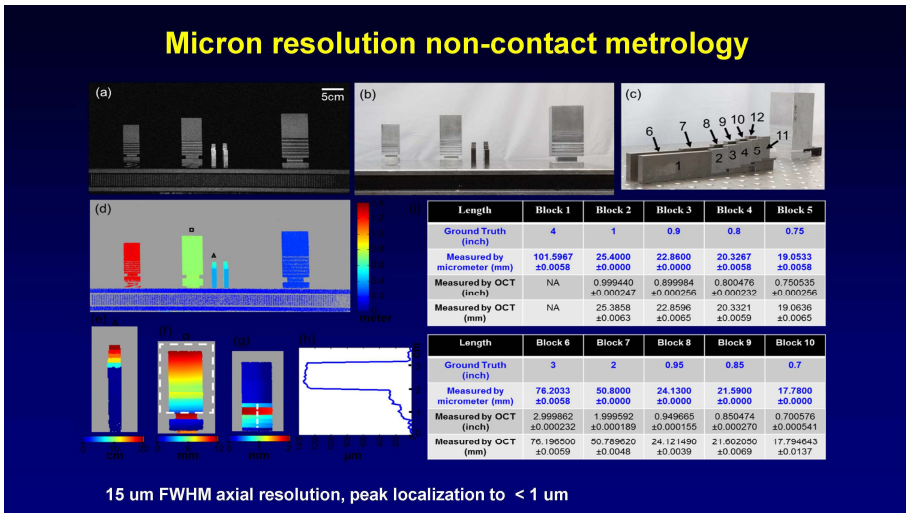


Fig. 127

〈Fig. 127〉 And, while this is not as interesting, it points out that this is actually a precision measurement where we can measure distances, displacements, to the micron level scale. For metallurgy, for process manufacturing, this type of capability is quite important.



Fig. 128

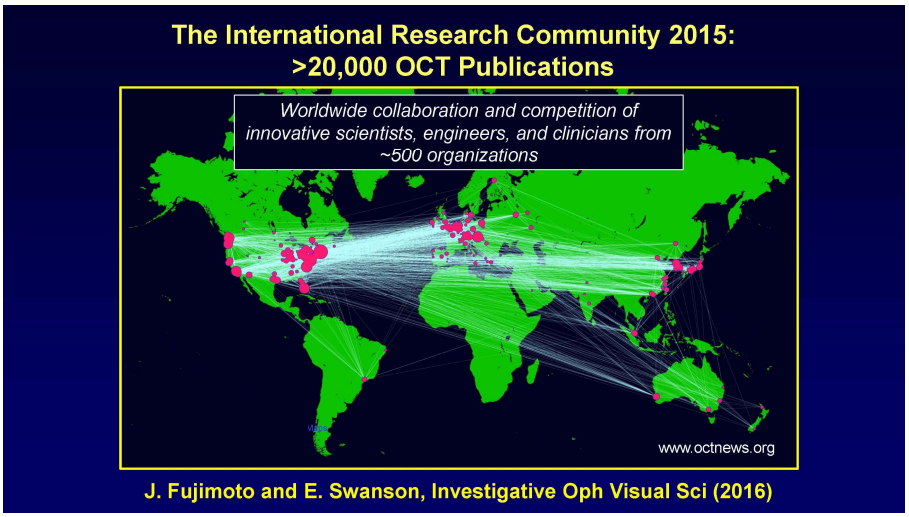


Fig. 129

〈Fig. 128 and 129〉 Now let's look at the impact of OCT. 〈Fig. 129〉 This would not have been possible without the international research community. The little red spots indicate the major research groups, the lines indicate collaboration between the groups showing the extensive international network with collaborative exchange of information.

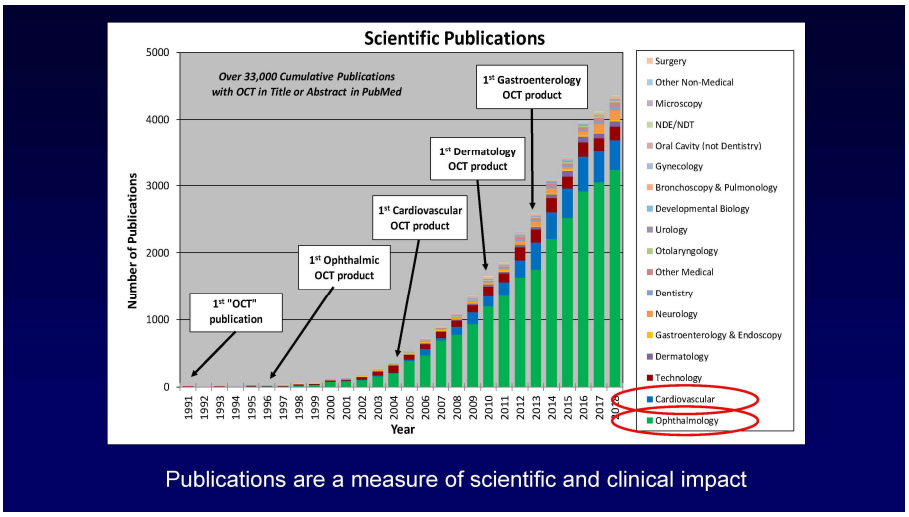


Fig. 130

〈Fig. 130〉 If we look at the publication history, this plots the number of publications per year in different areas, which closely parallels the commercial introduction of OCT. This is because commercialization made widespread use and investigation possible. The largest publication volume is in ophthalmology, the green portion of the plot. Cardiovascular is the blue portion, the second largest. We see multiple other applications that have potential for growth.



