

CHAPTER 22 COST EFFECTIVENESS

22.1 Economic burden of Colorectal Cancer in Australia

Colorectal Cancer is a major health concern in Australia. In 2001, it was the most common cancer reported to Australian cancer registries, and the second most common for men and for women following prostate and breast cancer respectively. By age, it was the third and second most common cancer for people aged 15–44 and 45–64 respectively, and the most common cancer for people aged over 65.¹ Colorectal Cancer is also the third most common cause of cancer deaths in both males and females.¹ Treatments for Colorectal Cancer include surgical resection, chemotherapy and radiotherapy. In recent years, efforts to improve survival have focused on pre-symptomatic diagnosis, adjuvant chemotherapy, intensive follow up, and modification of surgical techniques.

The estimated burden of disease attributable to Colorectal Cancer in Australia is outlined in Table 22.1. Years of life lost (YLL) due to Colorectal Cancer are considerably higher than years lost due to disability (YLD). This reflects the fact that the ‘burden of cancer is dominated by mortality rather than lengthy periods of disability’.²

Table 22.1 Burden of disease attributable to Colorectal Cancer in Australia, 1996

	Total		Males		Females	
	<i>Number</i>	<i>Per cent</i>	<i>Number</i>	<i>Per cent</i>	<i>Number</i>	<i>Per cent</i>
Deaths	4973	3.9				
YLL	55372	4.1	29223	3.9	26149	4.4
YLD	11579	1.0	6288	1.0	5291	0.9
DALYs <small>Disability Adjusted Life Year</small>	66951	2.7	35511	2.7	31440	2.7

Source: Mathers et al²

The Australian Institute of Health and Welfare has estimated the costs of Colorectal Cancer at a macro level. In 1993–94, cancer was estimated to account for 6% of total health care system costs in Australia. Colorectal Cancer accounted for 10.8% of the total cost of cancer care. It ranked second in terms of the most ‘expensive’ cancers in Australia, with total health care expenditure on Colorectal Cancer estimated at \$204.9 million in 1993–94.³ Colorectal Cancer ranks as the fifth most costly cancer for females aged 25–44, the first and third most costly cancer respectively for males and females respectively aged 45–64, and the third and second most costly cancer for males and females respectively aged over 65.³ Total treatment costs per case of Colorectal Cancer were estimated at \$A15,374 in 1993–94, which ranks eleventh in terms of the most costly cancer to treat.³ However, there is relatively little micro-level information available in Australia about treatment patterns and resource use for Colorectal Cancer.

22.2 Economic evaluation

Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences. Cost-effectiveness analysis is the form of economic evaluation in which the consequences of interventions, procedures or programs are measured in the most appropriate natural units, such as life-years gained, complications avoided, or cases correctly diagnosed. While many cost-effectiveness evaluations consider a single measure of output, others present an array of output or outcome measures alongside cost, allowing decision makers to form their own view of the relative importance of each measure.

In a cost-utility analysis (CUA), the consequences of an intervention, procedure or program are adjusted by health-state preference scores or utility weights. This means that the quality of the life

years gained can be assessed, which is particularly useful for interventions that extend life at the expense of side effects (such as some chemotherapy for cancer), or produce reductions in morbidity rather than mortality (such as some treatments for chronic conditions, e.g. arthritis).

Whatever form of economic evaluation is used, an intervention, procedure or program can be considered efficient relative to the alternatives if it can be shown to produce a given level of benefit for the minimum cost.

22.2.1 Role of economic evidence in the development of guidelines

The NHMRC has identified two main areas where economic evidence is important in the development of clinical practice guidelines:

- determination of the most cost-effective treatment alternatives
- determination of whether a proposed clinical practice guideline is cost-effective.

In the development of these guidelines, the emphasis has been in the first instance on identifying those interventions for which there is evidence of effectiveness, before addressing questions of cost-effectiveness. There is limited evidence available within Australia to assess the costs and cost-effectiveness of alternatives for screening, early diagnosis and management of Colorectal Cancer. However, there is a range of international literature that provides information about the relative cost-effectiveness of alternatives. This information can be used to inform the development of these guidelines.

The approach taken in reviewing the economic evidence involved:

- identifying those areas where economic evidence is likely to be important
- identifying those areas where economic evaluation evidence is available
- reviewing and summarising the economic evaluation literature.

However, it is important to note that international literature on economic evaluation is limited in its relevance to Australia because of differences in cost structures and reimbursement arrangements, and because the comparator in international studies may not reflect current practice in Australia.

A search was conducted using the databases Pre-Medline, Medline and Embase, covering the period January 1994–December 2004. Economic evaluation literature that pre-dates 1994 was considered to be of limited relevance because of changes in technology, cost structures and management practices. The key words included Colorectal Cancer, colon cancer, rectal cancer, economic evaluation, cost-effectiveness analysis, cost-benefit analysis, cost analysis and cost. Articles were included if they were judged to be economic evaluations, that is, if they involved comparison of alternative interventions in terms of costs and consequences. Articles were classified into nine main areas:

- prevention
- population screening
- screening based on family history
- screening patients with symptoms
- diagnosis
- follow up
- treatment — surgery

- treatment — chemotherapy
- treatment — other (radiotherapy and radiofrequency ablation).

These groupings reflected the main areas in which economic evaluations of interventions have been undertaken.

Of the 121 articles included in these guidelines 49 investigated the effect of an intervention on outcomes such as life years saved (LYS) or gained (LYG), or quality of life on utility (QALY), and seven were cost-benefit or cost-minimisation studies. A further 26 were cost and consequence analyses investigating the costs and effects of an intervention using limited measures of clinical outcome such as cancers detected, deaths prevented, cured/surviving patient, curative resection, recurrence/cured recurrence, treating complications, and so on, or in some cases, output such as length of stay (LOS). The remainder consisted of 13 economic analyses that measured costs and outcomes/or outputs separately, four cost analyses measuring costs only, and 22 reviews or combined review/analyses.

The 49 articles measuring outcomes such as LYS and QALY were reviewed using the criteria recommended in *How to compare the costs and benefits: evaluation of the economic evidence (NHMRC)*.⁴

Table 22.2 NHMRC’s criteria: Assessing evidence using shadow prices

Ranking of evidence on costs	Ranking of evidence on effects	
	High	Low
Strong	Recommend if: < \$70,000 per life year Do not recommend if > \$100,000 per life year	Recommend if < \$30,000 per life year Do not recommend if >\$70,000 per life year
Weak	Recommend if < \$30,000 per life year Do not recommend if > \$70,000 per life year	Recommend if < \$30,000 per life year Do not recommend if >\$30,000 per life year

Source: *How to compare the costs and benefits: evaluation of the economic evidence (NHMRC)*⁴ Table 6.1 pg 67.

The NHMRC provides comprehensive guidelines for evaluating the economic evidence for clinical practice guidelines. The evidence on both effectiveness and costs can be compared, providing a range of possibilities shown in the Table above. The threshold cost per life year should vary with the quality of evidence. The *lower* the ranking of the evidence, the more likely the decision will be to not recommend an option where the cost per life year falls between \$30,000 and \$100,000.

Table 22.2 shows that ‘if highly ranked evidence is available on effects and there is strong evidence on costs, then options that cost less than \$70,000 per life year saved are recommended and those that cost \$100,000 are rejected. Those that cost between \$70,000 and \$100,000 should be considered.’

