

# CANCER FORUM



**March 2014**

**Volume 38 Number 1**

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FORUM: Bowel cancer

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Tom Reeve Award for Outstanding Contributions  
to Cancer Care

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Australian behavioural research in cancer

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# CANCER FORUM



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# CANCER FORUM

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## Bowel cancer

# KEEPING ABREAST OF THE EVIDENCE IN MANAGEMENT OF COLORECTAL CANCER

**Finlay Macrae**

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The opportunity to host as Guest-Editor this issue of *Cancer Forum*, has indeed been timely. The unannounced rescindment by the National Health and Medical Research Council's Guideline of the Prevention, Early Detection and Management of Colorectal Cancer, as published on its website, met with ripples of discontent from the colorectal cancer clinical community.<sup>1</sup> Such solid effort was invested in those 2005 guidelines which have served the community well. Many could see that the baby was being thrown out with the bathwater. Secondary, unintended consequences were articulated - that now there are no guidelines, anyone's views prevail with a non-evidence based distortion of clinical practice that might follow.

Enter then the invitation to edit this issue of *Cancer Forum*. I have selected Australia's most authoritative academics, clinicians and researchers to address the chapters in this issue. Furthermore, I have charged them with a focus to move from the 2005 (rescinded) guidelines to a position that could be the foundation of thinking and systematic address for a new and updated version of the National Health and Medical Research Council (NHMRC) guidelines, which we believe is now much needed. My colleagues have done a magnificent job meeting this challenge. Some have juxtaposed the 2005 guidelines with new and updated considerations which are sound and influential. Others have taken topics which have evolved since 2005, and initiated concepts into evidence-based recommendations which were nascent in 2005, but are now viably part of clinical practice.

So we have seen a refinement of the data behind primary prevention brought forward by our CSIRO colleagues who, recognising the major importance of colorectal cancer (CRC) to the health of many Australians, have themselves invested substantial resources in CRC prevention through their pHealth program.<sup>2</sup> Drawing on recent reports from the World Cancer Research Fund, their recommendations are sound and comprehensive. Their assessment of aspirin in prevention of CRC is a ground-breaking message in terms of guidelines

internationally, and one which I am keen to see advocated internationally from Australia. After all, the first signal pointing to the benefit of aspirin in CRC prevention came from the Melbourne Colorectal Cancer study, lead by Professor Gabriel Kune, who insightfully asked the question about aspirin in his case control study. The recently published randomised control trial of aspirin in Lynch Syndrome showing a 50% reduction in CRC and other Lynch Syndrome cancers, was also internationally supported from Australia.

Graeme Young is the foremost clinical academic worldwide in the field of screening for colorectal cancer, leading the World Endoscopy Organisation's Colorectal Cancer Screening Committee over the last eight years to a position where its annual meetings are considered the most informative horizon scanning opportunities anywhere in the world on this topic. So his chapter on screening carries a wealth of understanding and foresight.<sup>3</sup>

The team from the University of Melbourne's School of Population Health, who are at the forefront of epidemiology in CRC, especially familial CRC, through their leadership in the US National Cancer Institute Colon Cancer Family Register, have assembled evidence relating to familial risk and its individualisation.<sup>4</sup> Aung Win's academic work on this topic has been recognised by the unique Premier's Award in 2013.

Nicholas Pachter, a rising star in clinical cancer genetics from Western Australia, paints the important picture of how the familial cancer clinics integrate in the matrix of CRC management.<sup>5</sup> Genomics undoubtedly will continue to push its importance, some would say peripherally, others centrally, into CRC clinical management. My belief is that it is central and our young trainees across many disciplines would do well to invest their time in grappling with, and understanding, the genomics and genetics revolution of which we are in the midst. Already, cancer multi-disciplinary team meetings include clinical genetics or organ specialists with a dedicated interest in the field of familial predisposition.

## GLOSSARY

**Glossary of terms used in this issue of *Cancer Forum***

5FU – 5-fluorouracil	MSI-H – Microsatellite instability high
ADR – Adenoma detection rate	MS-Stable – Microsatellite stable
APC – Adenomatous polyposis coli	MUTYH - Gene encoding a DNA glycosylase responsible for base excision repair
BRAF – Murine sarcoma viral oncogene homolog B1 encoding BRAF protein	NBCSP – National Bowel Cancer Screening Program
cCR – Clinical complete response	NCCN – National comprehensive cancer network
CRC – Colorectal cancer	NCI – National Cancer Institute
CRM – Circumferential resection margin	NRAS – Neuroblastoma RAS viral (v-ras) oncogene homolog
CRT – Chemoradiotherapy	NSAIDS – Non-steroidal anti-inflammatory drugs
DFS – Disease-free survival	NSP – Non-starch polysaccharides
EGFR - Epidermal growth factor receptor	OR – Odds ratio
EPA-FFA – Eicosapentaenoic Acid-Free Fatty Acid	OS – Overall survival
ESGE – European Society of Gastrointestinal Endoscopy	PAHs – Polycyclic aromatic hydrocarbons
eviQ – Cancer treatments online from the NSW Cancer Institute	pCR – Pathological complete response
FAP– Familial adenomatous polyposis	PCR – Polymerase chain reaction
FIT – Faecal immunochemical test	PEG – Percutaneous endoscopic gastrostomy
FOBT – Faecal occult blood test	PFS – Progression free survival
FOLFIRI – Irinotecan, fluorouracil and leucovorin chemotherapy	PI3K – Phosphoinositide 3-kinase
FOLFOX – Oxaliplatin, fluorouracil and leucovorin chemotherapy	PIK3CA – Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
gFOBT – Guaiac-faecal occult blood test	PR – Polypectomy rates
HCA – Heterocyclic amines	PTEN – Phosphatase and tensin homolog
HNPCC – Hereditary non-polyposis colorectal cancer	R0 – Complete resection of disease with histologically-free margins
HR – Hazard ratio	RCT – Randomised control trials
IHC – immunohistochemistry	RFS – Relapse-free survival
KRAS - Kirsten rat sarcoma viral oncogene homolog encoding KRAS protein	RT – Radiotherapy
LOH – Loss of heterozygosity	SCFA – Short chain fatty acids
LS – Lynch syndrome	SEMS – Self-expanding metallic stents
LV – Leucovorin	SNP – Single nucleotide polymorphisms
MMR– DNA mismatch repair	SSRIs – Selective serotonin reuptake inhibitors
MBO – Malignant bowel obstruction	TEMS – Transanal endoscopic microsurgery
MS – Microsatellite status	TKI – Tyrosine kinase inhibitors
MSI – Microsatellite instability	TME – Total mesorectal excision
	VEGF – Vascular endothelial growth factor

Personally, I am very grateful to Karen Barclay, a young and energetic colorectal surgeon, who filled the gap from the 2011 NHMRC updated guideline on colonoscopic surveillance after adenoma and CRC removal, with an easily read wall chart which should adorn the walls of all colonoscopy suites. She has sounded my contribution with a reassuring grasp of the literature herself.<sup>6</sup>

Professor Robyn Ward, scientist and clinician, describes the challenge and experience of determining personalised approaches to colorectal cancer chemotherapy, in a grounded presentation.<sup>7</sup> Robyn herself is a wonderful advocate for practical guidelines, developing the eviQ process supporting clinical oncological practice. Michael Michael and John Zalberg use the sharp tools of medical oncology to systematically answer practical clinical questions around chemotherapy and radiotherapy for CRC, firmly founded on their tool of trade – the randomised control trial.<sup>8</sup>

Academic surgery is no better remonstrated than by Michael Solomon's team at University of Sydney – Michael's academic disciplinary approach was the backbone of the 2005 guidelines, so his approach to issues of surgery for CRC in this issue carries the same measured and calibrated approach to the evidence around surgery.<sup>9</sup>

A major interest and focus professionally is being placed on quality of colonoscopy, picked up also by the National Bowel Cancer Screening Program, which has funded the National Endoscopy Training Initiative to upskill the colonoscopy community. Complacently, we have thought our practices and training of surgeons and physicians alike has been adequate if not good. But the 'Train the Trainer' and audit programs in the UK have challenged this complacency. No colonoscopist in Australia can ignore the messages in the chapter from Mark Appleyard, who has brought Queensland endoscopy near singlehandedly, to new heights of competency.<sup>10</sup>

Survivorship and palliation – so different but so integral to the population's journey from prevention to palliation, is presented through a unique consumer perspective. Mark Dunstan's frank account of his journey is a moving wakeup story to what otherwise could be stylised in clinical dispassionateness.<sup>11</sup> It is a refreshing work to bring us back to earth. Palliation, less recognised in 2005, is now a core discipline in cancer management. Brian Le's contribution promises to be the foundation for a new chapter in national guidelines.<sup>12</sup>

Our authors' efforts provide a firm basis for a much needed new version of the Australian guidelines. Lives are at stake through support of clinical decision-making, which otherwise may deviate unintentionally from contemporary best practice. Engaging the CRC community to bring such a process to fruition, including adequate impartial funding (who better than the National Health and Medical Research Council?), must be an Australian national priority given the 1 in 12 or more Australians who are diagnosed with CRC. All the more important given the NHMRC's programmed decision to rescind the guidelines, when most, but not all, are sound, and still extant in clinical practice.

My hope is that this issue will either support contemporary decision making to enshrine good practice, or form the kernel for a comprehensive but costly NHMRC 'bells and whistles' approach to updated guideline development, or both! Necessarily, we must place a disclaimer around the recommendations presented. Sound as they are, they are the views of the individual authors, and have not been presented for endorsement by Cancer Council, the NHMRC or indeed the Guest-Editor of this issue of *Cancer Forum*. That would require a greater investment in process, consultation and promulgation – though I suspect the content and message would ultimately be the same.

Meantime, I hope, as do my authors, that the distinguished contributions here presented, can inform your practice to deliver best care.

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# PRIMARY PREVENTION OF COLORECTAL CANCER

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## Abstract

Colorectal cancer is the third most common type of cancer worldwide, with the highest incidences in Australia, New Zealand, Europe and North America, and the lowest in Africa and South-Central Asia. Rates are substantially higher in males than in females. Bowel cancer is the most preventable cancer type in Australia, with an estimated 44% preventability achievable through improvements in diet and physical activity. In 2005, the National Health and Medical Research Council published *Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*. This chapter builds on the conclusions from these guidelines, drawing on the comprehensive review undertaken by the World Cancer Research Fund/American Institute for Cancer Research (Second Expert Report) published in 2007, and Continuous Update Project review published in 2011. The evidence is convincing that physical activity and foods containing dietary fibre protect from colon and colorectal cancer respectively, and that red and processed meat, ethanol from alcoholic drinks and body and abdominal fatness increase the risk of colorectal cancer. Strategies to support these lifestyle and dietary changes in practice should be strongly recommended. The smoking of tobacco probably causes colorectal cancer and foods containing garlic, milk and calcium probably protect against colorectal cancer. The use of anti-inflammatory drugs as prophylaxis against further adenoma development in individuals with familial adenomatous polyposis should be considered, especially where surgery is inappropriate; low dose aspirin in those at high familial or personal risk is recommended. Based on the current evidence, the level of protection offered by physical activity and dietary fibre, and the level of risk resulting from the consumption of red and processed meat and high body and abdominal fatness, is stronger and more conclusive than the evidence documented in previous reviews.

## Physical activity

The Second Expert Report (SER) (2007),<sup>1</sup> by the World Cancer Research Fund and American Institute for Cancer Research recommended people be moderately physically active, equivalent to brisk walking for at least 30 minutes a day, with the objective of  $\geq 60$  minutes of moderate or  $\geq 30$  minutes of vigorous physical activity every day, and to limit sedentary habits to prevent colorectal cancer (CRC).

The Continuous Update Project (CUP) (2011),<sup>2</sup> reviewed the outcomes of cohort studies published since 2007, and concluded that a lower risk of colon cancer was associated with higher overall levels of physical activity, with evidence of a dose-response effect within the range studied. The effect was strong for colon cancer, but there was no evidence of an effect for rectal cancer. The effect was strong and consistent for men, but less strong in women. The meta-analyses showed that recreational physical activity resulted in an 11% decrease in risk for colorectal and 12% decrease for colon cancer per 30 minutes of exercise per day. While these effects were independent of any effect of exercise on obesity, additional benefits of longer term, sustained, moderate physical activity may also be realised through reduced body fatness and may protect against colon cancer by decreasing inflammation, reducing insulin levels and reducing insulin resistance. More recently, physical activity and fewer sitting hours were found to significantly reduce colon cancer risk in both

the distal and proximal colon, although results for rectal cancer were mixed.<sup>3-5</sup>

## Obesity and abdominal fatness

The CUP review concluded that new cohort studies published between 2007 and 2011, investigating body mass index, showed increased risk of CRC with increased body fatness. The meta-analyses showed increased risks of 2, 3 and 1% per kg/m<sup>2</sup> for colorectal, colon and rectal cancers respectively. There tended to be a larger effect for men than women and the effect was stronger for the US and Asia than Europe. The CUP agreed with the SER finding that there was convincing evidence that greater body fatness is a cause of CRC. Similarly, the CUP found that all new cohort studies demonstrated that increasing waist circumference and/or waist to hip ratio measurements increased risk for CRC. The meta-analyses showed increased risks of 3, 5 and 3% (per inch for studies that did not adjust for body mass index) respectively for colorectal, colon and rectal cancers. In the UK, 13% of CRC has been attributed to overweight and obesity. In the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, individuals who gained >20kg of weight since age 20, had a 38% higher risk of colon, but not rectal cancer, compared to those whose weight remained stable. This association only applied to those with high attained waist circumference, suggesting fat accumulation in the abdominal area is important in



relation to CRC risk.<sup>6</sup> A recent review involving seven studies, found obese patients were more likely to have distal tumours, show intact DNA mismatch repair, and have increased lymph node metastases compared with normal-weight patients.<sup>7</sup> Other recent reviews made similar conclusions, with the risk of CRC from excess body fatness being stronger in men than women, rectal cancer being less affected by body fatness than colon cancer and with general and regional fatness both playing a role.<sup>8-12</sup> Body and abdominal adiposity may increase risk through systemic effects, in which insulin and oestrogen levels encourage carcinogenesis and discourage apoptosis.<sup>4</sup>

## Diet

### **Dietary fibre**

Dietary fibre is a heterogeneous group of plant-derived structural components not digested by human digestive enzymes, consisting largely of non-starch polysaccharides and resistant starch. The suggested mechanisms for protection from CRC from high dietary fibre include fibre diluting or absorbing digested carcinogens, reducing intestinal transit time, reducing secondary bile acid production, reducing colonic pH and increasing the production of short chain fatty acids.<sup>13</sup> The short chain fatty acid butyrate may play an important role,<sup>14</sup> as it enhances the deletion of genetically damaged cells by inducing cell cycle arrest, differentiation and apoptosis.<sup>15</sup> The CUP concluded that 13 of 18 studies published since the SER (2007) review showed decreased risk of CRC with increased intake of total dietary fibre. The updated meta-analyses showed a 12% decreased risk for men and an 8% decreased risk for women (per 10g dietary fibre/d), with a 21% decreased risk per three servings of wholegrains for CRC and a 16% decreased risk for colon cancer. Based on consistent evidence, with clear dose-response relationships for both women and men the CUP concluded that the protective effect of dietary fibre had strengthened from 'probable' to 'convincing'. The CUP agreed with the SER conclusion that evidence of protection from non-starchy fruits and vegetables was limited. The CUP review included a pooled analysis of 756,217 participants from 14 cohort studies, followed up for six to 20 years.<sup>16</sup>

### **Red and processed meat**

Based on the findings of nine of 12 studies published

between 2007-2011, the CUP agreed with the SER that there was convincing evidence that higher intakes of red and processed meat increase the risk of CRC. Meta-analysis showed a 17% increase in risk of CRC per 100g red meat consumed per day. This conclusion is further supported by more recent studies confirming red meat consumption is a risk factor for cancer of several sites, including colon and rectum, with no effect of cooking method.<sup>17</sup> Others have found an association between cooking method and CRC and rectal adenoma risk.<sup>18,19</sup> The risk of CRC and rectal cancer differ according to the subtype of red meat consumed.<sup>20</sup> The mechanism underlying the increase in risk may be associated with the presence of heme in red meat, which undergoes endogenous nitrosation with the formation of potentially carcinogenic N-nitroso compounds,<sup>21</sup> or due to the production of potentially carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons during the cooking of meat, or the presence of nitrites and nitrates.<sup>18</sup> In 10 of 13 studies reviewed by the CUP, increased risk of CRC with higher intake of processed meat was observed. The meta-analysis showed an 18% increased risk for CRC and a 24% increased risk of colon cancer per 50g processed meat/day intake. There was an indication of increased risk of rectal cancer, but the effect was not significant. The CUP concluded there was a dose-response relationship apparent from cohort studies and agreed with the SER that processed meat was a convincing cause of CRC. More recent studies have confirmed a positive association between red processed meat and proximal colon cancer,<sup>18</sup> and that in Europe the negative effect of processed meat was mainly driven by the consumption of sausages.<sup>22</sup>

### **Other nutrients**

The CUP and SER concluded milk probably protected from CRC with a 9% decreased risk for CRC per 200g milk consumed/day. This conclusion is supported by the EPIC study, which found dairy products protective irrespective of fat content of the products,<sup>23</sup> but not non-dairy calcium products. However, the CUP and SER reviews found that in six of seven cohort studies, calcium supplements reduced the risk of CRC, and the CUP panel concluded that calcium probably protected against CRC. Other nutrients or foods for which there is limited or inconsistent evidence to support their role in CRC protection or development are listed in table 1.

**Table 1: Summary of 2005 Guidelines and Updated Recommendations**

	<b>SUMMARY 2005 NHMRC GUIDELINES</b>	<b>2013 UPDATED RECOMMENDATIONS</b>
<b>Strongly recommended</b>	<p>Alcohol intake should be limited or avoided with men drinking under two standard drinks/day and women under one standard drink a day (10 g alcohol).</p> <p>Limit energy intake in most men to &lt;2500 calories (10,480 kJ) per day and in most women to &lt;2000 calories (8360kJ) per day.</p>	<p>Alcohol intake should be limited or avoided with men drinking under two standard drinks/day.</p> <p>Increase intake of cereal fibre, particularly poorly soluble cereal.</p> <p>Moderate intakes of lean red meat (up to 100g/d) can be eaten as part of a mixed diet. Charring of red meat is best avoided and consumption of processed meats should be limited.</p> <p>30-60 minutes/day of vigorous physical activity and avoid sedentary behaviour. Maintain weight in healthy BMI range and avoid abdominal fatness.</p> <p>Lynch Syndrome carriers should take aspirin, at least 100mg daily, except in carriers with indigestion, renal impairment, aspirin allergy or uncontrolled hypertension.</p>
<b>Recommended</b>	<p>Engage in 30-60 min/day of vigorous physical activity, and avoid excessive weight gain. Maintain weight in healthy BMI range.</p> <p>Avoid tobacco smoking.</p> <p>Reduce dietary fat to &lt;25% of calories as fat.</p> <p>Antioxidant supplementation is not advised.</p> <p>Use of anti-inflammatory drugs (aspirin) as prophylaxis against further adenoma development in those with previous removal of an adenoma.</p>	<p>Alcohol intake should be limited or avoided with women drinking under one standard drink/day.</p> <p>Avoid tobacco smoking.</p> <p>Garlic, milk and calcium probably protect against cancer.</p> <p>Use of anti-inflammatory drugs (aspirin) as prophylaxis against further adenoma development in those with previous removal of an adenoma.</p> <p>Individuals at familial risk of colorectal cancer (other than Lynch Syndrome) should take aspirin, at least 100mg daily, except in carriers with indigestion, renal impairment, aspirin allergy or uncontrolled hypertension. Where surgery is inappropriate, it is recommended FAP patients take NSAIDs (e.g. sulindac).</p>
<b>Equivocal</b>	<p>Moderate intakes of lean red meat can be eaten as part of a mixed diet. Charring of red meat is best avoided and consumption of processed meats should be limited.</p> <p>Fresh fruit and vegetable intake should be increased above national nutritional guidelines of two serves of fruit and five of vegetables.</p> <p>Increase intake of cereal fibre, particularly poorly soluble cereal, especially if at increased risk of CRC.</p> <p>Supplementation with calcium to 1000-1200mg/day in keeping with general dietary guidelines.</p> <p>Selenium supplementation.</p> <p>Hormone replacement therapy cannot be recommended as prophylaxis for CRC because of possible collateral risks.</p>	<p>Evidence that foods containing iron, cheese, animal fats and sugars cause cancer is limited.</p> <p>Evidence of protection from non-starchy vegetables, fruits and foods containing vitamin D is limited.</p> <p>Statin use is associated with reduced colorectal cancer incidence and can be considered as such when used for lipid reducing purposes.</p>

<b>Limited - no conclusion</b>	<p>No evidence of protection from foods containing folate, fish and selenium.</p> <p>Use of bisphosphonates as prophylaxis against further adenoma development in those with previous removal of an adenoma.</p>
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## Alcohol

The 15 new papers reviewed by the CUP showed an increased risk with increased intake of ethanol for CRC and colon cancers. The meta-analyses showed a 10% increased risk for CRC and rectal cancers, and an 8% increased risk for colon cancer per 10g ethanol consumed per day. The effect was stronger in men than women, with 11% increased risk in men compared to 7% in women. The CUP agreed with the SER conclusion that ethanol from alcoholic drinks as a cause of CRC in men was convincing, and was probably a cause of CRC in women. In the UK, 15.5% of CRC in men and 6.9% in women has been attributed to consumption of alcohol.<sup>24</sup> Alcohol interacts with tobacco by interfering with the repair of specific DNA mutations caused by smoking, and may also enhance the penetration of other carcinogenic molecules into mucosal surfaces.

## Tobacco smoking

Significant associations were found between daily cigarette consumption, duration, pack years and age of initiation with CRC incidence, with an increase in risk of 38% for every 40 cigarettes smoked per day.<sup>25</sup> Tobacco smoking is considered to be an established cause of CRC,<sup>26</sup> with 8.1% of CRC in the UK attributed to tobacco use.<sup>24</sup>

## Potential chemopreventative agents

Chemoprevention is the regular use of drugs to prevent or delay the development of cancers. As chemoprevention strategies require regular use of agents over many years by people who are disease free and may never develop cancers, chemopreventive agents need to be easily administered with a convenient dosing schedule, inexpensive and extremely low in side-effects. There is strong evidence supporting the chemopreventive activity of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) against CRC. However, data on the risk-benefit profile of these drugs is currently insufficient to allow definitive recommendations for their use at a population level for primary cancer prevention. Aspirin is the NSAID most likely to be used, largely because its cancer-preventive actions augment its already established cardiovascular benefits and its safety and efficacy profile is well understood.<sup>27</sup> Indeed, with the recent publication of data from the CAPP2 study, there is consensus among familial cancer clinics that daily aspirin use at a dose of at least 100mg per day be recommended for patients with Lynch Syndrome,<sup>28</sup> subject to consideration of their history of indigestion, peptic ulcer, *Helicobacter pylori* infection, renal impairment, allergy to aspirin and uncontrolled hypertension. In some circumstances, patients with familial adenomatous polyposis are currently treated with

traditional NSAIDs (e.g. sulindac) to reduce their risk of developing CRC, even though these drugs provide no cardio-protection.<sup>29</sup>

The commonly prescribed cholesterol-lowering statin drugs also have chemopreventive properties. They are very well tolerated and serious adverse effects of these drugs are rare. While currently less compelling than for aspirin, accumulating clinical evidence suggests a significant association of certain statins with lowered gastrointestinal (particularly colorectal) tumour occurrence, or increased patient survival when the drugs are taken for >3 years or >5 years in modest doses (e.g. 40 mg simvastatin; reviewed in.<sup>27</sup> These benefits are likely to be more marked in populations with a higher lifetime risk of cancer e.g. the hereditary colorectal cancer syndromes.

Patients with diabetes mellitus have an increased risk of CRC.<sup>30</sup> Metformin is an anti-hyperglycaemic drug, widely prescribed for the treatment of type-2 diabetes with few side-effects. Metformin lowers intestinal glucose absorption, hepatic glucose production and improves insulin sensitivity in the peripheral tissues, leading to lower levels of circulating insulin.<sup>31</sup> Elevated insulin levels have been associated with an increased risk of CRC. Two meta-analyses of cancer incidence in patients with type-2 diabetes have both shown an inverse association between metformin use and CRC.<sup>32,33</sup> Given the increased risk of CRC associated with type-2 diabetes, metformin's potent anti-hyperglycaemic activity and its protective activity against CRC make it an attractive drug for the management of diabetes patients.

Bisphosphonates are used in treatment of osteoporosis, multiple myeloma, for the treatment of bone overgrowth in malignancy and for the prevention or treatment of solid tumour metastases to the bone.<sup>34</sup> Their anti-cancer activity is likely mediated through inhibition of angiogenesis and cell proliferation, induction of cell-cycle arrest, and apoptosis in cancer cells, and immune cell activation.<sup>34</sup> Three studies in women found quite substantial reduction in the risk of CRC,<sup>35-37</sup> while analyses of data from the Women's Health Initiative and the Nurse's Health Study found no such reduction.<sup>38,39</sup> More research is needed to confirm the utility of bisphosphonates in the prevention of CRC and to quantify the benefits of bisphosphonates against the rare but serious adverse events.

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# SCREENING FOR COLORECTAL CANCER – NEW EVIDENCE IN THE LAST 10 YEARS

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### Abstract

The evidence base for screening for colorectal cancer has expanded at a rapid pace in the last 10 years. Faecal immunochemical tests for haemoglobin have been proven to be superior to guaiac-based faecal occult blood tests in terms of acceptability to screenees and analytic and clinical sensitivities for cancer and advanced adenomas. In addition, flexible sigmoidoscopy has been proven to reduce incidence and mortality from colorectal cancer, demonstrating that structural detection of preinvasive lesions will reduce its incidence. Both methods are now proven screening tool options and should be considered for implementation in screening programs. The requirements of screening programs are also much clearer. The monitoring and reporting outcomes of screening programs have been subject to consensus processes and have been clearly enunciated. They include quality, population acceptance, costs, adverse effects and measures of disease burden. The data needed to measure these should be an obligatory aspect of organised screening programs. The evidence base supporting communication strategies has expanded. These, combined with strategies proven to increase participation, should be part of all screening programs. Australian society is clearly benefitting from colorectal cancer screening and guidelines need revision to reflect the new evidence.

The last 10 years have seen considerable advances in screening for colorectal cancer (CRC), not only in terms of tests used, but in understanding of how to execute and how to judge the outcomes of population-based organised screening programs, including our own National Bowel Cancer Screening Program. Furthermore, the latest research points to newer technologies that seem likely to change the screening scene in the next 10 years. This short review will focus primarily on the new evidence base and what it means for Australia at this point in time.

### Nature of screening and WHO principles

Screening is a multi-step and multidisciplinary process.<sup>1,2</sup> The World Health Organisation (WHO) guidelines address the need for an evidence base for the test and its impact, issues around the screening process, the importance of the cancer for the community in question, and the need for community engagement. For the screening process to work, a significant proportion of the population should engage in the screening test, the screening test should be performed appropriately and correctly, colonoscopy must be undertaken with skill, and any therapy, whether colonoscopic, surgical, chemotherapeutic or radiological, must be done well. Each of these steps is crucial if we are to achieve a reduction in population mortality from CRC or in its incidence. Quality assurance at each step is vital. A screening program should seek to ensure all these aspects are in place, and should be monitored carefully for quality and to demonstrate value and feasibility.

Principles of the WHO,<sup>1</sup> while promulgated in 1968, continue to be the basis for this approach, although two aspects of the original standard need comment – reduction of cancer incidence, and the nature of the screening test.

The WHO principles always envisaged screening being undertaken using a simple screening test with follow-up of a 'positive' by diagnostic verification (in the case of CRC this would be colonoscopy). In some countries, CRC screening with the diagnostic test (colonoscopy) is underway and being performed with careful attention to quality and good population acceptance.<sup>3,4</sup> However, we still do not have randomised control trials (RCT) of average-risk populations assessed on an intention-to-screen basis to support such 'one-step' screening. Such trials are underway, but it will be a decade before the information is available.<sup>3</sup>

The WHO principles also focused on reducing cancer mortality, with little attention paid to incidence reduction. Clearly the latter will lead to the former. Given we now have evidence, discussed below, showing CRC screening can reduce incidence, we need to consider whether we should target not just early stage cancer, but also pre-invasive lesions, especially 'advanced adenomas'.

Targeting adenoma detection has a risk of leading to overdiagnosis, although there has been no evidence to emerge that suggests over-diagnosis is an issue for CRC. Over-diagnosis refers to detection of inconsequential disease that will not shorten one's life-span if left untreated. Overdiagnosis will occur when we focus on detection of adenomas, but it should be noted that the vast majority of these will be simply treated at colonoscopy.

### Screening contexts and outcomes

Organised screening programs are the preferred basis for implementing screening programs.<sup>5</sup> This ensures all

elements of the screening process are in place, that quality assurance is addressed systematically, or resourcing of key aspects such as colonoscopy are appropriately dealt with, population engagement can be addressed and improved and benefit to the community is readily understood. Screening by case-finding is ad hoc and quality assurance, as well as equitable population coverage, are difficult since screening is more than simply carrying out the screening test and referring people for diagnosis where indicated.

Invitation processes must be developed and carefully tested in the target population. The program should then ensure that a high level of compliance with diagnostic follow-up occurs. Practice standards for diagnosis, treatment and surveillance must be set. While we have done this most recently for CRC through the National Health and Medical Research Council guidelines of 2005, new approaches in aspects of CRC have emerged since the National Bowel Cancer Screening Program began in earnest in 2006.

Global standards have now emerged for monitoring CRC screening at the population level.<sup>6</sup> These generally cover the following categories of measurable events:

1. Population acceptance
2. Screening pathway adherence by screenees and health professionals
3. Test performance and lesion detection, including missed (or interval) lesions and technical aspects of the screening test
4. Quality measures (at all levels)
5. Adverse events
6. Cost-effectiveness
7. Burden of disease at the population level:
  - Cancer and advanced adenoma detection rates
  - Down-staging of cancer (a useful surrogate for mortality in the case of CRC screening)
  - CRC-specific mortality
  - CRC incidence.

Complete and accurate recording of relevant data on each person and every screening and diagnostic test performed is crucial. This places major demands on all involved in the screening pathway, and on data systems and processes for collating and monitoring data. Incorporating evaluation of the program into the protocols adopted for the screening process must be in place at the start. In this context of oversight, 'safety-net' systems can also be implemented. For example, nurse pathway coordinators serve to ensure program adherence and improvement in quality.<sup>7</sup>

### New evidence base for screening tests

Two key developments in simple screening tests have changed or are in the process of changing the nature of screening programs. The first relates to the revolutionary changes in faecal tests for occult blood (FOBT) brought about by faecal immunochemical tests (FIT) for haemoglobin. It should be noted that FIT is the preferred abbreviation for the latter since the technology, clinical performance, and population acceptance is very different

from the original guaiac-FOBT (gFOBT).<sup>8</sup>

As background, the relatively insensitive gFOBT Hemoccult offered biennially, reduced CRC-mortality by 15-20% on an intention-screen basis.<sup>9-13</sup> This improves to 33% with rehydration of Hemoccult offered annually, a process that increases sensitivity, but results in considerable deterioration in specificity.<sup>9</sup> The increased sensitivity achieved with rehydrated Hemoccult is also associated with a 20% reduction in CRC incidence when followed up for 18 years,<sup>14</sup> presumably resulting from increased detection and removal of adenomas. Together with this benefit on CRC mortality, the associated parameters regarding screening participation, test accuracy and cancer down-staging have been demonstrated.<sup>15</sup> For CRC screening, we can be confident down-staging will translate into survival benefit and reduced population mortality.

It is now clear that FIT provides better accuracy, including improved sensitivity for advanced adenomas as well as CRCs, and better acceptability when evaluated on an intention-to-screen basis.<sup>16,17</sup> When evaluated in a program involving repeated testing, two-thirds to three-quarters of cancers are detected by FIT.<sup>18</sup> Population-based and case-control studies support the value of this technology.<sup>19-26</sup> Further studies from the Netherlands confirm the value of FIT in a population RCT when analysed on an intention-to-screen basis relative to Hemoccult II.<sup>27</sup> While that study showed that FIT resulted in twice as many colonoscopies as gFOBT, more than twice as many advanced neoplastic lesions were detected, meaning that the number needed to colonoscope to detect one lesion was largely unchanged. All this evidence has led to recommendations that FIT replace gFOBT.<sup>2,28</sup> FIT technology has significantly better capacity to detect adenomas than gFOBT, and repeated testing improves detection.<sup>18,29</sup> In other words, when using this FOBT technology, there is capacity to reduce incidence as well as mortality.

Publications are now calling for the use of quantitative FIT, not just the qualitative versions, since these allow flexibility, including choice of preferred test performance characteristics and adjustment of the cut-off triggering colonoscopy, such that programs can be carefully matched to colonoscopic resources.<sup>30</sup> These tests are also readily automated and the endpoints are objectively ascertained, improving quality assurance in the laboratory.

Finally, FIT tests have now been shown in the absence of bias to lead to down-staging on an intention-to-screen, as well as a participant basis in the National Bowel Cancer Screening Program.<sup>31</sup> They have also been associated with down-staging in an extensive cancer register.<sup>32</sup> We can be confident of their value in reducing CRC mortality.

More recently, the results of three sigmoidoscopy screening RCTs consistently showed that endoscopic excision of colorectal adenomas is associated with a substantial reduction in CRC incidence (18%-23%) and mortality (26%-31%) on an intention-to-screen basis.<sup>33-35</sup> Considering subjects who were actually screened, the reduction in CRC incidence ranged between 31% and 33%, and CRC-specific mortality was reduced by 38%-43%. The observed protective effect refers to a follow-up of 11 years and was mainly limited to the distal colon. The

reduction in CRC incidence in the proximal colon was small and not statistically significant either in the UK (3%) or in the Italian (15%) trials.<sup>33, 34</sup> A statistically significant 14% reduction in CRC incidence in the proximal colon was documented only in the Prostate, Lung, Colorectal and Ovarian cancer screening trial,<sup>35</sup> but there was no mortality reduction in the trial.

Based on the effect observed for flexible sigmoidoscopy, it can be concluded that structural detection (i.e. visualisation at endoscopy) of lesions brings significant benefit in terms of reduced incidence, morbidity and CRC mortality. But it should be noted that the majority of adenomas would not progress to cancer during a person's life time if left in situ.<sup>36</sup>

Whether the benefit of polypectomy extends to the proximal colon is not yet certain. This uncertainty is underscored in observational studies that showed use of colonoscopy was not associated with a reduction in the risk of dying from right-sided CRC.<sup>37-40</sup> Only one case-control study has shown a reduction in proximal CRC incidence associated with self-reported use of colonoscopy in the preceding one to 10 years, and only in subjects older than 60 years.<sup>41</sup> These findings underscore how crucial the quality of diagnostic examinations is to maximising effectiveness in screening and to optimise the balance between potential harms and benefit. They also suggest effectiveness of one-step colonoscopic screening in practice might not be as great as is often assumed.

Therefore, even though colonoscopy improves detection of both invasive lesions and pre-invasive lesions (adenomas), adding the potential to prevent cancer, the benefit of colonoscopic screening, either in terms of CRC mortality, or incidence reduction, has not been assessed by mass population RCTs in the setting of mass population screening.<sup>42</sup> Such studies are, however, underway.<sup>3</sup> New guidelines for CRC screening need to specify FOBT technology and the superiority of FIT over gFOBT.

### Emerging tests

Molecular tests using multi-target DNA markers are being developed using faecal samples. They continue to improve, with promise of very good sensitivity and specificity for cancer and advanced adenomas. Their adoption will depend on logistics and cost. Blood based molecular markers also show promise, although at this stage they do not seem superior to FIT in terms of performance, and are limited in capacity to detect advanced adenomas.<sup>43</sup> Nonetheless, qualitative studies show that the concept of a blood test would be preferred by the majority.

### Communication and program

The target population should receive relevant information to enable them to make an informed decision about screening. CRC screening is more complex than for breast or cervix, especially in view of the more complex risk groups and wider range of test options. Communications need to address the anxiety this can raise.

The screening process needs to be clearly explained, as well as the fact that a positive test in two-step screening should be followed by colonoscopy. Similarly, programs must explain that screening tests are not perfect. While

many innovative studies are underway to address how best to do this, and some guidelines are providing guidance,<sup>2</sup> programs should clearly enunciate communication standards needed for the community context.

Communicating the value and appropriateness of screening aids participation as it moves people through the stages of pre-contemplation and contemplation to action. An advance letter improves uptake in the Australian environment and in many others, but this needs support from a wider media-based awareness campaign.<sup>44</sup>

FIT tests help to overcome some of the faecal sampling barriers due to their simpler sampling devices (compared to gFOBT) and removal of dietary restriction barriers inherent in gFOBT.<sup>16</sup> FIT also avoids the high false-positive rate of gFOBT in certain ethnic populations.<sup>45</sup> A trusted advocate, specifically a person's own general practitioner, increases screening participation rates and adherence to screening over multiple rounds.<sup>46</sup> It makes sense to develop methods to demonstrate to invitees that GPs are supportive. While most screening guidelines have traditionally restricted themselves to addressing tests, it is now time that guidelines for communication and proven participation-enhancing strategies are incorporated.

