## Table 1: NHMRC Evidence Statement for clinical question: SPT1-2a:

“What signs/symptoms alone or in combination are most predictive of colorectal cancer?”

<table>
<thead>
<tr>
<th>PICO SPT1-2a:</th>
<th>Report body of evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>In symptomatic patients without a colorectal cancer diagnosis, what signs or symptoms (persistent changed bowel movements, persistent diarrhoea or constipation, unexplained rectal bleeding, general or localised abdominal pain, unexplained palpable abdominal or rectal mass, unexplained weight loss, iron deficient anaemia, tiredness, fatigue, or any combination) correlate best with a diagnosis of colorectal cancer?</td>
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</tr>
</tbody>
</table>

### 1. Evidence base (number of studies (quantity), level of evidence and risk of bias in the included studies – see body of evidence tables in report)

<table>
<thead>
<tr>
<th>Rectal bleeding</th>
<th>A One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE reviewed 16 studies (N=134794) reporting rectal bleeding. Rectal bleeding according to age was reported in 10 studies (N=33874) while rectal bleeding was reported in three studies for men (N=103846) and three studies (N=103846) for women. Of the 16 studies reported, nine were at risk of bias and seven were of low risk of bias. Fourteen of these studies were of level III-2 evidence, one study of level III-3 evidence and another study of level IV evidence. One level II study (N=1003) and one level III-2 (N=1459) were identified in the NICE update for rectal bleeding and were at risk of bias.</td>
<td>Grade D</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abdominal pain</th>
<th>B One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE reviewed five studies (N=373796) reporting abdominal pain. Abdominal pain according to age was reported in one study (N=2093) while abdominal pain was reported in one study (N=43791) for men and one study (N=43791) for women. Of the five studies reported, three were at risk of bias and two were of low risk of bias. Four of these studies were of level III-2 evidence and one contained level III-3 evidence. One level II study (N=1003) and one level III-2 (N=1459) were identified in the NICE update for abdominal pain and were at risk of bias.</td>
<td>Grade D</td>
</tr>
</tbody>
</table>

| | C One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias |
| | | D Level IV studies or Level I to III studies/SRs with a high risk of bias |
Anaemia*
NICE reviewed 10 studies (N=89550) reporting anaemia. Anaemia according to age was reported in 1 study (N=2093) while anaemia was reported in two studies (N=118672) for men and two studies (N=118672) for women. Of the 10 studies reported, seven were at risk of bias and three were of low risk of bias. Nine of these studies were of level III-2 evidence and one study contained level III-3 evidence. Two level II studies (N=1295) and one level III-2 (N=1459) study were identified in the NICE update for iron deficient anaemia and were at risk of bias.

** The available data did not allow clear distinction between iron-deficiency and non-iron deficiency anaemia.

Grade D

Constipation
NICE reviewed two studies (N=2373) reporting constipation. Constipation according to age was reported in one study (N=2093) while constipation was reported in one study (N=43791) for men and one study (N=43791) for women. These two studies were both at risk of bias. One of these studies was of level III-2 evidence and the other was of level III-3 evidence. One level II study (N=1003) was identified in the NICE update for constipation and was at risk of bias.

Grade D

Diarrhoea
NICE reviewed two studies (N=2373) reporting diarrhoea. Diarrhoea according to age was reported in one study (N=2093) while diarrhoea was reported in one study (N=43791) for men and one study (N=43791) for women. The two studies reported were both at risk of bias. One of these studies was of level III-2 evidence and the other was of level III-3 evidence. One level II study (N=1003) was identified in the NICE update for diarrhoea and was at risk of bias.

Grade D

Change in bowel habit
NICE reviewed five studies (N=692916) reporting change in bowel habit. Change in bowel habit according to age was reported in two studies (N=71315) for men and two studies (N=71315) for women. Of the five studies reported,
two were at risk of bias and three were of low risk of bias. All five studies were of level III-2 evidence. One level III-2 (N=1459) was identified in the NICE update for change in bowel habit and were at risk of bias.

**Grade D**

**Weight loss**
NICE reviewed five studies (N=88222) reporting weight loss. Weight loss according to age was reported in one study (N=2093) while weight loss was reported in one study (N=43791) for men and one study (N=43791) for women. Of the five studies reported, three were at risk of bias and two were of low risk of bias. Four of these studies were of level III-2 evidence and one study contained level III-3 evidence. One level II study (N=1003) and one level III-2 (N=1459) study were identified in the NICE update for weight loss and were at risk of bias.

**Grade D**

**Dyspepsia**
NICE reviewed three studies (N=4476) reporting dyspepsia. All three of these studies were at risk of bias and were of level III-2 evidence.

**Grade D**

**Other single symptoms**
NICE reviewed 8 studies (N=1245637) reporting other single symptoms. Of the 8 studies reported, six were at risk of bias and two were of low risk of bias. Six of the reported studies were of level III-2 evidence and two were of level III-3 evidence.

