

1        **Application and Optimisation of the Comparison on Extreme Laboratory Tests (CERT)**  
2        **Algorithm for Detection of Adverse Drug Reactions: Transferability Across National**  
3        **Boundaries**

4        **SHORT RUNNING TITLE: Optimisation of CERT to Detect ADRs**

5        Mun Yee Tham,<sup>1</sup> Qing Ye,<sup>1,2</sup> Pei San Ang,<sup>1</sup> Liza Y. Fan,<sup>1,2</sup> Dukyong Yoon,<sup>3,4</sup> Rae Woong Park,<sup>3,4</sup>  
6        Zheng Jye Ling,<sup>5</sup> James W. Yip,<sup>5</sup> Bee Choo Tai,<sup>6</sup> Stephen Evans,<sup>7</sup> Cynthia Sung<sup>1,8</sup>

7  
8        <sup>1</sup> Vigilance and Compliance Branch, Health Sciences Authority, Singapore

9        <sup>2</sup> Genome Institute of Singapore, Agency for Science and Technology, Singapore

10       <sup>3</sup> Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea

11       <sup>4</sup> Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Korea

12       <sup>5</sup> Academic Informatics Office, National University Health System, Singapore

13       <sup>6</sup> Saw Swee Hock School of Public Health, National University of Singapore, Singapore

14       <sup>7</sup> Department of Medical Statistics, Faculty of Epidemiology and Population Health, London  
15       School of Hygiene and Tropical Medicine, London, UK

16       <sup>8</sup> Health Services and Systems Research, Duke-NUS Medical School, Singapore

17       **CORRESPONDING AUTHOR:**

18       Cynthia Sung

19       11 Biopolis Way, #11-03, Singapore 138667 | Tel: +65 8123 1495 | Fax: +65 6478 9069 |  
20       |cynthia\_sung@hsa.gov.sg |

21       **KEYWORDS:**

22       Adverse reaction

23       Data mining

24       Pharmacovigilance

25       Signal detection

26       Laboratory abnormality

27       Electronic Medical Records

28  
29       **KEY POINTS:**

30       1. The Comparison on Extreme Laboratory Tests (CERT) algorithm was implemented in the  
31       electronic medical records (EMR) of a major tertiary hospital in Singapore, the National  
32       University Hospital (NUH).

33       2. A modified version of CERT that requires a minimum of 400 cases to assess a drug-  
34       laboratory abnormality (CERT400) yielded higher positive predictive value and sensitivity.

35       3. CERT400 demonstrated potential in detecting drug induced hepatic and renal toxicities,  
36       but limited utility in detecting ADRs associated with haematopoiesis and coagulation.

37  
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50 **CONFLICT OF INTEREST**

51 The authors declare no conflict of interest.

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54

55 **This study has neither been previously published nor presented at any conferences.**

56

57 **Abstract**

58 **Purpose:** The Singapore regulatory agency for health products (Health Sciences Authority), in  
59 carrying out active surveillance of medicines and their potential harms, is open to new  
60 methods to achieve this goal. Laboratory tests are a potential source of data for this purpose.  
61 We have examined the performance of the Comparison on Extreme Laboratory Tests (CERT)  
62 algorithm, developed by Ajou University, Korea, as a potential tool for adverse drug reaction  
63 (ADR) detection based on the electronic medical records (EMR) of the Singapore healthcare  
64 system.

65 **Methods:** We implemented the original CERT algorithm, comparing extreme laboratory  
66 results pre- and post-drug exposure, and five variations thereof using 4.5 years of National  
67 University Hospital (NUH) EMR data (31,869,588 laboratory tests, 6,699,591 drug dispensings  
68 from 272,328 hospitalizations). We investigated six drugs from the original CERT paper and  
69 an additional 47 drugs. We benchmarked results against a reference standard we created  
70 from UpToDate® 2015.

71 **Results:** The original CERT algorithm applied to all 53 drugs and 44 laboratory abnormalities  
72 yielded a PPV and sensitivity of 50.3% and 54.1%, respectively. By raising the minimum  
73 number of cases for each drug-laboratory abnormality pair from 2 to 400, the PPV and  
74 sensitivity increased to 53.9% and 67.2%, respectively. This post-hoc variation, named  
75 CERT400, performed particularly well for drug-induced hepatic and renal toxicities.

76 **Discussion:** We have demonstrated that the CERT algorithm can be applied across national  
77 boundaries. One modification (CERT400) was able to identify ADR signals from laboratory  
78 data with reasonable PPV and sensitivity, which indicates potential utility as a supplementary  
79 pharmacovigilance tool.