### Conclusions

In the last 10 years, FIT has been proven to be superior to gFOBT in terms of acceptance and analytic and clinical sensitivities for cancer and advanced adenomas. In addition, flexible sigmoidoscopy has been proven to reduce incidence and mortality from CRC, demonstrating that structural detection of pre-invasive lesions will reduce incidence. Both need to be specifically included as proven screening tool options and should be explored for implementation in screening programs.

The outcomes of screening programs that should be monitored and reported have been subject to consensus processes and have been clearly enunciated. These should be obligatory aspects of organised screening programs. Some of the inadequacies of colonoscopy in CRC detection have been highlighted, and RCTs to help guide us are underway. The evidence base supporting communication strategies has expanded and the standards of such are being established. These, combined with strategies proven to increase participation, should be presented along with guidance about the screening tests themselves. CRC screening clearly brings benefit to Australian society. But given the advances over the last 10 years, the guidelines for screening need revision to reflect the expanding and more informative evidence base.

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# RISK PROFILING: FAMILIAL COLORECTAL CANCER

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## Abstract

Family history of colorectal cancer is a well-established and consistently strong risk factor for this disease. However, simply counting the number of affected relatives is an imprecise measure of colorectal cancer risk. We have reviewed current colorectal cancer screening guidelines from Australia, New Zealand, Canada, the US, and UK, and found that all, including the Australian National Health and Medical Research Council 2005 guidelines, assign people to risk categories largely based on age and rudimentary metrics of family history and recommend screening regimens. We claim that these guidelines are not sufficiently precise for a large proportion of people within these categories, as there is a substantial variation in colorectal cancer risk, even for people with the same family history, and even for people with a predisposing mutation in the same gene, or set of genes. If there was a tool to estimate individual colorectal cancer risk based on all known risk factors for the disease - personal and family history of cancer (including ages, ages at diagnoses, and genetic relationships across multiple generations), all known genetic factors (rare high-risk genetic mutations as well as common genetic variants), environmental factors and personal characteristics - then accurate prediction of future risk of colorectal cancer (personalised risk) may be possible. The development and utility of such a comprehensive risk prediction tool is important for appropriate personalised clinical management, including targeted colorectal cancer screening.

In Australia, a total of 14860 (8258 men and 6602 women) people were newly diagnosed with colorectal cancer (CRC) (12.7% of all cancer cases) and 3968 (2199 men and 1769 women) died of CRC (9.3% of all cancer deaths) in 2010, making it the second most commonly diagnosed and second most common cause of cancer-related death. On average, one in 19 men and one in 28 women will be diagnosed with CRC by age 75 years, and one in 10 men and one in 15 women will be diagnosed by age 85 years.<sup>1</sup> The problem with these statistics is that they are 'average' risks and therefore do not reflect the substantial heterogeneity of disease risk across the population due to varying risk factors. They apply to only a small fraction of the population.

## Quantifying risk based on family history

Apart from age, family history of CRC is one of the most well-established and consistently strong risk factors for this disease.<sup>2-4</sup> A person with one first-degree relative (parent, offspring, sibling) with CRC (approximately 10% of the population)<sup>5</sup> is, on average, twice as likely to be diagnosed with CRC compared with someone without a family history (i.e. two-fold familial risk). Even a second and third-degree family history of CRC has been shown to increase the risk of disease, especially when combined with first-degree family history.<sup>4</sup> The younger the age at diagnosis of the affected relative, and the more closely related the affected relative, the greater the CRC risk.<sup>4</sup> This familial risk is partly due to genetic factors passed from parent to offspring, and partly due to environmental risk factors shared by family

members. It should be noted that, none of the current CRC screening guidelines takes environmental risk factors into account to quantify CRC risk for the population, or to formulate screening recommendations.<sup>6-12</sup>

In the absence of known cause for a particular family history (e.g. no predisposing gene mutation has been identified), current CRC screening guidelines from Australia, New Zealand, US, Canada and UK, assign people to risk categories of CRC based only on a combination of age and family history (table 1).<sup>6-12</sup> People with no personal or family history of CRC are generally defined as being at average risk, those with some family history as being at moderate or increased risk, and those with a strong family history as being at high risk of CRC. While many guidelines use basic presence or absence of family history to define risk categories, some guidelines consider the number of affected relatives, the ages at diagnoses of CRC and the degree of relationship for risk categorisation. However, even among these guidelines there are inconsistencies in definitions used for risk categorisation. For example, the variation in the criteria required to define the moderate or increased risk categories (table 1), and the variation in the recommendations provided for screening (table 2). These inconsistencies illustrate our relatively limited understanding of the familial aspect of CRC. All the existing guidelines fail to provide clear level of risk cut-offs beyond the broad and uncertain risk categories currently in use. This uncertainty constitutes a major barrier to the translation of current evidence into the most effective risk-reduction strategies.

**Table 1:** Summary of family history profiles used in current guidelines to define colorectal cancer risk in the population.

Country	Institution	Definition of family history of colorectal cancer		
		Average risk	Moderate or increased risk	High risk
<b>Australia</b>	National Health and Medical Research Council. <sup>6</sup>	<p><i>“at or slightly above average risk”</i></p> <ul style="list-style-type: none"> <li>• No personal history of CRC, advanced adenoma, or chronic ulcerative colitis; and</li> <li>• No close relative with CRC; or</li> <li>• One FDR or SDR with CRC diagnosed at age 55 or older</li> </ul>	<p><i>“at moderately increased risk”</i></p> <ul style="list-style-type: none"> <li>• One FDR with CRC diagnosed before age 55; or</li> <li>• Two FDRs or one FDR and one SDR on the same side of the family with CRC diagnosed at any age</li> </ul>	<p><i>“potentially high risk”</i></p> <ul style="list-style-type: none"> <li>• Three or more FDRs or SDRs on the same side of the family diagnosed with CRC, or</li> <li>• Two or more FDRs or SDRs on the same side of the family with CRC, including any of the following high-risk features: <ul style="list-style-type: none"> <li>– Multiple CRCs in a relative</li> <li>– CRC diagnosed before age 50</li> <li>– At least one relative with endometrial, ovarian, stomach, small bowel, renal pelvic or ureter, biliary tract, or brain cancer (suspected HNPCC), or</li> </ul> </li> <li>• At least one FDR with a large number of adenomas throughout the large bowel (suspected FAP), or</li> <li>• At least one relative identified having a high-risk mutation in APC or an MMR gene.</li> </ul>
<b>New Zealand</b>	New Zealand Guidelines Group <sup>7</sup>	<p><i>“slightly increased risk”</i></p> <ul style="list-style-type: none"> <li>• One FDR with CRC diagnosed after age 55</li> </ul>	<p><i>“moderately increased risk”</i></p> <ul style="list-style-type: none"> <li>• One FDR with CRC diagnosed before age 55, or</li> <li>• Two FDRs on the same side of the family with CRC diagnosed at any age</li> </ul>	<p><i>“potentially high risk”</i></p> <ul style="list-style-type: none"> <li>• Family history of FAP, HNPCC, or other familial CRC syndromes, or</li> <li>• One FDR plus two or more FDRs or SDRs on the same side of the family with CRC diagnosed at any age, or</li> <li>• Two FDRs, or one FDR plus one or more SDRs, on the same side of the family with CRC, and one such relative diagnosed with: <ul style="list-style-type: none"> <li>– CRC before age 55, or</li> <li>– multiple CRCs, or</li> <li>– an extracolonic tumour suggestive of HNPCC (endometrial, ovarian, stomach, small bowel, renal pelvic, pancreas or brain cancer).</li> </ul> </li> <li>• At least one FDR or SDR with both CRC and multiple colonic polyps, or</li> <li>• A personal history or one FDR with CRC diagnosed before age 50, particularly where CRC IHC shows absence of protein expression for an MMR gene, or</li> <li>• A personal history or one FDR with multiple colonic polyps.</li> </ul>

Country	Institution	Definition of family history of colorectal cancer		
		Average risk	Moderate or increased risk	High risk
USA	American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, and American College of Radiology <sup>8</sup>	<p><i>"average risk"</i></p> <ul style="list-style-type: none"> <li>No family history of CRC<sup>87</sup></li> </ul>	<p><i>"increased risk"</i></p> <ul style="list-style-type: none"> <li>One FDR with CRC or adenoma diagnosed before age 60, or</li> <li>Two or more FDRs with CRC or adenoma diagnosed at any age</li> <li>One FDR with CRC or adenoma diagnosed at age 60 or older, or</li> <li>Two or more SDRs with CRC.<sup>87</sup></li> </ul>	<p><i>"high risk"</i></p> <ul style="list-style-type: none"> <li>FAP: genetic diagnosis of FAP or suspected FAP without genetic testing evidence, or</li> <li>HNPCC: genetic or clinical diagnosis of HNPCC or people at increased risk of HNPCC,<sup>87</sup> or</li> <li>Inflammatory bowel disease, chronic ulcerative colitis and Crohn's colitis.</li> </ul>
	Canadian Task Force <sup>9</sup>	<p><i>"at normal risk"</i></p> <ul style="list-style-type: none"> <li>Not defined in the statement paper.</li> </ul>	<ul style="list-style-type: none"> <li>One or two FDRs with CRC</li> </ul>	<p><i>"at above-average risk"</i></p> <ul style="list-style-type: none"> <li>FAP: Multiple adenomatous polyps throughout the colon; polyps first appear after puberty; and other lesions including gastric and duodenal polyps, desmoid tumours, osteomas and retinal lesions.</li> <li>HNPCC: defined by Amsterdam Criteria-II88</li> <li>Family history: More than two FDRs with CRC, but do not meet criteria for HNPCC.</li> </ul>
Canada	Canadian Association of Gastroenterology and Canadian Digestive Health Foundation <sup>10</sup>	<p><i>"at average risk"</i></p> <ul style="list-style-type: none"> <li>No family history of CRC</li> </ul>	<ul style="list-style-type: none"> <li>One FDR with CRC or adenoma diagnosed after age 60, or</li> <li>Two or more SDRs with CRC or adenoma at any age</li> <li>One FDR with CRC or adenoma diagnosed at before age 60, or</li> <li>Two or more FDRs with CRC or adenoma at any age</li> </ul>	<p><i>"high risk"</i></p> <ul style="list-style-type: none"> <li>HNPCC: defined by Amsterdam Criteria-II88; or</li> <li>FAP; or</li> <li>AAPC or AFAP</li> </ul>
UK	British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland <sup>12</sup>	<ul style="list-style-type: none"> <li>No family history of CRC</li> </ul>	<p><i>"high-moderate risk"</i></p> <ul style="list-style-type: none"> <li>Three relatives# with CRC in first-degree kinship,* at least one is a FDR of the consultand, none diagnosed before age 50, or</li> <li>Two relatives## with CRC in first-degree kinship,* at least one is a FDR of the consultand, both diagnosed before age 60 or their mean age before 60.</li> </ul> <p><i>"low-moderate risk"</i></p> <ul style="list-style-type: none"> <li>One FDR with CRC diagnosed before age 50, or</li> <li>Two FDRs with CRC diagnosed at age 60 or older.</li> </ul>	<p><i>"high-risk"</i></p> <ul style="list-style-type: none"> <li>At-risk HNPCC: fulfills Amsterdam Criteria-II88; or untested FDR of proven MMR gene mutation carrier</li> <li>MMR gene mutation carrier</li> <li>One FDR with MSI-H CRC and IHC shows absence of MSH2, MSH6 or PMS2 protein expression; MLH1 loss and MSI specifically excluded.</li> <li>At-risk FAP: member of FAP family with no mutation identified)</li> <li>MAP: MUTYH-associated polyposis.</li> </ul>

AFAP, attenuated familial adenomatous polyposis; AAPC, attenuated adenomatous polyposis coli; APC, adenomatous polyposis coli; CRC, colorectal cancer; FAP, familial adenomatous polyposis; FDR, first-degree relative; IHC, immunohistochemistry; SDR, second-degree relative; MMR, mismatch repair; MAP, MUTYH-associated polyposis; MSI, microsatellite instability.

\*First-degree kinship: first-degree relatives of each other

#Combinations of three affected relatives in a first-degree kinship include: a parent and a blood-related aunt/uncle and/or grandparent; OR two siblings/one parent; OR two siblings/one offspring; OR both parents/one sibling.

##Combinations of two affected relatives in a first-degree kinship include: a parent and grandparent; OR >2 siblings; OR >2 children; OR child and sibling.

Ages at diagnosis are quoted in years.

**Table 2:** Summary of colorectal cancer screening recommendations for asymptomatic adults, by country and category of risk.

Country	Institution	Title	Recommendations by category of risk		
			Average risk	Moderate or increased risk	High risk
<b>Australia</b>	National Health and Medical Research Council	<i>The prevention, early detection and management of colorectal cancer (2005)</i> <sup>6</sup>	<ul style="list-style-type: none"> <li>• FOBT/FIT every 2 years starting at age 50</li> <li>• Flexible sigmoidoscopy every 5 years starting at age 50</li> </ul>	<ul style="list-style-type: none"> <li>• Colonoscopy every 5 years starting at age 50, or 10 years earlier than the youngest age at diagnosis of CRC in the family, whichever comes first</li> </ul>	<ul style="list-style-type: none"> <li>• Genetic counseling; Refer to CRC specialist to plan appropriate surveillance and management.</li> <li>• FAP: Flexible sigmoidoscopy every 1–2 years, from age 12–15 to 30–35 until polyposis develops. If no polyposis develops, flexible sigmoidoscopy every 3 years after age 35 and change to population screening after age 55.</li> <li>• HNPCC: Colonoscopy every 1–2 years, starting at age 25, or 5 years earlier than the youngest age at diagnosis of CRC in the family, whichever comes first.</li> </ul>
<b>New Zealand</b>	New Zealand Guidelines Group	<i>Guidance on Surveillance for People at Increased Risk of Colorectal Cancer (2011)</i> <sup>7</sup>	<ul style="list-style-type: none"> <li>• FIT every 2 years starting at age 50 (Same strategy as for those with no FDR with CRC and no personal history of CRC, adenomas, or inflammatory bowel disease)<sup>89</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Colonoscopy every 5 years starting at age 50, or 10 years earlier than the youngest age at diagnosis of CRC in the family, whichever comes first</li> </ul>	<p>Refer to</p> <ul style="list-style-type: none"> <li>• a cancer genetic service or the New Zealand Familial Gastrointestinal Cancer Registry,</li> <li>• a bowel cancer specialist to plan appropriate surveillance and management.</li> </ul>
<b>USA</b>	American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, and American College of Radiology	<i>Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps (2008)</i> <sup>3</sup>	<p>For people aged 50 or older:</p> <ul style="list-style-type: none"> <li>• High-sensitivity gFOBT every year</li> <li>• High-sensitivity FIT every year</li> <li>• High-sensitivity sDNA (interval uncertain)</li> <li>• Flexible sigmoidoscopy every 5 years</li> <li>• Colonoscopy every 10 years</li> <li>• Double contrast barium enema every 5 years</li> <li>• Computed tomography colonography every 5 years</li> </ul>	<ul style="list-style-type: none"> <li>• For people with one FDR with CRC or adenoma diagnosed before age 60, or two or more FDRs with CRC or adenoma diagnosed at any age: Colonoscopy every 10 years starting at age 40, or 10 years earlier than the youngest age at diagnosis of CRC or adenoma in the family, whichever comes first</li> <li>• For people with one FDR with CRC or adenoma diagnosed at age 60 or older or two or more SDRs with CRC: same strategy as for average-risk people, but starting at age 40.</li> </ul>	<ul style="list-style-type: none"> <li>• Genetic counselling</li> <li>• FAP: Flexible sigmoidoscopy every year, starting at age 10–12</li> <li>• HNPCC: Colonoscopy every 1–2 years, starting at age 20–25, or 10 years earlier than the youngest diagnosis of CRC in the family, whichever occurs first.</li> <li>• Inflammatory bowel disease: Colonoscopy with biopsies for dysplasia every 1–2 years, starting at 8 years after onset of pancolitis, or 12–15 years after onset of left-sided colitis; refer to a centre for management of inflammatory bowel disease.</li> </ul>

Country	Institution	Title	Recommendations by category of risk		
			Average risk	Moderate or increased risk	High risk
Canada	Canadian Task Force	<i>Recommendation statement from the Canadian Task Force on Preventive Health Care (2001)</i> <sup>9</sup>	<ul style="list-style-type: none"> <li>• FOBT every 1–2 years starting at age 50</li> </ul>	<ul style="list-style-type: none"> <li>• Same strategy as for 'average risk' people</li> </ul>	<ul style="list-style-type: none"> <li>• Genetic counselling</li> <li>• FAP: Flexible sigmoidoscopy every 1–2 years, starting at puberty.</li> <li>• HNPCC: Colonoscopy (starting age and the interval were not specified).</li> </ul>
	Canadian Association of Gastroenterology and Canadian Digestive Health Foundation	<i>Guidelines on colon cancer screening (2004)</i> <sup>10</sup>	Starting at age 50: <ul style="list-style-type: none"> <li>• FOBT every 2 years</li> <li>• Flexible sigmoidoscopy every 5 years; or</li> <li>• Flexible sigmoidoscopy combined with FOBT every 5 years, or</li> <li>• Double contrast barium enema every 5 years, or</li> <li>• Colonoscopy every 10 years</li> </ul>	<ul style="list-style-type: none"> <li>• For people with one FDR with CRC or adenoma diagnosed after age 60, or two or more SDRs with CRC or adenoma: same strategy as for average-risk people, but starting at age 40.</li> <li>• For people with one FDR with CRC or adenoma diagnosed before age 60, or two or more FDRs with CRC or adenoma: Colonoscopy every 5 years starting at age 40, or 10 years earlier than the youngest diagnosis of CRC or polyp in the family, whichever comes first.</li> </ul>	<ul style="list-style-type: none"> <li>• HNPCC: Colonoscopy every 1–2 years from age 20 or 10 years earlier than the youngest diagnosis of CRC in the family, whichever occurs first.</li> <li>• FAP: Sigmoidoscopy every year, from age 10–12.</li> <li>• AAPC or AFAP: Colonoscopy every year, from age 16–18.</li> </ul>
	Canadian Association of Gastroenterology	<i>Position statement on screening individuals at average risk for developing colorectal cancer (2010)</i> <sup>11</sup>	<ul style="list-style-type: none"> <li>• FOBT (preferably FIT) every 2 years from age 50 to 75.</li> <li>• Flexible sigmoidoscopy every 10 years from age 50 to 75.</li> </ul>	na	na
UK	British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland	<i>Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (2010)</i> <sup>12</sup>	na	<ul style="list-style-type: none"> <li>• For high-moderate risk people: Colonoscopy every 5 years from age 50 to 75.</li> <li>• For low-moderate risk people: Once-only colonoscopy at age 55; if normal—no follow-up.</li> </ul>	Genetic counseling <ul style="list-style-type: none"> <li>• At-risk HNPCC or MMR gene mutation carrier or people with FDR with MSI-H/IHC-MMR absent CRC: Colonoscopy every 1.5–2 years, starting at age 25</li> <li>• At risk FAP: Colonoscopy or alternating colonoscopy and flexible sigmoidoscopy every year, starting from puberty to age 30; thereafter every 3–5 years until age 60.</li> <li>• MAP: Colonoscopy every 2 years, starting at age 25.</li> </ul>

AFAP, attenuated familial adenomatous polyposis; CRC, colorectal cancer; FDR, first-degree relative; FIT, faecal immunochemical test; FOBT, Faecal occult blood test; gFOBT, guaiac-based faecal occult blood test; HNPCC, hereditary non-polyposis colorectal cancer; MMR, mismatch repair; SDR, second-degree relative; sDNA: stool DNA test; na, not available.

Ages at diagnosis are quoted in years.

## Rare predisposing genetic mutations

In the last two decades, there have been great advances in the discovery of genetic causes of familial risk of CRC, beginning with the identification of the adenomatous polyposis coli (APC) gene, which when mutated, causes familial adenomatous polyposis.<sup>13</sup> The human homologs of the DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2) were discovered in the 1990s to be implicated in what is now referred to as Lynch Syndrome.<sup>14</sup> Since then, mutations in the genes MUTYH,<sup>15</sup> STK11,<sup>16</sup> BMPR1A,<sup>17</sup>

SMAD4 and PTEN,<sup>18</sup> have also been found to be genetic causes of CRC.

Approximately 5% of all CRC can be attributed to germline mutations in the CRC predisposing genes listed above, but this percentage is highly dependent on age. For example, 2-4% of all CRCs are attributable to Lynch Syndrome, but 10-15% of CRCs diagnosed before age 50 are attributable to Lynch Syndrome.<sup>19-27</sup> Approximately 1% of all CRC cases are due to familial adenomatous polyposis, and similarly, around 1% are due to MUTYH-associated polyposis and other polyposis syndromes (table 3).<sup>28</sup>

**Table 3: Colorectal cancer syndromes and their predisposing germline mutations.**

Syndrome	Phenotype OMIM ID	Genes	Genotype OMIM ID
<b>Non-polyposis syndromes</b> Lynch Syndrome (Hereditary non-polyposis colorectal cancer)	120435	MLH1 MSH2 MHS6 PMS2 EPCAM	120436 609309 600678 600259 185535
<b>Adenomatous polyposis syndromes</b> Familial adenomatous polyposis MUTYH-associated polyposis	175100 608456	APC MUTYH	611731 604933
<b>Hamartomatous polyposis syndromes</b> Juvenile polyposis syndrome	174900	SMAD4 BMPR1A	600993 601299
Peutz-Jeghers syndrome	175200	STK11	602216
Cowden disease (multiple hamartoma syndrome)	158350	PTEN	601728
Bannayan-Riley-Ruvalcaba syndrome	153480	PTEN	601728
<b>Other syndromes</b> Hereditary Mixed Polyposis syndrome	601228	GREM1	603054
Gorlin syndrome (Basal cell nevus syndrome)	109400	PTCH1	601309
Neurofibromatosis 1	162200	NF1	613113
Multiple endocrine neoplasia syndrome 2B	162300	RET	164761
Oligodontia-colorectal cancer syndrome	608615	AXIN2	604025
Other germline mutations for colorectal cancer		GALNT12 SMAD7 POLD1 POLE	610290 602932 174761 174762

OMIM, Online Mendelian Inheritance in Man (<http://omim.org>).

Familial adenomatous polyposis is an autosomal dominantly inherited disorder caused by germline mutations in APC (chromosome 5q21).<sup>13</sup> Prevalence of germline APC mutations in caucasian populations is estimated to be one

in 13,000.<sup>29</sup> APC mutation carriers are almost certain to develop hundreds to thousands of adenomatous polyps throughout the bowel before age 40 years. If prophylactic colectomy is not performed, CRC will occur by the sixth

decade of life in nearly all APC mutation carriers.<sup>30</sup> These mutation carriers also have an elevated risk of gastric, duodenal, thyroid and brain cancers.<sup>31</sup>

Lynch Syndrome, previously termed Hereditary Non-Polyposis Colorectal Cancer,<sup>32</sup> is an autosomal dominantly inherited disorder of cancer predisposition caused by germline mutations in one of the DNA mismatch repair genes: MLH1 (chromosome 3p21.3);<sup>33</sup> MSH2 (chromosome 2p22-21);<sup>34</sup> MSH6 (chromosome 2p16);<sup>35,36</sup> and PMS2 (chromosome 7p22.2);<sup>37,38</sup> or constitutional 3' end deletions of EPCAM (chromosome 2p21).<sup>39,40</sup> Estimates of prevalence of germline mutations of these genes in the population vary widely (depending on the assumptions used) from approximately one in 370 to one in 3100 people.<sup>41,42</sup> Risk of CRC to age 70 years for mismatch repair gene mutation carriers is estimated to be from 10% to

50%, depending on their sex and the gene that is mutated. Mutation carriers also have a substantial risk of subsequent primary (metachronous) CRC following colon, rectal, or endometrial cancer (table 4). Compared with the general population, mutation carriers are at increased risk of cancers of the colon, rectum, endometrium, stomach, ovary, ureter, renal pelvis, brain, small bowel and hepatobiliary tract, and the diagnoses of these cancers generally occur at younger ages than for the general population.<sup>43</sup> In addition, mutation carriers may also be at increased risk of cancer of the pancreas,<sup>44,45</sup> prostate,<sup>46-49</sup> breast,<sup>45,50-52</sup> and cervix,<sup>53</sup> although to a lesser extent than the cancers above. For people with Lynch Syndrome, colonoscopy is usually recommended every one–two years, starting at age 20–25 years or 10 years earlier than the youngest age at diagnosis of CRC in the family, whichever comes first (table 2).<sup>54</sup>

**Table 4:** Risks of colorectal cancer for people with germline mutations in mismatch repair genes or MUTYH.

Specific gene mutation	Hazard ratio (95% confidence interval)		Cumulative risk % to age 70 years* (95% confidence interval)	
	Male	Female	Male	Female
<b>Lynch Syndrome</b>				
<i>Risk of first colorectal cancer</i>				
MLH1 <sup>53</sup>	Age ≤40: 183 (102–328) Age 50: 84.3 (30.9–230) Age ≥60: 7.8 (1.5–41.5)	Age ≤40: 45.4 (19.4–106) Age 50: 74.1 (29.3–187) Age ≥60: 37.0 (12.7–108)	34 (25–50)	36 (25–51)
MSH2 <sup>53</sup>	Age ≤40: 139 (82.3–236) Age 50: 134 (66.1–274) Age ≥60: 34.6 (11.7–103)	Age ≤40: 120 (64.3–223) Age 50: 152 (67.5–344) Age ≥60: 18.3 (5.6–59.6)	47(36–60)	37 (27–50)
MSH6 <sup>90</sup>	8.6 (5.5–13.4)	6.4 (3.6–11.4)	22 (14–32)	10 (5–17)
PMS2 <sup>91</sup>	5.2 (2.8–9.7)	5.2 (2.8–9.7)	20 (11–34)	15 (8–26)
EPCAM <sup>92</sup>	not available	not available	75 (63–87)	74 (56–92)
<i>Risk of metachronous colorectal cancer following segmental resection for colon cancer</i>				
All genes combined <sup>93</sup>	not available	not available	10 years: 16 (10–25) 20 years: 41 (30–52) 30 years: 62 (50–77)	
<i>Risk of metachronous colon cancer following rectal cancer</i>				
All genes combined <sup>94</sup>	not available	not available	10 years: 19 (9–31) 20 years: 47 (31–68) 30 years: 69 (45–89)	
<i>Risk of colorectal cancer following endometrial cancer</i>				
All genes combined <sup>52</sup>	39.9 (27.2–58.3)		10 years: 20 (13–28) 20 years: 48 (35–62)	
<b>MUTYH mutation</b>				
<i>Risk of first colorectal cancer</i>				
biallelic <sup>61</sup>	108 (25.9–454)	129 (43.7–380)	75.4 (41.2–96.6)	71.7 (44.5–92.1)
monoallelic <sup>61</sup>	2.46 (1.54–3.93)	2.67 (1.67–4.26)	7.2 (4.5–11.2)	5.6 (3.5–8.7)

\*Cumulative risk of colorectal cancer to age 70 years for the Australian general population is estimated to be approximately 3.6% for males and 2.5% for females.

MUTYH-associated polyposis is an autosomal recessively inherited disorder caused by germline mutations in both alleles of MUTYH (biallelic mutation), whether they are homozygotes or compound heterozygotes.<sup>15</sup> Germline mutations in one allele of MUTYH (monoallelic mutation; heterozygote) are also associated with development of colorectal adenoma and cancer.<sup>55</sup> In the general population, the prevalence of monoallelic and biallelic MUTYH mutations in caucasians is estimated to be 1.7%, and 0.01% respectively.<sup>56</sup> In individuals with attenuated colorectal polyposis syndrome, the prevalence of monoallelic and biallelic MUTYH mutations is between 0-2% and 2-7% respectively.<sup>57</sup> Biallelic mutation carriers have a very high risk of CRC with 70% risk to age 70 years.<sup>58-60</sup> Monoallelic mutation carriers have approximately 6-7% risk of colorectal cancer to age 70 years.<sup>61</sup> Further, biallelic mutation carriers might also be at increased risk of duodenal, ovarian, bladder and skin cancers;<sup>62</sup> and monoallelic mutation carriers might also be at increased risk of gastric, endometrial and liver cancer.<sup>63,64</sup>

Given there is almost complete penetrance of CRC for biallelic MUTYH mutation carriers,<sup>58-60</sup> we recommend that biallelic MUTYH mutation carriers should consider colonoscopy screening every one-two years starting at age 20 years,<sup>65,66</sup> and consider prophylactic total colectomy with ileorectal anastomosis depending on the individual, age of presentation and number and size of polyps present.<sup>65,67,68</sup> Based on our recent estimates of CRC risk for monoallelic MUTYH mutation carriers,<sup>61</sup> we recommend that monoallelic MUTYH mutation carriers should consider colonoscopy beginning at age 40 years, with follow-up at intervals dependent on the presence or absence of polyps, but no less often than every five years if they have a first-degree relative diagnosed with CRC.

Recently, germline mutations in other genes have been identified as risk factors for the development of CRC including POLE and POLD1.<sup>69</sup> However, no study has been conducted to date to estimate risk of CRC for these mutation carriers. Until these age and sex-specific penetrance studies have been conducted, it will not be possible to make clinical recommendations including cancer screening.

### Common predisposing genetic variants

While much research capital has been spent on the search for new genes involved in CRC development in the last decade, there has been little success. However, genetic variants that are associated with the risk have been identified and have the potential to be used to identify people more likely to develop the disease. Genome wide association studies have identified single nucleotide polymorphisms (SNPs) associated with CRC risk at 15 genetic loci.<sup>70,71</sup> The minor alleles of each of these SNPs are carried by 5-50% of the population, and have been shown to be associated with small increases or decreases in CRC risk – the average effect size of the association (odds ratio) being approximately 1.2.<sup>72-80</sup> In total, these variants explain approximately 6% of the familial risk of CRC.<sup>81</sup> There is some support for the utility of genotyping for these SNPs to identify people at sufficiently high risk to justify more intensive CRC screening.<sup>81</sup> Clinical and population screening could

change dramatically if the underlying causal variants that explain the SNP associations are discovered and the cost of targeted genotyping reduces.

### Unexplained familial risks

All known genetic mutations and variants described above can only explain about 30% of the average two-fold familial risk of CRC.<sup>82</sup> The causes of the remainder of familial risk are presently unknown, but might consist of a combination of unmeasured minor genetic factors (often termed 'polygenic effect'), high-risk mutations in other CRC predisposing genes and environmental risk factors shared by relatives, that to date have either not been measured, or not been adequately measured.<sup>83</sup>

### Variation in CRC risks

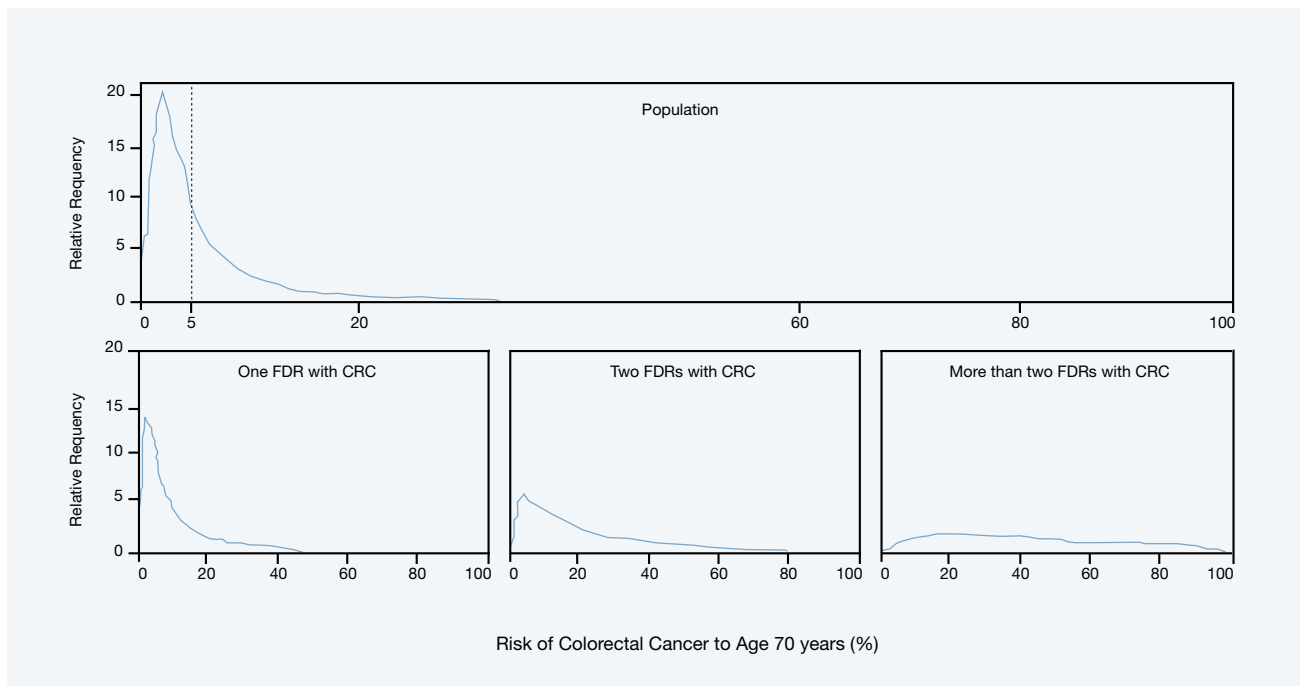
Given the personal differences in physical characteristics, family history of cancer, genetic factors and exposure to environmental risk factors, there is a wide spectrum of CRC risk across the population, ranging from almost zero to almost certainty. Even within a specific family history category, there is substantial heterogeneity of risk for CRC. Statistical modelling suggests that if all the familial/genetic risk factors act multiplicatively: (i) the risk of CRCs varies approximately 20-fold between the people in the lowest quartile for risk (average 1.25% lifetime risk) and the people in the highest quartile for risk (average 25% lifetime risk); and (ii) 90% of all CRCs occur in people who are above the median familial risk.<sup>84,85</sup>

Figure 1 shows the estimated distribution of lifetime risk (to age 70 years) of CRC for the overall population, and for three scenarios of having a family history of CRC. The shape of the distributions of risk are based on the fact that having an affected first-degree relative approximately doubles the risk, and presuming an underlying genetic risk model that involves multiple variants in multiple genes that have a multiplicative effect on risk.<sup>85</sup> It should be noted that: these distributions do not include the small proportion of people with inherited high-risk mutations in predisposing genes such as APC and the mismatch repair genes who have lifetime risks of approximately 100% and 50%, respectively.

The main diagram of figure 1 shows that while the average lifetime risk of CRC for the general population is approximately 5%, there is a wide spectrum of risk across the population, with the majority below 'average' risk. Lifetime risk of CRC for people with one affected first-degree relative (average two-fold increased risk) ranges from ~0% to ~40%. This overlaps substantially with lifetime risk of CRC for people with two affected first-degree relatives (average four-fold increased risk) whose risk ranges broadly from ~0% to ~80%, and for people with more than two affected first-degree relatives (average eight-fold increased risk) whose risk ranges from ~0% to ~100%. That is, simply counting affected relatives to define family history appears a rather naïve approach and an imprecise measure of actual familial risk of CRC, even more so if information on the ages of unaffected relatives, ages at diagnosis of affected relatives, and the genetic relationships between family members are not taken into account.<sup>86</sup>



**Figure 1:** Under the polygenic multiplicative model, for colorectal cancer (CRC) with average lifetime risk of 5%, the distribution of lifetime risk for: the population; people with one affected first-degree relative (FDR); people with two affected FDRs; and people with more than two affected FDRs. Modified the Figure 2 of Hopper (2011).<sup>85</sup>



### Variation in CRC risks for people with predisposing genetic mutations

Even for people with Lynch Syndrome, there is substantial variation in CRC risks. For example, a large study of 166 MLH1 and 224 MSH2 mutation families showed that on average, 34% of male MLH1 carriers, 47% of male MSH2 carriers, 36% of female MLH1 carriers, and 37% of female MSH2 carriers would be diagnosed with CRC by age 70 years (table 4). However, this average risk belies a wide of range risk between mutation carriers (standard deviation 1.6); a not insubstantial proportion of carriers being almost certain to be diagnosed with CRC (e.g. 19% of male MSH2 carriers have a risk of 90% or higher) while an even greater proportion are at only moderately elevated risk (e.g. 17% of male MSH2 carriers have a risk of 10% or less (see detail in Dowty et al.<sup>53</sup>).

A recent study also showed that there is a substantial variation of CRC risks for monoallelic MUTYH mutation carriers (standard deviation of 1.1). This translates that monoallelic MUTYH mutation carriers with a first-degree relative diagnosed with CRC, have about 10-12% risk of CRC to age 70 years, while the risk for all monoallelic mutation carriers irrespective of family history is about 6-7% (see detail in Win et al.<sup>61</sup>).

