An important first step in managing genital herpes is getting an accurate diagnosis. While that may seem like a simple concept, it can be more difficult than it appears. Even for many healthcare providers, knowing when to test, which test to use, and how to appropriately interpret test results can cause some confusion.

To help sort through and clarify some of the issues around herpes testing, The Helper spoke with a well-known expert on the subject, Rhoda Ashley Morrow, PhD, Professor of Laboratory Medicine at the University of Washington School of Medicine. Dr. Morrow has done extensive research in the area of herpes testing and offered her expertise and insight here on a subject that can be challenging to patients and providers alike.

**Which test is best?**

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Of course, there are some limitations for both viral culture and PCR. The latter, while highly sensitive, can be expensive and may not be easily available in all areas. With viral culture, accuracy is dependent upon timing. The best samples come from lesions that have not started to scab or crust over. Wait until the lesion has begun to heal, and the result may be a false negative. For those with recurrent lesions, one option offered by some specialty clinics is to take a swab test kit home and gather a sample yourself at the beginning of any symptoms. PCR, if available, is more sensitive than viral culture and transport conditions are not as critical for the accuracy of the test. So PCR is the preferred test for recurrent lesions, whether sampled by the patient or the clinician.

So while a patient experiencing typical lesions is a clear scenario for a PCR or culture test, many experience recurrent, less recognizable signs and symptoms. For these symptomatic patients, serology might be the answer. “I do feel that there is a clear role for serology to play in..."
the person who has recurrent, troubling symptoms,” says Dr. Morrow. “If you’re having itching or pain, or some kind of non-specific symptoms, I do think that serology can be very helpful in that scenario, since a positive culture may be difficult to obtain.”

But what about those without symptoms, who may have other reasons for getting tested? For those people, Dr. Morrow notes, “My first question is, are you clear on why you are getting this test? If you’re asymptomatic, and in a long-term monogamous partnership, why are you interested in herpes and should your partner be involved in this testing? If you have a new partner who wants to know your status, that’s legitimate. I think that both partners should be tested in that case.”

When these partners go in for a test, it is quite likely that they will be tested with one of the two most widely used tests available—the Focus ELISA (trade name HerpeSelect®) or the Trinity ELISA (trade name Captia™). These tests detect and measure IgG (Immunoglobulin G) antibodies and provide an index value—a number that is read to be positive or negative. But it often isn’t that simple.

“In general,” Dr. Morrow explains, “the more antibody you have the higher the index value.” Yet while this concept is relatively straightforward, the index number can cause a good deal of confusion. “People use the index value incorrectly in a couple of ways,” Morrow explains. “One is that they infer that a low index value means that infection has occurred recently. That’s not always true. We’ve shown that people with long term infections can have low index values.”

Just as there is no association between index values and the time and length of infection, neither is there an association between this value and recurrences. As Dr. Morrow states, “The second thing that people try to take out of index values is that a high index value means that I’m going to recur a lot. Or some people draw the opposite conclusion and think, ‘I have a high index value, therefore I have lots of antibody and I’m not going to recur very often.’ That’s not necessarily true either. Index values are not predictive of your natural history.”

The function of the index value is simply to indicate whether the test is positive or negative. “Index values are really only to tell whether you have detectable antibody or you don’t have detectable antibody, which leads to the third category of concern with index values, and that is, how high can it be before I can be completely confident that the test is really, truly positive. That’s the big question that people have.”
Stuck in the middle

Certain values are fairly clear cut, according to Dr. Morrow. “If you get an ELISA and an index value is reported to be over about 5 or under 0.9, you should believe the result.” Where questions come are with values in a low positive range. In this range, Dr. Morrow notes, there is some possibility for false negative as well as false positive results. While an index value that falls in this middle range is reported as a positive, and is indicated as such by test manufacturers, experience has shown there can be some room for question. As Dr. Morrow notes, “There’s some overlap, what lab people call ‘the gray zone,’ where there can be some uncertainty. With negatives, if enough time has passed from a possible infection to testing, we’re in good shape. With the higher positives, we’re in good shape. It’s the mid-range or gray zone that can give you problems.”

For those that have an index value that falls in a low positive range, between 0.9 and about 3.5, repeat or confirmatory testing is a reasonable option. Dr. Morrow summarizes the strategy she gives to people: “If, given all of your clinical and sexual history, and clinical presentation, you have reason to doubt a low positive test, your options include getting a confirmatory test.” For those looking for confirmation, there are three reasonably available and moderately expensive options that have data behind them to show they are useful: the Western Blot, Biokit Rapid assay, and the Focus recombinant inhibition HSV-2 ELISA (from Quest).

While confirmatory testing can clarify initially inconclusive results, Dr. Morrow cautions that the majority in the middle range are not falsely positive. “It’s good to remind people that most people who test in the gray zone confirm as positive.”