**Grade D**

**Rectal bleeding presenting with other symptoms**
NICE reviewed nine studies (N=5770) reporting rectal bleeding presenting with other symptoms. Of the nine studies reported, seven were at risk of bias and two were of low risk of bias. Seven of the reported studies were of level III-2 evidence, one study was of level III-3 evidence and another study contained level IV evidence.

**Grade D**
Other symptom combinations
NICE reviewed two studies (N=3494) reporting other symptom combinations. These two reported studies were both at risk of bias, one of which was of level III-2 evidence and the other contained level III-3 evidence.
Grade D

2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)

<table>
<thead>
<tr>
<th>Rectal bleeding</th>
<th>A</th>
<th>All studies consistent</th>
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<tbody>
<tr>
<td>Seven studies on rectal bleeding in the NICE review found varied PPV values ranging from 2.2%-15.8% for colorectal cancer. This range may reflect the tendency of these PPVs to decrease as study sample size increased. Two studies identified in the NICE update reported rectal bleeding (Rodriguez-Alonso et al., 2015; Koning et al., 2015) and contained more conservative estimates in reporting that rectal bleeding presenting in a primary care setting is associated with a PPV of 1.4% (Koning et al., 2015; 95%CI 0.5-3.9) and 2.0% (Rodriguez-Alonso et al., 2015; 95% CI=0.9-4.3) for colorectal cancer. Only one study with a case-control design (Hamilton et al., 2005) looked at rectal bleeding reported twice which held a PPV value of 6.8% (95%CI not reported) for colorectal cancer. There were no general trends with respect to the four studies reporting rectal bleeding containing dark blood (PPV ranging 7.4%-19%), three studies reporting blood seen on paper only (PPV ranging 2.4%-9%) or the five studies reporting blood mixed with stool (PPV ranging 4%-21%). Apart from one study (Robertson et al. 2006), patient numbers for these rectal bleeding combinations were as low as 31 which limited statistical power. Four studies reporting rectal bleeding with bright blood or no/not dark blood contained PPVs that were generally low (PPVs ranging 2.7%-10%), however, one study contained a small number of patients and 95%CI was not reported for another study which limits interpretation. Two studies reported blood seen on paper and either pan or in toilet bowl and were both low in PPV magnitude with blood seen on paper and in toilet bowl containing a slightly higher PPV (4.9% vs 11%) for colorectal cancer. Two studies compared rectal bleeding for the first time and while both had PPVs low in magnitude, their PPVs differed (4.7% vs 14.24%). The two studies that compared rectal bleeding not for the first time were similar in their small PPV values for unchanged bleeding pattern (3.8% vs 4.4%) whereas for those with changed bleeding pattern, the PPV for colorectal cancer was higher at 18.75% (95%CI=9.4-33.1%) and contained a wide confidence interval. These values were greater than one study that</td>
<td>B</td>
<td>Most studies consistent and inconsistency can be explained</td>
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<tr>
<td>C</td>
<td>Some inconsistency, reflecting genuine uncertainty around question</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Evidence is inconsistent</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable (one study only)</td>
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</tr>
</tbody>
</table>
reported rectal bleeding and previous history of rectal bleeding (PPV=0%, 95%CI=0-4.8%). Three studies in the NICE review reported blood not mixed with stool for rectal bleeding and were small in PPV for colorectal cancer ranging from 1.7%-7%.

The following rectal bleeding with other symptoms/signs were only reported once: blood seen in toilet bowl for rectal bleeding containing a low PPV of 14% (95%CI not reported) for colorectal cancer; large compared to small volume of blood lost from rectal bleeding which had small PPVs while small volume of blood lost had a slightly higher PPV of 5.3% (95%CI=2.7-9.9%) verse 1.3% (95%CI=0.07-7.8%) for colorectal cancer; rectal bleeding with blood on stool or mixed with stool only with a small PPV of 7% (95%CI not reported); others or combinations apart from “blood on stool or mixed with stool only”, not ‘dark blood and blood mixed with stool’, blood neither dark nor mixed with stool, not ‘blood neither dark nor mixed with stool’ all reported low PPVs for colorectal cancer; dark blood and blood mixed with stool and unknown how blood was seen contained slightly higher PPVs of 10.2% and 7% respectively.

Five studies in the NICE review reported rectal bleeding with family history of either colorectal cancer, abdominal disease, irritable bowel syndrome, diverticular disease or first degree relative with colorectal cancer which limited comparison between studies. These studies generally lacked statistical power due to patient numbers ≤96 or did not report patient numbers. Rectal bleeding and no history of irritable bowel syndrome or diverticular disease included in one study had similar PPVs to rectal bleeding only (3.9-4.4%).

