The Hospital for Sick Children

Technology Assessment at Sick Kids (TASK)

APPENDICES

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

Authors:

Richard M. Zur, Ph.D.
Research Project Manager, Child Health Evaluative Sciences,
The Hospital for Sick Children, Toronto

Lilla M. Roy, RN, BScN, M.Sc.
Research Project Coordinator, Child Health Evaluative Sciences,
The Hospital for Sick Children, Toronto

Wendy J. Ungar, MSc, PhD
Senior Scientist, Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto
Professor, Health Policy, Management & Evaluation, University of Toronto

Report No. 2015-03

October 7, 2015

Available at: http://lab.research.sickkids.ca/task/reports-theses/

Co-investigators:

Shinya Ito, MD, FRCPC
Division Head, Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Professor, Medicine, Pharmacology & Pharmacy, Department of Paediatrics, University of Toronto

Elizabeth Uleryk, MLS
Director, The Hospital for Sick Children Library, Toronto

Joseph Beyene, MSc, PhD
Department of Clinical Epidemiology & Biostatistics, McMaster University

Knowledge user partners:

Chris Carew, MBA
Centre for Genetic Medicine, The Hospital for Sick Children

James Whitlock, MD
Division Head/Chief Haematology/Oncology, The Hospital for Sick Children; Professor, Paediatrics, University of Toronto

ACKNOWLEDGEMENTS

This research was supported by a Canadian Institutes of Health Research Knowledge Synthesis Grant, grant #305352. We thank Mr. Ian Schiller, M.Sc., Division of Clinical Epidemiology, McGill University Health Centre and Dr. Nandini Dendekuri, Ph.D., Director, Technology Assessment Unit of the McGill University Health Centre for their technical assistance with this report. We thank Ms. Christine Millan for administrative assistance.

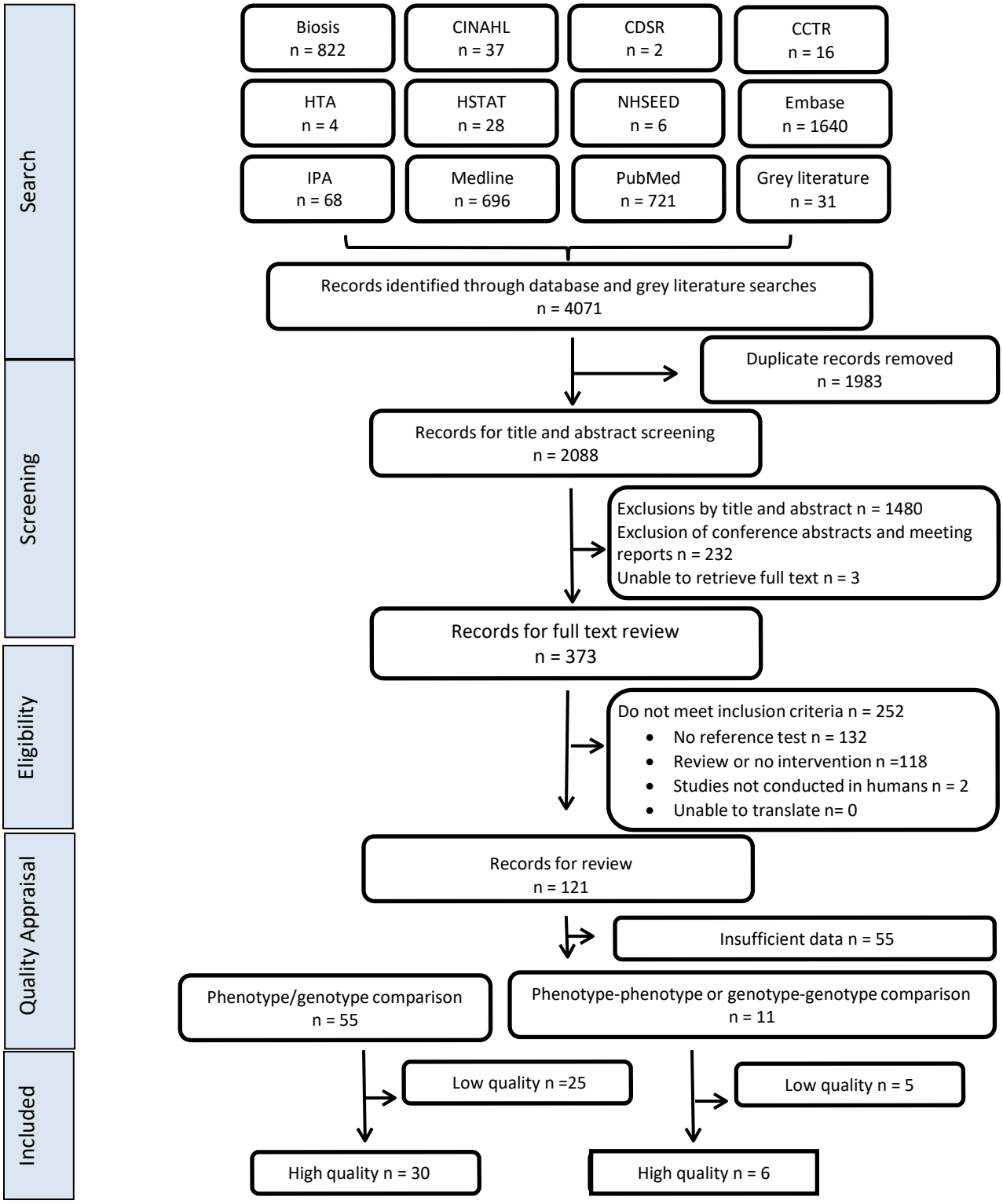
CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