‘If effectiveness evidence is ranked as low and the cost evidence as weak, options that cost more than \$30,000 per life year saved are rejected.’

'If neither of the above cases applies [that is, where one of the criteria (costs or effects) is weak and the other is strong], then options of less than \$30,000 are recommended and those greater than \$70,000 are rejected. Those that are between \$30,000 and \$70,000 should be considered.'⁴

Health care alternatives require further consideration if they fall between \$70,000-\$100,000 per life year saved and rank highly for effects and costs, or if they fall between \$30,000-\$70,000 per life year saved and rank highly on one but not the other. Issues that enhance the attractiveness of a health care option and move the threshold towards a higher price include equity implications, prevention of adverse flow on effects to other sectors, rare diseases with no other health options, improvement of survival and quality of life and severe and preventable conditions.⁴

This methodology has not been applied in the development of these Guidelines. Rather, the economic information has been summarised and presented, but not graded. Hence they have not been assessed applying NHMRC's criteria and shadow prices framework.

However, assessment of overseas economic evaluations and even some Australian economic evaluations in these terms should be treated with caution. Whether these costs and outcomes would be realised if the intervention were adopted in the Australian context depends upon a number of factors, but particularly on whether the comparator for the study reflects current practice in Australia. This also applies where cost-effectiveness evaluations are made in terms of clinical comparators, as is the case in the majority of studies.

Cost-effectiveness results from studies are presented as reported in the relevant studies, but also, for comparative purposes, converted to 2004 Australian dollars. The conversion was undertaken using the OECD purchasing power parity estimates (<www.oecd.org/std/ppp/>) for the relevant year of the study to convert to Australian dollars, then using the Australian Bureau of Statistics Health Price Index (weighted average of eight capital cities)⁵ to convert the relevant costs to 2004 Australian dollars. Results in terms of 2004 Australian dollars are reported in parentheses following the original results. However, in comparing across studies it should be noted that the results from different studies are not directly comparable. In particular, the scope of the studies may differ in terms of the range of costs and consequences considered, the perspective of the study, and the choice of comparator. In addition, particularly for earlier studies, there may be important changes in cost structures and technology that limit comparability. The indicative cost-effectiveness estimates in 2004 Australian dollars should be treated as providing a guide to the likely cost-effectiveness of the interventions in the Australian setting.

The findings of the literature review are summarised below. A summary table providing full terminology for all abbreviations used in the tables is presented in Appendix 4.

22.3 Prevention

A number of studies have investigated the cost-effectiveness of aspirin and non-steroidal anti-inflammatory drugs such as cyclo-oxygenase-2 specific inhibitors (COX-2) as chemoprevention agents. The results are summarised in Table 22.3. Neither COX-2 nor aspirin (ASA), as alternatives or adjuncts to screening with colonoscopy or combined flexible sigmoidoscopy (FSIG) and faecal occult blood testing (FOBT), have been found to be as effective or cost-effective. However, for persons already taking aspirin, the addition of screening may be potentially cost-effective. As there is only a limited number of studies evaluating each chemotherapy agent, and comparisons are not the same across studies, the results should be used as an indication only.

Table 22.3 Results of studies investigating the cost-effectiveness of COX-2 inhibitors and aspirin as chemoprevention agents

Study	Country	Study questions	Conclusion
Arguedas et al ⁶	United States	Comparison of COX-2 vs COL for average risk post-polypectomy patients (secondary prevention)	COX-2 in average risk patients is not a cost-effective strategy compared to COL. ICERs/LYG (discounted) vs no surveillance for COL and COX-2 were \$US27,970 and \$US407,498 (\$A49,225 and \$A717161). Undiscounted and discounted ICER/LYG of COX-2 vs COL is \$US1,613,333 and \$US1,715,199 (\$A2,839,324 and \$A3,018,599). Sensitivity analysis confirms results are robust.
Ladabaum et al ⁷	United States	Comparison of: <i>For average risk</i> COX-2 vs COL 10yrly vs FSIG 5yrly + FOBT yrly vs COX-2 + COL 10yrly vs COX-2 + FSIG 5yrly/FOBT yrly <i>For 1st- and 2nd-degree relatives</i> COX-2 vs COL 10yr vs COL 5yr vs COX-2 + COL 10yr vs COX-2 + COX-2 + COL 5yr	COX-2 is less effective and more costly than other strategies. For average risk persons, and for persons with two 1st-degree relatives, ICER/LYG vs no screening was \$US233,000 and \$US56,700 (\$A410,059 and \$A99,787) compared to \$US20,200 (\$A35,198) for COL 10yrly and \$US16,800 (\$A29,567) for SIG 5yrly + FOBT yrly; and \$US1200 and \$US2600 (\$2112 and \$A4576) for COL 10yrly and COL 5yrly. ICER of COX-2 as an adjunct to screening was \$US828,000 (\$A1,457,207) and \$US404,700 (\$A712,236). Results are highly sensitive to cost, and effect of COX-2 on cancer risk.
Ladabaum et al ⁸	United States	Comparison of no screening vs (ASA) vs FSIG/FOBT vs COL vs FSIG/FOBT + ASA vs COL + ASA	ASA should not be used for persons undergoing screening, or as a substitute for screening. ICERs/LYG vs no screening for ASA, FSIG/FOBT, COL were dominated, \$US16,844 and \$US20,172 (\$A26,305 and \$A31,502). ASA was dominated as an adjunct to FSIG/FOBT and had a high ICER/LYG as an adjunct to COL, of \$US149,161 (\$A239,940). In persons already taking ASA, screening with FSIG/FOBT or COL results in ICERs less than \$US31,000/LYG (\$A48,412).

Study	Country	Study questions	Conclusion
Suleiman et al ⁹	United States	Comparison of no intervention vs COL (10yrly or 3yrly if polyps) vs ASA vs COL (10yrly or 3yrly if polyps) + ASA	Compared with COL 10yrly, use of ASA as a preventative measure saves fewer lives (5301 vs 7951–5166/1000) at higher costs. Compared to no screening, COL is more cost-effective than ASA or COL+ASA (ICER = \$US10,983 [\$A18,821] vs \$US47,259 [\$A80,987] vs \$US41,929 [\$A71854]). COL + ASA saves more lives but at a prohibitive cost (ICER/LYG vs COL = \$US227,607 [\$A390,048]).
Sonnenberg ¹⁰	United States	Review of no intervention vs ASA vs ASA + COL	Chemo prevention with ASA is not cost-effective (ICER vs no intervention = \$US47,249 [\$A75,326])/LYG). If ASA is already being used, screening with COL10yrly results in ICER of \$US34,800 (\$A55,479)/LYG.
Inadomi ¹¹	United States	Review of no intervention vs ASA vs ASA + COL vs COL	The addition of ASA to COL is not cost-effective but if already using, ASA + COL may be cost-effective. ASA + COL vs ASA has ICER range of \$US31,000–34,836 (\$A45,801–51,468)/LYG.

22.4 Population screening

There have been numerous studies to investigate the effectiveness and cost-effectiveness of population screening. Methodologies used, and comparisons made, varied considerably across studies, with investigators comparing screening to no screening, different screening tests, different types of the same test, as well as different screening schedules or ages. There was also variation in terms of whether comparisons were made for single tests, combinations of tests, or both. The majority of the studies have been cost-effectiveness analyses, but there have also been several cost and consequences, economic and cost analyses, as well as numerous reviews. The results of studies conducting analyses are summarised in Table 22.4. Review studies are summarised in Table 22.5.

