EDITORIAL

Screening for Chronic Obstructive Pulmonary Disease
Unmet Needs and Future Considerations

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Chronic obstructive pulmonary disease (COPD) is a leading cause of treatable and preventable morbidity worldwide but often remains undiagnosed or incorrectly diagnosed, making it a condition for which screening could enhance disease recognition and diagnosis. Most COPD screening has focused on affluent countries,[1-3] with little or no attention given to enhancing COPD diagnosis in countries with fewer resources. Routine population-based spirometric screening in asymptomatic individuals has not been endorsed, but screening to identify symptomatic individuals at increased COPD risk may be appropriate.[2-5]

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The report by Siddharthan et al[6] in this issue of *JAMA* provides important information about general population COPD screening in 3 low- or middle-income country (LMIC) settings. This cross-sectional study of 10 709 adults in Nepal, Peru, and Uganda demonstrated substantial variation of spirometry-confirmed COPD prevalence in 3 communities in these regions (2.7% in Lima, Peru; 7.4% in Nakaseke, Uganda; and 18.1% in Bhaktapur, Nepal). Three previously developed screening tools (COPD in Low- and Middle-Income Countries Assessment [COLA-6],[7] COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk [CAPTURE],[8] and Lung Function Questionnaire [LFQ]) exhibited similar operating characteristics (area under the receiver operating characteristic curve [AUC], 0.717-0.791), and time to administer (mean, 7.6 minutes with 99.5% complete data).

Among the 1003 participants with screen-identified and research spirometry–confirmed COPD, 95.3% were previously undiagnosed and 16.4% had severe or very severe airflow obstruction. The diagnostic accuracy of the instruments was greater (weighted AUC, 0.742-0.895) among individuals with more symptoms (higher scores for the COPD Assessment Test and Modified Medical Research Council Dyspnea Scale), greater risk of exacerbation, or both, representing those most likely to have the greatest benefit from therapeutic interventions. The study also highlights important unaddressed considerations for the global expansion of COPD screening.

Screening tools identify individuals at high risk of having a given health condition and appropriate for further evaluation and diagnosis. When screening tools are developed, sensitivity and specificity are assessed, with the tool "optimized" by adjusting content (questions, tests) and scoring to achieve the appropriate balance of sensitivity and specificity for the target condition and setting. Higher sensitivity ensures that fewer people with the condition are missed but increases the number of false-positive results. The influence and implications of high sensitivity and therefore more false-positive results will vary by condition and region of the world. Missing the time-sensitive diagnosis of a curable condition is clearly undesirable. However, the implications of high sensitivity for a resource-limited region where higher false-positive rates may require more resources than are available must be considered. Siddharthan et al[6] report the frequency of false-positive results in the 3 LMIC regions studied. In resource-challenged or LMIC regions, these numbers of false-positive results are important because each requires spirometry evaluation to confirm or negate the screening results. Spirometry requires equipment, experienced staff, and bronchodilators; these resources may not be available locally or even regionally.

The social, emotional, and economic effects of false-positive test results on patients and families must also be addressed.[9] Assessments will need to include the possible concern, fear, or stigma[10] associated with a positive (including false-positive) test result and the economic costs for the patient and community. These considerations highlight the need for careful decision-making regarding the selection of threshold values for "positive" test results, including the idea of equalizing sensitivity and specificity and the potential influence on the rate of false-positive results.

Several tools are available for COPD screening.[5] How and where the tools were developed likely influence content and will need to be a consideration in selecting tools that can be tailored for specific regions.[2,7,8,11] Knowing the COPD risk factors and perhaps the sex-specific risk factors for a region may be important in the selection of specific screening tools. Siddharthan et al[6] did not describe an assessment of potential sex differences in screening results, but this may be an important factor based on the regions where women may be more likely to have greater biomass fuel exposure or on regions where primarily men smoke. The LFQ relies heavily on smoking and age.[11] The COLA-6 adds a question about biomass fuel that is not used in the other screening tools and includes questions about hospitalization, where hospitals may be not be equally available in all health care systems.[7] Candidate content for CAPTURE was based on data from the literature, prospective qualitative data from the target population in the US, and quantitative data from a US sample.[8] Some of these differences may explain the variations in AUC of the tools in the 3 study regions.[6]

The findings of Siddharthan et al[6] suggest that different tools are likely to variably affect resource use. Resource utilization will be influenced by the number, length, and complexity of questions in the tools; administration setting(s); ease of

scoring; and action steps. Short single-focus questions are likely easier to answer and translate to other languages. For example, compare "How often do you cough up mucus" (a single-domain question)[11] with "Have you brought up phlegm from your chest on most day or nights of the week during at least 3 months in a row in at least 2 years in a row?" (a question with stacked domains for mucus, days, months, and years).[7] Results by Siddharthan et al[6] support findings from previous studies that suggested that the addition of a peak flow assessment improves test specificity, at a cost of greater resource use (time, materials, complexity),[8] suggesting that a stepwise screening process, with peak flow measurement only for some groups, may be an option in resource-limited environments.