Correspondence:

Wendy J. Ungar, M.Sc., Ph.D.
Senior Scientist, Child Health Evaluative Sciences
The Hospital for Sick Children Peter Gilgan Centre for Research and Learning
11th floor, 686 Bay Street
Toronto, ON, Canada M5G 0A4
tel: (416) 813-7654, extension 303487
fax: (416) 813-5979
e-mail: wendy.ungar@sickkids.ca
http://www.sickkids.ca/AboutSickKids/Directory/People/U/Wendy-Ungar.html

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_{2j}). 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_{2j}, 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_1), which follows a normal distribution, where a positive results on T_1 corresponds to a higher value on Z_1 than a negative result. The model assumes that among patients with $D = 0$, $Z_1 \sim N\{-\alpha_j/2, \exp(-\beta/2)\}$ and when $D = 1$, $Z_1 \sim N\{\alpha_j/2, \exp(\beta/2)\}$. Conceptually, the model is a binomial regression model with a probit link.

Each study is assumed to use a different cut-off value, θ_j, in the latent variable space to define a positive result. Dendukuri et al. define a hierarchical prior distribution on the mean difference $\alpha_j \sim N(\Lambda, \sigma^2_\alpha)$, allowing for variation in the distribution of Z_1 in each study. A hierarchical prior distribution on the cut-off values is also defined: $\theta_j \sim N(\Theta, \sigma^2_\theta)$. Independent prior distributions for the parameters of each reference standard are defined for the sensitivity and specificities of the reference standards: $Se_{2j} \sim \text{Beta}(a_{Sej}, b_{Sej})$ and $Sp_{2j} \sim \text{Beta}(a_{Spj}, b_{Spj})$. 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 jth study is given by $Se_{1j} = \Phi\{-(\theta_j - \alpha_j/2)/\exp(\beta/2)\}$, while its specificity is given by $Sp_{1j} = \Phi\{(\theta_j + \alpha_j/2)/\exp(-\beta/2)\}$.

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

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

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 Λ, Θ, and β were selected so that the resulting marginal distributions in the pooled sensitivity or specificity were approximately uniform over (0, 1). The parameter Λ had a prior of U(-3, 3), β had a prior of U(-0.75, 0.75), and Θ had a prior of (-1.5, 1.5). Parameters σ_α and σ_θ were assigned prior distributions of U(0,2). The priors for π_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:

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

1. Dendukuri N, Schiller I, Joseph L, Pai. Bayesian meta-analysis of the accuracy of a test for tuberculous pleuritis in the absence of a gold standard reference, *Biometrics*. 2012 December ; 68(4): 1285–1293.
2. Nanidini Dendukuri's website. http://www.nandinidendukuri.com/software.