10.5 A Screening for Congenital Cytomegalovirus (CMV)

Some newborns acquire cytomegalovirus (CMV) from their mothers before birth. Congenital CMV can cause hearing loss and developmental delay (among other problems), and there is some evidence that treatment improves outcomes.[1] Boppana et al[2] tried screening newborns' dried blood spots (DBS) using a polymerase chain reaction (PCR) test. They reported that for a 2-primer DBS PCR test, specificity was 99.9%, positive predictive value was 91.7%, negative predictive value was 99.8% but the sensitivity was only 34.4%.

Here are their results:

		Congenital CMV D+	Congenital CMV D-	
2-Primer DBS PCR	Positive	11	1	**12**
	Negative	21	8985	**9006**
		32	**8986**	**9018**

Assume that this was a cross-sectional sample and the gold-standard determination of congenital CMV was valid.

One concern about screening for low prevalence conditions like congenital CMV is that even if the screening test has high specificity, the false positives will overwhelm the true positives, resulting in unnecessary follow-up testing and parental anxiety.

a) Based on the table above, what was the ratio of false-positives to true positives?

There were 1 false positive and 11 true positives, so the ratio was 1:11.

b) Based on this study, will this test lead to significant unnecessary follow-up testing and parental anxiety?

No. Only one false positive in 9000+ newborns.

Of course, the other problem is false negatives that might lead to false reassurance and failure to initiate treatment. Both the authors and the editorialist[3] recommended against screening using this test because it was not sufficiently sensitive.

c) Assume that newborns benefit from early diagnosis and that the cost of adding this test onto existing newborn screening is not significant. Additionally, assume that the alternative to using this screening test is not to screening. Do you agree that this sensitivity is too low to recommend screening? Why or why not?

If the cost of adding this test on all infants is insignificant, then for every ~10,000 babies screened, this test would result in early treatment of 11 CMV-infected babies in return for one false positive. If treatment is effective, this seems like a great deal. As long as it is clear that the test does not rule out CMV, it's hard to see how the 22 babies with false negative results are any worse off than they would have been without screening.

We think this is an example of false-negative confusion, as discussed in Chapter 2. This test has a positive predictive value of 11/12 = 91.7% and a negative predictive value of 8985/9006 = 99.77%. These are more clinically relevant than the sensitivity and specificity.

d. Now imagine that the reason for the false-negative PCR has become clear: there are two equally treatable types of CMV, which we'll call Types S and F. The DBS-PCR is 100% sensitive for Type S CMV, which makes up about 1/3 of CMV and 0% sensitive for Type F. So now we have a screening test with close to 100% sensitivity and 100% specificity, but it is for a less common disease (CMV Type S). How would the consequences of screening using the DBS-PCR test for CMV Type S differ from the screening studied by Boppanna et al and summarized in the table above?

The consequences would be the same, but we could claim we had a great screening test for CMV-Type S.

1. Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015;372(10):933-43.
2. Boppana SB, Ross SA, Novak Z, Shimamura M, Tolan RW, Jr., Palmer AL, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA. 2010;303(14):1375-82.
3. Bale JF, Jr. Screening newborns for congenital cytomegalovirus infection. JAMA. 2010;303(14):1425-6.

1. Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015;372(10):933-43.
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