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Xpert at 8 years: where are we now, and what should we do next?

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IN DECEMBER 2010, the World Health Organization (WHO) endorsed Xpert[®] MTB/RIF (Cepheid, Sunnyvale, CA, USA) for the diagnosis of tuberculosis (TB).¹ Since then, Xpert has been widely scaled up, and the WHO now recommends that Xpert be used rather than sputum smear microscopy as the initial diagnostic test for TB in all adults and children.² However, even 8 years later the impact of Xpert, compared to smear, on patient outcomes remains uncertain.

In this episode of the *Journal*, Agizew et al. address this uncertainty with a systematic review of 13 published studies.³ They conclude that, relative to smear, Xpert reduces time to diagnosis and treatment while increasing the proportion of TB diagnoses with bacteriologic confirmation—but without a significant improvement in treatment outcomes among individuals with TB.

What should we make of this evidence, and what should we do next? On one hand, we should not adopt a diagnostic test simply because it is more sensitive—especially when smear is inexpensive and easy to implement. On the other hand, there are many reasons why we should continue to implement Xpert and to study that implementation process.

First, for a diagnostic test to improve patient outcomes, it must be integrated into a system that can effectively translate improved diagnosis into patient benefit.⁴ If health systems are so weak that many patients never receive their diagnostic test results, solutions should focus first on strengthening these systems, with a longer-term goal of implementing the best test available. In other words, the question should not be whether to implement Xpert, but when.

Second, Xpert may have substantial benefits for people without TB. For these patients, a more definitive negative result may speed diagnosis and treatment of an alternative condition. Indeed, Agizew et al. found that Xpert reduced empiric anti-tuberculosis treatment, suggesting that a test with a higher negative predictive value for TB may have ancillary benefits by reducing unnecessary treatment and focusing diagnostic attention on other conditions. Future studies should consider the impact of Xpert on outcomes in patients who present with TB symptoms but do not have TB.

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Third, it is challenging to demonstrate improved patient outcomes in controlled patient populations and research environments where negative outcomes are rare. To demonstrate the impact on patient outcomes, we may need to study individuals most at risk, such as human immunodeficiency virus-positive patients at an advanced clinical stage, using highly pragmatic designs that intentionally disrupt existing health systems as little as possible.⁵

In summary, after 8 years, we still lack convincing evidence that Xpert improves treatment outcomes in patients diagnosed with TB. However, we do have ample evidence of other important benefits for patients, such as reduced time-to-treatment and improved diagnostic certainty, and a clear research agenda. Specifically, we need to understand better when and how to implement Xpert in weak health systems, investigate the effect of Xpert-based diagnosis for symptomatic patients without TB, and perform highly pragmatic implementation trials in high-risk populations. In terms of implementing and evaluating Xpert (and other high-quality TB diagnostic tests), the next 8 years should be exciting ones indeed.

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