Primary Care Imaging
using
Optical Coherence Tomography

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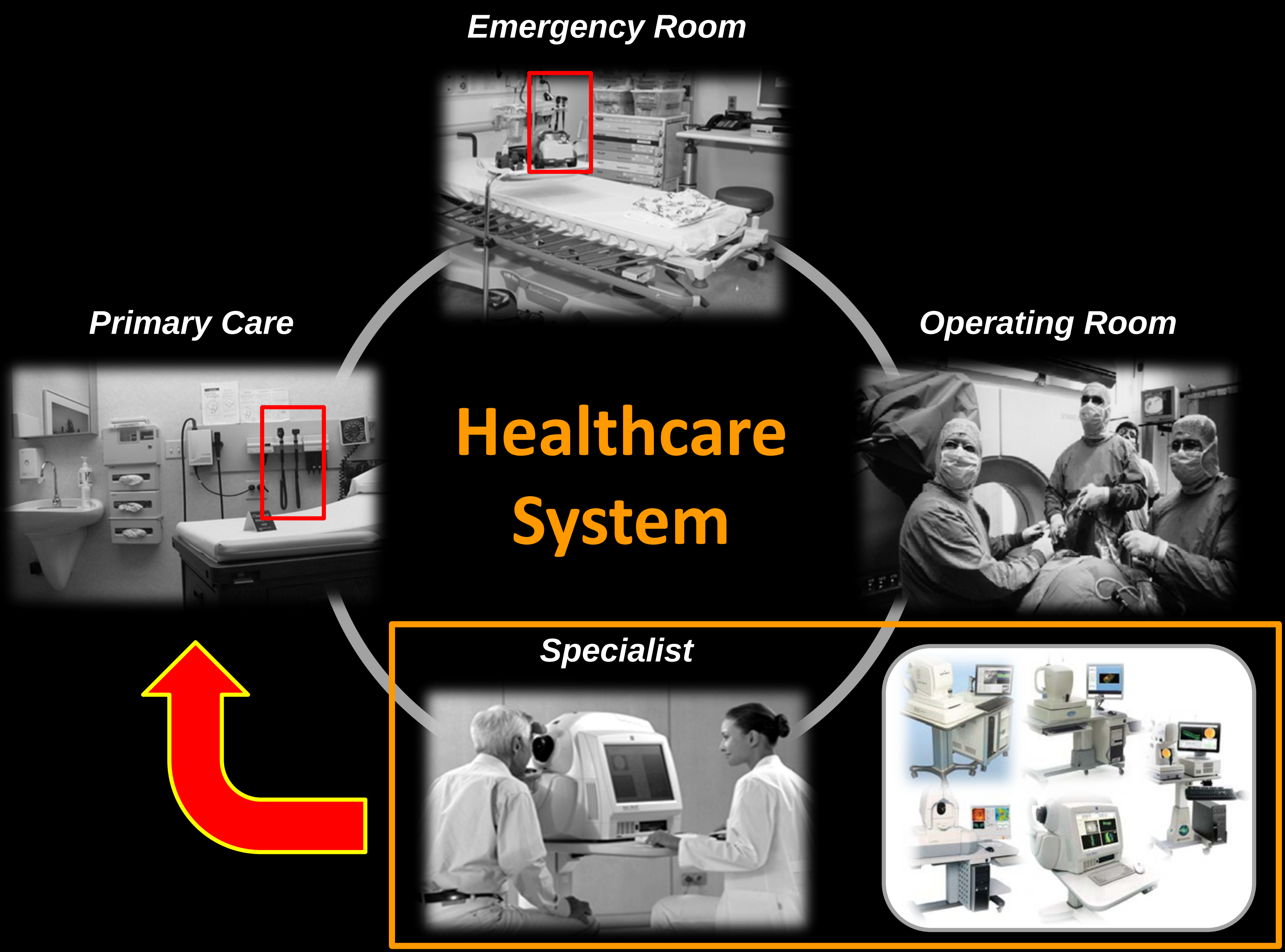
April 12, 2012

IEEE Engineering in Medicine and Biology Society
Syracuse Chapter
Health Tech Symposium

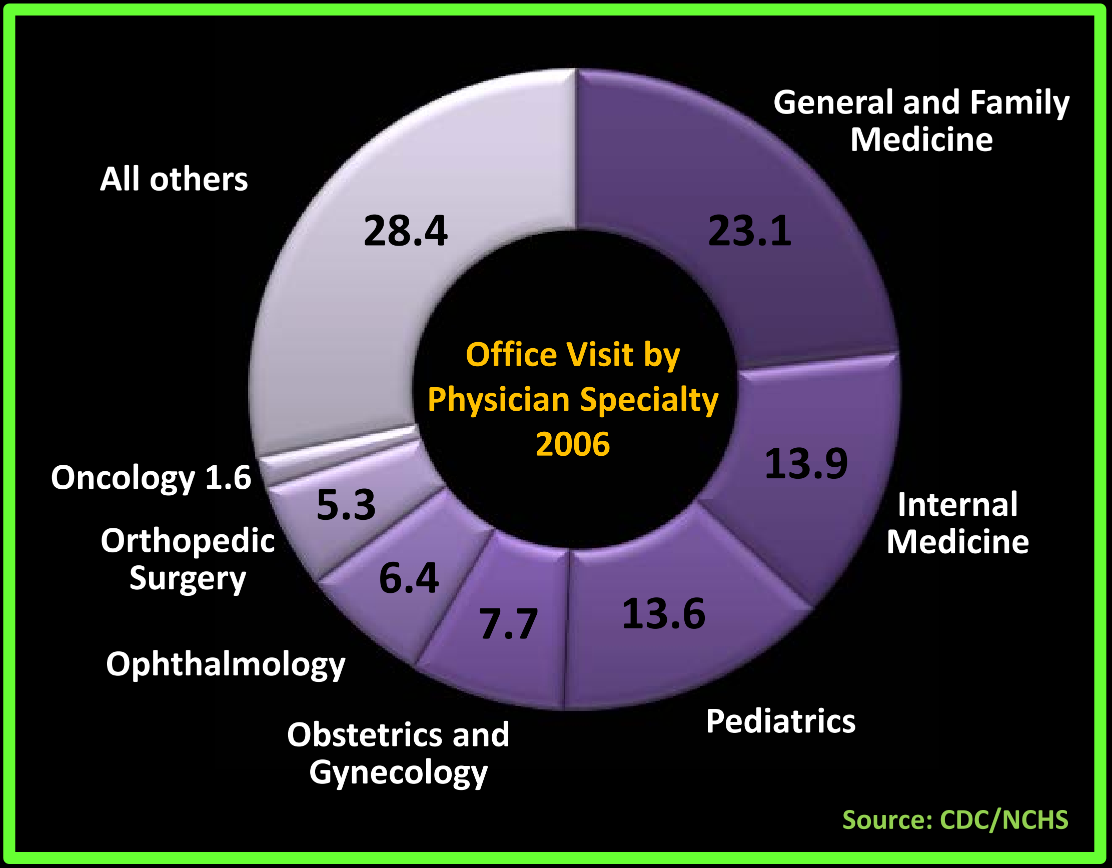
BIOPHOTONICS
IMAGING LABORATORY

Disclosure:
Royalties from patents licensed by MIT
Consultant and research funding from Welch Allyn, Inc., Texas Instruments, Inc., and Samsung, Inc.
Co-Founder and CMO of Diagnostic Photonics, Inc.



Emergency Room
Primary Care
Operating Room
Healthcare System
Specialist

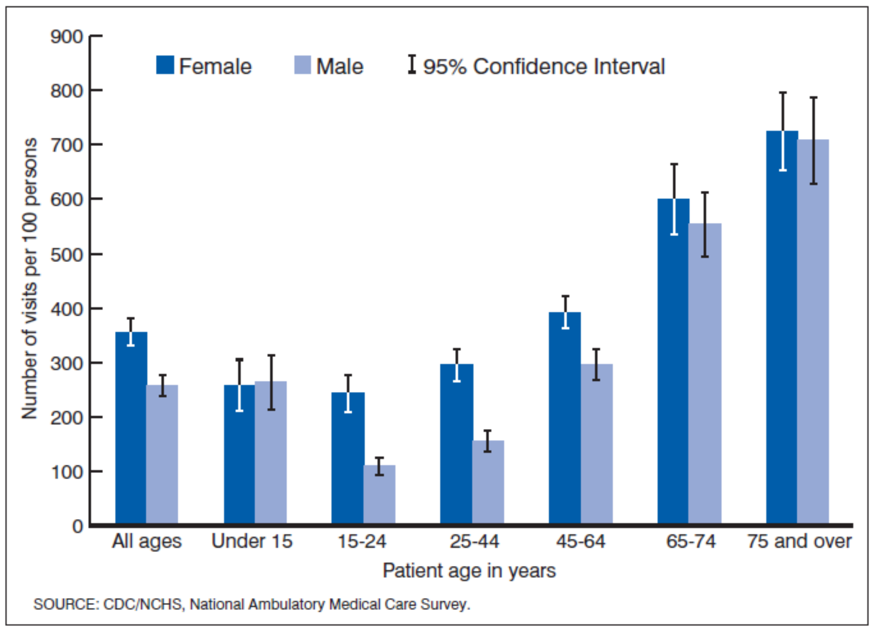
Motivation for this Research

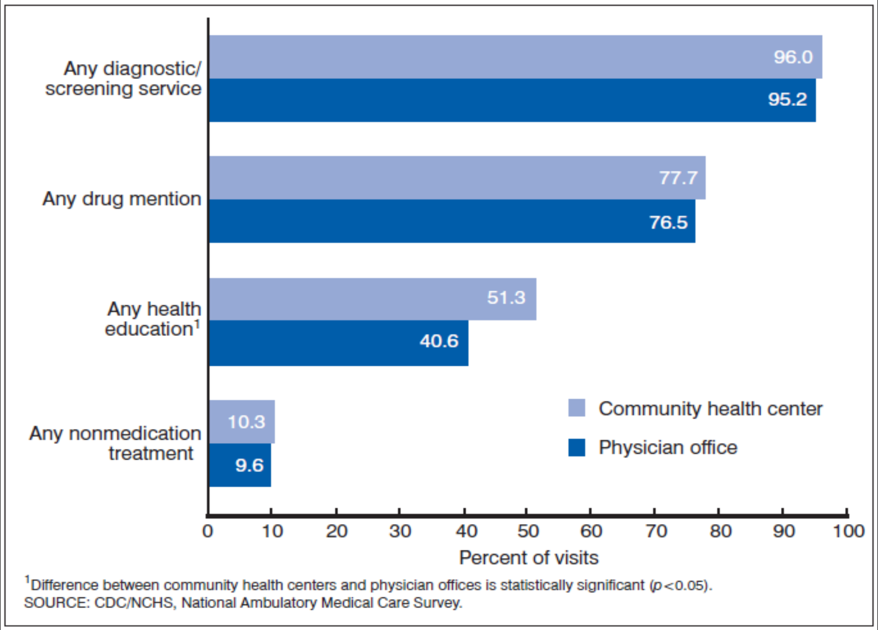


Objective

The development of an enhanced hand-held optical imaging instrument for use in the primary care office or general medical clinic.

Motivation for this Research





Result

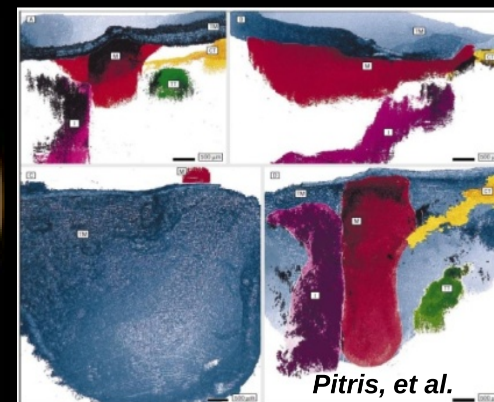
► Number of office visits increases dramatically in aging population, which is expected to continue to increase in the future.

► Majority of office visits are for diagnostic and screening services.

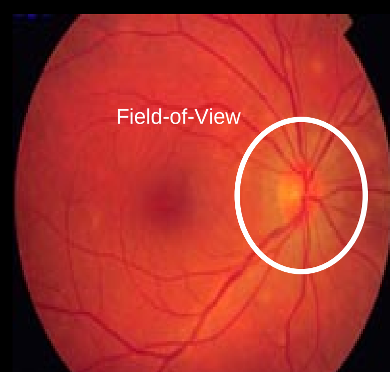
Advance Optical Biomedical Imaging Capabilities in the Front-Line Primary Care Instruments

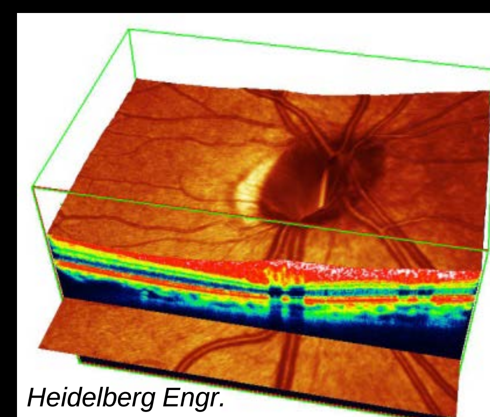
Standard Practice | **Standard 2-D View** | **Advanced 3-D OCT View**

Otoscopy

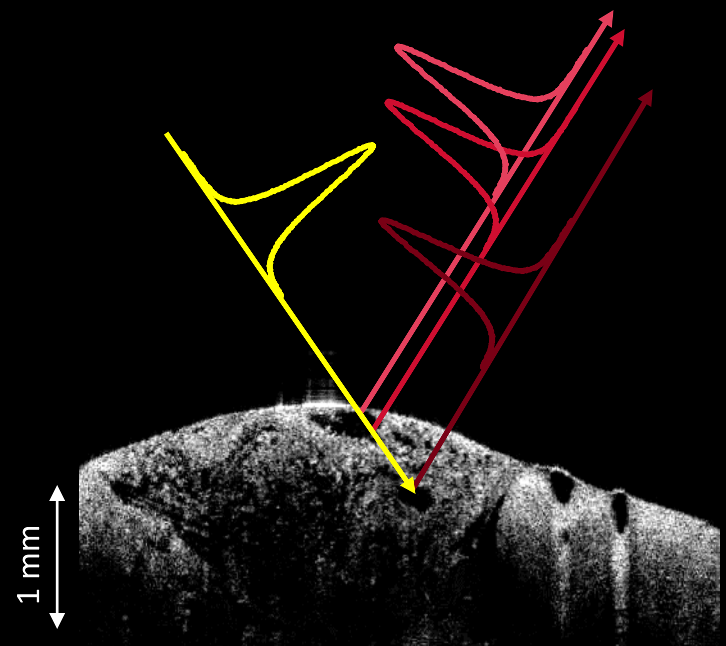


Ophthalmoscopy





Optical Coherence Tomography (OCT)



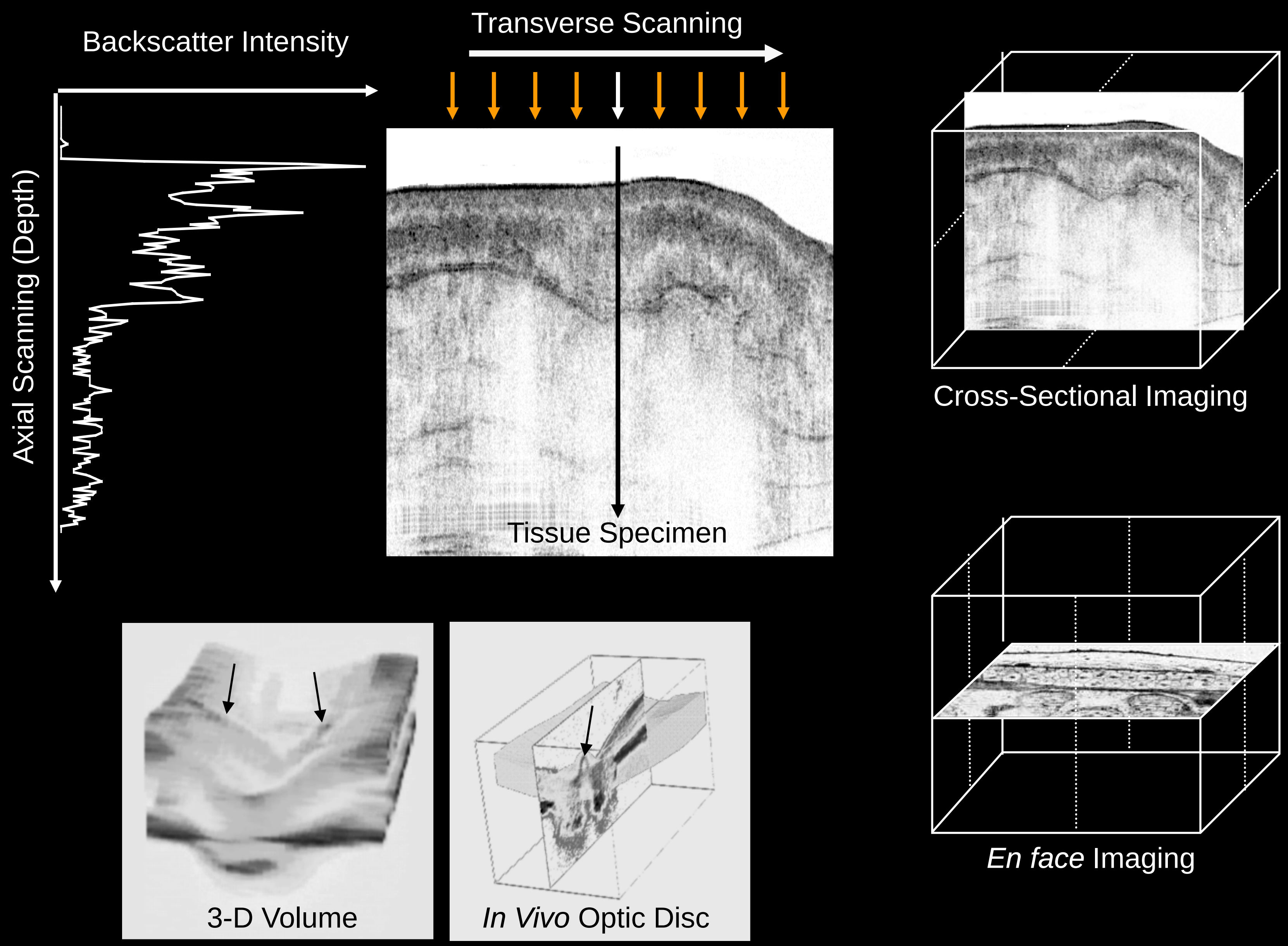
Analogous to ultrasound imaging, but with near-infrared light

