ONLINE MATERIALS THAT ACCOMPANY CHAPTER 13

Box 1. Screening for cervical cancer

The incidence of cervical cancer has decreased by an estimated 70% in the U.S. over the past fifty years. This public health success is attributable to the implementation of cytology-based screening programs (Wright 2007). Specifically, women undergo regular screening for cervical cancer using the Pap smear.

A meta-analysis of the Pap test indicated a mean sensitivity of approximately 53%, with ranges from 49% - 57% (Cuzick, Clavel et al. 2006). That is, approximately half of women with cancer pre-cursor lesions will not test positive for further evaluation using the Pap smear. Because of this low sensitivity, it is recommended that women undergo Pap tests on a regular basis (e.g., annually in many countries). Because cervical cancers are most often slow-growing tumors, regular screening with the Pap test mitigates the high rate of false negatives on any one test.

Advances in our understanding of the natural history and etiology of cervical cancer have led to reevaluation of the role of the Pap test in cervical cancer prevention. Human papillomavirus is a necessary cause of cervical cancer; that is, HPV is present and a component cause in every case of cervical cancer (though HPV is not sufficient; that is, not all women with HPV will develop cervical cancer). Given the causal role of HPV in the development of cervical cancer and the availability of minimally invasive tests for the presence of specific high-risk strains of HPV, there has been substantial development in HPV testing as an adjust for screening along with the Pap (American Congress of Obstetricians and Gynecologists 2012).

When used alone (without the Pap test), the sensitivity of the HPV test is high (Mayrand, Duarte-Franco et al. 2007, Kotaniemi-Talonen, Anttila et al. 2008, Ronco, Giorgi-Rossi et al. 2008); specifically, review studies indicate a mean sensitivity of 89% (median=91, IQR 84 - 97) (Hawes and Kiviat 2007). The increased sensitivity of the HPV test indicates that, compared with the Pap, screening intervals can be lengthened for women who screen negative. However, this increased sensitivity comes with a price, which is reduced specificity. Specifically, many women with HPV will clear the infection to an undetectable stage with no intervention; thus there is a risk of over-treating women with HPV.

Because the Pap test has low sensitivity but high specificity, while the HPV test has high sensitivity but low specificity, current US screening guidelines recommend that women over 30 be tested with both the Pap and HPV tests simultaneously (American Congress of Obstetricians and Gynecologists 2012). Women over 21 but under 30 are advised to undergo regular (every three years) screening with the Pap alone. The reason for differing guidelines by age is that the rate of HPV infection is extremely high among women in young adulthood (current estimates suggest that more than 70% of women in will test positive for at least one strain of HPV during their young adulthood). These infections often clear rapidly, but the rate of false positive assessment and the rate of unnecessary diagnostic procedures with HPV as a screening tool for cervical cancer would be too high to justify its use among women in this age group.

Citations

American Congress of Obstetricians and Gynecologists (2012). "New Cervical Cancer Screening Recommendations from the U.S. Preventive Services Task Force and the American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology." https://www.acog.org/About_ACOG/Announcements/New_Cervical_Cancer_Screening_Recommendations

Cuzick, J., C. Clavel, K. U. Petry, C. J. Meijer, H. Hoyer, S. Ratnam, A. Szarewski, P. Birembaut, S. Kulasingam, P. Sasieni and T. Iftner (2006). "Overview of the European and North American studies on HPV testing in primary cervical cancer screening." Int J Cancer 119(5): 1095-1101.

Kotaniemi-Talonen, L., A. Anttila, N. Malila, J. Tarkkanen, P. Laurila, M. Hakama and P. Nieminen (2008). "Screening with a primary human papillomavirus test does not increase detection of cervical cancer and intraepithelial neoplasia 3." European Journal of Cancer 44(4): 565-571.

Hawes, S. E. and N. B. Kiviat (2007). Screening for cervical cancer. Sexually Transmitted Diseases. K. K. Holmes, F. P. Sparling, W. E. Stamm et al. New York, McGraw-Hill Professional: 1075-1104.

