

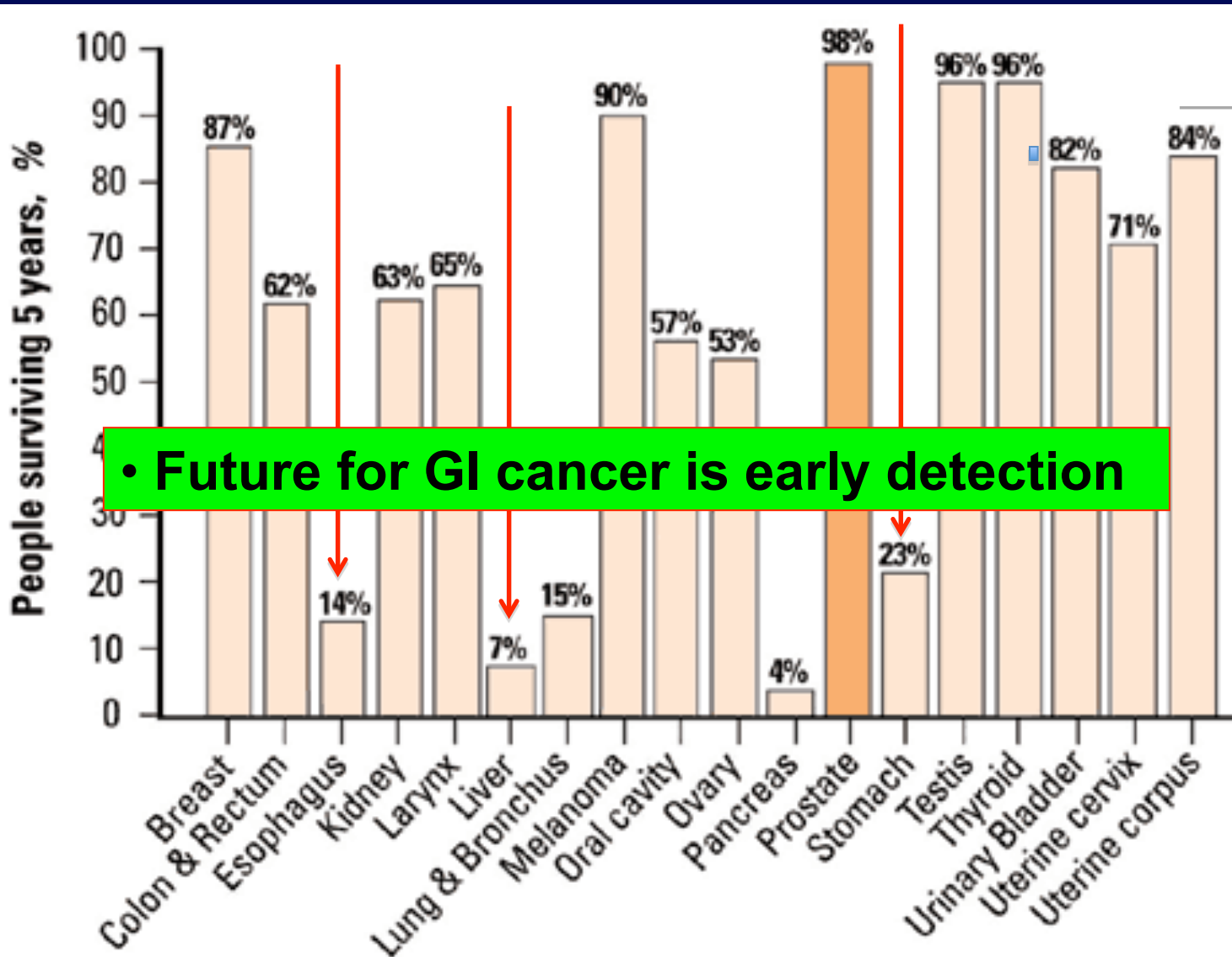
Innovative Fiber-optic Confocal Raman Endoscopy for Early Detection of Gastric Cancer

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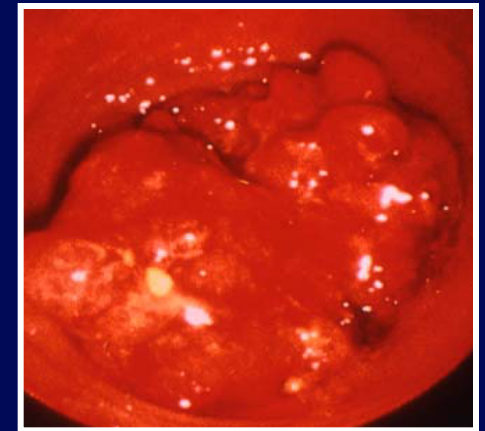
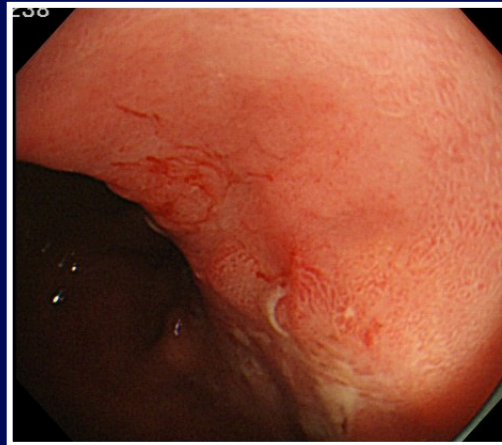
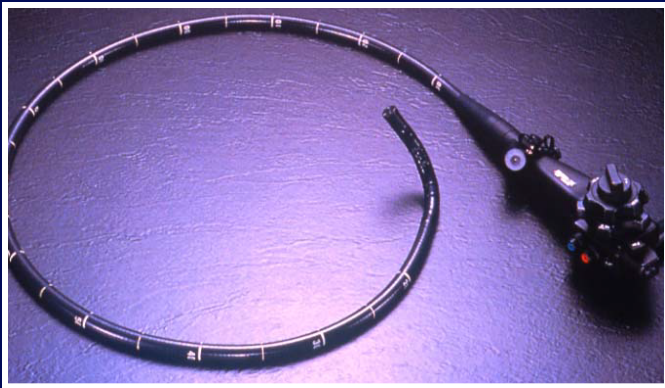
<http://www.bioeng.nus.edu.sg/people/PI/Huangzw/default.html>

Surviving Cancer in the US



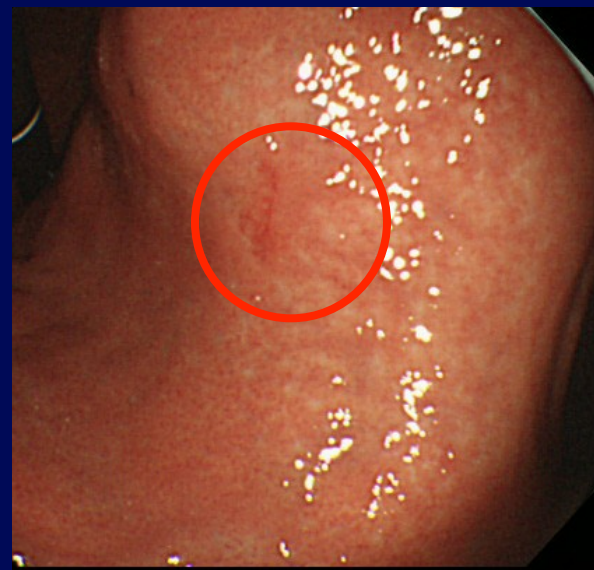
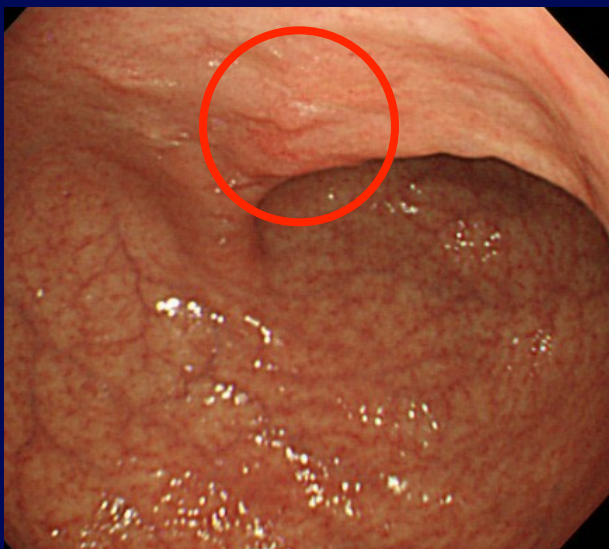
Screening of Gastric Cancer