In the main, and across all studies, screening has been found to be cost-effective compared to no screening, and is therefore recommended. However, due to differences in the compared tests, screening intervals, methods and assumptions used, and results across studies, at present it is not possible to recommend any one screening test (single or combination) over another. Similarly, recommendations cannot be made about the best options for screening intervals or commencement age, except that commencement before 50 years of age appears to be less cost-effective than commencement after 50 years of age. At this stage, therefore, screening is recommended, but an optimal screening strategy cannot be identified and choice may best be determined based on local context and policy.

Between 2002 and 2004, a pilot study was conducted to determine the feasibility, acceptability and cost-effectiveness of Colorectal Cancer screening among the Australian population. The results will inform government decisions about whether to introduce a bowel cancer screening program and if so, how. As part of the evaluation of the pilot program, a cost-effectiveness study is being sponsored by the Medical Services Advisory Committee. However, at the time of writing, the results of the economic evaluation were not available.

Table 22.4 Results of studies investigating effectiveness, costs and cost-effectiveness of population screening

Study	Country	Comparator/ screening test	Conclusion
Stone et al ¹²	Australia	FOBT vs no screening	There is support for a national program directed at 55–69yrs with extension to 70–74yrs if there are sufficient resources. Minimum or base program could avert 250 deaths per annum at a gross cost of \$A55M (gross ICER = \$A17,000/DALY gained). Sensitivity analysis indicates variation in parameters results in ICERs ranging from \$A13,000 to \$A52,000/DALY gained.
Whynes ¹³	United Kingdom	FOBT vs no screening	FOBT screening is cost-effective with an ICER of £1584 (\$A4007) LYG (with conservative assumptions). Results are sensitive to discount rates for survival benefits (6% increase results in 77.4% increase in ICER; if undiscounted, ICER falls 25.5%); survival estimates (if highest used, ICER falls 23.3%) and cost (if FOBT, investigation and treatment costs are doubled, ICER increases 59.6, 27.5 and 12.9%).
Whynes ¹⁴	United Kingdom	FOBT vs no screening	FOBT is cost-effective with an ICER of £1400–5700 (\$A3828–15,586)/QALY gained (depending on period of follow up). Results are sensitive to specificity (10% decrease doubles the ICER) and discount rate (3% rate raises ICER 50%).
Helm et al ¹⁵	United States	FOBT vs no screening	Screening is considered cost-effective over a wide range of projected costs and irrespective of trial on which analysis is based (CERs range from \$US2,500–20,500 [\$A4,072–33,384]/LYG). FOBT still limited to ≤ 15% reduction in mortality. Results are sensitive to variation in procedure costs (up to 50% variation in ICER).
Whynes et al ¹⁶	United Kingdom	FOBT vs no screening	Screening appears cost-effective with a cost/QALY gained range of £1371–5685 (\$A3,381–14,019). Results are highly sensitive to a number of test parameters, in particular cost and test specificity, but ICERs remain acceptable.

Study	Country	Comparator/ screening test	Conclusion
Bouvier et al ¹⁷	France	Assessment of 1st year treatment costs following implementation of screening programs (FOBT — Hemocult)	There is no significant cost decrease in 1st year of treatment with advance of diagnosis. Mean costs for stages 1 to 6 were €1276, €17,579, €21,858, €31,110, €17,384 and €15,365 (\$A2148, \$A29,858, \$A36,787, \$A52,358, \$A29,257 and \$A25,859) (total mean cost of €21,912 [\$A36,877]). Only stage 1 (4.2% of the sample), treated by polypectomy, had significantly lower costs.
Yamamoto and Nakama, ¹⁸	Japan	FOBT 1day vs, 2day vs 3day collection	Two-day method is suggested as it costs only slightly more than one day but has greater diagnostic accuracy. Sensitivity and specificity for 1, 2 and 3day tests were 58%, 96%; 89%, 96% and 100%, 94%. Cases detected were 13, 20.1 and 22.5 with costs/case detected of \$US5924.06, \$US6014.38 and \$US7122.91 (\$A10,629.68, \$A10,719.74 and \$A12,780.80).
Berchi et al ¹⁹	France	20yrs biennial automated immunological test (magstream) vs guaiac stool test (Haemocult)	Use of magstream leads to increased life expectancy of 0.0198yr with an ICER of €2980 (\$A4568)/discounted LYG. Although results are sensitive to numerous variables, ICER is still below €10,000 (\$A15,328)/undiscounted LYG, except when magstream sensitivity is 70% or 90% and cost of COL is €1000 (\$A1533).
Gyrd-Hansen et al ²⁰	Denmark	Hydrated Hemocult-II (HH-II), 55–74yrs vs HH-II, 50–74yrs vs hemeselect, 50–74yrs vs rehydrated H-II (RH-II), 50–74yr	The six most efficient H-II programs were 2yrly for 65–74yrs, 60–74yrs and 55–75yrs; 1.5yrly for 55–74yrs; and yrly for 55–74yrs and 50–74yrs. ICERs/LYG were DKK17,000, DKK18,896, DKK23,012, DKK28,802, DKK35,471 and DKK42,500 (\$A4197, \$A4665, \$A5682, \$A7110, \$A8757 and \$A10,492). Results are robust, except if future unrelated health care costs not included and if no discounting.

Study	Country	Comparator/ screening test	Conclusion
Gyrd-Hansen ²¹	Denmark	Unhydrated H-II, 55–74yrs 2yrly, vs hydrated H-II, 50–74yrs yrly vs hemeselect, 50–74yrs yrly, rehydrated H-II, 50–74yrs yrly	Unhydrated H-II test is cost-effective and preferable to other tests. Incremental cost/LYG with unhydrated H-II for 55–74yrs 2yrly is DKK17,500 (\$A4320). Ave costs/LYG with unhydrated H-II, 55–74yrs yrly, 50–74yrs yrly, Hemeselect, 50–74yrs yrly, rehydrated H-II, 50–74yrs yrly were DKK30,000, DKK39,000, DKK71,300 and DKK138,000 (\$A7,410, \$A9,628, \$A17,602 and \$A34,068). Sensitivity analysis suggests cost-effectiveness is dependent on specificity >97% for yrly screening. For 2yrly intervals, <97% is allowable. Efficiency curve results suggest rehydrated H-II test is a viable option for beyond 55–74yrs, 2yrly.
Castiglione et al ²²	Italy	1day RPHA vs 3day RG Haemocult	RPHA had higher efficacy. RPHA (+ and +/-) and RPHA (+ only) detected more cancers than RG Haemocult. All Dukes A were detected by RPHA (+ and +/-). RPHA is also more cost saving. Hemocult (-ve) had the highest cost/cancer or adenoma detected (\$US12,900 [\$A21,007]). RPHA (+) had the lowest cost per cancer detected (\$US9,020 [\$A14,689]) and RPHA (+ & +/-) had the lowest cost per person with adenoma (\$US1780 [\$A2899]).
Rae and Cleator 1994 ²³	Canada	Two-tier FOBT (HO Sensa + hemeselect) vs hemocult guaiac vs, HO Sensa guaiac vs hemeselect hemagglutination	The two-tier test is the most effective (specificity of 88.7% and 96.8% for high risk and asymptomatic/symptomatic, and a lower false negative rate). It is also the least expensive. For two tier vs the other tests, high-risk group costs/cancer detected and adenoma/polyp detected were \$US1842 vs \$US2261–3176 (\$A3693 vs \$A4533–6368) and \$US972 vs \$US1044–1444 (\$1940 vs \$A2093–2895). Asymptomatic/symptomatic group costs were \$US10,825 vs \$US20,948–27,165 (\$A21,704 vs \$A42,000–54,466). For asymptomatic alone, costs were \$US5476 vs \$US16,422–95,585 (\$A10,979 vs \$A32,926–191,647).
Whynes et al ²⁴	United Kingdom	Assessment of costs of FSIG screening in the UK	Total health service cost for screening plus subsequent management average approximately £91 (\$A210)/person. Costs vary across centres.

