Faecal Immunoassay Test

Pre-submission ID: 62

Full Submission ID: 25

Reviewer’s Questions in bold font

#Reviewer 1

1. **Provision of test device package inserts for further details.**

   **Response:**
   
   Auto sampling bottle. The device package for the patients’ use contains the needed consumables useful for the patient to perform the test, as self-test. An Auto sampling bottle is provided; it contains a sample probe with a spiral-shaped end to collect the faecal sample. Sampling bottle contains 2.0 mL of buffer solution, made with 50mM HEPES buffer [4-(2-hydroxyethyl)-1-piperazinethanesulfonic acid] and <0.1% sodium azide. The self-collected sample is ready for the automatized testing.

2. **Provision of pricing per test, cost of the automated analyzer and studies on the cost-effectiveness.**

   **Response:**
   
   An analysis from a third-party health-care payer perspective has been conducted, modelling chemical (guaiac) and FIT automated test for 40-year-old screening participants at average risk of colorectal cancer, in Ontario (Goede SL, Plos One 2017). Assuming a willingness-to-pay threshold of CAN$50,000 per QALY gained, FIT every year between age 45–80 years would be the preferred strategy over guaiac test, providing 49 QALYs per 1,000 participants. The costs estimated were lower for FIT than guaiac test, considering a higher detection of adenoma—a preinvasive lesion curable with endoscopic resection, so preventing the progression into invasive tumour (that requires more expensive treatments). Moreover, in a systematic review and cost-effectiveness analysis by Westwood M et al (Health Technol Assess. 2017), Faecal immunochemical testing is likely to be a clinically effective and cost-effective strategy for triaging people who are presenting, in primary care settings, with lower abdominal symptoms and who are at low risk for colorectal cancer. According to the manufacturer’s price to the public, the cost for one kit is 25 USD, in USA. According to more recent literature, the cost per person ranges from £25 to £62, in England. In South Africa, the test is sold at 1179 Rands (70 dollars), 60 USD in India.

3. **Change of the purpose as follows: “qualitatively detect occult blood in stool as an indication for a number of gastrointestinal tract abnormalities such as colorectal cancer, colonic polyps, haemorrhoids, Crohn's disease, ulcerative colitis”.”

   **Response:**
   
   I agree, perhaps I would restrict the possible diagnosis. Though the test is able to detect different sources of occult bleeding, the aim of the screening is to early diagnose colorectal cancer or pre-invasive tumours in asymptomatic patients, in the general population; the test is not supposed to screen for inflammatory bowel disease and benign conditions. This means that the test is not used in the setting of symptomatic patients, as it pertains to this submission, to orient the need of colonoscopy in patients with abdominal symptoms or iron-deficient anaemia. As it is supposed to be delivered at population-level for screening of colorectal cancer and not in a clinical referral pathway for symptomatic patients, I would suggest: “qualitatively detect occult blood in stool for the early diagnosis of colorectal cancer and adenoma”.
4. **It will be better if the assay format “Latex turbidimetric immunoassays”.**

   Response:
   Agree.

**#Reviewer 2.**

1. **Please provide more details regarding testing categorisation are required.**

   Response:
   FIT can be categorized in qualitative and quantitative test. In a meta-analysis of 4 qualitative and 4 quantitative FIT brands, the performance characteristics for colorectal cancer detection were similar. However, although the positivity rate of the qualitative test was 3 times higher than the quantitative one (8.1% vs 2.5% in Park MJ et al, Scand J Gastroenterol. 2012), there was an improved positive predictive value for cancer with the quantitative test (14.4% vs 5.2%), which is predictable using a more-specific, less-sensitive test (Lee JK et al, Ann Intern Med 2014). The position of the US Multi-Society Task Force on colorectal cancer is to propend more favourably for the quantitative assay, available as automated and well-studied device, appearing to have an advantage in consistency of performance, efficiency, and quality control. Issues of quality control for qualitative tests have been reported (Robertson DJ, GASTROINTESTINAL ENDOSCOPY 2017).

FIT can be also categorized according to the analytic sensitivity, intending the minimal quantity of occult blood that can be detected. Different formats are commercially available, ranging between 25 to 200 ng/ml minimal blood quantity detection. Three cohort studies, including one incidence-based mortality study, showed relative risks of death from colorectal cancer that were 10 to 40% lower among persons who had undergone FIT screening than among controls (Lauby-Secretan B et al, NEJM 2018). These cohorts are:

<table>
<thead>
<tr>
<th>Screening program</th>
<th>Kit used</th>
<th>Threshold of detection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>One Million Taiwanese Screening Program</td>
<td>Eiken OC-SENSOR</td>
<td>100 ng/mL</td>
<td>Han-Mo Chiu, Cancer 2015</td>
</tr>
<tr>
<td></td>
<td>Kyowa HM-JACK</td>
<td>8 ng/mL *</td>
<td></td>
</tr>
<tr>
<td>Reggio Emilia (Italy) organized screening program.</td>
<td>NR</td>
<td>NR</td>
<td>Rossi G et al, Am J Gastroenterol 2015</td>
</tr>
<tr>
<td>Florence district trial (Italy)</td>
<td>OC-Hemodia, Eiken,</td>
<td>100 ng/ml</td>
<td>Ventura L et al, Digestive and Liver Disease 2014</td>
</tr>
</tbody>
</table>

*no subgroup analysis per analytic sensitivity reported.