3-D Volume Acquisition

Dynamic Acquisition

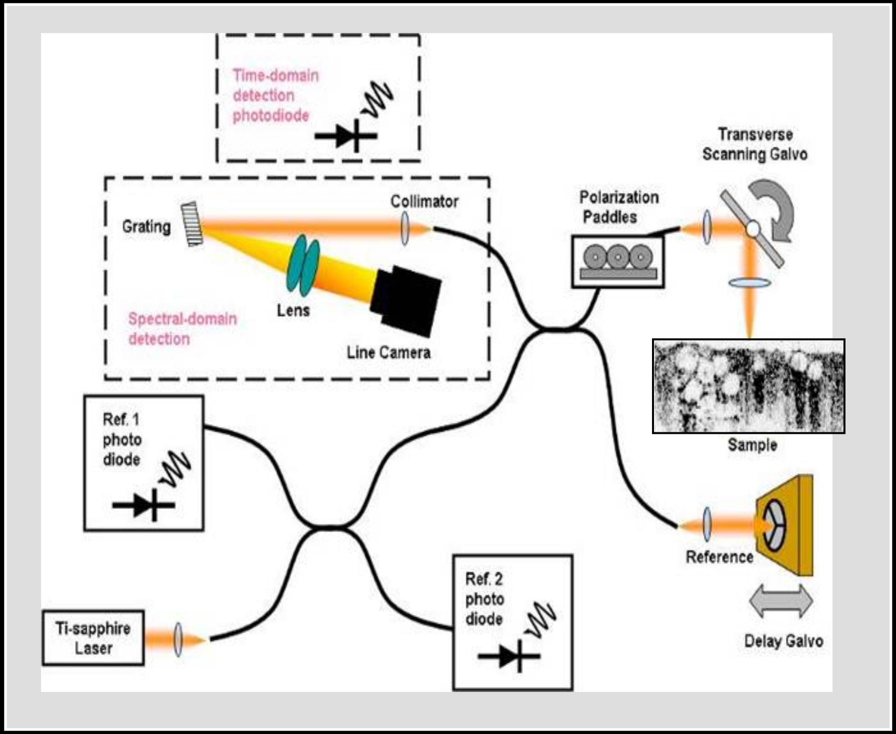
- ▶ Cellular-level resolution
- ▶ Real-time volumetric imaging
- ▶ Digital computational analysis
- ▶ Intra-operative & intra-procedure feedback

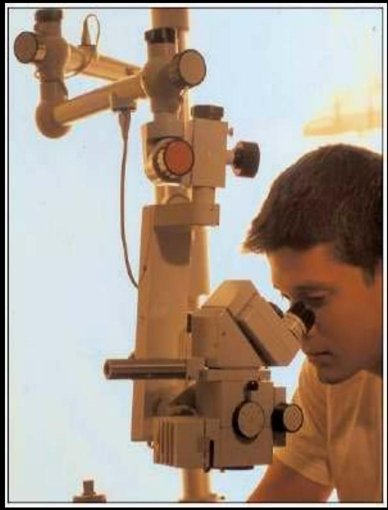
Multi-Dimensional OCT Imaging



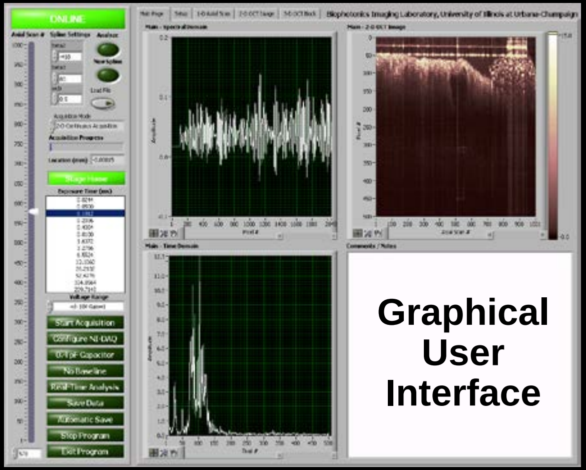
Portable & Modular OCT Imaging System

Portable OCT



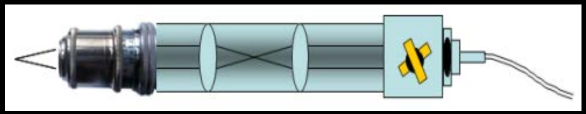


Surgical Microscope



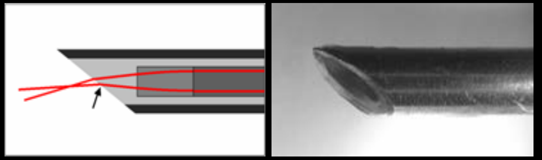
Graphical User Interface

Hand-Held Probe



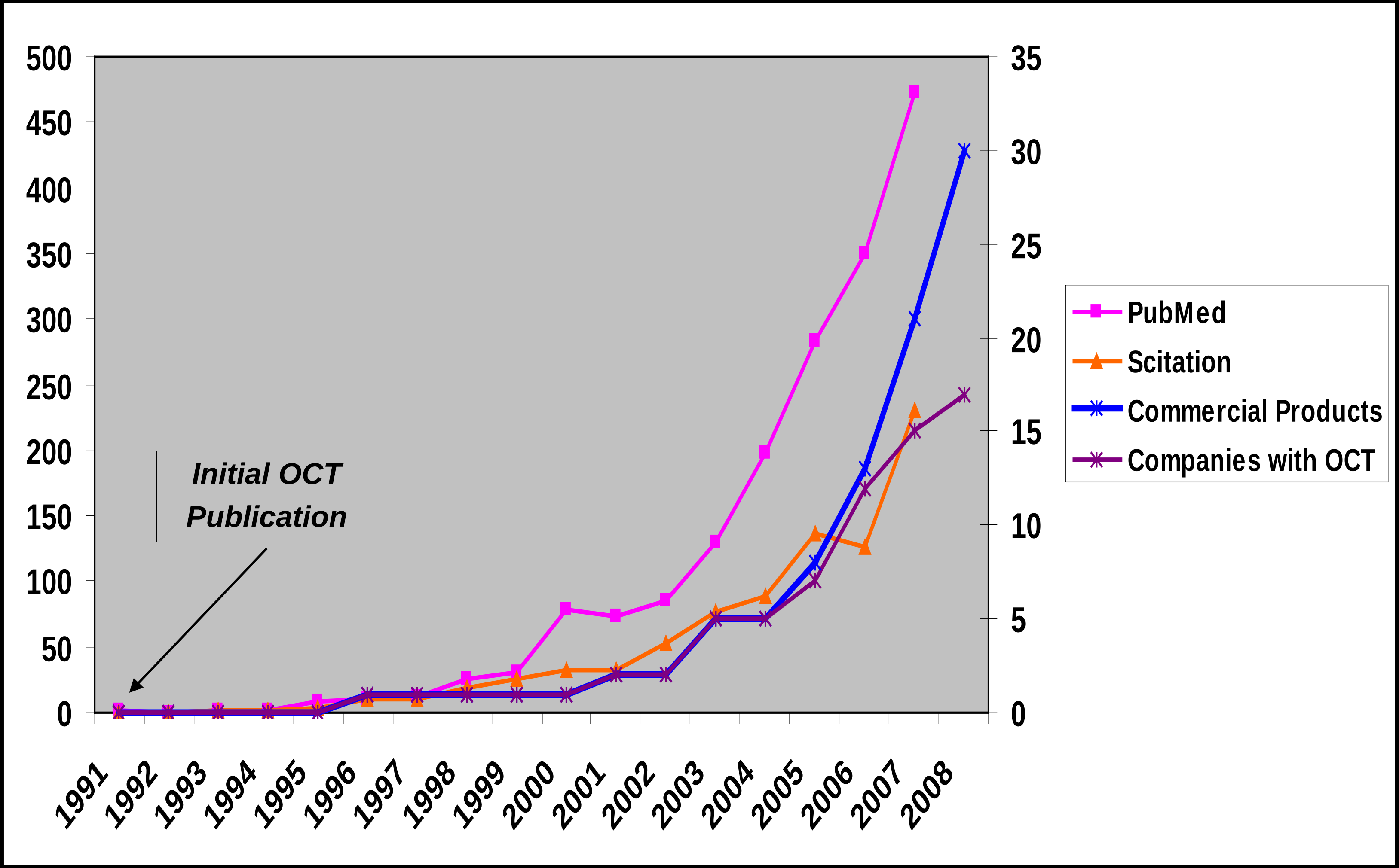
- ▶ Compact & portable clinical system
- ▶ User-friendly software interface
- ▶ Modular beam delivery devices

Needle Biopsy Probe



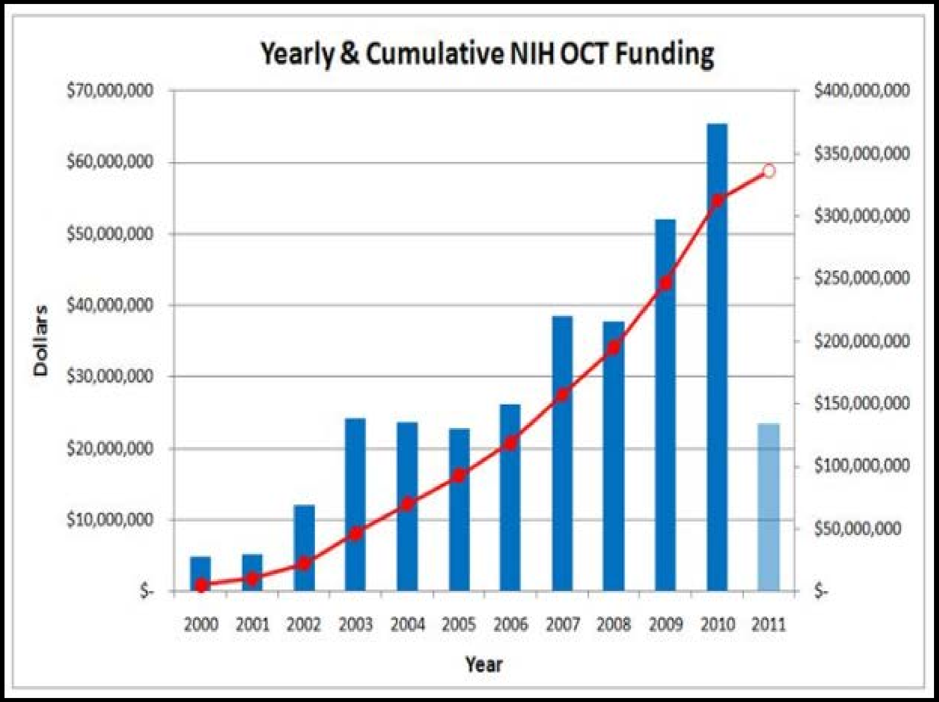
Optical Needle Probe

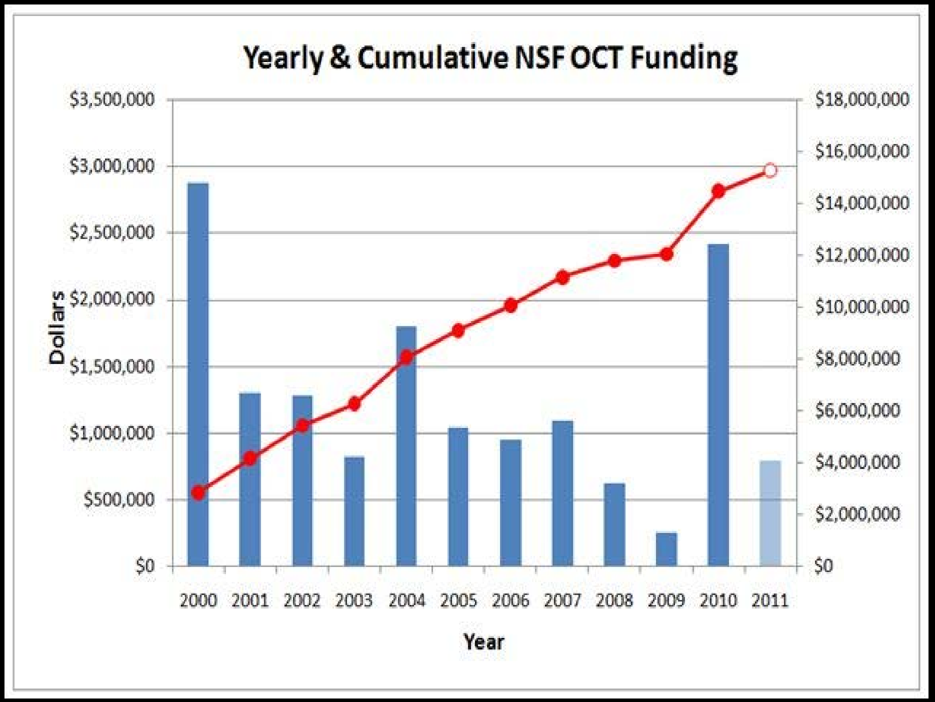
Optical Coherence Tomography
Rapid Development and Application



Zysk AM, Nguyen FT, Oldenburg AL, Marks DL, Boppart SA, J Biomed Optics, 12:051403, 2007

Optical Coherence Tomography
$500M of Federally-Funded Research over last Decade



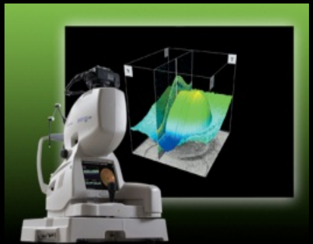


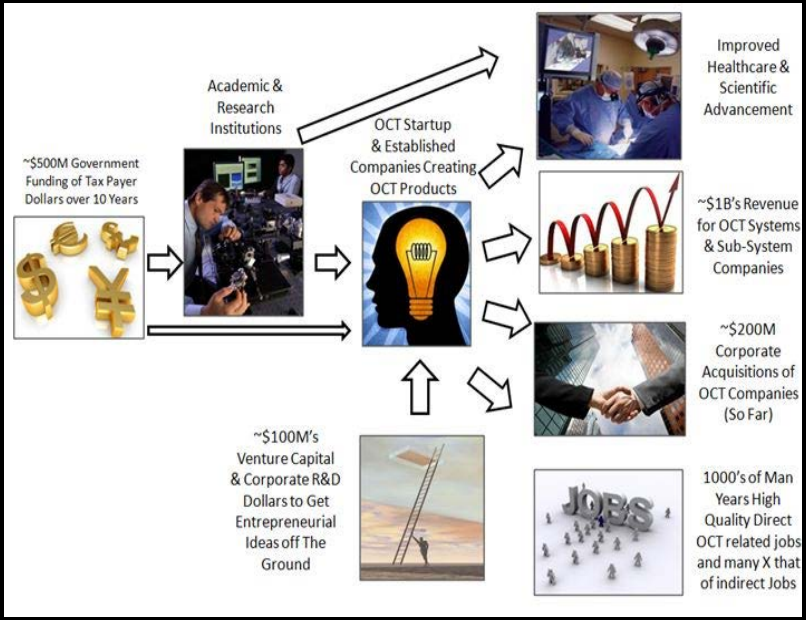
Swanson EA, OCT News, July 9, 2011

Optical Coherence Tomography

Rapid Commercial Development across Medical Specialties







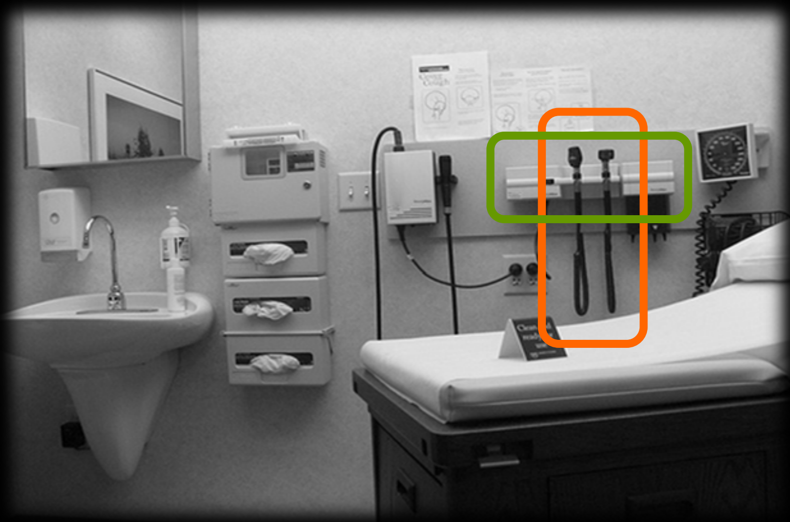







Swanson EA, OCT News, July 9, 2011

Objective of this Research



Transform OCT Technology from a Diagnostic Modality to a Screening Modality

- Advancing technology at the front-line
- Screening general population (normal/not?)
- Quantitative monitoring of chronic diseases
- Potentially more efficient and economic referral

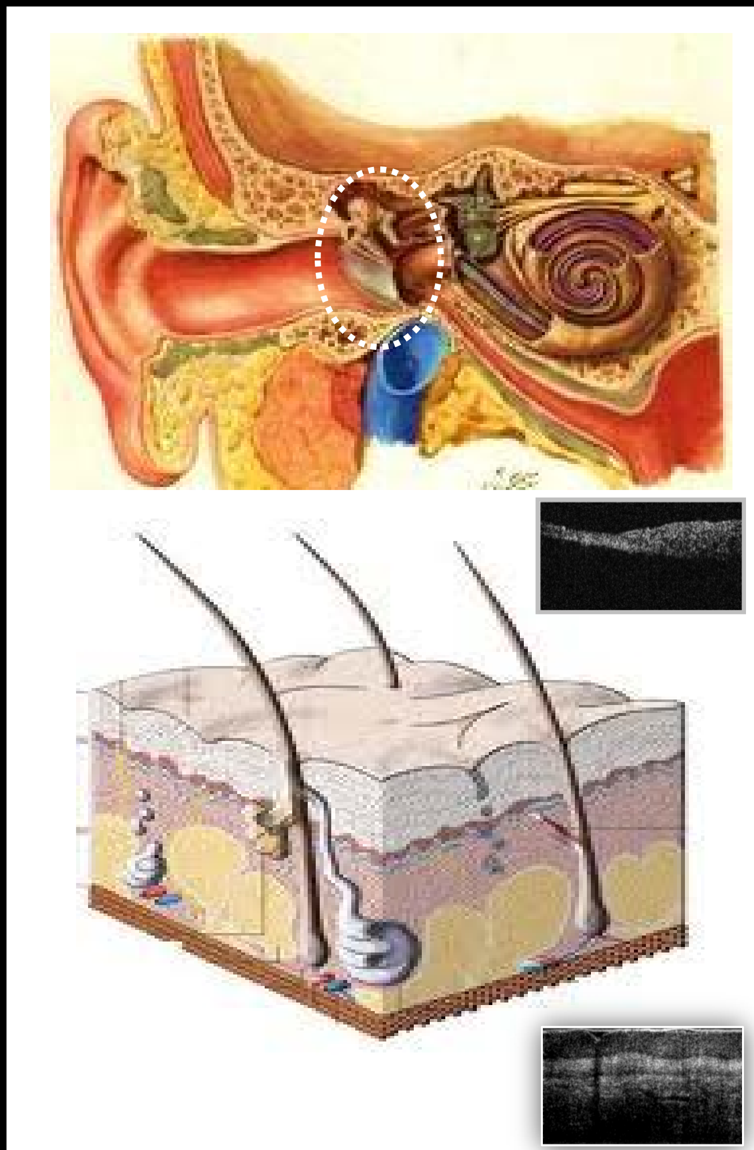
Advanced Handheld Probe

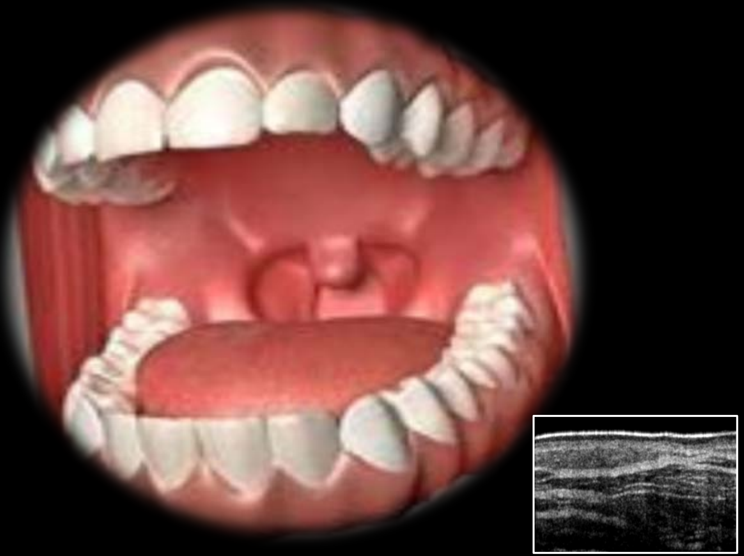
+

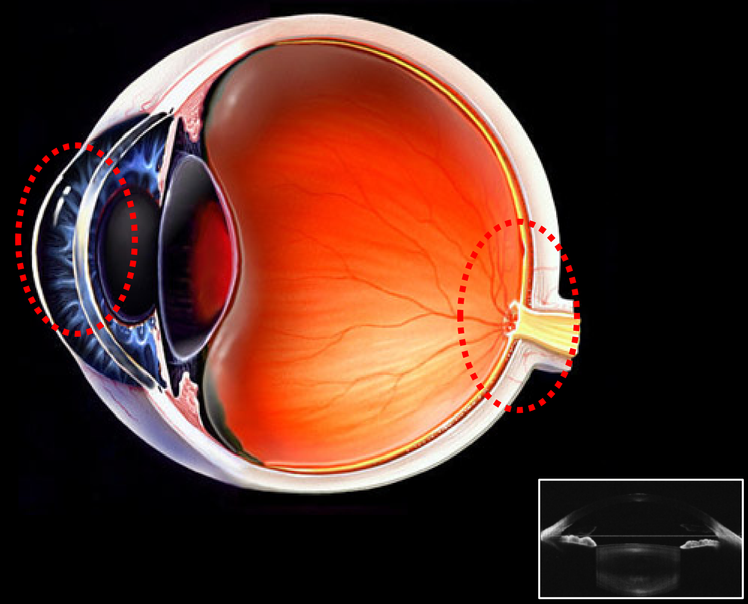
Compact OCT System

High speed, High resolution

Important Tissue Sites in Primary Care Medicine



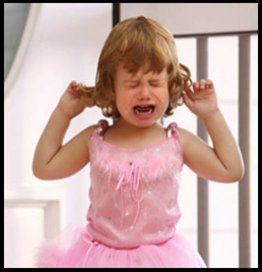




Noninvasive Assessment of Biofilm Growth in the Middle Ear using a Portable Low-Coherence Interferometry System