80

81 **Text**

## 82 **INTRODUCTION**

83 Traditionally, spontaneous reporting systems (SRS) have been the predominant data source  
84 for the detection of signals of adverse reactions.<sup>1-3</sup> This system, usually maintained by a  
85 government agency, receives suspected adverse drug reaction (ADR) reports submitted by  
86 healthcare professionals, pharmaceutical companies and consumers.<sup>1-3</sup> With the expanding  
87 use of electronic medical records (EMRs) in recent years, the pharmacovigilance community  
88 has another potentially rich source of information for drug safety surveillance.<sup>1,3</sup> The prospect  
89 of scanning EMRs is attractive, as it overcomes some of the limitations inherent in the SRS: (1)  
90 reliance mainly on voluntary reporting from its contributors, and susceptibility to under-  
91 reporting as well as over-reporting (e.g. due to media interest), (2) incomplete or missing data,  
92 hindering causality assessment, and (3) difficulty in detecting duplicate reports.<sup>1, 2</sup>

93 As EMRs are used for the clinical management of patients, they constitute an information-  
94 rich database<sup>3</sup> of patients' demographics, medications, past medical history, laboratory  
95 results, etc, which are commonly missing from ADR reports. The records reflect actual clinical  
96 practice, allowing for a more complete benefit-risk assessment. For specific ADRs, mining of  
97 EMRs has the added advantage of applying a consistent phenotype definition, thus  
98 overcoming variations in diagnostic criteria by different clinicians. However, unlike in SRS  
99 where a clinician has made a connection between the drug and an adverse event and files a  
100 report in a standardized format, much of EMR data are unstructured and housed in different  
101 databases. Pre-processing and data cleaning are required to extract and collate critical  
102 elements, such as drug exposure, concomitant medications, laboratory results, temporal  
103 relationships, and possible confounders.<sup>1</sup>

104 The Comparison of Extreme Laboratory Test (CERT) algorithm was developed by Korean  
105 researchers who applied it to 10 different drugs over 10 years of EMR data from Ajou  
106 University Hospital.<sup>4</sup> For each patient exposed to a particular drug, the algorithm selects the  
107 extreme laboratory test result (minimum or maximum) among multiple laboratory values  
108 from each of the pre-drug and post-drug exposure periods. CERT then determines whether a  
109 cohort of exposed patients demonstrates a significant change in abnormal laboratory values  
110 after drug exposure. As a regulatory agency seeking to build a toolkit of methods for active  
111 surveillance, the Health Sciences Authority (HSA), Singapore, sought to investigate the  
112 potential applicability of the CERT algorithm on the EMR in the Singapore healthcare system.  
113 The CERT algorithm had many desirable features that we were seeking, namely a temporal  
114 relation between drug exposure and a laboratory abnormality, the flexibility to evaluate any  
115 drug and laboratory test, and good performance metrics. Utilisation of numerical laboratory  
116 values before and after drug exposure made it potentially more portable across national  
117 boundaries, regardless of the language of the country. The objectives of this work were to  
118 implement and test CERT on the EMRs of the National University of Hospital (NUH), examine  
119 variations that could improve predictive performance, and assess its potential utility as a  
120 pharmacovigilance tool.

121

## 122 **METHODS**

### 123 Data source

124 De-identified EMRs were obtained from NUH, a 1,230-bed tertiary hospital, following  
125 approval of the study by the National Healthcare Group Domain Specific Review Board. The  
126 information retrieved included patient demographics, admission and discharge dates,  
127 inpatient drug dispensings, and laboratory test results over a 4.5 year period from July 2009  
128 to Dec 2013. The data comprised over 31 million (31,869,588) laboratory tests and 6 million  
129 (6,699,591) inpatient drug dispensed orders from 272,327 hospitalization visits for 158,096  
130 patients.

131

### 132 Selection of drugs for evaluation

133 Among the ten drugs analysed in the original CERT paper, one drug (ketorolac) was not used  
134 at NUH, while three oncologic drugs (etoposide, fluorouracil and methotrexate) were  
135 incompletely captured because oncologic drugs are mainly ordered and recorded in another  
136 database. In order to have a direct head-to-head comparison of algorithm performance from  
137 the EMRs of two different healthcare institutions, we first analysed only six drugs described  
138 in the original CERT publication (Round 1, Table 1).

139 In Round 2, we investigated an additional 47 drugs (Table 2). Factors considered in drug  
140 selection were drug usage volume and the likelihood of the drug being started during  
141 hospitalisation. Drugs with high usage were prioritised to provide sufficient number of cases  
142 for analysis. We also included negative controls (chlorpheniramine, metronidazole and  
143 risedronic acid) with no ADRs detectable by abnormal laboratory test results in the reference  
144 standard.

### 145 The CERT algorithm and variations

146 The original CERT algorithm paper examined 41 laboratory tests and 51 laboratory  
147 abnormalities. Six laboratory tests and seven laboratory abnormalities were not included in  
148 our evaluation because the laboratory results were infrequently ordered by clinicians in NUH  
149 (most of the 53 drugs had zero cases). Consequently, our evaluation included 35 laboratory  
150 tests and 44 laboratory abnormalities (Supplementary Table S1).

151 A common issue in assessing EMR data mining is the need for a benchmark reference standard  
152 to evaluate algorithm performance.<sup>1,4</sup> The original CERT publication used the 2010 version of  
153 UpToDate® Drug Information Database (UpToDate Inc, Waltham, MA, USA) to create a  
154 reference standard. We used the 2010 version of UpToDate® to directly compare our results  
155 with those previously published. To evaluate the performance of the original CERT algorithm  
156 and variations for all 53 drugs, two pharmacists constructed an updated reference standard  
157 from UpToDate® 2015 (Supplementary Table S3). As CERT utilises laboratory abnormalities  
158 as a surrogate of ADRs, the ADRs were mapped to their respective laboratory abnormalities  
159 using the mapping table described in the original CERT paper.<sup>4</sup>

160 In the original CERT algorithm, a case is defined when (1) the patient was prescribed the study  
161 drug at least once, and (2) at least one laboratory test result exists in each of the pre-drug and

162 post-drug periods. A minimum of two cases was required for CERT to run the statistical tests  
163 and generate output. If either the paired t-test or McNemar’s test had  $P < 0.05$ , the drug-  
164 laboratory-abnormality pair would be considered a positive signal.

