Editorial

The necessity of having asthma predictive scores in children

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Which infants and preschoolers with recurrent wheezing will have asthma once they have reached school age? This question is very important because asthma is one of the most prevalent chronic diseases in children; however, it is also one of the most difficult disorders for physicians to diagnose in infants and preschoolers. Approximately 40% of all young children worldwide have at least 1 episode of asthma symptoms, such as wheezing, coughing, or dyspnea.[1,2] Moreover, approximately 80% of asthmatic patients have the disease in the first years of life.[3] Fortunately, only 30% of preschoolers with recurrent wheezing still have asthma at age 6 years.[4]

In this issue of the *Journal*, Hafkamp-de Groen et al[5] present information for validating (discrimination and calibration) and updating (or improving) the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) risk score for predicting asthma at 6 years of age. The authors studied 2877 preschoolers with asthma-like symptoms in Generation R (a multiethnic prospective population based cohort in The Netherlands) and used the PIAMA risk score (a score developed in the PIAMA study, a prospective cohort of 3963 children followed from birth to 7-8 years of age in The Netherlands). The original PIAMA risk score has 8 predictors: male sex, postterm delivery, parental education, parental inhaled medication, wheezing/dyspnea apart from colds, wheezing frequency, presence of respiratory tract infection, doctor's diagnosis of eczema (ever), and presence of eczematous rash. The study reported that the discriminative ability of the original PIAMA risk score to predict asthma in Generation R was moderate and similar compared with that in the PIAMA cohort (concordance index = 0.74 vs 0.71). No differences in discriminative ability were found between different ages and ethnic and socioeconomic subgroups. For improving the score, the authors included preterm birth instead of the predictor postterm delivery and replaced parental inhalation medication for parental asthma. This updated PIAMA risk score had a slightly higher concordance index, sensitivity, and negative predictive value [NPV] versus the original risk score (0.75 vs 0.71, 64% vs 57%, and 97% vs 94%, respectively), but lower specificity and positive predictive value (PPV; 74% vs 76% and 12% vs 23%, respectively). The positive and negative likelihood ratios (LRs) were similar (2.4 vs 2.5 and 0.5 vs 0.5, respectively). The authors concluded that the PIAMA risk score had good external validity and called for the necessity to reproduce the predictive performance of the updated PIAMA risk score in other populations and settings and to assess its clinical relevance.

For developing diagnostic or prognostic prediction rules, the readers need to be aware that 3 steps are necessary. These steps include validity assessment, updating (if necessary), and impact assessment of clinical prediction rules. In general, 3 types of validation of previously developed prediction rules can be distinguished: temporal, geographic, and domain validations. In case of poor validation, the validation data can be used to update or adjust the previously developed prediction rule to the new circumstances. These updated methods differ in extensiveness, with the easiest method being a change in model intercept to the outcome occurrence at hand. Prediction rules with or without updating and showing good performance in (various) validation studies might subsequently be subjected to an impact study to demonstrate whether they change physicians' decisions, improve clinically relevant process parameters and patient outcomes, or reduce costs. Finally, whether a prediction rule is implemented successfully in clinical practice depends on several potential barriers to the use of the rule.[6]

The PIAMA risk score,[7] which was published in 2009, is one of the 3 published predictive scores for assessing developing asthma in children. The other 2 scores are the Asthma Predictive Index (API), which was described in 2000 in Tucson,[8] and the Isle Wight score,[9] which was described in 2003 in the United Kingdom. These 3 asthma indices are based on diverse variables, and that condition could make a difference as to which index would have more success in different populations worldwide. The API requires as an entry criterion recurrent episodes of wheezing during the first 3 years of life and had 5 parameters (major criteria: physician-diagnosed eczema or parental asthma; minor criteria: physician's diagnosis of allergic rhinitis, wheezing without colds, or peripheral eosinophilia >4%),[8] whereas the Isle of Wight score had 4 criteria (family history of asthma, recurrent chest infections in the second year of life, atopic sensitization at 4 years of age, and absence of recurrent nasal symptoms in the first year of life).[9] The API and Isle of Wight scores, in contrast to the PIAMA risk score, do not include environmental or socioeconomic information that can vary between populations, and thus their inclusion might reduce the generalizability of the tool.

These 3 indices varied in their statistical characteristics, such as sensitivity, specificity, PPV, and NPV. It is important to remember that sensitivity and specificity provide a population perspective that often exaggerates the diagnosis and certainty of the test. This is overcome by the use of the PPV and NPV, but these are influenced by the prevalence of asthma in the population studied. The stringent API score has the best combination of sensitivity