Finding and treating the source of chronic ear infections

Advance Point-of-Care Diagnostic and Imaging Technology in Primary Care Practice


<u>Otitis Media (OM) – Ear Infection</u>

Most frequent diagnosis for all children

- 60-80% have ≥ 1 OM by age 1
- 80-90% have ≥ 1 OM by age 3
- 17% have ≥ 3 OM by age 1
- 46% have ≥ 3 OM by age 3

<u>Diagnoses</u>

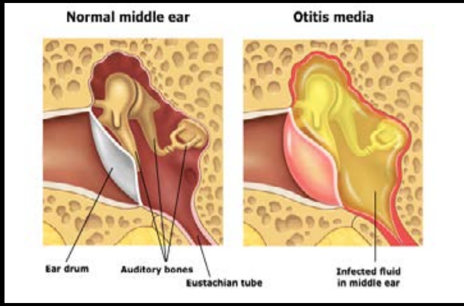
- Acute OM
- OM with effusion (OME)
  - serous or secretory
- Chronic suppurative OM

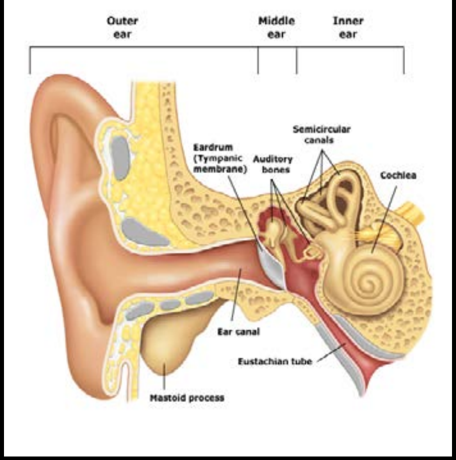
<u>Complications</u>

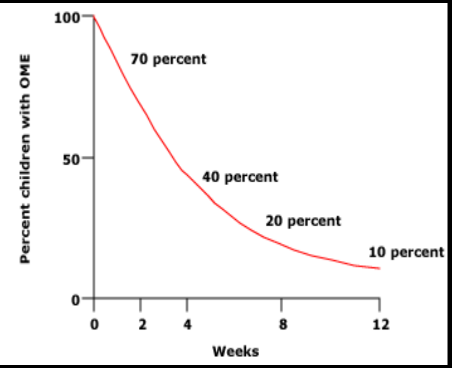
Hearing loss, speech, language delays

<u>Treatment</u>

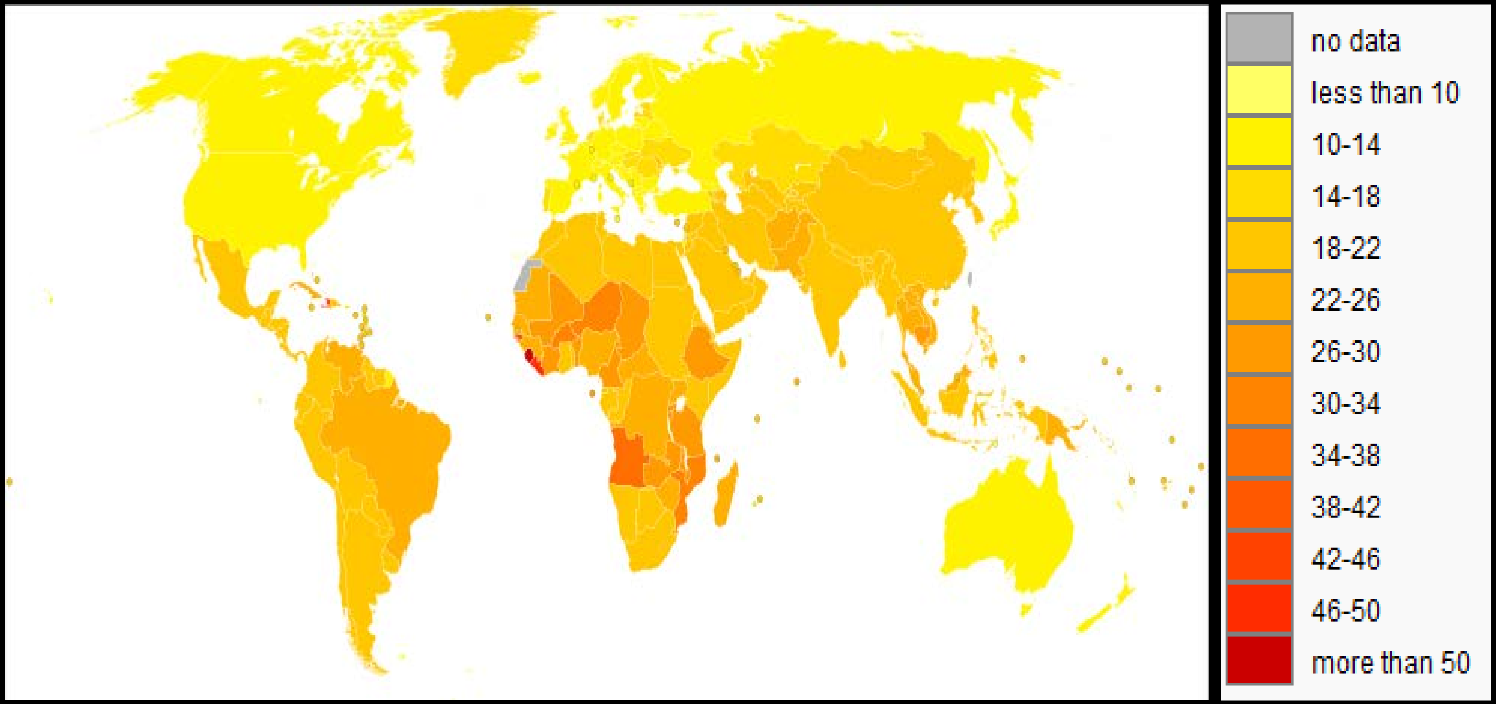
Antibiotics, surgery (tympanostomy), supportive care







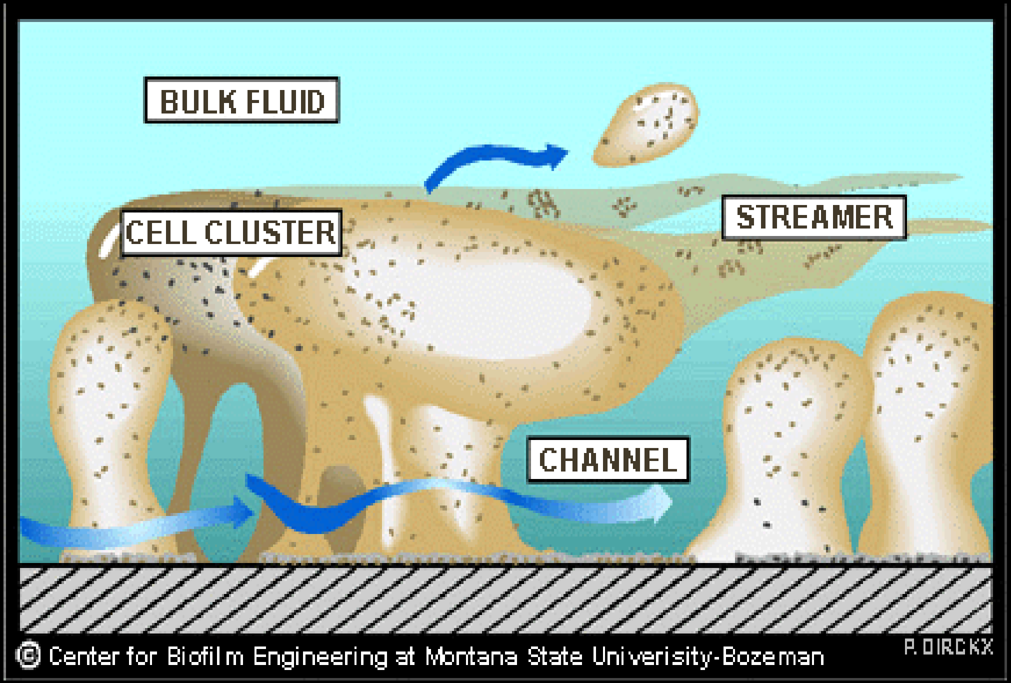
National and Global Impact on Disability

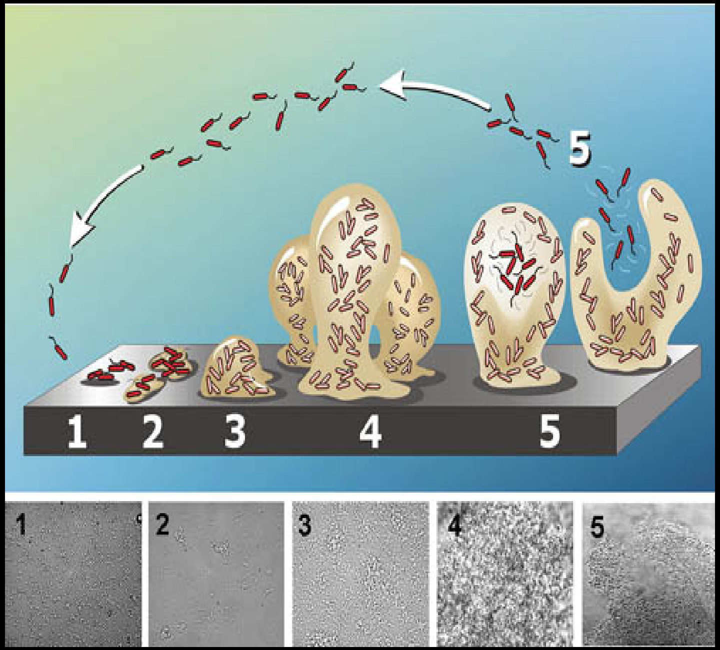


Age-standardized disability-adjusted life year (DALY) rates from otitis media by country (per 100,000 inhabitants)

Data from *Mortality and Burden of Disease estimates for WHO member states in 2002*

Biofilm Morphology and Growth

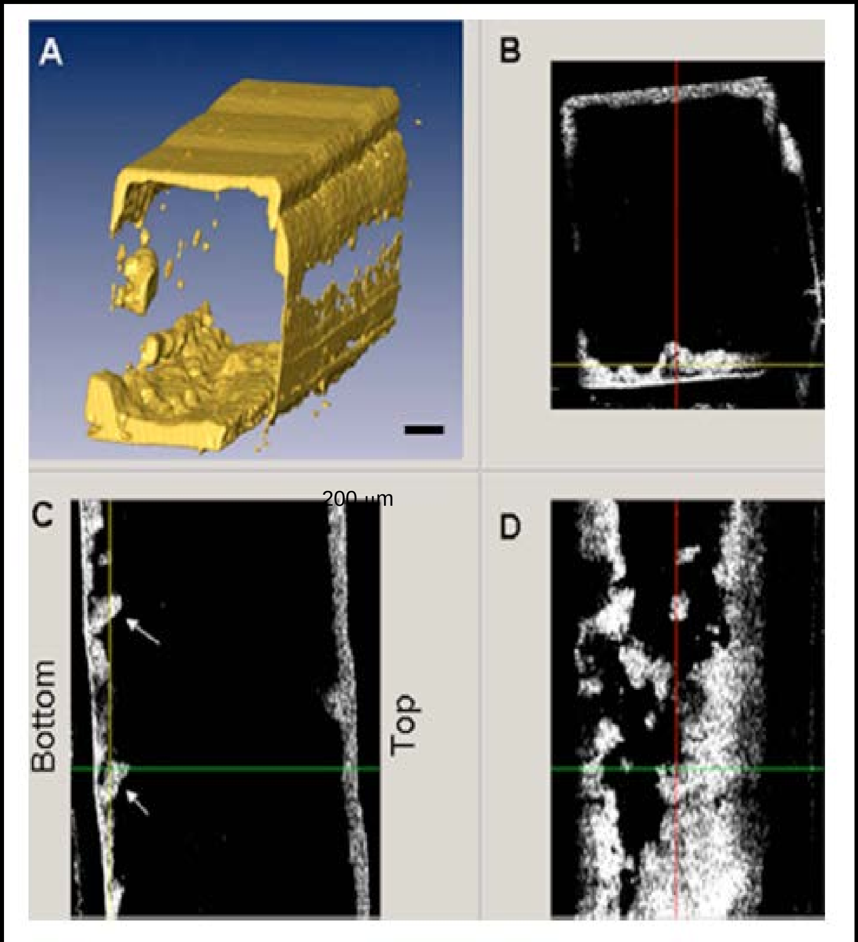




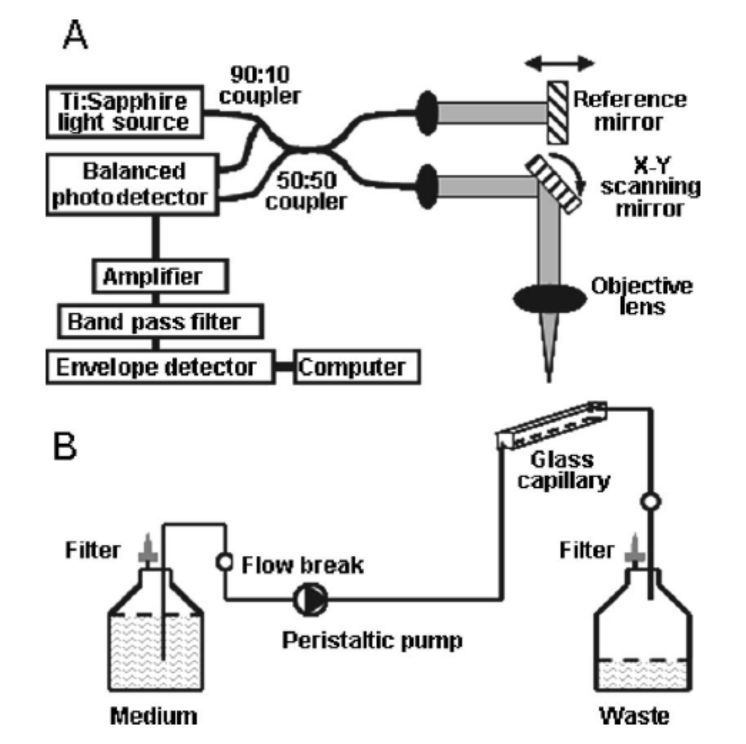
<u>Biofilms account for ~ 80% of all infections</u>
Urinary tract infections
Indwelling catheters
Dental plaque
Contact lenses
Prostheses

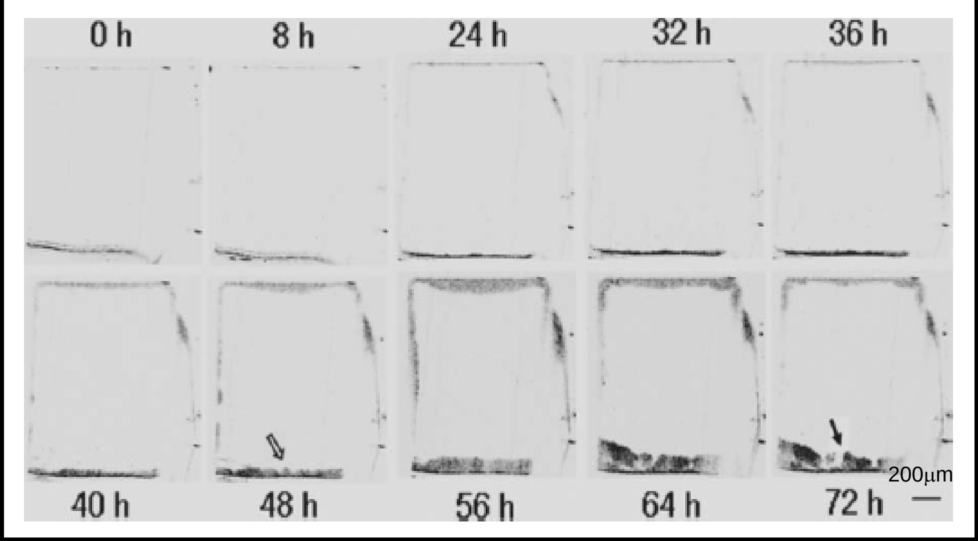
<u>Complex polymicrobial communities</u>
Protected from antibiotic exposure
Rapidly develop antibiotic resistance
Seed recurrent infections
Developmental processes unknown
Uncertain treatment protocols

