

**The Hospital for Sick Children
Technology Assessment at SickKids (TASK)**

APPENDICES

**HEALTH TECHNOLOGY ASSESSMENT OF THIOPURINE METHYLTRANSFERASE
TESTING FOR GUIDING 6-MERCAPTOPYRIMIDINE DOSES IN PEDIATRIC PATIENTS
WITH ACUTE LYMPHOBLASTIC LEUKEMIA**

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Report No. 2010-02

Date: 25 March 2010

Available at:

<http://pede.ccb.sickkids.ca/pede/task.jsp>

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ACKNOWLEDGEMENTS

We thank the following individuals for their clinical and technical expertise : Dr. Jack Hand, Pediatric Hematologist/Oncologist, Janeway Children’s Hospital, Eastern Health, St. John’s; Dr. Jules Doré, Associate Professor of Cell Biology, Memorial University of Newfoundland, St. John’s; Dr. Ed Randell, Chief of Clinical Biochemistry and Associate Professor of Laboratory Medicine, Eastern Health and Memorial University of Newfoundland, St. John’s; Dr. Phil Gordon, Chief, Department of Paediatric Laboratory Medicine and Ms. Elyse Zelunka, Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Canada.

Funding for this research was provided by the Atlantic Canada Opportunities Agency, the provincial government of Newfoundland and Labrador and Memorial University of Newfoundland and by a program grant from the Ontario Ministry of Health and Long-term care Drug Innovation Fund. In-kind support was provided by the Newfoundland and Labrador Centre for Health Information.

The views expressed in the material are the views of the authors and do not necessarily reflect those of the province of Ontario or Newfoundland and Labrador.

CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

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1 Appendix 1: Background of Subject Matter Experts

Table 1.1: Background of Subject Matter Experts

Name	Position(s)	Organization(s)
Dr. Proton Rahman	Rheumatologist and Genetic Epidemiologist	Eastern Health and Memorial University of Newfoundland, St. John's, Canada
Dr. Jack Hand	Pediatric Hematologist/Oncologist	Janeway Children's Hospital, Eastern Health, St. John's, Canada
Dr. Jules Doré	Associate Professor, Cell Biology	Memorial University of Newfoundland, St. John's, Canada
Dr. Ed Randell	Chief of Clinical Biochemistry and Associate Professor of Laboratory Medicine	Eastern Health and Memorial University of Newfoundland, St. John's, Canada
Dr. Phil Gordon	Chief, Department of Paediatric Laboratory Medicine	Hospital for Sick Children, Toronto, Canada

2 Appendix 2: Contingency Tables and Accuracy Values for Included Studies

2.1 Kham, 2008

	Mutation Present	Mutation Absent	Total
Test positive	14	0	14
Test Negative	8	457	465
Total	22	457	479

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	100.00%	98.28%	63.64%	100.00%
Standard Error	0.00%	0.59%	2.20%	0.00%
Confidence Limits	0.00%	1.16%	4.31%	0.00%

2.2 Yates, 1997

	Mutation Present	Mutation Absent	Total
Test positive	26	0	26
Test Negative	1	21	22
Total	27	21	48

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	96.30%	100.00%	100.00%	95.45%
Standard Error	2.73%	0.00%	0.00%	3.01%
Confidence Limits	5.34%	0.00%	0.00%	5.89%

2.3 Winter, 2007

	Mutation Present	Mutation Absent	Total
Test positive	11	0	11
Test Negative	6	113	119
Total	17	113	130

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	64.71%	100.00%	100.00%	94.96%
Standard Error	4.19%	0.00%	0.00%	1.92%
Confidence Limits	8.21%	0.00%	0.00%	3.76%

2.4 Schaeffeler, 2004

	Mutation Present	Mutation Absent	Total
Test positive	112	6	118
Test Negative	17	1079	1096
Total	129	1085	1214

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	86.82%	99.45%	94.92%	98.45%
Standard Error	0.97%	0.21%	0.63%	0.35%
Confidence Limits	1.90%	0.42%	1.24%	0.70%