Study	Country	Comparator/ screening test	Conclusion
Sonnenberg and Delco ²⁵	United States	Single COL (age 65yrs) vs repeated COL (from 50yrs) vs no screening	Compared to no screening, ICER/LYG for single and repeated COL is \$US2981 and \$US10,983 (\$A5109 and \$A18,821). Compared to single, ICER/LYG for repeated COL is \$US14,878 (\$A25,496). Sensitivity analysis shows single COL most effective if screening at 60yrs, most cost-effective after 70yrs. Depending on compliance, repeated COL is 2–3 times more effective than single COL. Repeated COL 10yrly is the best option. If high cost or low compliance renders this option not feasible, single COL at age 65yrs is a cost-effective alternative.
Sonnenberg et al ²⁶	United States	CT colonography vs COL vs no screening	COL is more cost-effective than CT colonography. ICER of CT colonography vs no screening, was \$US11,484 (\$A17,934)/LYG and ICER of COL vs CT colonography was \$US10,408 (\$A16,254)/LYG. Results are sensitive to cost and compliance. CT colonography cost <\$US336 (\$A525), or compliance rates 15–20% better than COL, would make it a cost-effective option.
Ladabaum et al ²⁷	United States	CTC 10yrly vs COL 10yrly	COL is the most cost-effective strategy with ICER/LYG of \$US18,000 vs \$US28,700 (\$A26,594 vs \$A42,403). Results are robust, except when cost of CTC ≤ 60% the cost of COL.
Norum ²⁸	Norway	FSIG + FOBT (followed by COL in selected risk groups) vs no screening	Screening with FSIG appears to be cost-effective vs no screening (ICER = £2889 (\$A7541)/LYG). Sensitivity analysis suggests a linear correlation between compliance and cancer detected and/or prevented would result in cost/LYG remaining almost constant. If LYG is reduced from 2 to 1, cost per year doubles.
Flanagan et al ²⁹	Canada	FOBT + COL vs no screening	Biennial screening of 67% population aged 50–74yrs results in estimated 10yr mortality reduction of 16.7%, with an average life expectancy increase of 15 days. CER = \$CAN11,907 (\$A14,475)/LYG.

Study	Country	Comparator/ screening test	Conclusion
Salkeld et al 1996 ³⁰	Australia	FOBT yrly + COL vs no screening	Screening is cost-effective compared to no screening, with an ICER/LYG = \$A24,660, but further evidence is needed for screening efficacy as results are sensitive to this parameter (ICER range \$A12,695–67,848) and to false +ve rate.
Banaszkiewicz et al ³¹	Poland	Assessment of screening (FOBT + COL) and treatment costs	Overall cost is lower within screening (costs/patient = 9,261PLN vs 10,513PLN (\$A6979 vs \$A7915). Increased expense due to screening is offset by lower costs of adjuvant therapy.
Nakama et al ³²	Japan	FOBT + COL 1day vs 2day vs 3day collection	For 1, 2, and 3day collection, cases detected were 0.2, 0.4 and 0.5%. The 2day method is the least expensive. Average costs/case detected were \$US3630.68, \$US3350.65 and \$US4136.36 (\$A6222.17, \$A5741.97 and \$A7088.44).
Fric et al ³³	Czech Republic	Haemocult + COL if +ve (7yr program for ages 45–60) vs no screening	The adapted program of screening 45–60yr olds is effective. A significantly higher proportion of Dukes A and B detected at no extra cost and GNP saving of approximately \$US18,500 (\$A53,849).
Nakama et al ³⁴	Japan	Immuno FOBT + COL at ages 40–49yrs, 50–59yrs, and 60+yrs)	Screening subjects under 50yrs is less effective and cost-effective than screening at over 50yrs. For ages 40–49yrs, 50–59yrs, and 60+yrs, detection rates are 0.3% vs 1.6% vs 1.7%, and average costs to detect are \$US6023.64, vs \$US1424 vs \$US1410.47 (\$A10,111.34 vs \$A2,385.98 vs \$A2,367.63).
Nakama et al ³⁵	Japan	1. FOBT + COL vs medical check up with COL if asymptomatic 2. 40–49yrs vs 50–59yrs vs 60+yrs	Screening efficiency and cost-effectiveness for subjects younger than 50yrs is less than for subjects over 50yrs. Detection rates and average detection costs at 40–49yrs, 50–59yrs and 60+yrs, for (i) population screening with FOBT + COL. and (ii) medical check up + COL if asymptomatic, are: 1. 0.09% vs 0.28% vs 0.29% and \$US13,352.38 vs \$US4554.59 vs \$US4461.17 (\$A7645.38 vs \$A7488.57 vs \$A10,886.43); 2. 0.3% vs 1.5% vs 1.7% and \$US6850.89 vs \$US1516.99 vs \$US1391.44 (\$A11,499.97 vs \$A2546.43 vs \$A2335.69).

Study	Country	Comparator/ screening test	Conclusion
O'Leary et al ³⁶	Australia	FSIG 10yrly vs FOBT yrly/ biennially vs COL 10yrly vs no screening	FSIG and COL are cost-effective strategies. Compared to no screening, ICERs/LYG for FSIG 10yrly, COL 10yrly, FOBT biennially and FOBT yrly were \$A16,801, \$A19,285, \$A41,183 and \$A46,910. Results are sensitive to several parameters, but order of effectiveness mostly remains unchanged.
McMahon et al ³⁷	United States	FSIG vs FOBT vs COL vs DCBE	Strategies including DCBE emerged as optimal. In average-risk persons, DCBE 3yrly, or 5yrly with FOBT yrly, had ICERs <\$US55,000 (\$A96,975)/LYG. However DCBE 3yrly + FOBT yrly was not cost-effective. More research is required.
Wong et al ³⁸	Singapore	FOBT, vs Immuno FOBT vs FSIG vs DCBE vs COL for ages 50–54yrs, 55–59yrs, 60–64yrs, 65–60yrs	All of the strategies increase life expectancy. Overall, FOBT is the most cost-effective method (cost/LYG = \$SING162.11 vs \$SING368.06 vs \$SING340.36 vs \$SING211.57 vs \$SING402.24). Cost/LYS decreases with screening age. ^a
Leshno et al ³⁹	Israel	Single COL vs FOBT + SIG vs Annual FOBT vs COL 10yrly vs DNA vs no screening	Screening average risk individuals beyond age 50yrs is cost-effective, with COL and FOBT + SIG dominating the other strategies. ICER of FOBT + SIG vs COL was 1268 New Israeli Shekels (NIS) (\$A487)/LYG. Results are robust across a large range of variables but compliance with follow up does affect the results (ICER/LYG = 5780NIS and 4980NIS [\$A2272 and \$A1914]) for 40% and 60% compliance.
McGrath et al ⁴⁰	Canada	FSIG vs FSIG + ACBE vs CTC vs COL	For 16.9% probability, advanced adenoma FSIG has lowest cost (\$CAN1930 [\$A\$2725]/ detection vs \$CAN2840, \$CAN3681 and \$CAN2290 [\$A4010, \$A5198 and \$A3233] for FSIG + ACBE, CTC and COL). However, detection rate is only 69% vs 96% for COL. With $\geq 33.5\%$ probability of adenoma, COL is most cost saving (\$CAN1235 [\$A1744]/detection). Considering incremental costs to investigate 1000 patients, COL is most effective and cost-effective (ICER/advanced adenoma = \$CAN29,902 [\$A32,337]).