Three-Dimensional OCT of Developing Biofilms



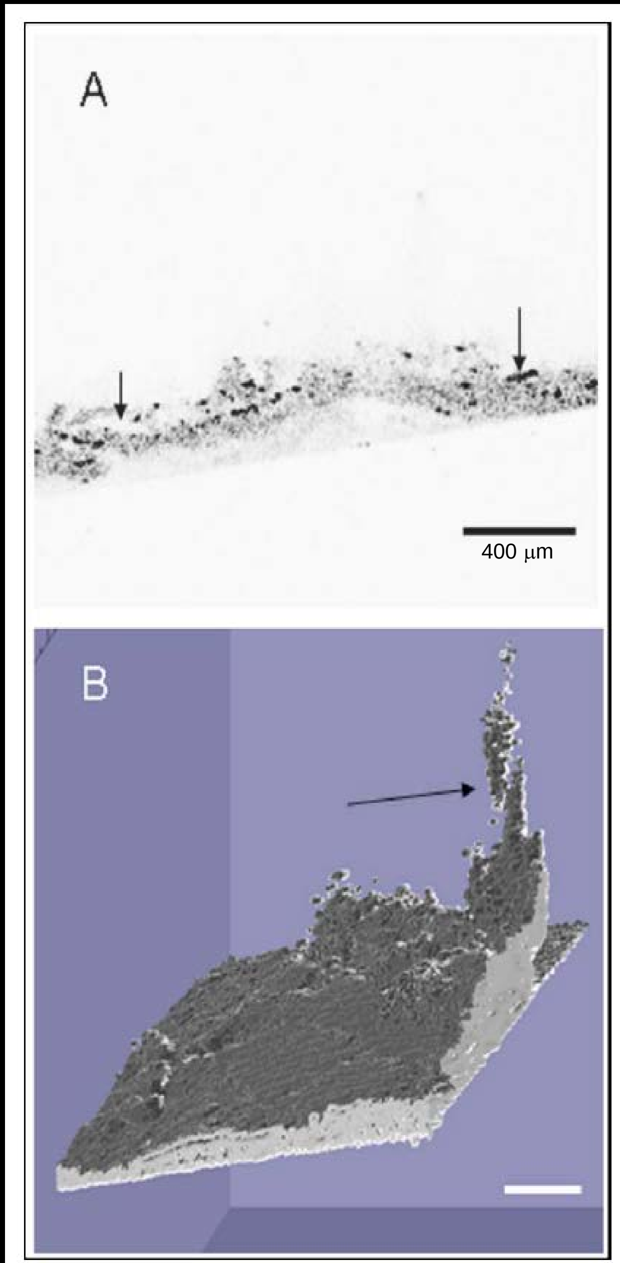
3-day-old *P.aerogenosa* biofilm



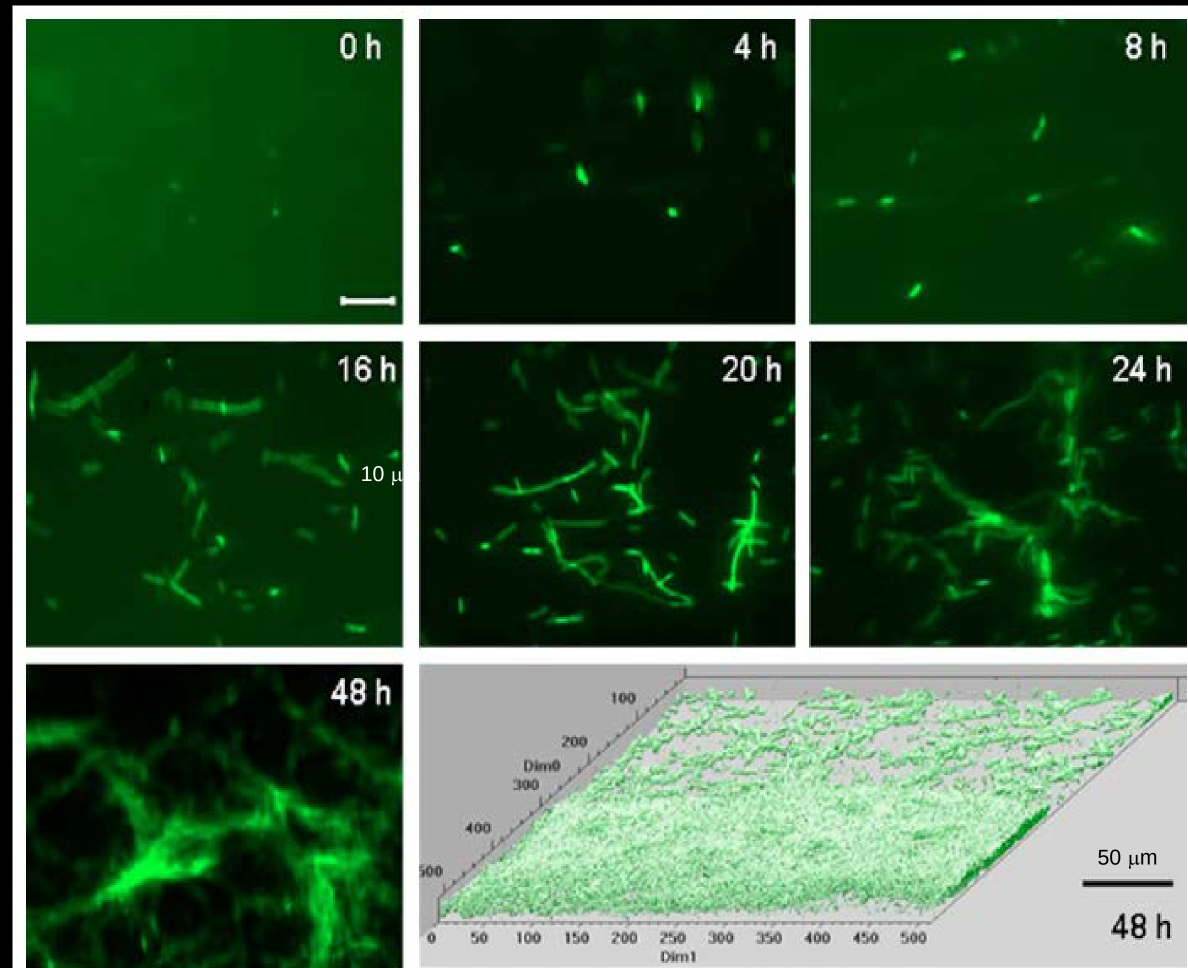


Xi, *et al.*, *J Biomedical Optics*, 11:034001, 2006

Comparison of Imaging Techniques



3-day-old *P.aerogenosa* biofilm

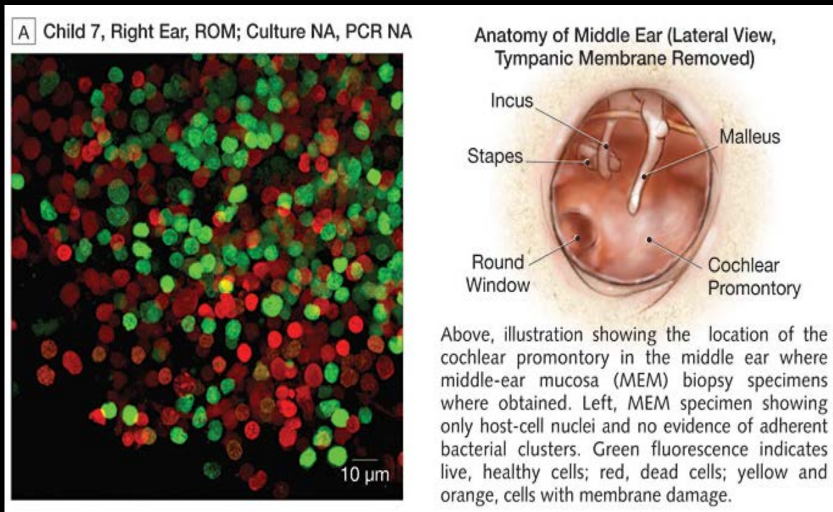


Fluorescence and confocal microscopy of the *P.aerogenosa* biofilm

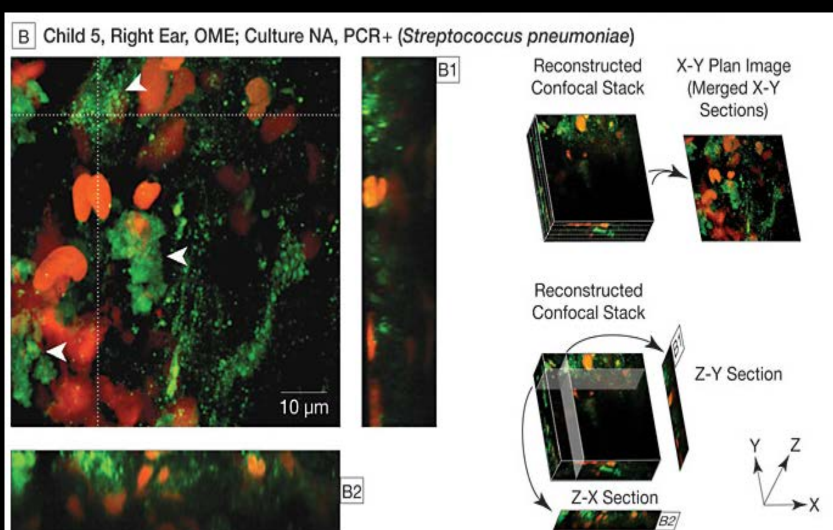
Xi, *et al.*, *J Biomedical Optics*, 11:034001, 2006

Direct Detection of Bacterial Biofilms on the Middle-Ear Mucosa of Children With Chronic Otitis Media

JAMA, 296:202-211, 2006



Above, illustration showing the location of the cochlear promontory in the middle ear where middle-ear mucosa (MEM) biopsy specimens where obtained. Left, MEM specimen showing only host-cell nuclei and no evidence of adherent bacterial clusters. Green fluorescence indicates live, healthy cells; red, dead cells; yellow and orange, cells with membrane damage.



<u>26 Children undergoing tympanostomy tube placement</u>
13 (50%) had OME   20 (77%) had recurrent OM
7 (27%) had both diagnoses
27 of 52 (52%) of ears had effusions
Biofilms visualized by CLSM in 46 (92%) of 50 middle-ear biopsies

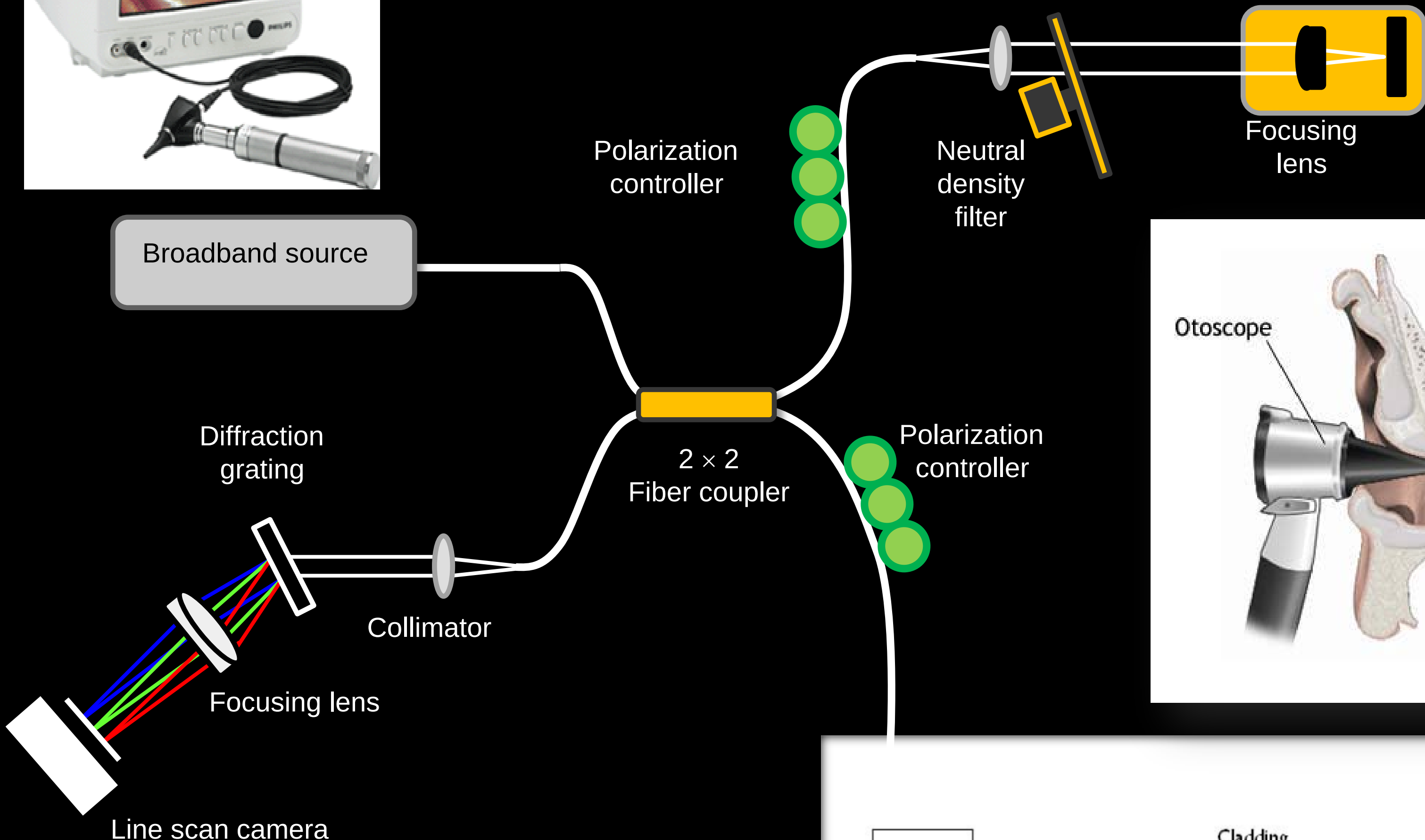
<u>3 children and 5 adults undergoing cochlear implantation (controls)</u>
No biofilms observed in any of these mucosal biopsies

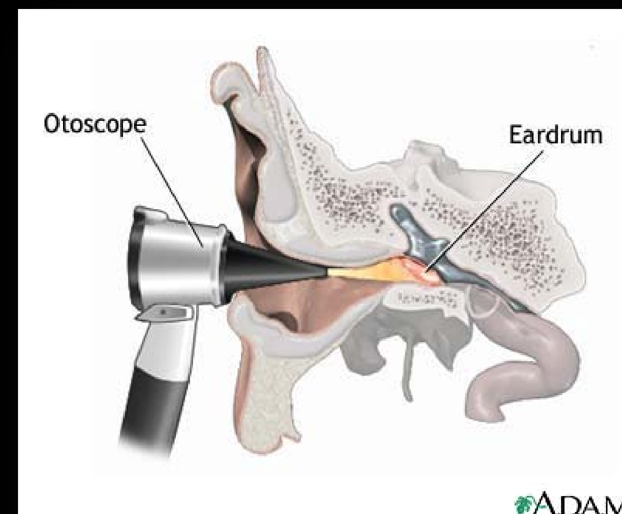
Will the diagnosis of a middle ear biofilm alter the antibiotic treatment protocol for chronic otitis media?

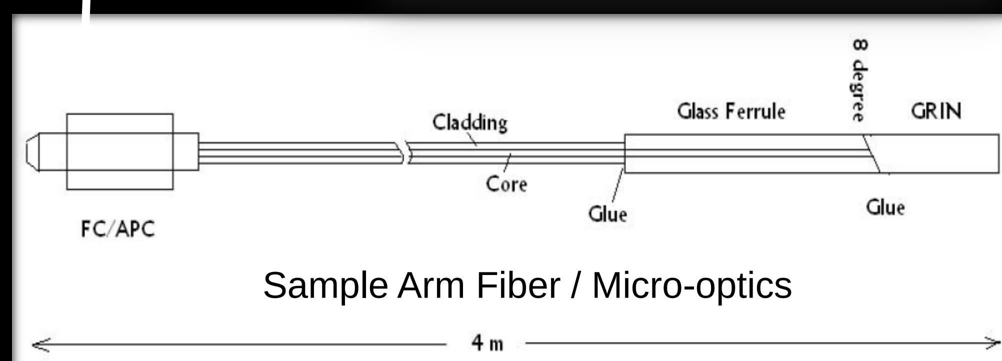
Can Low-Coherence Interferometry (LCI) or Optical Coherence Tomography (OCT) technology be used to determine the most appropriate therapy, most appropriate antibiotic, and follow response rates?

<u>Use LCI or OCT to:</u>
Diagnose, measure, and characterize biofilms.
Characterize and quantify effusions.
Measure precise TM changes under insufflation.

LCI Otoscopy System

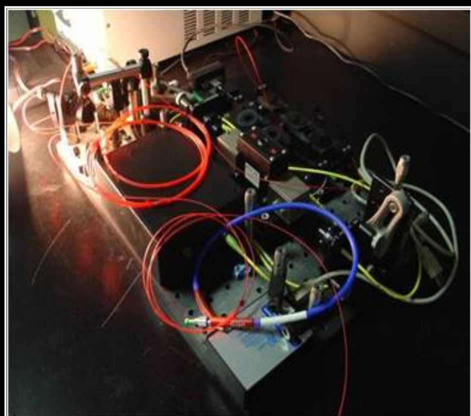


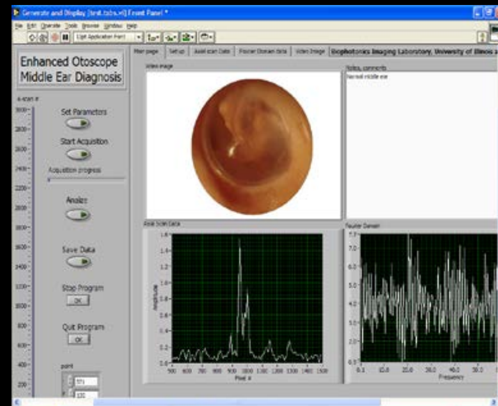


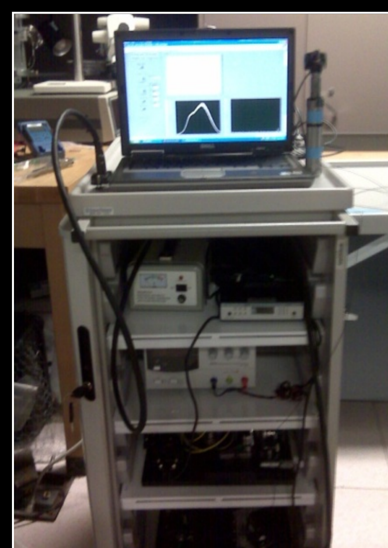


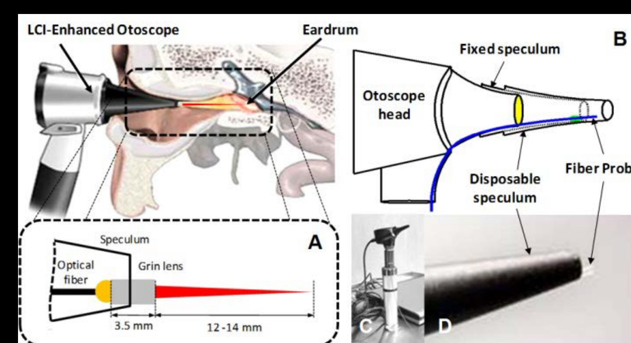
- Compact and portable clinical system
- Fiber / Micro-optics in ear speculum
- Compatible with existing otoscopes

