Appendix I

Definition of the Bayesian latent class model with conditional independence

Latent class models (LCMs) are a large model family that include, in the relationships between the parameters of interest and the observed variables, one or more discrete unobserved ("latent") variables to deal with some violations in traditional model assumptions. In diagnostic studies, LCMs are used to evaluate the performance of new test(s) (i.e. sensitivity and specificity) when a gold standard is not available to define the patient's current disease status ("Diseased" or "Non-Diseased" status). The target disease condition is a two-class "latent" variable and the observed outcomes of the diagnostic tests are considered as imperfect classifiers of the disease status (33,34).

To estimate diagnosis performance of two tests (T_1 and T_2) in the absence of a gold standard, the Bayesian LCM with conditional independence (35) includes five parameters of interest: the sensitivity (*Se1* and *Se2*) and specificity (*Sp1* and *Sp2*) of each diagnostic test, and the disease prevalence (π). The conditional independence assumption means that the two tests are independent, conditionally on the true disease status D, i.e. $\mathrm{P}\left(T_1 \cap T_2 \middle| D\right) = \mathrm{P}\left(T_1 \middle| D\right) \times P\left(T_2 \middle| D\right)$.

Four unique diagnostic test patterns could be observed ("+ +"; "+ –"; "– +"; "– –"); "+" denotes a positive result and "–" a negative result for each test. D_i is the latent status of subject *i*, defined by a binomial distribution as D_i~Binom(π,1).

The distribution of the joint results of the two tests Y_i is multinomial, $Y_i \sim Multi\left(P_{++i}, P_{+-i}, P_{--i}, 1\right)$ with the multinomial probabilities of each unique diagnostic test patterns calculated as shown below:

$$P_{++i} = D_i \times Se_1 \times Se_2 + \left(1 - D_i\right) \times \left(1 - Sp_1\right) \times \left(1 - Sp_2\right)$$

$$P_{+-i} = D_i \times Se_1 \times \left(1 - Se_2\right) + \left(1 - D_i\right) \times \left(1 - Sp_1\right) \times Sp_2$$

$$P_{-+i} = D_i \times \left(1 - Se_1\right) \times Se_2 + \left(1 - D_i\right) \times Sp_1 \times \left(1 - Sp_2\right)$$

$$P_{--i} = D_i \times \left(1 - Se_1\right) \times \left(1 - Se_2\right) + \left(1 - D_i\right) \times Sp_1 \times Sp_2$$

Method for prior elicitation of the parameters of the diagnostic Bayesian latent class model

The Bayesian latent class model with conditional independence used to estimate diagnosis performance of two tests in the absence of a gold standard includes five parameters of interest: the sensitivity and specificity of each diagnostic test, and the disease prevalence (35). Prior information in the form of a beta distribution will be assumed for each parameter.

Beta distribution for a parameter of interest θ was defined by two hyperparameters: α and β. Its mean and variance are defined by the two following equations:

$$E\left(\theta\right) = \frac{\alpha}{\alpha + \beta} \quad [1]$$

$$Var\left(\theta\right) = \sqrt{\frac{\alpha \times \beta}{\left(\alpha + \beta\right)^2 \times \left(\alpha + \beta + 1\right)}} \quad [2]$$

To elicit the prior of each parameter (33), its hyperparameters were estimated by matching the centre of the range of possible values of that parameter with the mean of the beta distribution, given by Eq. [1], and matching the standard deviation of the beta distribution, given by Eq. [2], with one quarter of the range of possible values.

The range of possible values were obtained by aggregating the data of literature synthesis in the field.

Stan code for Bayesian latent class model with conditional independence to estimate diagnosis performance of two tests in the absence of a gold standard

data {int y[4]; real<lower=0> alphapi; real<lower=0> betapi; real<lower=0> alphase1; real<lower=0> betase1; real<lower=0> alphase2; real<lower=0> betase2; real<lower=0> alphasp1; real<lower=0> betasp1; real<lower=0> alphasp2; real<lower=0>

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betasp2;}

parameters {real<lower=0,upper=1> pi; real<lower=0,upper=1> se1; real<lower=0,upper=1> se2; real<lower=0,upper=1> sp1; real<lower=0,upper=1> sp2;}

transformed parameters {simplex[4] p; p[1] = pi * se1 * se2 + (1-pi) * (1-sp1) * (1-sp2); p[2] = pi * se1 * (1-se2) + (1-pi) * (1-sp1) * sp2; p[3] = pi * (1-se1) * se2 + (1-pi) * sp1 * (1-sp2); p[4] = pi * (1-se1) * (1-se2) + (1-pi) * sp1 * sp2;}

model {pi ~ beta(alphapi, betapi); se1 ~ beta(alphase1, betase1); sp1 ~ beta(alphasp1, betasp1); se2 ~ beta(alphase2, betase2); sp2 ~ beta(alphasp2, betasp2); y ~ multinomial(p);}

References

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Table S1 Results of prior elicitation of the five parameters of the diagnostic Bayesian latent class model

Location	Parameter		Prior†	Beta distribution hyperparameters	
				α	β
All sites		π	[0.0–100.0]	1	1
	Radiography	Se_1	[50.0–87.1]	16.58	7.62
		Sp_1	[50.1–99.0]	8.65	2.97
	ULD-CT	Se_2	[50.0–94.2]	11.27	4.38
		Sp_2	[70.0–99.1]	20.21	3.70

† Priors presented as range of possible values (min and max); informative priors based on literature synthesis for sensitivities Se and specificities Sp; non-informative prior for fracture prevalence.

Table S2 Sensitivity analysis with (informative) or without (non-informative) a priori information included in the model used for the Bayesian approach

Parameter	Prior distributions			
	Informative		Non-informative	
	Median	95% CI	Median	95% CI
Fracture prevalence (π)	-	-	38%	[24–53]
Radiography sensitivity	76%	[71–81]	72%	[57–86]
Radiography specificity	93%	[87–97]	89%	[81–97]
ULD-CT sensitivity	90%	[87–93]	87%	[68–94]
ULD-CT specificity	96%	[93–98]	88%	[77–96]

ULD-CT: ultra-low dose computed tomography scan; 95% CI: 95% confidence interval.

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