(Bowel) Cancer Screening
an update

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Colorectal Surgeon
CD NZ Bowel Screening Pilot
Screening

• “The application of tests, examinations or other procedures .... to sort out apparently well persons who probably have a disease from those who probably do not.”

Wilson and Junger 1968

WHO Principles of Early Disease Detection

**Condition**
- The condition should be an important health problem.
- There should be a recognisable latent or early symptomatic stage.
- The natural history of the condition, including development from latent to declared disease should be adequately understood.

**Test**
- There should be a suitable test or examination.
- The test should be acceptable to the population.

**Treatment**
- There should be an accepted treatment for patients with recognised disease.

**Screening Program**
- There should be an agreed policy on whom to treat as patients.
- Facilities for diagnosis and treatment should be available.
- The cost of case-findings (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-findings should be a continuing process and not a ‘once and for all’ project.

Cancer screening programs in Australasia

- **Breast Cancer**
  - Australia: Mammograms every 2 years, 50 to 74 years of age
  - NZ: Mammograms every 2 years, 45 to 69 years of age
- **Cervical Cancer**
  - Australia: Pap Smear tests every 2 years, 18 to 69. Changing to Cervical Screening Test (Dec 2017): HPV smear test every 5 years, 25 to 74 years
  - NZ: Pap Smear tests every 3 years, 20 to 70 years
- **Bowel screening see later**
- **Lung cancer**
  - Australia: Screening not supported (last position paper 2015), emphasis on prevention by smoking reduction
  - NZ: No position papers and no screening, active anti-smoking programs
- **Prostate Cancer**
  - Australia: Position paper 2014 recommended against PSA screening
  - NZ: Position paper 2011 recommended against PSA screening, active public awareness campaigns from 2013 ongoing
- **Skin Cancer**
  - Australia and NZ: No formal screening but active publicity campaigns for recognition and prevention (slip slop slap etc)
Why Bowel Cancer

- 3rd commonest diagnosed cancer in the world
- Australasia has among the highest incidence in the world
- NZ second commonest cause of cancer death
  - 3158 new registrations in 2015
  - (pop 4.6 million)
  - ASI 44.2
- Australia
  - 10025 new registrations in 2013
  - (pop 23 million)
  - ASI 38.6
Why Bowel Cancer

Fig. 1. Trends in age-standardized incidence rates of colorectal cancer per 100,000 person-years (95% CI) by site for adults 25+ years.

Why Colon Cancer

Mismatch-repair gene inactivation
Microsatellite instability: BAT26

Mutation and loss
APC

Mutation
KRAS

Loss
SMAD2/4

Mutation and loss
TP53

Normal epithelium
Early adenoma/dysplastic crypt
Intermediate adenoma
Late adenoma
Carcinoma
Metastasis

Altered DNA methylation
Other genetic alterations
Why screen

If diagnosed at stage 1
97% of people survive for five years or more.

If diagnosed at stage 4
7% of people survive for five years or more.
“Although most studies suggested that screening for CRC is likely to be more cost-effective at saving life-years than cervical cancer screening or breast cancer screening, several studies pointed out that a CRC screening programme based on any screening modality will put additional pressure on the health system to increase the availability of colonoscopy and services used to investigate or follow-up on positive results. Any country considering a CRC screening programme must, therefore, consider whether the supply of such services can be increased to meet the expected increase in demand.”
Bowel Screening Techniques

- **Direct inspection**
  - Colonoscopy
  - Flexible sigmoidoscopy
    - Expensive, invasive, less frequent, left side only
  - CT colonography
  - Pill cam
- **Detection of blood in the stool**
  - gFOBT (original technique now obsolete)
  - FIT (immuno-faecal occult blood detects globin molecule)
    - Human specific, in theory only lower gi blood,
    - absolute measurement ng Hb/ml Buffer
  - Cancer DNA (panel of genes such as kras, p53, etc) excessive cost
## Table 1  Test performance per screening test in asymptomatic, average-risk adults