Study	Country	Comparator/ screening test	Conclusion
Glick et al ⁴¹	United States	DCBE 5yrly vs DCBE 5yrly + FOBT yrly vs FOBT yrly vs COL 5yrly vs SIG 5yrly vs SIG 5yrly + FOBT	All programs are cost-effective in the order of SIG, DCBE, SIG + FOBT, FOBT, COL, DCBE + FOBT (for 5yr polyp dwell time) and DCBE, FOBT, SIG + FOBT, FOBT, COL, DCBE + FOBT (for 10yr dwell time). CERs/LYG for 5yr and 10yr dwell times, range from \$US11,947–14,750 (\$A18,657–23,035) and \$US9435–12,815 (\$A14,734–20,013). DCBE 5yrly was sensitive to changes in test sensitivity and specificity, but CERs remain acceptable.
Sorrentino et al ⁴²	Italy	FOBT vs SIG vs FOBT+ SIG vs COL vs FC50 vs no screening	Screening programs based on SIG or COL are more cost-effective than FOBT. FC50 at age 50yrs appears to be most cost-effective. The 10yr cost/death prevented for FOBT, SIG, FOBT+ SIG, COL vs FC50 are \$US77,200, \$US15,500, \$US35,000, \$US15,100 and \$US14,000 (\$A135,685, \$A27,279, \$A61,597, \$A26,575, \$A24,639).
Shimbo et al ⁴³	Japan	Combinations of BFOBT or IFOBT with COL, BE, or BE/SIG with variations in screening intervals	Programs using IFOBT are the most cost-effective, with IFOBT 2yrly followed by COL if test +ve the most cost-effective (ICER = \$US13,100 [\$A26,265]/LYG). Beginning screening at 45yrs has best CER (\$US12,400 [\$A24,862]/LYG). However, commencement at age 40yrs is still cost-effective with ICER vs 45yrs of \$US16,800 (\$A33,643)/LYG. However, if compliance drops 10, 15 and 20% after each screening, commencement at 40yrs is dominated by later screening.
Lieberman ⁴⁴	United States	FOBT yrly vs FSIG (5yrly repeat if -ve) vs FSIG 5yrly/FOBT yrly vs COL 10yrly vs BE (5yrly repeat if -ve) over 10 year period	COL has the greatest impact on mortality. FOBT alone is the most cost-effective at 100% compliance. Cost/death prevented for FOBT, FSIG, FOBT/FSIG, COL, BE ranged from \$US225,000–280,000 (\$A420,118–522,813). At 50% compliance, ranges were \$US331,000–367,000 (\$A618,040–685,258). (FOBT becomes comparable with FS/FOBT and COL). FOBT cost-effectiveness is sensitive to detection rate, cost of care, cost of COL, and compliance with evaluation of +ve results.

Study	Country	Comparator/ screening test	Conclusion
Song et al ⁴⁵	United States	FDNA vs FSIG 5yrly vs FOBT yrly vs COL 10yrly vs FSIG/FOBT (all beg at age 50yrs) vs no screening.	FDNA 5yrly appears to be effective and cost-effective vs no screening, but is inferior to other strategies, all of which increase life expectancy at reasonable cost. ICERs/LYG vs no screening for FDNA, FSIG, FOBT, COL and FS/FOBT were \$US47,700, \$US15,500, \$US7200, \$US17,010 and \$US17,000 (\$A70,474, \$A22,162, \$A10,638, \$A25,131 and \$A25,116). FDNA was dominated by the other strategies; FOBT dominated FSIG; COL had ICER/LYG of \$US22,000 (\$A32504) vs FSIG; FSIG/FOBT had ICER/LYG of \$US22,100 (\$A32,651) vs FSIG and \$US16,300 (\$A24,082) vs COL. Significant improvement in sensitivity/specificity and a cost of \$US195 (\$A288) is required for FDNA to become comparable to COL.
Sonnenberg ¹⁰	United States	FOBT, FSIG 5yrly, COL, COL 10yrly, and FOBT/COL	For no intervention vs FOBT, FSIG, COL 10yrly and COL, ICERs/LYG were \$US9705, \$US36,509, \$US10,983, and \$US2981 (\$A16,631, \$A62,565, \$A18,821 and \$A4954). ICER of FOBT/COL vs no screening is \$US11,400 (\$A19,536). Single COL is the most cost-effective option. Sensitivity analysis suggests that overall, despite variations to parameters such as sensitivity/specificity, costs and compliance, COL remains the most cost-effective option.

Note ^a: Monetary values not converted to \$A due to unavailability of OECD PPP estimates for Singapore.

Numerous reviews of cost-effectiveness evidence relating to Colorectal Cancer screening have been published. These range from small reviews of a few articles to large systematic reviews. The findings are summarised in Table 22.5 and confirm the findings of this current evaluation. As previously stated, screening is cost-effective compared to no screening, but optimal tests, strategies or commencement age cannot be determined or recommended based on current evidence.

Table 22.5 Summary of findings from reviews of cost-effectiveness of screening

Study	Country	Study questions	Conclusion
Deenadayalu and Rex ⁴⁶	United States	Review of cost-effectiveness evidence of FDNA vs various strategies	Initial assessments indicate FDNA is cost-effective (studies cite cost/QALY gained ranges for FDNA of \$US674–9120 [\$A940–12,721] and FDNA 5yrly/COL10yrly of \$US14,528–17,095 [\$A20,265–23,845]). One study indicated FDNA 4yrly is cost-effective vs COL10yrly if sensitivity to detect cancer and adenoma = 90% and 70% respectively.
Redaelli et al ⁴⁷	United States	Review of evidence for alternative screening strategies	Most screening strategies have ICERs of approx \$US40,000 (\$A59,098)/LYG. FOBT has shown best positive results in terms of both clinical and economic outcomes.
Inadomi ¹¹	United States	Review of cost-effectiveness of screening for colorectal neoplasia	Several strategies (FOBT, FOBT/FSIG, COL, DCBE, alone or in combination) are cost-effective. Costs/LYG range from \$US8100–42,311 (\$A11,967–62,512). Cost/cancer detected range from \$US6851–13,352 (\$A10,123–19,727). However, determining ‘best’ strategy is difficult given the differences in studies (e.g. strategies compared, screening intervals, assumptions, costing methods).
Pignone et al ⁴⁸	United States	Systematic review of evidence for FOBT yrly vs FSIG 5yrly vs FOBT yrly + FSIG 5yrly vs DCBE 5yrly vs COL 10yrly	Screening appears cost-effective vs no screening, but a single optimal strategy cannot be determined. Cost-effectiveness ratios range from \$US5691–39,359 (\$A9073–62,747)/LYG (most between \$US10–20,000 [\$A15,943–31,885/LYS]). No one strategy was found to be consistently the most cost-effective or to have the best ICER. There is insufficient evidence to determine best starting and stopping age.
Pignone and Levin ⁴⁹	United States	Review of developments in screening with FOBT, BE, DCBE, COL, FSIG, DNA and CTC	Several methods are cost-effective vs no screening, but current evidence is not sufficient to determine most effective or cost-effective. ICERs range from \$US10,000–25,000 (\$A15,943–39,856)/LYG. DNA and CTC show early promise.