- **Conventional white-light endoscope is main instrument, followed by histopathology.**



Limitations of Endoscopy

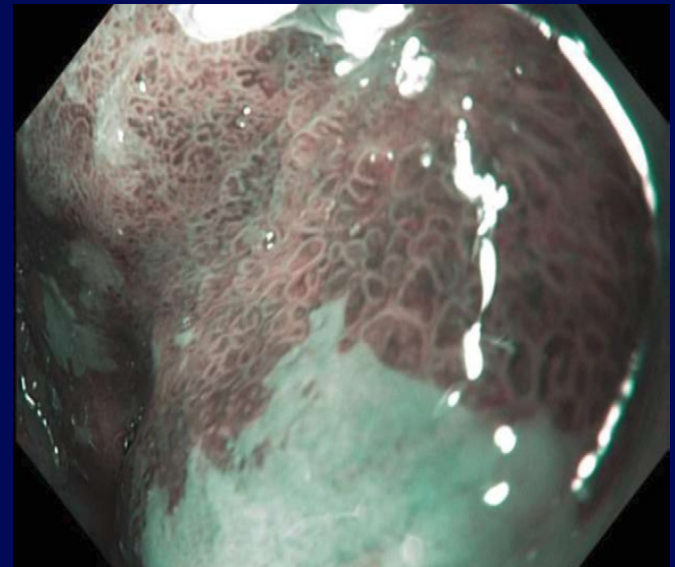
- Precancer/early cancers are difficult to detect by conventional endoscopy



- Appearance of dysplasia and early flat neoplasia in the gastric could be very subtle

Can newer imaging methods obviate need to take random biopsies during surveillance scope?

- **Narrow band imaging (NBI)**
- **Confocal endomicroscopy**



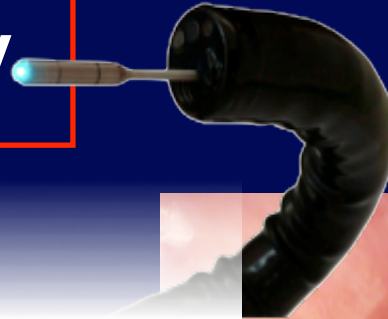
Olympus

Can newer imaging methods obviate need to take random biopsies during surveillance scope?

- **Narrow band imaging (NBI)**



- **Confocal endomicroscopy**



Pentax



**Is there any issue with these 2
technologies?**

Training effect on NBI

	Sensitivity		Accuracy	
	Pre	Post	Pre	Post
Average	65.9	74.9	63.6	68
Post-Pre	8.9		4.4	
(95%C.I.)	(-0.4, 18.3)			
P-value				

NBI is subjective, and dependent on operator's experience

Confocal endomicroscopy

ORIGINAL ARTICLE

Experienced versus inexperienced confocal endomicroscopy in the diagnosis of gastric adenocarcinoma: a comparison of confocal images

D. A. Gomez, M. A. Perez, Christopher J.L. Khor, Ming Teh, Y. S. Makova, Emily Shen, Supriya Srivastava, Khek Yu Ho

Site

Similarly, confocal endoscope is subjective, and dependent on operator's experience

Results: Interpretation of in vivo images by group 1 was associated with higher sensitivity (95.2% vs 61.9%, $P = .039$) and higher specificity (93.3% vs 62.2%, $P < .001$) for GIM than interpretation by group 2. The

GI cancer: low detection/diagnosis = high mortality



ART

=

YEARS OF TRAINING

SUBJECTIVE

- **We need to develop more advanced endoscopic screening technology that gives real-time & objective diagnosis and independent of operator's experience**

SOLUTION IS

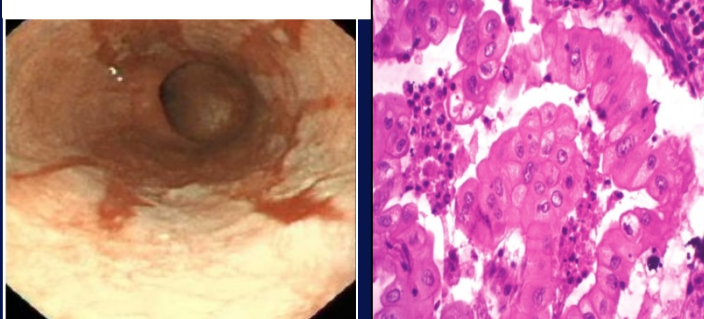
Face recognition



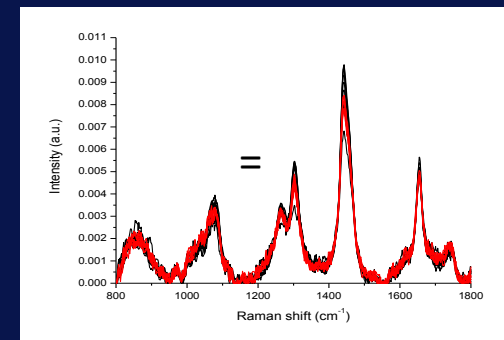
Fingerprint



Image



Molecular Fingerprint



Subjective visual interpretation

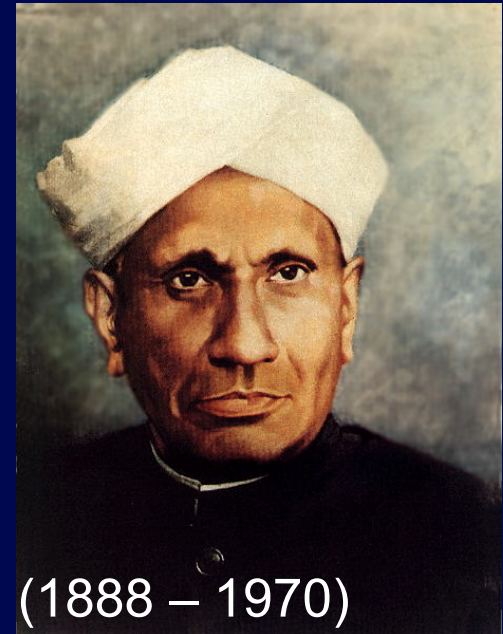
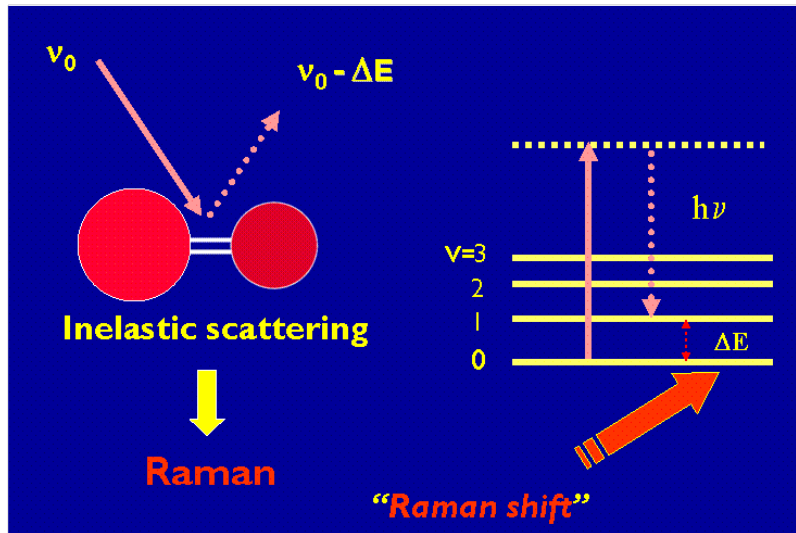
Objective, real time Dx

- **The Technology**

Raman Spectroscopy

A molecular vibrational technique that is capable of probing biomolecular changes associated with tissue and cellular transformation

