Diagnostic testing:
the importance of context

Holm and colleagues' study of the Kryptor®-PCT assay[1] illustrates the importance of undertaking diagnostic research in the appropriate setting. Their findings reveal the much lower discriminatory power of procalcitonin in primary care patients in comparison with hospitalised patients.

However, in interpreting the results of any such diagnostic research and assessing the importance of the findings, it is also helpful to consider two additional contextual factors: the other elements of the clinical assessment and the place of the new technology within a diagnostic processing pathway.

From the data provided by Holm *et al,* I have calculated positive and negative likelihood ratios (LRs) by comparing the blood results against the radiographic 'reference standard' (Table 1).

The magnitude of the LR provides a measure of the predictive ability of a clinical indicant (for example, symptom, sign, or test finding). Clinical indicants with LRs greater than 1 increase the chances of disease: the larger the LR the more compelling the argument for disease. Conversely, clinical indicants that have LRs between 1 and 0 decrease the probability of disease: the closer the LR to zero, the more convincing the finding argues against disease. The adjectives 'positive' or 'negative' indicate whether the LR refers to the presence of the clinical information (positive) or the absence of the clinical information (negative). Positive LRs with the highest value argue most for disease when the clinical information is present; negative LRs with the value closest to zero argue the most against disease when that clinical information is absent.

In my recently published book *Patient Centred Diagnosis*[2] I have assembled a number of LRs for clinical assessment. From this it seems that a duration of illness less than 24 hours before consulting a GP was the variable in the history with the highest positive LR for pneumonia diagnosis (Table 2).

The LRs for a number of more traditional clinical features used to determine whether an adult has a community-acquired pneumonia are shown in Table 3.

Although some individual findings, such as raised respiratory rate, elevated temperature, dullness to percussion, and bronchial breath sounds, provide substantial positive LRs, clusters of findings are more powerful, especially as some individual findings may be unreliable. The combination of temperature of greater then 37.8°C, heart rate more than 100 beats per minute, crackles, and diminished breath sounds in a patient without asthma provides a positive LR of 8.2, while the absence of this combination produces a negative LR of 0.3. In the study by Holm *et al* the interquartile range for procalcitonin was 0.04–0.08 ng/ml (median 0.05 ng/ml); with this in mind, it is worth noting that a procalcitonin level of ≥0.06 ng/ml only provides a positive LR of 2.06.

In using LRs in the context of clinical practice, Bayes' theorem is a very helpful tool to assist in the understanding of diagnostic processing. It is most clearly expressed in the form:

Posterior Odds = LR x Prior Odds

This formula emphasises that the interpretation of the significance of any new information should depend on our

Table 1. Positive and negative likelihood ratios for pneumonia diagnosis.

	LR+	LR–	% pneumonia (radiologically)
Procalcitonin >0.06 ng/ml	2.06	0.45	39
Procalcitonin >0.08 ng/ml	2.88	0.61	22
Procalcitonin >0.10 ng/ml	4.50	0.70	11
Procalcitonin >0.25 ng/ml	23.0	0.78	4
CRP >20mg/l	2.09	0.42	40

CRP = C-reactive protein. LR– = negative likelihood ratio. LR+ = positive likelihood ratio.

Table 2. Promptness of consulting and pneumonia diagnosis.

Duration of illness before consulting, days	LR+
<1	13.5
<4	2.0
>7	0.5

LR+ = positive likelihood ratio.

Table 3. Likelihood ratios for pneumonia diagnosis in adults.

Clinical feature	LR+	LR–
Cough	1.8	0.3
Dyspnoea	1.4	0.7
Sputum production	1.3	0.6
Fever	2.1	0.7
Chills	1.6	0.9
Night sweats	1.7	0.8
Respiratory rate >25 bpm	3.4	0.8
Heart rate >120 bpm	1.9	0.9
Temperature >37.8°C	4.4	0.8
Dullness to percussion	4.3	0.8
Decreased breath sounds	2.5	0.6
Crackles	2.7	0.9
Bronchial breath sounds	3.5	0.9

LR– = negative likelihood ratio. LR+ = positive likelihood ratio.

existing knowledge about the probability of a disease (the prior probability or prior odds of disease). Thus, a patient who comes to see their primary care physician about a cough will already have a prior (existing) probability of pneumonia. This probability will be modified by additional information derived from the medical history to arrive at a new (post-history) probability of pneumonia. This probability may, in turn, be further adjusted by data derived from the clinical examination to produce a post-examination probability that, after a procalcitonin test, could then become a post-test probability. Thus, in an idealised form, the diagnostic processing pathway can be seen as a number of probability steps increasing the certainty of disease (or absence of disease; Figure 1).