<table>
<thead>
<tr>
<th></th>
<th>gFOBT</th>
<th>FIT</th>
<th>FS</th>
<th>CTC</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%) for detecting advanced neoplasia</td>
<td>9 to 24&lt;sup&gt;43-48&lt;/sup&gt;</td>
<td>32 to 53&lt;sup&gt;43 44 47 49&lt;/sup&gt;</td>
<td>90 to 92&lt;sup&gt;*50&lt;/sup&gt;</td>
<td>88&lt;sup&gt;35&lt;/sup&gt; to 97&lt;sup&gt;43&lt;/sup&gt;</td>
<td>88 to 98&lt;sup&gt;51&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sensitivity (%) for detecting CRC</td>
<td>13 to 50&lt;sup&gt;44-46&lt;/sup&gt;</td>
<td>79&lt;sup&gt;52&lt;/sup&gt;</td>
<td>90 to 92&lt;sup&gt;*50&lt;/sup&gt;</td>
<td>100&lt;sup&gt;†53&lt;/sup&gt;</td>
<td>92 to 99&lt;sup&gt;50&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reduction in CRC incidence (%) intention-to-screen</td>
<td>No&lt;sup&gt;19 54&lt;/sup&gt;</td>
<td>Unknown</td>
<td>18&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Unknown</td>
<td>69&lt;sup&gt;§&lt;/sup&gt;&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reduction in CRC mortality (%) intention-to-screen</td>
<td>14 to 16&lt;sup&gt;19&lt;/sup&gt;</td>
<td>22&lt;sup&gt;¶15&lt;/sup&gt;</td>
<td>28&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Unknown</td>
<td>68&lt;sup&gt;§&lt;/sup&gt;&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Sensitivity is given for the distal colon.
† No CRCs were missed by CTC in six screening trials.
‡ No reduction in incidence was found in three of four RCTs included in meta-analysis.
§ Meta-analysis of observational studies; more results expected.
¶ Ecological study.
CRC, colorectal cancer; CTC, CT colonography; FIT, faecal immunochemical test for haemoglobin; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test; RCT, randomised controlled trial.

*Schreuders EH et al Gut 2015; 64: 1637-49*
Efficacy of Screening Tests

Table 2  Performance of a first round screening programme per screening test, based on screening indicators.

<table>
<thead>
<tr>
<th></th>
<th>gFOBT</th>
<th>FIT</th>
<th>FS*</th>
<th>CTC</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation rate (%)</td>
<td>16–47</td>
<td>17–77</td>
<td>30–84</td>
<td>18–34</td>
<td>16–93</td>
</tr>
<tr>
<td>Positivity rate† (%)</td>
<td>2.4–6.8</td>
<td>1.1–13</td>
<td>5.3–23</td>
<td>8.6–9.0</td>
<td>4.9–11</td>
</tr>
<tr>
<td>Advanced neoplasia detection rate‡ (%)</td>
<td>29–50</td>
<td>16–43</td>
<td>20–100</td>
<td>54–71</td>
<td>100</td>
</tr>
<tr>
<td>Detected advanced neoplasia per 1000 invited individuals§</td>
<td>2.1–6.3</td>
<td>1.1–21</td>
<td>23–39</td>
<td>8.8–21</td>
<td>14–73</td>
</tr>
</tbody>
</table>

References

*Relative detected advanced neoplasia per 1000 invited individuals is only for the area of the colon examined by FS.
†Those with a positive screen were recommended colonoscopy (except when colonoscopy was used as the primary screening test), which enabled the determination of the positive predictive value of the primary screen (the proportion of subjects that during colonoscopy were diagnosed with advanced neoplasia). The uptake of the test was multiplied by the positivity rate and positive predictive value to determine the number of true positives identified with advanced neoplasia per 1000 invited.
‡Proportion of subjects with a positive primary screening test that were found to have advanced colorectal neoplasia on secondary screening by colonoscopy.
§Detection rate per screening round.

CTC, CT colonography; FIT, faecal immunochemical test for haemoglobin; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test.

Schreuders EH et al Gut 2015; 64: 1637-49
Faecal Occult Blood Tests

- 4 large RCTs for gFOBT vs nothing
- Collectively enrolled 349642 participants
- Cochrane review of these by Holmes 2013 showed 14% (CI 95% 8 to 20%) reduction in CRC mortality
- Possible small reduction in CRC incidence of 5% (95% CI +2% to –ve 12%)
  - understandable as the sensitivity is low for fobt for advanced adenomas
- Takes a few years to see the effect
- Finnish trial Pitkäniemi et al BMJ 2015 showed no decrease in CRC mortality. Community based randomised health services trial (RHS) (68% uptake, 80% colorectal)
  - Started 2004 rolled out as a program but 1:1 randomisation
  - Average followup is only 4.5 years
  - Has treatment improved in the last 20 years?
Flexible sigmoidoscopy