165 Four variations of the original CERT algorithm were assessed on the set of 53 drugs (Table 3):  
166 (1) Limiting the period of observation to a defined period after the start of drug exposure, (2)  
167 Limiting the post-drug exposure observation period to a defined number of laboratory tests,  
168 (3) Taking an average of the two most extreme values instead of using only one extreme pre-  
169 and post-drug value, and (4) Using the paired t-test and non-parametric Wilcoxon’s signed-  
170 rank test instead of paired t-test and McNemar’s test. A fifth variation was also assessed post-  
171 hoc in which only drug-AE pairs with a minimum of 400 cases were included. The rationale for  
172 these variations is presented in the Discussion section.

### 173 Evaluation metrics

174 To evaluate the performance of CERT, we compared the drug-laboratory-abnormality pairs  
175 detected as significant signals by CERT with those identified in the reference standard. We  
176 then calculated the average positive predictive value (PPV), negative predictive value (NPV),  
177 sensitivity and specificity for each drug based on laboratory abnormalities. The F-score, which  
178 is the harmonic mean of PPV and sensitivity, is also reported (Supplementary Table S2). To  
179 contrast the results from different variations of the algorithm and get a pooled point estimate  
180 of the performance metrics and the 95% confidence interval, a random effects meta-analysis  
181 was performed to summarise a particular measurement of interest.

### 182 Creation of a reference standard

183 Supplementary Table S3 presents the reference standard created by mapping ADRs in  
184 UpToDate® 2015 for the 53 drugs to laboratory abnormalities. Researchers may find this a  
185 useful resource for benchmarking other algorithms intended to identify ADRs from laboratory  
186 abnormalities. However, it is worthwhile to note that this reference standard is not a list of  
187 confirmed ADRs, and is constantly being updated, and hence some may consider it a “silver  
188 standard” rather than a “gold standard”. While UpToDate® contains information from  
189 multiple sources about a drug’s safety profile, ADRs that occur in specific population could be  
190 overlooked, and it may be incomplete for drugs that have only been recently approved.

## 191 **RESULTS**

### 192 Evaluation of CERT performance

193 The PPV, NPV, sensitivity and specificity for Round 1 (6 drugs) are summarised in Table 4A.  
194 When comparing the same drugs between NUH and Ajou University, our results showed  
195 similar PPV (55.6% vs 58%) and better specificity (64.3% vs 52.2%). We had lower NPV (56.2%  
196 vs 66.7%) and sensitivity (48.9% vs 71.3%).

197 When the CERT algorithm was evaluated on a larger set of 47 drugs (Round 2) and  
198 benchmarked against an updated reference standard, PPV decreased to 48.5%, specificity was  
199 similar (65.2%), and sensitivity increased to 54.7%. Combining all 53 drugs evaluated in both

200 Rounds, overall PPV was 50.3%, specificity was 65.4%, and sensitivity was 54.1% for an F-score  
201 of 52.1% (Table 4B).

### 202 Performance across different laboratory panels

203 Consistent with Ajou University’s findings, the majority of the signals (93.6%) detected by  
204 CERT were from “haematopoiesis and coagulation”, “hepatobiliary enzymes” and “renal  
205 function and urine tests”, and these panels were associated with higher F-scores compared  
206 to the remaining laboratory panels. However, decreases in red blood cells, white blood cells,  
207 neutrophils, haematocrit, as well as haemoglobin were found for all of the drugs (with the  
208 exception of alendronic acid). Therefore, CERT may not be particularly discriminating for drug  
209 effects on those laboratory tests.

210 In “hepatobiliary enzymes”, ALT and AST showed good PPV (92%, 87%) and specificity (83%,  
211 83%), suggesting potential utility in detecting hepatotoxicity signals. The trade-off is the lower  
212 sensitivity (59%, 32%), potentially missing some valid signals. For the “renal function and urine  
213 tests”, creatinine showed good PPV (80%) and specificity (93%) but very low sensitivity (11%).  
214 BUN had good PPV (77%) and sensitivity (62%). Many signals for increased potassium were  
215 detected which were not reported in UpToDate®.<sup>5</sup> The lipid and metabolism, hormones and  
216 other panels also had high specificity (>87%) but low sensitivity (16-17%). PPV was also low,  
217 presumably because ADRs related to these abnormalities are rarer.

### 218 Performance across different variations

219 Among the four initial variations, Variations 1, 3 and 4 generally did not perform better than  
220 the original algorithm (Table 6, Figure 2). Variation 2 had the best specificity (76.8%, Table 6).  
221 However, this was accompanied by a large drop in sensitivity (38.3%). When we examined  
222 the evaluation metrics as a function of number of cases, we noted that sensitivity increased  
223 above 50% when there were 400 or more cases (Figure 1). Increasing the minimum number  
224 of cases from two to 400 cases for each drug-laboratory abnormality pair appears to better  
225 control the number of false negatives, as expected from increased power of a larger sample  
226 size. Hence, we performed a post-hoc analysis by imposing a threshold of 400 cases (Variation  
227 5). Variation 5, not surprisingly because of its post-hoc nature, gave the best overall  
228 performance (PPV 53.9%, sensitivity 67.2%, F-score 59.8%), and hereafter is referred to as  
229 CERT400.