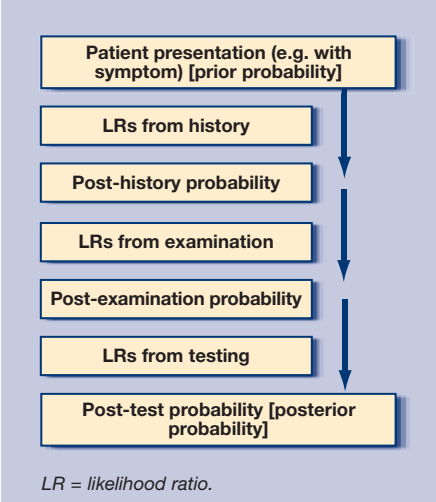

Figure 1. Diagnostic processing pathway.

It may be that, in many circumstances, the disease probability after the history and examination (the post-examination probability) is such that undertaking an investigation is actually unnecessary whatever its LR!

Nick Summerton

REFERENCES

1. Holm A, Pedersen SS, Nexoe J, *et al.* Procalcitonin versus C-reactive protein for predicting pneumonia in adults with lower respiratory tract infection in primary care. *Br J Gen Pract* 2007; **57(540):** 555–560.
2. Summerton N. *Patient centred diagnosis.* Abingdon: Radcliffe Publishing, 2007.

Mike Fitzpatrick

The end of the road for the campaign against MMR

'If the MMR vaccine was not the cause of my son's autism, then why has he got traces of measles virus in his bowels?' This was the question put to me 5 years ago by one of the parents involved in the litigation against the manufacturers of the MMR vaccine. He was a passionate supporter of the campaign led by the former Royal Free researcher Andrew Wakefield who first suggested a link between MMR and autism. The claim, made in 2002 by a team led by Dublin pathologist John O'Leary, that measles virus RNA had been detected in gut biopsies of children with autism, appeared to provide powerful vindication for Wakefield's hypothesis that a distinctive inflammatory bowel condition — dubbed 'autistic enterocolitis' — was the mediating link between MMR and autism.

Testimony in a US court last month by London-based molecular biologist Stephen Bustin (a world authority on PCR testing) exposed the unreliability of O'Leary's findings. Although this is good news for parents, Bustin's testimony was yet another blow for the anti-vaccine campaigners as Andrew Wakefield returns from his private clinic in Texas to face charges of professional misconduct at the General Medical Council. The hearings in the US mark the culmination of two parallel anti-vaccine campaigns. In the UK, parents of more than 1400 children were drawn into litigation against MMR, which collapsed in 2004 when the Legal Services Commission realised that, in the absence of scientific evidence, the claim had no chance of succeeding.

Meanwhile in the US, campaigners blame the mercury-based preservative thiomersal in some vaccines for the apparent increase in the prevalence of autism. The facts that the prevalence of autism has continued to rise after the removal of thiomersal from vaccines and that MMR has never contained thiomersal have not deterred campaigners from trying to link mercury and MMR in the causation of autism, through a series of speculative and improbable pathways. The court in Washington heard the first test case (of a total of 4800), that of 12-year old Michelle Cedillo whose parents believe, partly on the strength of results from O'Leary's lab, that the combination of vaccines containing thiomersal with MMR at 16 months rendered her autistic.

Unfortunately for the anti-vaccine campaigners there was no real contest — in terms of personal expertise or scientific substance — between the expert witnesses put forward in support of the vaccine-autism theory and those challenging this hypothesis. The evidence of videos revealing Michelle's autistic features long before she received MMR was particularly persuasive. In his investigation of the O'Leary lab, Stephen Bustin discovered problems at every step of the PCR process. His conclusions were categorical: 'the assay used was not specific for measles and it was not properly carried out.' The positive results were positive for DNA — confirming contamination, because 'if it's DNA it can't be measles' (measles is an RNA virus). For Bustin it was 'a scientific certainty' that the O'Leary lab had failed reliably to identify measles virus RNA in Michelle or any other child. Bustin's devastating testimony effectively destroyed the only piece of positive evidence that has been produced in support of the MMR–autism thesis since it was launched nearly a decade ago.

Bustin's revelations follow a series of studies, using the most rigorous techniques, which have failed to replicate O'Leary's results, while other researchers have disputed the existence of 'autistic enterocolitis' as a distinctive disease entity.[1–3] All these results are reassuring to parents of autistic children, whose anxieties have been needlessly provoked by the Wakefield campaign. Parents facing decisions about immunisation can also be reassured that the MMR autism scare has been shown to have no basis in science.

REFERENCES

1. Afzal MA. Absence of detectable measles virus genome sequence in blood of autistic children who have had their MMR vaccination during the routine childhood immunization schedule of UK. *J Med Virol,* 2006; **78:** 623–630.
2. D'Souza Y, Fombonne E, Ward BJ. No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder. *Pediatrics*, 2006; **118(4):** 1664–1675.
3. MacDonald TT, Domizio P. Autistic enterocolitis: is it a histopathological entity? *Histopathology* 2007; **50(3):** 371–379.