Raman Effect- Inelastic Light Scattering



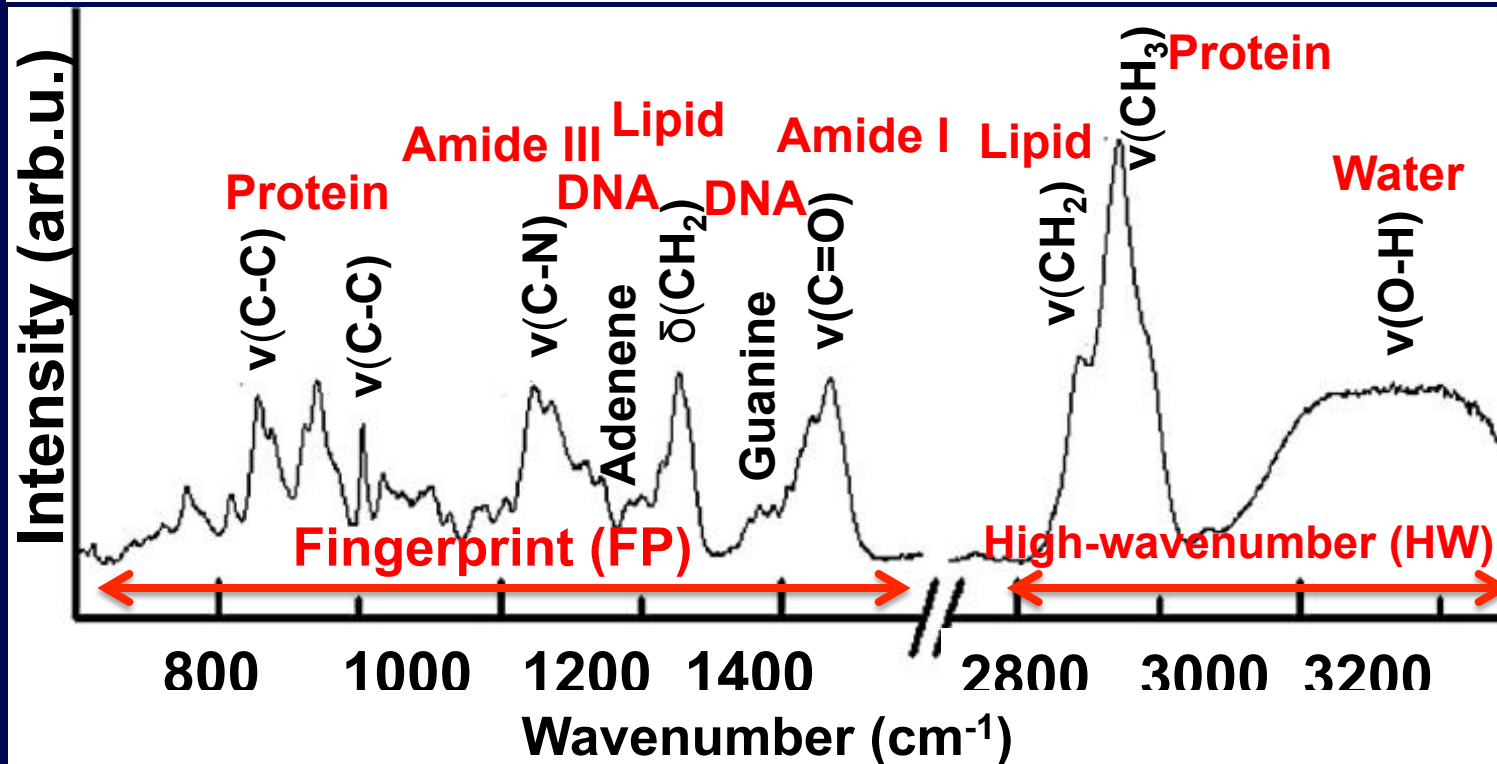
Professor Sir C.V. Raman

Won the Nobel Prize in Physics (1930)

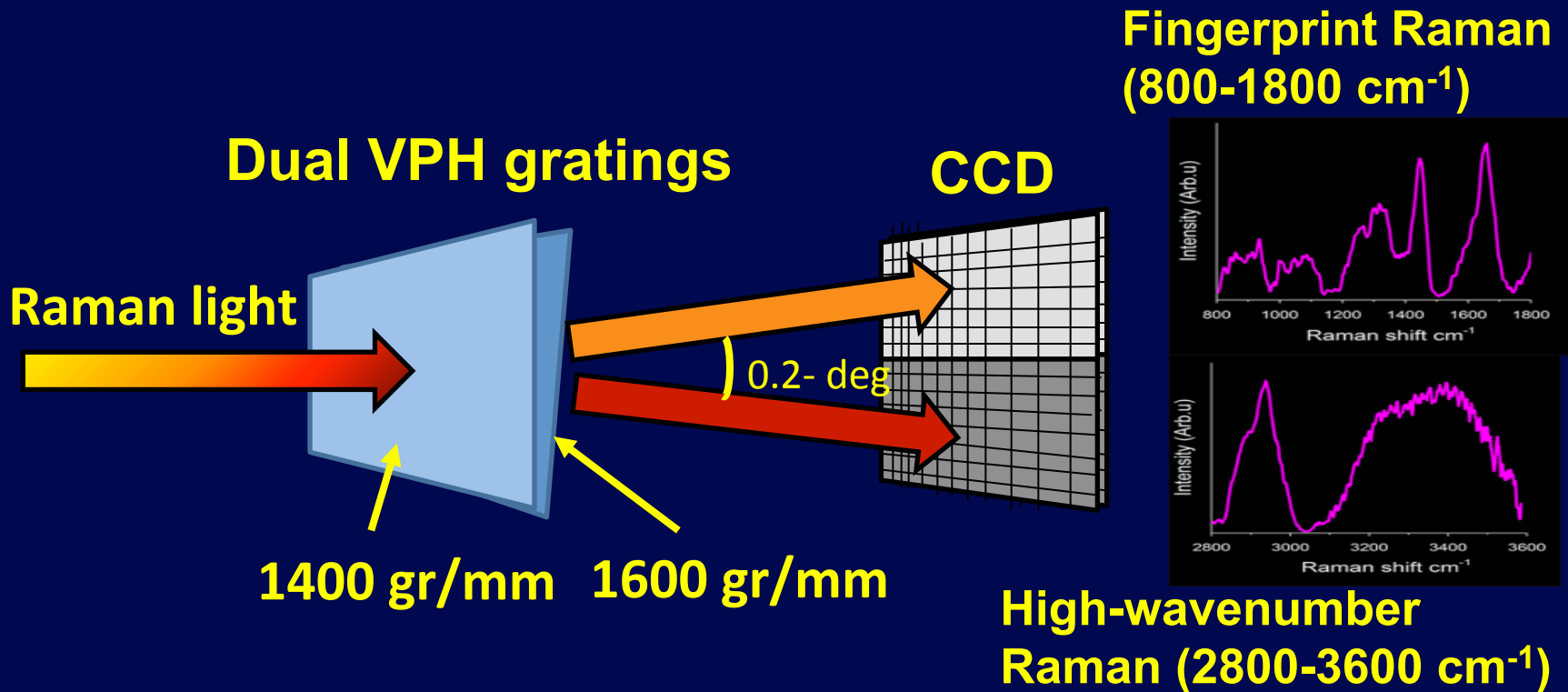
What can we obtain by Raman spectroscopy?

➤ Raman is molecular vibrational technique, providing fingerprinting signatures of specific biochemicals and biomolecules (e.g. proteins, DNA, nucleic acids, amino acids, lipids, carbohydrates) in cells and tissue.