2.5 Loennechen, 2001

	Mutation Present	Mutation Absent	Total
Test positive	23	0	23
Test Negative	1	236	237
Total	24	236	260

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	95.83%	100.00%	100.00%	99.58%
Standard Error	1.24%	0.00%	0.00%	0.40%
Confidence Limits	2.43%	0.00%	0.00%	0.79%

2.6 Spire-Vayron de la Moureyre, 1998

	Mutation Present	Mutation Absent	Total
Test positive	18	9	27
Test Negative	15	149	164
Total	33	158	191

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	54.55%	94.30%	66.67%	90.85%
Standard Error	3.60%	1.68%	3.41%	2.09%
Confidence Limits	7.06%	3.29%	6.69%	4.09%

2.7 Hon, 1999

	Mutation Present	Mutation Absent	Total
Test positive	18	0	18
Test Negative	5	23	28
Total	23	23	46

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	78.26%	100.00%	100.00%	82.14%
Standard Error	6.08%	0.00%	0.00%	5.65%
Confidence Limits	11.92%	0.00%	0.00%	11.07%

2.8 Reis, 2003

	Mutation Present	Mutation Absent	Total
Test positive	27	0	27
Test Negative	4	43	47
Total	31	43	74

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	87.10%	100.00%	100.00%	91.49%
Standard Error	3.90%	0.00%	0.00%	3.24%
Confidence Limits	7.64%	0.00%	0.00%	6.36%

2.9 Larovere, 2003

	Mutation Present	Mutation Absent	Total
Test positive	12	0	12
Test Negative	9	28	37
Total	21	28	49

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	57.14%	100.00%	100.00%	75.68%
Standard Error	7.07%	0.00%	0.00%	6.13%
Confidence Limits	13.86%	0.00%	0.00%	12.01%

2.10 Indjova, 2003

	Mutation Present	Mutation Absent	Total
Test positive	15	0	15
Test Negative	9	52	61
Total	24	52	76

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	62.50%	100.00%	100.00%	85.25%
Standard Error	5.55%	0.00%	0.00%	4.07%
Confidence Limits	10.88%	0.00%	0.00%	7.97%

2.11 Nasedkina, 2005

	Mutation Present	Mutation Absent	Total
Test Positive	15	0	15
Test Negative	0	43	43
Total	15	43	58

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	100.00%	100.00%	100.00%	100.00%
Standard Error	0.00%	0.00%	0.00%	0.00%
Confidence Limits	0.00%	0.00%	0.00%	0.00%

2.12 Schaeffeler, 2001

	Mutation Present	Mutation Absent	Total
Test positive	17	0	17
Test Negative	0	93	93
Total	17	93	100

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	100.00%	100.00%	100.00%	100.00%
Standard Error	0.00%	0.00%	0.00%	0.00%
Confidence Limits	0.00%	0.00%	0.00%	0.00%

2.13 Anglicheau, 2002 (RC)

	Mutation Present	Mutation Absent	Total
Test positive	3	8	11
Test Negative	0	50	50
Total	3	58	61

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	100.00%	86.21%	27.27%	100.00%
Standard Error	0.00%	4.42%	5.70%	0.00%
Confidence Limits	0.00%	8.65%	11.18%	0.00%

2.14 Anglicheau, 2002 (HPLC)

	Mutation Present	Mutation Absent	Total
Test positive	3	6	9
Test Negative	0	52	52
Total	3	58	61

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	100.00%	89.66%	33.33%	100.00%
Standard Error	0.00%	3.90%	6.04%	0.00%
Confidence Limits	0.00%	7.64%	11.83%	0.00%

2.15 Wusk, 2004

	Mutation Present	Mutation Absent	Total
Test Positive	18	27	45
Test Negative	0	195	195
Total	18	222	240

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	100.00%	88.74%	41.86%	100.00%
Standard Error	0.00%	2.04%	3.18%	0.00%
Confidence Limits	0.00%	4.00%	6.24%	0.00%

2.16 Rossi, 2001

	Mutation Present	Mutation Absent	Total
Test positive	11	3	14
Test Negative	0	89	89
Total	11	92	103