System Integration



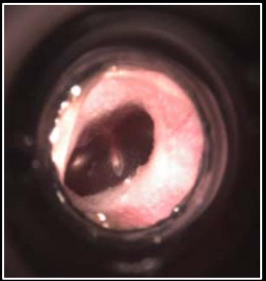


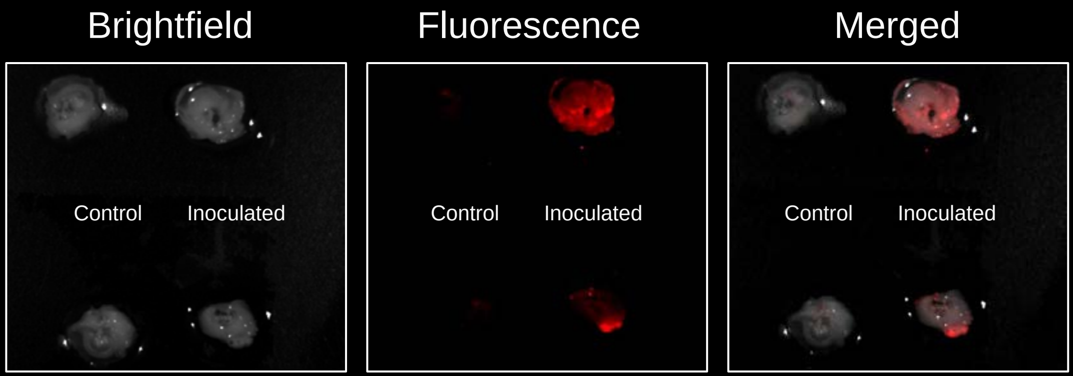




Otitis Media Induction Procedure in the Rat

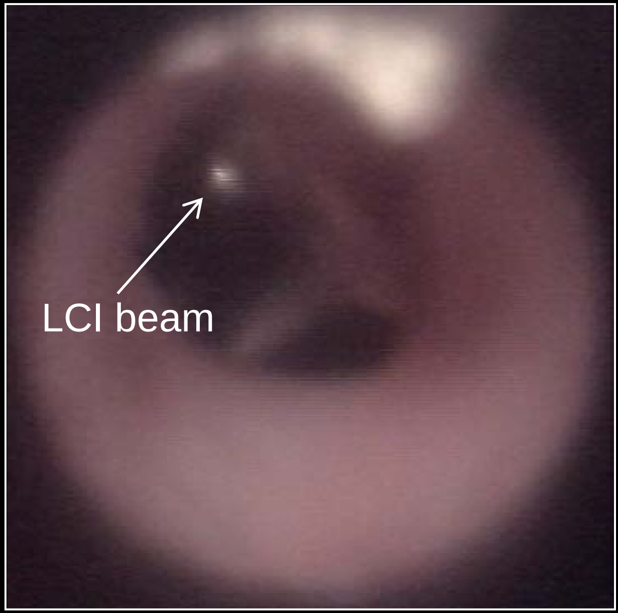
- Developed new animal biofilm model based on prior literature *
- 30 µl of *Streptococcus pneumoniae* bacteria in saline with 1% methylcellulose solution (10^{10} CFU/ml) inoculated into the nostrils of an anesthetized rat through a nasal cannula
- Immediately after inoculation, animal placed in a pressure chamber
- LCI otoscope used to examine the ears twice per week
- Entire procedure reproduced twice per week until the animal is unable to clear away fluid in the middle ear, and the presence of a biofilm is established
- Total 8 rats (6 infected, 2 control) over period of ~ 6 months

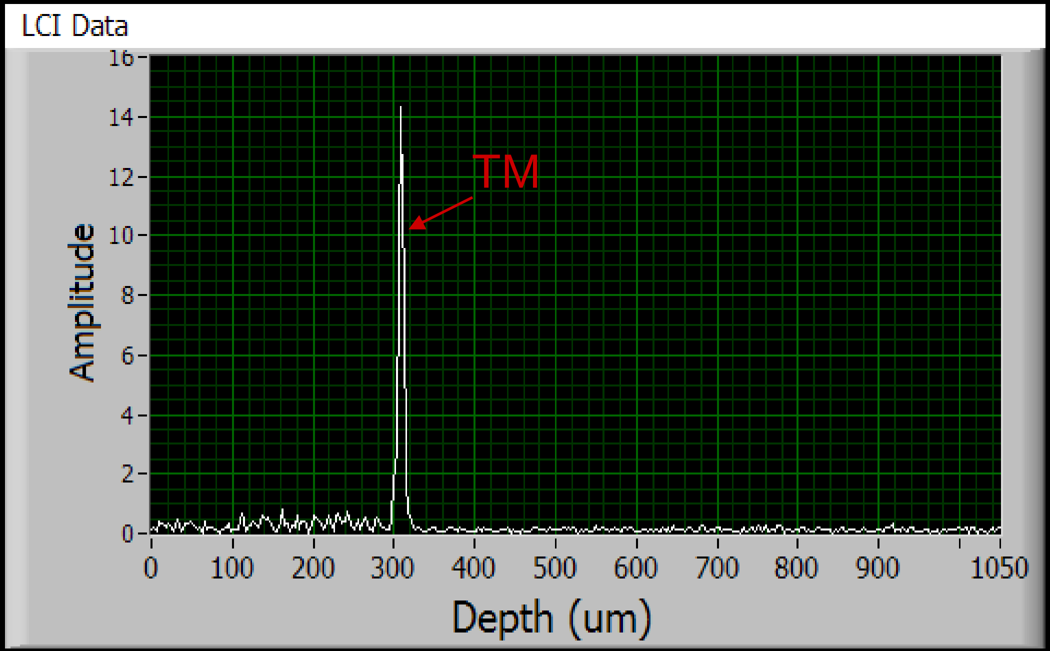




* Tonnaer, *et al*., Bacteria otitis media: a non-invasive rat model. Vaccine 21:4539-4544, 2003
Chaney, *et al*., Novel method for non-invasive induction of a middle-ear biofilm in the rat. Vaccine 29:1628-1633, 2011

Video Image and Typical LCI Data of Normal Rat TM

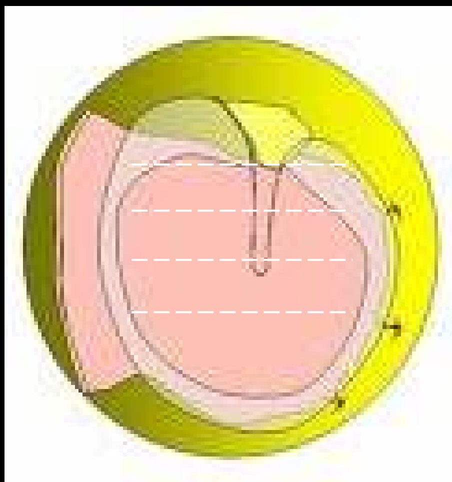


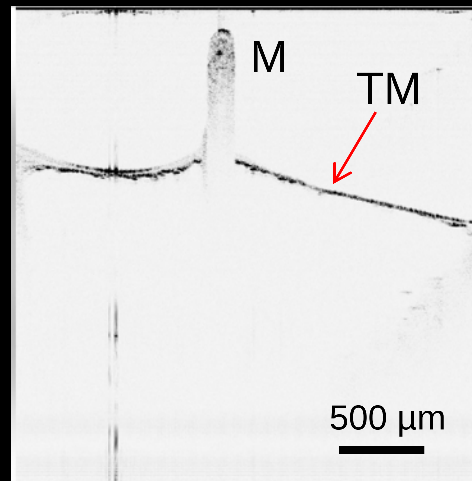


- Translucent membrane in otoscope video
- Thin LCI peak trace representative of a thin normal TM

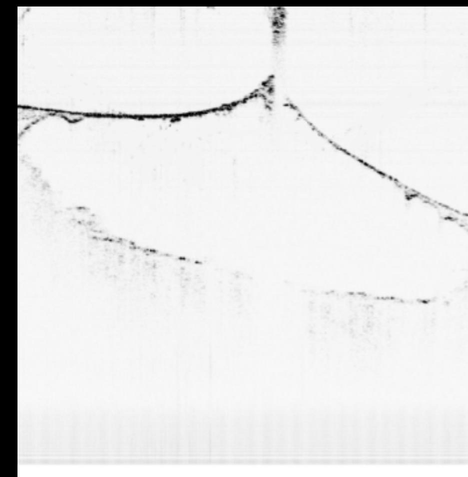
Nguyen, *et al*. Non-invasive optical interferometry for the assessment of biofilm growth in the middle ear. Biomedical Optics Express, 1:1104-1116, 2010

OCT and Histology of Normal Rat Tympanic Membrane

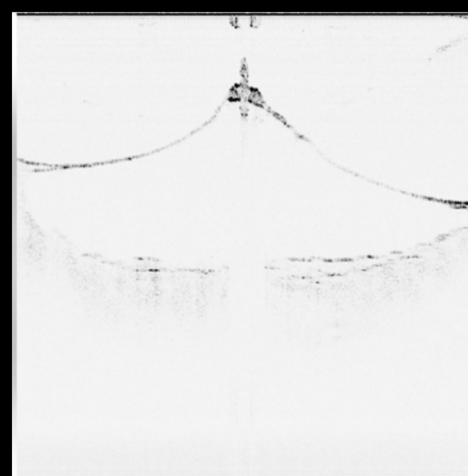

Scan Locations

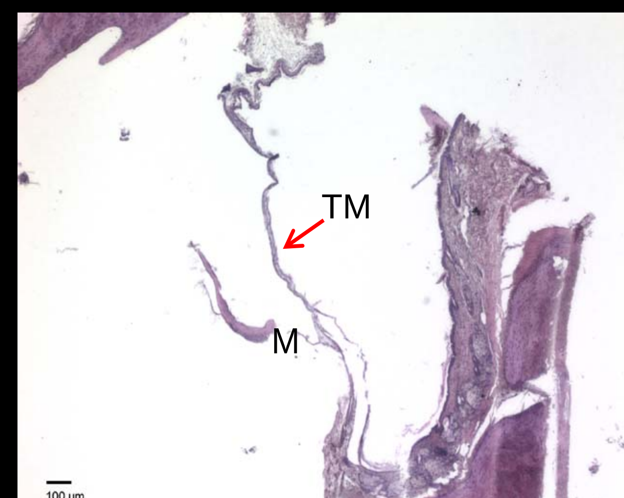


Position 1


Position 2

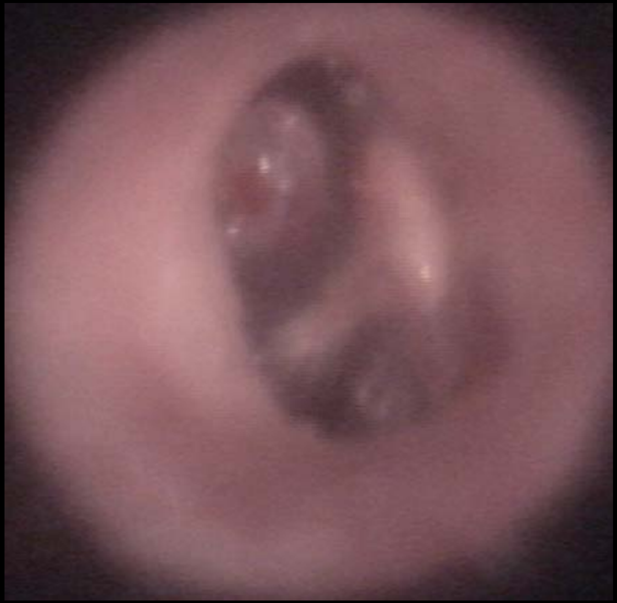

Position 3

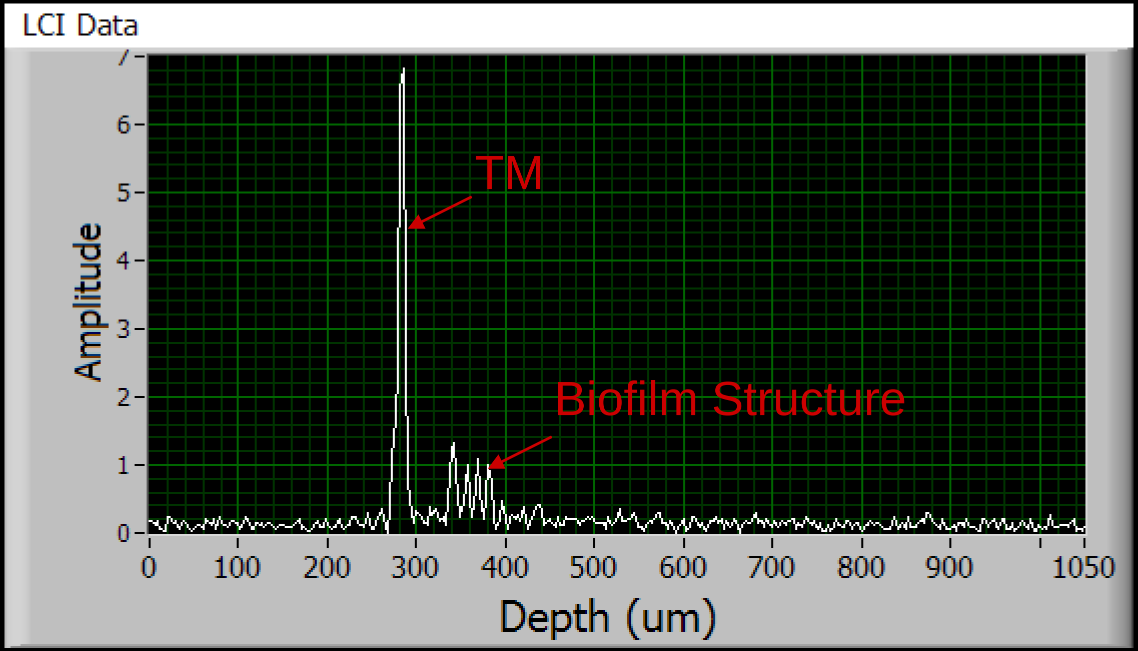

Position 4



Histology

Video Image and Typical LCI Data of Infected Rat TM

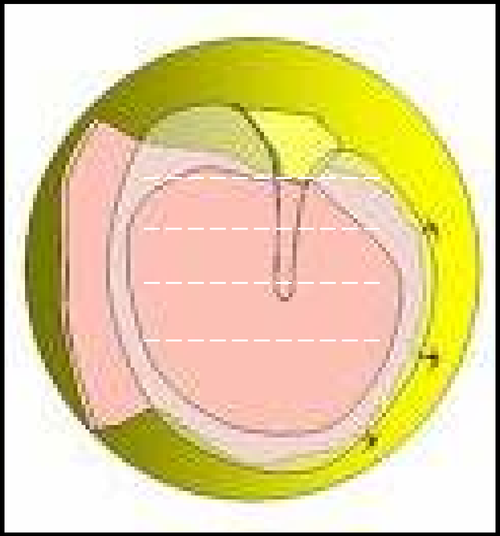




- Red membrane and focal areas in otoscope video
- Scattering layers representative of biofilm behind thin TM

Nguyen, *et al*. Non-invasive optical interferometry for the assessment of biofilm growth in the middle ear. Biomedical Optics Express, 1:1104-1116, 2010

OCT and Histology of Infected Rat TM



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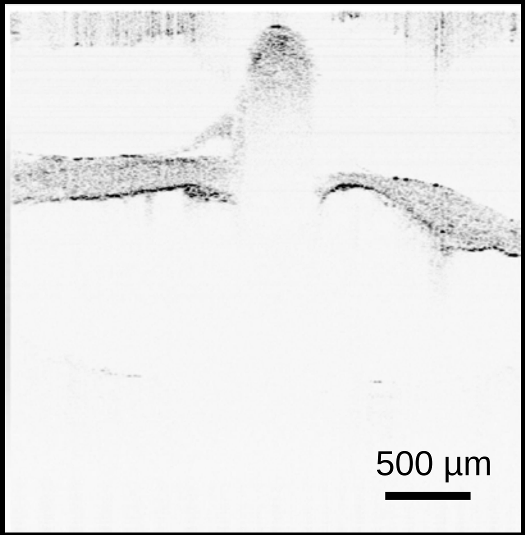

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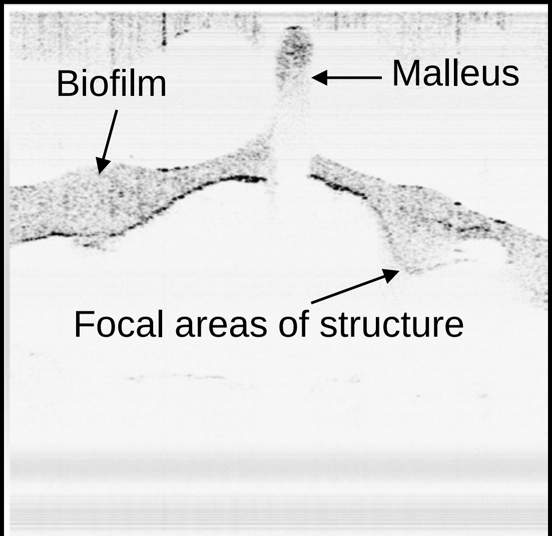
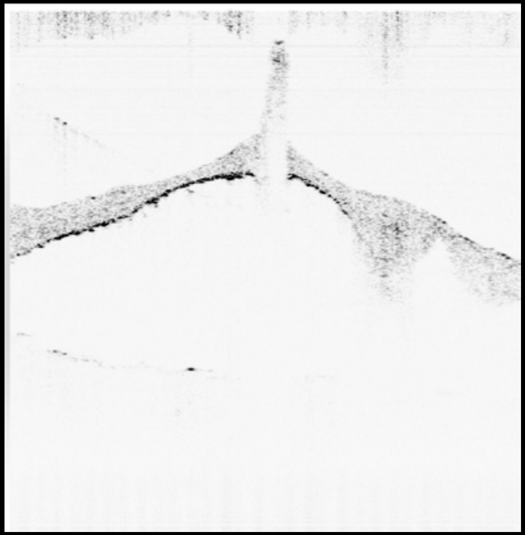
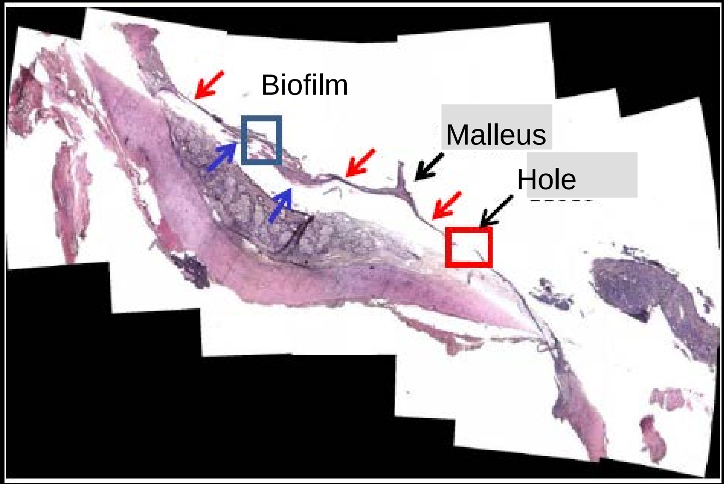


Position 2



Position 3

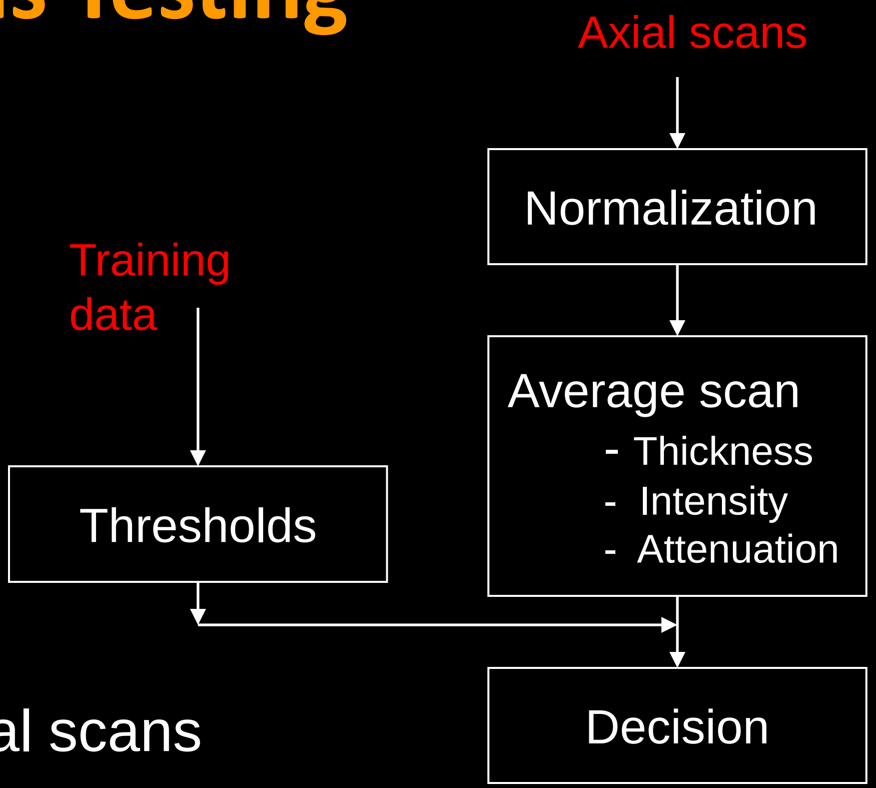
Position 4



Histology

Automatic Classification Algorithm
Hypothesis Testing

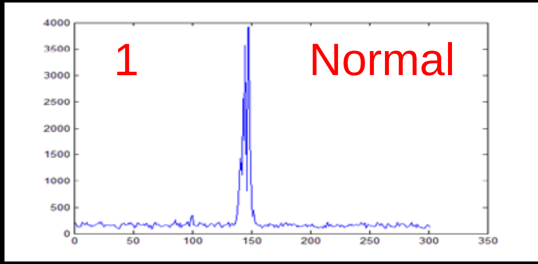
- Determine the existence of biofilm
  1. A-scan width (thickness)
  2. A-scan attenuation (density)
  3. A-scan intensity (structures)
- Pre-Classification process
  - Normalize the axial scans
  - Average the normalized axial scans
- Use training data to set thresholds and classify scans