Raman molecular signatures for objective diagnosis



Simultaneous fingerprint and high-wavenumber Raman technique

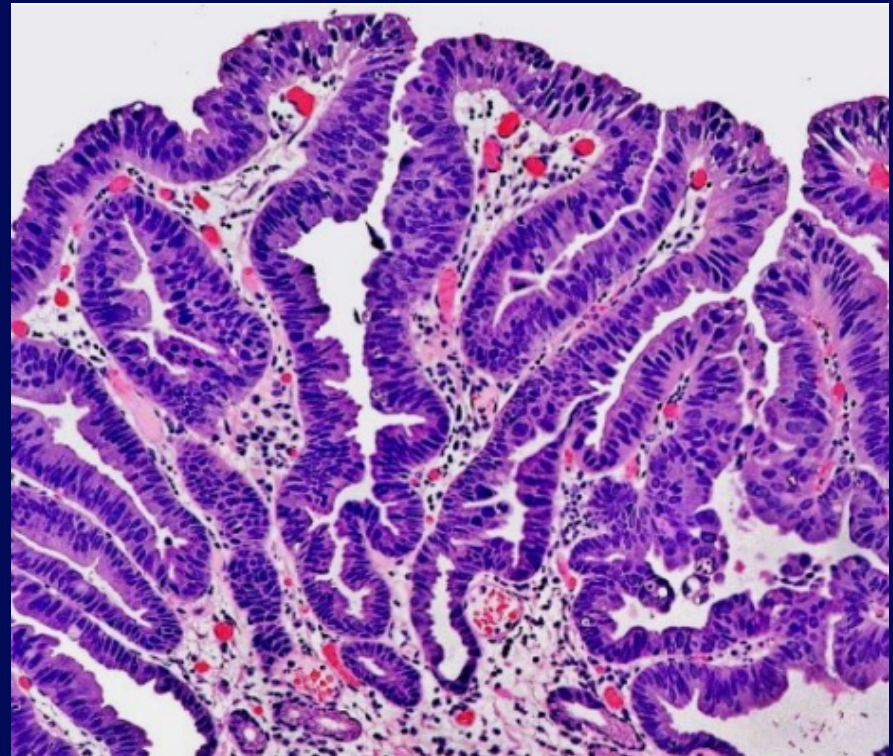


Broader spectral coverage (FP+HW) with good spectral resolution ($\sim 8 \text{ cm}^{-1}$)

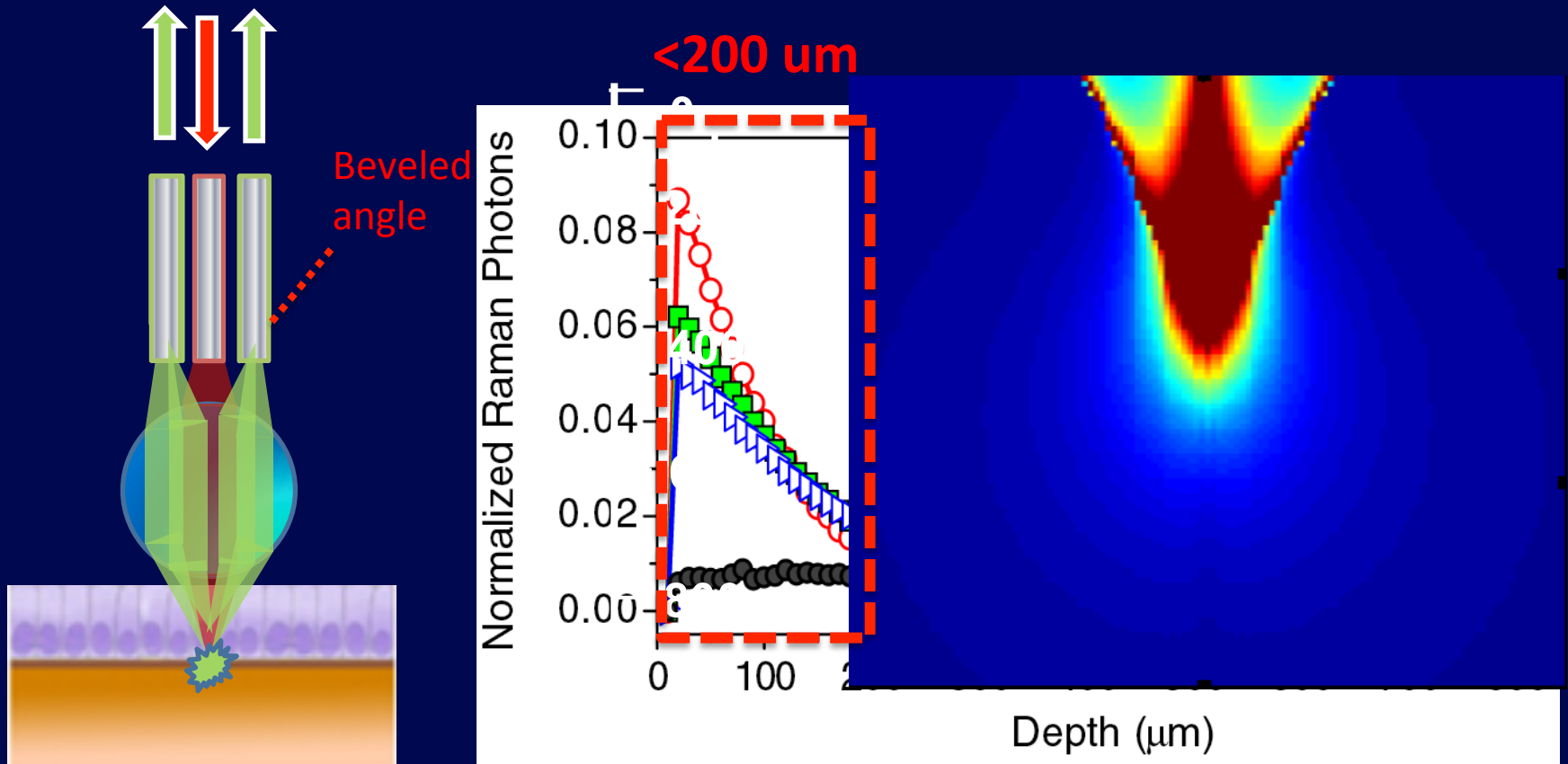
Novel confocal Raman probe with a ultra-short depth of focus

- Gastric carcinogenesis is an epithelial disease.
- The development of a confocal Raman probe would have two major advantages:

1. **Selective targeting of epithelium for increasing sensitivity to precancer**
2. **Reduction of interferences and Raman dilution from deeper bulky tissue.**



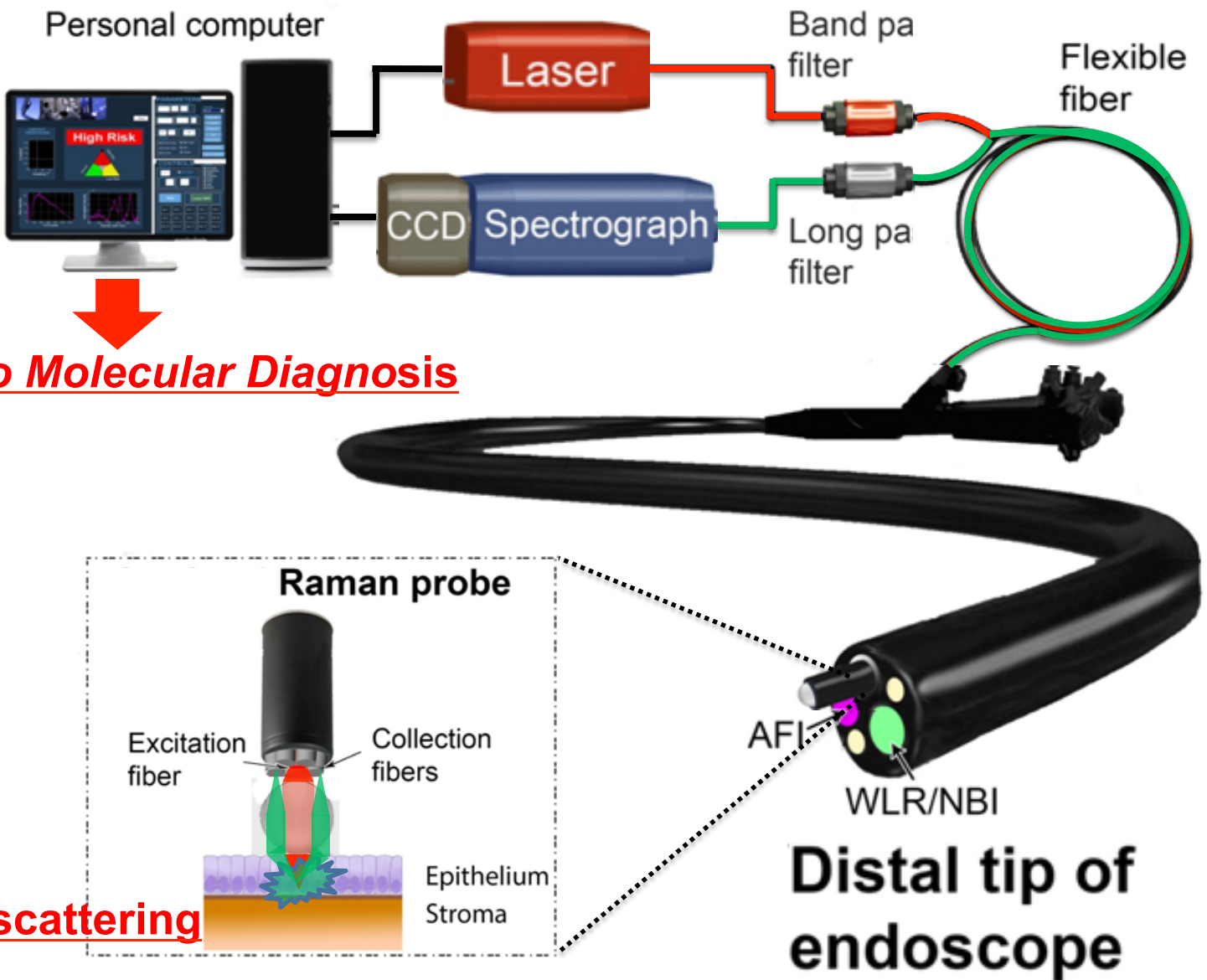
Controlling interrogation depths using beveled collection fibers