Study	Country	Study questions	Conclusion
Provenzale ⁵⁰	United States	Review of cost-effectiveness of screening for average-risk population	Screening is cost-effective with ICERs for the most effective strategies ranging from \$US10,000–40,000 (\$A15,943–63,769)/LYG. Variations in methods used, tests compared, screening intervals, etc. make it difficult to compare strategies.
Swaroop and Larson ⁵¹	United States	Review of cost-effectiveness of screening (FOBT yrly, FSIG 3yrly and 10yrly, FOBT yrly + FSIG 3yrly, FOBT or FSIG 5yrly, COL 10yrly, FOBT + FSIG 5yrly (plus 21 other combinations or tests))	Screening strategies have shown ICERs ranging from \$US9000–93,000 (\$A14,348–148,263)/LYG. Several options appear to be cost-effective, but a single best option cannot be determined. Compliance plays an important role in the efficacy of COL screening. Due to the number of tests available, physicians and patients have choices. The important thing is that screening is conducted.
McMahon and Gazelle ⁵²	United States	Review of cost-effectiveness evidence for available screening tests	Screening for average-risk individuals is cost-effective, but studies recommend that a wide variety of strategies and comparisons are difficult due to differences in strategies compared, assumptions, and outcomes reported. At present the important thing is that screening is effective. Choice of test is less critical than choice to get screened.
Crott ⁵³	Belgium	Review of most current economic studies analysing choice of optimal screening strategies (FOBT, FSIG, COL, DCBE, CTC, DNA)	Given current data, either FSIG or DCBE 5yrly, or a mix of both, offer reasonable cost-effectiveness, but at a loss of efficacy compared to COL, (though better than FOBT). FOBT is generally less cost-effective due to yearly/biennial repeat testing and high false +ve rate. COL is most effective but has high cost and is more invasive. Ultimate choice depends on local context, and is a function of threshold levels for policy makers.
Bolin et al ⁵⁴	Australia	Review of cost-effectiveness of screening strategies (FOBT, FSIG, COL)	Current data suggests FOBT (yrly and 3yrly), COL and FSIG/FOBT are all cost-effective (ICERs under \$A30,000/LYG).

Study	Country	Study questions	Conclusion
Gazelle et al ⁵⁵	United States	Review of current status and future outlook of screening and summary of cost-effectiveness literature	General consensus is that screening is cost-effective compared to no screening, but direct comparison of strategies is difficult. Costs/LYG range from \$US2057–15,168 (\$A3526–25,993) for FOBT (yrly or biennially) and \$US9287–22,170 (\$A15,915–37,992) for COL 10 yrly. There is evidence that cost-effectiveness of FOBT, and FSIG alone or in combination, is better than for BE or COL.
Frommer ⁵⁶	Australia	Review of effectiveness and cost-effectiveness of screening strategies (FOBT with Hemocult II, FSIG, COL)	All strategies are cost-effective. However, estimations of cost-effectiveness are affected by so many factors (poorly quantified studies, different strategies compared, etc.), it is not possible to conclude any one is significantly superior to another.
Wagner ⁵⁷	United States	Review of cost-effectiveness evidence for screening	Screening is cost-effective compared to none. Ranking varies depending on studies. DCBE is relatively favourable across studies.

22.5 Screening based on family history

There have been relatively few papers investigating the cost-effectiveness of screening and genetic screening for persons at above average/moderate or high risk of cancer based on family history. The majority of papers were cost-effectiveness studies or cost minimisation studies.

22.5.1 Screening for above average/moderate risk persons

One study conducted in Taiwan by Wu et al⁵⁸ investigated the costs and clinical effectiveness of screening for persons at above average/moderate risk. They compared colonoscopy to flexible sigmoidoscopy (FSIG) plus air contrast barium enema (ACBE) and found that costs for the two strategies were similar (2108 vs 2171 New Taiwan [NT]). However, 42% of cancers would be beyond the reach of detection by FSIG and 36% would be missed by ACBE because they were smaller than 0.5 cm. The authors concluded that colonoscopy is a more appropriate alternative. Monetary values for this study have not been converted to Australian dollars due to the unavailability of OECD PPP estimates for Taiwan. Results from this study should be taken as an indication only.

22.5.2 Screening for high-risk persons

Five studies were identified that investigated cost-effectiveness of genetic screening for persons at high risk. The studies varied in terms of gene mutations and screening strategies investigated and comparisons made.

Three United States studies investigated the cost-effectiveness of strategies to identify HNPCC carriers. Ramsey et al⁵⁹ conducted a cost-effectiveness study comparing alternative strategies¹ to identify HNPCC carriers among newly diagnosed patients. The results showed that following strategy 1 (Bethesda guidelines) is the most cost-effective approach to screening for HNPCC. Compared to no screening, ICERs/LYG (for probands, for probands plus relatives) for strategies 1, 2, 3 and 4 were \$US73,711, \$US11,865 (\$A117,512, \$A18,915); \$US213,290, \$US35,617 (\$A341,038, \$A56,782); \$US296,793, \$US49,702 (\$A473,156, \$A79,236); \$US1,625,787, \$US267,548 (\$A2,591,878, \$A426,533). Results were sensitive to survival benefits from aggressive surveillance in mutation carriers without Colorectal Cancer, and to the prevalence of HNPCC in the population. The ordering of the two main parameters remains unchanged, but the relative influence of each parameter varied substantially from strategy to strategy.

In another study, Reyes et al⁶⁰ conducted an economic analysis comparing effectiveness and costs (separately) of alternative strategies.² The results indicated that limiting genetic testing to persons meeting the Amsterdam criteria is not effective (7.8 carriers detected for every thousand screened), but testing all patients, though effective (67.6/1000), may be prohibitively expensive (ICER per carrier detected of \$US51,151 [\$A85,863]). The mixed strategy was the most cost-effective approach (59.6/1000 detected and an ICER compared to the Amsterdam strategy of \$US6441 (\$A10,812)/carrier detected). Sensitivity analysis confirmed the robustness of the results.