Fig. 131

〈Fig. 131〉 Fig. 131 shows other applications spanning the different medical specialties;, including gastroenterology, dermatology, pulmonology among others.

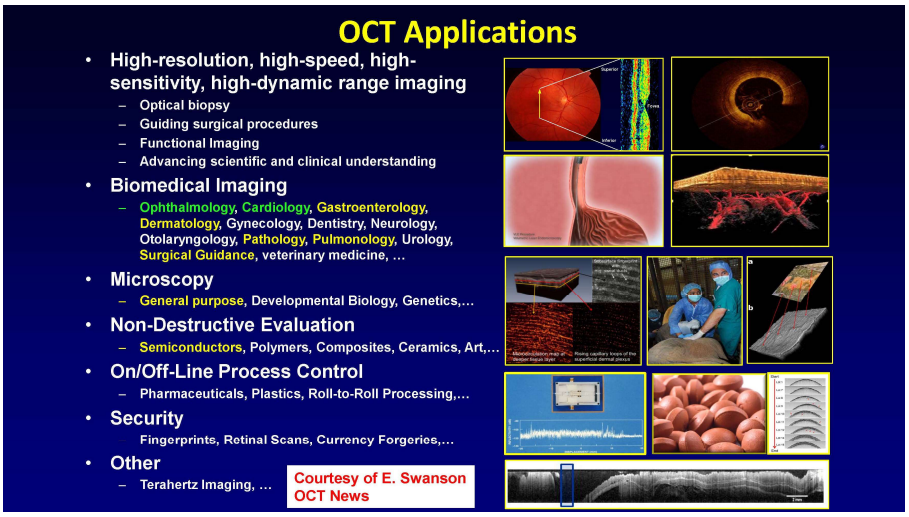


Fig. 132

〈Fig. 132〉 You can see multiple applications listed here.



Fig. 133

〈Fig. 133〉 But an important point is that for medical applications, the process of commercialization is long. There is a research phase, clinical feasibility studies, a commercial development phase, obtaining FDA approval, multi-center studies, early adopter studies, demonstration of efficacy which is required for reimbursement, and finally, we can start to realize significant sales, which occurs after reimbursement.



Fig. 134

〈Fig. 134〉 There is future potential, but the development cycle is challenging. We believe OCT will continue to play a key role in clinical ophthalmology and ophthalmology research. Commercial advances will enable wider spread access and we saw an example of this for disease screening, with a large potential impact on public health. I think this is very promising. There are applications in other specialties which will continue to develop, but each application has to be developed on a case-by-case basis. There is metrology, non-destructive evaluation, and process monitoring. We believe these more will become increasingly important. Photonic integration will enable very low cost and high performance. In general these advances require the international scientific and engineering community as well as the partnership of government, academics, medicine and industry.

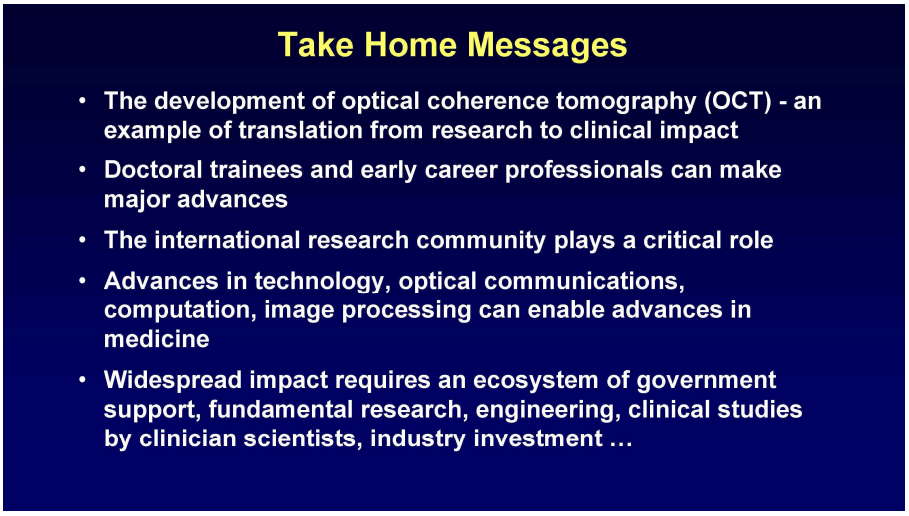


Fig. 135

〈Fig. 135〉 These are the important themes and the take home messages. The history of OCT shows that you can translate from research to clinical impact. OCT is one example of this; now there are many possible technologies that are being translated. Doctoral trainees and

early career professionals can make major advances, which shows potential for younger people in the science and engineering professions. The international research community played a critical role. Advances in technology, optical communications and other areas can enable advances in medicine and their translation to other applications. Widespread impact requires cooperation among many entities, or an ecosystem: government support, fundamental research, engineering, clinical studies by clinician-scientists, and industry investment.