### Future paradigms

The implications of the variation of CRC risk for the general population, for people with a family history, and for mutation carriers are considerable. Family history of CRC is only one of the risk factors for the disease, and is a crude way of capturing a wide variation in familial risk. Current CRC screening guidelines addressing familial risk (including the

Australian National Health and Medical Research Council (NHMRC) 2005 guidelines)<sup>6</sup> use only age and rudimentary metrics of family history after excluding those with a personal history of CRC, advanced adenoma, or inflammatory bowel disease, to stratify people in to different screening regimens. For a complex disease such as CRC, this binary concept is of limited relevance, particularly with regard to prevention and early treatment. Current CRC prevention policies fail to integrate and use: 1) critical information on the skewed distribution of CRC risk in the population; and 2) genetic and environmental risk factors that have been consistently shown to be associated with a higher risk of CRC. In such a context, risk prediction models appear to be a promising tool to incorporate and translate into practice a continuously growing body of knowledge on CRC risk and the genetic pathways of its development.

If it were possible to measure all the familial/genetic risk factors and accurately estimate personal risk of CRC, then those at high-risk could be identified and targeted for CRC screening by colonoscopy, leaving those at the lowest risk to be safely recommended faecal occult blood testing (FOBT), potentially at different ages or frequencies, thereby saving on screening costs. This would reduce the number of unwarranted invasive and expensive procedures for those who are at low-risk of developing CRC and are least likely to benefit from CRC screening, and result in fewer screening related injuries such as bowel perforation. As a consequence, effectiveness and cost-effectiveness for CRC screening could be increased.

Prediction tools for an individual's CRC risk can be designed based on their age, sex, personal and family history of cancer (including ages, ages at diagnoses,

and relationships across multiple generations), all known genetic factors (rare high-risk genetic mutations as well as common genetic variants), unmeasured genetic background, and environmental factors and personal characteristics.<sup>83</sup> These will be crucial developments to provide personalised risk of CRC and enable personalised screening, surveillance and genetic testing interventions beyond those currently available.

## Recommendations

In this chapter, we have focused on the rationale for familial risk profiling of CRC (rather than screening). We suggest that an update of the Australian NHMRC 2005 Screening Guidelines needs to consider a more advanced utility of familial risk profile. However, we are not able to propose specific changes at this stage, given that a comprehensive tool for personalised risk prediction of CRC is not yet available to enable a personalised screening approach.

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## FAMILIAL COLORECTAL CANCER CLINICS

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### Abstract

Familial cancer clinics strive to identify at-risk individuals with an inherited predisposition to cancer. Familial predisposition to colorectal cancer includes Familial Adenomatous Polyposis and Lynch Syndrome. The latter condition has no clear phenotype, leading to difficulties in its recognition. While family history remains an important tool in diagnosing inherited predisposition to cancer, many cases of Lynch Syndrome are diagnosed in the absence of a clear-cut family history. Therefore identification of Lynch Syndrome cases has moved in the direction of tumour-based testing, initially on cases selected for family history, young age of onset and tumour histological features, but now it has been suggested that Lynch Syndrome be screened for more widely via tissue testing of all newly diagnosed colorectal cancers under a certain age (e.g. < 60 years).

Familial cancer clinics are staffed by a multi-disciplinary team, comprising clinical geneticists, genetic counsellors, medical oncologists and other relevant specialists with expertise in colorectal cancer (CRC), such as gastroenterologists or colorectal surgeons. Familial cancer clinics aim to reduce the morbidity and mortality associated with CRC by identifying at-risk individuals with an inherited predisposition.

This is achieved firstly by working with the person referred to the clinic, usually on the basis of family history of cancer. The family history (pedigree) is collected and confirmed where possible, through obtaining histological reports, hospital notes or death certificates. The pedigree is then analysed for possible, familial cancer syndromes that fit the spectrum of cancers seen. For the individual, their cancer risk is estimated based on the family history and the presence of other established risk factors.

Communication is of utmost importance in the clinic. Discussion with the individual about risk, inheritance and testing of cancer predisposition genes (where appropriate) is undertaken. Individuals at high genetic risk and their managing doctors are advised about strategies for cancer screening, early detection and prevention. Individuals seeking genetic testing are counselled about the uncertainties, risks and benefits associated with positive and negative test results. The results of any genetic testing performed are given and carefully explained in terms of the impact on the individual and on their family members. Follow-up and review is provided where necessary. For the individual, follow-up may be provided via the provision of a registry-based reminder service for surveillance and screening programs.

Any individual attending a familial cancer clinic is also regarded as being part of a wider family and part of the clinic's role is to identify other high-risk relatives. Privacy legislation prevents direct contact from the clinic with such relatives, but strategies to spread the information within families are discussed with individuals and information

regarding local services is provided. Upon receiving contact from relatives, the cycle of communication with the individual and their family is re-commenced.

Finally, as inherited cancer and genetics is a rapidly evolving discipline in terms of knowledge and practice, familial cancer clinics serve as a rich resource for research and education.

### High-risk familial CRC syndromes

Approximately 15% of all CRCs demonstrate familial clustering and 1-5% are caused by specific germline genetic mutations. The two most common hereditary colon cancer syndromes are familial adenomatous polyposis (FAP), caused by germline mutations in the APC gene, and Lynch Syndrome, caused by germline mutations in the mismatch repair (MMR) genes. FAP is relatively easy to identify because of the distinctive phenotypic feature of hundreds to thousands of polyps present within the colonic wall. In contrast, Lynch Syndrome does not present with easily recognisable clinical features that distinguish it from sporadic colon cancer, thus many cases of Lynch Syndrome remain undiagnosed.

Lynch Syndrome accounts for approximately 1-2% of all CRCs and is also associated with an increased risk of extra-colonic cancers, including gastric, endometrial and urinary tract tumours.<sup>1</sup> This syndrome is caused by inherited mutations in one of the DNA MMR genes MLH1, MSH2, MSH6 or PMS2.<sup>2</sup> Carriers of a MMR gene mutation have a 45-90% lifetime risk of developing CRC.<sup>3,4</sup> Compared with the general population, the cancer risk in mutation carriers is also increased for uterine, ovarian, gastric, biliary tract uro-epithelial and kidney cancers, and central nervous system tumours.<sup>4</sup> The identification of MMR gene mutation carriers is of great benefit for the management of their individual and family risk of cancer. Early and regular colonoscopic surveillance can potentially prevent the development of CRC by detecting tumours at a pre-cancerous and thus more easily treatable stage.

Furthermore, the ability to exclude MMR mutation negative individuals in Lynch Syndrome families reduces the burden of participating in unnecessary high-risk surveillance and prevention programs.

### Challenges in the identification of Lynch Syndrome cases

Due to the high cost and technical difficulties associated with testing for germline mutations in MMR genes, the means of identifying likely mutation carriers among CRC patients has been a work in progress. In 1990, the International Collaborative Group on hereditary non-polyposis colorectal cancer was formed to develop clinical criteria that could help to identify patients with this hereditary condition. The specific aims were to establish a common nomenclature and to permit uniform identification of families for research and clinical purposes. The resulting criteria, known as Amsterdam 1 criteria (AC1), were quite rigid and focused entirely on a dense family history of early onset CRC.<sup>5</sup> Although there was widespread acceptance and use of these criteria within the expert community and among some clinicians, many classic Lynch Syndrome families were missed because the AC1 were not fulfilled and hence families were not investigated further for possible MMR gene mutations. The Amsterdam II criteria (ACII) were subsequently developed and included a spectrum of extra-colonic Lynch Syndrome cancers.<sup>6</sup> These new criteria were later modified again to take account of small families with insufficient members to fulfil the generational criteria. Although the Amsterdam criteria were highly specific for the detection of Lynch Syndrome families, their sensitivity was quite low.<sup>6</sup>

The Bethesda guidelines were subsequently formulated in 1996 at a meeting held at the National Cancer Institute. These guidelines were proposed as a cost-effective measure to improve the identification of Lynch Syndrome-like families who did not meet Amsterdam criteria but in whom pre-screening of their CRC tissue using the microsatellite instability (MSI) test was recommended.<sup>7</sup> The guidelines were revised in 2004 to include tumour features and a less stringent family history of cancer.<sup>8</sup> Compared with the Amsterdam criteria, the Bethesda guidelines demonstrated a higher sensitivity, but lower specificity for the detection of Lynch Syndrome families.<sup>8</sup> Approximately 20% of all diagnosed CRC cases meet the revised Bethesda guidelines, for which molecular evaluation of MSI and/or loss of MMR protein expression via immunohistochemistry (IHC) testing is recommended.<sup>9</sup>

MSI was recognised as a feature of hereditary colon cancer in the early 1990s.<sup>10</sup> The MSI phenotype is characterised by ubiquitous changes in the length of nucleotide repeat sequences in DNA, with mononucleotide repeat tracts (e.g. AAN) being particularly susceptible to deletions.<sup>11</sup> Testing for MSI is performed in the laboratory using polymerase chain reaction to amplify specific microsatellite sequences, followed by gel electrophoresis to identify changes in microsatellite length. Approximately 10% of sporadic CRCs also exhibit MSI. These tumours occur almost exclusively in the proximal colon and more often in older women.<sup>11</sup> The large majority of sporadic MSI+ CRCs arise because of acquired, methylation-induced transcriptional

silencing of MLH1 gene expression.<sup>12</sup> The MSI phenotype alone cannot therefore be used as a specific marker for Lynch Syndrome. However, the presence of a hot-spot point mutation (V600E) in the BRAF oncogene occurs in sporadic, but not familial cases of MSI+ CRC and can therefore be used to exclude sporadic cases that arise in the setting of Lynch Syndrome.<sup>13</sup> Methylation of the MLH1 gene promoter region can also be used as a marker to discriminate between sporadic and Lynch Syndrome CRC cases, with methylation being present in the former but not the latter.

Bi-allelic mutations in MMR genes almost always lead to the loss of protein expression, as evidenced pathologically on IHC analysis. The MMR proteins exist as heterodimers, thus loss of expression often occurs in pairs, with the loss of MLH1/PMS2 or MSH2/MSH6 pairs, most common, although other rarer patterns of loss have also been reported.<sup>14</sup>

There has been considerable debate as to whether MSI or IHC is the superior technical approach as the initial test for Lynch Syndrome screening.<sup>15</sup> IHC is a relatively rapid test that can be undertaken in most general pathology laboratories, is cheaper and can be used to ascertain which gene should begin the germline mutation search. However, IHC interpretation is subjective and highly dependent on the quality of the tissue, staining methods and reporting pathologist, thus there is much inter-observer variability in the evaluation of results. In Australia, technical protocols differ between laboratories and there is a lack of quality control measures at a national level. MSI does not require subjective interpretation, but is more expensive, labour intensive and requires involvement of a molecular genetics laboratory. There is, however, a high correlation in the results from both methods when used by experienced laboratories.<sup>16</sup>

### Moving towards population-based screening for Lynch Syndrome

Because of the complexities involved in applying the Amsterdam and Bethesda guidelines, there were concerns that many MMR gene mutation carriers in the population remained undetected.<sup>17-20</sup> The main reason for not utilising the proposed criteria and guidelines was that the primary onus was placed on clinicians to carefully document family history and to subsequently refer patients for genetic evaluation. The ongoing challenges relating to assessment, referral and follow-up were highlighted in a prospective study which found that of 228 CRC patients who may have benefitted by attending a familial cancer clinic, only 22% were referred and just 14% actually attended.<sup>21</sup>

The low rate of referrals to familial cancer clinics led to calls for the introduction of population-based screening for Lynch Syndrome based upon molecular analysis of MSI and/or IHC loss of expression of MMR proteins in the tumour.<sup>20,22</sup> Universal screening of all CRC patients for these markers is unlikely to be cost-effective because the majority of Lynch Syndrome cases occur in younger patients. A further difficulty is that the incidence of sporadic CRC with MSI+ tumours increases markedly after the age of 55 years, although these can be distinguished from

familial cases by additional testing for the presence of a specific BRAF oncogene mutation.<sup>13</sup>

A large retrospective study was carried out in the state of Western Australia to detect Lynch Syndrome among CRC patients aged <60 years at diagnosis and in the absence of any information on family cancer history.<sup>23</sup> This work established that MSI screening followed by testing for the BRAF mutation in the MSI+ cases was an effective strategy for the identification of previously unrecognised Lynch Syndrome mutation carriers in the Western Australia population. Based on these earlier findings, starting in 2008, routine MSI and/or IHC testing was recommended for all CRC patients (< 60 years) in Western Australia, regardless of their family history of cancer. A recent analysis of the population-based screening program for Lynch Syndrome in Western Australia has shown a significant increase in the number of new Lynch Syndrome cases identified each year.<sup>24</sup>

Although the laboratory tests used to screen for MSI, MMR protein loss, BRAF mutation and MLH1 methylation are not technically difficult or prohibitively expensive, their systematic introduction at a population level for the identification of Lynch Syndrome has proven challenging. This is because of the need for cooperation and effective communication between multiple disciplines, including gastroenterology, pathology, surgery, oncology and medical genetics.<sup>25</sup> Even greater diligence is required when the service providers are located at different sites or work for different organisations.

Based on the Western Australia experience with population-based screening, three key elements have been identified that are likely to be important for successful implementation of Lynch Syndrome screening in other states or regions. Firstly, reflex IHC testing should be carried out in accredited pathology services with ongoing quality control systems. This should be performed for all younger (<60 years) CRC patients, those with an individual and/or family history of cancer suggestive of Lynch Syndrome, and patients whose tumours have histological characteristics suggestive of Lynch Syndrome. Second, a state or region-wide reference laboratory for MSI testing is required to confirm all abnormal or equivocal IHC test results identified in the first screen by pathology service providers. In addition to MSI testing, the reference molecular pathology laboratory should be capable of performing BRAF mutation and/or MLH1 methylation assays so that sporadic MSI+ cases can be excluded,<sup>26</sup> thus preventing their unnecessary referral to familial cancer clinics.

The third critical element is the existence of a state or region-wide Lynch Syndrome coordinator to ensure that all potential germline mutation cases identified by laboratory testing are referred to and attend a familial cancer clinic for appropriate follow-up and germline testing. The position of Lynch Syndrome coordinator would ideally be embedded within a genetic service, or alternatively hosted by an independent organisation, such as a state or regional health department, or a state Cancer Council. The coordinator must have direct and regular communication with the molecular pathology reference laboratory and maintain a database of identified cases for their catchment area.

This allows monitoring of both referrals and attendance at familial cancer clinics. A recent study by the Cleveland Clinic demonstrated that direct contact of patients with MSI/IHC abnormalities by a genetic counsellor was an efficient means of ensuring attendance at a familial cancer clinic.<sup>27</sup> At present in Western Australia, only a small number of potential germline mutation cases are not being referred by clinicians to Geological Survey Western Australia (approximately 5/35 per year, 15%).

Finally, with regards to screening for Lynch Syndrome, several issues require further investigation. Firstly, what is the cost-effectiveness of laboratory-based screening for Lynch Syndrome? This has been investigated for single institutes,<sup>28,29</sup> but not for population-wide screening. Secondly, do Lynch Syndrome individuals and families identified by population-based laboratory screening have a different cancer penetrance to those identified in familial cancer clinics using the Amsterdam and Bethesda criteria? Finally, would routine IHC and/or MSI screening of endometrial cancers and other Lynch Syndrome-related cancers, particularly in younger patients, identify previously unrecognised cases of Lynch Syndrome?

## Recommendations

Clinicians need to be aware about the possibility of an underlying inherited predisposition when managing a patient with CRC. The implications of such a diagnosis apply not only to that individual, but to the wider family as well. A three generation family history remains the most important tool to alert clinicians towards a possible inherited predisposition, but tumour-based testing via IHC and/or microsatellite testing should also be considered in all patients diagnosed with colorectal cancer under the age of 60 years.

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## RISK PROFILING AND SURVEILLANCE: PREVIOUS ADENOMAS AND COLORECTAL CANCER

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### Abstract

The brief of this issue of *Cancer Forum* is to review information available since the 2005 publication of the National Health and Medical Research Council relating to risk management of individuals with previous adenomas or colorectal cancer. However, this can be abbreviated to the last three years, as Cancer Council Australia commissioned a review of colonoscopy in surveillance for colorectal cancer, which included adenoma and cancer follow-up. This has subsequently been endorsed by the National Health and Medical Research Council. Since then, there have been advances in some areas, although many questions remain and clinical judgement comes into play. In the current era of accountability, economic hardship and increasing demand, surveillance strategies should be proven effective and individualised, based on issues such as fitness, quality of life and personal preferences. International guidelines have aligned, although the simpler strategies specified in European guidelines are noted with interest. Despite clear recommendations, the lack of guideline use in routine practice is concerning and widespread promulgation of simple 'aid-memoirs' could help, along with incentives. Information supports risk related to multiplicity, size and histopathology of adenoma and cancer findings at the index colonoscopy. Quality issues relating to colonoscopy and pathology reporting are being driven through professional fora and training. The paradox of multiplicity and

quality colonoscopy needs addressing in a patient-centred response. Risk-stratification and adjustment over time is likely to gain increasing importance. The serrated pathway, its biology and epidemiology, have attracted attention for the rapid progression and association with interval cancers. Practice points for the management of malignant polyps continue to be topical. The effectiveness of intensive follow-up strategies following curative treatment for colorectal cancer remains unproven, although colonoscopic surveillance is still of value.

### Effectiveness of screening or surveillance for colorectal cancer

Before commencing on the issue of risk and what can be done to manage the risk, it is worth pausing to take stock of the evidence that the risk is modifiable. Risk assessment has little clinical relevance unless there are effective ways to modify that risk. Primary prevention, through reducing risk, has a role, and there is increasing evidence around strategies such as aspirin or calcium supplemental chemoprophylaxis, dietary modifications such as for red meat, fibre, cruciferous vegetables, and lifestyle factors such as exercise and healthy weight maintenance.<sup>1</sup> Additionally, following the positive results for polyp burden reduction in familial adenomatous polyposis, Eicosapentaenoic Acid-Free Fatty Acid (EPA-FFA) is currently under study through a randomised control trial (RCT) in high risk adenoma patients.<sup>2,3</sup> But colonoscopy with polyp detection and removal is the most likely, but not certain, strategy to prevent colorectal cancer.

Many commentators take it for granted that colonoscopic screening or surveillance reduces the incidence of and mortality from colorectal cancer (CRC) without critical evaluation. The non-randomised experience of colonoscopic surveillance in Lynch Syndrome is often quoted.<sup>4</sup> A recent report from the Nurses Health Study and Health Professionals Observational Follow-up Study also reports reduced CRC incidence in participants having a negative colonoscopy (HR 0.44 95% CI 0.38 to 0.52), as well as a reduced mortality from CRC (0.32 95% CI 0.24 to 0.45). For both incidence and mortality, the benefit included protection from proximal colon cancer.<sup>5</sup> However, by any good epidemiological standard, the answer would need to come from RCTs, where the intervention is colonoscopy at intervals (perhaps 10 years) versus a control group with no screening or, to be practical, standard screening advice in their setting. Reduced mortality from CRC associated with colonoscopy intervention would be the best endpoint. In fact, there have been no such trials published. Several long-term trials against different randomised control groups are under way: the Veteran's Administration trial in the US is against Faecal Immunochemical Testing (FIT); a large Spanish trial is also against FIT testing; a New York trial against standard US screening advice (measuring participation only of people responding to an initial invitation); and an important Scandinavian trial where the control group has no screening (screening is not implemented or advocated at a population level in Scandinavia).<sup>6-9</sup> The Spanish trial has published CRC incidence rates after the initial screening round and there were just as many CRCs detected in the FIT arm as the colonoscopy arm.<sup>8</sup> This gives pause for thought on cost benefit (poor for colonoscopy) and reach into the population (poor for colonoscopy). Of note, those that did participate in the colonoscopy arm - which were

substantially fewer than in the FIT arm - had as many CRCs as were detected in the larger proportion who accepted FIT testing. The advanced adenoma detection rate, however, was about three times higher in the colonoscopy arm, perhaps pointing to a longer term benefit of colonoscopy in preventing CRC within this trial.

There are RCTs demonstrating reduction in cancer mortality through the faecal occult blood test (FOBT) and in flexible sigmoidoscopy programs.<sup>10</sup> The question is relevant given the complication rate and (albeit low) mortality associated with colonoscopy.

The lack of RCTs addressing cancer incidence and mortality through colonoscopy screening also impinges on the rationale for management of risk for adenoma patients. In adenoma follow-up and indeed in general, the US National Polyp Study is often quoted as demonstrating that colonoscopy with adenoma removal prevents CRC.<sup>11,12</sup> This trial randomised participants to a more (zero, one and three years) versus a less (zero and three years) intensive surveillance schedule - showing no difference in adenoma or advanced adenoma outcomes. It did not have a control group of 'no colonoscopy'. The initial and later analyses did assess the cancer outcomes in comparison with population incidences of CRC, and historical groups of adenoma patients who did not have colonoscopy - pointing to the possibility that the participants did avoid CRC, as there were statistically fewer that developed within both trial arms compared with those control groups. It should be noted that many other long-term studies of adenoma patients in surveillance programs have not identified a reduced cancer incidence rate below the average incidence - though one assumes that the populations under study were above average risk for CRC to start with, given their propensity to form adenomas.

There is evidence that FIT testing, complementing scheduled colonoscopy in an adenoma and cancer surveillance program, can bring forward the time of detection of advanced adenomas and cancers.<sup>13</sup> This has not been formally addressed in any national screening guidelines, but is implemented in some organised programs in Australia,<sup>13</sup> including the authors'.

### Setting the scene: new international guidelines on adenoma and cancer follow up

A comparison of the US Multi-Society Task Force on Colorectal Cancer guidelines,<sup>14</sup> with the British Society of Gastroenterology Guidelines,<sup>15</sup> and more recently European guidelines,<sup>16,17</sup> has recently been published.<sup>18</sup> The greatest deviation from the Australian Guidelines and worthy of note, are the European Society of Gastrointestinal Endoscopy guidelines that recommend returning screenees to the

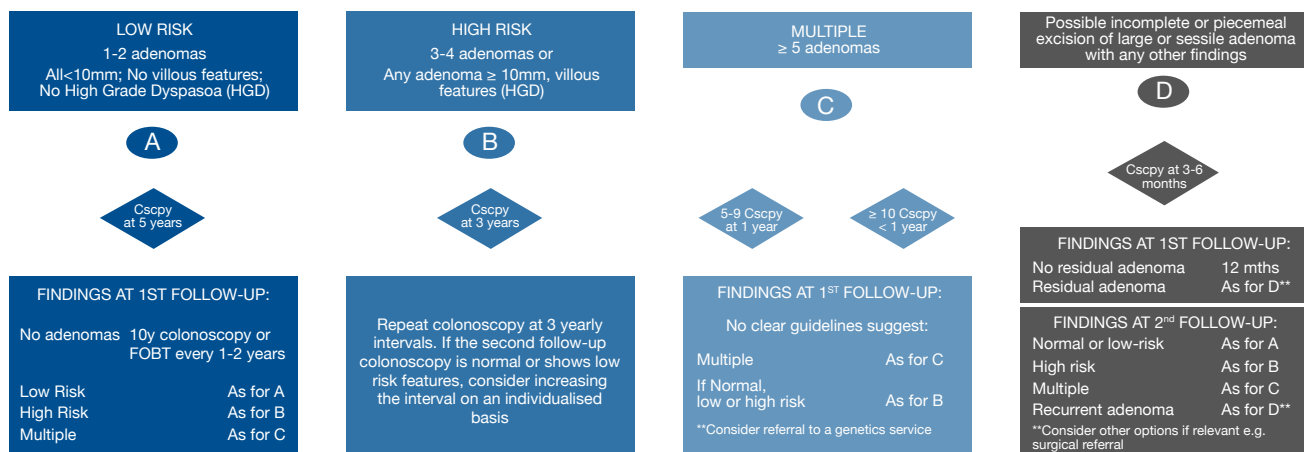


average-risk national screening program or a colonoscopy after 10 years if no screening program exists, in the low risk group (1-2 small adenomas with low-grade dysplasia), and an increase in interval from three years to five years after a normal follow up colonoscopy in the high risk group (3-4 adenomas, villous features or high grade dysplasia, or  $\geq 10$ mm in size).<sup>19</sup> Another strong recommendation, although backed only by low quality evidence, is that the endoscopist be responsible for providing a recommendation for the post-polypectomy surveillance schedule. Differences between US and Canadian guidelines have also been published, highlighting the standard of care for average risk (in low risk long-term adenoma follow-up), and differentiating between three or more, and 10 or more adenomas as do the Australian guidelines.<sup>19, 20</sup> The paper is worthy of review.<sup>20</sup>

## Implementation of the Australian Colonoscopy Guidelines for Adenoma and Cancer Surveillance

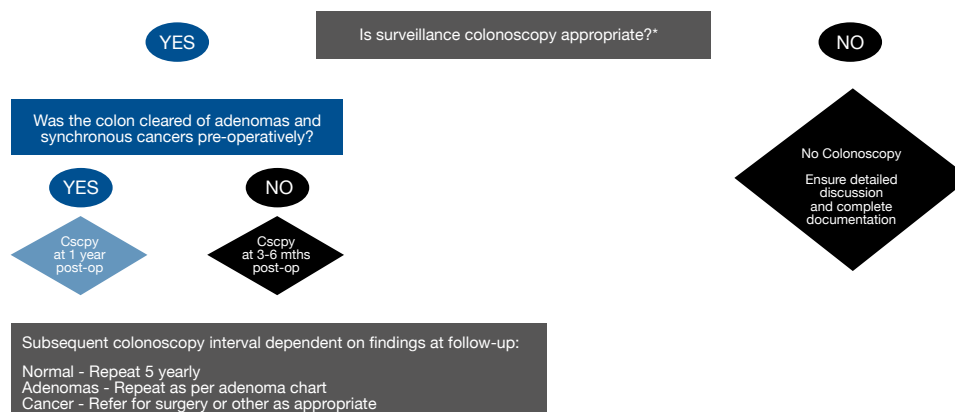
Despite considerable investment in the development of guidelines, numerous groups have shown barriers to their implementation and 'widespread ignorance of guidelines'.<sup>11</sup> Most societies or national bodies have provided funding to develop algorithms. The British Society of Gastroenterology published a handy wall chart summarising their guidelines.<sup>15</sup> Recently, such a wall chart presentation of the Australian 2011 Cancer Council/National Health and Medical Research Council (NHMRC) Guidelines for Colonoscopy in Surveillance for adenomas and CRC has been produced and is presented (figure 1 and 2). Although simple strategies such as this have been shown to be effective, barriers to the use of guidelines go beyond this.<sup>21-23</sup> Access to relevant past information may not be readily available (e.g. previous colonoscopy results, histology and family history) and the current procedure details may be inadequate (colon completely examined, clearance confirmed, exact number and sizes of the polyps noted, histology findings). Clinicians must also deal with patient anxiety and the fear of litigation. Linkage of guideline use to key performance indicators, bonuses and indemnity could enhance wider uptake.

Figure 1: Colonoscopic surveillance intervals - adenomas



NOTES: This algorithm is designed to be used in conjunction with the NHMRC Clinical Practice Guidelines for Surveillance Colonoscopy – in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease (December 2011) and is intended to support clinical judgement. Surveillance colonoscopy (cscopy) should be planned based on high-quality endoscopy in a well-prepared colon using most recent and previous procedure information when histology is known. Sessile serrated adenomas and serrated adenomas are followed up as for adenomatous polyps given present evidence, although they may progress to cancer more rapidly. Most patients  $\geq 75$ y have little to gain from surveillance of adenomas given a 10-20 year lead-time for the progression of adenoma to cancer. The finding of serrated lesions may alter management. Small, pale, distal hyperplastic polyps only do not require follow-up; consider hyperplastic polyposis syndrome if multiple proximal hyperplastic polyps are found. In the absence of a genetic syndrome, family history does not influence surveillance scheduling, which is based on patient factors and adenoma history. Follow-up of an advanced rectal adenoma by digital rectal examination, sigmoidoscopy or endo-rectal ultrasound should be considered independent of colonoscopic surveillance schedules.

Figure 2: Colonoscopic surveillance intervals – following surgery for colorectal cancer



NOTES: This algorithm is designed to be used in conjunction with the NHMRC Clinical Practice Guidelines for Surveillance Colonoscopy – in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease (December 2011) and is intended to support clinical judgement. \*Surveillance colonoscopy (cscopy) should be offered to those who have undergone curative treatment and are fit for further treatment if disease is detected. Ideally, the colon should be cleared pre-operatively to exclude synchronous cancers and adenomas by either colonoscopy (preferable) or other imaging (in the case of obstructing lesions) unless the proximal bowel is to be included in the resection. Those in whom a familial syndrome is probable or possible, or where there are other indications that the risk of metachronous cancer may be high (e.g. multiple advanced adenomas or cancers at diagnosis, hyperplastic polyposis, age less than 40 years) should be followed up more frequently (see full Clinical Practice Guidelines for Surveillance Colonoscopy). Follow-up of those with known syndromes is recommended in specialist clinics using Clinical Practice Guidelines for Surveillance Colonoscopy. Follow-up of rectal cancers with examination of the rectum by digital examination, sigmoidoscopy or endorectal ultrasound should be considered independent of colonoscopic surveillance.

Barclay Karen, Cancer Council Australia Surveillance Colonoscopy Guidelines Working Party. Algorithm for Colonoscopic Surveillance Intervals – Following Surgery for Colorectal Cancer. 2013. Cancer Council Australia would like to acknowledge and sincerely thank Ms Barclay for developing these algorithms based on the Clinical Practice Guidelines for Surveillance Colonoscopy – in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease (December 2011). ©2013 Barclay, Karen. This graphic is licensed under the Creative Commons Attribution-ShareAlike 3.0 Australia license.

## Risk related to multiplicity, size and histopathology of adenoma and cancer findings at the index colonoscopy

### Multiplicity

The Australian 2011 guidelines had some degree of complexity over frequency of surveillance colonoscopy, derived from the special consideration of risk associated with multiple adenomas. Different risks (and therefore follow-up intervals) were assigned to patients with 1-2 vs 3-4 vs 5 to 9 vs 10 or more adenomas.<sup>19</sup> Whether this needs simplification to enable it to be better accepted in clinical practice, or whether there is sufficient justification to promote that complexity, is a matter for discussion. The logic and data around the complexity is clear, but the complexity in itself may dilute the impact of the guidelines overall.

### Multiple adenomas - measured cumulatively or at the last colonoscopy?

A level of uncertainty exists in the literature on this question. The 2011 guidelines recognised the uncertainty, and followed the pragmatic option of accounting for adenomas only at the last colonoscopy, rather than attempting a cumulative history. Further predictive studies need to address this issue. Inherently, one would think that it is the cumulative number of adenomas over time which engages the risk for metachronous CRC most closely, as the timing and frequency of interventions to remove adenomas are somewhat incidental to the biological drive to multiplicity – and presumably its associated metachronous cancer risk.

Nevertheless, this has not been systematically teased out in adenoma follow-up studies.

### Cut and discard

The evolving practice to 'cut and discard' small polyps through cold snare guillotine techniques threatens the assessment of metachronous risk which, as we know, is most powerfully associated with multiplicity of adenomas of whatever size, over and above the other histological and polyp characteristics of size, villosity and dysplasia.<sup>24</sup> Although we are advocates for 'cut', we are not advocates for 'discard'. In Australian practice, there is no differential rebate for multiple polyp assessment (as there is in the US), so pathology costs are the same.

### Multiplicity and adenomatous polyposis syndromes

Multiplicity of adenomas plays very importantly into decisions around mutational analysis of the APC and MUTYH genes, again information lost with a 'discard' policy. In our Familial Cancer Clinic, we carefully record on a spreadsheet the entire colonoscopic history of patients referred, to inform decision-making. We will consider mutational analysis with as few as five documented adenomas. The predictive value of mutational analysis is directly related to the multiplicity.

### Size, histology and dysplasia

Size, histology and dysplasia are relatively easily measurable and accessible for the purposes of determining risk. Furthermore, their predictive value is consistent across many studies. The three factors are closely correlated,

so much so that the British guidelines take only size into account, being immediately assessable at the time of colonoscopy. If villosity and high grade dysplasia are not included in prediction algorithms, leaving only size and multiplicity of adenomas to determine high risk for metachronous advanced lesions, it does reduce the size of the high risk group slightly, with a minor shift in Receiver Operator Characteristic curves.<sup>18</sup>

### **Surveillance tailored multifactorial risk**

Risk algorithms, not favoured to date in the 2005 or 2011 Guidelines, may yet prove useful with access to easily computed and reliable algorithms even built into endoscopy surveillance management programs. More experience is needed with this approach.<sup>25</sup>

### **Quality of colonoscopy**

Another important theme relating to risk profiling is the number of adenomas and CRCs detected in relation to the quality of colonoscopy.<sup>26</sup> Attention has focused on measurement of quality and surrogates for quality. This includes the time taken to withdraw the colonoscope (during which inspection for polyps takes place),<sup>27</sup> adenoma detection rates,<sup>28</sup> bowel preparation cleanliness, retroversion of the colonoscope in the right colon and rectum,<sup>29</sup> and the thorny issue of missed cancers occurring at an interval after a colonoscopy.<sup>27-31</sup> Whereas quality of colonoscopy is the subject of another paper in this issue, it does bear reinforcement that all of these parameters have a logical connection to quality colonoscopy and point to ways of implementing quality control systems in colonoscopy.<sup>32</sup> Perhaps the most compelling data, now from two sources, is that a colonoscopist's adenoma detection rate in routine screening colonoscopy is indirectly but tightly related to the incidence of CRCs occurring in the years after colonoscopy – the interval cancer rate. This has been evident in both Polish and US studies.<sup>7,31</sup>

### **The multiplicity paradox**

The integration of the themes of risk associated with multiple adenomas, and the logical training and practice goal to increase adenoma detection rates, brings us to a paradox: those patients who are under the care of high quality colonoscopists with high adenoma detection rates will likely be found to have more polyps and adenomas, driving them under current guidelines (which are themselves, as noted, determined by multiplicity) to have even more frequent colonoscopies, inevitably towards points of diminishing return. On the other hand, individuals who are under the care of poor quality colonoscopists with low adenoma detection rates will be found to have few (or no) polyps, placing them in a 'lower' risk group, requiring less frequent colonoscopies on current guidelines – yet we know these people are the ones who develop the interval cancers. An anecdotal impression is that low quality colonoscopists compensate by offering frequent colonoscopies, outside guidelines. The answer to this dilemma must be to introduce quality control systems across all colonoscopy practices, including monitoring adenoma detection rates. With time, we may be able to introduce colonoscopy quality parameters into the guidelines such that the interval between

colonoscopies can be discounted (lengthened) where good quality colonoscopy has been documented through a range of parameters relating to the procedure and the colonoscopist. Notwithstanding that a colonoscopist's adenoma detection rate in US studies is calculated from the relatively homogeneous population of average risk patients undergoing screening colonoscopy (a population which is not within current Australian guidelines for clinical practice and is not reimbursable through Medicare), adenoma detection rates in other Australian settings can be used with some reliability. At the same time, there would need to be an economic incentive for the proceduralist to meet these standards (or disincentive if not). This should surely be in the patient's interests and attractive to the payers. This would then address the paradox.

### **Longer term surveillance: Does risk attenuate over time, where sequential colonoscopies are clear of polyps?**

The 2011 NHMRC guidelines are equivocal regarding the need to maintain surveillance at the interval determined by the polyp and patient characteristics at the time of the index (the last) colonoscopy. With follow up colonoscopies showing no further polyps, can the interval be relaxed? In some situations the answer is clearly 'no'. This would include the serrated polyposis syndrome discussed below, perhaps serrated polyps short of the syndrome, and the well characterised genotypically defined syndromes of Lynch Syndrome, familial adenomatous polyposis, MUTYH associated polyposis, Peutz Jeghers Syndromes (polyps grow quicker than adenomatous polyposis in the author's experience) and juvenile polyposis. Debate on the velocity of carcinogenesis in MUTYH associated polyposis has been engaging.<sup>33</sup> However, in the common adenoma patient, follow-up interval is less certain. In the Royal Melbourne Hospital-Flinders long-term experience (submitted for publication), there is a relatively high risk for advanced adenomas to be found within 18 months of an index colonoscopy, where an advanced adenoma is also identified and removed (we carefully reviewed the data to exclude patients from the analysis where the index advanced adenoma was not completely removed). With time, the risk did attenuate, but still there was a long tail of advanced adenoma detection that continued at a stable rate, suggesting an intrinsic continuing risk that needs to be addressed through a fixed frequency of colonoscopy – arguably three yearly from our data. This is supported from US experience. For small adenomas, the risk is small as reported in many series, such that the risk for metachronous cancer reverts to average risk or below average risk.<sup>6, 7, 27, 34</sup>

### **Sessile serrated polyps and serrated polyposis**

#### ***The serrated pathway***

The discovery and understanding of the serrated polyp pathway to CRC has been the focus of much attention since the last guidelines. There is now some evidence that identifies interval cancers in adenoma and other surveillance programs as being more likely to be associated with the serrated pathway, either through methylation of the MLH1 promotor, or more generally, having high CpG Island

Methylator Phenotype status.<sup>35,36</sup> Studies on antecedent polyps in these patients, especially as to their serrated architecture, are needed. Some evidence suggests that polyps pass through this pathway more rapidly than the more conventional microsatellite stable, APC gate-controlled pathway. Importantly, it would point to the need for more frequent surveillance in patients who have shown a propensity to develop sessile serrated polyps.<sup>37</sup> A consensus meeting dedicated to serrated lesions recommended particular attention (increased frequency) to patients with three or more sessile serrated adenomas/polyps or traditional serrated adenomas, especially if large (every two years) and any with dysplasia.<sup>38</sup> This question needs more data before implementing a change to the guidelines. The 2011 guidelines signalled an issue relating to this question, but did not spell out any alteration to the frequency of colonoscopy in follow-up for these patients, which are determined, as in conventional adenoma follow-up, by multiplicity and size of adenomas, with villosity and dysplasia also implicated through the definition of an advanced adenoma. Advanced adenomas in the current guidelines attract a three year interval for colonoscopy.