The third United States study, a cost-effectiveness study by Ramsey et al⁶¹ compared microsatellite instability (MSI) testing to no testing and found that screening patients with newly diagnosed cancer for HNPCC is cost-effective, especially if benefits to their immediate relatives are considered. Discounted ICERs/LYG for cancer patient, and for patient plus siblings and children, were \$US42,210 and \$US7556 (\$A70,854 and \$A12,684). Results were most sensitive to estimated survival gain from screening siblings and children, prevalence of HNPCC, and discount rate. Although these studies indicate that screening for HNPCC carriers is cost-effective, it is not possible to recommend any one particular strategy due to the variation in strategies evaluated.

Genetic screening can also be conducted for familial adenomatous polyposis (FAP). Only one study was identified that investigated this screening strategy. In Canada, Chikhaoui et al⁶² conducted a cost-minimisation study comparing clinical screening with genetic testing for FAP.³ The results showed that genetic testing is cost saving in comparison to clinical screening, and appears to be the optimal strategy. When FAP screening begins at puberty, costs for clinical screening compared to genetic testing were \$CAN3181 compared to \$CAN2259 (\$A4244, \$A3014). Cost savings continued up to a starting age of 36 years and the extent of savings was dependent on initial starting age (\$CAN922 (\$A1230) for starting age of 12 years) reduced to \$CAN211.67 (\$A282.40) for starting age of 30 years). The results were robust across a variety of assumptions.

The final study investigating genetic screening was a systematic review of the economic evidence for cancer genetic services conducted in the United Kingdom by Griffith et al in 2004.⁶³ Their findings stated that genetic testing has been shown to be cost saving and to prevent unnecessary invasive surveillance techniques with little or no loss of sensitivity in mutation detection. The extent of savings was dependent on the method used, with costs ranging from £653–5281 (\$A1416–11,453) if genetic

¹ **Strategy 1:** Bethesda guidelines (clinical/family history plus microsatellite instability testing and germline testing (MSI). Strategy 2: universal MSI. Strategy 3: germline test if meet clinical and family history criteria. Strategy 4: universal germline testing.

² **Modified:** tumour MSI if meet less stringent, modified, clinical criteria, and germline mutational if MSI-H tumour. **Test all:** tumour MSI for all, and germline mutational if MSI-H. **Mixed:** germline mutational testing if satisfy Amsterdam criteria and tumor MSI if meet less stringent criteria with substantial MSH2/MLH1 if MSI-H tumour. **Amsterdam:** germline MSH2 and MSH1 for high-risk persons meeting Amsterdam criteria.

³ **Clinical screening:** FSIG yearly for 12-25yr, biennially for 26-35yr and triennially for 36-60yr. **Genetic testing:** proband tested for APC. If positive, at-risk relatives tested. Clinical surveillance for positive at-risk relative, no surveillance for negative at-risk relatives. If proband negative, all at-risk relatives have clinical surveillance.

testing was conducted first, to £2781–5667 (\$A6031–12,291) for conventional screening. Population for testing for HNPCC mutation was found not to be cost-effective.

These studies provide some evidence for the cost-effectiveness of genetic screening, but due to the variations in strategies investigated and compared, the results should only be viewed as an indication of possible cost-effectiveness for particular screening options.

22.6 Screening patients with symptoms

A small number of studies were identified that investigated screening strategies for patients with symptoms. These consisted of only one cost-effectiveness study, three cost and consequences studies, one economic analysis and one review. The results are summarised in Table 22.6.

In general, the studies indicate that the strategies of FOBT, sigmoidoscopy (SIG), and rectosigmoidoscopy (RECT) plus immediate colonoscopy if polyps are found, are cost saving for the detection of cancer in symptomatic patients. For detection of both cancers and adenomas, FOBT plus endoscopy may be a cost-saving option. For patients with ulcerative colitis, colonoscopy every three years appears to provide cost-benefits. However, as these studies only evaluate costs and consequences, they provide, at best, an indication of possible cost savings.

The only cost-effectiveness study conducted indicated that flexible sigmoidoscopy (FSIG0 plus barium enema (BE) was cost-effective compared to FSIG for screening of patients with rectal bleeding. A definitive recommendation cannot be made on the basis of only one study. The results should be taken as an indication of possible cost-effectiveness with further research required.

Table 22.6 Results of studies investigating costs and outcomes of screening strategies for patients with symptoms

Study	Country	Study question	Conclusion
Ramsey et al ⁶⁴	United States	Comparison of screening vs evaluation of symptoms	Screening with FOBT can substantially reduce costs. Cancers detected by screening vs symptoms were 206 vs 717. Costs for the period 3mths pre-diagnosis to 12mths post-diagnosis were \$US24,636 vs \$US31,128 (\$A39,275 vs \$A49,625).
Sieg et al ⁶⁵	Germany	Evaluation of FOBT (faecal haemoglobin plus albumen) for symptomatic persons	Screening with FOBT is effective (99.5% specificity) and cost-effective. Cost/cancer detected = 8,667DM (\$A13,465); savings from cancer prevented exceeded costs by approx 2.3 times.
Manus et al ⁶⁶	Germany	Comparison of FOBT (hemofec) + endoscopy vs SIG for symptomatic and asymptomatic persons	For cancer detection, SIG for persons over 50yrs is advisable. For detection of both cancer and adenomas, FOBT + endoscopy is acceptable and cost-effective. The cost of identifying one cancer bearer was \$US1436 (\$A4180) (study A) and \$US271 (\$A789) (study B). Cost of identifying one cancer patient was \$US5435 (\$A15,819).
Arrigoni et al ⁶⁷	Italy	Comparison of RECT + ImmCOL, vs RECT + COL at subsequent examination, vs ImmCOL	If polyps are found during RECT, extending examination to the entire colon to remove all lesions found is a justifiable compromise to ImmCOL, reducing overall costs. Costs/lesion detected and cancer prevented for RECT + ImmCOL vs RECT + COL at subsequent examination, vs ImmCOL, were \$US898, \$US6703 (\$A1677, \$A12,516) vs \$US1243, \$US8227 (\$A2321, \$A15,361), vs \$US864, \$US7082 (\$A1613, \$A13,223).
Lewis et al ⁶⁸	United States	Comparison of FSIG vs FSIG + BE vs BE vs COL vs ANO + FSIG (or FSIG + BE or FSIG + COL) for young patients with rectal bleeding	For persons mid 30yrs+, evaluation of the entire colon yields greatest life expectancy at incremental cost comparable to other widely used strategies. FSIG + BE yielded greatest life expectancy with an ICER of \$US23,918 (\$A37,352)/LYG vs FSIG alone. For persons mid 20yrs and under, ANO + FSIG may be most cost-effective, with an ICER of \$US12,018 (\$A18,768)/LYG.

Study	Country	Study question	Conclusion
Lashner ⁶⁹	United States	Review of COL (at various screening intervals) for persons with ulcerative colitis	COL is more effective and less costly than no screening. The most reasonable strategy appears to be COL 3yrly. For patients with low-grade dysplasia, prophylactic colectomy is recommended. Persons at very high risk should have COL yrly, but if this is a concern, prophylactic colectomy is an alternative.

22.7 Diagnosis

A small number of cost and consequences studies have investigated various diagnostic procedures for Colorectal Cancer. The results are summarised in Table 22.7. Three studies evaluated positron emission tomography (PET) and found that the use of PET results in cost savings. However, these studies are limited in that they rely on estimates of sensitivity and specificity of PET based on case series, and the results are dependent on the assumption that PET did or would have changed management of the patient. Results should therefore be used as an indication of possible cost savings only.