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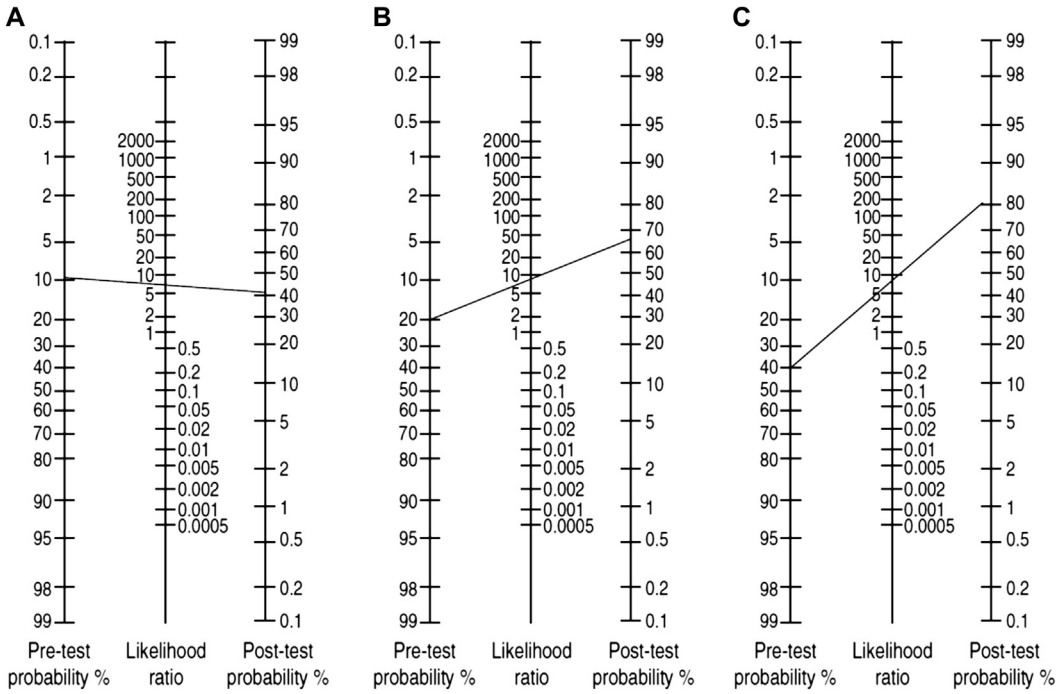

FIG 1. Application of the API at the LR (ie, 7.3) in hypothetical differing scenarios with populations at low **(A)**, moderate **(B)**, or high **(C)** risk of having asthma at school age.

(although it is low at 22%), specificity (97%), PPV (77%), and NPV (90%) of the indices compared. Another way to set cutoff points for diagnostic tests is through analysis of receiver operating characteristic curves. Only the PIAMA index includes this type of analysis in determination of the predictive score; determination of API scores does not require it.

Yet another approach to analyze the results (categorical or continuous) of a diagnostic test is to determine the LR, which is more relevant in clinical practice. The stringent API and the Isle of Wight index scores have the best positive LRs (7.3 and 7.9, respectively) and are good enough to apply in the general population and useful to certify the diagnosis of asthma.[10] This is justified by the fact that when a child goes to a clinic for recurrent wheezing episodes, the use of the API score increases the probability of a prediction of asthma by 4, 3, or 2 times (the pretest probability of asthma moves from 10% to 42%, from 20% to 62%, or from 40% to 80%, respectively; Fig 1).[11]

However, among these 3 indices, only the API score and the PIAMA risk score were validated in different populations. A small study conducted in a different scenario (ie, 130 preschoolers with recurrent wheezing who came to a tertiary outpatient clinic in Colombia)[12] was carried out to evaluate the discriminative properties of the API and PIAMA risk scores for diagnosis of asthma at 5 to 6 years of age. Both indices had similar results in terms of sensitivity, specificity, PPV, and NPV with respect to their developed original studies: 43%, 79%, 38%, and 83%, respectively, for the stringent API score and 55%, 79%, 75%, and 60%, respectively, for the PIAMA score. Leonardi et al[13] reported that the validation of the API to predictive asthma at age 6 to 7 years in 1954 children from the Leicester Respiratory Cohort (United Kingdom) was comparable with the Tucson Children's Respiratory Study, supporting the generalizability of the API score to other settings. The stringent API in the Tucson and Leicester cohorts had similar sensitivity (28% and 37%), specificity (96% and 93%), PPV (40% and 48%), and NPV (93% and 92%). The discrimination assessed by using the concordance index was moderate (0.62 and 0.65, respectively), and the overall predictive performance for the stringent API in the Leicester Respiratory Cohort was low (scaled Brier score, 16%). However, it is important to mention that for this API validation, the authors did not use the original API because they replaced 1 objective minor criterion (peripheral eosinophilia >4%) with a "surrogate" of wheeze or cough triggered by food at age 2 years. Also, the authors compared the API score with simpler prediction rules based on early frequency of wheeze, but the simpler rules had even lower overall predictive performance (scaled Brier score, 9%). However, the authors still state that "a simple question about frequency of preschool wheeze predicts asthma at school age with accuracy comparable to the API and might thus be preferable." Curiously, the same group[14] recently published a study with 1226 children from the Leicester Respiratory Cohort reporting a new tool for predictive asthma at 5 years of age using 10 predictors (sex, age, wheeze without colds, wheeze frequency, activity disturbances, shortness of breath, exercise-related and aeroallergen-related wheeze/cough, eczema, and parental history of asthma/bronchitis). The scaled Brier scores for the internally validated model and tool were 20% and 16%, respectively. For a score cutoff of 5 or greater, sensitivity was 72%, specificity was 71%, PPV was 49%, NPV was 86%, positive LR was 2.5%, and negative LR was 0.4%. Therefore, we can conclude that the stringent API still has the best positive LR to be successfully implemented in clinical practice.

Therefore, because no accurate screening tests[15] (using genetic or single biochemical markers) have been developed yet to determine which young children with recurrent wheezing will have asthma at school age, our diagnosis should be based on clinical predictive scores.

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