Cardiovascular diseases and cancer are the number one and two killers in the United States and in most parts of the world. Novel medical imaging technologies capable of quantifying relevant biomarkers nondestructively and in situ could assist in every stage of the clinical management of these diseases, from screening and early diagnosis, all the way to treatment selection, guidance and monitoring, as well as recurrence surveillance. In this seminar, we will provide a succinct overview of our current efforts to both develop and clinically validate quantitative optical image-guided clinical tools to enable precision medicine and ultimately improve the clinical management of cardiovascular and cancer patients. We will highlight current efforts toward improving: 1) the timely clinical detection of high-risk atherosclerotic plaques to prevent acute coronary events, 2) the early clinical detection of epithelial pre-cancer and cancer of the oral mucosa and skin, and 3) the intraoperative detection of surgical margins of malignant and invasive brain tumors.