Nine studies in the NICE review reported rectal bleeding according to age while one study looked at new onset or changed pattern rectal bleeding according to age. There was a general trend amongst the nine studies for PPV for colorectal cancer to increase according to age bracket with a peak generally occurring at ages around 70 years. PPVs were generally low except for two studies which, along with two other studies had low patient numbers around this age bracket. Ages were bracketed differently across studies which made it difficult to determine consistency. For the study reporting new onset or changed pattern rectal bleeding according to age (Nørrelund et al., 1996), PPVs for colorectal cancer were greater in magnitude than all other studies for ages ≥70 years, however, this age range contained lower numbers of patients which may have...
inflated PPVs.

Five studies in the NICE review reported rectal bleeding for men at all ages and were consistent in their small PPVs ranging 1.8%-5.9% for colorectal cancer with slight reduction at 6 months (PPV 1.8% 95%CI 1.5-2.2) and 3 years (PPV 2.4% 95%CI 2.1-2.8). The same five studies reported rectal bleeding for women at all ages and similarly contained low PPVs (1.3-2.1%) with no trends at 6 months or 3 years. Three studies reporting rectal bleeding in men by age brackets tended to report PPVs that increased by age bracket and peaked at ages around 80 years (PPVs in these brackets ranging 4.5-9.13%). This trend was also seen for women in the same studies (peak PPVs ranging 2.9-7.2%), however, PPVs for women overall tended to be slightly lower than men. One study reported rectal bleeding for men below 50 years which had a PPV of 0% (95%CI 0-7.7%), another study reported rectal bleeding for men ≥40 years (PPV=9%, 95%CI not reported). Another study reported a PPV for new onset or changed pattern rectal bleeding in men ≥40 years which had a higher PPV than other studies of 17.26% (95%CI=12-24%). This was the same case from this study for women with a higher PPV value of 12.76% (95%CI 8.6-18.4%).

Grade D

Abdominal pain

Four of the five studies on abdominal pain included by NICE reported consistent PPVs ranging between 0.5%-3.9% for colorectal cancer. These were consistent with two studies identified in the NICE update which reported abdominal pain with PPVs of 2.7% (Rodriguez-Alonso et al., 2015; 95%CI=1.4-5.0) and 1.3% (Koning et al., 2015; 95%CI 0.6-2.7%) for colorectal cancer. These findings were in contrast to one study reported by NICE (Panzuto et al., 2003) on abdominal pain which had a higher outlier PPV of 13.5% (95%CI=9.4-18.8) for colorectal cancer.

Abdominal pain increased from a PPV of 0.65% for colorectal cancer for those below age 70 to 2% for those ≥70 years in a case-control study (Hamilton et al., 2005) which was of slightly greater value to another study but consistent in direction in that the low PPVs for each gender (males PPV=0.15-1.2%; females PPV=0.01-0.9%) tended to increase by nine year age bracket. Between gender PPVs for colorectal cancer also tended to be consistent in magnitude.

Grade B
**Anaemia**

Three of the 10 studies on anaemia in the NICE review found consistent PPVs which ranged from 1.5%-3.4% for colorectal cancer. This was also consistent with one of the studies identified in the NICE update which had a PPV for low haemoglobin of 2.7% (Koning et al., 2015; 95%CI 1.5-4.9%). These studies were lower in magnitude than four other studies in the NICE review which found PPVs for anaemia ranging between 6.9%-8.6% for colorectal cancer. Two other studies identified in the NICE update were consistent with this latter range in reporting that iron deficient anaemia presenting in a primary care setting is associated with a PPV of 10.2% (95%CI=4.6-17.3%) or 12% (95%CI=8-16%) for colorectal cancer. One study reported by NICE greatly differed from all other studies reporting anaemia (Panzuto et al., 2003) in finding an outlier PPV of 40.6% (95%CI=29.1%-53.1%) for colorectal cancer. The PPVs of anaemia for the risk of colorectal cancer between and within genders over the age of 50 were low and consistent (ranging 1.38-3.38%) within one study and remained consistent between three studies for women and two studies for men, however, one study (Yates et al., 2004) differed in PPV value in containing a higher value for men over age 20 (18.2%, 95%CI=12.6-25.4%). Two studies in the NICE review reported PPVs by haemoglobin level ranges for colorectal cancer which resulted in minimal variation magnitude of PPVs (ranging 0.3%-2.3%) between the studies. Only one study reported different levels of haemoglobin stratified by gender and age group (see other single symptoms for detail).

* The available data did not allow clear distinction between iron-deficiency and non-iron deficiency anaemia.

**Grade C**

**Constipation**

One out of the two studies reported by NICE separated constipation into reported once or twice which had similar PPVs low in magnitude (0.42-0.81%) for colorectal cancer which differed from the second study reporting a PPV greater in magnitude of 15.7% (95%CI=10.2-23.2%). This latter study tended to contain outlier values across all symptoms (Panzuto et al. 2003). The study identified in the NICE update reporting constipation (Rodriguez-Alonso et al., 2015) fell between the NICE reported PPVs in that constipation presenting in a primary care setting was associated with a PPV of 2.5% (95%CI 0.6-7.4) for colorectal cancer.