### **Serrated polyposis syndrome**

Serrated polyposis Syndrome (previously known as Hyperplastic polyposis) is increasingly being recognised by colonoscopists. It is defined by five serrated polyps proximal to the sigmoid colon, with two one cm or over in size, or 20 (some say 30) serrated polyps spread throughout the colon. The third definition is any serrated polyps in a first degree relative of a patient with serrated polyposis. This remains tantalisingly without a genetic predisposition identified, whereas all other multiple polyposis syndromes have had their germline predisposition identified. Perhaps this is not surprising, as Mendelian inheritance is not commonly seen in the families of patients with serrated polyposis syndrome. The colonoscopist needs to treat this syndrome respectfully: although the absolute risk of CRC is not well defined, it is undoubtedly high.<sup>39</sup> Most colonoscopists have experienced interval CRCs occurring during surveillance of these patients, even within the recommended two year interval. Although this could be due to the inherent difficulty in detecting the subtle, flat and sessile serrated polyps with their indiscernible margins in the right colon (though perhaps flagged through its mucus cap), the evidence around the real possibility of a rapid pathway through diffuse methylation of suppressor genes or other mechanisms needs constant scrutiny. The high risk of CRC in the first degree relatives of patients with the serrated polyposis syndrome needs addressing in surveillance.<sup>40</sup>

### **Management of the malignant polyp**

Little new information has emerged to change the recommendations for management of malignant polyps, which balances the risk of surgical intervention (after malignant polypectomy) versus the risk of nodal metastases with ultimate progression within the lifetime of the patient.<sup>41</sup> Attention has been given to the importance of pathology reporting for decision-making. The recent publication by the Royal College of Pathologists of Australia of a structured reporting protocol for polypectomy and local resections of the colon and rectum are likely to be beneficial.

### **Follow-up and surveillance: CRC patients**

This section addresses the risk of metachronous CRC in patients who have already developed CRC and the role that colonoscopy plays in managing this. A more comprehensive analysis of the contemporary literature is available, which points to the limited benefit of surveillance after CRC resection, duration of follow-up, intensity and methods of follow-up, cost-effectiveness, and identifying RCTs in progress further addressing the question.<sup>42</sup> Colonoscopies should be done with the same quality in cancer follow-up as in adenoma follow-up.

The main change introduced in the 2011 guidelines was the introduction of a colonoscopy at one year after resection. Although the need for peri-operative total colonoscopy to seek synchronous cancers overlooked either due to incomplete index colonoscopy due to obstructing lesions, or other considerations, has long been recognised, the importance of a routine colonoscopy at 12 months from follow-up studies was brought to the fore in the 2011 guidelines. This holds true and may, incidentally, have a message for patients with advanced adenomas at index colonoscopy as well – notwithstanding the National Polyp Study noted above. Perhaps not surprisingly, the risk of metachronous adenomas and cancers is generally lower after cancer resection, than in adenoma follow-up. Counterintuitive? Probably not, as the resection reduces the epithelial mass available for adenomas and cancers to develop.

The metachronous risk of CRC after segmental oncological resection in Lynch Syndrome is now very clear: it is high - up to 60% at 40 years. Thus there is a strong rationale for suspecting, then diagnosing (preferably molecularly) and counselling patients with Lynch Syndrome to undergo extensive colonic surgical resection prior to resection of the index cancer or other advanced lesion in the colon. At a minimum, in the appropriate circumstance such as an early age onset index colon cancer, immunohistochemistry on the cancer should be done as part of the diagnostic work up. This information should usefully help decision-making around the surgical approach. Family history of cancer and the pattern of loss of expression in the cancer would all play into this decision-making.

### **Conclusion**

Evidence is accumulating on risks for metachronous adenomas and cancers in patients with adenomas or CRC. Risk reduction through appropriate colonoscopic surveillance has been described in the 2011 NHMRC Clinical Practice Guidelines for Surveillance Colonoscopy. However, implementation of these guidelines has been limited by lack of resources to promote the guidelines in clinical practice, except for their publication on the NHMRC website. This will be addressed in part by the algorithmic depiction of the guidelines now available, and published here, for dissemination at points of service, be it general practice, endoscopy services in private and practice and through dedicated and managed follow-up programs. Further, the need and implications of quality practice in colonoscopy, especially with respect to adenoma detection

rates, will need leadership and buy in by the endoscopic community and professional bodies.

Points of continuing clinical research attention include systems to integrate cumulative adenoma detection in

patients into risk and surveillance planning, the biology of the serrated pathway with its implications for surveillance scheduling, and further attention to early follow-up risk in patients with advanced adenomas.

**Table 1: Recommendations**

Summary of 2011 NHMRC recommendations for patients with previous adenomas or CRC	Practice recommendation	Status	Considerations for updated recommendations based on current evidence – if applicable
<p><b>Patients with adenomas and risk of developing CRC</b> Determination of risks for patients with adenomas must clearly distinguish between:</p> <ol style="list-style-type: none"> <li>Variables that relate to the likelihood of any particular adenoma having a malignant focus and</li> <li>Variables that relate to patient, pathological and epidemiological characteristics which predict metachronous adenomas and cancers.</li> </ol> <p>Patients whose only polyps are small, pale, distal, hyperplastic polyps require no colonoscopic follow-up.</p>	Practice Point: Recommend	No change	N/A
Patients whose only polyps are small, pale, distal, hyperplastic polyps require no colonoscopic follow-up.	Practice Point: Recommend	No change	N/A
<p><b>Location of adenomas and cancer: protection against right sided cancer in adenoma follow-up</b> Proximal location of adenomas may be a risk factor for metachronous neoplasia.</p>	Practice Point: Strongly recommend	Upgrade	Further attention to issues relating to the biology of right sided lesions, especially CIMP status, and the interface with quality of colonoscopy, especially relating to right sided colonoscopy, imaging and documentation of same.
<p><b>Models of risk assessment</b> Because of the complexity of multivariate analyses to predict individual patient risk of metachronous polyps, their use currently is difficult to apply to day to day practice.</p>	Practice Point: Recommend	Upgrade	The feasibility of these needs assessment through academic programs such as the NHMRC Centre for Research Excellence: Reducing the Burden of Colorectal Cancer by Optimising Screening - Evidence to Clinical Practice
<p><b>General considerations relating to polypectomy</b> All polyps should be considered for removal. Diminutive polyps may be too numerous to be cleared completely. In patients with small polyps, a sample should be taken for histological study. However, if syndromic diagnosis is under consideration, then sampling of many polyps is important, to guide decisions on which gene should be subjected to mutational analysis.</p>	Practice Point: Recommend	No change	The 'cut and discard' policy gaining credibility in colonoscopy practice needs to be modified to take into consideration syndromic diagnoses – which are becoming increasingly broader (less polyps) in consideration.
<p><b>Tattooing polypectomy sites</b> Tattooing any polyp site where there is a possibility of surgical resection will be needed is important at the primary colonoscopy if at all possible. This is necessary even for conventional surgery, as the site of polypectomy may well be impalpable, but particularly important where follow-up treatment may be laparoscopic, as the surgeon has no capacity to palpate the area.</p>	Practice Point: Recommend	No change	Raising a preliminary bleb with saline and injecting into the bleb helps to localize the tattoo to the site of injection.
<p><b>Malignant polyps</b> In general, malignant polyps which:</p> <ol style="list-style-type: none"> <li>Have a clear margin of excision pathologically</li> <li>Are well or moderately well differentiated</li> <li>Lack lymphatic or venous invasion</li> <li>Are endoscopically judged totally removed.</li> </ol> <p>They can be managed without subsequent surgery, but the decision needs to be individualised with respect to patient comorbidities and age.</p>	Practice Point: Strongly recommend	No change	N/A

<p><b>Quality of colonoscopy</b> High quality colonoscopy is critically important for good practice and patient safety. Adenoma detection rates (ADRs) should be monitored, though they will be influenced by patient mix (e.g. age, indications). ADRs within the NBCSP provide a sound basis for bench marking.</p>	Practice Point: Strongly recommend	No change	N/A
<p><b>Approach to adenoma follow-up in surveillance</b> Colonoscopy surveillance intervals should be planned when the colonoscopist is satisfied that the colon has been completely cleared of polyps and the polyp histology is known.</p>	Practice Point: Recommend	No change	N/A
<p><b>Follow-up for patients with low risk adenomas</b> Patients with one or two small (&lt;10mm) tubular adenomas can be scheduled for follow up colonoscopy at five years. If that colonoscopy is normal, then that patient can be considered as at average risk, with colonoscopy at 10 years or by FIT at least every two years.</p>	Grade B: Strongly recommend	Upgrade	These patients are considered at average risk on follow up evidence.  This patient might simply continue within the National Bowel Cancer Screening Program.
<p><b>Follow-up of patients with high risk adenomas</b> Surveillance colonoscopy should take place at a three year interval for patients with high risk adenomas (three or more adenomas, &gt;9mm, or with tubulo-villous or villous histology or high grade dysplasia).</p>	Grade A: Strongly recommend	No change	Surveillance intervals after a clear colonoscopy needs further research.
<p><b>Follow-up of patients with sessile adenomas and laterally spreading adenomas</b> If large and sessile adenomas are removed piecemeal, follow-up should be at three to six months to ensure complete removal. If removal is complete, subsequent surveillance should be based on histological findings, size and number of adenomas.</p>	Grade B: Recommend	No change. Consideration for update	Consideration should be given to referring these patients to centres of endoscopic excellence, experienced in managing these polyps. The first attempt to remove the polyp is the best attempt.
<p><b>Follow-up following resection of serrated adenomas (SAs and sessile serrated adenomas (SSAs)</b> At present, there is not enough evidence to differentiate follow-up protocols for sessile serrated adenomas from standard follow-up guidelines. Follow-up should be determined as for adenomatous polyps, taking into account size, number and presence of high grade dysplasia.</p>	Practice Point: Recommend	Update to strong recommendation	Anecdotal experience and biological studies have highlighted these polyps may progress rapidly, elevating an early metachronous risk.
<p><b>Follow-up of patients with multiple adenomas</b> As multiplicity of adenomas strongly determines risk of metachronous advanced and non-advanced neoplasia, follow up should be at 12 months for those with five or more adenomas and, because the likelihood of missed synchronous polyps being present, sooner in those with 10 or more adenomas. If a polyposis syndrome accounts for the findings, follow-up should be within one year for patients with five or more adenomas at one examination. FAP and MUTYH associated polyposis should be considered with as few as 10 adenomas and referred to a Familial Cancer Clinic (FCC).</p>	Grade B: Strongly recommend	No change. Consideration for update  Change	Complexity versus utility in practice of this guideline needs evaluation in practice. Further studies needed on whether the 'count' is cumulative needed.  FAP and MUTYH patients should have annual flexible sigmoidoscopy or colonoscopy regardless of findings at any one examination. The number of adenomas generating a referral for mutational analysis differs across FCCs and is resource dependent. It should be noted that 30% of MUTYH associated colorectal cancer patients have no synchronous adenomas.
<p><b>Interaction of age and family history</b> Family history should be considered separately when planning colonoscopy surveillance. Intervals should be predominantly determined by the adenoma characteristics, unless a syndromic risk mandates more frequent surveillance</p>	Equivocal	No change	N/A
<p><b>Follow up based on two or more examinations</b> If advanced adenomas are found during subsequent surveillance, maintaining a three yearly schedule is prudent but the choice should be individualised. The interval can be lengthened if advanced adenomas are not found.</p>	Grade B: Strongly recommend		Further evidence on attenuation of risk with time, or not, such as the Royal Melbourne Hospital Flinders data, needs to be sourced.

<p><b>Cumulative adenoma counts</b> Endoscopists should be encouraged to assess not only the current colonoscopy findings but those of any previous colonoscopies.</p>	Practice Point: Recommend	Consideration for update	Reporting systems and endoscopy databases need to be developed to take account of cumulative findings to facilitate decision making, and decisions on referral to familial cancer clinics.
<p><b>Hyperplastic polyposis</b> Risk of cancer in hyperplastic polyposis is still being defined, however there is sufficient evidence to identify these patients as being at high risk. Colonoscopy, with the aim of complete polyp removal, including the right sided sessile serrated polyps, should be the aim. Risks of polypectomy, notable because of the number and sessile nature of polyps, should be explained. Surgery is an acceptable alternative in patients with well defined hyperplastic polyposis.</p>	Practice Point: Recommend	No change. Consideration for update	Now called Sessile Serrated Polyposis, or Jass Syndrome. Consideration should be given to referring these patients to centres of endoscopic excellence, experienced in managing these large sessile polyps. The first attempt to remove the polyp is the best attempt. Referral to FCC if the patient has a mixed adenoma/serrated polyposis phenotype, as MUTYH mutations can be found in this subset

Summary of 2011 NHMRC recommendations for patients or CRC	Practice Recommendation	Status	Considerations for updated recommendations based on current evidence – if applicable
<p><b>Role of pre and peri operative colonoscopy in CRC patients</b> A peri-operative colonoscopy should be attempted in all patients with a newly diagnosed CRC. Colonoscopy should be performed three to six months after resection with obstructive XCRC in whom complete perioperative colonoscopy was not performed and in whom there is residual colon proximal to the obstructing cancer.</p>	Grade B: Strongly recommend  Grade B: Strongly recommend	No change	N/A
<p><b>Risk factors for metachronous neoplasia following resection for CRC</b> Patients with Lynch Syndrome should continue to have annual surveillance performed post operatively because of the apparent rapid progression of neoplasia from adenoma to carcinoma.</p>	Practice Point	Upgrade to recommend	N/A
<p><b>Surveillance of the residual colonic mucosa in patients with cancer in FAP</b> Should follow recommendations elsewhere in the 2005 NHMRC guidelines.</p>	Practice Point	No change	
<p>Patients including those</p> <ol style="list-style-type: none"> <li>whose initial diagnosis was made younger than 40 years of age</li> <li>with probable or possible HNPCC (ie. Patients whose tumours are MSI-High and less 50 years old at the time of initial cancer diagnosis but not proved by genetic testing to have Lynch Syndrome)</li> <li>with hyperplastic polyposis and BRAF mutations</li> <li>with multiple synchronous cancers or advanced adenomas at initial diagnosis should be considered following surgery to continuing with more frequent surveillance than would otherwise be recommended.</li> </ol>	Practice Point	No change	N/A
<p><b>Intervals for surveillance colonoscopy following resection for CRC</b> Colonoscopy should be performed one year after the resection of a sporadic cancer, unless complete post operative colonoscopy has been performed. If this colonoscopy reveals an advanced adenoma, then the next colonoscopy should be three years. If the colonoscopy performed at one year is normal or identifies one or two non advanced adenomas, then the interval before the next colonoscopy should be five years.</p>	Grade B: Strongly recommend  Grade C: Recommend  Grade C: Recommend	No change	N/A
<p>Patients undergoing either local excision or or ultra-low anterior resection of rectal cancer or advanced adenomas should be considered for six monthly endoscopies and digital examinations, independently of the colonoscopies as above.</p>	Practice Point: Recommend	No change	N/A

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# TARGETING TREATMENT FOR COLORECTAL CANCER: THE EGFR ANTIBODY STORY

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## Abstract

Frequent overexpression of the epidermal growth factor receptor in colorectal cancer was the rationale for the development of anti-epidermal growth factor receptor antibodies. The development of the drug cetuximab, led to considerable expectations in terms of clinical and commercial success. The registration of the anti-epidermal growth factor receptor antibodies, cetuximab and panitumumab, was granted on the basis of improvement in progression free survival. Other drugs targeting the epidermal growth factor receptor, such as the oral tyrosine kinase inhibitors, have minimal efficacy in colorectal cancer when used alone, and are too toxic when combined with chemotherapy. Cetuximab and panitumumab have activity only in patients with metastatic disease who have a reasonable performance status. Retrospective analyses of tumour samples collected from trial enrollees showed the presence of KRAS mutations in exon 2 were a negative predictor of response to the anti-EGFR antibodies. Recent data suggests that patient selection should be based on a more extensive analysis of KRAS, NRAS, BRAF and potentially other genes. The anti-EGFR antibodies have been used alone or in combination with other chemotherapies, however use with oxaliplatin appears to compromise patient outcomes. When used as monotherapy, toxicities include rash and fatigue, however more severe adverse effects are observed when used with chemotherapy. Anti-epidermal growth factor receptor treatments for colorectal cancer demonstrate the complexity of using targeted treatments. They remain a useful treatment in colorectal cancer, but have not fulfilled their initial expectation of being highly effective and non-toxic treatments.

Targeted therapies were expected to deliver a new treatment paradigm for cancer, characterised by improved efficacy and reduced treatment related toxicity. The term 'targeted therapy' encompasses a variety of treatments, including biologic agents such as monoclonal antibodies and oral tyrosine kinase inhibitors (TKI). The targets are molecules involved in the initiation or progression of cancer. Some drugs, like the anti-epidermal growth factor receptor (EGFR) antibodies, interact with one receptor. Other drugs, like TKIs, are promiscuous because they have multiple off-target effects. Also, the targets may be found in specific tumour types or in many. In the case of colorectal cancer (CRC), EGFR was identified as a potential therapeutic target, as the receptor is overexpressed as a consequence of gene amplification and other mechanisms.<sup>1,2</sup> Over a decade ago, the development of the anti-EGFR antibody cetuximab (also called Erbitux and C225), raised hopes that the era of targeted therapy for CRC had arrived. Since then, a number of clinical trials have clearly demonstrated that anti-angiogenic and anti-EGFR targeted therapies deliver a modest (around three months) delay in progression free survival for patients with metastatic CRC. Unfortunately, these agents have not had any impact on the adjuvant treatment of this disease. The story of targeted therapies for CRC and in particular, the controversies associated with the development and use of anti-EGFR antibodies, highlight many lessons about targeted therapies and help us place their value in perspective.

## History of the development of EGFR antibodies for use in clinical practice

Cetuximab is a recombinant chimeric human-mouse antibody, which acts by blocking and down regulating EGFR, and promoting the killing of targeted cells by antibody-dependent, cell-mediated cytotoxicity, and complement fixation.<sup>3</sup> Cetuximab was initially developed with the support of public funding in 1985.<sup>4</sup> In 1994, permission was sought by its patent owner, the New York based biotechnology company ImClone Systems Inc, to conduct human trials. Given the limited treatments for patients with CRC, the successful anecdotes and preliminary data from studies of cetuximab were met with enthusiasm from scientists and clinicians alike.<sup>5</sup> The market also responded positively and the share prices for ImClone soared.<sup>6</sup> On October 29th 2001, a \$2 billion deal between Bristol-Myers Squibb and ImClone came into effect: the CEO of ImClone, Samuel Waksal and his brother Harlan, sold \$111 million of their stock in the company. In December 2001, the first application for Food and Drug Administration approval for cetuximab in second line therapy for metastatic CRC was rejected. Among other things, the experts who reviewed the protocol on which the application was based, considered the study was fundamentally flawed and inappropriate for a registration trial. In May 2002, the data on cetuximab was presented at the American Society of Clinical Oncology (ASCO) meeting and therapeutic targeting of EGFR was discussed by Dr John Mendelson at the prestigious

Karnofsky lecture. No mention was made of the controversy surrounding the clinical development of cetuximab, yet Sam Waksal resigned as CEO of ImClone a few days following the ASCO meeting in the midst of investigations by the US Department of Justice and Securities and Exchange Commission. Eventually, both Sam Waksal and the business celebrity, Martha Stewart, were convicted of charges related to ImClone insider trading.<sup>7,8</sup> In 2004, Food and Drug Administration registration approval of cetuximab was granted on the basis of the phase III BOND trial, which showed an improvement in progression free survival in patients with metastatic CRC treated with cetuximab. Perhaps reassured by the success of using HER2 overexpression to identify breast cancer patients for treatment with Trastuzumab, the FDA approved a companion diagnostic for qualitative immunohistochemistry (IHC) for the detection of EGFR.<sup>9</sup> It was proposed that overexpression of EGFR could predict those patients likely to benefit from cetuximab. Unlike Trastuzumab, the relationship between anti-EGFR antibodies and overexpression of EGFR has not stood the test of time.

In 2008, a fully humanised recombinant anti-EGFR monoclonal antibody, panitumumab, was granted Food and Drug Administration approval on the basis of an improvement in progression free survival in a non-blinded phase III study that compared panitumumab with best supportive care in patients with treatment refractory CRC. The development of panitumumab has in many respects mirrored cetuximab. However, unlike cetuximab, a benefit in overall survival has not been demonstrated in any trials of panitumumab, although this has been explained by the fact that patients in the control arm were allowed to cross-over to panitumumab on progression.

The small molecule TKIs, such as erlotinib and gefitinib, interact with the intracellular domain of the EGFR. These orally available drugs have not proved to be effective in CRC. Erlotinib and gefitinib as single agents have shown minimal activity in metastatic CRC.<sup>10,11</sup> Clinical trials of combinations of erlotinib and cytotoxic chemotherapy, with or without the vascular endothelial growth factor inhibitor bevacizumab, were closed prematurely because of significant toxicities.<sup>12</sup> Erlotinib has also been investigated in combination with other treatments in different schedules, including maintenance and intermittent dosing schedules, however no benefits in response rate, progression free survival or overall survival have been observed.<sup>13, 14</sup>

### Who should be treated with EGFR antibodies?

A number of factors are influential in selecting patients for treatment with anti-EGFR antibodies. These include the molecular profile of the tumour, disease stage and the performance status of the patient.

Although it might be intuitive to propose that overexpression of EGFR is a likely biomarker for response to the anti-EGFR antibodies, this assumption has not proven to be correct. Specifically, response to antibody therapy does not correlate with EGFR over-expression as determined by immunostaining, somatic EGFR mutations or EGFR gene amplification. Certainly patients lacking EGFR expression

have responded to cetuximab and panitumumab.<sup>5,15</sup> The signal transduction downstream of the EGFR receptor includes multiple cell signalling pathways connected through complex cross-talk and feedback loops.<sup>3</sup> Most cancers show mutations in one or more of the downstream signalling pathways such as RAS-RAF-MAPK and PI3K-AKT. Preclinical studies show that tumours with mutations in KRAS have downregulation and suppression of upstream EGFR signalling and are thus refractory to drugs which block EGFR. This observation has been validated in the clinic by a retrospective analysis of KRAS status in tumours from patients enrolled in clinical trials of cetuximab or panitumumab. This analysis showed that patients with KRAS mutant tumours did not derive a benefit from either antibody.<sup>16-18</sup> Since KRAS mutations are present in about 40% of CRCs, analysis of KRAS status has proven to be a useful, if imperfect, negative predictor of response to the anti-EGFR antibodies.<sup>16</sup>

The results of a pooled meta-analysis of 11 trials of anti-EGFR antibodies is summarised in table 1.<sup>16</sup> This analysis shows that 50-65% of patients with KRAS wild type CRC remain resistant to the anti-EGFR antibodies. This finding could be explained by tumour heterogeneity, the presence of undetected less common KRAS mutations, or other RAS mutations such as in NRAS. Until very recently, all analyses have confined mutation testing to codons 12 and 13 of exon 2 of KRAS. There is now increasing evidence that gene mutations in NRAS, BRAF (V600E), or PI3K (PIK3CA), or loss of PTEN expression are associated with lack of response to anti-EGFR antibodies.<sup>19,20</sup>

The benefits of targeted therapies in CRC remain confined to individuals with metastatic disease. Targeted therapies have failed to improve outcomes when used in the adjuvant setting. There are several possible explanations for this. Firstly, the increased toxicity of combination treatment may lead to decreases in the dose of cytotoxics or premature discontinuation of adjuvant therapy. Further, some investigators have postulated that there is a negative interaction between some chemotherapy agents and anti-EGFR antibodies in patients with micro-metastatic disease. Finally it has been suggested that in the adjuvant setting, tumour cells are undergoing epithelial-mesenchymal transition and are not dependent on EGFR signalling.<sup>21</sup>

Age was not used as part of the selection criteria for most clinical trials of the anti-EGFR antibodies, however enrolment was restricted to patients with a functional status of ECOG 2 or less. The side-effects of the anti-EGFR antibodies include skin reactions, including acneiform rash (in up to 90% of patients), dry skin, pruritus and nail changes, diarrhoea, infusion related reactions (including hypersensitivity reactions), cardiac events and hypomagnesaemia. A high degree of fatigue and asthenia has also been reported. When used in combination with chemotherapy, severe side-effects are more frequent. In the adjuvant N0147 trial, elderly patients had more toxicity.<sup>22</sup> Thus the goal of minimal side-effects from a targeted treatment has not been realised in the case of the anti-EGFR antibodies, and performance status is very influential in selecting patients for treatment.

**Table 1:** Design characteristics and progression free survival results of published randomised studies grouped by partner chemotherapy.<sup>16</sup>

Paper	Trial phase	Treatment comparisons	Line of therapy	Study participant		Median progression free survival (months)			
				n	KRAS wild type where evaluable (%)	KRAS wild type		KRAS mutant	
						With anti-EGFR antibody therapy	No anti-EGFR antibody therapy	With anti-EGFR antibody therapy	No anti-EGFR antibody therapy
<b>Monotherapy</b>									
Amado, 2008 <sup>17</sup>	3	BSC vs BSC + Pmab	3rd	463	56.9	2.8	1.7	1.7	1.7
Karapetis, 2008 (CO.17) <sup>18</sup>	3	BSC vs BSC + Cmab	3rd	572	58.3	3.7	1.9	1.8	1.8
<b>Irinotecan</b>									
Van Cutsem, 2009(CRYSTAL) <sup>35</sup>	3	FOLFIRI vs FOLFIRI +Cmab	1st	1198	64.4	9.9	8.4	7.4	7.7
2010 - update <sup>38</sup>					62.7				
Peeters, 2010 <sup>39</sup>	3	FOLFIRI vs FOLFIRI +Pmab	2nd	1186	55.1	5.9	3.9	5.0	4.9
<b>Oxaliplatin</b>									
Bokemeyer, 2009(OPUS) <sup>26</sup>	2	FOLFOX-4 vs FOLFOX-4 +Cmab	1st	337	57.5	8.3	7.2	5.5	8.6
2009 - update <sup>25</sup>					56.8				
Maughan, 2011 (COIN) <sup>27</sup>	3	Ox, 5FU vs Ox, 5FU + Cmab*	1st	1630	44.0 †	8.6	8.6	NR	NR
Douillard, 2010(PRIME) <sup>40</sup>	3	FOLFOX4 vs FOLFOX4 +Pmab	1st	1183	59.9	9.6	8.0	7.3	8.8
2013 -update <sup>41</sup>					48.0 †				
Tveit, 2010(NORDIC VII) <sup>28</sup>	3	FLOX vs FLOX +Cmab*	1st	566	60.8	7.9	8.7	9.2	7.8
<b>Bevacizumab</b>									
Hecht#., 2009 (Ox) (PACCE) <sup>34</sup>	3B	Ox-CT/Bev vs Ox-CT/ Bev +Pmab	1st	823	60.8	10.0	12.5	8.3	11.9
Hecht#., 2009 (Iri) (PACCE) <sup>34</sup>	3B	Iri-CT/Bev vs Iri-CT/ Bev +Pmab	1st	230	57.2	9.8	11.5	10.4	11.0
Tol, 2009(CAIRO2) <sup>42</sup>	3	Cap, Ox, Bev vs Cap, Ox, Bev + Cmab	1st	736	60.3	10.5	10.6	8.1	12.5

#Differing drug regimens described in one paper. \* additional randomisation undertaken but not reported in this analysis. † excluding KRAS, other RAS and BRAF mutations. BSC, Best supportive care; Cmab, cetuximab; Pmab, panitumumab; Iri, Irinotecan; Ox, oxaliplatin; Ox-CT = oxaliplatin based chemotherapy; Iri-CT, irinotecan based chemotherapy; Bev, bevacizumab; Cap, capecitabine; FOLFOX, fluorouracil + leucovorin + oxaliplatin; FOLFIRI, fluorouracil + leucovorin + irinotecan; FU, 5fluoruracil. ns, not stated in paper; NR, not reported.

## Which antibody – are they all equal?

After years of separate development, a direct comparison of the efficacy of cetuximab and panitumumab in the chemo-refractory setting was reported this year.<sup>23</sup> Overall survival, progression free survival and response rates were similar in this non inferiority study. Much has been made of the chimeric nature of cetuximab when compared with panitumumab, with claims that increased immunogenicity would be both positive in promoting a stronger immune and

tumour response, and negative, with increased side-effects. While panitumumab has less infusion related side-effects than cetuximab and a different administration schedule, otherwise the drugs are currently interchangeable. This year, the first phase III trial to prospectively test for the KRAS mutation status to determine patients' randomisation and treatment in chemo-refractory CRC was reported.<sup>24</sup> The PICCOLO study revealed no overall survival benefit when panitumumab was added to irinotecan, when compared to irinotecan alone in patients known to be wild type for KRAS

(without the common mutations in codons 12, 13 and 61). The secondary endpoints of progression free survival and response rates were improved in the combination arm. A grouped analysis for mutations such as BRAF, NRAS, KRAS (codon146) and PIK3CA was performed and showed that treatment outcomes for this group were compromised compared with patients without mutations.

### Combinations with chemotherapy – are all partners equal?

A number of studies have noted a negative interaction between cetuximab and oxaliplatin. In all studies with oxaliplatin as the chemotherapy partner (OPUS,<sup>26</sup> COIN,<sup>27</sup> NORDIC VII,<sup>28</sup> N0147<sup>29</sup> and PETACC 8<sup>30</sup>), none were able to reach a significant result for the primary study end points. This observation was confirmed in a meta-analysis for both cetuximab and panitumumab, when used in combination with oxaliplatin based chemotherapy, showing no benefit in survival or response rates.<sup>31</sup> Possible explanations for this include negative interactions for oxaliplatin on the action of cetuximab and vice versa. Src has been observed to be activated by oxaliplatin in CRC cell lines, suggesting a possible mechanism of induced resistance through activation of a downstream signalling pathway to the EGFR receptor.<sup>32</sup> A suggested mechanism for the latter is reduced effectiveness of oxaliplatin in KRAS wild type CRC cells when treated with cetuximab. Oxaliplatin efficacy relies on an intracellular redox reaction which is inhibited by the cetuximab EGFR interaction through the Nox1 pathway.<sup>33</sup> Supporting these observations, the PACCE trial showed that the addition of panitumumab to bevacizumab and FOLFOX (oxaliplatin, fluorouracil and leucovorin) chemotherapy increased toxicity and decreased progression free survival.<sup>34</sup>

### When to use EGFR inhibitors?

Having shown some activity as a single agent or as a partner with irinotecan in the treatment refractory metastatic CRC setting, the anti-EGFR antibodies were tested in first line and adjuvant settings. Cetuximab in combination with first line FOLFIRI (irinotecan, fluorouracil and leucovorin) chemotherapy has been shown to have a small statistically significant improvement in progression free survival in unselected patients (8.9 vs 8.1 months). The progression free survival outcome is enhanced by selecting KRAS wild type patients for the combination treatment (9.5 vs 8.1 months).<sup>35</sup> The OPUS study used overall response rates as the primary endpoint and found in a retrospective subset analysis that there was a 2.54 times increase in response rates in patients with KRAS wild type tumours receiving cetuximab and FOLFOX (oxaliplatin, fluorouracil and leucovorin). When given as neoadjuvant treatment prior to liver resection, the rate of R0 resection achieved was doubled, however this was based on small patient numbers (6/61 vs 3/73 patients).<sup>26,25</sup>

The duration of antibody treatment has been studied as a continuous therapy until progression or unacceptable toxicity in all the randomised trials. A recent study in patients whose disease progressed after initial response, found acquired new KRAS mutations in six out of 10 cases, suggesting that this is a common resistance pathway to

anti-EGFR treatment.<sup>36</sup> Another study suggested that treatment with anti-EGFR antibodies select resistant clones present in heterogenous tumours at the outset, and that the time to recurrence is simply the interval required for the subclone to repopulate the lesion.<sup>37</sup> This raises the question as to whether continuous treatment with anti-EGFR antibodies is advisable.

### Future directions

The long history of development of anti-EGFR therapies for CRC illustrates the conceptual fallacy of the single target-single treatment model. It was tantalising to think that EGFR inhibitors targeting the commonly overexpressed EGFR would translate to a paradigm shift in CRC therapy. In fact, the EGFR has proven to be an inexact target, with downstream signals compromising the efficacy of anti-EGFR antibodies. For CRC, anti-EGFR antibodies help a minority of patients and every day more contraindications, such as the presence of other RAS and BRAF mutations, are being uncovered. Optimists may see an expected role for the anti-EGFR antibodies within select patient populations, yet others may question the declining marginal benefit of such treatments in an era of limited public resources and competing cancer care needs.

### Recommendations

Anti-EGFR antibodies are effective in the treatment of metastatic but not early CRC. Patients are selected for treatment on the basis of the molecular profile of their cancer. The effectiveness of standard chemotherapy may be reduced when used with anti-EGFR antibodies.

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## ADJUVANT THERAPY FOR COLORECTAL CANCER

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**Abstract**

Patients with resected colon cancer (stage III [T1 to T4, N1-N2] or high-risk stage II [T3 or T4, N0]) or stage II/III rectal cancers (T3 or T4, N0-2) are at significant risk of local and distant failure, with reduced survival due to microscopic residual disease. To reduce this risk, adjuvant therapy has been the standard of care for both cancer populations, as stated in the 2005 *Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer* developed through Cancer Council Australia's Clinical Guidelines Network. This review provides an update to the guidelines. Patients with resected stage III colon cancer should, where possible, be offered six months of adjuvant chemotherapy. The optimal regimen is oxaliplatin-5FU or -capecitabine, based on relevant clinical factors. For patients with resected stage II colon cancer, adjuvant 5FU-based chemotherapy should be considered for those at particularly high risk of relapse. For patients with stage II/III rectal cancer, treatment approaches include: (i) short course radiotherapy and immediate total mesorectal excision; or (ii) neoadjuvant chemoradiotherapy (with 5FU infusion or capecitabine) followed by TME. Post-operative adjuvant chemotherapy should be offered to all medically fit patients. At present, there are no markers to identify patients who may not require neoadjuvant chemoradiotherapy or who can avoid surgery.

Approximately 70-80% of newly diagnosed cases of colorectal cancer (CRC) undergo curative resection, however 40% of these develop incurable recurrent disease due to undetected micrometastases.<sup>1-2</sup> In particular, patients with stage III (T1 to T4, N1-2) or Dukes' C colon cancer have a five-year survival rate of between 44-88%, with a three-year disease-free survival (DFS) ranging from 45 to 52%. Those with stage II (T3 or T4, N0) or Dukes B colon cancer have a five-year survival rate of between 45-60% and three-year DFS of 64-75%.<sup>1, 3</sup> The inability to cure all such patients is a direct consequence of residual disease left behind after surgery. Over the last two decades, adjuvant chemotherapy has been offered to such high risk patients with the aim to decrease relapse and improve overall survival (OS) by attempting to eliminate this microscopic residual disease.

