Ovarian cancer is the deadliest gynecologic malignancy and the fifth-leading cause of cancer deaths in women, responsible for approximately 14,000 deaths in the United States each year. Survival correlates strongly with stage at diagnosis: cases diagnosed in Stage I are associated with five-year survival rates exceeding 90%, whereas cases of advanced, metastatic disease have survival rates around 30%. Ovarian cancer is therefore a disease for which earlier detection may correlate directly into improved outcome for patients. The FDA-approved biomarker CA125 is used for monitoring response to treatment and reporting on disease recurrence in women undergoing therapy. CA125 is not considered a reliable reporter for population-wide screening of asymptomatic women. This talk will report on two ongoing efforts to improve the clinical utility of CA125. In one study, we use bottom-up proteomics to address the question of whether CA125 composition differs among individuals and whether individual-level differences can convey clinically useful information. In another effort, we are selecting single-stranded nucleic acid affinity probes (aptamers) that may complement—and ideally improve upon—the antibodies that form the basis of the test currently in clinical use.