**Grade D**
**Diarrhoea**

One out of the two studies reported by NICE separated diarrhoea into reported once or twice which had similar PPVs low in magnitude (0.94-1.5%) for colorectal cancer which differed from the second study reporting a PPV greater in magnitude of 11.8% (95%CI=6.1-21%) with a wide range. This greater PPV was reported from a study containing outlier values across all symptoms (Panzuto et al. 2003). The study identified in the NICE update reporting diarrhoea (Rodriguez-Alonso et al., 2015) fell between the NICE reported PPVs in that diarrhoea presenting in a primary care setting was associated with a positive predictive value of 3.4% (95%CI=1.5-6.6) for colorectal cancer.

**Grade D**

**Change in bowel habit**

One out of the five studies in the NICE review (Panzuto et al., 2003) reported change in bowel habit in all patients and reported a PPV with a wide range of 14% (95%CI=6.7-23.3%) for colorectal cancer. This contrasted to the PPV reported for change in bowel habit in a study found in the NICE update which was 0.8% (Koning et al., 2015; 95%CI 0.04-4.9%). The latter PPV and range is more consistent with three of four studies in the NICE review that reported change in bowel habit in men above 60 years. One of the four studies reported PPVs slightly larger in magnitude for men over 60 years (6.89-7.73%) than the other three for colorectal cancer. The two studies reporting change in bowel habit for women over 60 years had lower and consistent PPVs (1.3-4.09%) for colorectal cancer which were slightly lower than in men over 60 years of age. As noted by NICE, two studies (Hamilton et al., 2009 & Collins et al., 2012) reporting on change in bowel habit shared a large proportion, if not, complete overlap of data.

**Grade C**

**Weight loss**

Four of the five studies included in the NICE review reported consistent PPVs for weight loss (0.8-1.4%) for colorectal cancer regardless of whether patients reported this symptom once or twice. Two studies identified in the NICE update reporting weight loss were slightly higher in PPV for weight loss presenting in a primary care setting with a PPV of 5.2% (Rodriguez-Alonso et al., 2015;95%CI=2.5-9.2%) and 3.8% (Koning et al., 2015; 95%CI 0.7-14.3%) for
colorectal cancer. These studies contrasted to the larger PPV and range reported by Panzuto et al., 2003 of 35.7% (95%CI=22-52%). This study tended to contain outlier values across all symptoms. Only one study reported weight loss by age and reported a slightly higher PPV for patients ≥70 years of 2.5% (95%CI not reported) for colorectal cancer compared to 0.74% (95%CI not reported) for ages 40-69 years. Two studies in the NICE review reported weight loss within and between genders which were low and consistent in PPV (0.06-1.5%) for colorectal cancer regardless of weight loss percentage. As noted by NICE, the two studies (Hamilton et al., 2009 & Collins et al., 2012) that reported on weight loss for women shared a large proportion, if not, complete overlap of data.

**Grade C**

**Dyspepsia**

All three studies on dyspepsia in the NICE review reported small and consistent PPVs (0-1.14%) for colorectal cancer. PPVs by age or gender were not reported for dyspepsia.

**Grade A**

**Other single symptoms**

Symptoms in the NICE review that were reported by very few studies were not included in the meta-analysis. Two studies reported on loss of appetite and two other studies reporting on non-acute abdominal complaints were highly consistent with their small PPV for colorectal cancer. One study in the NICE update (Koning et al., 2015) also reported loss of appetite and also contained a small PPV of 0% but had a large range (95%CI 0-60.4%) due to the small number of participants for that symptom (n=4).

Abdominal tenderness, abnormal rectal exam, positive faecal occult blood, blood sugar >10 mmol/L, history of diabetes were all reported by the same study with the first two symptoms reported low PPVs. Deep vein thrombosis was only reported by one paper and contained a low PPV for colorectal cancer (PPV=0.7%, 95%CI=0.2-2.2%). Bloating was reported by one study with a PPV for colorectal cancer of 13.2% (95%CI=8.6-19.5%), however, this study tended to contain outlier values across all symptoms (Panzuto et al. 2003).

Two studies in the NICE review reported PPVs by haemoglobin level ranges for colorectal cancer which resulted in minimal variation magnitude of PPVs.
Only one study reported different levels of haemoglobin stratified by gender and age group. In this study, PPVs for men above 60 years with haemoglobin levels with or without indicators of iron deficiency were small in magnitude and consistent between 9 and ≥13 g/dL but increased in magnitude for men above age 60 with haemoglobin levels of ≤9.9 g/dL (PPVs ranging 4-8.8%) and particularly for those with indicators of iron deficiency (PPVs ranging 13.3-31%). Women above 60 years tended to have slightly smaller PPVs over haemoglobin levels than men with or without indicators of iron deficiency. PPV values for haemoglobin level of <9 g/dL increased to a peak of 8.6% (95%CI 5.4-14%) for women 70-79 years while for haemoglobin levels of <9-10 g/dL with indicators of iron deficiency, PPV values increased to a peak of 10% for colorectal cancer, with values higher for the age category of 70-79 years.