Another issue for people to consider is that of time. While some people will develop enough antibodies to be detected by a serologic test within a few weeks, others may take a few months. For those who have an inconclusive result, a repeat test in a month or two might provide a more clear answer. If the repeat test yields a positive result, it doesn’t necessarily indicate that the initial result was incorrect. As Dr. Morrow explains, “The values less than 0.9 are really quite accurate in those tests. If you come up with a negative, you really don’t have to re-test unless you have reason to feel you may have been recently infected. If you were recently infected, you may not have enough antibodies to show at that point.”

While people who have experienced signs or symptoms may not only accept but also expect a positive result, for asymptomatic patients, a positive may be more difficult to believe. The bottom line for those who question the result: retesting is an option. As Dr. Morrow
recommends, if your result is positive, “Do all the things you need to do to put your life around that and move ahead. If it’s a total shock, if you really need to have this confirmed, I think it’s actually worth the money to go get your blood drawn and repeat the test or ask for a second type of test if that’s available.”

While the type-specific IgG serologic tests available are highly sensitive, there always remains some room for error. This, Dr. Morrow explains, is not the fault of the tests or the laboratories but rather “the inevitability of any kind of serum test”

What about IgM?

One test you would not feel confident about, however, is an IgM test. This test looks for IgM antibody, the first antibody that appears after infection. While used to test for other viral infections, IgM testing for herpes has very limited utility. The rate of high positive IgM tests has been a concern. Lacking a good way to definitely identify an uninfected person, it is hard to determine the exact accuracy of these tests. As Dr. Morrow states, “I don’t recommend that people use them. They just aren’t accurate enough. There are a lot of reasons why…Nobody has really been able to make an excellent type-specific IgM test.”

So why are they ordered? Dr. Morrow explains: “Most often, physicians are used to ordering an IgM and an IgG together when diagnosing other infections. We know that IgM comes up early followed by IgG, and then in most viral infections, IgM wanes. So if a person is positive for IgM it means that they recently acquired that infection. But with herpes, IgM keeps re-appearing. About a third of people with recurrent HSV-2 outbreaks have IgG and also IgM.” The presence of IgM is not a good marker of recent infection in HSV infections.

Yet the persistence of IgM testing for herpes isn’t only due to providers following an established custom. Some patients may think IgM can provide additional information, as Morrow notes. “I think patients have a surprising amount of sophistication. They’ve gleaned from the Internet that IgM often means early viral infection. So if you’re afraid you’re infected and your IgG test is negative, you think ‘Well, an IgM test picks up earlier, so I want that one.’” However, another reason not to rely on IgM is that type-specific IgM tests are not available on the market.

In short, patients who look to IgM for answers to the questions of when they were infected will only be disappointed. “Nobody that I know has figured out how to use serology to definitively show who gave what to whom and—when that occurred,” explains Dr. Morrow.
Knowledge is power…and prevention
The test alone can’t necessarily provide all of the answers, and that’s where the help of a provider comes in. While direct-to-lab testing services have become more widely available, allowing patients direct access to testing and results without the intervention of a healthcare provider, this approach is not one Dr. Morrow advocates. “I’m not a fan, simply because there are just so many issues around herpes. Psychosocial, sexual history, it’s a complicated arena. Anyone who has herpes needs to be talking to a good practitioner,” she states. “I know other people feel really strongly that it’s a breakthrough. It may capture somebody who otherwise wouldn’t be diagnosed and for some people, that might be appropriate. On the other hand, I think there are a lot of arguments against it right now.” Specifically, she cites circumstances that would require specialized counseling, such as pregnancy, as well as issues around risks for HIV transmission or acquisition for those with genital herpes.

Providers can also certainly help patients understand and deal with results and address issues and questions that accompany diagnosis—including results that may be unexpected. “It’s actually very surprising how often people who think they have herpes don’t, and how often people who don’t think they have herpes do,” notes Dr. Morrow. In testing couples in the context of research studies, Dr. Morrow and her colleagues have found that, not only are people who have herpes unaware of their infection, but many who thought they were infected were in fact negative. In one large study, she notes, “we were surprised to find couples whose HSV-2 status was reversed from what they assumed. They came in because he thought he had it and she thought she didn’t, and it was the opposite.”

Examples such as this demonstrate how important an accurate test result can be, not only in the context of prognosis and treatment options, but for prevention as well. “You can imagine a scenario where you think you’re positive and your partner tests positive and ends up transmitting to you because you think you’re concordantly positive,” Dr. Morrow explains. Such a scenario highlights the role that testing—for both partners—can play in prevention.

Prevention. Treatment and management options. Prognosis. Peace of mind. There are so many reasons why an accurate diagnosis is so important. With the availability of highly accurate confirmatory tests, and the help of a good provider, there is no reason for you not to get a result you can feel confident about.

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