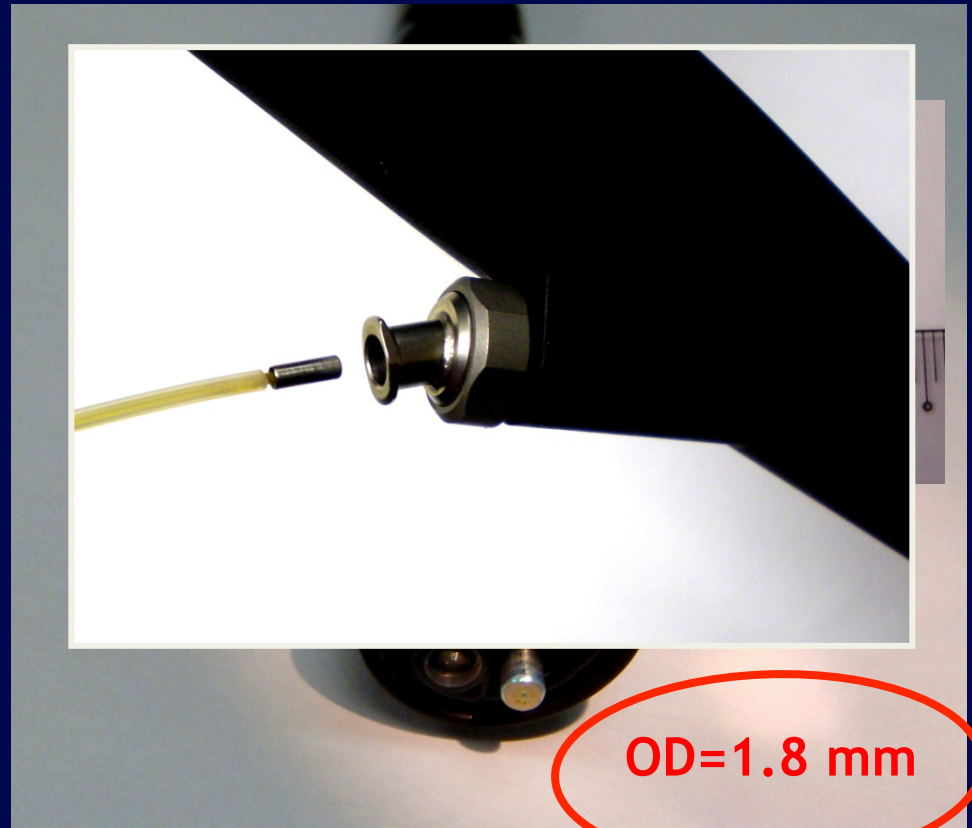
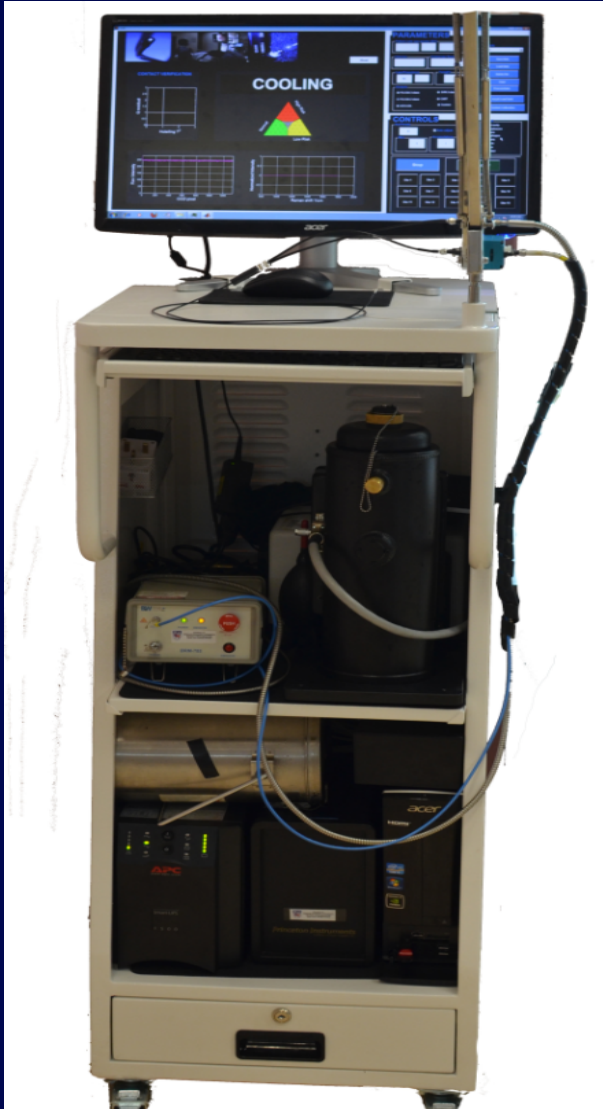
Wang et al. Opt. Letts. 38, 2321 (2013).

Bergholt et al. Gastroenterology, 146, 27 (2014).

The INNOVATION: World's first Objective, Real Time In-Vivo Molecular Diagnostic (IMDX) System



IMDX System



Z Huang et al., Opt Lett., 34(6), 758 (2009).
J Wang et al., Opt Lett., 38(13), 2321(2013).

Online Raman software for real-time diagnosis

The screenshot displays the software interface with several key components:

- Top Left:** An 'About' section with a small image of a person using the device.
- Top Center:** A large red box with the text 'High risk'.
- Top Right:** A 'PARAMETERS' control panel with fields for 'Clinician', 'Endoscope RoomNo', 'LaserPower(mw)' (set to 30), and 'Temp(C)' (set to 25). It also includes 'Analysis' options (PLS-DA 3 class and PLS-DA 2 class) and 'Diagnosis' options (ON and OFF). A 'Controls' dropdown is set to 'N(1,7)'. Buttons for 'Save Data', 'Load Data', 'Delete Spec', 'Clear Files', 'ProcessData', 'Load Dark', and 'System Calibration' are present.
- Middle Left:** A 'CONTACT VERIFICATION' graph showing 'Q residual' on the y-axis (scaled by $\times 10^{-7}$) with two vertical bars.
- Middle Right:** A triangular risk indicator with a red top section labeled 'High Risk' and a blue bottom section labeled 'Low Risk'. A black dot is positioned near the boundary.
- Center:** A large white box with red text: 'Real-time diagnosis (< 1 sec) (Auditory feedback)'. Below this, the text 'Low Risk' is visible.
- Bottom Left:** Two graphs. The left graph is 'CCD pixel vs. Raw Intensity' with the y-axis scaled by $\times 10^4$. The right graph is 'Raman shift (1/cm) vs. Normalized Intensity' with the y-axis scaled by $\times 10^{-3}$.
- Bottom Right:** A 'RUN' button and a 'Laser OFF' button. Below them is a 3x5 grid of buttons labeled 'Site 1' through 'Site 15'. To the right of this grid is a list of anatomical sites with radio buttons: 'Colon', 'Cervix', 'Bladder', 'Larynx', 'Esophagus', and 'Gastric'.