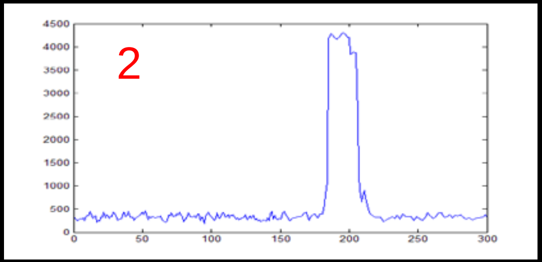


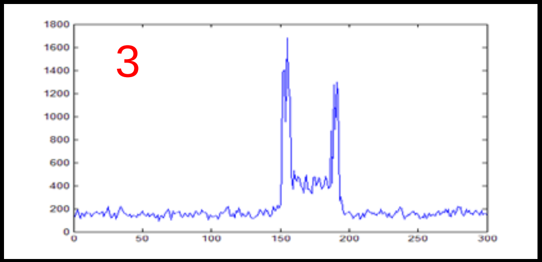
Classification Models

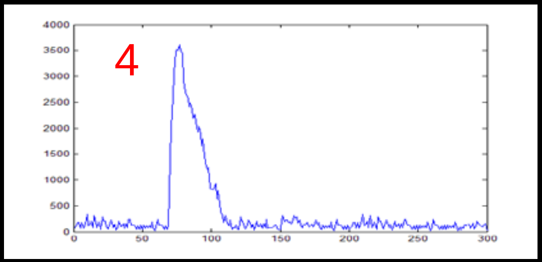
I. Normal	Normal, thin (animal)	1. Normal, thin
	Normal, thick (edge, human)	2. Normal thick 1 3. Normal thick 2
II. Biofilm or effusion present	Effusion present	4. Thick effusion 5. Clear effusion
	Biofilm present	6. New biofilm 7. Uniform biofilm
	Biofilm + effusion present	8. Uniform biofilm + clear effusion 9. Uniform biofilm + thick effusion
		10. New biofilm +clear effusion 11. New biofilm + thick effusion

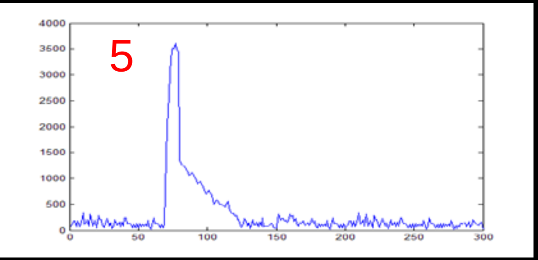
Signal models 12-19 and 20-27 are repeated using 4-11 for normal and thick types (2, 3)

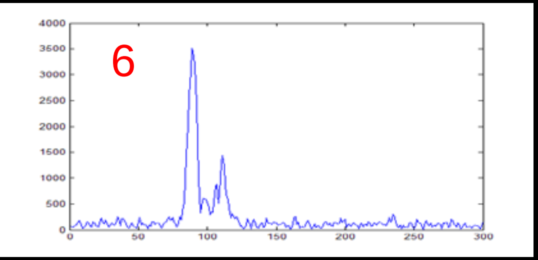


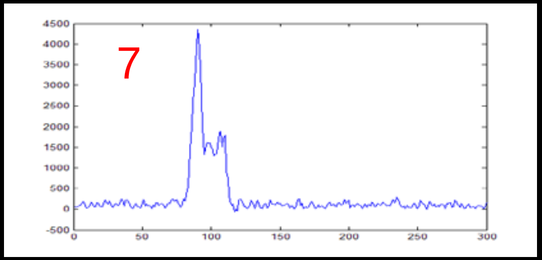


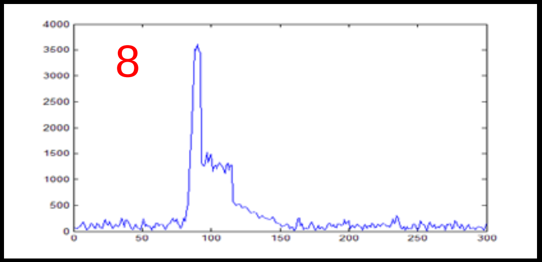


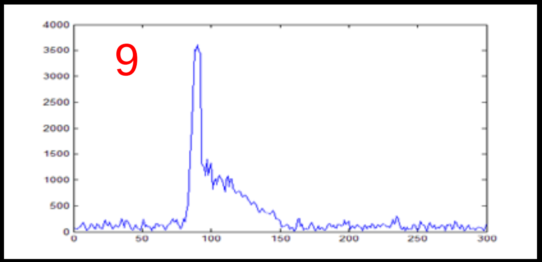


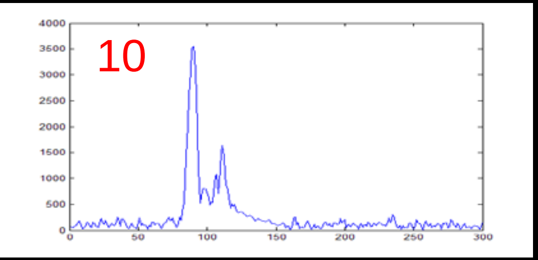


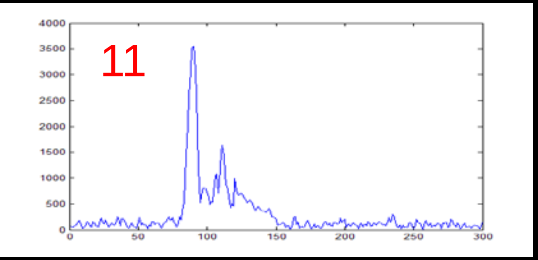












Classification of A-Scan Data

A-Scans \ Histology	Positive	Negative
Positive	TP = 1,430	FP= 225
Negative	FN = 167	TN = 1,561

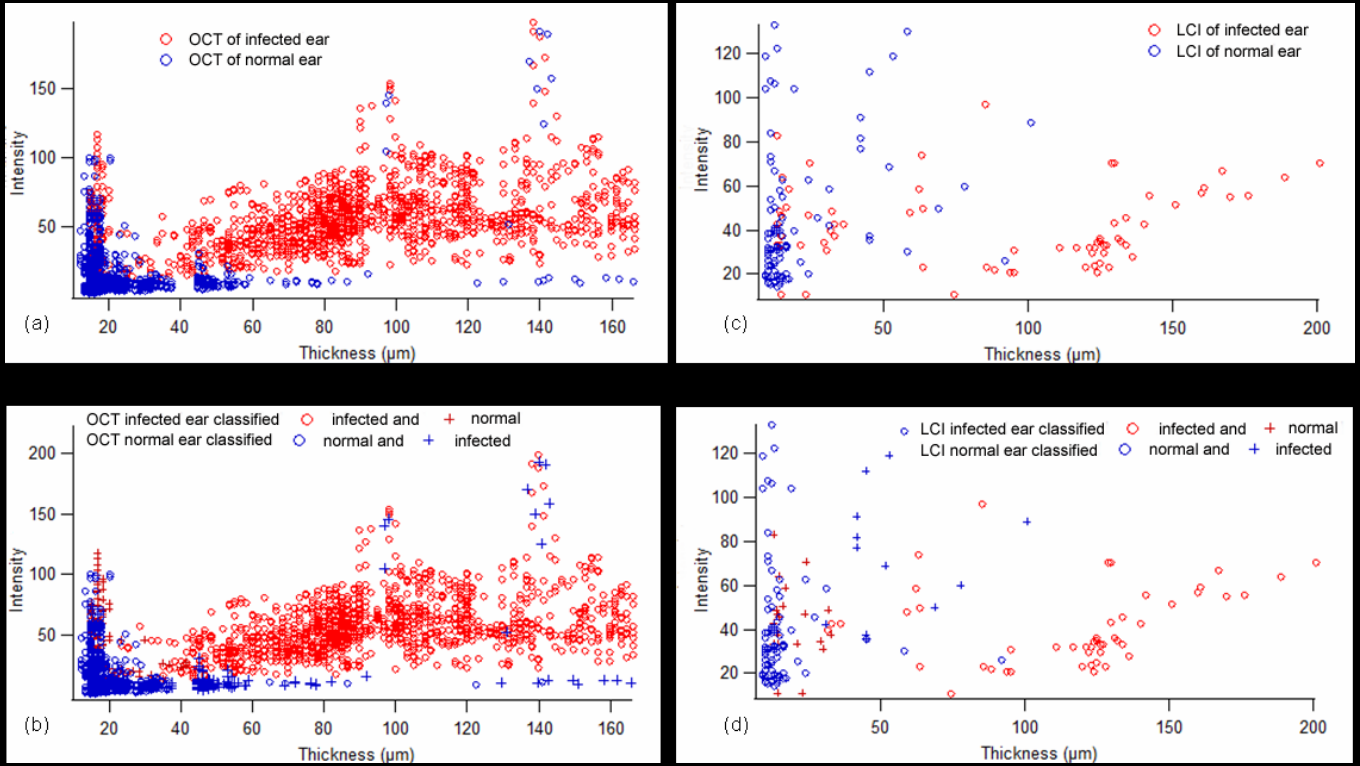
Sensitivity = 87%

Specificity = 90%

<u>Current methods:</u>

Standard otoscopy 74% and 60%

Tympanometry 70-90%

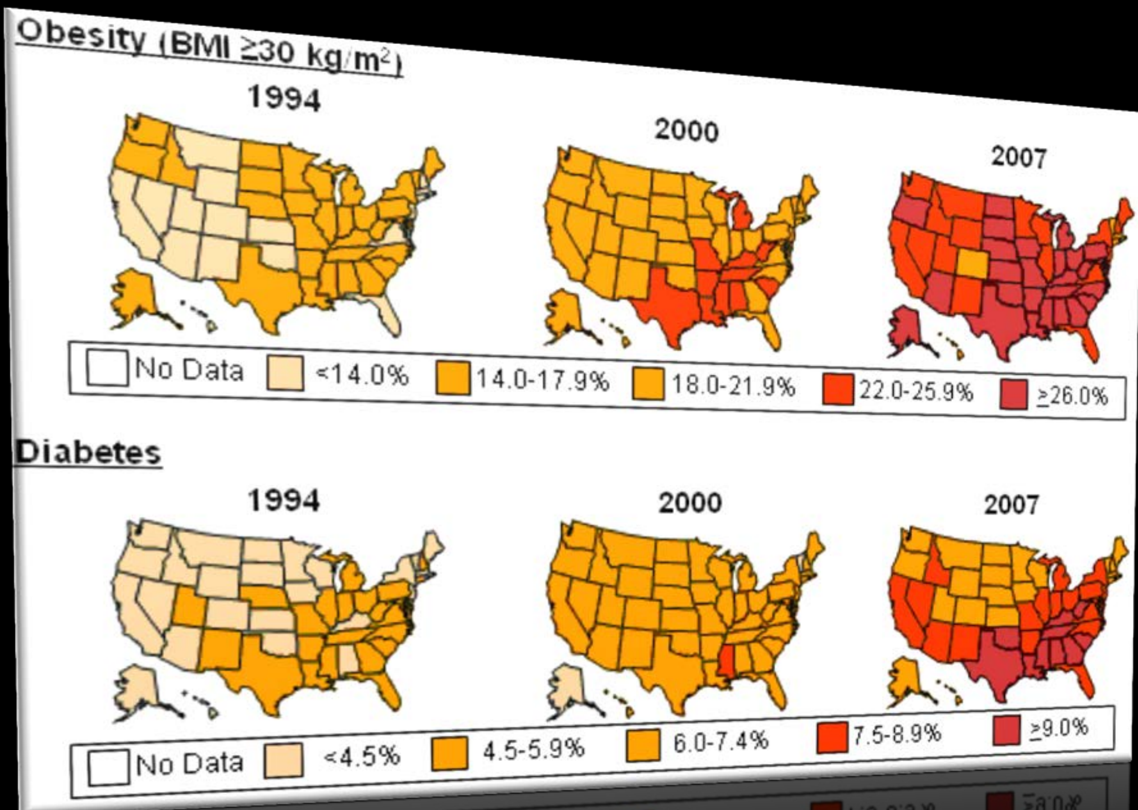


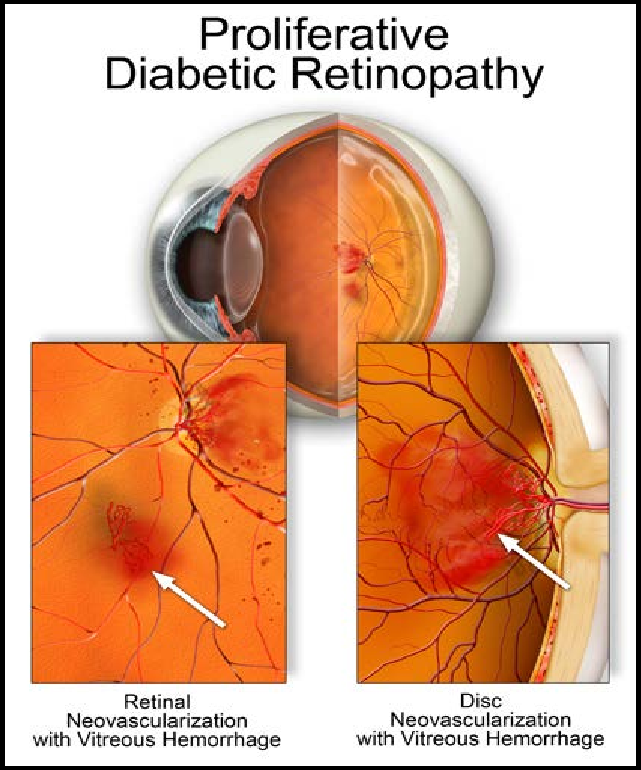

OCT Ophthalmoscopy
for Screening and Monitoring
of Diabetic Retinopathy

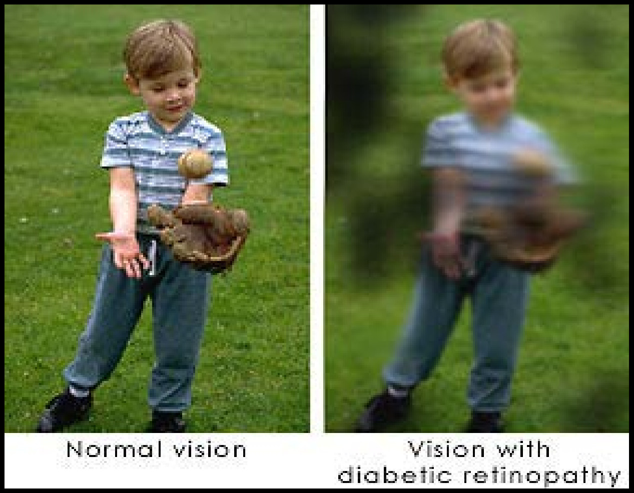
Obesity, Diabetes, and Diabetic Retinopathy

- ► **One-third (33.8%) of U.S. adults are obese**
- ► **Over one-third of children and adolescents are obese or overweight**

Reference: NHANES, CDC



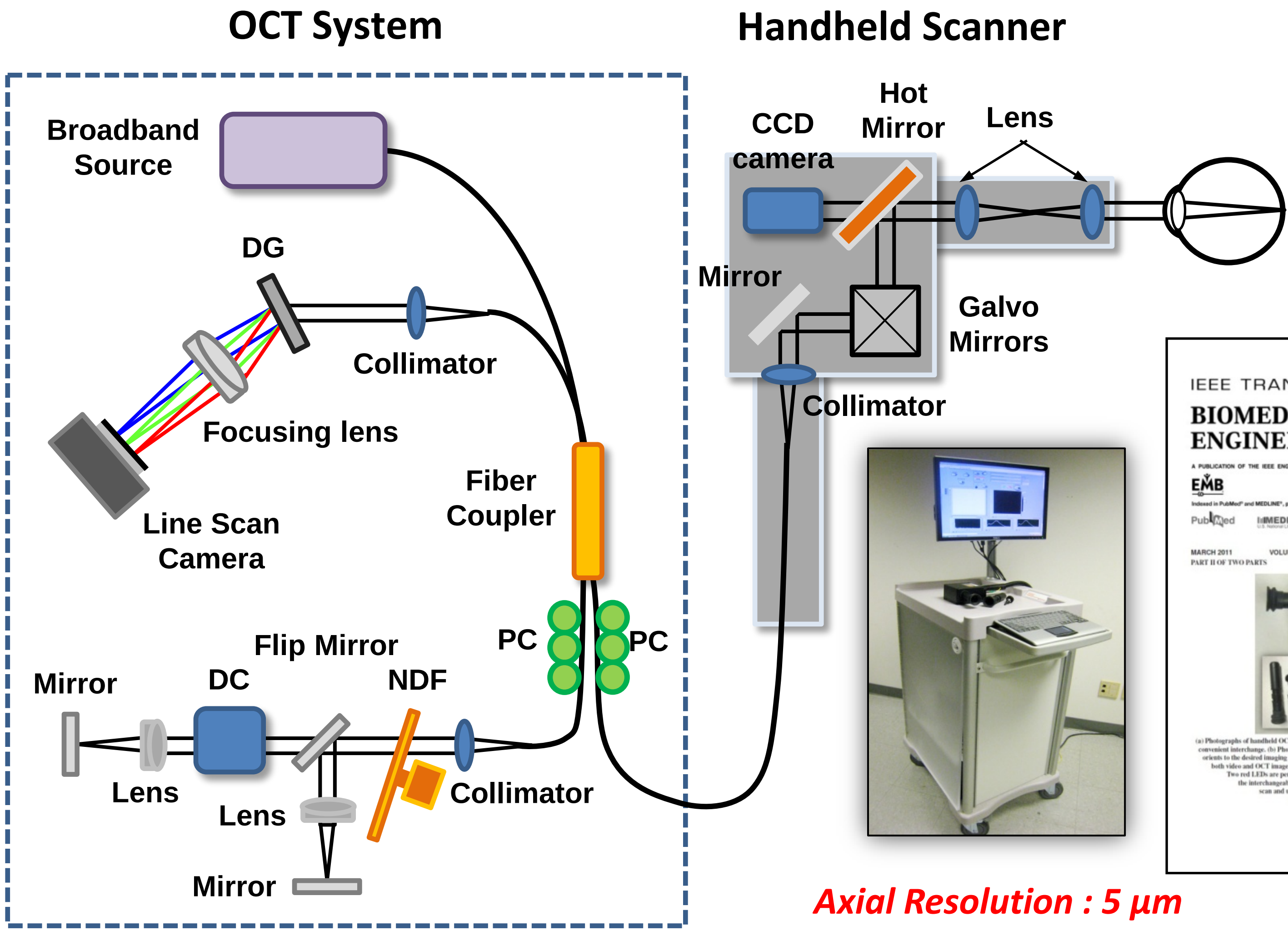




- ► **1 in 10 (552 million) are expected to have diabetes by 2030**
- ► **40-45% of diabetics will have diabetic retinopathy**

