Variation in f-Hb concentration means that two samples are better than one.

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Outline

• Variation between samples and between clinical phenotypes.
• Result concordance (1\textsuperscript{st} and 2\textsuperscript{nd} samples) by cut-off and phenotype.
• What happens with simultaneous adjustment of the two test parameters: cut-off and sample-number.
  • Sensitivity for advanced colorectal neoplasia (ACN)
  • Population positivity rate at equivalent sensitivity
• Modelling number needed to colonoscope (NNC) to detect one case with ACN (a surrogate for cost-effectiveness).

Background

- Quantitative faecal immunochemical tests (FIT) allow flexibility in screening for colorectal neoplasia (by adjusting operating characteristics to suit goals).
- But we know that there is day to day variation in the faecal haemoglobin concentration (f-Hb).
- Consequently, sampling just one stool rather than two increases the risk of missing a significant lesion, especially advanced preinvasive lesions which bleed less than cancers.
- There has been little consideration of the workload implications when positivity cut-off is assessed in relation to the number of samples collected.
  - Many organised screening programs adjust the positivity cut-off so as to control the colonoscopy workload in the context of requiring just one sample.
Key consideration

- If lesions bled into the same sized stool at the same rate each day we would only need one sample.
- But as you can see from the hundreds of samples studied here, that is not the case.
CONTEXT AND AIMS

In an elevated-risk population undergoing 3rd-5th yearly colonoscopy and undertaking 2-sample FIT in the intervening years (the SCOOP program), we performed an observational study which explored:

• Variation in f-Hb between samples
• Sensitivity of FIT for ACN, and the associated population test positivity (colonoscopy workload) rates, across a range of independently-adjusted combinations of
  • F-Hb cut-off for positivity, and
  • Sample number.
• Colonoscopic effort needed to detect one ACN lesion (relevant to cost-effectiveness)
Case disposition and phenotypes

- Active in colonoscopy surveillance program (July 2008 – April 2019) N=31,530 patients
- Offered FIT N=19,229 patients
- Returned FIT N=12,713 patients
- Returned FIT with 2 correctly completed samples N=12,710 patients; N=32,413 occasions
- Colonoscopy performed within 12 months of FIT N=3,499 patients
- Quality colonoscopy with verified diagnosis N=3,349 patients; N=4,037 occasions

Data used for population test positivity rate and within-individual f-Hb variation

7.0% positive; 2-sample @20µg/g

Graph:
- Fecal Hemoglobin (µg/g feces)
- Data used for sensitivity estimations
- Median, IQR
- P<0.001 vs all others
- P=0.08
Variation between 1st and 2nd samples

Faecal haemoglobin concentration (µg/g)

Case number

Advanced adenoma

f-Hb (µg/g faeces)

Sample 1 Hb (µg/g)
Sample 2 Hb (µg/g)
Concordance between 1\textsuperscript{st} and 2\textsuperscript{nd} samples*

- A positive in both samples was most likely for cancer and for lower cut-offs (both p<0.001).
- The proportion positive in just one was higher if including adenomas.
- No systematic fixed bias.
- There was large within-subject variability; the ratio for the 2\textsuperscript{nd} to the 1\textsuperscript{st} sample was:
  - up to 18-fold for all cases, and
  - up to 56-fold for ACN

*Bland-Altman analysis
ACN sensitivity by number/cut-off combo

![Graph showing sensitivity vs. positivity threshold (μg Hb/g feces)]
Population positivity by number/cut-off combo
Population positivity by equivalent sensitivity

- 1-sample sensitivity
- 2-sample sensitivity
- 1-sample positivity
- 2-sample positivity

Sensitivity (CRC and AA) vs. Population Positivity rate

Positivity threshold (µg Hb/g feces)
Modelling number needed to colonoscopy

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Sample number</th>
<th>Population positivity rate (% , 95% CI)</th>
<th>Sensitivity for advanced neoplasia (% , 95% CI)*</th>
<th>Number of lesions found (n)*</th>
<th>Number needed to colonoscopy (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10μg Hb/g</td>
<td>1-sample\textsuperscript{a}</td>
<td>7.9 (7.6, 8.2)</td>
<td>44.1 (40.2, 48.1)</td>
<td>276</td>
<td>9.29 (8.31, 10.42) \textsuperscript{a}</td>
</tr>
<tr>
<td></td>
<td>2-sample</td>
<td>12.1 (11.7, 12.5)</td>
<td>59.7 (55.8, 63.6)</td>
<td>374</td>
<td>10.49 (9.52, 11.58)</td>
</tr>
<tr>
<td>25μg Hb/g</td>
<td>1-sample\textsuperscript{b}</td>
<td>3.7 (3.5, 3.9)</td>
<td>29.6 (26.0, 33.3)</td>
<td>185</td>
<td>6.52 (5.71, 7.49)</td>
</tr>
<tr>
<td></td>
<td>2-sample\textsuperscript{a}</td>
<td>5.9 (5.7, 6.2)</td>
<td>46.6 (42.7, 50.6)</td>
<td>292</td>
<td>6.59 (5.93, 7.36) \textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} pair “a” on the previous slide
Three-dimensional modelling

Sensitivity for Advanced Neoplasia (%)

Number needed to colonoscope (N Ninety) per lesion detected, effort.
An International Comparison

Australian settings* vs those of another.

<table>
<thead>
<tr>
<th>Parameter combination</th>
<th>No. needed to colonoscopy</th>
<th>Positivity rate (%)</th>
<th>Sensitivity for ACN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-FIT @ 20μg/g*</td>
<td>6.71</td>
<td>7.0%</td>
<td>54.3%</td>
</tr>
<tr>
<td>1-FIT @ 40μg/g</td>
<td>6.70</td>
<td>2.4%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

This 2-sample@20 FIT detects almost 3 times more ACN at similar NNC (cost effectiveness)
Key Findings

- There is large variation in f-Hb between samples.
- Variation in f-Hb between samples is such that both parameters are crucial determinants of sensitivity and workload; independent adjustment of each should be considered.
- Advanced adenomas are especially at risk of being missed when sampling one stool, and especially when using a higher test cut-off.
- When a program’s goal aims for a higher sensitivity for cancer plus advanced preinvasive lesions and where a colonoscopy workload of >5% is feasible, a 2-sample test requires less colonoscopic effort per lesion detected.