**Grade: N/A**

**Rectal bleeding presenting with other symptoms**

Two studies in the NICE review reported rectal bleeding and constipation which were consistently low in PPVs for colorectal cancer (2.4-2.6%) as well as rectal bleeding and diarrhoea which were similarly consistently low (3.4-7.4%). However, patient numbers were ≤39 or not reported in these two studies which limits interpretation of PPVs. Similarly, three studies reported on the combination of rectal bleeding and change in bowel habit and were consistently low in PPV (9.2-11%), however, one study did not report patient numbers and another study contained ≤39 patients. Lack of patient numbers reported also limited interpretation for a number of studies. This was the case for one study that reported rectal bleeding and abdominal tenderness (PPV=4.5%, 95%CI not reported) and rectal bleeding and abnormal rectal exam (PPV=8.5%, 95%CI not reported), another study that reported rectal bleeding and feeling or no feeling of incomplete evacuation of rectum as well as rectal bleeding and pain or no pain on defecation which resulted in low PPVs (7-12%) and another study that reported rectal bleeding and spasm which resulted in a low PPV of 5.4% (2-11.4%). This was also the case for two studies reporting consistently low PPVs for colorectal cancer as a result of rectal bleeding and fatigue (PPV=7.1%, 95%CI not reported) or rectal bleeding with haemoglobin levels of 10-13 g/dL or <10g/dL (3.2-3.6%). Another study reported rectal bleeding and nausea as well as rectal bleeding and decreased appetite which both resulted (ranging 0.3%-2.3%) between the studies.
in a low PPV of 2% (95%CI not reported), however, patient numbers were not reported such that interpretation is limited. This limitation was also present for rectal bleeding and pale conjunctivae reported by the same study as well as for one study reporting rectal bleeding and non-gastrointestinal symptoms which resulted in PPV of 5% for colorectal cancer. For rectal bleeding and no non-gastrointestinal symptoms reported within the same study, the PPV for colorectal cancer was within the range of PPVs that were found in studies reporting rectal bleeding only (PPV=12%, 95%CI not reported). Lack of patient numbers reported also limited interpretation of PPVs for two studies reporting rectal bleeding and perianal eczema or no anal itch which reported PPVs below 18% and another study reporting rectal bleeding and abnormal proctoscopy which resulted in a PPV of 0% (95%CI=0-14.1).

PPVs for three studies reporting rectal bleeding and no change in bowel habit were consistently low (0-8.75%), however, one study did not report patient numbers. One study also reported new onset or changed pattern rectal bleeding and change in bowel habit (PPV=26.85%, 95%CI=19-36.4%) or uncertain change (PPV=25%, 95%CI=8.3-52.6%) in bowel habit which both had similarly higher PPVs, however, the latter symptom combination contained ≤16 patients which might have resulted in an inflated PPV. Two studies reported rectal bleeding with change in bowel habit (loose ± frequent) and both contained low PPVs (4.8-12%), however, the smaller study may have contained an inflated PPV due to ≤83 patients included. One of these studies additionally reported rectal bleeding and no ‘increased frequency/loose motions’ which resulted in a PPV for colorectal cancer within the range of rectal bleeding alone (PPV=2.8%, 95%CI=1.4-5.5%). One study also reported rectal bleeding and change in bowel habit (hard ± infrequent) which found a PPV of 2.8% (95%CI=0.1-16.2%), however, there were only 36 patients which limits interpretation. Only one study reported rectal bleeding and perianal or no perianal symptoms where both PPVs were small in magnitude (1.97-11.1%), however, PPVs for rectal bleeding and no perianal symptoms may have been inflated due to ≤63 patients included. Another study reported rectal bleeding and different degrees of discomfort whereby PPVs for uncertain (PPV=23.08, 95%CI=9.8-44.1%) and certain discomfort (PPV=16.67%, 95%CI=10.1-26%) may have been inflated due to patient numbers ranging 26-96 while patients with rectal bleeding and no discomfort displayed PPVs in the range of studies that reported rectal bleeding only (PPV=13.22%, 95%CI=9.3-18.3%). One
study reported rectal bleeding and associated slime which resulted in a PPV for colorectal cancer of 10.7% (95%CI=2.8-29.4%), however, patient numbers were ≤28 which may have led to an inflated estimate. Another study reported rectal bleeding and dyspepsia or rectal bleeding (visible blood in stools only) and dyspepsia which were both low in PPV (2.6-4%). Three studies in the NICE review reported rectal bleeding and haemorrhoid (including rectal palpation or identified by GP) and were consistent in their low PPVs for colorectal cancer (3.1-10%). Two of these studies reported rectal bleeding and no haemorrhoids whereby one study fell within the range of PPVs that were found for studies reporting rectal bleeding only (PPV=4.6%, 95%CI=2.4-8.3%) and the other study reported a 17% PPV for colorectal cancer but interpretation was limited due to no patient numbers provided. One study reported rectal bleeding and anal protrusion noticed by the patient which provided a PPV for colorectal cancer of 3% (95%CI not reported), where rectal bleeding and no anal protrusion noticed by patient yielded a PPV value of 13%, however, patient numbers were not reported and so interpretation of these values are again limited. Another study reported rectal bleeding and palpable tumour with a higher PPV of 31.5% (95%CI=12.5-56.5%), however, patient numbers were not reported which limits meaningful interpretation of this PPV. Two studies that reported on rectal bleeding and pain (at night for one study) were consistent in their 0% PPV values for colorectal cancer. Six studies reported rectal bleeding and abdominal pain where PPVs were consistently low for five studies (1.7-9%), while one study was inconsistent and higher in PPV value for both certain and uncertain abdominal pain (22.22-23.33%) but contained 9-90 patients. Three studies reported rectal bleeding and no abdominal pain which were in the range of PPVs for colorectal cancer found in studies reporting rectal bleeding alone. Seven studies in the NICE review reported on rectal bleeding and weight loss, however, interpretation of PPVs for colorectal cancer were limited due to patient numbers ≤63 or not being reported. This also applied to one study reporting rectal bleeding and uncertain weight loss. Three studies that reported rectal bleeding and no weight loss fell in the range of PPVs for colorectal cancer found in studies reporting rectal bleeding alone (3.6-13.07%).

