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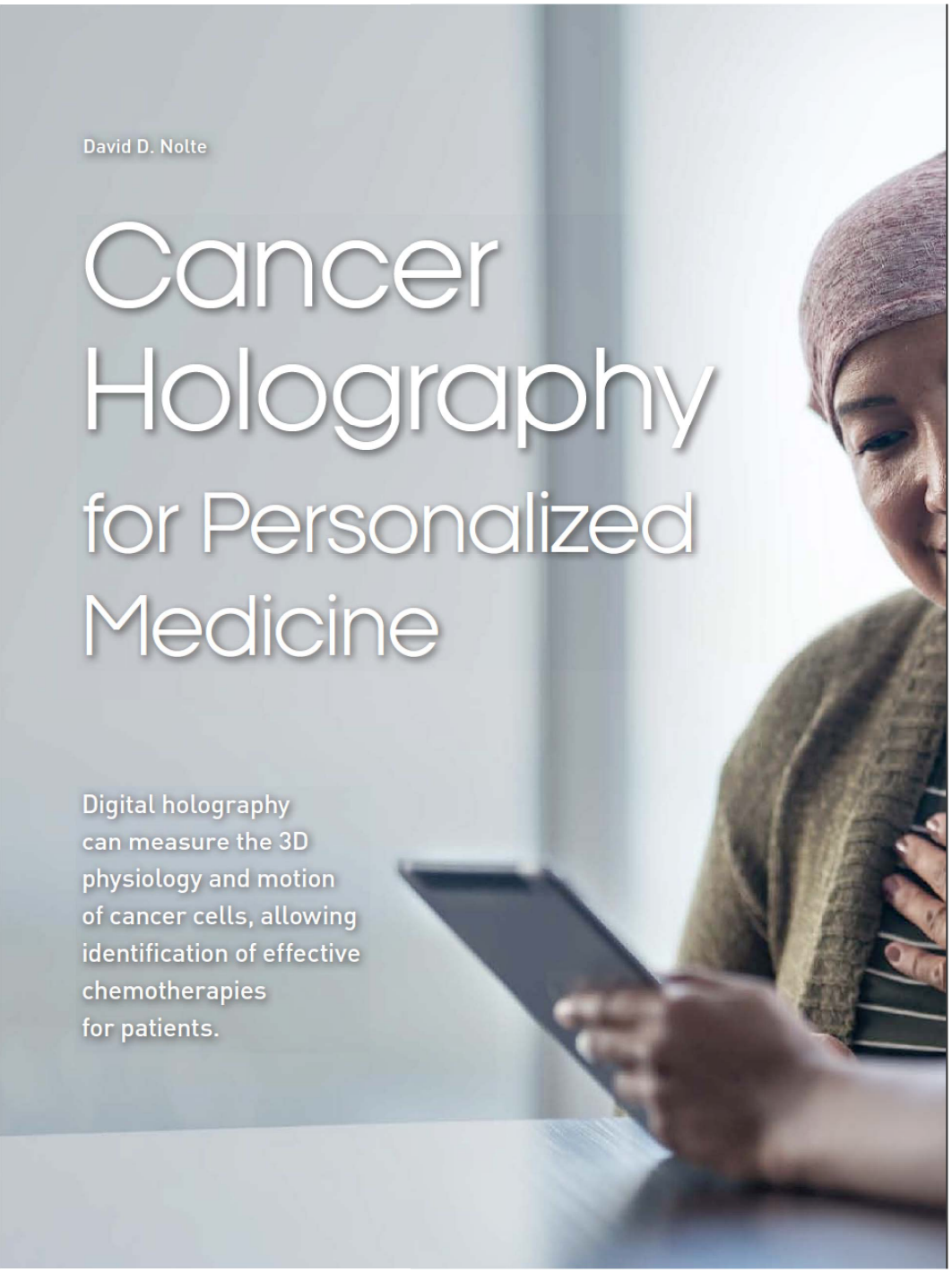
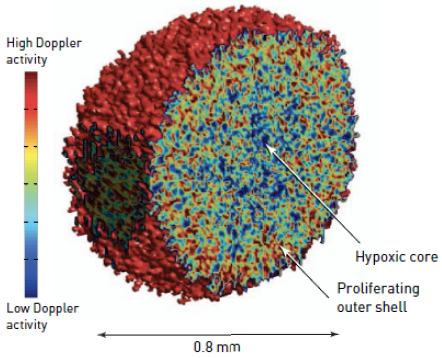
# Cancer Holography for Personalized Medicine