Fig. 136

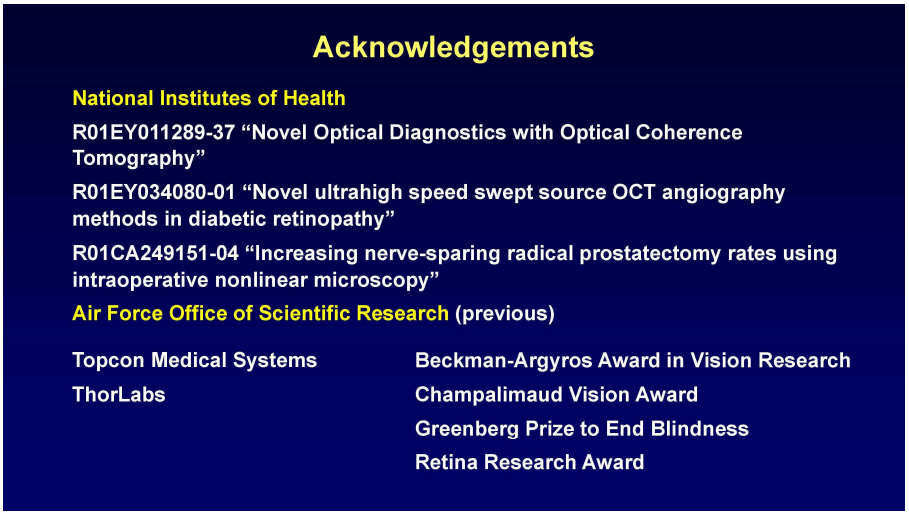


Fig. 137

〈Fig. 136 and 137〉 I'd like to acknowledge all of our collaborators, including current collaborators and many of our past collaborators who are too numerous to list here. 〈Fig. 137〉 and I'd like to acknowledge support from the government agencies, the National Institute of Health, the Air Force Office of Scientific Research, industry sponsorship from Topcon Medical Systems, ThorLabs, as well as a number of foundations.

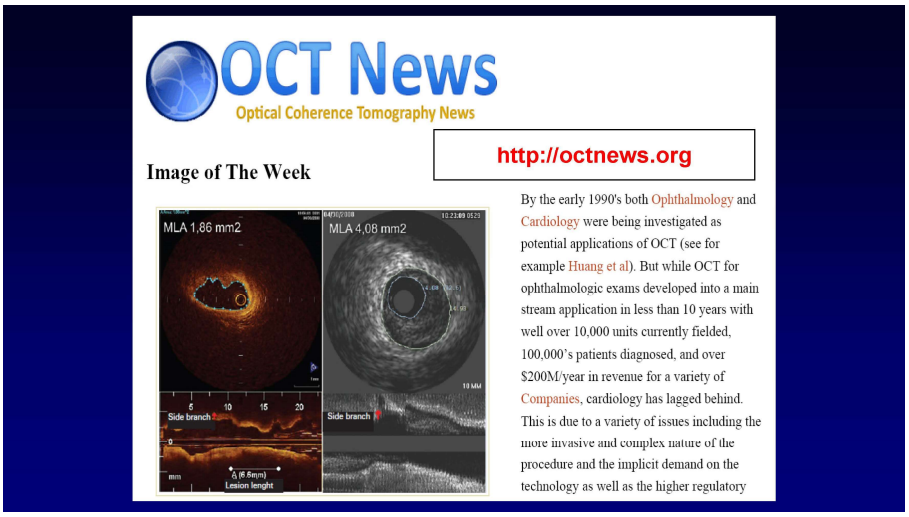


Fig. 138

〈Fig. 138〉 If you're interested in OCT, there's a website which is run by Mr. Swanson: OCT News. This website tracks industry development, venture capital funding and activity and, of course, scientific and clinical publications.



Fig. 139

〈Fig. 139〉 Again, I'd like to express my sincerest thanks to the Honda Foundation and to the selection committee. It's really a great honor and privilege to be selected as a recipient of the Honda Prize, and to be here with you today.

Thank you very much.

■ This report can be viewed in the Honda Foundation's website.
You may not use the proceedings for the purposes other than personal use without the express written consent of the Honda Foundation.



HONDA FOUNDATION

YANMAR TOKYO Bldg., 6F
2-1-1, Yaesu, Chuo-ku, Tokyo 104-0028 Japan
Tel. +81 3 3274-5125 Fax. +81 3 3274-5103
www.hondafoundation.jp/en

Editor in Chief : Masaki Tsunoda