One study reported multiple symptom combinations (Robertson et al., 2006). For rectal bleeding and change in bowel habit and abdominal pain or no abdominal pain, comparable PPVs of 9% and 9.6% for colorectal cancer were respectively reported. However, ≤67 patients were included for these symptom
combinations such that values may be inflated. Rectal bleeding and haemorrhoids and bright red blood not mixed with stools resulted in a low PPV of 1.9% (95%CI=0.5-5.8%) while rectal bleeding and haemorrhoids and no other symptoms except bright non-mixed bleeding resulted in a similarly low PPV, however, patient numbers were lower in this instance. Rectal bleeding and no ‘haemorrhoids and bright red blood not mixed with stools’ as well as rectal bleeding and no ‘haemorrhoids and no other symptoms except bright non-mixed bleeding’ had PPVs within the range of studies reporting rectal bleeding only (3.8%-4.5%). The study also reported rectal bleeding and deprivation category whereby all categories contained PPVs lower than 5.8%, however, trends could not be established due to patient numbers of ≤74 included for four out of seven categories.

One study in the NICE review reported rectal bleeding and change, uncertain change or no change in bowel habit by patient age but no trends could be interpreted due to likely inflation by low patient numbers ranging 2-62 for nearly all age categories.

**Grade D**

**Other symptom combinations**

Other symptom combinations presenting in a primary care setting were reported in two studies in the NICE review, however, the combinations were not comparable between studies. Apart from seven studies, all symptom combination PPVs for colorectal cancer were consistently low (ranging 0-4.7%). The symptoms that were higher in magnitude ranged in PPV from 5.8% (95%CI not reported) for abdominal tenderness and abnormal rectal exam to 13.51% (95% CI=5-29.57%) for dyspepsia and anaemia. However, the study that reported dyspepsia and anaemia as well as dyspepsia and jaundice (PPV=0%, 95%CI=0-48.32) contained patient numbers ≤37 such that interpretation of PPV is limited.

**Grade: N/A**

### 3. Clinical impact

See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)

<table>
<thead>
<tr>
<th>The present evidence suggests that PPVs for colorectal cancer based on each symptom category in a primary care setting were relatively low (below 15.7%)</th>
<th>A</th>
<th>Very large</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Substantial</td>
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</tbody>
</table>
and tended to increase with age both in men and women. The NICE guideline developers considered symptoms with a PPV of ≥3% for colorectal cancer to be a sufficient threshold to prompt referral for those symptoms. Out of the five symptoms pooled in the NICE meta-analysis, the symptoms which reached ≥3% PPVs for colorectal cancer were rectal bleeding (PPV=4.5%, 95%CI=3.2-6.3%) and anaemia (PPV=4.09%, 95%CI=2.24-7.34%) when higher risk patient studies were excluded. Symptoms with a PPV of ≥3% for colorectal cancer from Rodriguez-Alonso et al., 2015 included in the NICE update were iron deficient anaemia (PPV=10.2%, 95%CI=4.6-17.3%, N=97), weight loss (PPV=5.2%, 95%CI=2.5-9.2%, N=201) and diarrhoea (PPV=3.4%, 95%CI=1.5-6.6%, N=244). In addition, the symptom of iron deficient anaemia reported in Chowhundy et al. 2014 from the NICE update also fell above a PPV of 3% (PPV=12%, 95%CI=8-16, N=292) and weight loss as reported in Koning et al., 2015 also had a PPV above 3% (PPV=3.8% 95%CI 0.7-14.3%).