Reference: International Diabetes Foundation

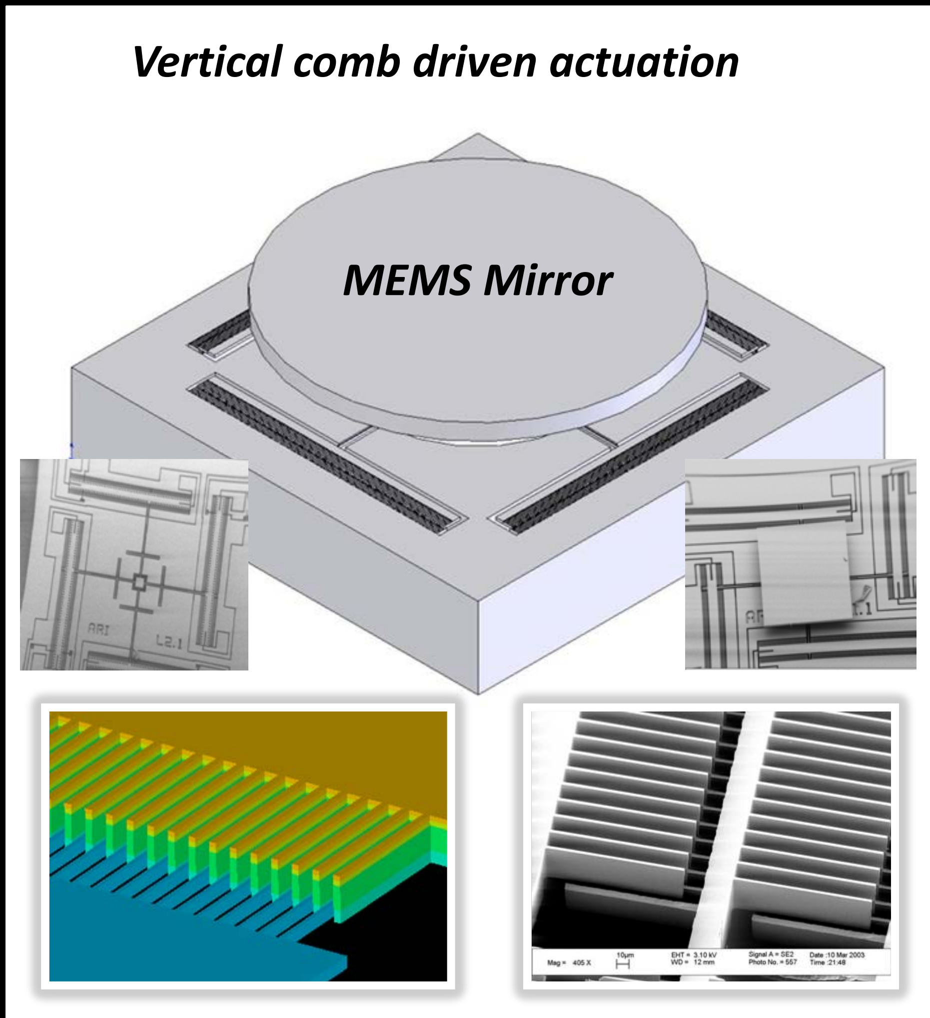
Portable OCT System

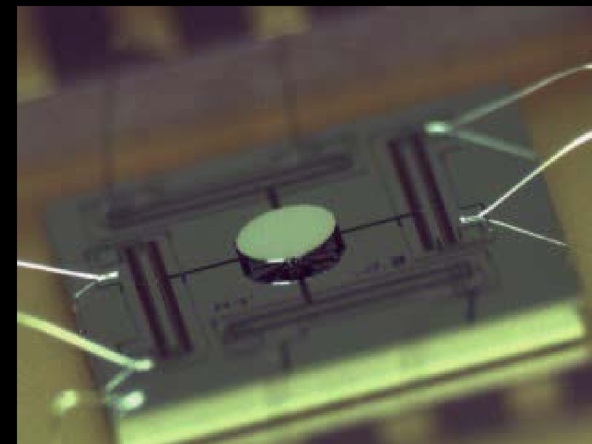


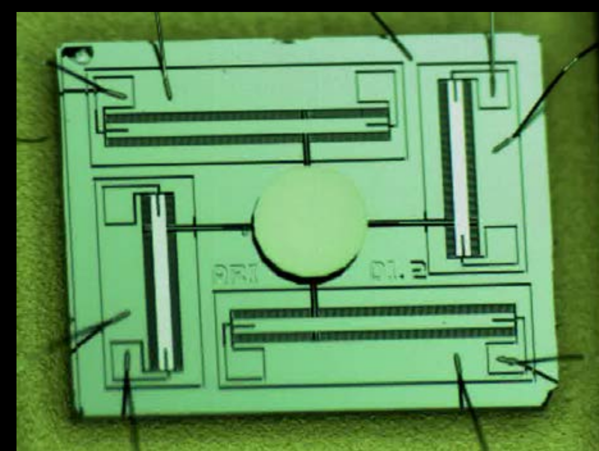
Axial Resolution : 5 µm
Lateral Resolution: 15 µm

Jung, *et. al.*, IEEE TBME 58:741, 2011

Four Quadrant 2 Axis Scanning MEMS Mirror







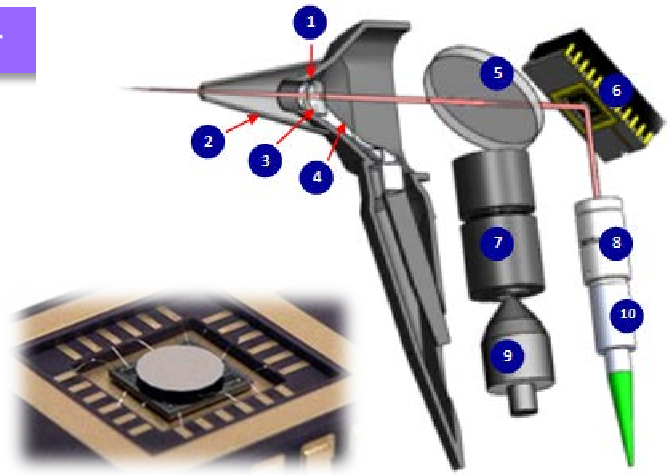
Unique Gimble-free linkage configuration

AdvancedMEMS

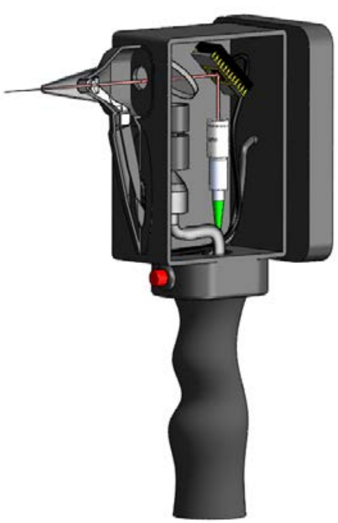
Handheld Probe using MEMS Scanner

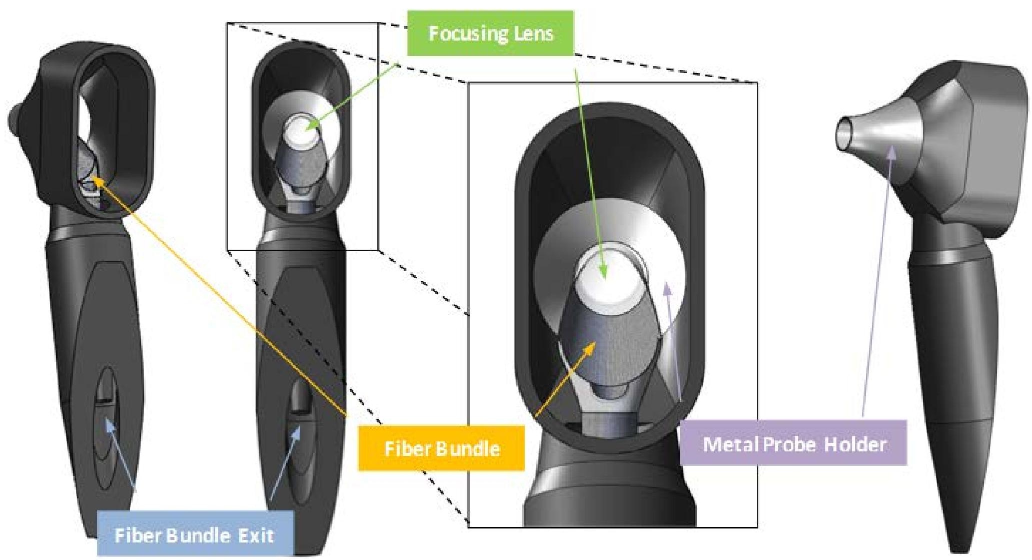
Anatomy of MEMS Probe

1. Metal Probe Holder
2. Ear Speculum
3. Focusing Lens
4. Fiber Bundle
5. Cold Mirror

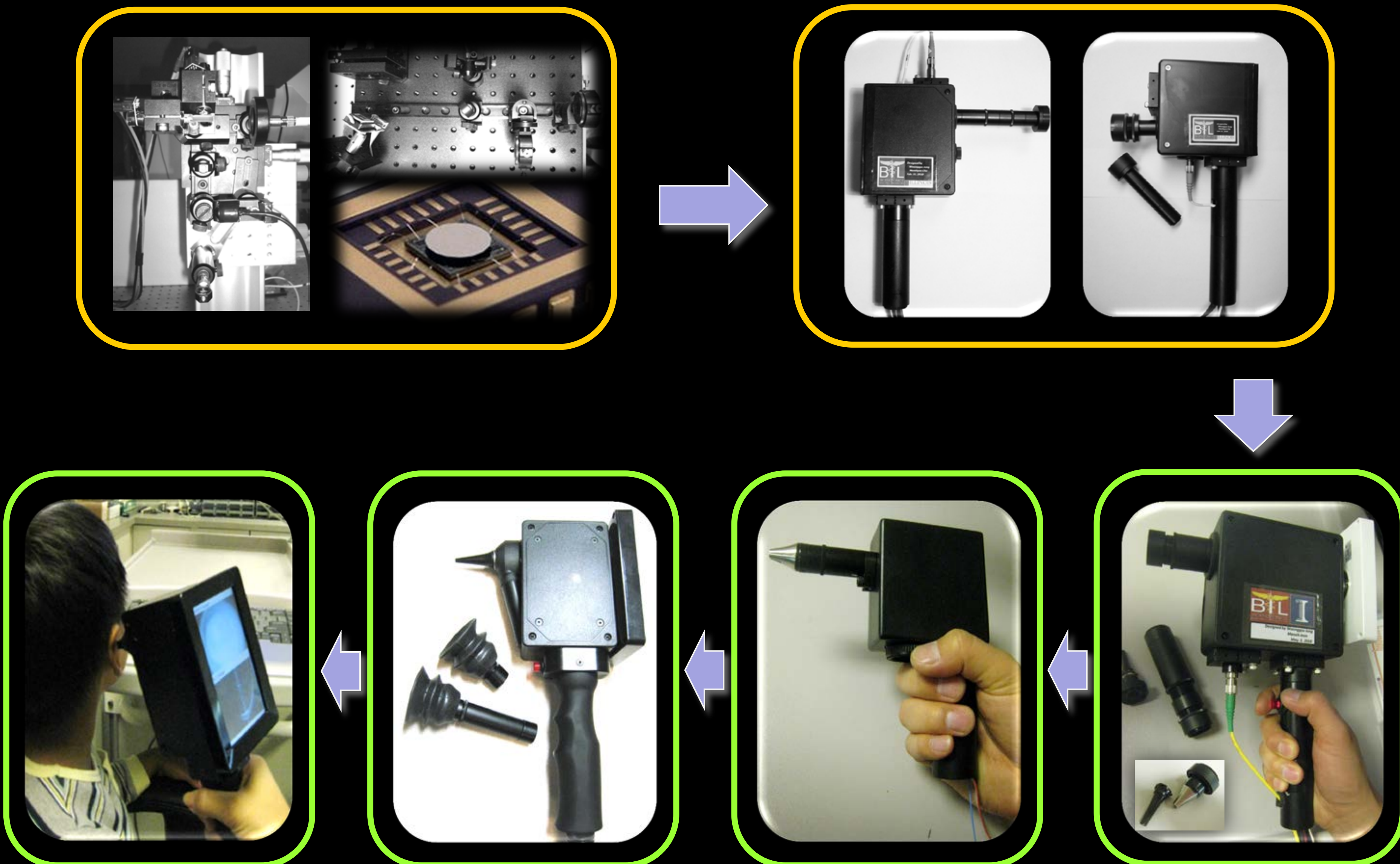


6. MEMS Scanning Mirror
7. Magnifier
8. Collimator
9. CCD Camera
10. Optical Fiber

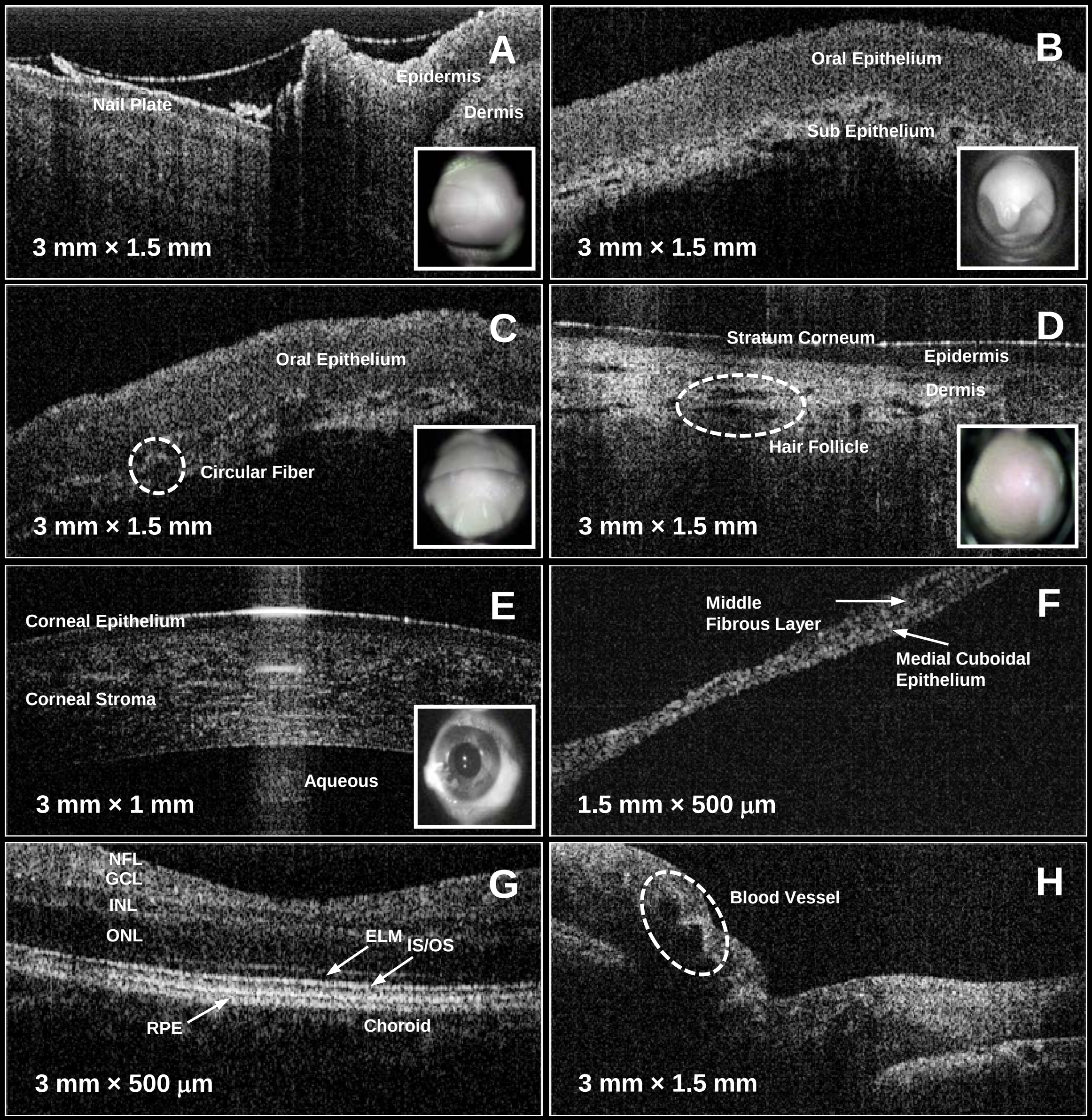


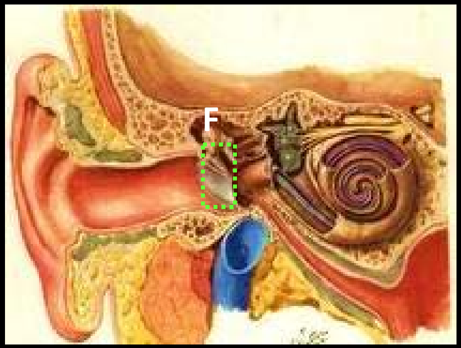


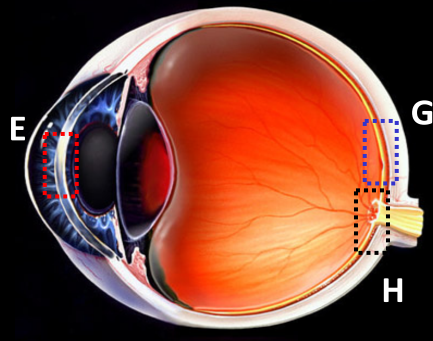
Various Probe Designs



In vivo OCT and Video Images (Human)







