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Smear to GeneXpert: Reassessing Diagnostic Priorities in Tuberculosis Screening

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E D I T O R I A L

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Tuberculosis (TB) remains a leading cause of morbidity and mortality in low- and middle-income countries (LMICs), where socioeconomic barriers, densely populated settings, and limited health resources fuel continued transmission. Despite the advent of novel molecular diagnostics such as GeneXpert MTB/RIF and its derivatives, TB detection in many high-burden settings continues to confront significant challenges related to cost, infrastructure, and diagnostic yield [1]. As global health strategies evolve, there is increasing debate about the over-utilization of GeneXpert as a universal screening tool, and whether policy should shift back to emphasize more cost-effective methods such as smear microscopy, particularly where GeneXpert positivity rates are low among presumptive cases [2].

Acid-fast bacilli smear microscopy, primarily using Ziehl–Neelsen staining, historically served as the backbone of TB screening in resource-limited settings for decades due to its low cost, operational simplicity, and rapid turnaround time. While known to have limited sensitivity, particularly in paucibacillary disease and smear-negative patients, its role in identifying individuals with high bacterial loads often the most infectious has been foundational to TB control programs worldwide. In many developing countries, smear positivity correlates with advanced disease and higher transmission risk, making it a valuable triage tool for immediate initiation of treatment and infection control measures. Although technological advancements have introduced sophisticated diagnostics, AFB smear remains indispensable where laboratory infrastructure is constrained [1].

The introduction of the Xpert MTB/RIF assay marked a significant milestone in TB diagnostics, offering rapid molecular detection of *Mycobacterium tuberculosis* and rifampicin resistance within hours. Numerous studies highlight its superior sensitivity over microscopy, especially in smear-negative patients, and its capacity to detect drug resistance early in the disease course [3]. For example, GeneXpert can achieve sensitivity rates above 90% in some settings, compared to microscopy's approximately 70–75% sensitivity when culture is used as gold standard. In Pakistan and other high TB burden regions, local research has further confirmed GeneXpert's diagnostic strength. A cross-sectional study demonstrated that GeneXpert has high diagnostic accuracy in both smear-positive and smear-negative pulmonary TB, reinforcing its role in early and definitive diagnosis. Additionally, evaluations of GeneXpert MTB/XDR further extend this utility by estimating performance in detecting drug-resistant TB beyond rifampicin alone [4].

However, this performance advantage has come with unintended consequences. GeneXpert's molecular

detection characteristics mean it often identifies non-viable organisms or residual DNA, leading to possible false-positive interpretations in treated patients and overestimation of TB prevalence in large, unchecked screening campaigns. Furthermore, the assay's high per-test cost, equipment maintenance requirements, and need for stable power and climate-controlled environments place significant strain on health budgets in LMICs. The widespread adoption of GeneXpert as a universal screening tool among all TB suspects has led to diminishing positivity rates in many programs, raising concerns about cost-effectiveness. As resources are finite in LMICs, deploying expensive molecular diagnostics indiscriminately irrespective of pre-test probability can divert funds from other critical TB control activities, such as treatment support, contact tracing, and active case finding [5]. This over-reliance can also yield laboratory bottlenecks. With high numbers of GeneXpert tests requested for routine screening including many patients with low likelihood of TB turnaround times can be delayed, and laboratory capacity stretched thin. This paradoxically undermines one of GeneXpert's key strengths: rapid diagnosis.

The AFB smear microscopy, though less sensitive than GeneXpert, remains a critical, affordable screening tool with several advantages:

- *Cost-effectiveness:* Smear microscopy is significantly cheaper than GeneXpert, making it viable for high-volume screening in peripheral health centers where GeneXpert may be unavailable or overburdened.
- *Immediate Results:* Smear microscopy yields same-day results without the need for specialized reagents or uninterrupted electricity, making it ideal for rapid triage.
- *Public Health Relevance:* Smear positivity generally correlates with higher bacterial burden and increased transmission risk, making it highly relevant for infection control and prioritization.
- *Integration with Diagnostic Algorithms:* Combining smear microscopy with symptom screening, chest radiography, and selective GeneXpert use can improve diagnostic yield while conserving resources.

While molecular diagnostics enhance sensitivity, smear microscopy's specificity and simplicity justify its continued use as a frontline test, especially where GeneXpert utilization is financially unsustainable. Given these realities, global and national TB programs should consider policy recalibration that balances cost, access, and diagnostic yield. Possible approaches include:

- Targeted GeneXpert deployment; prioritizing its use for high-risk groups (e.g., HIV-co-infected individuals, retreatment cases, drug-resistant suspects), while reserving smear microscopy for initial screening in low-risk groups.
- Algorithm-based diagnostics; initiating evaluation with symptom screening and smear microscopy, followed by GeneXpert only when initial tests are inconclusive or in contexts where resistance detection is critical.
- Cost-benefit assessment; periodically reviewing national TB data to determine positivity rates and adjusting screening policies to ensure funds are optimized for maximal public health impact.
- Training and quality assurance; strengthening microscopy quality, ensuring slide reading proficiency, and embedding external quality assessment (EQA) programs to sustain dependable smear performance.

The fight against TB in developing countries must ground itself in evidence-based, context-appropriate diagnostics. While GeneXpert has revolutionized TB detection, its overuse as a blanket screening tool is not financially sustainable in many high-burden settings and can lead to an inflated perception of disease burden with limited added benefit for large swathes of presumptive cases. Re-emphasizing AFB smear microscopy within national screening algorithms not as a replacement for molecular diagnostics but as a strategic, cost-effective first-line tool can ensure broader access, improved resource allocation, and sustained public health impact. Policymakers should embrace hybrid diagnostic pathways that leverage the strengths of both technologies while safeguarding the viability of TB control programs in resource-limited environments.

Competing interests

The author declares no competing interests.

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