Development and preliminary validation of a dynamic, patient-tailored method to detect abnormal laboratory test results

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Background

• Most clinical decisions involve lab results.
• Failure to follow up laboratory test results is a major concern in primary care.
• Electronic Health Records (EHRs) can support General Practitioners (GPs).
• GPs spend ~1 hour per day processing alerts.

Alert fatigue and patient safety issues
Example

Series of potassium observations for one patient

Observation value [mmol/l]
Population-based reference intervals

Series of potassium observations for one patient
Methods:
Mixed-effects model

If $y_{ij} \sim N(\alpha_i, \sigma^2)$, $\alpha_i \sim N(\mu, \omega^2)$, then $\alpha_i \mid \bar{y}_{ij} \sigma^2, \mu, \omega^2 \sim N(\tilde{\mu}_{ij}, V_{ij})$ where

$$
\tilde{\mu}_{ij} = \frac{\mu \omega^{-2} + \bar{y}_{ij} n_{ij}}{\omega^{-2} + \frac{n_{ij}}{\sigma^2}}
$$

and

$$
V_{ij} = (\omega^{-2} + \frac{n_{ij}}{\sigma^2})^{-1}
$$

Equivalently,

$$
\tilde{\mu}_{ij} = \mu \lambda_{ij} + (1 - \lambda_{ij}) \bar{y}_{ij}
$$

(1)

$$
\lambda_{ij} = \frac{\omega^{-2}}{\omega^{-2} + \frac{n_{ij}}{\sigma^2}} = \frac{\sigma^2}{\omega^2 + \frac{\sigma^2}{n_{ij}}} = \frac{V_{ij}}{V_{ij} + \omega^2}
$$

(2)

• $\mu$ and $\omega^2$ are population mean and variance;
• $y_{ij}$ is the jth observation of patient i;
• $\alpha_i$ is the mean of patient i;
• $\sigma^2$ is the intra-patient variance;
• $\bar{y}_{ij}$ and $n_{ij}$ are the sample mean and number of observations for patient i after j observations;
• $\tilde{\mu}_{ij}$ and $V_{ij}$ are the maximum likelihood estimates of $\alpha_i$ and $\sigma^2$;
• $\lambda_{ij}$ is the shrinkage factor.
Mixed-effects model: Example on patient data

Series of potassium observations for one patient

- Observation value [mmol/l]

- Pt observations
- Patient-tailored 95% RI
- Population-based 95% RI
- Patient-tailored alert
- Population-based alert
Methods: data source and study design

- Salford Integrated Record database (population ~234k, UK).
- Registered patients aged 18-85 between 1990-2012.
- Potassium measurements.
- Training dataset ~150k patients.
- Test dataset 500 patients.
- Clinical relevance of alerts assessed by a survey administered to GPs (gold standard).
Series of potassium observations, gender= M, age= 43

What colour this value (black dot) should be flagged?

- Green (normal value; i.e. no actions required)
- Yellow (probably abnormal; i.e. repeat in more than a week, do further test, change medication)
- Red (definitely abnormal; i.e. repeat urgently, hospital admission)
Survey: respondents characteristics

- Survey administered to 43 GPs in Manchester (UK)
- Response rate 44% (19 out of 43)
- Each value was assessed by a median of 3 GPs

<table>
<thead>
<tr>
<th>Respondent characteristic</th>
<th>Reply</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days per week in practice</td>
<td>1-3 days</td>
<td>10 (52.6%)</td>
</tr>
<tr>
<td></td>
<td>4-5 days</td>
<td>9 (47.4%)</td>
</tr>
<tr>
<td>Years of experience</td>
<td>&lt;10 years</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td></td>
<td>10-20 years</td>
<td>5 (26.3%)</td>
</tr>
<tr>
<td></td>
<td>&gt;20 years</td>
<td>12 (63.2%)</td>
</tr>
<tr>
<td>Opinion about tests alerts in general practice</td>
<td>Not enough</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td></td>
<td>About right</td>
<td>7 (36.8%)</td>
</tr>
<tr>
<td></td>
<td>Too much</td>
<td>8 (42.1%)</td>
</tr>
</tbody>
</table>
# Results: Alerts prevalence, PPV and sensitivity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard method</th>
<th>Patient-tailored method</th>
<th>Combined method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence (N) in test dataset (n=4,144)</td>
<td>11.3% (470)</td>
<td>9% (372)</td>
<td>7.3% (301)</td>
</tr>
<tr>
<td>Prevalence (N) in values assessed by GPs (n=152)</td>
<td>50% (76)</td>
<td>50% (76)</td>
<td>25% (38)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.51</td>
<td>0.41</td>
<td>0.38</td>
</tr>
<tr>
<td>PPV</td>
<td>0.66</td>
<td>0.67</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Results: Mixed-effects logistic regression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard method pos. vs neg.</td>
<td>24.5* [5.3,113.7]</td>
</tr>
<tr>
<td>Patient tailored method pos. vs. neg.</td>
<td>6.2* [2.0,19.1]</td>
</tr>
<tr>
<td>Weekly working days in GP: 4-5 days vs 1-3 days</td>
<td>2.2 [0.4,11.3]</td>
</tr>
<tr>
<td>Years of experience in GP: 10-20 years vs &lt;10 years</td>
<td>3.5 [0.4,11.3]</td>
</tr>
<tr>
<td>Years of experience in GP: &gt;20 years vs &lt;10 years</td>
<td>6.0 [0.3,103.1]</td>
</tr>
<tr>
<td>Opinion about tests alerts in GP: not enough vs about right</td>
<td>0.5 [0.7,3.7]</td>
</tr>
<tr>
<td>Opinion about tests alerts in GP: too much vs about right</td>
<td>0.2 [0.1,1.3]</td>
</tr>
</tbody>
</table>

Estimated variance of the random effects:

- assessor: 1.5 (SD:1.2)
- value: 0.4 (SD: 0.6)

*statistically significant
Conclusions:

• personalising alerts for lab results could provide useful information to clinicians;

• by combining both methods together systems could be used to prioritise alerts.

Future work:

• introduce time-dependency;

• extending evaluation to other lab tests (i.e. eGFR, calcium, creatinine);

• further alert personalisation with info in EHR (i.e. age, gender, comorbidities etc).
Presented project in collaboration with

Thanks for your attention

A partnership between

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