Mayrand, M.-H., E. Duarte-Franco, I. Rodrigues, S. D. Walter, J. Hanley, A. Ferenczy, S. Ratnam, F. Coutlee, E. L. Franco and G. the Canadian Cervical Cancer Screening Trial Study (2007). "Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer." N Engl J Med 357(16): 1579-1588.

Ronco, G., P. Giorgi-Rossi, F. Carozzi, M. Confortini, P. Dalla Palma, A. Del Mistro, A. Gillio-Tos, D. Minucci, C. Naldoni, R. Rizzolo, P. Schincaglia, R. Volante, M. Zappa, M. Zorzi, J. Cuzick and N. Segnan (2008). "Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test." J Natl Cancer Inst 100(7): 492-501.

Wright, T. C. (2007). "Cervical Cancer Screening in the 21st Century: Is it Time to Retire the PAP Smear?" Clinical Obstetrics and Gynecology.

Box 2. Two-stage screening

Screening for a health indicator of interest can be done in two stages. A two-stage approach is commonly used when there are two screening tests available and one is higher cost or more invasive, or when sensitivity and specificity differ between the two tests. In two-stage screening, we take all individuals who screened positive on the first test and then screen them with the second test. An example is given below.

We have two screening measures. The first, Test A, has 95% sensitivity and 95% specificity. The

second, Test B, has 85% sensitivity and 95% specificity. Let us determine how two-stage screening affects our ability to identify cases in this situation.

First, we use Test A, with the following results.

Box 2, Table 1. Results from Test A

	Diagnosis positive	Diagnosis negative	**Total**
Screen positive	950	170	1120
Screen negative	50	3500	3550
Total	1000	3670	4670

$$\text{Sensitivity: } \frac{950}{950+50} = 0.95 \text{ or } 95\%$$

$$\text{Specificity: } \frac{3500}{3500+170} = 0.95 \text{ or } 95\%$$

$$\text{PPV: } \frac{950}{950+170} = 0.85 \text{ or } 85\%$$

$$\text{NPV: } \frac{3500}{3500+50} = 0.99 \text{ or } 99\%$$

With a sensitivity of 95%, we would expect to miss 50 true cases of disease among 1,000 of those with disease. With a specificity of about 95%, we would expect about 170 false positives out of 3,670 individuals who are disease negative.

Now, only those who screened positive on the first test will be sent for the follow-up screening tests. Notice now that the totals of diseased and non-diseased for Test B equal the totals that screened positive on Test A. Test B has the following results.

Box 2, Table 2. Results from Test B

	Diagnosis positive	Diagnosis negative	**Total**
Screen positive	808	9	817
Screen negative	142	161	303
Total	950	170	1120

Those who screened positive in Test A

$$\text{Sensitivity: } \frac{808}{808+142} = 0.85 \text{ or } 85\%$$

$$\text{Specificity: } \frac{161}{161+9} = 0.95 \text{ or } 95\%$$

$$\text{PPV:}\frac{808}{808+9} = 0.99 \text{ or } 99\%$$

$$\text{NPV:}\frac{161}{161+142} = \ 0.53 \text{ or } 53\%$$

Using our second screening test, Test B, we obtain 85% sensitivity and 945% specificity, as shown above.

Now that we have our final results across two tests, let us summarize and evaluate the total sum of disease that we detected.

Among those with the disease (N=1,000), we will detect a total of 808 cases. Based on Test A we detected 950 potential cases, and of those 950, 808 were confirmed cases on Test B. So our total, or net, sensitivity is 808/1,000 = 0.81 or 81%.

Among those without the disease (N=3,670), we will detect a total of 3,661 disease-free individuals. Based on Test A, we confirmed 3,500 out of the 3,670 as disease free; the remaining 170 were re-evaluated in Test B. With Test B, 161 of the 170 were confirmed to be disease free. Thus, the total number of disease free individuals detected as disease free in our two tests is 3,500+161=3,661. Thus, the total, or net, specificity is 3,661/5,000=0.73 or 73%.

In summary, the net sensitivity and specificity of the two-stage testing is 81% and 73%, respectively. Note that net sensitivity is lower than either test alone – this is common in two-stage testing, because the individuals who are false negatives in Test A will not be re-evaluated at any time so do not have the opportunity for a correct placement at the second stage.