Patients with rectal cancer are at even greater risk of local recurrence following surgery alone, relative to the more proximal colon primaries.<sup>4</sup> In particular, tumours that have penetrated the rectal wall (T3 or T4) and/or with nodal involvement (N1-2) are at increased risk of local or distant relapse, with recurrence rates up to 25-65%.<sup>5</sup> A positive circumferential resection margin (CRM) (tumour  $\leq$ 1mm of resection margin) is an important independent prognostic marker, accounting for up to 85% of local recurrences,<sup>6-7</sup> and correlates with lymphovascular/perineural invasion and nodal involvement.<sup>8</sup> Hence the optimum strategy to improve the outcome of rectal cancer patients must address the problems of local and distant recurrence.<sup>9</sup> Multimodality treatment comprising total mesorectal excision (TME), with chemotherapy and radiotherapy, has been the standard of care for locally advanced (stage II and III) rectal cancer. The current nomograms include preoperative short course RT or preoperative chemoradiotherapy (CRT), followed by TME and adjuvant chemotherapy, and in limited patients, post-operative CRT, with adjuvant chemotherapy.<sup>9</sup> These

approaches have dramatically reduced local recurrence, however approximately one-third of patients will expire from their disease within five years.<sup>10</sup>

This article will review the current data and practice regarding the adjuvant treatment of both colon and rectal cancers, and will serve as an update beyond the 2005 *Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*, developed through Cancer Council Australia's Clinical Guidelines Network and approved by the National Health and Medical Research Council (NHMRC).<sup>9,11</sup>

**Adjuvant therapy of resected colon cancer**

Adjuvant chemotherapy is offered to high risk patients with the aim of decreasing relapse and improving OS by attempting to eliminate this microscopic residual disease. Its benefits must outweigh the risks from chemotherapy-related toxicities. For over two decades, it has been offered to patients with stage III disease as standard therapy,<sup>12</sup> a practice reinforced by two recent meta-analyses.<sup>13-14</sup>

In the case of patients with stage II disease, the role of adjuvant therapy is controversial given the difficulty in identifying patients at the highest of risk who would benefit the most from adjuvant therapy.<sup>15</sup> The recognised poor prognostic markers for patients with stage II disease include: (1) poorly differentiated histology,<sup>16</sup> (2) obstruction or perforation at presentation;<sup>17</sup> (3) lymphovascular invasion;<sup>18</sup> (4) less than 12 lymph nodes retrieved during primary resection;<sup>17,19-21</sup> and (5) T4 disease (with invasion into adjacent organs).<sup>16, 22</sup> The issues regarding treating patients with stage II disease will be addressed below.

**Adjuvant chemotherapy for resected stage III colon cancer (T1-4, N1-2, M0)**

Adjuvant chemotherapy has been the standard of care

for stage III disease for the last two decades. Initial efforts concentrated on the evaluation of 5-fluorouracil (5FU)-based regimens and 5FU biomodulation, and more recently the evaluation of oral 5FU prodrugs.<sup>11</sup> Two recent meta-analyses have shown a significant reduction in mortality by biomodulation of 5FU.<sup>13-14</sup> Subsequent large randomised trials have demonstrated that a weekly 5FU-low dose leucovorin (LV) regimen is preferred, based upon efficacy and toxicity relative to alternative regimens, or the use of 5FU-Levamisole with six months as the optimal duration of therapy. The randomised phase III X-ACT trial has also demonstrated the equivalent efficacy, and near superiority of the oral 5FU prodrug, capecitabine, (24 weeks, 1250 mg/m<sup>2</sup> b.i.d, days 1-14, 1 week rest) relative to six months bolus 5FU-LV as adjuvant therapy for stage III colon cancer, both in terms of survival parameters, toxicity and pharmacoeconomics.<sup>11, 23-24</sup>

The advances in the treatment of metastatic disease, including oral 5FU prodrugs, oxaliplatin, irinotecan and the biologicals (including epidermal growth factor receptor [EGFR] and anti-vascular endothelial growth factor [VEGF] monoclonal antibodies), have led to these agents being evaluated in patients with stage III disease. The evidence will be summarised in the sections below. It must be noted that during this time, three year DFS rate has been validated as an appropriate endpoint for adjuvant trials given its strong correlation with five-year OS,<sup>25</sup> and recently six-year OS.<sup>26</sup> In modern adjuvant trials, six or seven years may now be required to demonstrate OS improvements.<sup>27</sup>

### **Oxaliplatin and 5FU or Capecitabine**

The efficacy of oxaliplatin plus 5FU in the adjuvant setting was demonstrated by two pivotal trials - the MOSAIC,<sup>28</sup> and the more recent NSABP C07 trials.<sup>29</sup> In the MOSAIC trial, 2246 patients who had stage II or III colon cancer were randomised to receive a combined bolus/infusional 5FU regimen (LV5FU2) alone, or with oxaliplatin (FOLFOX4), for six months. The primary end point was DFS.<sup>28</sup> A total of 1123 patients were randomly assigned and on final analysis reported in 2009, the five-year DFS rates were 73.3% and 67.4% in the FOLFOX4 and LV5FU2 groups respectively (HR =0.80; P <0.005). Six-year OS rates were 78.5% and 76.0% in the FOLFOX4 versus LV5FU2 groups respectively (HR =0.84; P<0.05). The corresponding six-year OS rates for patients with stage III disease were 72.9% and 68.7%, respectively (HR =0.80; P <0.05). There was no difference in OS seen in the stage II population.<sup>30</sup>

The NSABP C07 trial, published in 2007, randomised 2492 patients with stage II and III colon cancer to either 5FU 500mg/m<sup>2</sup>, plus LV 500mg/m<sup>2</sup>, both IV weekly for six weeks during each eight-week cycle (Roswell Park regimen) for three cycles, or the same 5FU-LV regimen with oxaliplatin 85 mg/m<sup>2</sup> IV administered on weeks one, three and five of each eight-week cycle for three cycles.<sup>29</sup> The additional benefit provided by oxaliplatin in terms of DFS, as observed from the MOSAIC trial, was confirmed.<sup>29</sup>

A subsequent study, the NO1968 trial, compared capecitabine plus oxaliplatin (XELOX; oxaliplatin 130mg/m<sup>2</sup> on day one plus capecitabine 1000 mg/m<sup>2</sup> b.i.d on days one to 14, every three weeks for 24 weeks) with bolus 5FU-LV (Mayo Clinic for 24 weeks or Roswell Park

for 32 weeks) in patients with stage III colon cancer.<sup>31</sup> The three-year DFS rate was 70.9% with XELOX and 66.5% with 5FU-LV (HR =0.80, P <0.005). XELOX is thus considered an additional adjuvant treatment option for these patients.<sup>31</sup>

The efficacy of adjuvant oxaliplatin therapy has also been evaluated in the elderly. A subgroup analyses of the NO1968 trial above, demonstrated reduced risk of recurrence in all groups receiving oxaliplatin, including patients <65 years of age and those ≥65 years of age, however in the latter group the trend was not significant.<sup>31</sup> A post-hoc analysis of the NSABP C07 trial also demonstrated that oxaliplatin significantly improved OS in patients younger than age 70 (HR, 0.80; P <0.05), but no positive effect was evident in older patients.<sup>32</sup>

### **Irinotecan and 5FU**

Despite the activity of irinotecan in the treatment of advanced CRC, randomised phase III trials in the adjuvant setting (including CALBG 89803, PETACC3 and ACCORD 2 trials) have failed to demonstrate an added benefit relative to 5FU-LV alone.<sup>33-35</sup>

### **Biological agents + combination adjuvant chemotherapy**

In the metastatic setting, the antiangiogenic agent, bevacizumab, a monoclonal antibody to VEGF, and the EGFR monoclonal antibodies, cetuximab and panitumumab, have shown added benefit when added to conventional chemotherapy backbones, whether oxaliplatin-,<sup>36</sup> or irinotecan-based,<sup>37</sup> or 5FU-LV.<sup>38-39</sup> However, recent phase III trials in the adjuvant setting have demonstrated that these biological agents provide no additional benefit and may actually be detrimental when added to a chemotherapy backbone, usually oxaliplatin-5FU. These have included the NSABP C08 and AVANT trials for bevacizumab and the NCCTG-N0147 trial for cetuximab.<sup>40-42</sup> The mechanisms for this lack of synergy with chemotherapy and the biological agents in this setting are not clear, but may be explained by the induction of therapy resistance mechanisms by VEGF or EGFR inhibition; this has been discussed elsewhere.<sup>43</sup>

In terms of bevacizumab, two large relevant trials await reporting: the QUASAR 2 study, randomising patients to capecitabine +/- bevacizumab; and the ECOG E5202,<sup>44</sup> discussed below. Cetuximab is being further assessed in the PETTAC-8 trial. The FoxTROT trial evaluating FOLFOX or XELOX ± panitumumab is also to be reported.<sup>45</sup>

### **Adjuvant therapy of patients with resected stage II colon cancer**

#### **The case for and against?**

In the case of patients with stage II disease, the role of adjuvant therapy is controversial given the difficulty in identifying patients at the highest risk who would benefit the most from adjuvant therapy whilst avoiding potential toxicity in patients who would not benefit.<sup>15</sup>

The efficacy of systemic adjuvant chemotherapy for patients with stage II cancer has still not been confirmed.<sup>11</sup> The previously reported analyses from the IMPACT-B group,<sup>46</sup> the pooled analysis of the NSABP C01-4 trials,<sup>47</sup> and the

large phase III QUASAR trial,<sup>48</sup> have been inconsistent. In terms of modern combination therapy, there is relevant data from the MOSAIC and the NSABP C07 trials, above, in patients with stage II disease. In terms of the MOSAIC trial, 899 patients with stage II disease were randomised,<sup>30</sup> and with a median follow-up of 6.8 years, the five-year DFS was 79.9% versus 83.7% (HR =0.84, P>0.05) and the six-year OS 86.8% versus 86.9% (P >0.05).<sup>30</sup> From the NSABP C07 trial, 29% overall had resected stage II disease and the four year DFS was 81% versus 84.2% in favour of oxaliplatin-5FU.<sup>29</sup>

A recent Cochrane analysis considered all randomised trials or meta-analyses containing data on stage II colon cancer patients undergoing adjuvant therapy versus surgery alone; overall 8642 patients were considered.<sup>49</sup> In terms of the effect of adjuvant therapy, the pooled relative risk ratio for OS was 0.96 (95% CI 0.88-1.05), and for DFS 0.83 (95% CI 0.75-0.92). Hence the benefit was in terms of DFS only.<sup>49</sup>

Thus the overall the benefits of adjuvant systemic chemotherapy in patients with stage II patients are modest, but should be discussed in those with high risk features. The co-morbidities and likelihood of tolerating adjuvant systemic chemotherapy should be considered as well.<sup>49</sup>

### Identifying high risk stage II patients

Given the modest benefit for adjuvant therapy in such patients, there is an urgent need to better characterise high risk patients who would gain the greatest benefit. At present the identifiers of high risk relate to the tumour as well as clinical factors, as listed above, albeit inconsistently.<sup>15</sup> Considerable effort has been directed to identify molecular prognostic and predictive factors. However, as expected, there is considerable heterogeneity in terms of the cohorts evaluated, prospective versus retrospective analyses, and analytical methodology. The markers evaluated thus far include aneuploidy/tetraploidy DNA, 18q allelic loss, as well as microsatellite status (MS), p53, Kras, BRAF and thymidylate synthase.<sup>50-54</sup> A detailed review of these molecular factors with regard to stage II disease has been published recently.<sup>55</sup>

### MSI

The assessment of microsatellite instability (MSI), which serves as a marker for DNA mismatch repair (MMR) system function, has emerged as a useful tool for risk stratification of patients with stage II colon cancer. It seems clear, by retrospective studies and meta-analyses, that patients with stage II and III tumours classified as MSI-High (MSI-H) or defective MMR [dMMR]), have a better prognosis, independent of adjuvant therapy, relative to MS-Stable tumours.<sup>56-58</sup> While the prognostic importance of MSI has been confirmed, its importance in predicting response to adjuvant chemotherapy is unclear.<sup>51</sup> However, it appears from two retrospective studies that patients with dMMR do not benefit from adjuvant 5FU therapy.<sup>59-60</sup> Based on the body of current data, with the caveat that MSI status is still to be validated prospectively as a predictive biomarker, the current NCCN guidelines recommend that where adjuvant therapy is being considered in patients with stage II disease, MSI status must be assessed and those with MSI-H tumor should not be offered 5FU-based therapy.<sup>17,44</sup>

It is unclear whether this also applies to oxaliplatin-5FU adjuvant regimens. A recent study investigated the clinical implication of MSI-H/dMMR and p53 expression in 121 patients with resected colon cancer (13 stage II and 108 stage III disease) who received post-operative FOLFOX therapy.<sup>61</sup> The study observed that MMR status was not associated with DFS or OS, and thus adding oxaliplatin to adjuvant chemotherapy may overcome the negative impact of 5-FU on colon cancers with MSI-H/dMMR.<sup>61</sup> There is also preclinical evidence that MSI-H/dMMR tumour cells may be equally sensitive to oxaliplatin and possibly more sensitive to irinotecan.<sup>62</sup>

### 18q Allelic Imbalance (18qAI)

Chromosome 18q, contains the tumor suppressor genes deleted in colon cancer and the SMAD4 gene, which are lost in the oncogenic development of CRC.<sup>63</sup> The allelic loss of 18q is manifested as a loss of heterozygosity (LOH). The 18qLOH or 18 allelic imbalance (18qAI) have been correlated with a poorer prognosis in patients with stage II and III disease, albeit inconsistently.<sup>64-65</sup> The recently closed ECOG E5202 study had randomised stage II patients, stratified by MSI status and 18q allele imbalance, to observation for low risk patients (MS-S or MSI-Low with retention of 18q or MSI-H) and high risk patients (MS-S/18qLOH or MSI-L/18qLOH) to FOLFOX4 +/- bevacizumab. It was closed early following the reports that demonstrated the lack of benefit of bevacizumab in the adjuvant setting. We are still awaiting its final analysis.<sup>44</sup>

### Gene expression approaches

Quantitative gene expression assays have been evaluated to assess recurrence risk, though with less utility for the benefits from chemotherapy in patients with stage II disease. There are at present, two commercially available gene expression classifiers (ColoPrint and Oncotype DX) that have been developed and subsequently validated to prognostically classify patients with early stage colon cancer at high risk of relapse, rather than to determine their predictive ability in terms of outcomes from adjuvant chemotherapy.<sup>66-67</sup> Others have also been reported and are or are being validated.<sup>68-69</sup>

### Adjuvant therapy of rectal cancer

As stated above, patients with rectal cancer are at greater risk of local recurrence following surgery alone relative to the more proximal colon primaries.<sup>4</sup> An increased risk of local or distant relapse is observed, especially in tumours that have penetrated the rectal wall (T3 or T4) and/or with nodal involvement (N1-2).<sup>5</sup> A positive circumferential resection margin (CRM) (tumour ≤1mm of resection margin) is also an important independent prognostic marker, accounting for up to 85% of local recurrences.<sup>6-8</sup> Hence the optimum strategy to improve the outcome of rectal cancer patients must address the problems of local and distant recurrence.<sup>9</sup>

Multimodality treatment comprising of TME, with chemotherapy and radiotherapy, have been the standard of care for locally advanced (stage II and III) rectal cancer, as discussed in the 2005 Australian guidelines.<sup>9</sup> The current treatment nomograms will be discussed below, and include preoperative short-course radiotherapy or preoperative CRT followed by TME and adjuvant chemotherapy, and in select



patients post-operative CRT with adjuvant chemotherapy.<sup>9</sup> These approaches have dramatically reduced local recurrence, however approximately one-third of patients will still die from their disease within five years.<sup>10</sup> Current work is also now being directed towards identifying low risk patients who may avoid pre-operative radiotherapy or even surgery.

## Current treatment nomograms for rectal cancer

### **Short-course preoperative radiotherapy (25Gy in 5 fractions) followed by TME**

The advantages for preoperative radiotherapy include possible tumour downstaging, reduction of radiation field size and hence toxicity, and increasing radiosensitivity of the well-oxygenated un-manipulated tumour bed. Three meta-analyses have confirmed that preoperative radiotherapy is associated with a reduced local recurrence rate and reduction in cancer-specific mortality relative to surgery alone,<sup>70-72</sup> which extended to 10 years.<sup>71</sup> Short intensive course preoperative radiotherapy appeared to be as effective as longer schedules.<sup>71</sup> The pivotal Dutch Colorectal Cancer Group phase III trial, confirmed the benefit of preoperative radiotherapy (25Gy in five fractions) followed by TME one week later relative to TME alone in terms of local recurrence rate.<sup>73</sup> Follow-up data at five years, reported in 2007, had demonstrated that local recurrence was 5.6% versus 10.9%, respectively ( $P < 0.001$ ), but there was no OS difference.<sup>74</sup> As expected, short-course radiotherapy followed by immediate TME had not induced downstaging of the primary.<sup>75</sup>

### **Short-course preoperative radiotherapy (25Gy in 5 fractions) followed by TME versus TME and selective post-operative CRT**

As TME reduces the risk of local recurrence, it was suggested that the role of preoperative radiotherapy needed to be reassessed. The MRC-C07 trial had compared short-course preoperative RT (25Gy/5 fractions) versus immediate surgery, with selective postoperative CRT (45Gy/25 fractions with concurrent 5FU) in patients with positive resection margins.<sup>76</sup> Overall, 1350 patients were randomised and the primary outcome measure was local recurrence. At four years follow-up, there was a 61% reduction in the relative risk for local recurrence in patients receiving preoperative radiotherapy (HR = 0.39,  $P < 0.0001$ ), with an absolute difference at three years of 6.2% (4.4% versus 10.6%). The relative improvement in DFS was 24% for pre-operative radiotherapy (HR 0.76,  $P < 0.05$ ).<sup>76</sup>

### **Preoperative (long-course) CRT versus short course preoperative radiotherapy**

This has been directly compared in three randomised phase III trials.<sup>77-79</sup> A Polish study randomised 316 clinical stage T3–T4 rectal cancer patients to short-course radiotherapy (25Gy/5 fractions) plus TME one week later, versus long-course CRT (50.4Gy plus bolus 5F-LV) plus surgery. The primary endpoint was sphincter preservation.<sup>78</sup> There was no difference between the arms in terms of survival, local recurrence, late toxicity or sphincter preservation. The rates of positive CRM involvement though, were lower in the CRT arm (4% versus 13%,  $P < 0.05$ ).<sup>78</sup> A smaller Lithuanian phase III trial ( $n = 83$ ) compared the downstaging post long-

course CRT versus short-course radiotherapy. The former resulted in a significant greater tumoural downsizing and downstaging ( $P > 0.05$ ), but there was no difference in the R0 resection rates.<sup>77</sup>

The third study is the Australian TROG 01.04 trial that randomised 326 patients to short-course radiotherapy (5x5 Gy) versus long-course preoperative CRT (with daily bolus 5FU–LV, weeks one and five), followed by surgery and post-operative adjuvant chemotherapy.<sup>79</sup> The primary endpoint was local recurrence, which was not statistically significant between the arms 7.5% versus 4.4%, respectively. Nevertheless, in patients with distal tumours, long-course CRT did appear to be associated with lower rates of local recurrence. There were no differences between the arms for distant recurrence, relapse-free survival, OS or late toxicity.<sup>79</sup>

Based on current evidence, pre-operative long-course CRT, where downstaging effects are more pronounced, may be preferable, particularly for patients with distal or low rectal tumors or those with threatened radial margins. For patients with small, relatively proximal tumors for whom the duration of therapy is an important consideration, short-course preoperative radiotherapy appears to be appropriate.<sup>80</sup>

### **Preoperative CRT versus postoperative CRT**

The comparison between preoperative and postoperative CRT has been addressed by two pivotal phase III trials, updated since the guidelines.<sup>9</sup> The first is the German CAO/AIO/AIO-94 trial which randomised 800 patients with clinical stage T3/T4 or node-positive disease with OS as the primary endpoint.<sup>9,81</sup> The initial results from 2004 were confirmed when updated in 2012.<sup>82</sup> At a median follow-up of 134 months, OS at 10 years was approximately 60% in both arms ( $P > 0.05$ ), and there were no significant differences for DFS and 10-year cumulative incidence of distant metastases. However, the 10-year cumulative incidence of local relapse was 7.1% versus 10.1% in the pre and postoperative CRT arms, respectively ( $P < 0.05$ ).<sup>82</sup>

The NSABP R 03 trial, reported in 2009, randomised patients with T3–T4 or node-positive rectal cancers to either: (i) preoperative therapy - weekly bolus 5FU-LV for six weeks, followed by CRT (50.4Gy/28 fractions with bolus 5FU-LV). Patients then proceeded to surgery followed by 24 weeks of weekly 5FU-LV; or (ii) post-operative therapy - surgery followed by CRT (50.4Gy/28 fractions with bolus 5FU-LV) and then followed by 24 weeks of weekly 5FU-LV. The trial was closed prematurely, with only 267 of the planned 900 patients recruited.<sup>83</sup> In the preoperative arm, sphincter preservation occurred in 48%, compared with 39% of patients in the postoperative group ( $P > 0.05$ ). The five year DFS for the preoperative group was significantly higher (65% versus 53%;  $P < 0.05$ ).<sup>83</sup> Thus preoperative CRT is preferred to postoperative CRT.<sup>84</sup>

## The optimal chemotherapy backbone for concurrent long course pelvic radiotherapy

### **5FU-based therapy: Infusion and oral 5FU prodrugs**

The use of continuous infusion 5FU over bolus 5FU has become the standard of care in the CRT treatment of

rectal cancers, primarily for its low toxicity profile.<sup>85</sup> Two randomised phase III studies have now confirmed the equivalent efficacy of capecitabine as a radiosensitizing agent in preoperative CRT. A German phase III trial randomised patients to either: (i) preoperative CRT 50.4Gy plus capecitabine (825mg/m<sup>2</sup> b.i.d), days 1-38 and post-surgery capecitabine 1250 mg/m<sup>2</sup>/day b.i.d days one–14, q3 weeks for five additional cycles; or (ii) preoperative CRT 50.4Gy with infusional 5-FU and post-surgery four additional cycles of bolus 5FU.<sup>86</sup> At a median follow-up of 52 months, the local recurrence rate was equal (capecitabine 6% versus 5-FU 7%,  $P>0.05$ ), but with significantly fewer patients developing distant metastases in the capecitabine arm (18.8% vs 27.7%;  $P<0.05$ ).<sup>87</sup> The five-year OS rate was 75.7% for the capecitabine group and 66.6% for the 5FU group ( $P>0.05$ ).<sup>86</sup>

The second, the NSABP R-04 trial, was a 2x2 factorial design randomising patients to continuous infusion 5FU during preoperative RT versus capecitabine (825mg/m<sup>2</sup> b.i.d) on the days of radiotherapy only, and the second randomisation was with and without oxaliplatin.<sup>88</sup> In terms of the capecitabine versus 5FU, no differences were seen with regards to pathological complete response (pCR), tumour downstaging, or sphincter-sparing surgery. Local recurrence and overall survival have yet to be reported.<sup>88</sup>

It thus appears that capecitabine is a reasonable alternative to infusional 5FU as a radiosensitiser in pre-operative CRT, especially in those patients seeking an oral regimen or where a central venous access device is not preferred.

### **The utility of other chemotherapy agents and biologicals concurrent with long-course radiotherapy**

With the advances in systemic therapy in advanced CRC, there has been considerable effort to increase the effectiveness of CRT in terms of pathological downstaging, and systemic control. At this stage, based on trials discussed below, there has been no change from the 5FU (infusion or oral prodrug) chemotherapy backbone for CRT.

#### **1. Oxaliplatin**

There have been five reported phase III trials evaluating oxaliplatin with 5FU backbone versus 5FU alone as part of preoperative CRT. The STAR-01,<sup>89</sup> NASBP-R04,<sup>88</sup> and the PETACC-6,<sup>90</sup> trials all demonstrated the absence of additional benefit for tumoral pathological response or downstaging, but with an increased rate of toxicity. The German CAO/ARO/AIO4-04,<sup>91</sup> showed that patients who received oxaliplatin with 5-FU during CRT relative to 5FU alone had a pathological complete response (pCR) of 17.6% versus 13.1% ( $P<0.05$ ). The Accord 12/0405-Prodige 2 trial of oxaliplatin plus capecitabine versus capecitabine during CRT, demonstrated a similar trend: 19.2% versus 13.9% ( $P>0.05$ ).<sup>92</sup> To date, no DFS or OS advantage has been demonstrated. At this stage oxaliplatin cannot be a standard of care in preoperative CRT.

#### **2. Monoclonal antibodies to VEGF and EGFR**

Phase I and II trials of bevacizumab,<sup>93-96</sup> and cetuximab,<sup>97-99,100</sup> or panitumumab,<sup>101-102</sup> have been combined with neoadjuvant CRT. The reported pathological response rates range from 0-25%, not providing a significant advantage in this regard, but

associated with increased gastrointestinal toxicity and issues with wound healing.<sup>80, 103-104</sup> Thus the use of monoclonal antibodies cannot be considered as standard of care in preoperative CRT.

### **Current issues regarding the adjuvant therapy of rectal cancer**

#### **The role of post-operative adjuvant therapy patients undergoing neoadjuvant CRT or radiotherapy treatment**

The role of post-operative adjuvant therapy in patients treated in the neoadjuvant setting is unclear. It is standard practice to offer patients adjuvant therapy to reduce distant disease failure and improve OS. The optimal regimen and whether some patients, based upon pathological response or baseline stage, can be spared treatment is unclear. The only trial to evaluate this question was the EORTC Radiotherapy Group Trial 22921, which randomised patients to preoperative radiotherapy, preoperative CRT, preoperative radiotherapy plus postoperative chemotherapy, or preoperative CRT plus postoperative chemotherapy.<sup>10</sup> This showed no significant difference in OS or DFS between those that received post-operative chemotherapy versus those who did not ( $P>0.05$ ).<sup>10</sup> However, it must be noted that 43% of patients only completed the planned postoperative chemotherapy.<sup>105</sup>

Several retrospective series have shown that patients post-neoadjuvant CRT who achieve a pCR may have no, or minimal benefit from adjuvant chemotherapy.<sup>106-107</sup> A post-hoc analysis of patients who underwent neoadjuvant CRT or radiotherapy and post-operative chemotherapy from the EORTC 22921 trial above, demonstrated an improved DFS and OS in those with resected pT0-2 versus pT3-4 disease ( $P<0.05$ ).<sup>108</sup> Thus patients that have tumoural downstaging post CRT or radiotherapy do benefit from adjuvant chemotherapy,<sup>108</sup> an observation confirmed by others.<sup>109-110</sup> For treatment non-responders, it is not clear if additional 5FU chemotherapy or even multi-agent chemotherapy improves their poor outcomes.<sup>111</sup> Prospective data are required.

Hence at present, adjuvant chemotherapy should be offered to all medically fit patients with locally advanced, completely resected rectal cancer post-preoperative CRT or short-course radiotherapy. However, it is not clear which patients derive the most benefit from this approach. Patients treated with pre-operative CRT should have four months of a 5FU-LV or capecitabine regimen, and those post short-course radiotherapy a six month course postoperatively. If there is nodal disease at baseline or in the resected specimen, they should be offered an oxaliplatin-5FU/capecitabine based regimen, unless contraindicated.<sup>105</sup>

#### **Role of TME after pre-operative CRT**

Overall, approximately 15-20%,<sup>89, 92, 112</sup> of patients achieve a pCR at the time of TME post CRT, which is associated with substantially improved local control, distant control and DFS.<sup>82, 113-116</sup> A recent meta-analysis, involving 16 studies and 3363 patients, evaluated the long-term outcomes of patients found to have a pCR post neoadjuvant CRT.<sup>113</sup>

Overall, 1263 had a pCR with a mean local recurrence rate of 0.7% (range 0-2.6%). Compared with non-responders, a pCR was associated with fewer local recurrences (OR 0.25;  $P < 0.005$ ), reduced distant failure ( $P < 0.001$ ), and a greater OS (OR 3.28,  $P < 0.005$ ) and DFS (OR 4.33,  $P < 0.001$ ) at five years.<sup>113</sup> At present, there are no validated predictive biomarkers that identify patients most likely to undergo a pCR post-neoadjuvant therapy.<sup>117</sup>

Given these outcomes of pCR, some have advocated avoiding surgical resection totally in very select patients achieving clinical CR (cCR) post neoadjuvant CRT. However, the ability to predict cCR using clinical parameters is not robust.<sup>118-119</sup> The evidence is based upon a number of retrospective trials or prospective series,<sup>120-126</sup> without randomised data. A recent systematic review of 30 publications (9 series, 650 patients) evaluated a non-operative approach after CRT.<sup>127</sup> Overall the cCR rates varied from 10.9 to 56%.<sup>127</sup> The most recent Habr-Gama series,<sup>123</sup> reported a loco-regional failure rate of 4.6%, with five-year OS and DFS of 96% and 72%, respectively. These variable results reflect the significant heterogeneity in study design, including aspects of baseline and post-treatment staging, the definition of cCR and the nature of follow-up. The avoidance of TME requires, at the least, long-term prospective observational and randomised studies. Validated methods are also required to distinguish residual scar from viable tumor and document residual mesorectal deposits. Current MRI,<sup>128-129</sup> or PET,<sup>130-132</sup> imaging data have been inconsistent in this regard. A number of European prospective trials are evaluating this question.

### **Novel alternative neoadjuvant approaches**

These include intensifying systemic chemotherapy prior to neoadjuvant CRT or radiotherapy and surgery in an effort to reduce systemic failure, especially as 20%-40% of patients do not receive post-operative adjuvant chemotherapy.<sup>10, 84</sup> A phase II trial in high risk patients (distal lesions, threatened CRM, cT4 or cN2),<sup>133</sup> and a prospective study,<sup>134</sup> have evaluated an induction oxaliplatin-capecitabine combination pre-CRT. The studies have observed reduced toxicity,<sup>134</sup> higher response rates with favourable survival parameters.<sup>133</sup> Phase III trial data are required to validate the utility of such induction chemotherapy.

Other approaches have been to identify patients with low risk disease at baseline, who can proceed with surgery alone without neoadjuvant therapy. There is retrospective evidence indicating that there is a subgroup of patients with early T3N0 disease who may not benefit from additional therapy, apart from surgery.<sup>135-136</sup> The MERCURY study evaluated 374 patients with stage I-III rectal cancer, who underwent baseline high resolution pelvic MRI imaging.<sup>137</sup> Overall, 33% of these patients were deemed to have good prognosis, based upon predicted clear CRM (T2-T3a/b disease), and thus underwent surgery alone. The five-year DFS for stage II-III patients in this category was 85%, with a 3% local recurrence rate.<sup>137</sup> There is also the current US Intergroup PROSPECT phase II/III trial, evaluating the need for pre-operative radiotherapy in patients with mid to high rectal tumors who are candidates for TME with sphincter

preservation. Patients are randomised to a standard arm of neoadjuvant CRT with 5FU, followed by TME and adjuvant chemotherapy. In the experimental arm, patients will receive neoadjuvant chemotherapy alone with FOLFOX, but will only receive post-operative radiation therapy if they have a  $< 20\%$  pathological response to chemotherapy.<sup>138</sup>

### **Conclusions**

In conclusion, adjuvant therapy is recommended for patients with resected stage III colon cancer. Patients, based on fitness and preference, with completely resected stage III cancer, should be offered six months of adjuvant chemotherapy, which optimally should start within eight weeks of surgery. The optimal regimen is oxaliplatin in combination with 5FU-LV or capecitabine, based on relevant consideration of the therapeutic ratio, especially in regard to neurotoxicity, and perhaps age. Patients not considered suitable for oxaliplatin should be offered 5FU-LV or capecitabine.<sup>50</sup> Current trials are now investigating the optimal length of therapy i.e. three versus six months, and the additional benefit of the EGFR monoclonal antibody panitumumab, (the FOxTROT trial).<sup>43</sup>

In terms of patients with resected stage II disease, adjuvant chemotherapy may be discussed with patients at high risk of disease relapse, based upon clinico-pathological factors discussed above and while considering the patients' comorbidities, age and the risk of therapy-related toxicity. MSI status must be assessed for those patients being considered for adjuvant therapy. Those with a MSI-H tumor should not be offered 5FU-based therapy.<sup>17,44</sup> The utility of oxaliplatin-based therapy in this setting is controversial, given the marginal benefit and greater risk of toxicity. Where available, commercial gene expression classifiers may also be considered to further classify patients based on risk of relapse. However, at this stage they cannot identify patients who are likely to respond to therapy.

For patients with stage II/III rectal cancer (T3 or T4 and/or with nodal involvement [N1-2]), the optimal strategy is to reduce local and distant recurrence. Current treatment approaches may include: (i) short-course radiotherapy and immediate TME (especially in proximal tumours); or (ii) long-course neoadjuvant CRT (with 5FU infusion or capecitabine) followed by TME. Post-operative adjuvant chemotherapy should be offered to medically fit patients. Postoperative CRT therapy may be preferred, for example where patients who have undergone surgery for very small or proximal T3 tumors, or tumors that are either T2/3. In these circumstances, post CRT and adjuvant chemotherapy should be considered if unexpected nodal involvement or a positive margin is identified. At present, there are no validated markers that can identify patients who may not require neoadjuvant radiotherapy, or who can be safely spared surgery post CRT or radiotherapy, though these are areas of active research. In an effort to increase pCR, the intensification of neoadjuvant chemotherapy is also being evaluated.

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# SURGERY FOR COLORECTAL CANCER

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### Abstract

Surgery is the mainstay in the treatment of colorectal cancer. Considerable progress has been made in the past eight years since the publication of the most recent clinical practice guidelines for colorectal cancer by the National Health and Medical Research Council. The most notable changes in surgery are the result of trials in minimally invasive approaches, including laparoscopic cancer resection, new advances yet to be tested such as robotic assisted cancer resection and the use of self-expanding metallic stents in patients with curable malignant obstruction. This paper provides an overview of these minimally invasive techniques and summarises the recommendations that could be considered for inclusion or update in the next edition of the guidelines.

Surgery is the mainstay treatment for colorectal cancer (CRC). With the exception of medically contraindicated patients or patients who decline surgery, most patients, including those with locally advanced or metastatic disease, will require some form of surgical intervention, which may be preceded by or followed by adjuvant therapy.

Although progress continues to be made on all fronts in the treatment of CRC, from a surgical standpoint, minimally

invasive and maximally invasive resection techniques have made the most progress over the past eight years, since the publication of the most recent clinical practice guidelines by the National Health and Medical Research Council.<sup>1</sup> Table 1 summarises the existing practice guidelines and areas where updates could be considered based on the available literature.

**Table 1:** Summary of 2005 recommendations and updated recommendations. Based on the authors' interpretation of available evidence and may not be representative of the Journal's opinion.

Summary of 2005 NHMRC recommendations	Practice recommendation	Status	Considerations for updated recommendations based on current evidence – if applicable
High ligation of the lymphovascular pedicle does not confer any oncological benefit. Resection where feasible should extend to the origin of the segmental vessels.	Equivocal	No change. Consideration for update	For colon cancers, sharp fascial dissection with preservation of the mesocolon package and central vascular ligation requires further assessment <sup>61</sup>
The no-touch isolation technique has no oncological benefit.	Recommend	No change	N/A
Segmental resection is equivalent to extended resection in outcome.	Equivocal	No change	N/A
Sutured and stapled anastomosis have equivalent outcomes.	Strongly recommend	No change	N/A
Omental wrapping of anastomosis has no benefit.	Strongly not recommend	No change	N/A
Bilateral oophorectomy should be performed if there is obvious malignant disease of one or both ovaries.	Recommend	No change	N/A
Prophylactic bilateral oophorectomy for colon cancer cannot be supported by the available evidence.	Strongly not recommend	No change	N/A
In experienced hands, laparoscopic surgery for colon cancer has equivalent outcome to conventional surgery.	Recommend	No change	N/A

Elective surgery for rectal cancer should be carried out by a surgeon who has undergone a period of special exposure to this form of surgery during surgical training, and who has maintained satisfactory experience in the surgical management of rectal cancer.	Recommend	No change	N/A
Local excision of T1 rectal cancer may be used in selected cancer patients according to the following guidelines: -mobile tumour < 3 cm -T1 on endorectal ultrasound -not poorly differentiated on histology (biopsy).	Equivocal	No change	N/A
A distal margin of 2cm (fresh) is recommended in most instances, or 1cm fixed.	Recommend	No change. Consideration for update	A 1cm distal margin may be acceptable in selected patients. <sup>62,63</sup>
Sphincter-saving operations are preferred to abdominoperineal resection except in the presence of:  -tumours such that adequate distal clearance (> 2 cm ) cannot be achieved -the sphincter mechanism is not adequate for continence -access to the pelvis makes restoration technically impossible (rare).	Equivocal	No change. Consideration for update	A 1cm distal margin may be acceptable in selected patients to allow a restorative procedure. <sup>62,63</sup>
For mid-to-low rectal tumours, the principles of extra fascial dissection and total mesorectal excision (TME) are recommended.	Recommend	No change	N/A
Where technically feasible, the colonic reservoir is recommended for anastomosis within 2cm from anorectal junction.	Strongly recommend	No change. Consideration for update	The use of coloplasty is an alternative to a colonic reservoir.
Routine drainage should only be considered for rectal cancers.	Equivocal	No change	N/A
N/A	N/A	Consideration for update	In experienced hands, laparoscopic rectal resection is safe and seems to have equivalent outcomes to open surgery.
N/A	N/A	Consideration for update	The use of robotic colorectal resection needs to be further assessed in prospective randomised trials.
Primary resection of obstructing carcinoma is recommended unless the patient is moribund.	Recommend	No change. Consideration for update	Routine use of self-expanding metallic stents as a bridge to surgery for curable obstructing cancer cannot be supported based on available evidence.
N/A	N/A	Consideration for update	Enhanced recovery programs should be considered in the care of colorectal patients undergoing elective resection.