(A) nail fold (B) uvula

(C) gum (D) arm (E) cornea

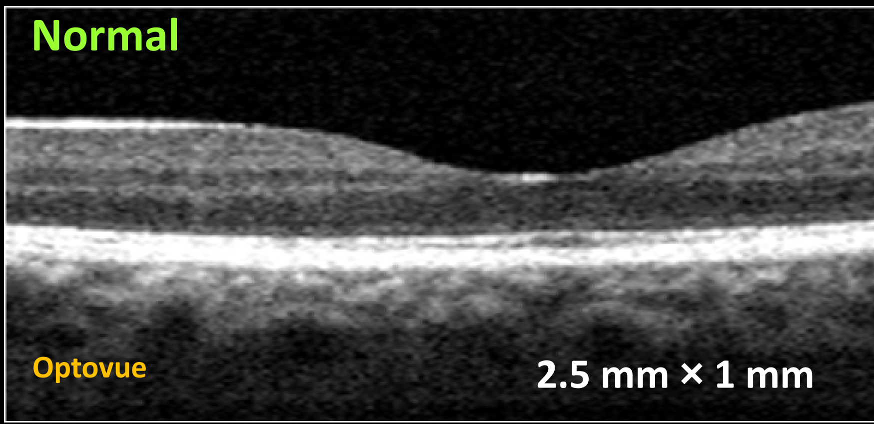
(F) tympanic membrane

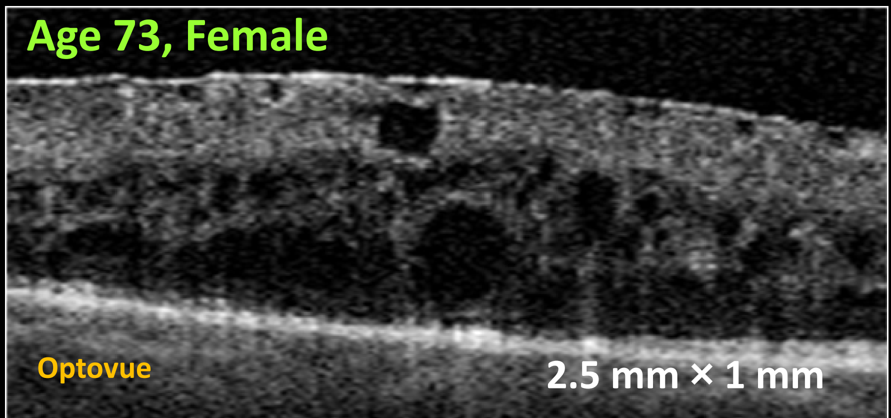
(G) retina around fovea

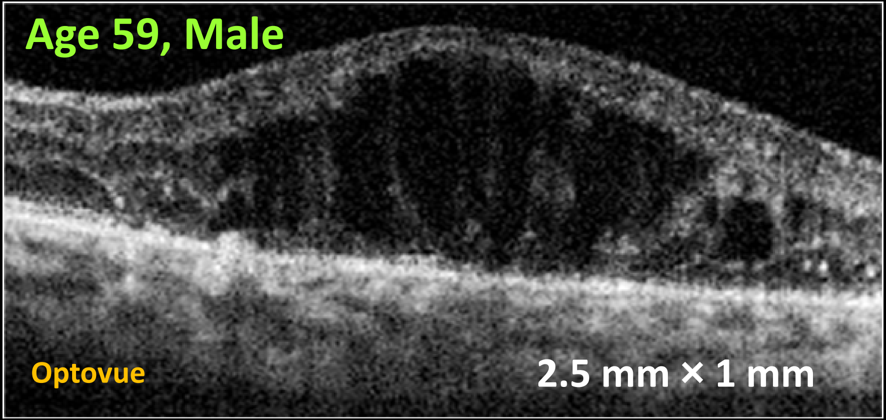
(H) optic nerve head

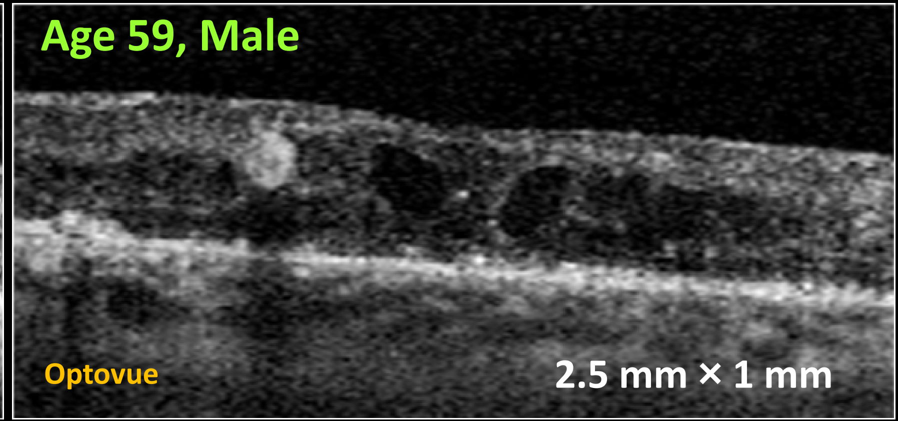
Jung, *et. al.,* IEEE TBME 58:741, 2011

Retinal OCT Images from Diabetic Patients

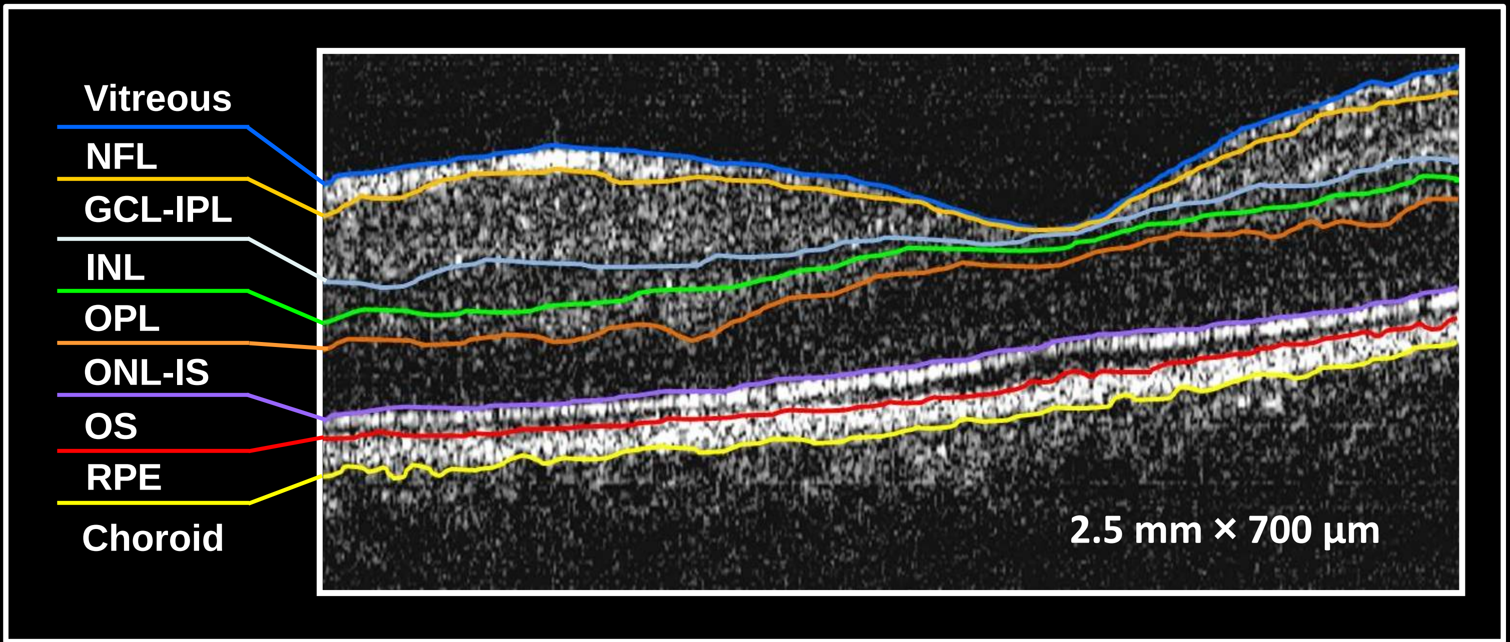








Structure of Retinal Layers

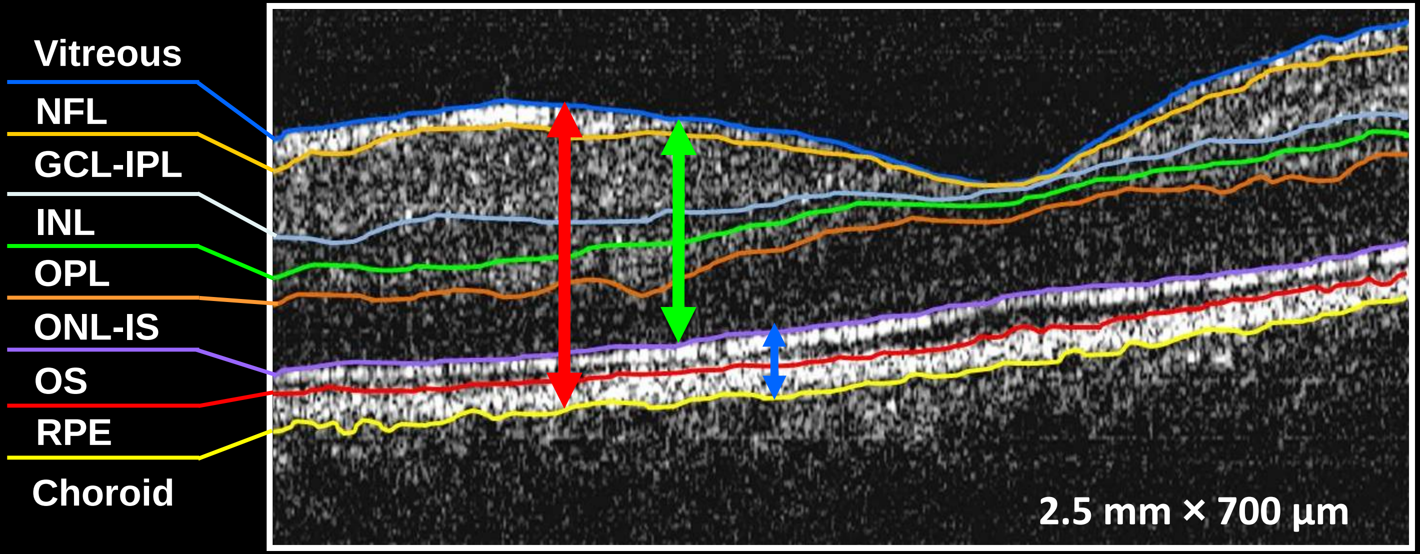


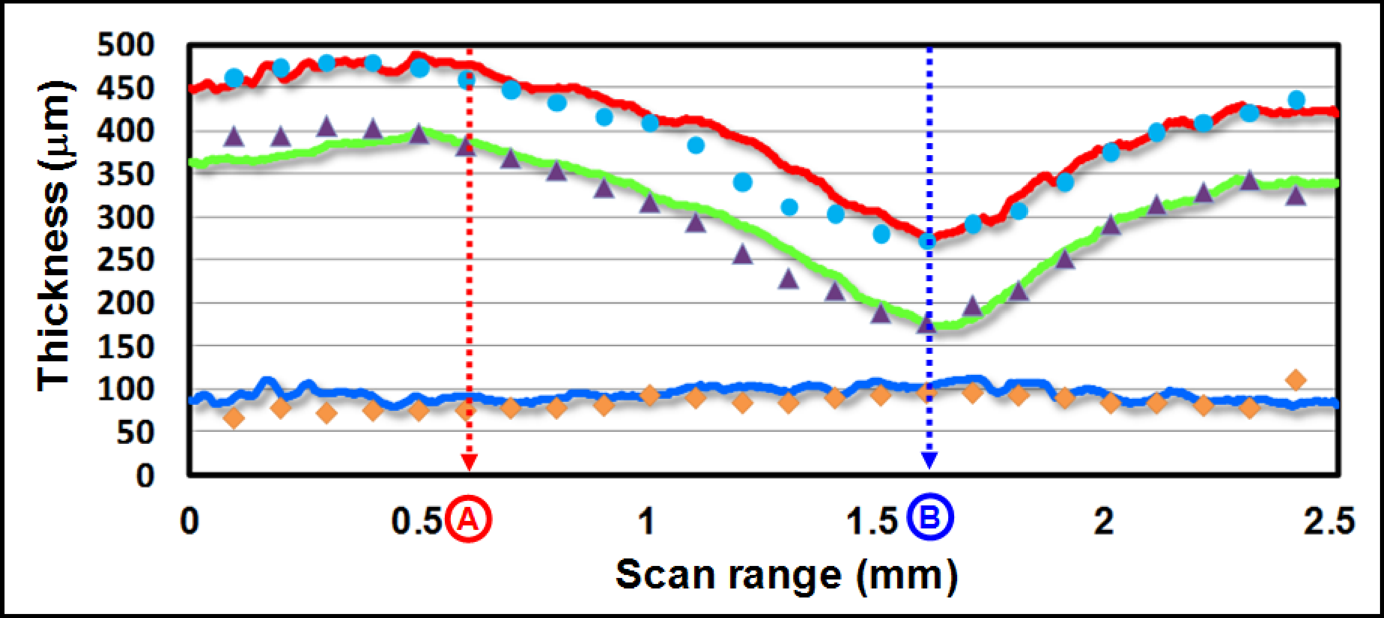
NFL: Nerve fiber layer
GCL: Ganglion cell layer
IPL: Inner plexiforn layer
INL: Inner nuclear layer
OPL: Outer plexiforn layer

ONL: Outer nuclear layer
IS: Inner segment
OS: Outer segment
RPE: Retinal pigment epithelium

Diabetic retinopathy is a change in the thickness of retinal layers

Segmentation of Retina Layers

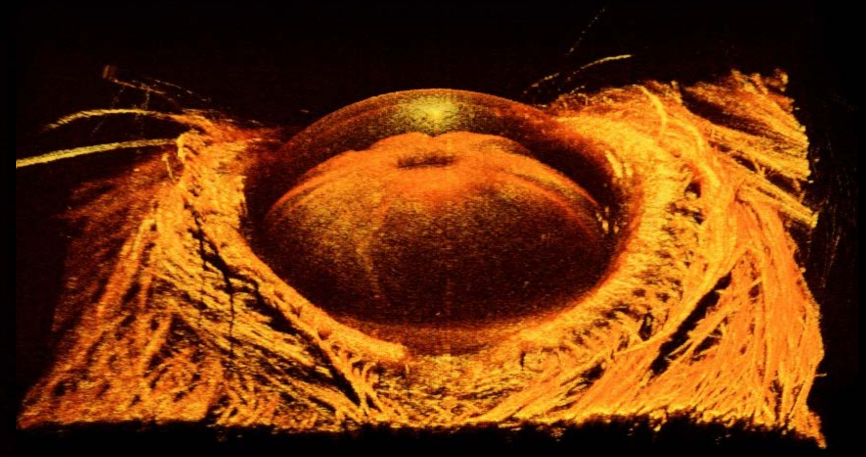




Solid line: Manual segmentation; Dotted line: Automatic segmentation

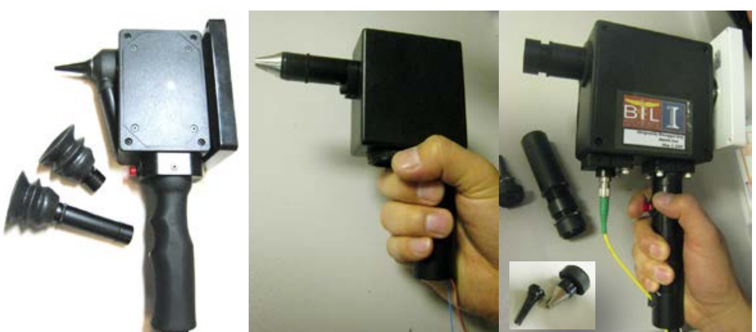
Conclusions

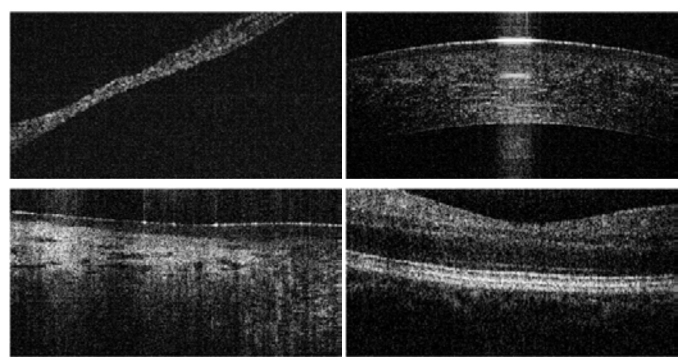
- Vision for new technology and research in Primary Care Imaging using novel handheld scanners and portable OCT/LCI systems.
- Primary Care Imaging enables new technology at the front-line of healthcare for screening, quantitative monitoring, and potentially more effective referral practices.
- Experimental results show potential for advances in fundamental medical science of middle ear biofilms and retinal layer changes in diabetic retinopathy.
- Transform OCT to be a Screening Modality.

Primary Care Imaging Research Partnership

NIH - NIBIB Bioengineering Research Partnership R01 EB013723





Acknowledgments

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for Advanced Science and Technology

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Daniel McCormick, Ph.D.

National Institutes of Health (NIBIB, NCI)
National Science Foundation
Carle Foundation Hospital
Welch Allyn, Inc. & Blue Highway, LLC
Texas Instruments, Inc.
Samsung, Inc.

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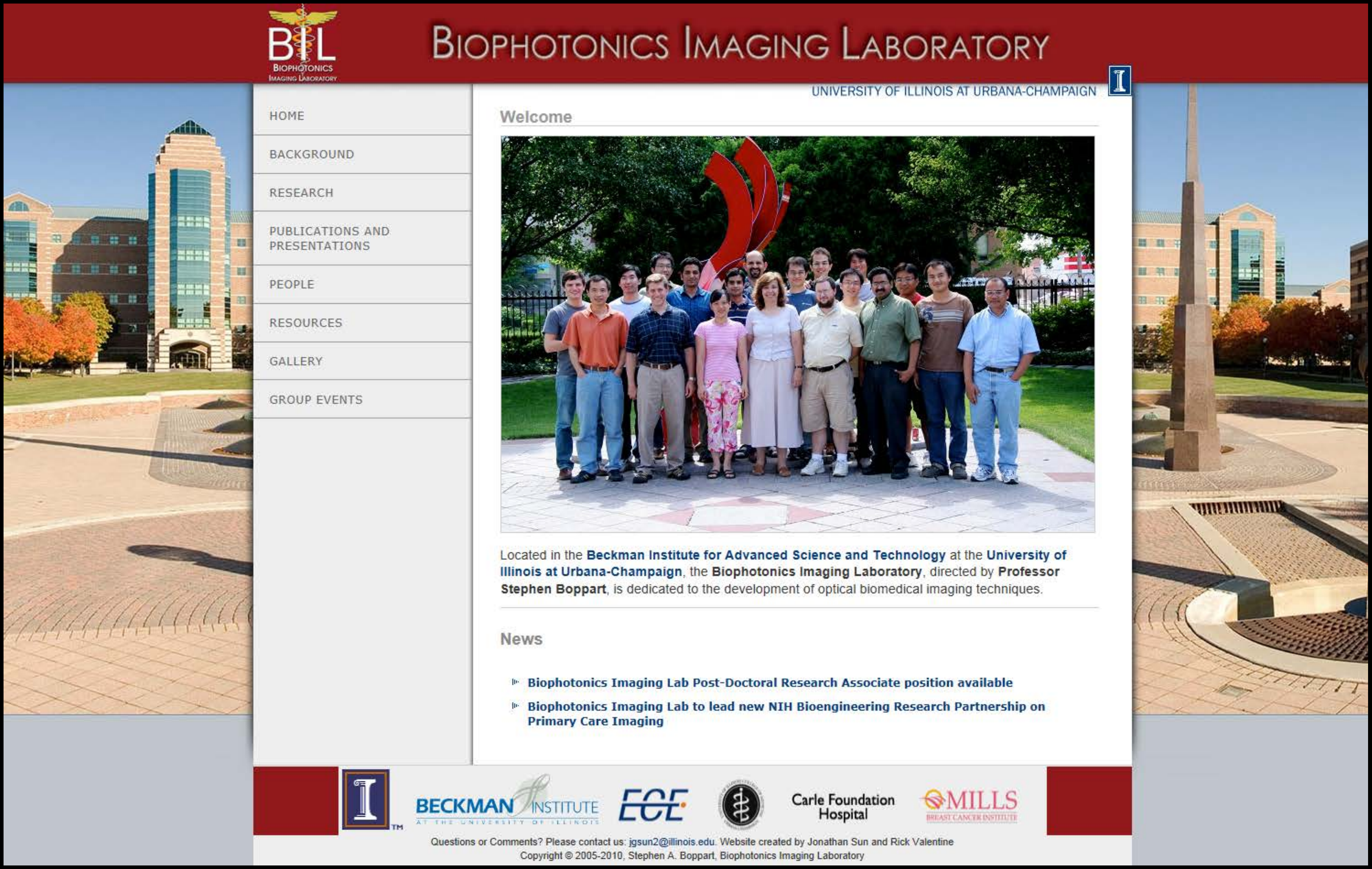


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