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### Authors' reply

Elif Hindié and colleagues ask about optimal radionuclides for use with prostate-specific membrane antigen (PSMA)-targeted approaches in the treatment of prostate cancer, and whether radionuclides other than lutetium-177 (<sup>177</sup>Lu) might deepen and extend the duration of responses. The TheraP trial<sup>1</sup> used [<sup>177</sup>Lu]Lu-PSMA-617, a radiolabelled small molecule that binds to PSMA to deliver beta particles resulting in double stranded DNA damage and subsequent cell death. Therapies using beta emissions require a relatively high number of particles to enter a cell to be effective. Other radionuclide therapies including alpha particles<sup>2</sup> or auger electrons need fewer particles for cell death and have a shorter path length. Whether these characteristics improve therapeutic responses is unknown. An advantage and disadvantage of <sup>177</sup>Lu is its relatively long path length of around 1 mm. This enables a so-called cluster bomb effect that kills adjacent cells, including

those with low PSMA-expression.<sup>3</sup> This effect could overcome intralesional tumour heterogeneity—a fundamental limitation of many therapies in oncology. Conversely, for microscopic residual disease, a 1 mm path length might not result in effective targeting of the smallest deposits. Radionuclides with shorter path lengths could be more effective in targeting microscopic disease at the cost of inferior targeting of adjacent low PSMA-expressing cells. This limitation might be overcome by using tandem radionuclides—ie, radionuclides that have multiple emissions,<sup>4</sup> or novel combinations with other effective systemic agents.

Ugo De Giorgi and colleagues ask whether PET imaging or genomic features of the tumour could enable better selection of men for [<sup>177</sup>Lu]Lu-PSMA-617 therapy. Although not reported in this initial publication of TheraP, all gallium-68-PSMA-11 and fluorine-18-fluorodeoxyglucose (<sup>18</sup>F-FDG) PET-CT imaging data and germline and multi-timepoint plasma samples were centrally collected. Analysis of these samples will enable us to define predictive and prognostic biomarkers. TheraP was one of the first studies that used quantitative PET parameters for patient selection. We hypothesise that PSMA intensity is predictive of response to [<sup>177</sup>Lu]Lu-PSMA-617, whereas tumour metabolic volume on <sup>18</sup>F-FDG PET-CT has prognostic value.<sup>5</sup> Depending on the outcomes, it might be possible to select patients most likely to benefit on the basis of molecular imaging and genomic alterations. In particular, identifying the subset of men least likely to have clinically meaningful responses to [<sup>177</sup>Lu]Lu-PSMA-617 would be of great clinical value. More broadly, given the expanding number of treatments for men with advanced prostate cancer, this might enable better personalised medicine, optimising sequencing of [<sup>177</sup>Lu]Lu-PSMA-617 relative to or in combination with other therapies.

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### Lung health in LMICs: tackling challenges ahead

We welcome Jamilah Meghji and colleagues' Review<sup>1</sup> about improving lung health in low-income and middle-income countries (LMICs), and we are particularly encouraged by the focus on the frequently neglected field of

chronic respiratory diseases. However, we find that insufficient attention was paid to the role of primary care, which is the keystone for universal health coverage and, therefore, the route to improved prevention, diagnosis, and individualised and holistic treatment for most of the population.<sup>2</sup> The interconnection between primary care and public health can address the social determinants of health and promote community participation, which are crucial to lung health across the lifecourse.<sup>3,4</sup>

Challenges to be addressed include inadequate investment in recruitment and reimbursement; education; status; and power in decision making processes,<sup>5</sup> as well as the limited respiratory prescribing rights of family doctors. The potential of primary care leadership is not considered. Nevertheless, primary care is essential for prioritisation at the individual patient level and the community level to manage all non-communicable diseases. Common risk factors such as air pollution, tobacco dependence, insufficient physical activity, and poverty affect the prevalence of all non-communicable diseases.

In situations where there is no family medicine strategy, the Practical Approach to Care Kit approach might be important; however, there is much more to be gained by promoting a service led by family medicine that is funded, implemented, evaluated, and endorsed by governments, academics, and disease specialists with the support of international research and advocacy organisations, such as the International Primary Care Respiratory Group. Without this vision, tackling respiratory diseases will remain challenging.

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Jamilah Meghji and colleagues<sup>1</sup> deliver a welcome wake-up call about chronic respiratory diseases in stretched health systems. However, the proposed solutions in their Review could be strengthened by a preventive approach addressing crucial contributors of chronic respiratory diseases. In short, we expected a stronger plea for clean air to improve lung health in low-income and middle-income countries (LMICs).

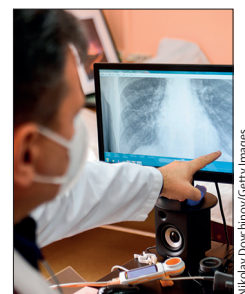
Although air pollution contributes substantially to the burden of

cardiorespiratory diseases in LMICs,<sup>2</sup> the Review barely evokes the high amounts of urban air pollution in LMICs<sup>3</sup> and the urgent need to reduce emissions from anthropogenic sources. Meghji and colleagues acknowledge the adverse effects of exposure to biomass smoke, but they temper these effects because of the limited success of clean stove trials. However, these largely unsuccessful trials do not imply that biomass smoke is harmless for the lungs.<sup>4</sup>

Furthermore, work-related chronic respiratory diseases received scant attention in the Review. “Occupational exposures” is mentioned just once and the terms work, dust, mining, and silicosis are absent.<sup>1</sup> Nevertheless, most commodities—including metals needed for modern technology—are extracted, sometimes by children, from mines in LMICs, often in extremely unhealthy conditions,<sup>5</sup> thus possibly leading to silicosis and increased likelihood of tuberculosis.<sup>6</sup> Lung-damaging exposures also occur in manufacturing, construction, agriculture, transport, street vending, or menial jobs across formal and informal sectors, contributing to various chronic respiratory diseases.<sup>7</sup> Putting work-related chronic respiratory diseases on the agenda will enhance awareness of this important field of pulmonology among policy makers and clinicians, many of whom are unfamiliar with occupational diseases. The rationale for including working conditions in strategies to improve lung health is that they are probably more amenable to prevention by regulatory measures than are those caused by poverty, inadequate health services, or general pollution.

In conclusion, we applaud the authors’ proposals to improve lung health, but we urge that consideration goes beyond medical solutions towards a global health approach. The respiratory community must advocate, together with patients and civil society, for the right to breathe clean air in homes, cities, and workplaces.

For more on the **Practical Approach to Care Kit** see <https://knowledge.translation.co.za/pack/>



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