## Laparoscopic colon resection

Laparoscopic colectomy for cancer is a safe alternative to open surgery, provided the same surgical and oncological principles are adhered to. Short-term surgical outcomes such as intra-operative blood loss, post-operative pain, return of gastro-intestinal function and length of hospital stay, have all been consistently shown to improve, although only marginally, with laparoscopic surgery.<sup>2-5</sup> However, the oncological outcomes of laparoscopic

CRC resection remained a concern until more recently, when the long-term follow-up data from several large multi-centre randomised control trials (RCTs), such as the Australasian Laparoscopic Colon Cancer Study (ALCCaS trial), Clinical Outcomes of Surgical Therapy (COST), Colon Cancer Laparoscopic or Open Resection I (COLOR I), Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASIC) and Barcelona trials became available. All confirmed the equivalence of laparoscopic assisted resections to open procedures in terms of long-



term oncological outcomes, with no confirmation of initial suggestions that laparoscopic colectomy may be associated with increased risk of port site metastases.<sup>6-9</sup> These results have re-affirmed the previous guidelines that laparoscopic colon resection can be considered now with Level 1 evidence to be safe, however laparoscopic rectal cancer surgery should remain in the confines of prospective RCTs (see later).

The ALCCaS, COST and CLASSIC trials have published short-term data with only marginal improvements in subjective outcomes in the laparoscopic groups consistent with previous meta-analyses, however the longer term oncological outcomes are all equivalent. In 2008, Lacy et al published the long-term follow-up results from the Barcelona trial at a median follow-up of 95 months, where recurrence rates, overall mortality and cancer related mortality were 18% vs 28% ( $p>0.05$ ), 36% vs 49% ( $p>0.05$ ) and 16% vs 27% ( $p>0.05$ ) respectively for laparoscopic and open arms.<sup>9</sup> Although local recurrence rates and survival favoured the laparoscopic group, these did not reach statistical significance.<sup>9</sup> Jayne et al reported the long-term follow-up data from the CLASSIC trial in 2007.<sup>10</sup> Although comparable oncological outcomes have been demonstrated, early reports from the CLASSIC trial were somewhat alarming because of the high conversion rate (29%) and increased mortality, as well as morbidity, with open conversion.<sup>3</sup> Much debate has stemmed from these and other trial results suggesting that if the conversion rates are lowered, then the benefit of the laparoscopic procedure will be increased. However, maintaining the intention to treat analyses and inherent bias of this post-hoc analysis cannot support this, widespread assumption. Several meta-analyses pooling data from the large Barcelona, COST, COLOR I, CLASSIC I and ALCCaS RCTs have confirmed that laparoscopic colectomy is at least oncologically equivalent to open surgery and can be reasonably offered as an alternative to the open procedure, and that this choice is based on surgeon and patient preferences.<sup>2,11,12</sup>

### Laparoscopic rectal resection

More recently, laparoscopy has also been extended to treat rectal cancer. To date, multiple large case series, uncontrolled comparative studies and non-randomised controlled trials have demonstrated that laparoscopic rectal resection confers the same short-term surgical benefits as laparoscopic colectomy, and that laparoscopic proctectomy is associated with less blood loss, reduced post-operative pain, earlier return of gastrointestinal function and shorter duration of inpatient stay.<sup>13-16</sup> As randomised trial confirmation of the long-term oncological data are currently lacking for laparoscopic proctectomy, there are concerns about its oncological safety, just as there were initial concerns about the oncologic safety of laparoscopic colectomy.

Rectal cancer outcomes are directly related to the quality of surgery, where local recurrence rates have been shown to halve after the surgeons are trained to perform high quality total mesorectal excision (TME).<sup>17</sup> However, although local recurrence is a useful marker of surgical quality, it is at best an indirect marker of quality of surgery. Further, as local

recurrence requires large numbers of patients with long-term follow-up, it limits its usefulness for immediate feedback or early recognition and implementation of strategies to improve surgical quality. The completeness of excision and integrity of the mesorectum of the resected rectal specimen is not only a surrogate for quality surgery, it has also been shown to correlate with oncological outcomes such as local recurrence.<sup>18,19</sup> In a sub-study of the Dutch TME trial, Nagtegaal et al reported that an incomplete mesorectum is associated with an increased risk of overall recurrence (35.6% vs 21.5%) and local recurrence (15.0% vs 8.7%).<sup>19</sup> Using the grading system described by Nagtegaal et al, Maleskar et al demonstrated stepwise incremental risk of local recurrence with progressive deterioration in the quality of TME, where the risks of local recurrence were 1.6%, 5.7% and 41% with a complete, near complete and incomplete mesorectum respectively. The importance of an intact mesorectum is currently being further assessed in the Australian Laparoscopic Cancer of the Rectum Trial (A La CaRT) trial, which is an Australasian multi-centre trial comparing laparoscopic and open rectal resection for cancer.<sup>20</sup>

A number of prospective randomised trials have either been completed or are currently ongoing to assess laparoscopic rectal resection.<sup>10,20-25</sup> In the CLASSIC trial, patients undergoing laparoscopic rectal resection were twice as likely to have an involved circumferential margin as patients undergoing open rectal surgery, although interestingly, this did not translate to a local recurrence or survival difference at three years follow-up.<sup>3,10</sup> Ng and Leung et al have published several studies comparing laparoscopic and open rectal resection, including a 10 year follow-up study which showed that there was no difference in survival between the two groups (overall survival 83.5% vs 78%  $p>0.05$ , disease free survival 82.9% vs 80.4%  $p>0.05$ ).<sup>21,22</sup> Ongoing trials include the Comparison of Open versus laparoscopic surgery for mid and low REctal cancer After Neoadjuvant chemoradiotherapy (COREAN) trial from South Korea, COLOR II trial from Europe, the Australian Laparoscopic Cancer of the Rectum Trial (A La Cart) trial from Australia, and the Laparoscopic-Assisted or open resection rectal cancer trial from the United States.<sup>20,23-25</sup> The first two trials have completed recruitment and are due to complete their three year follow-up by the end of 2013, while the latter two trials are still currently recruiting.<sup>23,24</sup> Interim reports from the former two trials found no differences in lymph node yield, macroscopic quality of the TME or involvement of circumferential resection margin between laparoscopic and open surgery, thereby providing some evidence that laparoscopic surgery may be oncologically equivalent to open surgery.<sup>23,24</sup> However, long-term follow up data are still required before definite conclusions can be drawn.

### Robotic colorectal surgery

Laparoscopic TME is a technically challenging procedure which can be made even more challenging in the setting of neoadjuvant chemoradiation, a narrow male pelvis or obesity. Improving surgical access within the confines of a bony pelvis may therefore improve the quality of TME while minimising inadvertent pelvic nerve injury, thus improving cancer outcomes as well as urinary and sexual

function.<sup>26</sup> Robotic assisted surgery has the potential to mitigate some of the limitations of laparoscopy through its stable operating platform, improved depth perception and enhanced dexterity, while offering improved ergonomics for the surgeon to minimise fatigue. However, availability and costs hamper widespread dissemination of the technique.

Although robotic surgery is increasingly utilised in pelvic surgery, the collective international experience remains in its infancy. As far as the authors are aware, only one small RCT has been published to date comparing outcomes between robotic and laparoscopic total mesorectal excision, although a number of multi-centre randomised trials are currently underway to assess the safety and efficacy of robotic surgery for rectal cancer.<sup>27,28</sup> Several large series and at least two systematic reviews have been published which suggest that robotic surgery is safe and that it is associated with less open conversion, with no differences in surgical morbidity, length of hospital stay and rates of involved margin.<sup>29-31</sup> Promising as it is, until more data becomes available, there is insufficient evidence from a functional or oncological outcome perspective to justify the additional costs of robotic surgery.

### Self-expanding metallic stents for CRC

The use of self-expanding metallic stents for obstructing CRC as definitive treatment in a palliative setting is well established.<sup>32,33</sup> As experience with self-expanding metallic stents grows, its indications have also expanded to include curable obstructing CRC as a bridge to elective surgery. This approach is attractive because not only does it reduce the morbidity associated with an emergency resection, it also permits bowel preparation and pre-operative colonoscopic assessment of the proximal colon, the use of laparoscopic resection while minimising the likelihood of requiring a stoma. However, the use of self-expanding metallic stents as a bridge to surgery is also contentious because of the potential for tumour dissemination from stent related perforation, which may convert a curable CRC into an incurable cancer.

Although self-expanding metallic stents have been assessed in numerous studies, few of these studies are prospective randomised trials.<sup>34,35</sup> Further, while the short-term safety of self-expanding metallic stents has been established, the same cannot be said about the oncological safety of self-expanding metallic stents as a bridge to surgery, because most studies do not report long-term outcomes.<sup>35</sup> Studies by Saida et al, Dastur et al and Kavanagh et al did not reveal any differences in survival, but alarmingly, in a recent publication by Sabbagh et al, five year overall survival and cancer related mortality were both worse in the self-expanding metallic stents group compared to the group that underwent surgical decompression.<sup>36-39</sup> Further, five year disease free survival and time to recurrence also tended to favour the surgical decompression group. Although this was not statistically significant, it might have been related to the small sample size in that study.<sup>37</sup> More long-term follow-up data are required to determine the safety of self-expanding metallic stents as a bridge to surgery in patients with curable CRC.

### Pelvic exenteration for locally advanced and recurrent rectal cancer

Since the last guidelines, numerous international and national publications have confirmed the safety and survival advantage of pelvic exenteration for recurrent rectal cancer.<sup>40-42</sup> Provided a clear microscopic resection margin can be achieved, five year overall survivals of 30-50% have been reported.<sup>40</sup> With improved surgical techniques and experience with extra-anatomical dissection, local recurrences in challenging anatomical locations such as the pelvic side wall, recurrences involving proximal sacral segments or pubic bone are increasingly being offered curative surgery.<sup>43,44</sup> Specialised units with an interest in maximally invasive surgery have also pushed the boundary of resectability further by offering pelvic exenteration in patients with isolated resectable metastasis of the liver or lung. Although morbidity of pelvic exenteration remains high, long-term oncological benefit of pelvic exenteration coupled with good quality of life outcomes have cemented the role of pelvic exenteration for locally recurrent rectal cancer.<sup>45</sup>

### Role of local excision for rectal cancer

Transanal excision of rectal cancers has traditionally been reserved for old and medically frail patients who are unable to tolerate a major resection. However, in selected rectal cancers, namely early rectal cancers (T1 cancers) with no adverse features on histology, patients may be spared the morbidity of a major resection or a permanent colostomy without compromising oncological outcomes.<sup>46,47</sup> The major disadvantage with the conventional local excision technique though, is the quality and completeness of resection, as well as access difficulties which limit the applicability of the technique to the low rectum. With the advent of transanal endoscopic microsurgery, the incidence of surgical site recurrence has reduced and the quality of the specimen improved.<sup>48</sup> Although the risk of loco-regional recurrence from unrecognised nodal involvement remains, the risk of this is low provided case selection is appropriate.<sup>49</sup> Unfortunately, because of the limitations of existing staging modalities and our understanding of tumour biology, some cancers will recur despite seemingly appropriate case selection. Outcome of surgical salvage in the event of local recurrence is variable and further highlights the importance of accurate staging of the primary and appropriate case selection. To minimise the risk of local recurrence, selected centres are offering neoadjuvant chemoradiotherapy as an adjunct to local excision.<sup>50,51</sup> However, the safety and morbidity of this approach remains under-studied and needs further evaluation before it can be recommended.

### Care of the post-operative patient

The principle of enhanced recovery after surgery, also known as fast track surgery, is to minimise surgical trauma thereby reducing ileus and post-operative pain.<sup>52</sup> In doing so, time to resumption of diet, surgical morbidity and length of stay in hospital have all been proven to reduce.<sup>53-55</sup> Although initially described for elective open colectomy, the principles of enhanced recovery programs are also increasingly applied to laparoscopic procedures and rectal surgery with similar benefits.<sup>56,57</sup>

Notwithstanding the compelling evidence from existing literature about enhanced recovery programs, there remains reticence among many colorectal surgeons about the safety and efficacy of enhanced recovery protocols. Separate surveys conducted in New Zealand, the UK and Europe have indicated that less than 50% of respondents have adopted enhanced recovery programs.<sup>58-60</sup>

## Conclusions

Considerable progress has been made in the surgical treatment of CRC. Notable changes relate to minimally and maximally invasive approaches to cancer resection, as well as care of the post-operative surgical patient. Inclusion of these developments in the next edition of CRC practice guidelines should be considered.

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## COLONOSCOPY AND COLORECTAL CANCER

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### Abstract

Colonoscopy has a central role in the detection and prevention of colorectal cancer. This is based on the fact that most colorectal cancer develops from premalignant adenomatous or serrated polyps, which can be removed at colonoscopy and hence prevent the development of colorectal cancer. The success of colonoscopy in preventing bowel cancer is dependent on the quality of the colonoscopy performed. This review highlights the key performance indicators measuring quality of colonoscopy, including consent, indication, preparation, caecal intubation rates, polyp detection and removal, withdrawal time and complication rates, and sets minimum target recommendations for each of the key performance indicators.

### Does colonoscopy prevent colorectal cancer?

The evidence for colonoscopy reducing the incidence of colorectal cancer (CRC) comes mostly via indirect evidence from a number of observational, cohort studies.<sup>1-5</sup> While the National Polyp Study demonstrated a risk reduction in the development of CRC of 76 per cent to 90 per cent post polypectomy,<sup>3</sup> other studies have shown a more modest risk reduction.<sup>6-8</sup> In addition, more recent evidence suggests that in real world community practice, colonoscopy affords a greater level of protection against the

development of cancers on the left side of the colon than the right side.<sup>5,9-11</sup> The reason for this is not entirely clear, but could include patient factors (bowel prep and tumour biology), colonoscopist factors (technique, knowledge, personality and perceptual factors), system drivers and equipment factors.<sup>4</sup> The more aggressive biology of right sided cancer might be a factor and a recent study has confirmed that a higher proportion of right sided cancers after recent colonoscopy are microsatellite unstable.<sup>5</sup> However, low polypectomy rates and a high proportion of incomplete colonoscopies seem a common theme in many

of these studies, suggesting that the quality of colonoscopy is a more important factor.<sup>10</sup> A recent German study has suggested that well performed colonoscopy does indeed protect patients from both left and right sided cancer.<sup>12</sup>

### Quality in colonoscopy

Overall high quality colonoscopy is dependent on a number of factors, including patient-related factors, operator-related factors, system related factors and equipment.<sup>13</sup> Operator factors include appropriate training and experience of the colonoscopist, proper risk assessment of the patient, complete examination to the caecum with adequate mucosal visualisation and bowel preparation, the ability to detect and remove polyps safely, adequate documentation, timely and appropriate management of adverse events, follow-up of histopathology and appropriate screening and surveillance intervals based on published guidelines.<sup>14</sup> Therefore, in order to maintain a high level of performance and quality in the colonoscopy procedure, a number of working groups have proposed key performance indicators. *Improving Colonoscopy Services in Australia* was published by a quality working group tasked by the Australian Department of Health and Ageing to provide a reference guide for colonoscopy alongside the roll-out of the National Bowel Cancer Screening Program.<sup>15</sup> Several other international societies have also recently published colonoscopy quality guidelines, including the American, Canadian and European societies.<sup>16-18</sup> The Australian National Health and Medical Research Council (NHMRC) 2005 guidelines identify four key performance areas that need to be monitored for quality assurance.<sup>19</sup> These are:

1. Procedure: indication, consent, preparation, technique
2. Facility and equipment
3. Documentation and reporting systems and training
4. Certification and credentialing.

Here we aim to focus on the colonoscopy procedure and the key performance indicators (KPIs) within this domain that have been identified for quality assurance. Key areas for quality KPIs for the colonoscopy procedure include consent, indication, preparation, caecal intubation rates, polyp detection and removal, withdrawal time and complication rates.<sup>20</sup>

### Consent

Patients must provide informed consent to undergo any endoscopic procedure. The requirements for an adequate bowel preparation form part of the consent, along with a full explanation of the procedure, including any risks and potential complications, why it is indicated and any alternative investigation options. Patients must be given the opportunity to ask questions and receive advice.<sup>15</sup> Provision of this information prior to colonoscopy helps to minimise withdrawal of consent on the day of procedure, and therefore reduces loss of facility time and other economic consequences.<sup>17</sup> It is important that this information is given prior to the commencement of bowel preparation. While European colonoscopy guidelines state that patients should also have the opportunity to withdraw consent during the examination,<sup>17</sup> this is less relevant in Australia where anaesthetic support is more commonly used and

patients are often more deeply sedated.

### Indication

The Australian Quality Working Group recommended that prior to colonoscopy, the colonoscopist should ensure that the indication for performing the colonoscopy is documented.<sup>18</sup> The indications for asymptomatic patients should conform to the NHMRC guidelines and include a family history of CRC, personal history of CRC or polyps, colitis surveillance or a positive faecal blood test.<sup>19</sup> The use of colonoscopy for screening asymptomatic patients is not supported by the Australian Government, though this is not the case in other countries including the United States. Symptomatic patients should have relevant symptoms documented on the colonoscopy report.

### Preparation

Effective bowel preparation is obligatory for high quality colonoscopy. Good bowel preparation facilitates polyp detection and optimises caecal intubation.<sup>21-25</sup> Conversely, poor preparation is associated with prolonged procedures and failure to detect disease.<sup>21-26</sup>

The data on the superiority of type of bowel prep is conflicting. While preparations containing sodium phosphate are lower volume and may be better tolerated,<sup>27-29</sup> polyethylene glycol solutions have an improved safety profile and are favoured for use in the elderly and patients with other medical comorbidities.<sup>27-29</sup> However, tolerability and quality of high volume PEG prep is improved by splitting the dose,<sup>30-31</sup> with the aim of finishing bowel prep within hours of the colonoscopy start time. Several societies suggest the poor preparation should be present in less than 10% of studies,<sup>17-18</sup> but poor preparation is probably more precisely defined by the requirement to repeat the examination.

### Caecal intubation rates

Caecal intubation is defined as deep intubation into the caecum with the tip of the colonoscope being able to touch the appendiceal orifice.<sup>17</sup> Caecal intubation demonstrates a complete examination of the colon, and is fundamental for CRC screening.<sup>17</sup> The intubation of the caecum should ideally be documented by an image of the appendiceal orifice and/or terminal ileum if intubated.<sup>17</sup> The Australian Quality Working Group sets unadjusted (i.e. includes studies with poor prep and obstructing cancer) caecal intubation rates of 90% for general patients and 95% for patients undergoing screening colonoscopy.<sup>15</sup> This is comparable to the National Health Service (NHS) Bowel Cancer Screening Program with a recommended minimum, unadjusted caecal intubation rate of 90%.<sup>32</sup> The US Multi-Society taskforce has set a minimum intubation rate of 95% for screening colonoscopy and 90% for symptomatic colonoscopy,<sup>33-34</sup> whereas the Cancer Care Ontario Standards are a completion rate of 95%,<sup>35</sup> though this excludes cases with obstructing lesions and poor bowel preparation.

Low colonoscopy volume, i.e. less than 200 procedures per annum, has been associated with lower caecal intubation rates for colonoscopists with less than five years' experience.<sup>36</sup> While the Australian Conjoint Committee

currently requires a minimum of 200 colonoscopies for initial certification, there are no current recommendations for minimum annual colonoscopy numbers for ongoing colonoscopy practice.

### Withdrawal time

Withdrawal time is the time taken to remove the colonoscope from the maximal extent of insertion at the caecum to withdrawal from the anus. Longer withdrawal times are associated with increased adenoma detection.<sup>37,38</sup> The Australian quality working group recommends that the mean colonoscopy withdrawal time from the caecum for each proceduralist should be six minutes or greater for procedures where there is no polypectomy performed.<sup>15</sup> This recommendation is similar to European guidelines,<sup>17</sup> which recommend a minimum withdrawal time of six minutes in at least 90% of purely diagnostic examinations, and the joint task force of the American College of Gastroenterology and American Society for Gastrointestinal Endoscopy which recommends that average withdrawal time should exceed six minutes in normal colonoscopies in which no polypectomies or biopsies were performed, though notes that this withdrawal time should not be applied to individual cases.<sup>39</sup> However, withdrawal time is likely to be a surrogate marker for adenoma detection rates and as such should not be relied upon as an independent marker of quality.<sup>40</sup>

### Polyp detection, removal and retrieval

The NHS Bowel Cancer Screening Program defines 'adenoma detection rate' (ADR) as "the number of colonoscopies at which one or more histologically confirmed adenomas is found, divided by the total number of colonoscopies performed".<sup>17</sup> It is the best validated KPI for colonoscopy, though the number of adenomas per colonoscopy is a less well studied, but potential alternative.<sup>41</sup> Evidence of ADR variability between endoscopists has been demonstrated by studies comparing ADR between gastroenterologists in the same group. These studies report a three to six fold difference in ADR between endoscopists.<sup>37,42-44</sup> Similarly, the detection of serrated polyps also differs between endoscopists.<sup>45,46</sup> The degree of variation is higher than traditional adenomas, with one study reporting a 25% difference in proximal serrated polyp prevalence per colonoscopy between endoscopists.<sup>46</sup>

A study by Kaminski et al demonstrated a significant increase in interval cancers in individual colonoscopists with an ADR below 20%.<sup>47</sup> The European Society of Gastrointestinal Endoscopy guidelines recognise that there is a difference between populations in whom screening colonoscopy is performed (e.g. US, where suggested ADR are 15%/25% for women/men) and for colonoscopy populations enriched with patients with positive faecal occult blood testing, in whom the ADR should be nearer to 35%.<sup>17</sup> The ESGE guidelines recommend that a minimum of 90% of resected polyps should be retrieved.<sup>17</sup>

ADR measurement often requires manual calculation and is time consuming to generate in endoscopy units without electronic linking between endoscopy reporting systems and histopathology reports. In order to overcome

difficulties in measurement of ADR, a recent suggestion of using polypectomy rates (PR) as a surrogate for ADR has been studied and validated.<sup>48,49</sup> However, a study by Boroff et al warns that while the correlation with ADR is reliable in the right colon, it is not in the left colon.<sup>50</sup> Therefore, while PR measurement cannot be recommended as an alternative to ADR measurement, for endoscopy units that have difficulty in measuring ADR, PR is a reasonable first step but should not reduce attempts to be able to measure adenoma detection rates.

A number of newer technologies such as cap-assisted colonoscopy, chromoendoscopy, Third Eye Retroscope and electronic image enhancement techniques, such as narrow band imaging (NBI) have, been developed to enhance mucosal inspection and adenoma detection rates. The impact of these on adenoma detection has been modest compared with the potential improvements from removing individual variation among colonoscopists.<sup>4</sup> Indeed, it seems clear that colonoscopy technique and individual characteristics are much more important than equipment.<sup>40</sup>

The Australian Quality Working Group recommends the adenoma detection rate for each proceduralist is more than 20 per cent in patients over 50 years undertaking an initial colonoscopy.<sup>15</sup> The Joint Advisory Group from the British Society of Endoscopy Guidelines suggests an adenoma detection rate of >10% for flexible sigmoidoscopy and colonoscopy.<sup>51</sup> The American College of Gastroenterology/American Society for Gastrointestinal Endoscopy taskforce recommends ADR targets for individual endoscopists of identifying one or more adenomas in at least 25% of men and 15% of women aged 50 years and older, undergoing screening colonoscopy,<sup>33,39</sup> whereas European guidelines recommend adenoma detection rates be recorded, but leave targets to the discretion of individual screening boards – presumably due to variation among recommendations for screening (allcomers or faecal blood positive enriched), surveillance and symptomatic populations.

### Complications

There is some evidence to suggest that an increased volume of colonoscopy performed by colonoscopists results in fewer complications.<sup>52-54</sup> As a result, the UK NHS Bowel Screening Program suggests a lifetime experience of 1000 colonoscopies and an annual number of 150 colonoscopies prior to being certified to perform bowel cancer screening program colonoscopy.<sup>55</sup>

The two most feared complications of colonoscopy are perforation and bleeding (usually post polypectomy). However, a missed cancer or advanced polyp is likely to be the biggest overall risk for the patient. Perforation in screening colonoscopy approximates 1/1000 and could be used as a useful indicator of colonoscopy safety in large colonoscopy units or in national screening programs.<sup>56</sup> This increases to around 1/500 post polypectomy,<sup>56</sup> but it is likely that not all post polypectomy perforations are recognised clinically. The rates are higher when resecting larger polyps.<sup>57</sup> For screening populations enriched with positive faecal blood, the likelihood of adenomas and advanced adenomas is increased and the overall colonoscopy complication

rate is likely to be higher than with screening colonoscopy populations.<sup>17</sup> This needs to be considered when applying historical complication rates in enriched colonoscopy populations. The requirement for surgery has reduced with the ability to close perforations with endoscopic clips (particularly post polypectomy).<sup>58</sup>

The British Joint Advisory Committee and the Australian Quality Working Group guidelines state colonoscopy perforation rates should be <1:1000 while Rex et al suggest perforation rates greater than one in 500 for all colonoscopies or one in 1000 for screening colonoscopies require evaluation of practice.<sup>15,51,39</sup>

Post polypectomy bleeding is defined as rectal blood loss following a colonoscopy that requires a blood transfusion that may occur up to two weeks post polypectomy.<sup>17</sup> Bleeding is affected by many factors, including the definition of bleeding, use of antiplatelet and anti-thrombotic medication, lesion characteristics, colonoscopist volume and different diathermy settings.<sup>57,59-61</sup> Due to this wide range of variables that impact on post polypectomy bleeding, there is a large range of reported incidence

in the literature, with rates ranging from 1:10 to 1:300 colonoscopies.<sup>62,63</sup>

Rex et al suggested post-polypectomy bleeding rates should be less than 1% and the Joint Advisory Group on GI Endoscopy from the British Society of Gastroenterology recommends post polypectomy bleeding requiring transfusion should be <1:100 (for >1cm polyps).<sup>39,51</sup> The Australian Quality Working Group recommends post-polypectomy bleeding should be less than one in 100 patients who have had a polypectomy, whereas the European Society of Gastrointestinal Endoscopy recommends that less than 5% of post-polypectomy bleeding should require surgical intervention.<sup>15,17</sup>

Colonoscopy has the most validated set of quality indicators of all endoscopic procedures. Many national and international societies have developed specific KPIs similar to those suggested in this article. Many of these quality indicators are deliverable from electronic reporting systems, so should be measured by colonoscopists and endoscopy units and be required by accreditation bodies.

**Table 1: Recommendations**

Colonoscopy quality indicator	Recommendation
Consent	Suitable information should be provided to patients prior to the commencement of bowel preparation for colonoscopy.
Indication	The indication for screening colonoscopy in asymptomatic patients should conform to the NHMRC guidelines. Symptomatic patients should have the relevant symptoms documented on the colonoscopy report.
Preparation	Less than 10% of patients should require repeat procedure due to poor bowel preparation.
Caecal intubation rates	Unadjusted rates for caecal intubation should be ≥90% for symptomatic and ≥95% for screening patients. Photo documentation of the appendiceal orifice +/- terminal ileum should be performed to confirm a complete examination.
Polyp detection, removal and retrieval	Adenoma detection rate for each proceduralist of >20% in patients over 50 years of age undertaking an initial colonoscopy.
Complications	Perforation rates post colonoscopy should be <1/1000. This is more relevant for population programs and large endoscopy units rather than individual colonoscopists.

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# SURVIVING BOWEL CANCER

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Surviving bowel cancer is not just about avoiding death. This article may not contain the means of achieving that end, but describes a personal journey which has suggestions for the patient and observations which may add to a medical professional's understanding. My survival story would not have been possible without the important assistance of family, professionals and friends. My reflections on the experience of diagnosis, treatment and recovery are described with some candour, while recognising that individual approaches vary enormously. The body of research into the long-term survival of cancer patients has grown rapidly, and the material available from health professionals, researchers and cancer organisations is respected and recommended as a critical resource. It is hoped that the comments here contribute further to that understanding.

## Background and diagnosis

In 1993, I felt overwhelmingly sick. After weeks of increasing pain and discomfort, the discovery of a malignant tumour was not as devastating as it sounds. At least there was a diagnosis and the prospect of remedial action. It must be shattering for someone who receives a cancer diagnosis when otherwise fit and well. Perhaps some individuals have approached their local general practitioner to assess a small lump, with the thought of cancer as a horrifying possibility at the very back of their mind. They will become unwell, whether from the tumour or the treatment, and their life may thus be threatened. I could at least hope for improvement, if things went well.

Let the battle begin. The clichéd description of a battle may wrongly give the impression that a patient's prospects of survival may be influenced by their actions. Sadly, I'm sure there are instances where there is as much likelihood of changing the ultimate outcome as there is battling an on-coming train. The professional advice comfortingly suggested that my prospects of survival were quite good. As the surgeon listed the risks, I felt that my age and general health would give me a head start in the survival stakes.

Even before any pathology, the tumour was diagnosed as almost certainly malignant. Its size and location gave away its deadly nature. The tumour was large, located in the upper right area of the transverse colon and had breached the wall of the colon into the duodenum. While still groggy from the colonoscopy sedative, the information being conveyed did not have the impact on me that others frequently describe. There were no emotional outbursts or feelings of impending doom. Step one in the journey was clear: just do what would be necessary to get better and continue. That meant surgery.

It had taken weeks to progress from my doctor's comforting suggestions of minor bowel problems. In reality, that delay could have been avoided. At 33 years of age, I was on the radar of those specialists researching families with unusually high rates of bowel and other cancers. It was the early nineties and the research was embryonic, but I had been warned. Even then, testing by way of colonoscopy was recommended for at-risk family members over 30. At some future point, I imagined I would start the screening program. Why rush, when I was relatively young, healthy and feeling bulletproof?

The faulty mismatch repair gene is genetically inherited from my mother's side of the family. Not only was I unaware that I had inherited the gene, but that my mother would succumb to colorectal cancer almost 10 years later. I can reflect now on the concept of a battle and be comforted by the knowledge that there can be benefits and successes, even during an ultimately futile campaign.

I really don't know if I made a conscious decision to plan my approach to a cancer diagnosis. Perhaps I made a decision to really avoid making a decision, just to continue on with as minimal disruption as possible. Have the surgery, discuss the need for chemotherapy, get back to work, go to cricket training. Simple approach. That might be achievable if there were others to absorb and work the details. Like the sportsman who thinks he need only be left alone to perform, the work done by others is easily forgotten, allowing the player his room to perform. Everyone has an important job to do.

When the mind is emotional and scrambled, the details conveyed by specialists, surgeons and others are easily confused or forgotten. The presence of a partner in all these consultations is more than just emotionally supportive. Preferably, bring at least one clear thinking and inquisitive brain to all consultations. In that regard, I was extremely fortunate. Not only was the advice able to be analysed, but the entire journey was observed and recorded. This proved enormously valuable as the process developed. As incidents occurred later, I had the recorded memories and resources to which I could refer.

That same brain came with a heart and soul that carried me through the early days, handling all the communication with friends and family when my only focus was to survive. The decision to go public and to select a comfortable level of detail apparently causes difficulty for many patients. For me, there was never any thought to do other than issue detailed medical updates to family and friends and work colleagues. In the era prior to social media, this required bulletins for work noticeboards and frequent phone calls.

The response to these bulletins was intriguing. Not surprisingly, those with frequent and open contact can approach discussions with ease. Their questions and enquiries are without embarrassment and discomfort and the details can be discussed. For example, in a shared dressing room, discussing reactions to surgery and chemotherapy can be frank and a bountiful source of humour. By knowing how different people have varying levels of comfort in their enquiries, an environment of ease can be created.

After diagnosis, patients have expressed a temptation to make impulsive decisions. Having said that, I just wanted to continue my life unchanged, but there were nevertheless occasions when my thoughts turned to seemingly urgent matters. Fortunately, I was surrounded by family and work colleagues who rejected such ill-considered thoughts as: "Do I check my superannuation arrangements and resign from work immediately?" In recent years, Cancer Council Victoria has created two comprehensive information booklets for people who have finished active treatment for cancer. They are *Living Well After Cancer* and *Loss and Grief*.

## Surgery and chemotherapy

My surgery would be urgent and radical. My plumbing through the stomach, duodenum, small and large bowels would be irreversibly altered and would become idiosyncratic. There should however, be an immediate improvement. The pain, discomfort and cramps should disappear with the tumour. But even if successful, it would bring on inconveniences and represent only the first step in the overall plan for recovery. The surgery was successful and the pathology indicated that the cancer had not spread to the lymph nodes. It was only then that the specialists confided their surprise at the containment of the cancer, given its apparent aggression.

Chemotherapy started with several consecutive days of treatment, followed by a break, before commencing the weekly sessions. The plan was to have weekly chemotherapy on Mondays, so as to feel well enough to play cricket by Saturday. I could sit behind a desk and tackle the requirements of the rest of the week, although my contribution to my employer and the economy may have been minimal on some days.

Attending chemotherapy sessions was not accompanied by the dread that many would expect. The group of about a dozen patients was cheerful and chatty as they sat around attached to their intravenous drips. Nurses who administered the treatment helped to create a positive mood. Sadly, the reality of the situation was brought home when some patients stopped attending and there was the obvious apprehension associated with making enquiries about their fate.

The combination of post surgery factors and chemotherapy implications took a while to grasp. While some general advice about coping with chemotherapy was useful, it was the personal discoveries that really worked. Chemotherapy left me with difficulty overcoming a chemical taste and smell that would take days to disappear. It wasn't in the instruction manual, but a session of massage and

aromatherapy succeeded in overcoming that taste and smell. However, the unfortunate consequence is that the scent of lemongrass, used in those massage treatments, is now forever associated in my mind with feelings of nausea and discomfort. I am reminded of the possibly true story of a patient, who years after receiving chemotherapy, was exposed to the same perfume as that worn by a nurse during her treatment, who unexpectedly vomited in the cosmetics section of a department store.

The drugs caused dryness and cracking of my skin, especially on my hands. Going to bed wearing rubber gloves over my hands smothered with moisturiser was not some strange predilection, but a worthwhile adjuvant treatment. It was an unexpectedly pleasant surprise that my hair did not noticeably thin during treatment.

Eating became problematic. I became fussier than a delicate child and took on passions and fetishes for food usually associated with pregnant women. For me, it meant that Japanese food was compulsory on Mondays. Alcohol became less appealing. Beer and wine were only manageable for social purposes and it often felt that they were only imbibed through social habit, not desire. My bodily reactions suggested that fish and vegetables have a well deserved reputation for promoting health. At one time, I couldn't get enough fruit cake. At another, grapes became compulsory eating.

Irritability has also been known to occur with chemotherapy patients. My opinions became strongly held, extremely valid in my mind and forcefully presented. That hasn't changed, and I don't know whether that can be associated with treatment or just being a grumpy older man. My previous concerns about being a fence-sitter disappeared quickly.

Chemotherapy, particularly when used as a preventative measure, is speculative. The drugs I received at that time were professionally recommended, but not necessarily universally adopted. There was also much discretion in the prescribing of anti-nausea drugs in combination with the chemotherapy. It was therefore interesting to have two sessions of chemotherapy while travelling overseas. The abiding memory is of the cost of medical services in the United States. However, the exposure to a variety of anti-nausea drugs proved valuable and resulted in a change to my local treatment.

## Recovery and consequences

There is considerable research available on the psychological impact of suffering and recovering from cancer. Post-traumatic stress disorder has become a recognised affliction and I can identify aspects of that syndrome in my subsequent behavior. Alcoholism and depression are not a necessary consequence of cancer, but the possibility of suffering both appears to increase. To adopt a sporting metaphor, batsmen respond differently after a dropped catch gives them another opportunity. Some take extra caution to ensure the most of the opportunity, while others engage in riskier shotmaking. I will admit to a few agricultural shots as my innings continues.

Jefford reviews the evidence which supports the view that psychosocial support results in broad benefits for patients.

From a clinical viewpoint, the challenge is to identify those at risk and with unmet needs.<sup>1</sup> Supportive care is widely available and the various bodies have significantly extended the promotion and availability of their services inside and outside the clinical setting.

People ask whether I need to be careful with my diet. The answer is that from a health perspective, my requirements are no different from anybody else. However, a really exciting and useful by-product of my bowel surgery, is that my body immediately registers the quality and nutritional value of food I eat. Within minutes, I will feel genuinely nauseous after eating highly fatty or processed food. Vanilla slices may win awards, and at times, they can't be resisted, but their impact is diabolical. My body's responses have enabled me to prepare a league table of food quality. It has become clear to me that the products of a particularly well known hamburger chain should not be eaten and that a well known pastry manufacturer's party products should not be eaten at the conclusion of cricket committee meetings.

In the immediate post surgery period, there are extremely vivid memories. Travels and events are remembered because of the inconveniences that arose. With only minimal large bowel remaining, I have a need to do about five times a day what others accept as a daily ritual. During chemotherapy, I had to carefully plan when and what I would eat prior to a boat trip on a Louisiana bayou. Even golf and walks on the beach took some planning. Sad as it may be, my memory of Rottneest Island in the weeks after initial chemotherapy, revolve around discretely vomiting. Similarly, I became well acquainted with the bathroom of a famous New Orleans restaurant after foolishly attacking the local oyster shooters.