- 5 RCTs looking at Flexisig vs nothing
- Collectively enrolled 414744 participants for a one off flexi sig (4/5)
- Cochrane review 2013 Holme et al showed
  - Reduction in crc mortality by 28% (95% CI 21 to 35%)
  - Reduction in crc incidence 18% (95% CI 10 to 26%)
- Referral rates to colonoscopy depended on the definition of a positive result
  - UK Atkin 5.2% (4.4% fobt)
  - Italy Segnan 8.2% (8.8% Swedish and 8.5% Danish fobt)
  - US Schoen 16.5% (28% usa fobt biennial fobt)
  - NORCCAP Hoff 23% (Flexi + FOBT)
- Major complication 8/10,000
colonoscopy

- Tends to be used in opportunistic programs particularly in the USA
- Case control studies from USA, Canada and Germany show that long term use of colonoscopy in a community will decrease the incidence of colorectal cancer in a community.
- Brenner et al Gastroenterology 2014, > 3000 in each arm showed that a colonoscopy for screening reasons reduced the risk of colorectal cancer by 80-90% in the subsequent 10 years.
- At least 4 big trials looking at colonoscopy as a screening modality underway but results not expected until 2025 to 2034
  - NordICC, COLONPREV, SCREESCO, CONFIRM
Australian Bowel Screening

- Pts sent FIT kit directly from NBCSP register
- +ve result sent to pt and gp
  - (pt advised to see gp to discuss results and referral
- Colonoscopy public or private
- National program register for data collection, quality control, reporting.
- Problem is much outcome data is non mandatory data therefore quite a bit is missing
NBCSP Australia Invitation based FIT testing

- Pilot testing Nov 2002 to June 2004
- 2006 kits sent to 55 and 65 year olds
- 2009 50 55 and 65
- 2013 50, 55, 60 and 65
- 2015 50, 55, 60, 65 and 70
- 2015 50, 54, 55, 58, 60, 64, 68, 70, 72, 74
- 2019 onwards plan for a biennial FIT testing for all 50 to 74 year olds
<table>
<thead>
<tr>
<th></th>
<th>Pilot 2002-04</th>
<th>2008</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation rate</td>
<td>45.4%</td>
<td>42.5%</td>
<td>35%</td>
<td>33.4%</td>
<td>36%</td>
</tr>
<tr>
<td>FOBT positivity rate</td>
<td>9%</td>
<td>7.6%</td>
<td>7%</td>
<td>7.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>GP follow-up rate</td>
<td>unknown</td>
<td>44%</td>
<td>63%</td>
<td>58%</td>
<td>61.5%</td>
</tr>
<tr>
<td>Colonoscopy rate</td>
<td>55%</td>
<td>64%</td>
<td>72%</td>
<td>70.4%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Stage data for screened vs non-screened patients (%)

- Stage A: P<0.001 Cole 2013
- Stage D: screening 34.8 vs non-screened 19.2
- Stage D: screening 12.4 vs non-screened 5.4
NZ Bowel Cancer Screening

- NZ Bowel Cancer Screening Pilot
- Oct 2011 to dec 2015 but extended for a further 2 years to end 2017
- Waitemata DHB (north and west Auckland pop of 600,000)

- National Program
- Commenced Hutt/Wairarapa July 2017
- Rolling out sequentially around the country completing 2020
NZ bowel screening Pilot WDHB

- Pilot started in Waitemata DHB 2012
  Bienial FIT test
- (oc-sensor, Eiken)
- Register with direct invites to eligible participants
- 50 – 74,
- FIT positive threshold 75 ng/ml buffer
- Excluded those with IBD, on surveillance programs (prev ca), those who had had colo in last 5 years

- GPs have 10 days to refer for colonoscopy
- If no referral then the Unit takes over
- Participants re-enrolled for screening or surveillance or treatment
- All outcomes including pathology and treatment data entered onto the national register
## NZ Bowel Screening Pilot results

<table>
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<tr>
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<tbody>
<tr>
<td><strong>Participation rate</strong></td>
<td>56.8%</td>
<td>55.2%</td>
<td>54.9%</td>
</tr>
<tr>
<td><strong>FOBT positivity rate</strong></td>
<td>7.5%</td>
<td>5.9%</td>
<td>5.5%</td>
</tr>
<tr>
<td><strong>invitation rate</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Colonoscopy rate</strong></td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
</tr>
</tbody>
</table>

![Stage data for the first 4 years of the BSP vs Non Screened Cancers Piper Project*](image)

*Jackson C et al The Piper Project 2015*
What can we do with our current resource?