Duraipandian et al., JBO, 17, 081418 (2012).

Bergholt et al., Anal. Chem. 85, 11297 (2013).

Shining new light on gastric cancer:

Confocal Raman endoscopy



NUH

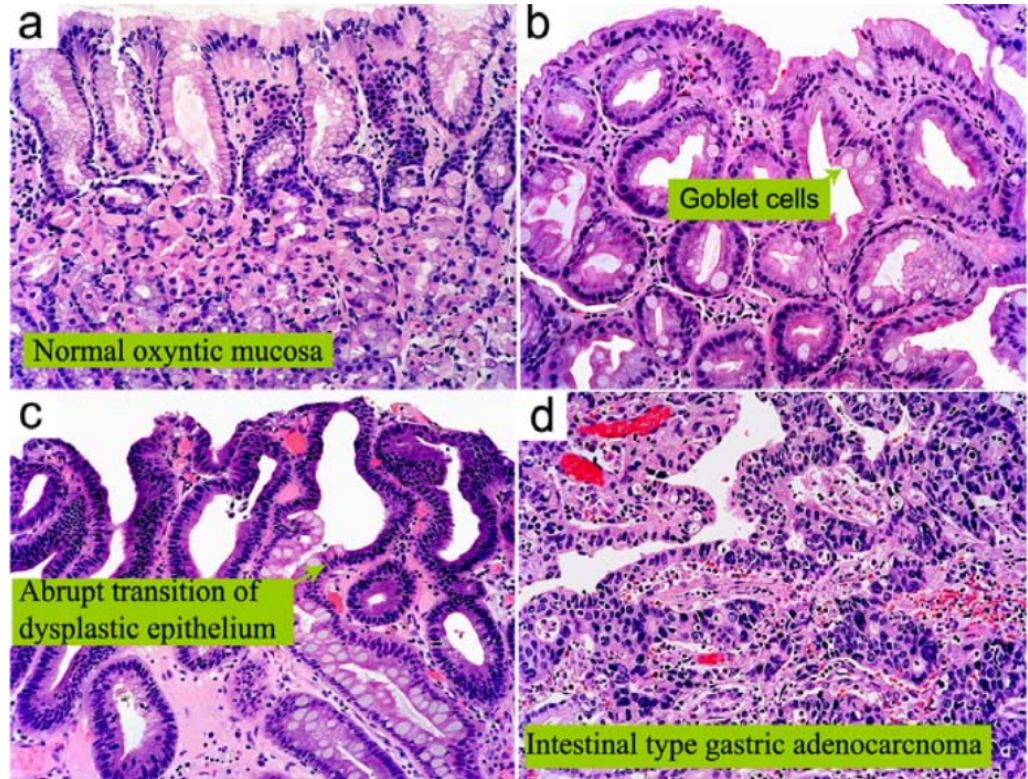
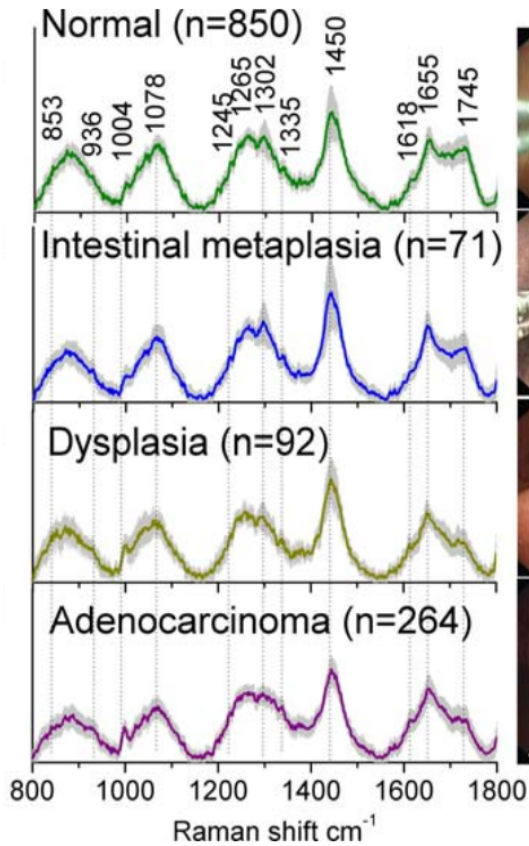
National University
Hospital



NUS

National University
of Singapore

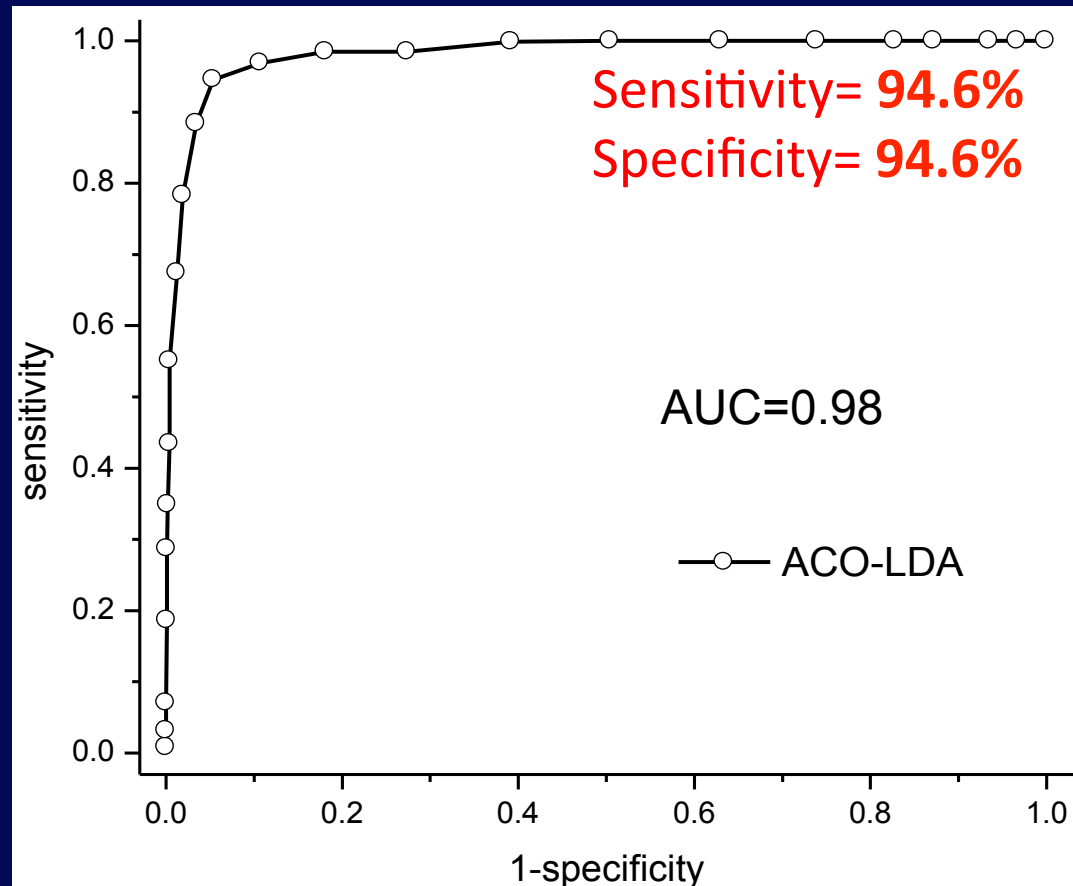
Raman endoscopy reveals progressive biomolecular changes in intestinal-type gastric carcinogenesis



