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Optical Biopsies Can Transform Pathology

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Histopathology has long been the gold standard for disease diagnosis. Many of the processes date back to the late 1800s. Immunohistochemistry (IHC) evolved in the late 1900s, providing a means to target molecular receptors and cell or tissue features that were more specific to molecular subtypes of disease. Despite the historical significance and reliance on H&E and IHC histopathology, the processes by which we go about using these methods for diagnostic decision-making is both problematic and outdated.

Histopathology is time-intensive and labor-intensive. In the U.S. alone, more than 27,000 trained histotechnologists produce an estimated 40 million tissue blocks each year, resulting in more than 300 million microscope slides. The 15,000 pathologists that view these slides have years of training and experience, and they rely on pattern-matching, mental database searching skills and shared interpretation to make a subjective diagnosis. All of this requires tissue to be removed from a patient, with associated costs, effort, pain and anxiety.

The **biophotonics** dream of an optical biopsy promises a better way. Advances in microscopy with the generation of many new forms of image contrast, along with advances in artificial intelligence (AI), machine learning and computer-aided diagnosis algorithms, present a profound opportunity to realize this dream.

New label-based and label-free microscopy technologies have expanded the traditional set of contrast mechanisms. A wide range of molecular targets are accessible using fluorescent dyes and probes. Functional metabolic signatures based on three- and two-photon autofluorescence of nicotinamide adenine dinucleotide and flavin adenine dinucleotide are detected via nonlinear imaging. Fluorescence lifetime microscopy measurements of endogenous fluorophores reveal cell dynamics and cell death processes. Molecular vibrational signatures are extracted by coherent anti-Stokes Raman scattering or stimulated Raman scattering. Polarization-sensitive and elastographic measurements are possible, as are many other forms of optical contrast that carry signatures and diagnostic determinants for disease.

While new label-based methods will expand our armamentarium for ex vivo analysis of tissue

procedure.

The acceptance and adoption of digital pathology has been far slower than the pace of advances in optical microscopy. It is now possible for a pathologist to use a digital image of a scanned histology slide to make a diagnosis, but the glass histology slide must still be prepared. As a consequence, the time and labor required have been increased rather than reduced because of the addition of slide scanning, digital image data management and archiving. The digital image, however, should not be discounted. When combined with AI and machine learning, the next generation of automated detection and diagnosis methods will emerge.

AI and machine learning have only begun to permeate biomedical imaging and pathology. High-profile examples include the use of digital photos to detect and diagnose skin lesions for melanoma, eye fundus images for diabetic retinopathy, chest x-rays for lung nodules, and histology slides for micrometastases in lymph nodes. Sensitivity and specificity percentages are matching or even outperforming the expert-trained dermatologist, radiologist or pathologist.

AI provides a means to recognize patterns and features that the human eye and brain cannot. The more contrast mechanisms, features and data, the more accurate and reliable these methods will become.

New advances in light sources, imaging systems and multimodal optical contrasts will continue to widen the diagnostic capacity of digital pathology and machine learning. Instead of looking with our eyes, we need to turn that first look over to AI, which will do a far better and more objective job of finding the small and subtle molecular and structural changes that are telltale indicators of disease.

Tomorrow's optical biopsy will be done in real time, in vivo, without stains and without slides. Enormous volumes of digital image data will be generated. These will be fed into AI algorithms for automated analysis, ready sharing among pathologists and physicians, and centralized comparison to thousands if not millions of similar images backed by known diagnoses and patient outcomes. This will ultimately replace the glass slide and define a new gold standard that will not only rely on structural changes of disease, but also be sensitive to molecular and metabolic changes that will likely predate the structural changes.

In the future, will disease be diagnosed by the structural alterations it causes in cells and tissues? Will the molecular and metabolic signatures provide an earlier and more dynamic diagnostic assessment? Will genomic data interface more readily with digital molecular pathology or structural pathology? It is all possible. Collectively, the convergence of optical imaging hardware with AI software technologies will bring about profound changes in the way we visualize, detect

Meet the author

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