### 230 Negative controls

231 We tested CERT on three negative controls: chlorpheniramine, metronidazole and risedronic  
232 acid. These drugs have no signals in the reference standard that would be indicative of  
233 laboratory abnormalities. Yet, for all three drugs, CERT detected decreases in red blood cell,  
234 white blood cell, neutrophil, haematocrit, haemoglobin, and protein, as well as increases in  
235 platelets and alkaline phosphatase (ALP). As noted above, most haematopoeisis tests  
236 returned positive results for all drugs, therefore these tests are of limited utility for ADR signal  
237 detection using CERT.

## 238 **DISCUSSION**

239 As a drug regulatory authority responsible for monitoring the post-market safety of drugs,  
240 HSA has been interested in supplementing SRS with other methodologies to strengthen the  
241 system for identifying drug safety signals. Knowledge of the full safety profile of a drug,  
242 particularly for rarer adverse reactions, only becomes available through post-marketing  
243 surveillance from drug usage in actual clinical practice across a broad population.<sup>6</sup> With EMRs,  
244 new opportunities have arisen to mine these information-rich resources for safety signals.  
245 Here, we have shown that the CERT algorithm, which utilises laboratory test data in a  
246 temporal relationship with drug exposure, can be implemented on EMR data in a healthcare  
247 institution from another country with a different population. We have examined the  
248 performance of CERT for 53 drugs, of which direct comparison could be performed for 6 drugs  
249 in both countries. We also investigated 5 variations of the original CERT algorithm, and  
250 identified two that improve specificity and/or sensitivity.

251 The PPV of CERT was high for the liver enzymes ALT and AST and renal tests serum BUN and  
252 creatinine (92%, 87%, 77% and 80%, respectively), thus a positive signal from CERT is likely to  
253 signify hepatic and renal toxicity. However, the aminoglycosides gentamicin and amikacin,  
254 which are known to be nephrotoxic, did not show a positive signal with either increased  
255 creatinine or BUN. This could be a result of close monitoring of renal function and/or  
256 therapeutic drug monitoring by clinicians to prevent any acute renal injury, thereby  
257 dampening the incidence of a well-known signal. CERT did detect a signal of raised creatinine  
258 for other drugs with known nephrotoxic potential (e.g. hydrochlorothiazide, ranitidine,  
259 cefazolin), but sensitivity of the serum creatinine test was low (11%). However, sensitivity for  
260 BUN was much higher at 62%.

261 CERT appears to be less discriminating for the hematopoiesis and coagulation panel, as nearly  
262 every drug had one or more signals in this panel. This may be more a reflection of the course  
263 of the disease or treatment. Similarly, the high number of false positives with potassium may  
264 be due to the high incidence of hyperkalaemia (up to 10%) in hospitalised patients, as many  
265 conditions can affect potassium levels (e.g. transcellular shifts, impaired excretion, or increase  
266 in potassium intake).<sup>5</sup> Indeed, a major limitation of the CERT algorithm is the lack of  
267 adjustment for confounding factors. The CLEAR algorithm<sup>7</sup>, also developed by the Ajou  
268 University group, controls for confounder effects with the use of matched controls having the  
269 same admitting department and diagnosis but who had not taken the drug, but CLEAR is much  
270 more computationally intensive. Another limitation is the lack of an actual gold standard for  
271 ADRs. Even though we created a reference standard using UpToDate 2015, we cannot confirm  
272 that the ADRs listed are indeed true ADRs. In addition, for chronic medications (e.g.  
273 simvastatin, enalapril), patients might already be taking them prior to admission. As such, the  
274 pre-exposure laboratory test results retrieved by CERT for these cases may not be true,  
275 potentially diluting any positive signals.

276 In the original CERT algorithm, all tests in the pre- and post-drug exposure period were  
277 included. However, it was often the case that many more tests were ordered during the post-  
278 drug exposure period, which tends to inflate the chance finding of an abnormal result in the  
279 post-drug exposure period. By limiting the number of tests in the post-drug exposure period  
280 to two more than the number in the pre-drug exposure period (Variation 2), we observed an



281 increase in the specificity of CERT from 65.4% to 76.8%. The original CERT algorithm counted  
282 a drug-laboratory abnormality pair if there were at least two cases. We found that raising the  
283 minimum to 400 cases for each drug-laboratory abnormality pair (CERT400) helped to reduce  
284 the false negative rate, increasing the sensitivity from 54.1% to 67.2%. However, since the  
285 choice of 400 is based on results in these data, these estimates may be biased upwards.  
286 Although these performance metrics are not sufficiently high to solely rely on CERT400 for  
287 active surveillance, it promises to be a valuable addition to the toolkit for postmarket  
288 surveillance. A drug-laboratory abnormality pair identified by an automated CERT400  
289 algorithm could then be further evaluated by other methodologies such as text mining of  
290 discharge summaries<sup>8-10</sup> to determine the validity of the signal. In the case of infrequently  
291 ordered laboratory tests, rarely used drugs, or newly approved drugs where usage has yet to  
292 pick up, the use of CERT400 may hinder detection of safety signals, since there may be  
293 insufficient cases to meet the minimum. With the growth of electronic data in healthcare  
294 databases and linkages across multiple institutions, however, we anticipate that the rising  
295 volume of data will overcome the limitation of having this threshold of cases for evaluating  
296 the algorithm.

