UK screening programme is the diversity of the population. In the UK about 4% of children diagnosed with CF are non-Caucasian in origin. A DNA panel comprising the most common 31 CF mutations will detect 97% of mutations in a Caucasian population, but only just over 65% of mutations in a non-Caucasian population. The gene frequency of $\Delta F508$ in the UK Indian subcontinent CF population is less than half that in the UK Caucasian CF population.⁶ Thus a three stage IRT-DNA-IRT protocol is likely to increase the chances of detecting CF in non-Caucasian infants. The main disadvantages of IRT-DNA-IRT are its complexity and the anxiety generated for families who have to wait for the result of a second IRT. Babies with one mutation and a normal second IRT still carry a small risk of having CF. The precise "unexpected false negative rate" and the true value of a second IRT using the

IRT-DNA-IRT approach in the UK, can only be determined by careful prospective monitoring.

There is no "ideal" protocol for CF screening and variations will be influenced by local circumstances. A recent study from France suggests that it may yet be possible to screen with acceptable sensitivity and specificity without the use of genetic tests.⁷ As screening becomes more widespread, each new screening programme should be monitored carefully and reviewed. The meticulous recording of data over many years in New South Wales sets an excellent example.

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Diagnosis

Can we predict vesicoureteric reflux?

J H Baumer

Commentary on the paper by Leroy *et al* (see page 241)

Many children are investigated for vesicoureteric reflux (VUR) following a urinary tract infection (UTI), but the imaging technique of a voiding cystourethrogram (VCUG) is unpleasant for the child and not without risk. A clinical scoring system capable of confidently predicting VUR would therefore be an attractive alternative approach.

The original study by Oosterbrink and colleagues¹ seemed to suggest that a score derived from the combination of clinical factors (age, sex, and positive family history), ultrasound findings and C reactive protein (CRP) result could predict the presence of VUR with high sensitivity, albeit with rather low specificity. A diagnostic test with 100% sensitivity can be useful in ruling out a condition when it is negative, even when it has low specificity (that is, cannot be relied upon when positive). This has been referred to as a "SnNout" (when a test has a high Sensitivity, a Negative result rules out the diagnosis).² However, the lower the specificity, the smaller would be the expected proportion of children without reflux

who have a negative result, and thereby avoid an unnecessary imaging investigation. A negative result, excluding VUR, was seen in 17% of children without VUR in Oosterbrink's series.

Leroy and colleagues³ are to be commended on repeating the work of Oosterbrink. When a group of patients is used to develop a diagnostic test, the performance of that test tends to be overestimated. This is particularly true when the test is composed of a number of elements, and when continuous variables (such as age, CRP) are categorised and weighted in such a way as to produce the best discrimination. A second, validation study should therefore be conducted in an independent group of patients.

Leroy *et al* found a lower specificity (3% versus 17%) for all grades of VUR using a threshold score of 0, and lower sensitivity (93% versus 100%) and specificity (13% versus 38%) for grade 3 to 5 VUR using a threshold score of 5. With a second study showing a less good performance from the decision rule, what are we to conclude? The first question is how well the second study

was conducted. A key issue is whether an independent reference or "gold standard" test was applied blind to all patients (that is, whether those interpreting the gold standard test did so unaware of the result of the clinical decision rule and vice versa). In this case the reference test was the VCUG, with the radiologist reporting the VCUG being unaware of the VUR risk score. It is not clear whether all the components of the VUR score were obtained blind to the VCUG result. The CRP result and age and gender are objective measures, and as long as the family history was obtained before the parents knew the VCUG result, these were all very unlikely to have been influenced by the latter. If the ultrasound examinations were sometimes conducted after the VCUG, however, knowledge of the latter could have influenced the interpretation of the former.

Another issue is what proportion of eligible children had all necessary information available. Ten children who did not have a VCUG performed were excluded from the study. A further six children with inadequate clinical information were excluded from analysis. All other children had both the relevant clinical information and test results available. This is a relatively small proportion (around 10%) with missing information.

The study therefore appears to have been conducted satisfactorily, apart from the one or two uncertainties about the independence of the tests. If the tests were not performed fully independently, the study could be expected to

have overestimated the performance of the decision rule.

The second question is whether the children were similar in both studies and representative of children likely to be seen in clinical practice. This largely appears to be the case, although the rate of grade 3 to 5 VUR was approximately double in the Oostenbrink population. We can therefore conclude that with a few reservations the study appears to be valid and relevant to children presenting with a febrile UTI.

The performance of this clinical decision rule can be illustrated by considering a child similar to those in this study, who has had a febrile urinary tract infection. Before even applying the decision rule, we can anticipate that the child will have a 1 in 4 (25%) risk of having vesicoureteric reflux, as this is the expected frequency. Using Bayes' theorem we can calculate the likelihood ratios, both for a positive and negative result from the clinical decision rule, based on its sensitivity and specificity. The likelihood ratio for a (positive) score above "0" is 1.03 (based on a sensitivity of 100% but specificity of only 3%). This results in the probability of reflux after applying the decision rule changing from 25% to 25.6%, hardly clinically helpful! This probability only increases to 29% using the sensitivity and specificity results of Oostenbrink¹ (likelihood ratio 1.2 for a positive score).

With an observed sensitivity of 100%, then the decision rule when negative ("0" or below) will reduce the probability of VUR from 25% to 0%. This would only have applied to 3% of children, however. In addition, the 95%

confidence limits for sensitivity are relatively wide (because of the small number of children involved in the study), and even a small reduction in sensitivity in the presence of such a poor specificity would increase the post-test probability with a negative test considerably.

What use would be a score of 5 or less in reducing the likelihood of vesicoureteric reflux? The sensitivity for any degree of reflux is reduced to 89%, with a specificity of only 13% (table 2 in Leroy *et al*³). Using the same calculation, a child with a score of 5 or less would have a 21% probability of VUR (compared to 25% before applying the decision rule), which is clinically unhelpful in excluding reflux.

What therefore is the clinical benefit of this decision rule? As it stands, only in a few children with very low scores of "0" or below would it be possible to be reasonably confident that they do not have vesicoureteric reflux.

Should an attempt be made to improve the decision rule? The key consideration is how important it is to know whether a child who has had a documented urinary tract infection has vesicoureteric reflux. A recent systematic review of imaging in children under the age of 5 years following a UTI, reported in *Effective Health Care*,⁴ concluded: "given the lack of evidence of a link between reflux and renal scarring, and the unproven benefit of treating reflux promptly, it is difficult to justify the routine use of MCUG in children with UTI". A recent publication by Moorthy and colleagues⁵ also concluded that in those children with a normal

renal ultrasound, cystography contributes little to the management of young children with a UTI. A recent systematic review of randomised controlled trials of treatments for vesicoureteric reflux⁶ concluded that "it is uncertain whether the identification and treatment of children with VUR confers clinically important benefit".

The benefit of routine imaging of children for vesicoureteric reflux following UTI is therefore doubtful. Perhaps it would now be sensible also to accept that we do not have a useful clinical decision rule to predict vesicoureteric reflux.

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