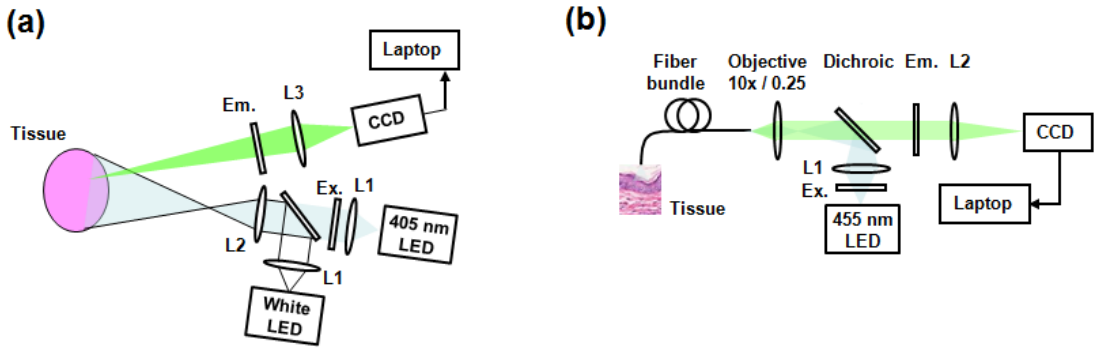
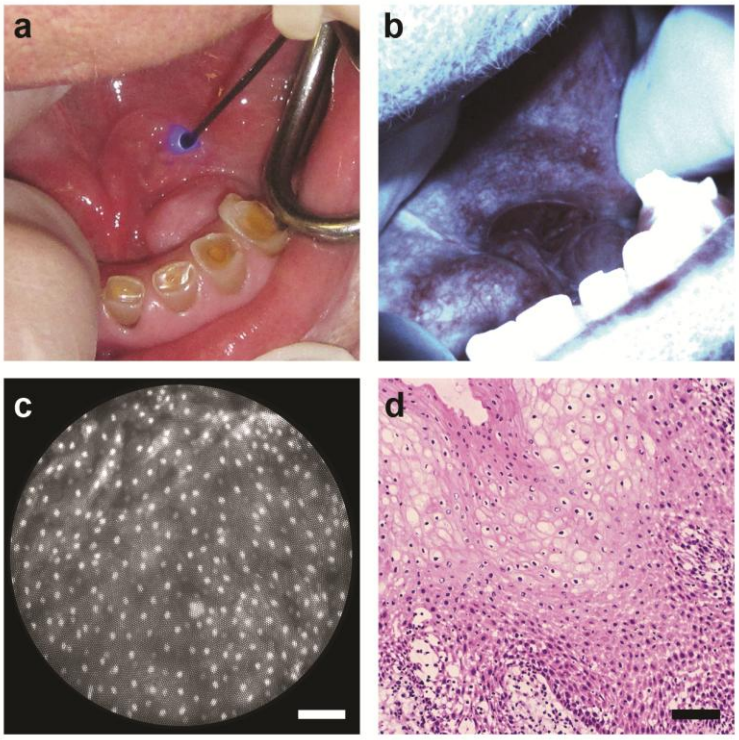
Supplementary Figure 1:



Schematic diagrams of the imaging systems used in this study. (a) The wide-field autofluorescence imaging system. Abbreviations: L1-3, lenses, Ex: Fluorescence excitation filter, Em: Fluorescence emission filter, LED: Light-emitting diode, CCD: Charge-coupled device (camera). The system images a 45 mm diameter field of view at a 250 mm working distance, with spatial resolution of 0.1 mm. A broad spectrum white light emitting diode (LED) is used for conventional illumination, with a separate 405 nm wavelength LED (Thorlabs M405L1) and 385-425 nm bandpass filter (Chroma HQ405/40X) for autofluorescence excitation. During AFI, a 435 nm long-pass filter (Omega XF3088) is additionally placed in the imaging path to reject scattered illumination light. Images were acquired by a compact color CCD camera (Point Grey Research, GRAS-14S5C-C) and transferred to a laptop computer for real-time video display at 10 frames per second. Recording of individual images was initiated by the camera operator, with acquisition of a pair of white-light / autofluorescence images completed in less than one second.

(b) The high-resolution microendoscope imaging system. This system operates as a compact, battery-powered fluorescence microscope, coupled to a flexible, 1 mm diameter fiber-optic imaging probe. LED illumination with a center wavelength of 455 nm is delivered from the HRME unit, through the imaging probe, to the tissue surface. Light returning from the tissue is transmitted through the same probe back to the HRME unit and imaged onto a CCD camera. Images are displayed on a laptop computer screen in real-time at 12 frames per second. The probe used in the current study provides a 720 μm diameter field-of-view with 4.4 μm spatial resolution. After imaging each patient, the fiber-optic probe was disinfected with Cidex OPA.

Supplementary Figure 2:



Multimodal imaging at the floor-of-mouth of a 73-year old female with a lesion on the floor-of-mouth, indicated in (a) by arrows. This site appeared "abnormal, high-risk" by clinical impression and autofluorescence imaging, but was found to be normal on high-resolution imaging and by histopathology. Autofluorescence imaging (b) revealed a distinct loss of fluorescence within the entire area of concern, which included the specific measurement site for this study (arrow). On placement of the high-resolution probe at this site, nuclei appeared small and evenly spaced throughout the field of view, consistent with normal epithelium (c). This appearance was uniformly observed on surveying the mucosa throughout the entire lesion with the high-resolution probe (data not shown). Histopathology from the site shown in panels (a-c) indicated normal epithelium, with hyperplasia and mild to moderate chronic inflammation (d). Following removal of the lesion, the entire surgical specimen was determined to be free of dysplasia or cancer by pathology. Scale bars represent 100 μm.