As time has moved on, my bodily functions have fortunately become more predictable. I am grateful for the enormous improvement in public facilities over the last 20 years. The French have, if it can be said, taken leaps and bounds in this regard.

As a genetic victim, are there any other matters which arise? Being a statistic and research model has its advantages. It is comforting to receive individual treatment. However, requests posed to me for assistance with research usually involve frequent blood tests. The increasing privacy requirements make the sharing of information between interested parties more difficult to arrange. This has its frustrations. After a year of chemotherapy, my veins may not cooperate and it can be a test of nursing staffs' abilities to extract blood samples.

Our health system does not provide an obvious integrated model for a patient's overall care. Each type of need can be met by accessing the appropriate provider, but it can be difficult to co-ordinate an overall plan. The earlier comments about needing a supportive, clear thinking

and well-organised companion are particularly true in this context. Reconciling the sometimes conflicting views, and avoiding falling into any cracks in care, takes considerable concentration. It is not part of a patient's typical care plan to arrange a meeting between the colorectal specialist, the surgeon, the dietician, the oncologist and the physiotherapist. There are times when such a meeting could be valuable.

My good fortune was to be recommended to a team of specialists and surgeons in which I could have total faith. In addition, their age at the time and their ongoing involvement has provided a continuity of care. Being able to access immediate advice is comforting and has proved valuable on numerous occasions.

A real risk arising from abdominal surgery, is the threat of adhesions. Within six months of the initial surgery, I experienced the first enormously painful blockage, which rectified itself overnight with the assistance of morphine. However, they became more frequent and worrying. The diagnosis was uncertain without further investigative surgery. Typically the dozens of attacks would come at the most inconvenient times and require a dash to emergency and an overnight hospital stay. The first surgical treatment was a scheduled event, but the two subsequent procedures within the next two years, were unplanned. Something worked and there have been no blockages since 1995. But all that surgery must have had some physical impact. Some years later, my duodenum, for unexplained reasons, perforated and required another unexpected, middle of the night callout for my surgeon.

Screening is still an annual event, but, with only minimal large bowel, I am absolved from the discomfort of taking the widely despised bowel preparations. As well, the improvements in anaesthetics are a boon. At a recent colonoscopy, or more accurately, a flexible sigmoidoscopy, I enquired if such a relaxing anaesthetic was broadly available for recreational purposes. Apparently, it was the same type used frequently and understandably, but not successfully, by Michael Jackson.

After 20 years of observing my reactions to events, I should know the triggers for depressive behaviour. While compiling these reflections, I am aware of signs which should be recognised. They include survivor guilt about inadequately showing gratitude for the assistance of family, friends, work colleagues and cricket mates, and pressures and consequences of not maximising opportunities. This coincided with the date of my late mother's birthday and while anticipating a weekend interstate trip.

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# PALLIATIVE CARE AND COLORECTAL CANCER

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## Abstract

Recent advances in anti-cancer treatment have seen improvements in survival for patients with metastatic colorectal cancer. Increasingly, patients with advanced disease are living longer, sometimes with significant morbidity related to the disease or its treatment. Integration of palliative care in the management of patients with advanced malignancy improves symptom control and quality of life for patients and their families. This article reviews the role of palliative care and provides an overview of current management for commonly experienced symptoms in patients with colorectal cancer.

Palliative care is defined by the World Health Organisation (WHO) as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”.<sup>1</sup> Palliative care encompasses symptom control and the provision of practical support across physical and psychosocial domains for patients and their carers, from first referral through terminal care and into bereavement.<sup>1</sup>

There is increasing recognition of the benefits of early integration of specialist palliative care can have for patients, particularly when provided concurrently with anti-cancer therapy.<sup>2</sup> A landmark study published in 2010 demonstrated a range of benefits to patients with newly diagnosed stage IV non-small cell lung cancer.<sup>3</sup> This study randomised patients at the time of diagnosis to early palliative care intervention with standard oncologic care or standard oncologic care alone. As expected, early palliative care involvement resulted in objective improvements in quality of life, symptom management and a reduction in ‘aggressive therapies’ at end of life. More surprisingly, patients in the early palliative care intervention arm had an increased median survival of 2.7 months compared to those who received standard oncologic care alone.<sup>3</sup> The basis for this observed improvement in survival is the subject of ongoing discussion and research.<sup>4</sup> With randomly allocated and evenly matched intervention groups for performance status, age, gender and disease stage, the survival benefit has been attributed to improvements in symptom control, quality of life and mood. This is supported by evidence of an association between increased symptoms, in particular dyspnoea and drowsiness, and shorter survival in cancer patients.<sup>5</sup>

The benefits of palliative care involvement on quality of life for cancer patients and their families have been demonstrated in two recent systematic reviews.<sup>6,2</sup> Notwithstanding the methodological challenges related to research in this population, improvements were reported across a number of outcome measures including quality of life, patient satisfaction and end of life care.<sup>6,2</sup> These results have been

replicated across different palliative care settings, including hospital based consultation teams, community services and specialist inpatient units.<sup>6</sup>

## Palliative care and colorectal cancer

Despite improvements in survival, colorectal cancer (CRC) is the second most common cause of cancer death in Australia.<sup>7</sup> The prognosis for patients with advanced disease remains poor, with a five-year survival of 59% for stage III and 8% for stage IV disease.<sup>8</sup> Both Australian and international data show patients with metastatic CRC experience significant symptoms throughout the course of their disease.<sup>9,10,11</sup> Pain has been reported by up to 50% of patients,<sup>11</sup> with other common symptoms including nausea, vomiting, bowel dysfunction and anorexia.<sup>9,11</sup>

## Symptom management

### Pain

Pain is a common complication of advanced cancer and is prevalent in all stages of disease.<sup>12</sup> Uncontrolled pain is a source of significant distress, morbidity and disability for patients with cancer. Despite evidence-based pain management guidelines, there is significant variation in pain treatment, with inadequate pain control reported in over 80% of patients in some series.<sup>12,13,14</sup> Effective management of cancer pain requires a holistic, multimodal and mechanism-based approach, regardless of disease stage.<sup>13,15</sup> Multidisciplinary assessment is required to guide therapies such as radiotherapy and chemotherapy for the management of pain, and psychosocial supportive therapies are important to address concurrent sequelae of cancer pain.

There is strong evidence to support the effective and safe use of opioids in the management of cancer pain.<sup>16</sup> More specific to CRC, they may be particularly efficacious in visceral type pain. Oral morphine, oxycodone and hydromorphone all have similar efficacy and toxicity in opioid-naïve patients.<sup>17</sup> Recent guidelines from the European Association for Palliative Care suggest that any of these opioids can be used as first line for the management of cancer pain.<sup>18</sup> Prescription of ‘around the clock’ coverage

with long-acting opioids, plus access to doses of immediate release 'breakthrough' analgesia, remains best practice for moderate to severe cancer pain.<sup>13</sup> Doses should be carefully titrated according to individual pain requirements and response.<sup>12</sup> Pre-emptive use of immediate release opioids should be considered for predictable episodes of breakthrough pain.<sup>18</sup> In patients with co-morbid renal impairment, opioids should be used with caution and at reduced dose or frequency,<sup>12</sup> with buprenorphine, fentanyl and methadone being safer alternatives, due to inactive metabolites and reduced adverse effects in significant renal impairment.<sup>12</sup> However, transdermal patches (fentanyl and buprenorphine) are best used in patients with stable opioid requirements, and methadone has wide variability in individual dosing and duration of action, with guidelines recommending its use only by experienced clinicians.<sup>12</sup>

Neuropathic pain may occur in patients with CRC as a consequence of disease or its treatment. Recent evidence-based guidelines recommend two classes of medications for use as first-line adjuvants in the management of neuropathic pain: antidepressants (including tricyclics, venlafaxine and duloxetine); and anticonvulsants (including pregabalin and gabapentin).<sup>12,19,20</sup> Opioids are effective in the management of neuropathic pain and are recommended in conjunction with adjuvant medications.<sup>13,19</sup> Bisphosphonates are an effective adjunct in the management of malignant bone pain in addition to radiotherapy.<sup>12</sup> Non-steroidal anti-inflammatory drugs may also be useful adjuvants, particularly in somatic-type pain, but can be associated with significant adverse effects.<sup>12</sup>

### **Nausea**

Nausea is a common symptom in patients with advanced CRC.<sup>11</sup> The causes of nausea and vomiting are often multifactorial, including metabolic disturbance, partial or complete mechanical obstruction and iatrogenic causes. Aside from in post-chemotherapy or post-operative settings, there is limited high-level evidence to guide the management of nausea and vomiting in patients with advanced disease. Consideration should be given to the treatment (where appropriate) of reversible contributing factors such as hypercalcaemia, infection and known emetogenic medications.

Traditionally, decisions around antiemetic therapy have been mechanistically based, with management targeted at the proposed neurotransmitter pathways involved. However, the lack of strong evidence supporting this approach means that in practice, antiemetic choices are often derived from expert opinion or clinician familiarity.<sup>21</sup> A recent systematic review concluded there was no evidence to favour either a mechanistic or empirical approach to the management of nausea in advanced cancer.<sup>21</sup> Further studies, including a randomised phase III multicentre Australian study, are underway to better guide therapy for this common symptom.<sup>21, 22</sup>

A systematic review of antiemetics in advanced cancer found that metoclopramide had the greatest evidence to support its use.<sup>21</sup> There was some evidence supporting serotonin (5HT<sub>3</sub>) antagonists, although they can be associated with worsening constipation.<sup>21</sup> The butyrophenone anti-psychotic haloperidol is commonly

prescribed for nausea in palliative care practice, however support for its efficacy as an anti-emetic is based on uncontrolled studies and expert opinion.<sup>22,23</sup> Similarly, other antiemetics including corticosteroids, cyclizine and levomepromazine, which are often utilised as second-line agents, have only low-level evidence supporting their use.

### **Bowel obstruction**

The development of malignant bowel obstruction is frequently associated with distressing symptoms, including pain and intractable nausea and vomiting.<sup>24</sup> While malignant bowel obstruction may occur at any time in the disease process, risk increases in the advanced stages with reported rates of 4% to 24% for CRC.<sup>24, 28</sup>

Surgical options to relieve malignant bowel obstruction in advanced cancer can be limited due to poor performance status or multilevel obstruction.<sup>24</sup> Less invasive endoscopic stenting can be an option for selected patients with good results for symptomatic control described in the literature.<sup>25</sup> Venting percutaneous endoscopic gastrostomy can be used to reduce vomiting in patients for whom other surgical procedures are not appropriate.<sup>24</sup>

For many patients, invasive treatments are not appropriate and therefore medical management remains the mainstay of treatment. Medical management of malignant bowel obstruction by specialist palliative care utilises a combination of medications aimed at relieving symptoms and aiding resolution of the obstruction. These can include analgesics, corticosteroids, antisecretory agents (hyoscine, glycopyrrolate, ranitidine and octreotide) and antiemetics.<sup>24,26</sup> A Cochrane review from 1999 concluded that the use of parenteral corticosteroids may facilitate the resolution of malignant bowel obstruction,<sup>27</sup> although concerns have been raised about methodological flaws in studies addressing this question.<sup>28</sup> Postulated mechanisms for this effect include direct anti-inflammatory activity and a reduction in malignant peri-tumoural oedema.<sup>27</sup> A systematic review comparing ranitidine with proton pump inhibitors suggested that ranitidine is a more effective agent for reducing the volume of secretions and may therefore be valuable as an antisecretory agent in malignant bowel obstruction.<sup>29</sup>

Octreotide, a somatostatin analogue, has been used in malignant bowel obstruction to reduce gastric secretions and minimise symptoms, although evidence supporting its use is mixed. A systematic review from 2007 reported that octreotide was more effective at relieving symptoms of inoperable bowel obstruction than the antisecretive hyoscine butylbromide, although patient numbers were relatively small in the included studies.<sup>28</sup> However, recently concluded, yet to be published Australian multicentre randomised trial, did not demonstrate significant benefit for octreotide in either reducing malignant bowel obstruction associated vomiting or pain and nausea scores.<sup>30</sup>

### **Constipation**

Constipation has been defined as "the passage of small, hard faeces infrequently and with difficulty".<sup>31</sup> Chronic constipation is the commonest side-effect of opioids, and occurs in 40-70% of patients treated for cancer pain with oral morphine.<sup>32</sup> Additionally, there are multiple other highly

prevalent causes of constipation in this patient population, including other medications, metabolic abnormalities (e.g. hypercalcaemia, uraemia), decreased mobility, neurological disorder/damage, autonomic neuropathy, altered dietary intake and depression.<sup>31,33</sup>

Despite the prevalence of constipation in palliative care patients, it is underdiagnosed and undertreated.<sup>34</sup> Reports suggest that up to 70% of patients with advanced cancer treated with laxatives continue to experience symptomatic constipation.<sup>35</sup> Examination of the patient should include a focused rectal examination to assess faecal impaction and pelvic floor.<sup>34</sup> Recent evidence suggests that plain abdominal x-rays, while frequently ordered in the investigation of constipation, correlate poorly with colonic transit time, faecal loading and symptoms of constipation, highlighting the importance of thorough clinical assessment.<sup>34,36</sup>

While laxatives remain the mainstay of management, consideration must be given to modifying any contributing factors.<sup>31</sup> There is no strong evidence to support the choice of a specific laxative, however guidelines suggest using a combination of stimulant and softening agents.<sup>31</sup> Peripheral opioid receptor antagonists as separate therapy (e.g. methylnaltrexone) have been shown to be effective for refractory opioid induced constipation, although their use is not recommended in patients with bowel pathology.<sup>37</sup> Combination opioid plus naloxone formulations have been reported to reduce opioid induced constipation without impacting on analgesia or precipitating withdrawal.<sup>38</sup> These medications however, are contraindicated in liver dysfunction and inappropriate for patients with high opioid requirements and therefore their use in patients with advanced CRC may be limited.

### Psychosocial care and bereavement

Patients with life limiting illness face many psychological challenges: grief about current or anticipated losses; fear and uncertainty about the future; regrets from their past; existential or spiritual issues and concerns about loved ones. Each person brings with them a unique burden of social and psychological vulnerabilities, balanced by their individual coping resources.<sup>39</sup> Whether the patient with cancer has support or feels supported are major factors in how they manage socially, spiritually, physically and emotionally.<sup>40</sup> Health professionals, particularly physicians, are perceived as important sources of support for patients and their families in time of serious illness.<sup>41</sup>

Depression and other psychiatric disorders have a significant impact on the ability of patients to negotiate the challenges of life-limiting illness and are associated with significant suffering for patients and families.<sup>42</sup> Depression leads to reduced quality of life, prolonged hospitalisation and causes significant distress for patients, caregivers and families.<sup>42</sup> Identification of depression in palliative care patients is challenging, due to confounding effects of advancing disease.<sup>42</sup> Approach to treatment should include good symptom management, fostering of social connections and relationships, pastoral and spiritual care.<sup>43</sup> Choice of treatment modality must take patient function and prognosis into consideration. A recent Cochrane review demonstrated the effectiveness of psychotherapy

in patients with incurable cancer, although onset of therapeutic effect can take up to six weeks and requires intensive patient participation.<sup>44</sup>

Effectiveness of antidepressants in the treatment of depression in palliative care is widely agreed throughout the literature, however there are few controlled or comparative studies.<sup>42</sup> Choice of pharmacotherapy must take into account patient factors such as prognosis, renal function, previous antidepressant history and comorbidities.<sup>42</sup> Clinical guidelines based on current evidence recommend the use of selective serotonin reuptake inhibitors or mirtazapine as first line pharmacotherapy for depression in palliative care patients.<sup>42</sup> In selected patients where prognosis is very limited (less than four weeks), a trial of psychostimulant medication may be appropriate.<sup>45</sup>

Grief and bereavement is a normal response to the death of a loved one. Each loss is a unique experience with the requirement for bereavement support depending on resilience and the diverse needs of each person affected.<sup>46</sup> Complicated grief is defined as a grief response that is severe and/or prolonged and is associated with a range of negative social, psychological and physical outcomes for bereaved carers, including increased morbidity and mortality.<sup>47</sup> While evidence suggests that provision of bereavement counselling to resilient individuals is not beneficial and may actually be harmful, the literature consistently demonstrates benefit to those experiencing or at risk of complicated grief.<sup>46</sup> Clinical practice guidelines suggest that all cancer services should screen carers for the risk of complicated grief, which includes factors such as limited social support networks, symptoms experienced and timing and location of death.<sup>48,49</sup>

### Conclusion

Early integration of palliative care is increasingly recognised as an effective component of multidisciplinary cancer care. Despite this, there is little specific reference to palliative care in many of the international colorectal practice guidelines. The European Society for Medical Oncology clinical practice guidelines for patients with metastatic CRC, for example, while emphasising that optimal treatment should be discussed in a multi-disciplinary setting and that care should be seen as a continuum determined by appropriate goals of care, does not mention palliative care.<sup>50</sup> In Australia, the 2005 National Health and Medical Research Council colorectal cancer clinical practice guidelines makes only brief reference to the benefit of palliative care in the management of advanced disease.<sup>51</sup> Given the symptom burden associated with advanced colorectal disease, the ongoing expansion of clinical trials designed to optimise approaches to symptom management and the increasing evidence base supporting an integrative approach between oncology and palliative care, this situation will hopefully change in coming years and palliative care will become a more prominent feature of future clinical guidelines for colorectal and other cancers.

Table 1: Recommendations

Guideline – Palliative Care should be integrated early following diagnosis of advanced disease, even in the absence of physical symptoms.	Level of Evidence	Practice recommendation	Refs
Palliative care interventions should be introduced early as a component of care as they can improve the quality of life of patients with cancer.	II	Recommend	2, 4, 5
Guideline – Patients with colorectal cancer should be assessed regularly and routinely for pain and other symptoms.	Level of Evidence	Practice recommendation	Refs
Symptoms in advanced colorectal cancer are common and can usually be effectively managed.	I	Strongly recommend	9, 10, 12
Guideline – Psychosocial interventions including bereavement support are important.	Level of Evidence	Practice recommendation	Refs
Psychosocial care can improve the quality of life for patients, and bereavement support for those with complicated grief improves outcomes.	III	Recommend	39, 41, 44, 49

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# AWARDS

## TOM REEVE AWARD FOR OUTSTANDING CONTRIBUTIONS TO CANCER CARE

The Tom Reeve Award for Outstanding Contributions to Cancer Care, offered annually by the Clinical Oncology Society of Australia, formally recognises a national leader who has made a significant contribution to cancer care.

Since its inception in 2005, where the inaugural award was presented to Professor Tom Reeve himself, there have been eight recipients of this prestigious award. In 2013, the winner of the Tom Reeve Award was Professor Ian Frazer AC. Best known for his work on the HPV vaccine, Professor Frazer is currently CEO and Director of Research at the Translational Research Institute, Queensland (and a good friend of COSA).

Professor Frazer accepted the award and delivered his oration at the COSA Annual Scientific Meeting in Adelaide on 13 November 2013, where he spoke about some of the progress in cancer research over the last 40 years and offered some suggestions for the future.



It is a great honour to be asked to give an oration in the name of Professor Tom Reeve. Tom is one of those people who achieve great things quietly, and almost without recognition. His efforts over many years to catalyse the production and use of guidelines for management of patients with specific cancers will undoubtedly have saved many lives, and significant amounts of health dollar expenditure, to the great benefit of the Australian community. Continued effort at this sort of translational research, as highlighted in the McKeon Committee report last year, is one key to ensuring the best outcomes for patients through medical research.

It's fitting, when COSA is celebrating a 40th birthday, and its substantial contribution to cancer control over the last 40 years, to look at where COSA might expand its efforts

in cancer control in the future, now that it has reached maturity. I believe that societies, like people, should reinvent and repurpose themselves regularly, to maintain interest and momentum.

The McKeon committee's report to government on medical research in Australia touched on several themes, with the overarching aim of giving better outcomes for patients and the country through the re-embedding of health and medical research into health service delivery. While it's a long document, the summary is a useful starting place, and if even that's too much, there is a two page summary of the summary for those who live in the era of 140 character 'tweets'. The newspapers and electronic media tend to focus their reporting of medical research on 'breakthroughs'

# AWARDS

in the laboratory, with promises of better outcomes for patients in the future.

The McKeon committee recognised that basic research on the pathophysiology of disease is clearly the engine that drives medical progress. However, it commented on the need for more effort in translational research, an equally important component of medical research, and one that falls squarely within the remit of members of COSA, as it examines whether we are using best practice health care, and if not, why not. This area of research is not so sexy or newsworthy, but it does have the greatest potential for significant and immediate impact on health outcomes and health costs. I believe that we should each lobby strongly within our area of cancer related health care practice for funding for research on this topic, and we should use COSA as a vehicle to coordinate such efforts within the discipline of cancer care across the country.

Another area in which I believe that COSA can contribute usefully as a peak body in the clinical delivery of cancer services, is in supporting outreach activities in cancer control within our region. Australians are privileged to have access to cancer care which approaches world standard, albeit with some evident loopholes e.g. in delivery of an optimal bowel cancer screening program and in prompt access to some of the newer targeted cancer medications.

Further, we are world leading in many areas, being among the first, for example, to provide government funded

programs for vaccination against HPV associated cancers for both boys and girls. Within a short distance of Australia, however, there are many countries where access to cancer services is either limited or non-existent, and cancer deaths, particularly from breast and cervical cancer, are substantial contributors to mortality in most of these countries. COSA is already active to some extent in this area, but I think that we should take the opportunity to see if we can do better.

Where countries themselves seek advice, we can provide expert help through education and advice on establishing programs matched to the resources of the country. We can also help with training of staff, and with support for their ongoing professional development. My own involvement with the Vanuatu Government in establishing cervical cancer prevention programs there has shown the opportunities (and, I must admit, the challenges) of being involved. It's great fun to get involved, and I believe also that we have a moral responsibility to offer help where there is local interest. Further, engagement with limited resource countries also helps us to provide training and experience for our own professional colleagues.

I leave these thoughts with you for your consideration, and take the opportunity to wish COSA well for the next 40 years, and to thank the society for inviting me to give the 2013 Tom Reeve oration.

*Ian Frazer AC, Director, Translational Research Institute, Brisbane.*

*Searching for evidence-based information on cancer?*

## Cancer Guidelines Wiki

Web-based clinical practice guidelines - accessible  
**ANYWHERE, ANYTIME**

**Online, evidence-based recommendations for:**

- Lung cancer treatment
- Advanced prostate cancer
- Early stage endometrial cancer
- Nutritional management for head and neck cancer
- Approach to gastroenteropancreatic neuroendocrine tumours
- Psychosocial management of AYAs diagnosed with cancer
- Surveillance colonoscopy
- Sarcoma
- Cancer pain management
- Early detection of cancer in AYAs
- Fertility preservation for AYAs diagnosed with cancer

**with more guidelines regularly being added**



## AUSTRALIAN BEHAVIOURAL RESEARCH IN CANCER

### **Behavioural Research and Evaluation Unit (BREU) Cancer Council SA**

#### ***Feasibility of workplace physical activity programs***

Physical inactivity is related to the development of chronic diseases such as cardiovascular disease, diabetes and some cancers. However, by addressing insufficient physical activity through the promotion and support of health enhancing behaviours, many of these diseases can be prevented or delayed. We are currently undertaking a study looking at the feasibility of workplace physical activity programs.

Paid employment is now predominantly comprised of physically inactive and sedentary tasks, and along with other factors like long work hours and a reduction in the use of active transport, have all contributed to low levels of physical activity in the community. Workplace health promotion programs are an effective means of promoting regular physical activity, which benefits individuals, employers and the wider community. The workplace is a suitable setting to reach a large number of people from a variety of backgrounds to encourage and support the adoption of health enhancing behaviours. It is possible to modify health behaviours through multiple levels of influence.

There are a number of key factors contributing to the success of workplace physical activity initiatives. This study aims to further our understanding of employers' perspectives of workplace physical activity by identifying those organisational factors that are perceived as most critical to the success of workplace physical activity, and ultimately whether these factors are predictive of overall support for workplace physical activity.

#### ***Who smokes during pregnancy? Identifying high-risk subgroups among the Aboriginal and non-Aboriginal populations in South Australia***

The rate of smoking in pregnancy is disproportionately high among Aboriginal women. In collaboration with the Pregnancy Outcomes Unit (SA Health), we are working on a research project investigating the socio-demographic characteristics associated with smoking in pregnancy. The project aims to identify Aboriginal and non-Aboriginal women most at risk of smoking in pregnancy.

This study involved retrospective analysis of data collected for all births by midwives in South Australia from 2000 to 2010. Socio-demographic variables were entered into a multivariate logistic regression analysis to determine the factors which were significantly and independently associated with smoking in pregnancy for Aboriginal and non-Aboriginal women separately.

Antenatal care attendance is also a significant factor in the area of reproductive health. Our findings indicated that attendance was lower among women who smoked, compared to their non-smoking counterparts. Given this finding, and the potential to improve antenatal care attendance, the data are being explored to identify socio-

demographic characteristics associated with lower antenatal care among smokers.

The broader aims of the research are to help identify interventions specifically for: (i) reducing smoking during pregnancy among Aboriginal women; and (ii) increasing smokers' participation in antenatal care.

### **Centre for Behavioural Research in Cancer (CBRC), Victoria**

#### ***Television advertising to promote NHMRC guidelines for low risk alcohol consumption: experimental study***

In 2009, the National Health and Medical Research Council (NHMRC) released guidelines advising that Australian adults should limit consumption to two standard drinks per day to reduce the risk of lifetime harm, and four standard drinks on any single occasion to avoid short-term harm. However, given the absence of government investment in a large scale communication strategy to promote these guidelines, it is unsurprising that the majority of adults either do not know or overestimate the safe levels of alcohol consumption.

Supported by an NHMRC project grant, our study will experimentally assess the impact of television advertising that promotes the guidelines for low risk drinking on adults' estimates of drinking levels associated with a higher risk of short-term and long-term harm.

A set of potential tagline messages to communicate the drinking guidelines will initially be assessed using friendship pair qualitative interviews. The strongest taglines will then be edited on to the end-frame of up to 16 existing alcohol harm prevention television ads deemed appropriate for the Australian context.

An online pre-testing study will be conducted to identify the top four performing short-term and long-term harm ads respectively (i.e. eight ads in total) for inclusion in the experimental study. The experiment will use a naturalistic advertising viewing situation, incorporating both implicit and explicit post-viewing measures of advertising effects, as well as a one-week follow-up interview.

Findings from this research will identify how the NHMRC guidelines might best be promoted via mass media campaigns to positively influence perceptions of alcohol-related harm and drinking norms in the whole population.

#### ***ShadePlus: a built environment intervention to improve park usage in disadvantaged neighbourhoods***

There is a paucity of research on the health outcomes of changes to the built environment. With the support of a three-year NHMRC partnership grant, we will conduct a natural experiment assessing the impact of the ShadePlus intervention on health behaviours and its acceptability to local residents.

ShadePlus involves the installation of built shade, walking paths, quality playground equipment and other



features in degraded community parks in disadvantaged neighbourhoods. This project partners with Brimbank City Council, who will develop, implement and fund the park improvements. Outcomes will be assessed at three parks selected for the improvements and at three other geographically separate control parks (matched on size and suburb features).

The study methods include a pre-test and post-test assessment of a broad range of health-related and behavioural measures of local residents recruited via letter-box surveys, and observations and intercept surveys of park goers in spring and summer months. At the end of the study, residents living close by the intervention parks will be invited to participate in focus group discussions about their use of the newly developed park facilities. This study will provide unique and significant data assessing the potential of park renewal interventions to promote park usage, physical activity, sun protection behaviours and mental well-being in a low SES population.

## **Newcastle Cancer Control Collaborative (New-3C), NSW**

### **Advance care planning**

Patients' preferences in relation to end of life care are the 'gold standard' and should determine the care patients receive. However, patient preferences may not be clearly communicated. Often, providers will rely on their personal views, or surrogates' perceptions as representative of patient preferences. The usefulness of these views is dependent on their agreement with the patient's actual preference.

With funding from NHMRC and in partnership with Cancer Council NSW, we are undertaking a study to examine whether the preferences of cancer patients can be reliably predicted by cancer care providers and surrogate decision makers.

Three end-of-life care options will be described in video format to participants, including: 1) comfort care (maximising comfort and relieving pain and suffering); 2) life-prolonging care (doctors doing all they can to maintain life); and 3) provider decides on patient's behalf (doctor determines what they consider to be appropriate care). Patients will then be presented with hypothetical clinical vignettes and asked to indicate the type of end of life care they would choose in relation to each vignette. Vignettes will vary by anticipated benefits to survival and quality of life, and treatment burden.

Providers and surrogates will be presented with the same vignettes and asked to answer survey questions from the patient's perspective (what they think the patient would prefer). Patients and surrogates will complete the survey three months later to examine changes over time. An economic analysis will explore the costs of health resources required for different end of life care pathways.

### **Online and phone assistance for lung cancer**

Lung cancer patients can experience poorer prognosis and more pronounced psychosocial distress than patients with other major cancers. An accessible and sustainable source of personalised support for cancer patients is Cancer Council Helpline, which provides telephone-based information and

support from an oncology nurse consultant.

Lung cancer patients are under-represented among Helpline users and less than one-third report being aware of its services. Three key issues have emerged for the Helpline model: 1) how to engage patients who may benefit from the service; 2) whether the model of low intensity information and support can improve relevant psychosocial outcomes; and 3) whether on-line modes of support are acceptable to and beneficial for patients.

With funding from NHMRC and in partnership with Cancer Council NSW, the proposed trial will address these issues via patients newly diagnosed with lung cancer and attending an appointment with thoracic and respiratory physicians recruited via the Australian Lung Foundation.

The patient-randomised control trial will compare the relative effectiveness of: 1) a printed *Understanding Lung Cancer* information booklet; 2) proactive telephone-delivered support and information from a trained oncology nurse consultant; and 3) proactive online delivered (email and live chat) support and information from a trained oncology nurse consultant.

Six-month follow-up assessments of general wellbeing and self-efficacy in managing health will provide robust evidence of whether the Helpline model of information and support improves wellbeing, and whether an electronic approach can provide equivalent outcomes to a telephone-based approach. These results will have relevance for decisions about how community-based information and support is provided.

## **Cancer Council Queensland Viertel Centre for Research in Cancer Control (VCRCC)**

### **Accessing supportive care through the internet for people with cancer**

Approximately 35% of people diagnosed with cancer will experience persistent psychological distress and unmet psychological supportive care needs. Some of the barriers to receiving adequate psychological care include a lack of available or easily accessed services and geographical barriers.

The internet is a unique way to deliver psychological care that has the potential to overcome these barriers. The CancerCope project, led by Cancer Council Queensland and Griffith University, has been funded through a National Health and Medical Research Council Partnership Grant.

This two-phased study will adapt an existing manualised tele-based and evidence-based cognitive behavioural intervention to a web-based environment. Semi-structured interviews will be used to: improve our understanding of the nature of the intervention; assess specific components/tools delivered and the mechanisms of change; and provide an in-depth analysis of patients' responses to the intervention.

The randomised control trial will involve 490 newly diagnosed colorectal and melanoma patients, recruited through the Queensland Cancer Registry, and will compare a static patient education website with the individualised, interactive, internet-based psychology intervention – CancerCope. This research will provide recommendations on the effectiveness

of Internet based psychology interventions to improve the mental health of people with cancer by reducing cancer related distress and improve quality of life.

## **A randomised control trial of a mindfulness intervention for men with advanced prostate cancer**

Men with advanced prostate cancer report higher levels of psychological distress, poorer quality of life, and have an increased risk of suicide compared to men with localised disease. The Living Well with Prostate Cancer Study, with funding from the National Health and Medical Research Council, is trialling a mindfulness-based cognitive therapy (MBCT) group intervention to improve psychological well-being in men with advanced prostate cancer.

In collaboration with the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group and Griffith University, we will compare patient education with the tele-based MBCT group intervention.

The MBCT intervention involves eight weekly group

mindfulness sessions conducted over the telephone with up to seven men, facilitated by a health professional with experience in oncology and professional training in MBCT. Participants are encouraged to participate in daily home practice of mindfulness meditation. Patient education includes standard medical management and existing evidence-based patient education materials.

A sample of 190 men diagnosed with advanced prostate cancer is being recruited through clinicians in the ANZUP Cancer Trials Group and in major treatment centres in Queensland, New South Wales, Victoria and Western Australia. Participants will be assessed at baseline, three, six and nine months post-recruitment and intervention commencement, to examine anxiety, depression, cancer-specific distress and quality of life.

To date, over 110 participants are enrolled in the study. Outcomes from the study will help to identify an effective way to reduce psychological distress, and improve quality of life for men with advanced prostate cancer.

## CANCER COUNCIL AUSTRALIA

### **Cancer Council and eftpos launch new initiative to help protect students' skin**

Cancer Council has been selected alongside Diabetes Australia to be a recipient of eftpos' Giveback campaign for 2013, with a \$1 million donation to Cancer Council's Sunshade for Secondary Schools initiative.

Secondary schools around Australia have been invited to submit an application to Cancer Council for a shade grant of up to \$25,000. The grant will allow the selected schools to purchase permanent or temporary shade for their school.

The grants will be divided proportionally across the nation based on state and territory school populations.

### **Sporting venues rival beaches as sunburn hotspots**

Australians are at the same risk of being sunburnt at sporting venues as they are at the beach, according to Cancer Council research.

The findings from Cancer Council's National Sun Protection Survey, show sporting venues are clearly linked with sun damage, with 22 per cent of Australians at sports grounds and centres getting sunburnt – the same percentage of Australians at the beach, local lake or river who got sunburnt.

Cancer Council released the findings during National Skin Cancer Action Week (17-23 November) as a reminder to Australians to protect themselves outdoors, as well as monitor their skin for changes so cancers are picked up early.

Chair of Cancer Council Australia's Skin Cancer Committee, Louise Baldwin, said over the next three years, 44,000 Australians would be told they had the deadliest form of skin cancer, melanoma. Almost two in three would be men.

"Cancer Council is reminding Australians that the 'slip, slop, slap, seek and slide' message doesn't just apply at the beach," Ms Baldwin said.

### **New online asbestos course for DIY renovators**

Cancer Council Australia and the Department of Health in Western Australia have released a free online course aimed at helping home renovators identify and safely handle asbestos.

The course was developed in the face of growing concern about a 'third wave' of people contracting the deadly disease, mesothelioma, from exposure to asbestos while doing their own renovations.

Chair of Cancer Council Australia's Occupational and Environmental Cancer Risk Committee, Terry Slevin, said short-term or low-level exposure to asbestos from people doing home renovations could prove as big a threat as the death toll from asbestos mining.

"We're sadly all too aware of the thousands of tragic deaths of asbestos mine workers from mesothelioma, as well as those who worked with asbestos-containing materials such as builders, electricians and plumbers," Mr Slevin said.

"But with the burgeoning interest in DIY home renovation, we're now facing a third wave of people being diagnosed with mesothelioma. It's largely due to ignorance - people aren't sure how to handle asbestos, or even recognise asbestos in their homes."

The course, 'kNOw asbestos in your home', has been designed to give the DIY renovator basic knowledge about asbestos, and the risks and safe practices when working with or removing, small amounts of asbestos-containing material.

Mr Slevin said the course was easy to access and complete online. "It's a great way for DIYers to educate themselves and ensure they know what they are doing when embarking

on any renovation job around the house, big or small," he said.

## CLINICAL GUIDELINES NETWORK

### ***Clinical practice guidelines for the management of adult onset sarcoma***

These guidelines were launched by Cancer Council Australia and the Australasian Sarcoma Study Group at the ASSG Research Meeting in November 2013.

The guidelines are designed to be used as a resource for the sarcoma community, both clinicians and consumers, and to help to assist in identifying priority research areas. Paediatric and gynaecological topics will be added to future iterations.

### ***Algorithms for colonoscopic surveillance intervals in adenoma follow-up; following curative resection of colorectal cancer; and for colorectal cancer screening (family history)***

Algorithms based on the *Clinical practice guidelines for surveillance colonoscopy* and the *Clinical practice guidelines for the prevention, early detection and management of colorectal cancer* have been developed and reviewed.

The algorithms are now available on Cancer Council Australia's Cancer Guidelines Wiki to accompany the clinical practice guidelines as a derivative resource for health professionals working in this specialty area.

- Algorithm for Colonoscopic Surveillance Intervals – Adenomas
- Algorithm for Colonoscopic Surveillance Intervals – Following Surgery for Colorectal Cancer
- Algorithm for Colorectal Cancer Screening – Family History

An algorithm for colonoscopic surveillance intervals in inflammatory bowel disease is being planned.

### **New guidelines in development**

### ***Clinical practice guidelines for the diagnosis and management of Barrett's oesophagus and mucosal neoplasia***

Working party authors are assessing the literature and developing their topic content and evidence-based

recommendations. The draft guidelines are planned to be released for public consultation on the Cancer Guidelines Wiki around April 2014. Relevant organisations, experts and interested parties will be consulted.

### ***Clinical practice guidelines for PSA testing and management of test-detected prostate cancer***

These guidelines are undergoing a systematic literature review. Cancer Council Australia, together with the Prostate Cancer Foundation of Australia, aim to release the draft guidelines for public consultation by June 2014.