297 Other groups have been investigating a variety of data mining methodologies to query health  
298 records for identification of ADRs based primarily on clinical features.<sup>11-16</sup> One notable effort  
299 is the Sentinel Initiative funded by the United States Food and Drug Administration. Specific  
300 queries of interest are submitted to the Sentinel coordinating center, which sends computer  
301 programs to data partners to extract and aggregate data on administrative and insurance  
302 claims data of over 180 million subjects.<sup>17</sup> The Sentinel group successfully identified  
303 intussusception after rotavirus vaccination in infants<sup>13</sup> and risk of coeliac disease in patients  
304 on long-term therapy with olmesartan<sup>18, 19</sup> from algorithms applied to their extensive  
305 databases. The Observational Medical Outcomes Partnership investigated methods that  
306 relied primarily on diagnosis codes in administrative databases.<sup>11, 20, 21</sup> Our dataset had  
307 limited structured diagnostic coding, which made it challenging for us to explore algorithms  
308 that rely on codes such as ICD-9.

309 Methods using abnormal laboratory values for identifying ADRs have been investigated  
310 previously. In a study by Levy et al<sup>22</sup>, automatic laboratory signals were generated when a  
311 specific laboratory value met a pre-defined criteria and tested on a prospective cohort of 192  
312 patients. A list of cases was generated for further manual review. The false positive rate  
313 throughout the entire study period was 83%, which is a likely barrier to implementation.  
314 Ramirez et al implemented a prospective program based on automatic laboratory signals (ALS)  
315 for 54,525 hospitalisations in Spain.<sup>23</sup> The algorithm flagged patients whose laboratory values  
316 met the criteria specified for six serious ADRs, but did not include a temporal relationship with  
317 drug intake, hence the cases needed to be manually reviewed to determine if the timing of  
318 drug intake could account for the abnormal laboratory values. The authors concluded that  
319 this was an intensive manual process requiring considerable effort.

320 Liu et al<sup>3</sup> aimed to have a more automated methodology that incorporated a temporal  
321 relationship with drug exposure. Abnormal laboratory results were correlated with specific  
322 drug administration by comparing the outcomes of drug-exposed and a matched unexposed

323 group; higher thresholds for categorizing a laboratory result as abnormal were used and a  
324 minimum of 25 cases was required. When benchmarked with two reference datasets (the  
325 same 10 drugs evaluated by Yoon et al. or 9 other drugs), the reporting odds ratio (ROR)  
326 method performed best when applied to an EMR database containing four times more unique  
327 patients than the NUH database (PPV 77% and 58% respectively, sensitivity 61% and 67%,  
328 respectively).

329 In summary, we have demonstrated the transferability of the CERT algorithm to a health care  
330 institution of another country. We have developed a reference standard of drug-laboratory  
331 abnormalities for 53 drugs based on the 2015 version of UpToDate® to evaluate CERT on our  
332 data, and which can also be used to benchmark other published algorithms. CERT400, a  
333 modification of CERT which only accepts results generated from more than 400 drug-  
334 laboratory abnormality cases, gave the best overall performance with a PPV of 53.9% and  
335 sensitivity of 67.2% (F-score 59.8%). High PPV for increased AST and ALT enzyme levels, BUN  
336 and serum creatinine suggests that CERT would be particularly useful for identifying drug-  
337 induced hepatic and renal toxicities. The ability of CERT400 to sift through a large volume of  
338 laboratory tests obtained before and after drug exposure and identify potential signals with  
339 reasonable positive predictive value and sensitivity indicates that it will be a useful tool to add  
340 to a pharmacovigilance programme.

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342 **Tables and Figures**

343

344 **Table 1: Database size and number of patient visits used for CERT comparison between Ajou**  
345 **University Hospital and NUH**

	<b>Ajou University Hospital</b>	<b>NUH</b>
Number of patient visits*	1,011,055	272,328
Drug	Number of Visits	
Ciprofloxacin	16,706	17,576
Clopidogrel	19,188	28,672
Levofloxacin	9,059	4,673
Ranitidine	68,995	7,474
Rosuvastatin	4,811	2,252
Valproic acid	11,523	4,300

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347 \*Number of hospitalizations during which the patient received at least one dispensing of the drug.

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350 **Table 2: Number of patient visits for 47 drugs used in Round 2**

<b>Drug</b>	<b>No. of patient visits</b>	<b>Drug</b>	<b>No. of patient visits</b>
Aciclovir	5,353	Ezetimibe	2,809
Alendronic acid	2,009	Famotidine	23,590
Allopurinol	8,694	Fenofibrate	6,552
Amikacin	1,629	Fluconazole	3,566
Amoxicillin-Clavulanic Acid	116,511	Gentamicin	13,512
Ampicillin	4,850	Gliclazide	8,622
Azithromycin	5,812	Hydrochlorothiazide	6,811
Carbamazepine	1,373	Imipenem-cilastatin	3,509
Carvedilol	40,013	Isoniazid	1,610
Cefazolin	26,750	Itraconazole	629
Ceftazidime	7,228	Levetiracetam	7,955
Ceftriaxone	74,834	Losartan	19,158
Celecoxib	3,266	Meropenem	26,273
Chlorpheniramine	26,790	Metformin	55,881
Clarithromycin	17,382	Metronidazole	22,212
Clindamycin	3,869	Omeprazole	163,999
Cloxacillin	6,505	Phenytoin	5,136
Cotrimoxazole	14,969	Piperacillin-Tazobactam	14,843
Digoxin	17,338	Pyrazinamide	1,061
Domperidone	10,004	Rifampicin	1,758
Doxycycline	1,813	Risedronic acid	1,551
Enalapril	57,621	Simvastatin	81,590
Entecavir	1,368	Vancomycin	34,028
Ethambutol	1,328		

