Need for early, minimally invasive cancer diagnosis

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We have read the article in PNAS by Mittal et al. (1) and would like to congratulate the authors on an excellent piece of work demonstrating spectroscopy's capability for accurately subtyping epithelial cells and the tumor-associated microenvironment. Herein, we would like to add some insight and to comment on how this work could take the field forward.

In their recent paper, Mittal et al. (1) employ a high-definition Fourier transform infrared imaging method using a quantum cascade laser source for the characterization of a 100-case breast tissue set. This advancement has the potential to facilitate label-free molecular histopathology and bring spectroscopy one step closer to the clinic. Undoubtedly, this method would be of great benefit with regard to expediting the diagnostic workflow and in terms of saving the pathologist's and/or surgeon's precious time and reducing caseloads, in addition to providing high-quality data. Having said that, the most critical points with regard to patient benefit still remain unanswered: Could this technique be used for improving cancer patients' prognosis and survival? And could this method allow for an earlier, noninvasive diagnosis while there is still room for timely intervention and favorable outcomes (2, 3)?

For instance, the technological development of handheld spectroscopic devices and fiber optics has previously shown tremendous promise when it comes to characterization of cancer and could be used for in vivo diagnostics without the need for tissue resection (4–6). Recent studies have also shown the promise of biological fluids for minimally invasive and presymptomatic cancer detection (7–9). Different types of machine learning algorithms have been developed to interpret spectroscopic data (10), with the aim of detecting cancer. A major field will be the development of predictive algorithms to identify presymptomatic patients who are destined to develop the disease; this would allow earlier intervention.

The results presented in Mittal et al.'s (1) carefully conducted work are undeniably a progressive step toward an accurate and differential diagnosis; however, we also propose that further spectroscopic/clinical research should focus on the development of screening tools for an earlier and minimally invasive detection of cancer.

1 Mittal S, et al. (2018) Simultaneous cancer and tumor microenvironment subtyping using confocal infrared microscopy for all-digital molecular histopathology. *Proc Natl Acad Sci USA* 115:E5651–E5660.
2 Richards MA (2009) The national awareness and early diagnosis initiative in England: Assembling the evidence. *Br J Cancer* 101:S1–S4.
3 Hiom SC (2015) Diagnosing cancer earlier: Reviewing the evidence for improving cancer survival. *Br J Cancer* 112:S1–S5.
4 Mohs AM, et al. (2010) Hand-held spectroscopic device for in vivo and intraoperative tumor detection: Contrast enhancement, detection sensitivity, and tissue penetration. *Anal Chem* 82:9058–9065.
5 Wang W, Zhao J, Short M, Zeng H (2015) Real-time in vivo cancer diagnosis using Raman spectroscopy. *J Biophotonics* 8:527–545.
6 Mackanos MA, Contag CH (2010) Fiber-optic probes enable cancer detection with FTIR spectroscopy. *Trends Biotechnol* 28:317–323.
7 Baker MJ, et al. (2016) Developing and understanding biofluid vibrational spectroscopy: A critical review. *Chem Soc Rev* 45:1803–1818.
8 Shaw RA, Mantsch HH (2000) Infrared spectroscopy in clinical and diagnostic analysis. *Encyclopedia Anal Chem* 1:83–102.
9 Gajjar K, et al. (2013) Fourier-transform infrared spectroscopy coupled with a classification machine for the analysis of blood plasma or serum: A novel diagnostic approach for ovarian cancer. *Analyst* 138:3917–3926.
10 Goodacre R (2003) Explanatory analysis of spectroscopic data using machine learning of simple, interpretable rules. *Vib Spectrosc* 32:33–45.

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