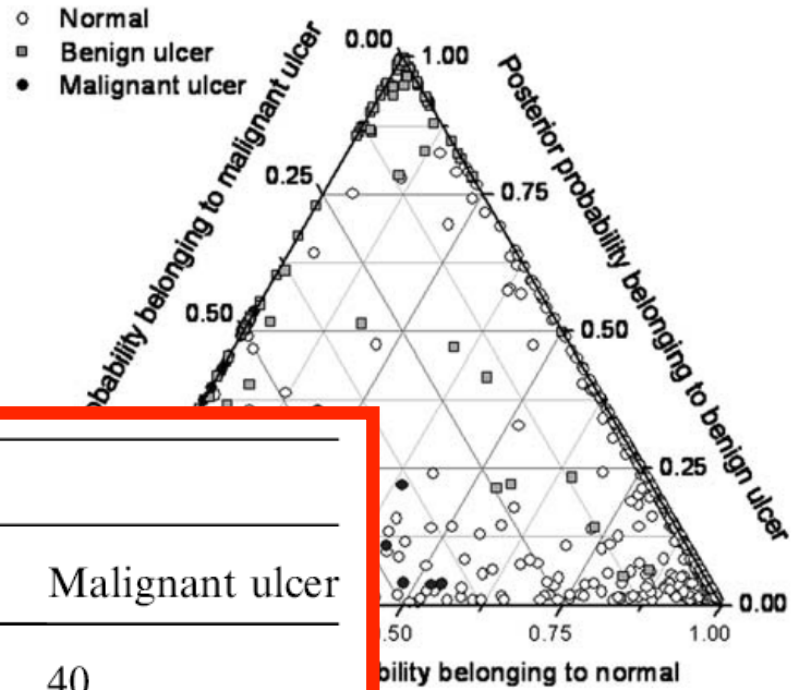
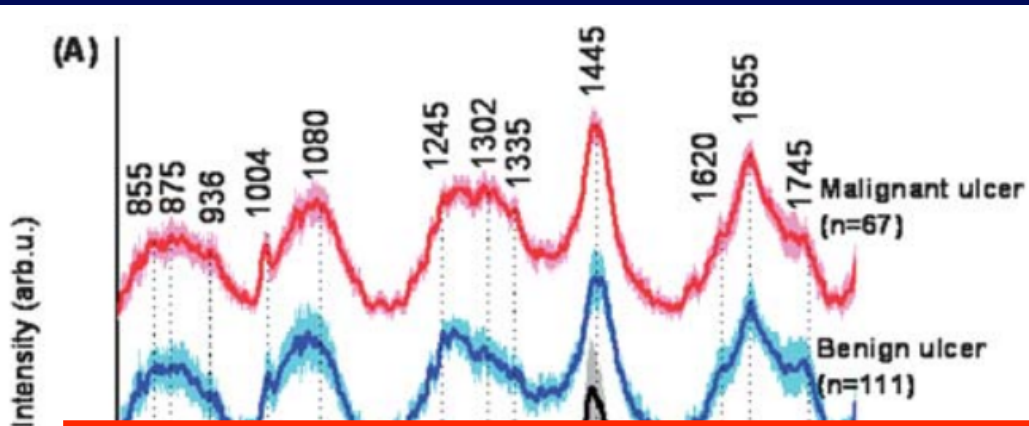
Each pathology has unique molecular fingerprint

Raman endoscopy detects gastric cancer

In vivo diagnosis of gastric cancer using Raman and ant colony optimization (ACO)-LDA techniques.

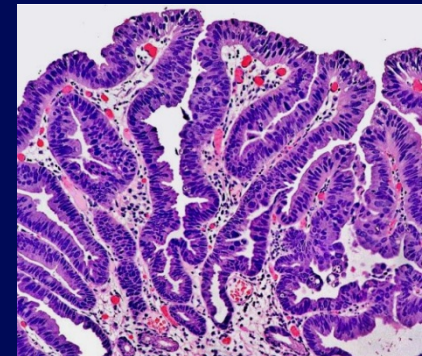
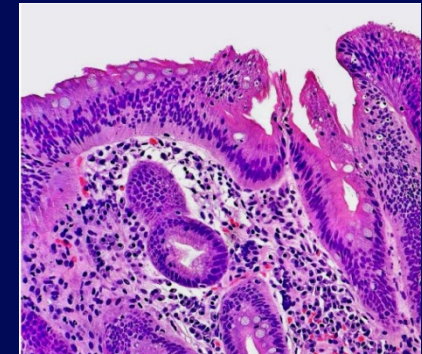
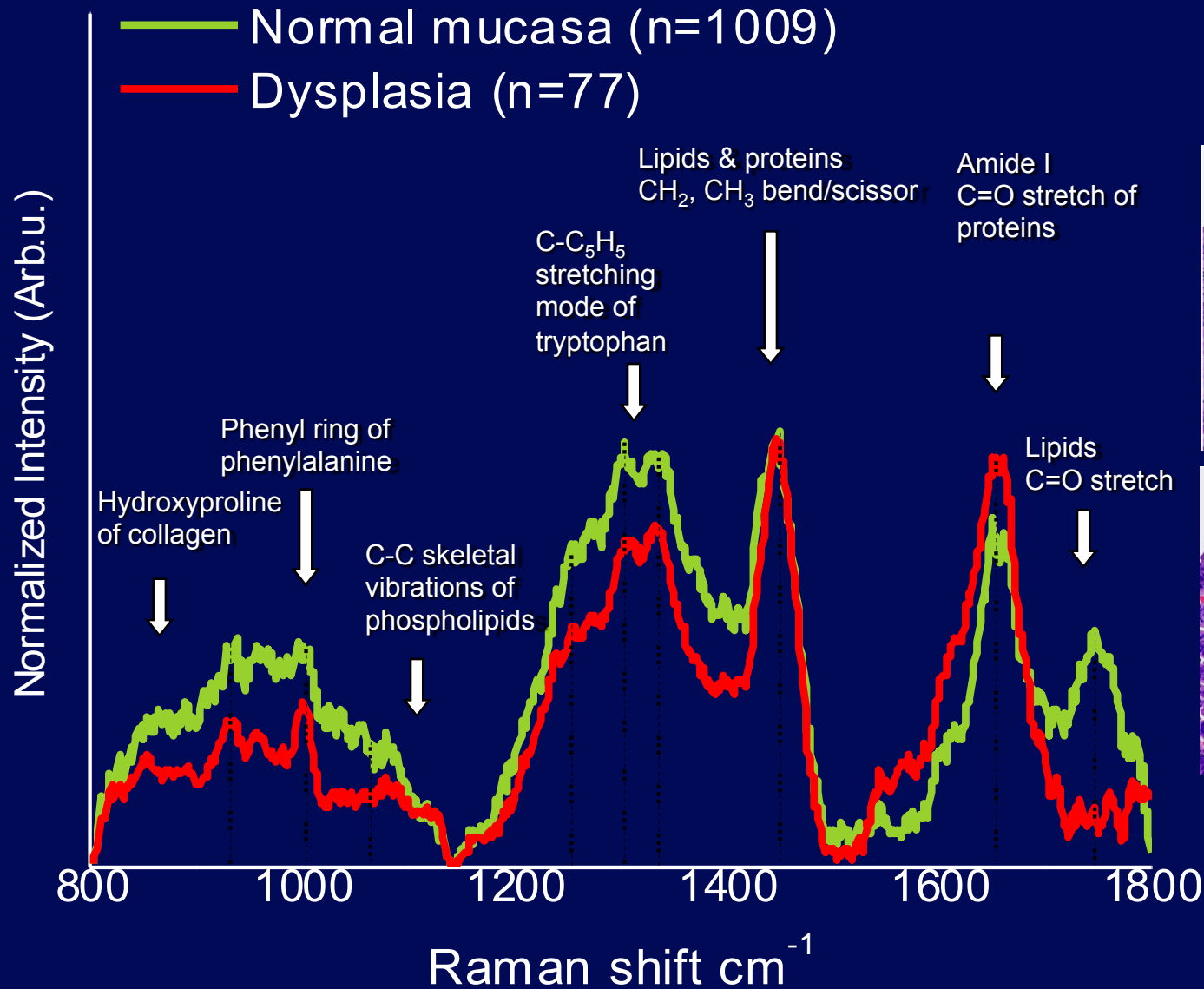