• Reduce age range to 60 to 74 yr olds
• Increase threshold from 75 to 200ng Hb/ml buffer
• Reduce colonoscopy numbers by 50%
• Pick up just over 60% of cancers found on the BSP
• Commenced July 2017 Hutt/Wairarapa finishes end 2020

• National coordination centre
  • (Homecare Medical)
  • Send out invites, notify gp/screening units of +ve results
  • Manage active followup and national publicity
  • Central registry/database
• 4 regional coordination centres
  • Publicity, clinical support
• 20 DHBs who will host screening units (endoscopy)
  • Local treatment
Figure 1  Overview of screening programmes 2014. Regional differences within one country are, except for North-America, not taken into account in these figures. (A) Overview of screening programmes in European region. (B) Overview of screening programmes in region of the Americas. (C) Overview of screening programmes in Western Pacific, South-East Asia and Eastern Mediterranean region. FIT, faecal immunochemical test for haemoglobin; gFOBT, guaiac faecal occult blood test.
Novel screening techniques

- Biomarker stool tests +/- FIT
- Blood tests for Methylated SEPT9 DNA (sensitivity for crc of 48%)
- Colon Capsule Endoscopy
- Magnetic resonance colonography
- Genetics and genomic testing
- Microbiota profiling
The Future...Personalised (targeted) screening

- Family history
  - First degree relatives esp when under age of 50
- Lifestyle
  - Excess body fat/lack of physical exercise
  - Alcohol consumption
  - High intake of certain foods (eg processed meat)
  - Smoking
  - Exposure to ionising radiation
- Medications
  - Asprin (nsaids) decrease risk
  - HRT in women decrease risk
- Genetics
  - Probably about 10 to 20% of bowel cancers (FAP, HNPCC, MYH...........)

Source: United European Gastroenterology EU affairs
“Alcohol and Digestive cancers across Europe, Time for a Change”
Targeted screening

- Study by Imperiale et al JNCI J Natl Cancer Inst 2017 showed good correlation between future cancer risk and current risk of advanced neoplasia.
- Study by Dekker et al Eur J Cancer (2011) showed 6% of pts in the dutch screening program were high risk for crc (>10% lifetime risk)
- Similar study by Worthley et al Eur J gast hepatol 2006 found 4.2% in Australian participants had > 10% lifetime risk
Thanks
Bowel cancer burden attributed to selected risk factors (DALYs and proportion), 2011

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Attributable DALYs</th>
<th>Proportion of bowel cancer burden (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical inactivity</td>
<td>28,570</td>
<td>30.9</td>
</tr>
<tr>
<td>High body mass index</td>
<td>11,819</td>
<td>12.8</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>7,213</td>
<td>7.8</td>
</tr>
<tr>
<td>Diet high in processed meat</td>
<td>7,124</td>
<td>7.7</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>4,830</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Sources: AIHW 2016a, 2017b (BMI estimates); AIHW analysis of ABDS 2011 (unpublished data).
National roll out as per WDHB (age 50-74 yrs.)

Colonoscopy demand 2014-2026 with National Bowel Cancer Screening from 2017 for New Zealand

- Demand: Colonoscopy by Symptomatic Demand
- Demand: Follow up Colonoscopy after CT Colonography
- Demand: Colonoscopy, NBSP
- Demand: Surveillance Colonoscopy - NBSP
- Supply: The Current Capacity (2014)
National implementation from 2017
Age 60-74 yrs. adjusted FIT threshold
National implementation from 2017
Age 60-74 yrs. adjusted FIT threshold
Pink block represents colonoscopy shortfall

Additional demand for colonoscopies with full BCS rollout compared to anticipated supply

- Supply: The Current Capacity (2014)
- Supply: Extra GE (3 sessions per week = 600 procedures per year)
- Supply Shortfall
- Demand: Follow up Colonoscopy after CT Colonography
- Demand: Surveillance Colonoscopy - NBSP
- Supply: CT Colonography
- Supply: Extra GS (1 session per week= 200 procedures per year)
- Demand: Colonoscopy by Symptomatic Demand
- Demand: Colonoscopy, NBSP


Demand vs Supply Graph