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Commentary

A promising whole-blood biomarker to aid Leprosy control

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Blood biomarkers can be useful in strategies to control leprosy, a neglected chronic infection that affects thousands of people in endemic countries. Early detection of leprosy is the cornerstone to providing timely treatment that interrupts *Mycobacterium leprae* (*M. leprae*) transmission and prevents physical disabilities and deformities. Years of life lost to disability by leprosy are calculated to be between 2 to 6 in 10,000 people, being highest in males than in females [1].

The onset and perception of signs and symptoms of leprosy may take several years while *M. leprae* replicates at large, especially in people who lack adequate cellular immune response, which is essential to suppress this obligate intracellular bacterium. Thus, the transmission chain persists without notice. Conversely, people with adequate immune response, show an imperceptible bacterial load and may have few uncharacteristic lesions, making it difficult to diagnose with the current available serological and molecular tests [2]. In the end, clinical and epidemiological diagnosis prevail in these cases, relying on the clinicians' experience. Hence, leprosy is a complex disease with a broad spectrum of clinical and immunologic features for which there is an urgent need for reliable tests for the prompt identification of cases in endemic countries.

In this context, Tió-Coma M *et al.* [3] report on a blood biomarker, the RISK4LEP signature that allowed identifying people affected by leprosy up to 5 years after enrolment among a large cohort of household contacts (HC) of people affected by leprosy. This is a comprehensive translational developmental study that integrated transcriptomic and genomic, with epidemiological and clinical parameters. The authors take the reader through the whole development process towards the final 4-gene signature (*MT-ND2, REX1BD, TPGS1*, and *UBC*), designated as RISK4LEP, that has acceptable sensitivity and specificity to predict the development of borderline leprosy in individuals at high risk of leprosy in Bangladesh. The model included internal validation using the set of genes selected from those with commercially available probes for reverse transcription quantitative-PCR.

The systematic study of the gene expression profiles obtained from the transcription of genetic material in the cell, through ribonucleic acid (RNA) sequencing and bioinformatic analysis is enhancing the development of new biomarkers for many diseases. Investigating the changes in expression patterns in response to pathogens, at the level of both the transcriptome and proteome, has helped us gain a deeper understanding of the host-pathogen relation and the disease processes [4]. We know that replication and disease progression depends on host cellular transcription and gene regulation in *M. leprae*-specific target cells. Both bacterial and host factors are implicated in this differential regulation [5,6]. Gene arrays and transcriptome analyses could shed light on why some infected individuals remain asymptomatic. A similar model such as presented by Tió-Coma *et al.* [3], could be used to search for blood biomarkers to predict the immune-inflammatory events known as leprosy reactions or nerve damage progression. These two complications reduce the patient's quality of life and can lead to disabilities, consequently, patients at risk would benefit from preventive intervention.

Under the operational plan of the Global Leprosy Strategy [7], HC and/or social contacts should be screened for leprosy shortly after the detection of the index case, and then, they are supposed to be screened annually for 5 years. However, contact surveillance for such a long period is challenging to the primary health service, and costly for the health system, especially in low resource areas. In addition, even though the infected exposed persons are expected to be at higher risk of leprosy, they may not evolve to have the disease [8]. Therefore, there is great potential in finding a predictive gene signature of leprosy in HC. It can allow identifying individuals that could benefit from the use of preventive measures and would help target a more specific intervention.

A major task is ensuring that promising biomarkers use technology and methods easily reproduced by other researchers and in different settings. Assays should ideally use platforms that can be easily transferred, or adapted, for use in the clinic and the field. The incorporation of gene signatures into clinical decision-making is a slow process and is limited in various aspects. Independent validation studies are critical to further evaluate the predictive accuracy and usefulness of the RISK4LEP signature in clinical practice, and provide the high-quality evidence needed of its predictive utility. It is important to notice that all incident cases developed indeterminate leprosy or forms from the tuberculoid spectrum of the disease. Although this

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type of leprosy is more frequently diagnosed in cohorts of HC [8], it is of greater interest to predict the development of the more severe and transmissible lepromatous forms of the disease. Therefore, prospective studies are needed to verify both the clinical validity and the utility in different settings and population samples to corroborate the predictive significance. We expect the test can achieve enough level of sample throughput and assay affordability to allow its transfer to point-of-care and incorporation to use under programmatic conditions.

Declaration of Competing Interest

The author has no conflicts of interest to disclose.

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