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**Table 3: Variations of the original CERT algorithm**

Algorithm	Input (laboratory test results)	Observation period after drug exposure	Minimum no. cases required	Statistical test
Original	Extreme values	Till discharge	2	Paired t-test & McNemar's test
Variation 1	Extreme values	12 days	2	Paired t-test & McNemar's test
Variation 2	Extreme values	(n+2) laboratory test results	2	Paired t-test & McNemar's test
Variation 3	Average of the two most extreme values	Till discharge	2	Paired t-test & McNemar's test
Variation 4	Extreme values	Till discharge	2	Paired t-test & Wilcoxon's signed-rank test
Variation 5 (CERT400)	Extreme values	Till discharge	400	Paired t-test & McNemar's test

**Variation 1:** Limit the unit of observation to 12 days after drug exposure, which is the mean (7.1 days) plus 2 times the standard deviation (2.6 days) of the time from drug administration to the time the extreme post-drug laboratory value was taken for all true positive cases.

**Variation 2:** Limit the unit of observation to a maximum of (n+2) laboratory test results for each encounter, where n is the number of laboratory tests before the drug was started.

**Variation 3:** Take the mean of the two most extreme values for both the pre- and post-drug periods, to minimize the possibility that a single extreme value, such as one caused by measurement error, would unduly influence the result.

**Variation 4:** Use the non-parametric Wilcoxon's signed-rank test to replace the McNemar's test.

**Variation 5 (Post-hoc variation):** Impose a minimum of 400 cases for each drug-laboratory test pair based on results shown in Figure 1.

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359 **Table 4A: Performance Metrics of CERT: Comparison between NUH and Ajou\***

	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	F-score (%)	Avg. No. of signals detected per drug
NUH	57.0	58.1	48.6	63.9	52.5	113/6 = 18.8
Ajou University Hospital	57.4	66.6	69.4	52.1	62.8	155/6 = 25.8

360 *Average performance for the 6 drugs from original paper*

361 *\*Results are benchmarked according to the 2010 Version of UpToDate used in original CERT paper. Six*  
362 *drugs included in the comparison are ciprofloxacin, clopidogrel, levofloxacin, ranitidine, rosuvastatin,*  
363 *and valproic acid*

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366 **Table 4B: Performance Metrics of CERT: Comparison between Rounds 1 and 2 based on NUH EMR**  
367 **data\***

	No. of evaluated drugs	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	F-score (%)	Avg. No. of signals detected per drug
Round 1	6	63.4	55.1	49.8	66.8	55.8	113/6 = 18.8
Round 2	47	45.6	70.6	55.5	64.4	50.1	885/47 = 18.8
Total	53	47.6	68.9	54.8	64.6	51.0	998/53 = 18.8

368 *\*Results are benchmarked according to 2015 Version of UpToDate*

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374 **Table 5: Performance Metrics of CERT algorithm for 53 drugs – Comparison across Laboratory**  
 375 **Panels\***

376 **A) Analysis according to the original CERT algorithm for laboratory panels or**  
 377 **selected tests**

<b>Laboratory Panel or Test</b>	<b>Avg. no. of cases</b>	<b>No. of positive Signals</b>	<b>PPV (%)</b>	<b>NPV (%)</b>	<b>Sensitivity (%)</b>	<b>Specificity (%)</b>	<b>F-score (%)</b>
Hemato- poiesis and coagulation	2634	600	44.7	71.7	67.3	49.8	53.7
Hepatobiliary enzymes	1507	228	63.6	31.5	59.7	35.2	61.6
AST	1532	15	86.7	26.3	31.7	83.3	46.4
ALT	1533	26	92.3	37.0	58.5	83.3	71.6
Renal function and urine tests	3867	75	61.3	35.7	46.0	50.8	52.6
BUN	3835	30	76.7	39.1	62.2	56.3	68.7
CRE	3848	5	80.0	29.2	10.5	93.3	18.6
K	3917	40	47.5	53.8	76	25	58.5
Lipids and metabolism	80	32	25.0	82.8	16.7	88.9	20.0
Hormones	104	14	14.3	89.1	16.7	87.2	15.4
Others	1158	49	34.7	71.1	15.5	87.7	21.4

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**B) Analysis according to the CERT400 algorithm for laboratory panels or selected tests**