Raman endoscopy differentiates between benign and malignant gastric ulcers



Tissue type	Raman prediction		
	Normal	Benign ulcer	Malignant ulcer
Normal	839	45	40
Benign ulcer	8	94	9
Malignant ulcer	3	9	55
<i>Sensitivity</i>	90.8%	84.7%	82.1%
<i>Specificity</i>	93.8%	94.5%	95.3%

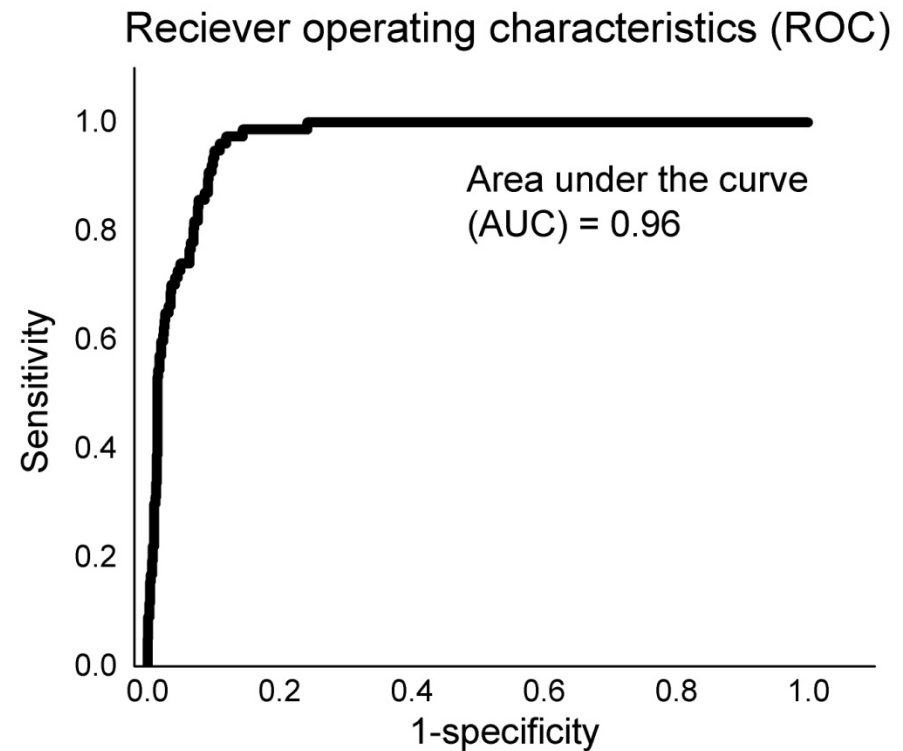
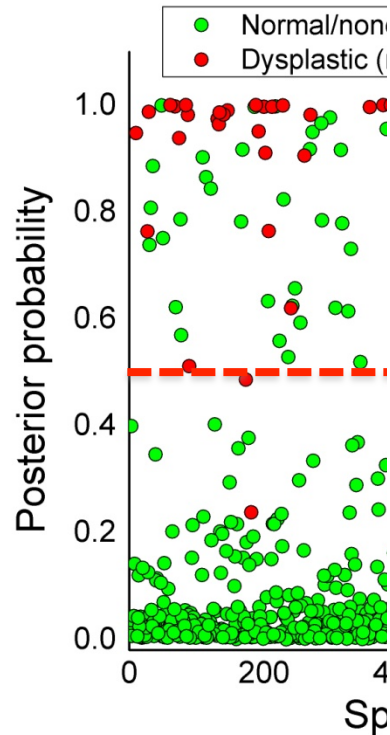
Real-time confocal Raman endoscopy for detecting dysplasia



Real-time confocal Raman endoscopy for detecting dysplasia

Sensitivity = 90.4%

Specificity = 90.9%



In vivo confocal Raman diagnosis in human patients

Biosensors and Bioelectronics 26 (2010) 383–389

Journal of Biomedical Optics 17(8), 081418 (August 2012)



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Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Real-time Raman spectroscopy for *in vivo*, online gastric cancer diagnosis during clinical endoscopic examination

Shiyamala Duraipandian,^a Mads Sylvest Bergholt,^a Wei Zheng,^a Khek Yu Ho,^b Ming Teh,^c Khay Guan Yeoh,^b Jimmy Bok Yan So,^d Asim Shabbir,^d and Zhiwei Huang^a

In vivo detection of epithelial neoplasia in the stomach using image-guided Raman endoscopy

- > 800 patients with esophageal, gastric, & colorectal lesions, cervix, head & neck, etc
- > 90% of diagnostic sensitivity and specificity
- >40 publications

Diagnosis of gastric cancer spectroscopy and classification techniques

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Abstract
Raman
technique
cancer
diagnosis
validation
effect
difference
lecter

Fiberoptic Confocal Raman Spectroscopy for Real-Time *In Vivo* Diagnosis of Dysplasia in Barrett's Esophagus

Mads Sylvest Bergholt,¹ Wei Zheng,¹ Khek Yu Ho,² Ming Teh,³ Khay Guan Yeoh,² Jimmy Bok Yan So,⁴ Asim Shabbir,⁴ and Zhiwei Huang¹

¹Optical Bioimaging Laboratory, Department of Biomedical Engineering, Faculty of Engineering, ²Department of Medicine, Yong Loo Lin School of Medicine, ³Department of Pathology, Yong Loo Lin School of Medicine, ⁴Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore

High-quality Raman spectra in the 800 to 1800 cm⁻¹ are acquired from gastric tissue with improved *in vivo* diagnosis of gastric cancer diagnostic sensitivity and specificity of the learning data and 95.7%; and the predictive sensitivity and specificity

Mads Sylvest Bergholt^a, Wei Zheng^a, Kan Lin^a, Khek Yu Ho^b, Ming Teh^c, Khay Guan Yeoh^b, Jimmy Bok Yan So^d, Zhiwei Huang^{a,*}

GASTROENTEROLOGY IN MOTION

Ralf Kiesslich and Thomas D. Wang, Section Editors

M. Teh, M.D.³
K. G. Yeoh, M.D.²
J. B. Y. So, M.D.⁴
Z. Huang, Ph.D.^{1*}

ics

te/bios

d Raman spectroscopy

Value



ASGE TECHNOLOGY COMMITTEE SYSTEMATIC REVIEW AND META-ANALYSIS



ASGE Technology Committee systematic review and meta-analysis
assessing the ASGE PIVI thresholds for adopting
real-time endoscopic assessment of the histology of
diminutive colorectal polyps

1) Functional diagnosis for real-time decision:

- Biopsy or not → Where?
- Resect or not → How ?



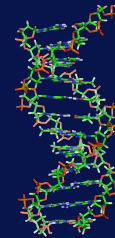
ASGE Technology Committee systematic review and meta-analysis
assessing the ASGE PIVI thresholds for adopting
real-time endoscopic assessment of the histology of
diminutive colorectal polyps **2015**

- For a “**diagnose-and-leave**” strategy for diminutive polyps predicted to be non-neoplastic based on optical biopsy, PIVI recommends that endoscopic diagnosis should provide a $\geq 90\%$ NPV for adenomatous histology
- For a “**resect-and-discard**” strategy for diminutive adenomas, PIVI recommends that endoscopic characterization of polyp histology by optical biopsy should provide a $\geq 90\%$ agreement in assignment of postpolypectomy surveillance intervals compared with decisions based on pathology assessment

IMPACT

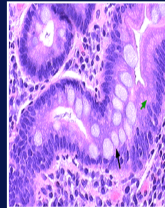
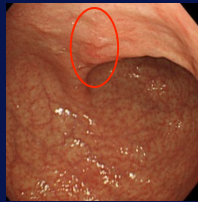
From subjective recognition to objective assessment

Objective



From training operator to training software

No learning curve - scaleable



0 Lag time

From days to instant



Summary

- Fiber-optic confocal Raman endoscopy realizes real-time, in vivo detection and diagnosis of gastric precancer and cancer with high accuracy, suggesting the potential to be a routine diagnostic tool for mass screening and surveillance of gastric patients at high risk.

Acknowledgements

Prof Ho Khek Yu, MD
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D Shiyamala, PhD
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Nursing staff and GCEP team