The highest PPV values for colorectal cancer came from one study (Panzuto et al. 2003) with 280 patients which tended to contain outlier PPV values for all reported symptoms. These symptoms were constipation (PPV=15.7%, 95%CI=10.2-23.2%), change in bowel habit (PPV=14%, 95%CI=6.7-26.3%), bloating (PPV=13.2%, 95%CI=8.6-19.5%) and diarrhoea (PPV=11.8%, 95%CI=6.1-21%).

Most of the studies included in the NICE review as well as the updated studies included ages <50, however, mean ages tended to be >50 years. The magnitude of influence on PPVs for each symptom, however, is difficult to determine.

In relation to commonly used FOB tests for screening asymptomatic population with average risk of colorectal cancer, the PPVs reported for these symptoms is comparable.

**Grade D**

### 4. Generalisability

*(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)* For study population characteristics see table of study characteristics in report

All studies were conducted in western populations, with the majority based on European populations, particularly in the UK which contained 16 studies. The only non-European studies were conducted in Australia (Mant et al., 1989) and
another in the US (Hefland et al., 1997). Excluding studies that contained higher risk individuals, the evidence is generalisable to the Australian population at average risk of developing colorectal cancer.

5. Applicability (Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)

Apart from one study conducted in the US, all of the studies were conducted in countries with few barriers to primary care services due to universal, free or affordable access healthcare which is relatable to the Australian healthcare context. In addition, the cost of colonoscopy in some countries of included studies might be beyond reach for certain socio-economic groups. In terms of geographic barriers to health services, most included studies would differ from the Australian healthcare context whereby this issue would need to be considered in rural/regional Australian settings.

Other factors (Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).)

EVIDENCE STATEMENT MATRIX
Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

<table>
<thead>
<tr>
<th>Component</th>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence base</td>
<td>D</td>
<td>For all symptoms/outcomes reported - Level IV studies or Level I to III studies/SRs with a high risk of bias</td>
</tr>
</tbody>
</table>
| 2. Consistency | D | Rectal bleeding - Evidence is inconsistent  
| | B | Abdominal pain - Most studies consistent and inconsistency can be explained  
| | C | Anaemia - Some inconsistency, reflecting genuine uncertainty around question  
| | D | Constipation - Evidence is inconsistent  
| | D | Diarrhoea - Evidence is inconsistent  
| | C | Change in bowel habit - Some inconsistency, reflecting genuine uncertainty around question  
| | C | Weight loss - Some inconsistency, reflecting genuine uncertainty around question  
| | A | Dyspepsia - All studies consistent  
| | N/A | Other single symptoms - Not applicable (one study only)  
| | D | Rectal bleeding presenting with other symptoms - Evidence is inconsistent  
| | N/A | Other symptom combinations - Not applicable (one study only)  
| 3. Clinical impact | D | Slight/Restricted  
| 4. Generalisability | B | Evidence directly generalisable to target population with some caveats  
| 5. Applicability | B | Evidence applicable to Australian healthcare context with few caveats |
**Evidence statements:** Rectal bleeding presenting in primary care was associated with a PPV for colorectal cancer of up to 4.8% (95% CI 3.3 to 6.8). This PPV tended to increase with age in both men and women.

Abdominal pain presenting in primary care was associated with a PPV for colorectal cancer of up to 2.0% (95% CI 0.5 to 7.6). This PPV tended to increase with age in both men and women.

Anaemia* presenting in primary care was associated with a PPV for colorectal cancer of up to 5.8% (95% CI 2.6 to 12.0). This PPV tended to increase with age in both men and women. Two new studies since the meta-analysis estimated the PPV for anaemia in referred populations as 10.2% (95% CI 4.6 to 17.3) and 12.0% (95% CI 8.0 to 16.0).

**Weight loss** presenting in primary care was associated with a PPV for colorectal cancer of up to 3% (95% CI 0.3 to 22.9). This PPV tended to increase with age in both men and women. One new study since the meta-analysis estimated the PPV for weight loss in a referred population as 5.2% (95% CI 2.5 to 9.2).

Dyspepsia presenting in primary care was associated with a PPV for colorectal cancer of up to 0.6% (95% CI 0.3 to 1.4).

Constipation presenting in primary care in two studies was associated with a PPV for colorectal cancer of 0.4–2.5%. In one further small study in selected patients the estimated PPV was 15.7% (95% CI 10.2 to 23.2).

Diarrhoea presenting in primary care in two studies was associated with a PPV for colorectal cancer of 0.9–3.4%. This PPV tended to increase with age in both men and women. In one further small study in selected patients the estimated PPV was 11.8% (95% CI 6.1 to 21%).