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	100.00%	96.74%	78.57%	100.00%
Standard Error	0.00%	1.75%	4.04%	0.00%
Confidence Limits	0.00%	3.43%	7.92%	0.00%

2.17 Alves, 2001

	Mutation Present	Mutation Absent	Total
Test positive	11	3	14
Test Negative	1	128	129
Total	12	131	143

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Point Estimate	91.67%	97.71%	78.57%	99.22%
Standard Error	2.31%	1.25%	3.43%	0.73%
Confidence Limits	4.53%	2.45%	6.73%	1.44%

3 Appendix 3: Results of Quality Appraisal Using the Modified CASP Tool

Table 3.1: Quality Appraisal Using the Modified CASP Tool

Question	Kham, 2008	Yates 1997	Winter, 2007	Schaeffeler, 2004	Loennechen 2001	Spire-Vayron de la Moureyre, 1998	Hon, 1999	Reis, 2003
Was there a clear question for the study to address?	No	No	Yes	No	No	Yes	Yes	Yes
Was there a comparison with an appropriate reference standard?	Yes	Yes	Yes	Yes	Yes	Yes	Cannot tell	Yes
Was there a sample size calculation?*	No	No	No	No	No	No	No	No
Did all patients get the test and the reference standard?	Yes	No	Yes	No	Yes	Yes	No	No
Could the results of the test of interest have been influenced by the reference standard?	No	No	No	No	No	No	No	No
Were the diagnosticians blinded to the results of the other test?	Cannot tell	Cannot tell	Cannot tell	Cannot tell	No	No	No	No
Is the disease status of the population clearly described?	Yes	Yes	Yes	Yes	No	No	Yes	No
Were concurrent	Cannot tell	Cann	Cannot	Yes	No	No	No	No

medications accounted for?*		ot tell	tell					
Were blood transfusions accounted for?*	Sample of blood donors	No	No	Sample was blood donors	No	No	No	No
Were the methods for performing the test described in sufficient detail?	Yes	Yes	No	Yes	Yes	Yes	No	No
Are sensitivity and specificity and/or likelihood ratios presented?	Yes	Yes	Yes	Yes	No	No	No	No
Are the results presented in such a way that you can work them out?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Could the results have occurred by chance?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are there confidence limits?	No	No	No	No	No	No	No	No

*These questions were not included in the original *Critical Appraisal Skills Program* tool (Public Health Research Unit, 2006)

Table 3.2: Quality Appraisal Using the Modified CASP Tool

Question	Larovere, 2003	Indjova, 2003	Nasedkina, 2005	Lu, 2005	Schaeffeler 2001	Anglicheau 2002	Wusk, 2004	Rossi, 2001	Alves, 2001
Was there a clear question for the study to address?	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Was there a comparison with an appropriate reference standard?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there a sample size calculation?*	No	No	No	No	No	No	No	No	No
Did all patients get the test and the reference standard?	No	No	Yes	Yes	Yes	Yes	Cannot tell	Yes	Yes
Could the results of the test of interest have been influenced by the reference standard?	Yes	No	No	No	No	No	No	No	No
Were the diagnosticians blinded to the results of the other test?	No	No	No	Yes	Cannot tell	Yes	Cannot tell	No	No
Is the disease status of the population clearly described?	Yes	No	No	No	No	Yes	Yes	Yes	Yes
Were concurrent medications accounted for?*	No	Yes	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	No	Yes**

Were blood transfusions accounted for?*	Yes	Yes	No	No	No	No	No	No	No
Were the methods for performing the test described in sufficient detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are sensitivity and specificity and/or likelihood ratios presented?	No	No	No	No	Yes	No	Yes	No	No
Are the results presented in such a way that you can work them out?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Could the results have occurred by chance?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are there confidence limits?	No	No	No	No	No	No	No	No	No

*These questions were not included in the original *Critical Appraisal Skills Program* tool (Public Health Research Unit, 2006)

** Alves, et al. (2001) this study only accounted for diuretics not other medications (eg. thiopurines) that may influence the results.