### **Guidelines under revision**

### ***Clinical practice guidelines for the prevention, diagnosis and management of lung cancer***

The prevention and diagnosis section of the 2004 guidelines is planned for revision and will be updated as online guidelines on the Cancer Guidelines Wiki in 2014.

The Lung Cancer Screening Guidelines Working Party has developed topic groups, key clinical questions and search strategies for the guidelines.

### ***Clinical practice guidelines for the management of melanoma***

Revision of the 2008 melanoma guidelines will commence later this year.

The literature review is to be informed by the German S3 Melanoma Guidelines, published by Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V., which Cancer Council Australia is looking to adapt for this revision.

For more information contact Christine Vuletich, Clinical Guidelines Network Manager on 02 8063 4100 or [christine.vuletich@cancer.org.au](mailto:christine.vuletich@cancer.org.au)

Clinical practice guidelines can also be accessed from Cancer Council Australia's website at [cancer.org.au/clinicalguidelines](http://cancer.org.au/clinicalguidelines)

## CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA

### **ASM 2013**

The 40th COSA Annual Scientific Meeting (ASM) was held in Adelaide from 12-14 November. The theme for the conference was 'Cancer Care Coming of Age', focusing on

the emerging field of geriatric oncology. The disease theme was gastro-intestinal cancers.

Attended by over 850 delegates, the program featured 10 international and 41 local invited speakers and included a

broad range of multidisciplinary sessions, presentations from opinion leaders and discussion of key issues in cancer management.

The opening plenary 'The burden of cancer in the elderly' set the scene for a stimulating conference by defining the problem of cancer in the elderly.

Epidemiologist, Dr David Roder, opened the plenary, highlighting some of the statistics. The proportion of cancers diagnosed in people aged  $\geq 75$  years will increase two to three fold over the next 30 years and risk of death will increase three to four fold. Also, the complexity of the disease will rise with increases in comorbidity and loss of living independently.

Professor Harvey Cohen from Duke University defined what geriatric oncology is and how the two specialities of geriatrics and oncology could come together to help older people with cancer, as well as the need for survivorship plans for this population. The session closed with an address from ex South Australia Health Minister, John Hill, who discussed the impact of a growing health budget, and the need for rationalisation of services bringing evidence into current clinical practice.

The 2013 Tom Reeve Award for Outstanding Contributions to Cancer Care was awarded to Professor Ian Frazer AC, at the conference dinner on Wednesday night. Best known for his work on the HPV vaccine, Professor Frazer delivered an outstanding oration on the impact of his work, the development of skin cancer vaccines and the importance of a good work/life balance.

The COSA Presidential Lecture on Thursday was delivered by Professor Ian Maddocks, renowned palliative care physician and Senior Australian of the Year 2013. Professor Maddocks drew upon his experiences in New Guinea to reflect on the process of dying with dignity and the importance of cultural aspects of grieving. His talk highlighted the challenges health professionals face due to our ageing population and the increased burden of cancer on our community. His message was clear – listen to the elderly and engage with the aged.

## ASM 2014

The 41st COSA ASM will be held in conjunction with the Union for International Cancer Control World Cancer

Congress in the first week of December 2014, at the Melbourne Convention and Exhibition Centre. The COSA ASM will run Tuesday 2 to Thursday 4 December, and World Cancer Congress 4 to 6 December, with Thursday 4th being a joint day. Discounts are on offer for people registering for both events.

The theme for COSA's 41st ASM will highlight cancer survivorship, supportive care and palliative care – all important areas of interest for COSA members, and hopefully will also prove attractive to World Cancer Congress delegates. COSA's disease theme in 2014 will be lung cancer and metastases. We anticipate that the Australasian Metastases Research Society will hold a satellite meeting on Monday 1st December 2014, and encourage their delegates to attend the COSA ASM on Tuesday 2nd December when the clinical aspects of metastases will be covered.

Visit [www.cosa2014.org](http://www.cosa2014.org) for more information.

## Leadership in improving cancer control

In December, COSA released two important position statements on single nucleotide polymorphisms testing, and the safe handling of monoclonal antibodies.

In collaboration with the Human Genetics Society of Australasia, The Royal College of Pathologists of Australasia and the Royal Australian College of General Practitioners, COSA released a position statement regarding the role of single nucleotide polymorphisms testing for personalised breast cancer risk prediction. The position statement recommends testing should only be undertaken after an in-depth discussion led by a clinical professional familiar with the implications of genetic risk assessment and genetic testing, including the potential insurance implications.

The COSA Cancer Pharmacists Group released a position statement on the safe handling of monoclonal antibodies in healthcare settings. A comprehensive literature search was undertaken to identify published information in the area of safe handling of monoclonal antibodies. Input was sought from members of COSA and the Cancer Nurses Society of Australia and incorporated in the final document.

Both position statements are available on the COSA website [www.cosa.org.au](http://www.cosa.org.au)

*Marie Malica, Executive Officer, COSA*

## MEDICAL ONCOLOGY GROUP OF AUSTRALIA, MOGA

The Medical Oncology Group of Australia officially welcomed Associate Professor Phillip Parente (Melbourne, and Deputy Chair, Special Advisory Committee-Medical Oncology, Royal Australasian College of Physicians), and Dr Zarnie Lwin (Brisbane) to the Executive as newly elected members and, Dr Ashayana Malalaskera (Sydney), as the new National Trainee Representative, at our Annual General Meeting in August.

Recent submissions to Cancer Australia include the review of 'Recommendations for the management of breast cancer in

women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation' and 'Recommendations for the use of first-line chemotherapy for the treatment of women with epithelial ovarian cancer'.

Professor Paul de Souza, Foundation Chair, Medical Oncology, School of Medicine University of Western Sydney and Director, Medical Oncology, Liverpool Hospital, has taken on the role of Convenor for the Association's 2014 Annual Scientific Meeting (Sydney Hilton, 6-8 August). The MOGA Meeting is the premier national meeting for

Australian medical oncologists, attracting close to 300 delegates from Australia and the Asia-Pacific region. The meeting has experienced significant growth in the last three years courtesy of its cutting-edge scientific program.

The 2014 meeting, Integrating Molecular and Immunologic Advances into Practice, will focus on the latest advances in a number of tumour streams, including breast, lung and colorectal cancers, and their relevance to clinical practice. It will also cover other developments at the forefront of cancer treatment and management globally, including immunotherapy, next generation sequencing, circulating tumour cells and molecular profiling and bioinformatics. Bioinformatics is a powerful multidisciplinary research approach to analysing biological data. Best of ASCO Australia, highlighting current oncology developments, will follow the meeting on 9 August.

Dr Mark Shackleton, Group Leader with the Melanoma Research Laboratory at the Peter MacCallum Cancer Centre, has taken over the convenorship of the Sciences of Oncology Program (8-9 November 2014, Melbourne). This program is only open to MOGA trainees and will focus on translational sciences and research, as well as current advances in cancer treatment and their relevance to the clinic, such as developmental biology, immunology, genetics, canceromics and pharmacology.

MOGA's Australia and Asia Pacific Clinical Research Development (ACORD) Workshop will run from 14-20 September 2014 at Coolumb in Queensland. ACORD, celebrating its 10th anniversary, is open to candidates with training in medical, radiation, gynaecological, paediatric, geriatric, surgical oncology and psycho-oncology, palliative care, nursing, pharmacology, haematology, pathology, and allied health disciplines. Applicants must write and submit a short concept outline for a proposed clinical research project to be developed at the workshop with supporting referee materials. This week-long intensive training program on clinical trials design for cancer researchers in all oncology subspecialties from Australia and the Asia Pacific region, is the regional equivalent of programs run by the European Society for Medical Oncology and the American Society for Clinical Oncology.

While drugs shortages and access issues around high costs drugs continue to be of interest to the media, clinical oncology drugs and treatment issues have remained high on the MOGA agenda over the last few months. The Annual Roundtable on November 29 provided a lively forum for the consideration of key national issues relating to oncology drugs access and the findings of the Association's Annual Horizon Scanning Report, highlighting major developments in oncology drugs and research, as well as their implications for Australian clinicians. There is now real movement towards improving and eventually creating a national system that will allow our patients access to new effective oncology drugs and an opening up of the regulatory process

to address some of the long-term systemic problems. This reflects a great deal of work by the many members who have assisted us with submissions and professional advice over the last few years. After extensive lobbying, effective 1 December dabrafenib and genetic testing for the BRAF mutation for patients with advanced or metastatic melanoma; and, sunitinib for unresectable pancreatic neuroendocrine tumours were listed on the Pharmaceutical Benefits Schedule (PBS). EGFR testing with the TKIs and dabrafenib with BRCA testing have also gone forward for approval by the Minister.

On November 30, the Government announced it will make more than \$82 million available each year through the PBS for essential chemotherapy drug infusions. The new arrangements also make overdue provision for oncology clinicians to be able to use a patient's medication chart to dispense and claim PBS medicines. Not only does the new funding arrangement allow for continuation of the vital role of 'chemotherapy pharmacist', but also supports the viability of chemotherapy administration in rural and regional areas. It also paves the way for the universal streamlining of authority drugs and electronic prescribing – two issues we have been fighting for since 2007.

MOGA has also engaged in ongoing discussions with the regulatory bodies and industry regarding approved indications in the Australian Register of Therapeutic Goods, product information and how this could be changed to reflect: evidence and changes in clinical practice; changes to listings and indications for older, off-patent and orphan oncology drugs; listing tamoxifen for breast cancer prevention; streamlined authorities for various drugs for a long time and the disparity between the public and private sectors authority requirements; the development of a structured approach to drug shortages and the introduction of a process similar to that available in the US, Europe and Canada; conducting a review and report on the outdated listings for metastatic breast cancer that were developed in the 1990s; advice on any other listing areas where the information is also outdated; and the use of GCSF primary prophylaxis after treatment for early breast cancer, particularly the combination of docetaxel and cyclophosphamide.

On November 21 MOGA participated in Parliamentarians Supporting Cancer Causes, a parliamentary briefing on the Medicines Australia 'Access to cancer medicines in Australia' report. This event enabled parliamentarians to hear about the challenges the Australia health system faces, the growing burden of cancer, the emergence of new cancer treatments and the expectation that these new advances should be made available to patients in a timely manner. The MOGA presentation, Treating cancer in Australia, covered the increasing understanding of cancer as a disease, changes in cancer treatment and issues from a clinician perspective.

*Associate Professor Gary Richardson, MOGA Chairman*



## FACULTY OF RADIATION ONCOLOGY, RANZCR

The end of another year allows us an opportunity for reflection on the changes within our profession and within the health care environment more generally.

Despite the solid investment in workforce and resources that has occurred since the release of the Baume report in 2002, resulting in many more patients benefitting from radiation therapy, we are still not able to provide access to all who might need it. At the same time, the other oncological disciplines are struggling with how to ensure adequate resources for service provision, particularly in the realm of the expensive and niche biological agents coming onto the market.

Despite a decade of sound work, the profile of radiation oncology as an essential component of care for many cancer patients still needs to be raised further for the benefit of our patients. The Faculty has started a number of initiatives of consumer involvement, to educate the public as to who we are, what we do, and how we can benefit society.

In 2014, we will build on the strength of our achievements to date, to ensure the cancer control community as a whole remains centre-stage on the political and funding agenda. As the leading cause of mortality in Australia and in New Zealand, and of significant morbidity when cure is not achieved, cancer control must remain a top health priority. The national health and hospital reform changes in Australia are still evolving, and we are monitoring the process and intervening when required.

### Radiation Oncology Targeting Cancer Campaign

The Faculty of Radiation Oncology is very excited to have officially launched the 'Radiation Oncology Targeting Cancer' campaign at the RANZCR Annual Scientific Meeting in October. This awareness campaign, which is relevant to both Australia and New Zealand, aims to increase recognition of radiation oncology and demystify radiation therapy as a treatment option. The campaign is mainly targeted at consumers (patients and their carers), but will also be relevant for health consumer organisations, the medical sector, governments and other stakeholders.

Key messages of the campaign:

- One in two cancer patients would benefit from radiation therapy (if they knew it was an option for them, and if they had access to it).
- Radiation therapy is effective and cost-effective, and is delivered by a highly skilled professional team using sophisticated technology.

The campaign website is now live and can be accessed at [www.targetingcancer.com.au](http://www.targetingcancer.com.au) or [www.targetingcancer.co.nz](http://www.targetingcancer.co.nz). It includes simple information about radiation therapy and the professional team involved in delivering it, short personal videos from real patients and supporters on the value of radiation therapy, as well as links to specific cancer site material. Patients and their carers can also find

details of their nearest radiation oncology centre, a list of issues to discuss with their doctor and answers to some frequently asked questions on the website.

Please support this exciting initiative in any or all of the following ways:

- Visit the website and register your support
- Follow the campaign on Twitter (@TargetingCancer)
- Visit and 'like' the Facebook page
- Connect to the campaign on LinkedIn
- Request a resource pack from [info@targetingcancer.com.au](mailto:info@targetingcancer.com.au)
- Email us your ideas and suggestions for media stories to help drive traffic to the website.

The website also contains a page for supporter statements. The Faculty values endorsement and support from our stakeholders for this initiative, which is essential to enhance the effectiveness and outcomes of the campaign. Please contact us at [faculty@ranzcr.edu.au](mailto:faculty@ranzcr.edu.au) if you would like to provide a supporter statement and/or reciprocal link to the website. We need and value your support of the website.

### Radiation oncology consumer forum

The Radiation Oncology Tripartite Committee hosted a consumer forum at the RANZCR office in August, to discuss common priorities and agendas with a group of informed consumers.

The forum aimed to:

- inform and educate consumers on radiation therapy and its role in cancer care
- identify areas of information need for consumers in relation to radiation therapy, with the intention of increasing the profile of radiation therapy in Australia to ensure optimal care of the patient with cancer
- present the Tripartite National Strategic Plan for Radiation Oncology 2012–2022
- identify areas and opportunities for consumers to become involved in driving the priorities of the Tripartite Strategic Plan.

A report on the consumer forum is available from the College website at <http://www.ranzcr.edu.au/about/faculty-of-radiation-oncology/faculty-initiatives/tripartite-strategic-plan-consultation>.

Consumers who attended the forum are very engaged and have already undertaken many advocacy activities, particularly with regards to implementation of the Radiation Oncology Practice Standards. The Tripartite Committee is exploring avenues for continued consumer engagement, and ways to assist consumers in their advocacy efforts.

*Prof Gill Duchesne  
Dean, Faculty of Radiation Oncology  
Chair, Radiation Oncology Tripartite Committee*

# CALENDAR OF MEETINGS

## AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
<b>March</b>			
4-5	Clinical Oncology Society of Australia (COSA) Cancer Care Coordination Conference 2014	Sydney, New South Wales	ASN Events Pty Ltd Website: <a href="http://www.asnevents.net.au">www.asnevents.net.au</a> Email: <a href="mailto:eg@asnevents.net.au">eg@asnevents.net.au</a> Phone: +61 3 5983 2400
19-21	Palliative Care Clinical Studies Collaborative (PaCCSC) Research Forum 2014	Sydney, New South Wales	Palliative Care Clinical Studies Collaborative Website: <a href="http://www.caresearch.com.au/caresearch/tabid/2993/Default.aspx">www.caresearch.com.au/caresearch/tabid/2993/Default.aspx</a> Email: <a href="mailto:paccsc@flinders.edu.au">paccsc@flinders.edu.au</a> Phone: +61 8 8275 1926
26-30	Australia New Zealand Gynaecological Oncology Group (ANZGOG) & Australian Society of Gynaecological Oncologists (ASGO) Annual Scientific Meeting 2014	Canberra, ACT	YRD (Aust) Pty Ltd Website: <a href="http://www.anzgog.org.au">www.anzgog.org.au</a> Email: <a href="mailto:admin@yrd.com.au">admin@yrd.com.au</a> Phone: +61 7 3368 2422
<b>April</b>			
1-4	Trans-Tasman Radiation Oncology Group (TROG Cancer Research) Annual Scientific Meeting 2014	Sunshine Coast, Queensland	Dean Bradley, Conference Organiser Website: <a href="http://www.trog2014.com">www.trog2014.com</a> Email: <a href="mailto:dean@cmnzl.co.nz">dean@cmnzl.co.nz</a> Phone: +61 4 479 4162
3-5	10th Australian Lymphology Association Conference	Auckland, New Zealand	Australasian Lymphology Association Website: <a href="http://www.alaconference.com.au">www.alaconference.com.au</a> Email: <a href="mailto:info@lymphology.asn.au">info@lymphology.asn.au</a> Phone: +61 3 9895 4486
9-11	10th Asia Pacific Musculoskeletal Tumour Society (APMSTS) Meeting	Melbourne, Victoria	Alison Fallon, Conference Manager Website: <a href="http://www.apmsts2014.aoa.org.au">www.apmsts2014.aoa.org.au</a> Email: <a href="mailto:alison.fallon@aoa.org.au">alison.fallon@aoa.org.au</a> Phone: +61 2 8071 8000
10-12	6th Exercise & Sports Science Australia (ESSA) Conference	Adelaide, South Australia	Exercise & Sports Science Australia Website: <a href="http://www.essa.org.au/2014conference">www.essa.org.au/2014conference</a> Email: <a href="mailto:conference@essa.com.au">conference@essa.com.au</a> Phone: +61 7 3862 4122
13-16	Australian Pain Society (APS) Annual Scientific Meeting 2014	Hobart, Tasmania	DC Conferences Website: <a href="http://www.dconferences.com.au/aps2014">www.dconferences.com.au/aps2014</a> Email: <a href="mailto:aps2014@dconferences.com.au">aps2014@dconferences.com.au</a> Phone: +61 2 9954 4400
<b>May</b>			
6-9	Australasian Leukaemia & Lymphoma Group (ALLG) Annual Scientific Meeting 2014	Melbourne, Victoria	Australasian Leukaemia & Lymphoma Group Website: <a href="http://www.allg.org.au/events.html">www.allg.org.au/events.html</a> Email: <a href="mailto:dilupa.uduwela@petermac.org">dilupa.uduwela@petermac.org</a> Phone: +61 2 9656 9011
17-18	Clinical Oncology Society of Australia (COSA) CGP Clinical Skills for Cancer Pharmacy Practitioners Course	Brisbane, Queensland	ASN Events Pty Ltd Website: <a href="http://www.asnevents.net.au">www.asnevents.net.au</a> Email: <a href="mailto:eg@asnevents.net.au">eg@asnevents.net.au</a> Phone: +61 3 5983 2400
<b>June</b>			
19-21	Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG) 2014 Annual Scientific Meeting	Sydney, New South Wales	MCI Australia Website: <a href="http://www.anzchog2013.org">www.anzchog2013.org</a> Email: <a href="mailto:info@anzchog2013.org">info@anzchog2013.org</a> Phone: +61 2 9213 4000

# CALENDAR OF MEETINGS

## July

13-15	Australian and New Zealand Urogenital and Prostate (ANZUP) Annual Scientific Meeting 2014	Melbourne, Victoria	YRD (Aust) Pty Ltd Website: <a href="http://www.anzup.org.au">www.anzup.org.au</a> Email: <a href="mailto:anzup@yrd.com.au">anzup@yrd.com.au</a> Phone: +61 7 3368 2422
16-19	2014 Australia & New Zealand Breast Cancer Trials Group (ANZBCTG) Annual Scientific Meeting	Wellington, New Zealand	ANZBCTG Business Department Website: <a href="http://www.bcia.org.au/content.aspx?page=asmpublic">www.bcia.org.au/content.aspx?page=asmpublic</a> Email: <a href="mailto:asm@anzbctg.org">asm@anzbctg.org</a> Phone: +61 2 4925 5255
24-26	Cancer Nurses Society of Australia (CNSA) Winter Congress 2014	Melbourne, Victoria	Chillifox Events Website: <a href="http://www.chillifoxevents.com.au">www.chillifoxevents.com.au</a> Email: <a href="mailto:cnsa@chillifoxevents.com.au">cnsa@chillifoxevents.com.au</a> Phone: +61 2 8005 1867

## August

1-3	Royal Australian and New Zealand College of Radiologists (RANZCR) NZ Branch Annual Scientific Meeting	Wellington, New Zealand	Outshine Website: <a href="http://www.ranzcr2014.co.nz">www.ranzcr2014.co.nz</a> Email: <a href="mailto:ranzcr@outshine.co.nz">ranzcr@outshine.co.nz</a> Phone: +64 7 823 2316
20-22	16th Australasian Gastro-intestinal Trials Group (AGITG) Annual Scientific Meeting	Brisbane, Queensland	ASN Events Pty Ltd Website: <a href="http://www.agitg.asnevents.com.au">www.agitg.asnevents.com.au</a> Email: <a href="mailto:eg@asnevents.net.au">eg@asnevents.net.au</a> Phone: +61 3 9329 6600
31-2 Sep	15th Asia-Pacific Prostate Cancer Conference 2014	Melbourne, Victoria	ICMS Pty Ltd Website: <a href="http://www.prostatecancercongress.org.au">www.prostatecancercongress.org.au</a> Email: <a href="mailto:pcwc2013@icms.com.au">pcwc2013@icms.com.au</a> Phone: +61 1300 792 466x

## September

2-5	Australian and New Zealand Society of Palliative Medicine (ANZSPM) Conference 2014	Gold Coast, Queensland	Australian and New Zealand Society of Palliative Medicine Website: <a href="http://www.etches.com/ehome/65181">www.etches.com/ehome/65181</a> Email: <a href="mailto:anzspm@willorganise.com.au">anzspm@willorganise.com.au</a> Phone: +61 2 4973 6573
14-19	Australia and Asia Pacific Clinical Oncology Research Development Workshop (ACORD)	Coolum, Queensland	Medical Oncology Group of Australia (MOGA) Website: <a href="http://www.moga.org.au">www.moga.org.au</a> Email: <a href="mailto:moga@moga.org.au">moga@moga.org.au</a> Phone: +61 2 8247 6210

## October

9-11	Australasian Breast Congress	Surfers Paradise, Queensland	Australasian Breast Congress Website: <a href="http://www.asbd.org.au">www.asbd.org.au</a> Email: <a href="mailto:info@asbd.org.au">info@asbd.org.au</a> Phone: +61 7 3847 1946
16-18	BreastScreen Australia Conference 2014	Melbourne, Victoria	Think Business Events Website: <a href="http://bsaconference.com.au">bsaconference.com.au</a> Email: <a href="mailto:bsa@thinkbusinessevents.com.au">bsa@thinkbusinessevents.com.au</a> Phone: +61 3 9417 1350
24-25	7th Cooperative Trials Group for Neuro-Oncology (COGNO) Annual Scientific Meeting	Melbourne, Victoria	Cooperative Trials Group for Neuro-Oncology Website: <a href="http://www.cogno.org.au">www.cogno.org.au</a> Email: <a href="mailto:cogno@cogno.org.au">cogno@cogno.org.au</a> Phone: +61 2 9562 5000
26	Australasian Lung Cancer Trials Group (ALTG) Meeting	Sydney, New South Wales	Australasian Lung cancer Trials Group Website: <a href="http://www.altg.com.au">www.altg.com.au</a> Email: <a href="mailto:enquiries@altg.com.au">enquiries@altg.com.au</a> Phone: +61 7 3251 3648

# CALENDAR OF MEETINGS

## November

8-11	15th Biennial Meeting of the International Gynaecological Cancer Society (IGCS)	Melbourne, Victoria	International Gynaecological Cancer Society (IGCS) Website: <a href="http://www.igcs.org">www.igcs.org</a> Email: <a href="mailto:adminoffice@igcs.org">adminoffice@igcs.org</a> Phone: +61 502 891 4575
11-14	Australasian Leukaemia & Lymphoma Group (ALLG) Annual Scientific Meeting 2014 (Sydney)	Sydney, New South Wales	Australasian Leukaemia & Lymphoma Group Website: <a href="http://www.allg.org.au/events.html">www.allg.org.au/events.html</a> Email: <a href="mailto:dilupa.uduwela@petermac.org">dilupa.uduwela@petermac.org</a> Phone: +61 9656 9011
16-19	Australian Health and Medical Research Congress	Melbourne, Victoria	ASN Events Pty Ltd Website: <a href="http://www.asnevents.net.au">www.asnevents.net.au</a> Email: <a href="mailto:eg@asnevents.net.au">eg@asnevents.net.au</a> Phone: +61 3 5983 2400

## December

2-4	Clinical Oncology Society of Australia's (COSA's) 41st Annual Scientific Meeting	Melbourne, Victoria	ASN Events Pty Ltd Website: <a href="http://www.asnevents.net.au">www.asnevents.net.au</a> Email: <a href="mailto:eg@asnevents.net.au">eg@asnevents.net.au</a> Phone: +61 3 5983 2400
4-6	Union for International Cancer Control (UICC) World Cancer Congress	Melbourne, Victoria	Union for International Cancer Control Website: <a href="http://www.worldcancercongress.org">www.worldcancercongress.org</a> Email: <a href="mailto:congress@uicc.org">congress@uicc.org</a> Phone: +41 22 809 1834

## INTERNATIONAL

### March

12-13	Maximising the value of Imaging in Oncology Drug Development	London, United Kingdom	SMi Group Website: <a href="http://www.smi-online.co.uk">www.smi-online.co.uk</a> Email: <a href="mailto:events@smi-online.co.uk">events@smi-online.co.uk</a> Phone: +44 20 7827 6000
17-21	12th International Congress on Obesity	Kuala Lumpur, Malaysia	International Association for the Study of Obesity (IASO) Website: <a href="http://www.iaso.org/events/ico/ico-2014">www.iaso.org/events/ico/ico-2014</a> Email: <a href="mailto:enquiries@iaso.org">enquiries@iaso.org</a> Phone: +44 20 7685 2580
22-25	Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer	Tampa, United States	Society of Gynecologic Oncology Website: <a href="http://www.sgo.org">www.sgo.org</a> Email: <a href="mailto:sgo@sgo.org">sgo@sgo.org</a>
26-28	3rd Asia Pacific Research Ethics Conference (APREC)	Singapore	Asia Pacific Research Ethics Conference Website: <a href="http://www.aprec-nhg.com.sg">www.aprec-nhg.com.sg</a> Email: <a href="mailto:aprec-nhg@eventslineup.com">aprec-nhg@eventslineup.com</a>

### April

2-5	International Symposium on Oncology Pharmacy Practice (ISOPP 2014)	Montreal, Canada	Sea to Sky Meeting Management Inc Website: <a href="http://www.isoppxiv.org">www.isoppxiv.org</a> Email: <a href="mailto:register@isoppxiv.org">register@isoppxiv.org</a> Phone: +1 778 338 4142
11-13	6th Asian Oncology Summit 2014	Kuala Lumpur, Malaysia	Marie-Claire Morley, Project Lead Website: <a href="http://www.asianoncologysummit.com">www.asianoncologysummit.com</a> Email: <a href="mailto:m.morley@elsevier.com">m.morley@elsevier.com</a> Phone: +44 1425 616891

# CALENDAR OF MEETINGS

## May

6-9	Royal Australasian College of Surgeons (RACS) Annual Scientific Congress 2014	Marina Bay Sands, Singapore	Royal Australasian College of Surgeons Website: <a href="http://www.surgeons.org">www.surgeons.org</a> Email: <a href="mailto:college.sec@surgeons.org">college.sec@surgeons.org</a> Phone: +61 3 9249 1200
26-28	Euroson 2014 - 26th Congress of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB)	Tel Aviv, Israel	EUROSON Website: <a href="http://www.euroson2014.org">www.euroson2014.org</a> Email: <a href="mailto:secretariat@euroson2014.org">secretariat@euroson2014.org</a> Phone: +972 3 5767711
30-3 June	American Society of Clinical Oncology's (ASCO's) 50th Annual Scientific Meeting	Chicago, United States	American Society of Clinical Oncology Website: <a href="http://www.asco.org">www.asco.org</a> Email: <a href="mailto:meetings@asco.org">meetings@asco.org</a> Phone: 571 483 1599

## June

12-14	European Society of Thoracic Imaging (ESTI) Annual Scientific Meeting	Amsterdam, The Netherlands	European Society of Thoracic Imaging (ESTI) Website: <a href="http://www.myesti.org">www.myesti.org</a> Email: <a href="mailto:office@myesti.org">office@myesti.org</a> Phone: +43 1 5322165
26-28	Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO) International Symposium on Supportive Cancer in Cancer 2014	Florida, United States	Kenes International Website: <a href="http://www.mascc.org/mascc-symposia">www.mascc.org/mascc-symposia</a> Email: <a href="mailto:mascc@kenes.com">mascc@kenes.com</a> Phone: +41 22 908 0488
26-28	International Association of Cancer Registries (IACR) 2014	Ottawa, Canada	International Association of Cancer Registries Website: <a href="http://www.iacr2014.org">www.iacr2014.org</a> Email: <a href="mailto:iacr@iacr.fr">iacr@iacr.fr</a> Phone: 217 698 0800
26-28	OIC 2014 - Oncologic Imaging Course	Dubrovnik, Croatia	ECR Office Vienna Website: <a href="http://www.oncoic.org">www.oncoic.org</a> Email: <a href="mailto:office@oncoic.org">office@oncoic.org</a> Phone: +43 1 533 4064 0
28-29	St Jude-VIVA Forum in Paediatric Oncology	Singapore	St Jude-VIVA Forum Website: <a href="http://www.viva.sg/stjude">www.viva.sg/stjude</a> Email: <a href="mailto:sjvf@nuhs.edu.sg">sjvf@nuhs.edu.sg</a>
30-2 July	International Symposium on Paediatric Neuro-Oncology	Singapore	International Symposium on Paediatric Neuro-Oncology Website: <a href="http://www.ispno2014.com">www.ispno2014.com</a> Email: <a href="mailto:info@ispno2014.com">info@ispno2014.com</a> Phone: +65 6411 6687

## September

11-13	3rd World Congress on Controversies in Hematology (COHEM) ESMO	Istanbul, Turkey	ComtecMed Website: <a href="http://www.comtecmed.com/cohem/2014">www.comtecmed.com/cohem/2014</a> Email: <a href="mailto:cohem@comtecmed.com">cohem@comtecmed.com</a> Phone: +972 3 5666166
26-30	European Society for Medical Oncology (ESMO) 2014 Congress	Madrid, Spain	European Society for Medical Oncology Website: <a href="http://www.esmo.org">www.esmo.org</a> Email: <a href="mailto:esmo@esmo.org">esmo@esmo.org</a> Phone: +41 0 91 973 19 00

## October

16-19	18th Senologic International Society (SIS) World Congress on Breast Healthcare	Orlando, United States	Kenes International Website: <a href="http://www2.kenes.com/sis/Pages/Home.aspx">www2.kenes.com/sis/Pages/Home.aspx</a> Email: <a href="mailto:sis2014@kenes.com">sis2014@kenes.com</a> Phone: +41 22 908 0488
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# CALENDAR OF MEETINGS

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20-24	16th World Congress of Psycho-Oncology and Psychosocial Academy	Lisbon, Portugal	International Psycho-Oncology Society Website: <a href="http://www.ipos2014.com">www.ipos2014.com</a> Email: <a href="mailto:info@ipos-society.org">info@ipos-society.org</a> Phone: +1 434.293.5350
29-31	34th Congress of the European Society of Surgical Oncology (ESSO) in partnership with BASO	Liverpool, United Kingdom	ECCO - the European Cancer Organisation Website: <a href="http://www.ecco-org.eu/ESSO34">www.ecco-org.eu/ESSO34</a> Email: <a href="mailto:ESSO34@ecco-org.eu">ESSO34@ecco-org.eu</a> Phone: +32 2 775 02 01
<b>December</b>			
9-13	37th Annual San Antonio Breast Cancer Symposium	San Antonio, United States	Rich Markow, Director Website: Email: <a href="mailto:sabcs@uthscsa.edu">sabcs@uthscsa.edu</a> Phone: 210 450 1550

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## CANCER COUNCIL AUSTRALIA

Cancer Council Australia is the nation's peak independent cancer control organisation. Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.



### MEMBERS

Cancer Council ACT  
Cancer Council New South Wales  
Cancer Council Northern Territory  
Cancer Council Queensland  
Cancer Council South Australia  
Cancer Council Tasmania  
Cancer Council Victoria  
Cancer Council Western Australia

### AFFILIATED ORGANISATIONS

Clinical Oncology Society of Australia

### CEO

Professor I Olver AM

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## CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA

The Clinical Oncology Society of Australia (COSA) is a multidisciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.

It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with Cancer Council Australia.



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*Cancer Council Australia nominee*  
Professor Ian Olver

### MEMBERSHIP

Further information about COSA and membership applications are available from:

[www.cosa.org.au](http://www.cosa.org.au) or [cosa@cancer.org.au](mailto:cosa@cancer.org.au)

Membership fees for 2013  
Medical Members: \$170  
Non Medical Members: \$110 (includes GST)

### COSA Groups

Adolescent & Young Adult  
Biobanking  
Breast Cancer  
Cancer Biology  
Cancer Care Coordination  
Cancer Pharmacists  
Clinical Trials Research Professionals  
Complementary & Integrative Therapies  
Developing Nations  
Epidemiology  
Familial Cancer  
Gastrointestinal Cancer  
Geriatric Oncology  
Gynaecological Cancer  
Lung Cancer  
Melanoma & Skin Cancer  
Neuroendocrine Tumours  
Neuro-Oncology  
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Paediatric Oncology  
Palliative Care  
Psycho-Oncology  
Radiation Oncology  
Regional & Rural Oncology  
Social Work  
Surgical Oncology  
Survivorship  
Urologic Oncology

## Information for contributors

*Cancer Forum* provides an avenue for communication between all those involved in cancer control and seeks to promote contact across disciplinary barriers. To this end, articles need to be comprehensible to as wide a section of the readership as possible. Authors should provide sufficient introductory material to place their articles in context for those outside their field of specialisation. *Cancer Forum* is primarily a review journal, with each issue addressing a particular topic in its 'Forum'. The Forum topic and appointment of Guest Editor(s) are determined by the Editorial Board, which welcomes suggestions. Proffered papers containing primary research findings will be considered for publication in *Cancer Forum* in limited circumstances. Articles will be considered by the Editorial Board and then published subject to two peer-reviews. Generally speaking, authors are encouraged to submit their primary research findings to established cancer research or clinical oncology journals. The following information is provided for contributors invited to prepare manuscripts for *Cancer Forum*.

### Format

Prospective authors are encouraged to examine recent editions of *Cancer Forum* for an indication of the style and layout of Forum papers ([www.cancerforum.org.au](http://www.cancerforum.org.au)). All manuscripts should be submitted by email to the Forum's Guest Editor(s) and Executive Editor ([rosannah.snelson@cancer.org.au](mailto:rosannah.snelson@cancer.org.au)) as MS Word documents.

Length: 2000-2500 words.

Font: Arial - 20pt for title, 12pt for headings and 10pt for text.

Following the title, include your full name, organisation and email address.

Include introductory headings and sub-headings that describe the content.

Number pages in the footer.

### Abstract

All manuscripts must include an abstract of approximately 200 words, providing a summary of the key findings or statements. No references or abbreviations should be included in the abstract.

### Abbreviations and acronyms

Abbreviations and acronyms should only be used where the term appears more than five times within the paper.

They must be explained in full in the first instance, with the abbreviation in brackets.

The Editorial Board reserves the right to remove the heavy use of abbreviations and acronyms that may be confusing to the diversity of our readership.

### Photographs, tables and graphs

Photographs and line drawings can be submitted via email, preferably in tiff or jpeg format. If images are not owned by the author, written permission to reproduce the images should be provided with the submission. A maximum of five illustrations and figures and three tables can be submitted with the manuscript. Inclusion of additional items is subject to approval by the Editorial Board. Unless otherwise specified by the authors or requested by the Editorial Board, all images, graphs and tables will be printed in black and white. All figures – including tables and graphs – will be reproduced to *Cancer Forum*'s style. Figures containing data (eg. a line graph) must be submitted with corresponding data so our designers can accurately represent the information. Figures and images should be labelled sequentially, numbered and cited in the text in the correct order e.g. (table 3, figure 1). Tables should only be used to present essential data. Each must be on a separate page with a title or caption and be clearly labelled.

### Referencing

Reference numbers within the text should be placed after punctuation and superscripted. The maximum number of references is 75. Only papers closely related to the subject under review should be quoted and exhaustive lists should be avoided. Only one publication can be listed for each number. Citation of more than one reference to make a point is not recommended. The Editorial Board prefers a focus on more recent references (in the last 10 years). The list of references at the end of the paper should be numbered consecutively in the order in which they are first mentioned and be consistent with the National Library of Medicine's International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals. i.e. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med*. 2002 Jul 25;347(4):284-7.

A full guide is available at [www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html) a guide to abbreviation of journal names can be found at [https://www.library.uq.edu.au/faqs/endnote/medical\\_2010.txt](https://www.library.uq.edu.au/faqs/endnote/medical_2010.txt)

**The Editorial Board will make the final decision on inclusion of manuscripts and may request clarifications or additional information.**

For further information or confirmation of the above, please contact:

#### **Rosannah Snelson**

Cancer Forum Executive Editor

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