**Change in bowel habit** presenting in primary care in two studies was associated with a PPV for colorectal cancer of 2.8–2.9%. This PPV tended to increase with age in both men and women. In one further small study in selected patients the estimated PPV was 14% (95% CI 6.7 to 23.3%).

Combinations associated with higher estimated PPVs included:
- abdominal tenderness and abnormal rectal examination (PPV 5.8%; 95% CI not reported)
- dyspepsia with anaemia (PPV 13.5%; 95% CI 5 to 29.57%).

Combination of symptoms: Nine studies that examined the PPVs for rectal bleeding in combination with other symptoms reported wide-ranging estimates. Some studies reported other combinations of symptoms.

Combinations associated with higher estimated PPVs included:
- abdominal tenderness and abnormal rectal examination (PPV 5.8%; 95% CI not reported)
- dyspepsia with anaemia (PPV 13.5%; 95% CI 5 to 29.57%).

Several of the estimates from these studies are likely to be artificially inflated due to small numbers of participants with specific combinations of symptoms.
<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>GRADE OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.</td>
<td>C</td>
</tr>
</tbody>
</table>

The urgency of colonoscopy to investigate symptoms suggestive of colorectal cancer should be based on an assessment of patient age, symptom profile and results of simple investigations including full blood count, iron studies and iFOBT (see Table 10.1 for consensus-based colonoscopy triage categories).
Timely diagnosis of colorectal cancer is important for improving survival. The triage criteria are designed to improve the efficiency of the referral and triage processes for people with symptoms suggestive of colorectal cancer, but further evidence is required on the impacts of their implementation.

Table 2: Unresolved issues

<table>
<thead>
<tr>
<th>UNRESOLVED ISSUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.</td>
</tr>
<tr>
<td>Timely diagnosis of colorectal cancer is important for improving survival. The triage criteria are designed to improve the efficiency of the referral and triage processes for people with symptoms suggestive of colorectal cancer, but further evidence is required on the impacts of their implementation.</td>
</tr>
</tbody>
</table>

Table 3: Implementation of recommendation

<table>
<thead>
<tr>
<th>IMPLEMENTATION OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.</td>
</tr>
<tr>
<td>Consensus based recommendation:</td>
</tr>
<tr>
<td>In people with symptoms other than overt rectal bleeding, immunochemical faecal occult blood testing (iFOBT) can be used as part of the diagnostic assessment in primary care</td>
</tr>
<tr>
<td>Practice point:</td>
</tr>
<tr>
<td>Immunochemical faecal occult blood testing (iFOBT) is of particular use in the following circumstances to support diagnostic assessment and inform urgency of colonoscopy:</td>
</tr>
<tr>
<td>• people over 50 years with either unexplained weight loss or abdominal pain</td>
</tr>
<tr>
<td>• people under 60 years with either altered bowel habit or anaemia.</td>
</tr>
</tbody>
</table>

PRACTICE POINT (CONSENSUS-BASED RECOMMENDATION)

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation (practice point) can be given.

Consensus based recommendation:

In people with symptoms other than overt rectal bleeding, immunochemical faecal occult blood testing (iFOBT) can be used as part of the diagnostic assessment in primary care

Practice point:

Immunochemical faecal occult blood testing (iFOBT) is of particular use in the following circumstances to support diagnostic assessment and inform urgency of colonoscopy:

• people over 50 years with either unexplained weight loss or abdominal pain
• people under 60 years with either altered bowel habit or anaemia.
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will this recommendation result in changes in usual care?</td>
<td>YES</td>
</tr>
<tr>
<td>The triage categories, while moderately complex, are designed for use by endoscopy units to assess the urgency of referrals for colonoscopy. GPs should apply this evidence to inform their use of simple investigations in primary care (full blood count, iron studies and iFOBT) as part of their assessment of patients with symptoms suggestive of colorectal cancer. It should also be noted which patients are identified in this guideline as not requiring referral for colonoscopy.</td>
<td></td>
</tr>
<tr>
<td>Are there any resource implications associated with implementing this recommendation?</td>
<td>YES</td>
</tr>
<tr>
<td>Endoscopy units may need dedicated staff to apply the triage criteria consistently.</td>
<td></td>
</tr>
<tr>
<td>Will the implementation of this recommendation require changes in the way care is currently organised?</td>
<td>YES</td>
</tr>
<tr>
<td>Health services and endoscopy units should consider implementing specific GP referral proformas designed to capture the information needed to apply the triage criteria</td>
<td></td>
</tr>
<tr>
<td>Are the guideline development group aware of any barriers to the implementation of this recommendation?</td>
<td>NO</td>
</tr>
<tr>
<td>Primary Health Networks should support this implementation in general practice as part of the national Optimal Care Pathways for colorectal cancer.</td>
<td></td>
</tr>
</tbody>
</table>