Digital holography can measure the 3D physiology and motion of cancer cells, allowing identification of effective chemotherapies for patients.

The overarching characteristic of animate matter is that it moves. Living systems move at all scales, including motions that run rampant within cells. And cancer, as a dynamic disease, is characterized fundamentally by altered states of that intracellular motion.

Detecting variations in slow intracellular movements—some as small as nanometers per second—is a technological challenge. In the past ten years, holography has helped to meet this challenge through digital holographic imaging techniques that include quantitative phase imaging (QPI) of isolated cancer cells; 3D tracking of cancer cells migrating through a biological matrix; and biodynamic imaging of biopsied cancer tissues to measure subtle changes in intracellular motions in response to anticancer drugs. These techniques draw on the partial coherence of light to map the 3D properties of cancer cells and tissues, and thereby to better understand the disease and care for patients.




A 3D reconstruction of a small living cancer tumor, acquired using low-coherence digital holography that performs laser ranging up to 1 mm deep into tissue, is color-coded for intracellular Doppler activity, displaying the high activity (red) of dividing cells and low activity (blue) in the low-oxygen core. Adapted from Z. Li et al., Appl. Opt. **60**, A222 (2021)

## Digital holography of cancer cells

Thin biological specimens are essentially transparent, with little light scattering. That makes it difficult to observe cells in high contrast, either in transmission or reflection, using conventional microscopy. Specimens do, however, significantly modify the phase of transmitted and reflected waves; these scattered fields are the basis of phase-contrast microscopy, which converts phase to amplitude by interference of scattered light fields with transmitted fields inside microscope optics.

Holography—invented by Denis Gabor as a method to correct aberrations in electron microscopy, and later translated to light imaging—similarly uses interference between scattered light and a reference field, and it has great flexibility in the manipulation and properties of the reference field. QPI, for instance, can use holographic interferometry to measure the refractive-index profiles inside isolated cells and to track changes in internal cell morphology and intracellular motion.

The holographic approach to QPI uses an off-axis reference wave to produce an interference fringe pattern on a digital light sensing array, such as a CCD or CMOS camera chip. The technique is called digital holography, as the hologram is recorded digitally and images are reconstructed using computational algorithms. Holograms are famous for providing partial 3D information about a target, but to achieve quantitative 3D performance requires that multiple holograms be acquired, either at successive depths inside a sample or via multiple illumination angles.

Used primarily in transmission, and on isolated cells or small groups of cells, QPI relies on translucent targets to modulate the phase of the transmitted field that interferes with the reference field. By numerically inverting the holograms from illumination at multiple angles, a full 3D quantitative map of the refractive-index variations inside a cancer cell can be reconstructed.

Holography is well-suited for 3D cell tracking of cell movement, such as metastatic cancer cell migration, through translucent 3D biological matrix samples. Biological matrices are composed of fibrous elements like collagen and are translucent, making them available for transmission studies. The 3D reconstruction capabilities of digital holography make it possible to track and measure cell-crawling behavior that can be related back to the biological and genetic characteristics of the cancer cell. For example, the generation of locomotion forces by a crawling cell, coupled to the elasticity of the matrix, creates local deformations that can be measured holographically in 3D, in addition to cell size, mass and morphology.

Migrating melanoma and breast cancer cells have been used to better understand how cancer cells migrate to new locations in the body to form metastatic cancer sites. In this cell-tracking application, digital holography can be performed with a wide field of view to allow many crawling cells to be tracked in 3D at the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