In LMIC regions COPD diagnostic confirmation with spirometry assessment is often not readily available. It is possible that in such regions "screening" tests could become the equivalent of a "diagnostic" test for COPD. The data reported by Siddharthan et al[6] help focus this concern. If a COPD screening test becomes a default diagnostic test, all persons with false-positive results would be considered to have COPD, and the limited resources for caring for people with COPD would be disproportionally given to the higher number of those with false-positive "COPD" compared with true-positive results. Introducing screening in any region must take this potential outcome into account, along with consideration of the implications for individuals with false-negative results.

Concerns about false-negative results are often dismissed by assuming that these individuals will likely be identified in repeat screening episodes.[6] The assumptions that future screening will occur and what it will entail are seldom addressed with any evidence basis. When rescreening a population, the target cases are not the prevalent "missed cases" identified during initial screening events but rather are primarily incident cases and potentially the false-negative prevalent cases. In most regions of the world, incident rates are much lower than the COPD missed prevalent case rates targeted in initial screening. Thus, the positive predictive value and negative predictive value must be reassessed along with resource use or costs per case identified in rescreening and are important aims for future translational studies.

A key question that remains unanswered is the feasibility and ultimate effects on patient and health care outcomes of implementing large-scale screening approaches across populations and health care systems.[3] Prior work with targeted case finding has been encouraging,[12] with questions raised as to its overall clinical benefit.[13] The GECo (Global Excellence in COPD Outcomes) investigators have proposed a next phase, testing a self-care approach that includes COPD education, facilitated self-management action plans for COPD exacerbations, and monthly visits by community health workers for newly diagnosed patients identified using one of this study's screening strategies and confirmed by spirometry.[14] In countries with low health care resources, self-care may be an important part of COPD management, but first it is necessary to understand if implementing screening can result in necessary COPD diagnostic evaluations that are feasible and acceptable in the community. A comprehensive approach to COPD screening validation includes region-specific adjustments to existing local systems as well as assessment of acceptability to patients and clinicians.[15] An important step in the validation process will be testing the ability of screening and diagnostic confirmation to occur and be adapted to using local health care staff rather than research staff.

The results of the study by Siddharthan et al[6] in this issue of *JAMA* represent a crucial step in the development of feasible COPD screening programs in LMIC regions. Next steps will include understanding and communicating patient- and society-level risks and benefits; developing and testing an effective and efficient locally based and administered screening procedure that reflects country-specific needs, risk factors, and action steps; ensuring commitment of the health care system and clinical staff; and engaging the patient community by raising awareness of undiagnosed COPD and the importance of prevention and treatment. As with most published research, Siddharthan et al have identified meaningful problems, opportunities, and issues for future studies.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Yawn reported serving on COPD-related advisory boards for GlaxoSmithKline, Boerhinger Ingelheim, AstraZeneca, TEVA, and Novartis; receiving grants from GlaxoSmithKline and the National Heart, Lung, and Blood Institute (NHLBI); and formerly serving as chief clinical officer for the COPD Foundation. Dr Leidy reported that her employer, Evidera, received funding to support the development of the CAPTURE instrument. Dr Martinez reported receiving grants from NHLBI, Chiesi, and Sanofi/Regeneron; receiving personal fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Gala, GlaxoSmithKline, Novartis, Polarean, Sunovion, Teva, and Theravance/Viatris; receiving consulting fees from Pulmatrix, Pulmonx, Verona, Bristol Myers Squibb, Bridge Biotherapeutics, CSL Behring, Genentech, IQVIA, Sanofi, Shionogi, XAR, and Zambon; serving on a adjudication committee for Medtronic; serving on steering committees for Afferent/Merck and Bayer; serving on an advisory board and data and safety monitoring board (DSMB) for Boehringer Ingelheim; serving on a steering committee and DSMB for Biogen; serving as consultant and steering committee member for DevPro; serving on steering committees for Nitto, Patara/Respivant, ProMedior, and Veracyte; and receiving presenting fees from United Therapeutics.

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