<b>Laboratory Panel or Test</b>	<b>Avg. no. of cases</b>	<b>No. of positive Signals</b>	<b>PPV (%)</b>	<b>NPV (%)</b>	<b>Sensitivity (%)</b>	<b>Specificity (%)</b>	<b>F-score (%)</b>
Hemato- poiesis and coagulation	3663	512	48.8	64.9	74.9	37.2	59.1
Hepatobiliary enzymes	2255	177	64.4	33.9	73.5	25.0	68.7
AST	2042	12	91.7	26.9	36.7	87.5	52.4
ALT	2000	23	91.3	37.5	67.7	75.0	77.8
Renal function and urine tests	4408	69	62.3	36.2	49.4	49.0	55.1
BUN	4372	27	74.1	36.8	62.5	50.0	67.8
CRE	4386	5	80.0	29.3	12.1	92.3	21.1
K	4466	37	51.4	66.7	86.4	25	64.4
Lipids and metabolism	639	5	40	40	40	40	40
Hormones	567	1	0	100	Not valid	50	Not valid
Others	2682	45	33.3	73.6	34.1	73.0	33.7

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*\*Results are benchmarked according to 2015 Version of UpToDate*



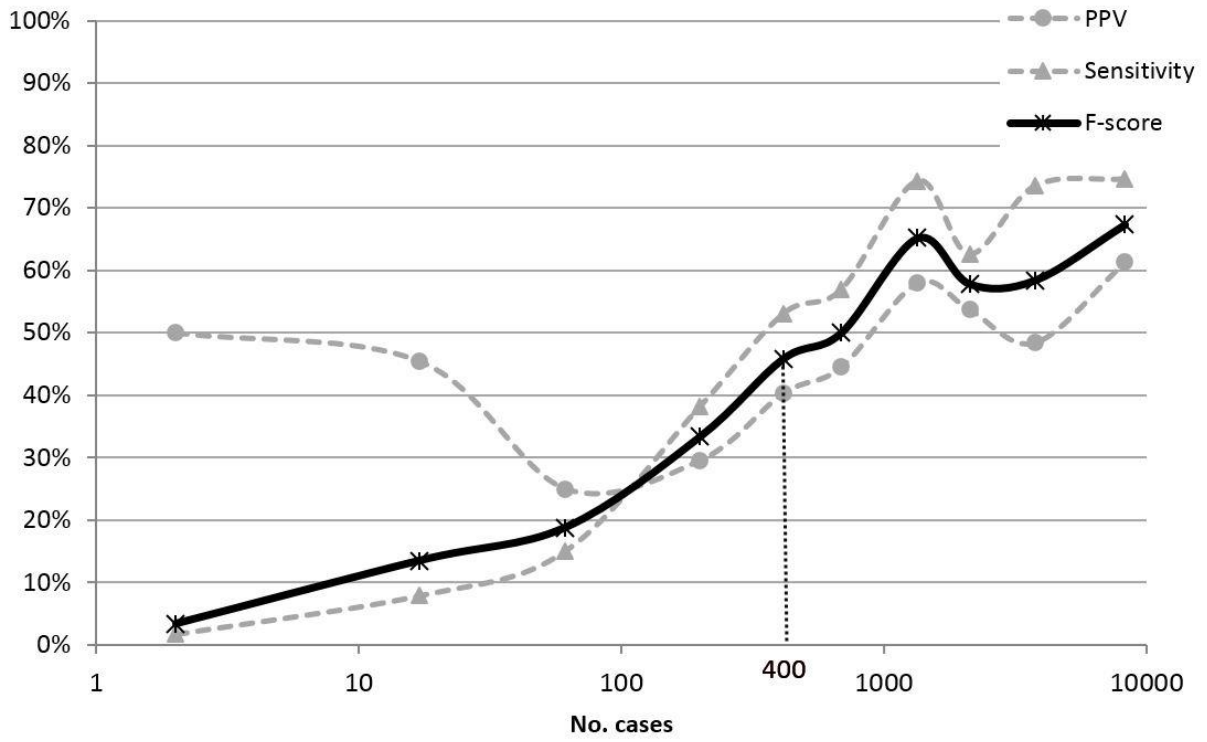
385 **Table 6: Performance Metrics for the Original CERT Algorithm and 5 Variations\***

Variation	No. of cases (Avg)	No. of positive Signals	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	F-score (%)
Original	1899	998	50.3	67.2	54.1	65.4	52.1
Variation 1	1853	761	50.6	64.5	40.3	74.1	44.9
Variation 2	1899	707	51.6	64.6	38.3	76.8	44.0
Variation 3	1833	905	49.1	65.6	48.4	68.2	48.7
Variation 4	1898	1385	44.8	64.4	66.9	45.0	53.7
Variation 5 (CERT400)	2969	792	53.9	53.5	67.2	42.3	59.8

386 *\*Results are benchmarked according to 2015 Version of UpToDate for 53 drugs and 44 laboratory*  
 387 *abnormalities*

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406 **Figure 1: CERT Algorithm: Dependence of PPV, Sensitivity and F-score on Number of Cases\***

