APPENDICES

THIOPURINE S-METHYLTRANSFERASE TESTING FOR AVERTING DRUG TOXICITY IN PATIENTS RECEIVING THIOPURINES: A META-ANALYSIS OF DIAGNOSTIC TEST ACCURACY

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CONFLICTS OF INTEREST
The authors have no conflicts of interest to disclose.

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Appendix 1. PRISMA flowchart
Appendix 2. Technical Appendix

The Bayesian estimation of a hierarchical summary receiver operating characteristic (HSROC) model for diagnostic meta-analysis as implemented by Dendukuri et al. (1) is described here. We assume that J diagnostic studies are included in the meta-analysis, and each study provides the cross-tabulation between the index test ($T_1$) and one reference test ($T_2$). All tests are assumed to be binary, taking a value of 1 when positive and 0 when negative. All tests are assumed to be imperfect measures of a common underlying binary latent variable $D$, the true disease status. Let $t_1j$ and $t_2j$ denote the vectors of results from study $j$ for $T_1$ and $T_2$, respectively. The sensitivity of the reference test is defined by $Se_{2j} = P(T_{2j} = 1 | D = 1)$ and its specificity is defined by $Sp_{2j} = P(T_{2j} = 0 | D = 0)$.

The model of Dendukuri et al. assumes that there is a continuous latent variable ($Z_j$), which follows a normal distribution, where a positive results on $T_1$ corresponds to a higher value on $Z_j$ than a negative result. The model assumes that among patients with $D = 0$, $Z_1 \sim N\{-a_j/2, \exp(-\beta/2)\}$ and when $D = 1$, $Z_1 \sim N\{a_j/2, \exp(\beta/2)\}$. Conceptually, the model is a binomial regression model with a probit link.

Each study is assumed to use a different cut-off value, $\theta_j$, in the latent variable space to define a positive result. Dendukuri et al. define a hierarchical prior distribution on the mean difference $a_j \sim N(\Lambda, \sigma_\alpha^2)$, allowing for variation in the distribution of $Z_1$ in each study. A hierarchical prior distribution on the cut-off values is also defined: $\theta_j \sim N(\Theta, \sigma_\theta^2)$. Independent prior distributions for the parameters of each reference standard are defined for the sensitivity and specificities of the reference standards: $Se_{2j} \sim \text{Beta}(a_{Se_j}, b_{Se_j})$ and $Sp_{2j} \sim \text{Beta}(a_{Sp_j}, b_{Sp_j})$. When the same reference standard is used in two different studies $j$ and $j'$, we assume the accuracy is the same in both studies (i.e., $Se_{2j} = Se_{2j'}$ and $Sp_{2j} = Sp_{2j'}$).

Based on the assumptions of the model, the sensitivity of $T_1$ in the $j$th study is given by $Se_{1j} = \Phi\{-\theta_j + a_j/2)/\exp(\beta/2)\}$, while its specificity is given by $Sp_{1j} = \Phi\{(\theta_j + a_j/2)/\exp(\beta/2)\}$.

The likelihood function of the observed data can be expressed in terms of the sensitivities, specificities, and prevalence in the $j$th study, $\pi_j = P(D = 1 | \text{Study} = j)$ as follows:

$$L(\Theta, \Lambda, Se_{2j}, Sp_{2j}, \sigma_\alpha^2, \sigma_\theta^2, \beta, \pi_j, a_j, \theta_j, j = 1, ..., J | t_{1j}, t_{2j}, j = 1, ..., J) = \prod_{j=1}^J \left[ \pi_j \Phi\{-\frac{\theta_j - a_j/2}{\exp(\beta/2)}\} Se_{2j} + (1 - \pi_j) \right] t_{1j}^{t_{1j}} t_{2j}^{t_{2j}} \times \left[ \pi_j \Phi\{-\frac{\theta_j - a_j/2}{\exp(\beta/2)}\} (1 - Se_{2j}) + (1 - \pi_j) \right] t_{1j}^{(1 - t_{1j})} t_{2j}^{(1 - t_{2j})} \times \left[ \pi_j \Phi\{\frac{\theta_j + a_j/2}{\exp(\beta/2)}\} Sp_{2j} + (1 - \pi_j) \right] t_{1j}^{(1 - t_{1j})} t_{2j}^{(1 - t_{2j})}.$$ 

Priors need to be specified over the set of unknown parameters to performed Bayesian estimation. Our strategy was to use noninformative priors for most parameters. The priors for $\Lambda$, $\Theta$, and $\beta$ were selected so that the resulting marginal distributions in the pooled sensitivity or specificity were approximately uniform over (0, 1). The parameter $\Lambda$ had a prior of U(-3, 3), $\beta$ had a prior of U(-0.75, 0.75), and $\Theta$ had a prior of (-1.5, 1.5). Parameters $\sigma_\alpha$ and $\sigma_\theta$ were assigned prior distributions of U(0,2). The priors for $\pi_j$, $Se_{2j}$, and $Sp_{2j}$ were Beta(1, 1) distributions.
A Gibbs sampler algorithm was used to obtain a sample from the marginal posterior distributions of the parameters of the model. The WinBUGS code obtained from Dendukuri (2) is provided below. A total of 50,000 iterations of the model was run with the first 10,000 iterations dropped and the remaining 40,000 used to report summary statistics.

The code is as follows:

```winbugs
model {

  for(i in 1:l) {

    theta[i] ~ dnorm(THETA, prec[1])
    alpha[i] ~ dnorm(LAMBDA, prec[2])

    p[1,i] <- phi(-(theta[i] - 0.5*alpha[i])/exp(beta/2))
    p[2,i] <- phi(-(theta[i] + 0.5*alpha[i])*exp(beta/2))

    prob[i,1] <- pi[i]*( p[1,i] * s2[ref[i]] ) + (1-pi[i])*( p[2,i] * (1-c2[ref[i]]) )
    prob[i,2] <- pi[i]*( p[1,i] * (1-s2[ref[i]]) ) + (1-pi[i])*( p[2,i] * c2[ref[i]] )
    prob[i,3] <- pi[i]*( (1-p[1,i]) * s2[ref[i]] ) + (1-pi[i])*( (1-p[2,i]) * c2[ref[i]] )
    prob[i,4] <- pi[i]*( (1-p[1,i]) * (1-s2[ref[i]]) ) + (1-pi[i])*( (1-p[2,i]) * s2[ref[i]] )

    results[i,1:4] ~ dmulti(prob[i,1:4], n[i])
    n[i] <- sum(results[i,1:4])

    pi[i] ~ dbeta(1,1)
    se[i] <- p[1,i]
    sp[i] <- 1-p[2,i]
  }

  for(j in 1:2) {
    prec[j] <- pow(sigma[j],-2)
    sigma[j] ~ dunif(0,2)
  }

  THETA ~ dunif(-1.5,1.5)
  LAMBDA ~ dunif(-3,3)
  beta ~ dunif(-0.75,0.75)

  S_overall<-phi(-(THETA-LAMBDA/2)/exp(beta/2))
  C_overall<-phi( (THETA+LAMBDA/2)*exp(beta/2))

  theta_new ~ dnorm(THETA, prec[1])
  alpha_new ~ dnorm(LAMBDA, prec[2])

  S_new<-phi(-(theta_new-alpha_new*0.5)/exp(beta*0.5))
  C_new<-phi( (theta_new+alpha_new*0.5)*exp(beta*0.5))
}
```
for(h in 1:k) {
    s2[h] ~ dbeta(1,1) ;
    c2[h] ~ dbeta(1,1) ;
}

REFERENCES