The World endoscopy Organization (Colorectal cancer screening committee) suggested a cut-off of 75 ng/ml, as more cost-effective and to pilot the screening programs starting with a cut-off of 50 ng/ml. A scoping revision of the FIT used across the countries, revealed differences and heterogeneities. The majority of countries reported a device with a cut-off 100 ng/mL (Canada, England, Italy, Uruguay). REF: http://www.worldendo.org/wp-content/uploads/2016/08/weo_expert_working_group_fit_meeting_report_orlando2013.pdf

A study from Thailand explored the optimal cut-off level of the fecal immunochemical test for colorectal cancer screening in a country with limited colonoscopy resources (Aniwan S et al, Asian Pac J Cancer Prev. 2017). The authors reported that all cut-off points provided a high negative predictive value (NPV) (>90%). For colorectal cancer, the miss rate for FIT 25ng/ml to FIT 150ng/ml was the same (21%), whereas that with FIT 200 ng/ml increased to 35%. The cut-off 150ng/ml was considered appropriate for the context of the country in term of clinical performance and resource utilization.
The aim of the submission is to acknowledge the FIT as a screening device for colorectal cancer, consistently with the indications of the International Agency for Research on Cancer (IARC). Speculations can be applied for the resource utilization and policy-dialogue for the optimal threshold, ranging between 50-100 ng/ml (high-income countries standards) and 150ng/ml (selected countries). Quantitative test are preferred.

2. Its use in testing environmental conditions is required. Specifically, sample stability is what I think they want here.

Response:
A head-to-head comparison of Hb stability in a standardized fashion for various FIT tests was provided, assessing quantitative and qualitative FITs. “Stability” was studied, defined as the number of days until the percentage of hemoglobin (Hb) recovery was predicted to drop below 80% of the baseline concentration, at day 0 (Catomeris P et al, Archives of Pathology & Laboratory Medicine 2018).

<table>
<thead>
<tr>
<th>FIT test</th>
<th>Manufactures</th>
<th>FIT type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb NS-Plus</td>
<td>Alfresa Pharma Corporation (Chuo-ku, Osaka, Japan)</td>
<td>Quantitative</td>
</tr>
<tr>
<td>OC-Sensor Diana</td>
<td>Eiken Chemical Co, Ltd (Taito-ku, Tokyo, Japan)</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Hema-Screen SPECIFIC</td>
<td>Immunostics, Inc (Eatontown, New Jersey)</td>
<td>Qualitative</td>
</tr>
<tr>
<td>FOB Advanced</td>
<td>uli med (Ahrensburg, Germany)</td>
<td>Qualitative</td>
</tr>
<tr>
<td>Hemoccult ICT</td>
<td>Beckman Coulter, Inc (Brea, California)</td>
<td>Qualitative</td>
</tr>
</tbody>
</table>

The performance of the tests was compared, with regard to the stability at different temperatures:
- frozen, −20° to −15°C (~4° to 5°F)
- refrigerated, 2°C to 8°C (36°F to 46°F)
- ambient, 20°C to 22°C (68°F to 72°F)
- elevated, 45°C (113°F).

Freezing the devices produced an initial decrease of 20% in Hb recovery, but then Hb recovery remained stable over time thereafter for that temperature condition. There were decreasing recoveries with increasing temperature and increasing time for the other temperature conditions. Across all temperature conditions, there was a tendency toward better stability for one of the quantitative devices (NS Plus). The period of stability of frozen samples ranged between 4.5 and 9.9 days, for the quantitative devices; as refrigerated, range was 37.4 and over 60 days; at ambient temperature, 4.6-6 days and 0-0.5 days at 45°C. Interestingly, no FIT performed well at 45°C; as comparison, the guaiac-based Immunostics seemed to better perform at elevated temperature (19.8 days).

The report is consistent with previously evidence, highlighting the importance of a timely and time-defined sampling and return of the test sample, addressing temperature-related issues in the preservation of the samples (van Roon AH et al, Am J Gastroenterol. 2012; Grazzini G et al, Gut 2010).