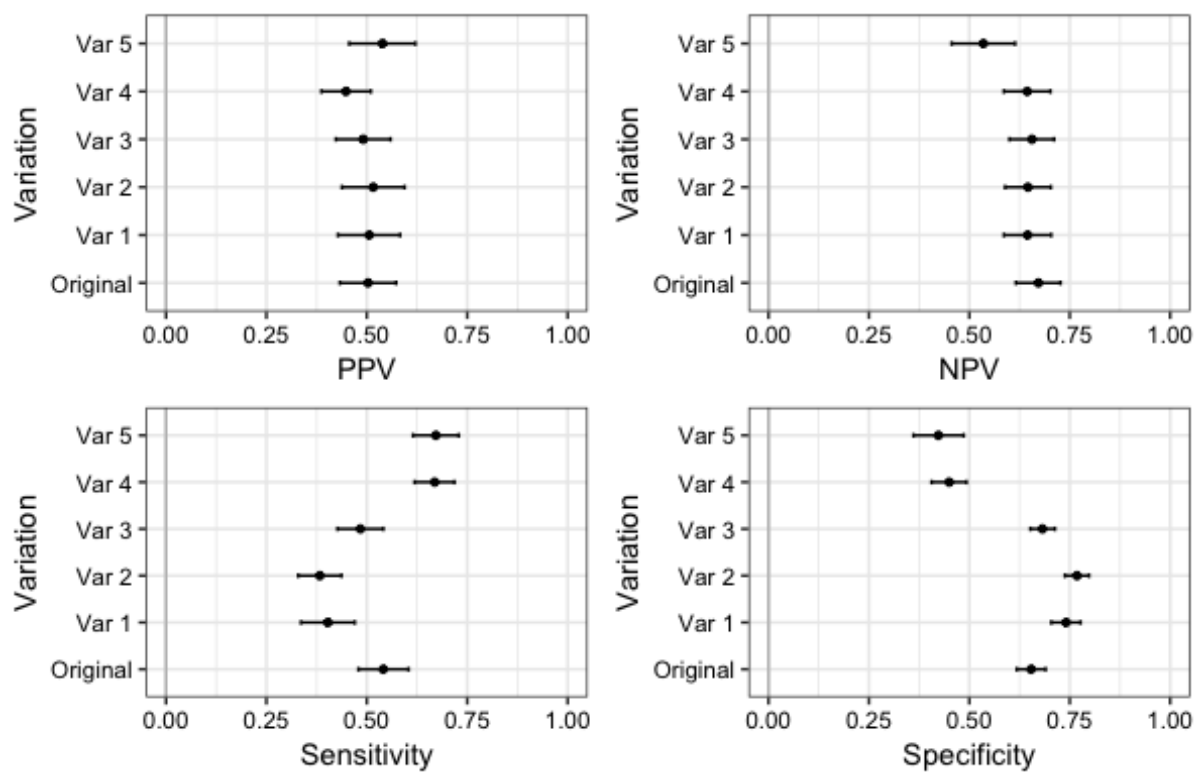


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408 \*53 drugs, 44 laboratory abnormalities

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410 **Figure 2: Performance metrics and 95% confidence interval based on random effects meta-analysis**  
411 **for all the 53 drugs.**



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414 **Supplementary tables: (Recommended to put as additional supporting information online)**

415 Table S1: List of the 44 selected laboratory test abnormalities according to the laboratory panels.

<b>Hematopoiesis and coagulation</b>		<b>Renal function and urine tests</b>	
Activated partial thromboplastin time	Increased	Blood urea nitrogen	Increased
	Decreased	Creatinine	Increased
Basophil	Decreased	Potassium	Increased
Eosinophil	Increased	<b>Lipids and metabolism</b>	
	Decreased	Cholesterol	Increased
Fibrinogen	Decreased	Glucose	Increased
Hematocrit	Decreased		Decreased
Hemoglobin	Increased	LDL cholesterol	Increased
	Decreased	Triglyceride	Increased
Lymphocyte	Increased	<b>Hormones</b>	
Neutrophil	Decreased	Free thyroxine	Increased
Platelet	Increased		Decreased
	Decreased	<b>Others</b>	
Prothrombin time	Increased	Ammonemia	Increased
	Decreased	Amylase	Increased
Red blood cell	Decreased	Creatine kinase	Increased
Reticulocyte	Increased	Lactate dehydrogenase	Increased
	Decreased	Lipase	Increased
White blood cell	Increased	Sodium	Decreased
	Decreased	Uric acid	Increased
<b>Hepatobiliary enzymes</b>			
Alanine transaminase	Increased		
Alkaline phosphatase	Increased		
Aspartate transaminase	Increased		
Direct bilirubin	Increased		
Gamma-glutamyl transpeptidase	Increased		
Protein	Decreased		
Total bilirubin	Increased		

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419 Table S2 (a): Evaluation metrics PPV, NPV, sensitivity (sens), specificity (spec) and F-score.

Algorithm Result	2010/2015 Version of UpToDate		
	Present	Absent	
Positive	$TP$	$FP$	$PPV = \frac{TP}{TP + FP}$
Negative	$FN$	$TN$	$NPV = \frac{TN}{FN + TN}$
	$sens = \frac{TP}{TP + FN}$	$spec = \frac{TN}{FP + TN}$	$F - score = \frac{2 \times PPV \times Sensitivity}{PPV + Sensitivity}$

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421 Table S2 (b): Example to show the performance metrics for ALT laboratory test abnormality on the  
 422 53 drugs we tested.

Algorithm Result (for ALT)	2015 Version of UpToDate (for ALT)		
	Present	Absent	
Positive	24	2	$PPV = \frac{24}{26} = 92\%$
Negative	17	10	$NPV = \frac{10}{27} = 37\%$
	$sens = \frac{24}{41} = 59\%$	$spec = \frac{10}{12} = 83\%$	$F - score = 72\%$

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425 Table S3: Reference Standard of drug ADRs developed from UpToDate® 2015\*

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**Table S3 - Ref  
Standard 1.pdf**



**Table S3 - Ref  
Standard 2.pdf**

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428 \*This table is uploaded separately online as well.

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