The other two studies investigated a range of diagnostic procedures including computerised tomography (CT), magnetic resonance imaging (MRI), digital rectal examination (DRE) and transrectal ultrasound (TRUS) or endoluminal ultrasound (EUS). However, as the studies did not compare the same strategies it is not possible to determine the most cost-effective option and the findings should be taken as indicative of potential cost savings for certain diagnostic options.

Table 22.7 Results of studies investigating costs and consequences of various diagnostic procedures

Study	Country	Study question	Conclusion
Miles ⁷⁰	Australia	Evaluation of FDG–PET costs for preoperative evaluation of recurrent cancer and comparison of decision-tree analysis results with actual experience	Studies using decision-tree analysis suggest a cost saving of \$A2301.27/patient, with sensitivity analysis indicating the results are robust. Studies based on actual experience suggest a smaller saving of \$A230.75. The discrepancy suggests decision-tree models may not reflect actual practice.
Valk et al ⁷¹	United States	Evaluation of effectiveness, impact and costs of PET for patients with of recurrent cancer	PET shows more sensitivity (93% vs 69%) and specificity (98% vs 96%) than CT. PET may avoid unnecessary surgery, thereby reducing costs. Total PET costs were \$US140,400 (\$A247,092). Savings from surgery avoided would be \$US3003 (\$A5285)/patient.
Valk et al ⁷²	United States	Assessment of impact and costs of PET for patients with recurrent cancer	PET suggested change in surgical management in 35% patients. Costs for procedures that would have been avoided and PET were \$US300,000 (\$A601,497) and \$US112,000 (\$A224,559), a savings/cost ratio of 2:5. If PET replaced CT, the net cost would be \$US68,000 (\$A136,339), a savings/cost ratio of 4:4.
Harewood and Wiersema ⁷³	United States	Comparison of abdominal and pelvic CT vs abdominal CT + EUS vs abdominal CT + pelvic MRI	Abdominal CT+ EUS is the most cost-effective approach (recurrence-free rate of 87%, CER = \$US24,668 (\$A39,326)/yr). It dominated the other two strategies. Results are sensitive to sensitivity and specificity of EUS and pelvic MRI but remained mostly cost-effective if the sensitivity of EUS >66% and pelvic MRI <90%, and the specificity of EUS >78% and pelvic MRI <90%.
Brown et al ⁷⁴	United Kingdom	Comparison of MRI vs DRE vs EUS in staging CRC	MRI shows clinical and cost benefits over DRE and EUS. Agreement between staging and histological assessment was 94% vs 65% vs 69%. Cost per additional successful and accurately staged patient was £67,164 (\$A145,666) for MRI vs DRE, and £92,244 (\$A200,060) for MRI vs EUS. Sensitivity analysis suggests an MRI cost of £1079 (\$A2340) is required for MRI to equate with EUS. Ignoring resource implications of incorrect staging would result in cost per additional successful and accurately staged patient of £151 (\$A327) for MRI vs EUS and £288 (\$A625) vs DRE.

22.8 Follow up

Several cost-effectiveness/utility studies and cost and consequences studies were identified that investigated the effectiveness and costs of follow up. In addition, one review was found. Two studies compared follow up with no follow up, three investigated various follow-up tests, and another five compared different schedules. The studies comparing follow-up schedules were predominately cost-effectiveness/cost-utility studies. The results are summarised in Table 22.8.

Findings suggest that follow up is expensive, but effective. In general, carcinoembryonic antigen testing (CEA) has been identified as the most cost-effective individual follow-up test. Results regarding scheduling of follow up differ across studies, with intensive follow up identified as cost-effective in some studies but not in others. Risk-adapted follow up has been identified as a cost-effective alternative.

The studies provide some evidence that follow-up costs are justified and that CEA is potentially cost-effective. However, in relation to follow-up scheduling, as the studies evaluate different schedules, not only in terms of comparisons but also in, for example, what intensive or standard follow up involves, at this stage it is not possible to recommend any one follow-up schedule over another. Results should be used as an indication only.

Table 22.8 Results of studies investigating costs, effectiveness and cost-effectiveness of follow-up strategies

Study	Country	Study question	Conclusion
Ketteniss et al ⁷⁵	Germany	Comparison of follow up following resection vs no follow up (focus on patients with liver metastases)	Costs are high, but justified by good outcome in patients for whom early diagnosis is made (26.7% of patients with liver metastases are detected at early stage, when resection can be performed). Cost/LYG is 28,258DM (\$A47,945).
Audisio et al ⁷⁶	Italy	Comparison of follow up vs none following curative surgery	Postoperative follow up is expensive (cost/patient cured = \$US106,383 [\$A190,885]), but potentially effective (25% of detected recurrences are suitable for potentially curative second surgery). However, follow up should be tailored according to stage/site of the primary to reduce costs.
Matasar et al ⁷⁷	United States	Review of CEA, chest x-ray, COL, physical examination, standard follow up, and intensive/aggressive follow up for elderly patients	CEA appears most cost-effective and intensive follow up has also been identified as a cost-effective option. However more research is needed.
Bleeker et al ⁷⁸	The Netherlands	Assessment of costs and outcomes for symptoms vs CEA vs chest x-ray vs COL vs CT/ultrasound vs combination, vs physical examination as follow up for Dukes C patients	Mean cost of diagnostic procedure/curative resection is \$US9011 (\$A15,126). Ultrasound/CT and COL identified 22 recurrences at a cost of \$US11,970 (\$A20,093) per patient, while CEA, x-ray and physical examination identified a further six at a cost of \$US19,850 (\$A19,892) per patient.
Graham et al ⁷⁹	United States	Comparison of CEA vs chest x-ray vs COL vs physician examination for detecting recurrent disease	CEA is the most cost-effective surveillance procedure for curable and potentially curable patients. Costs per recurrence for CEA, chest x-ray, COL, physical examination were \$US5696, \$US10,078, \$US45,810, no benefit (\$A10,636, \$A18,818, \$A85,536, no benefit).

Study	Country	Study question	Conclusion
Michel et al ⁸⁰	France	Comparison of seven postoperative management strategies ^a for patients with stage II or III resected cancer	Current standard strategy may not be the most cost-effective strategy. Cost per surviving patient for strategies 1–7 were \$US10,788, \$US9118, \$US7373, \$US6781, \$US12,421, \$US9308 and \$US8954 (\$A18,986, \$A16,947, \$A12,976, \$A11,934, \$A21,860, \$A16,381 and \$A15,758).
Worthington et al ⁸¹	Australia	Review of evidence for intensive vs conventional follow up	Available data indicate intensive follow up using CEA would be of benefit in terms of lives saved (studies suggest CEA would be 1st indicator of recurrent disease in 38% and 89% of patients), and cost-effectiveness. Application of Australian values to results in overseas studies suggest CER is \$A23,812/LYG.
Renehan et al ⁸²	United Kingdom	Comparison of intensive vs conventional follow up	Intensive follow up is economically justified with an ICERs for the 5yr and 4yr trials of £3402 (\$A7378)/LYG and £3077 (\$A6673)/LYG. Sensitivity analysis confirmed the results are robust.
Staib et al ⁸³	Germany	Comparison of minimal vs intensive vs proposed risk-adapted follow up	Intensive follow up has low efficacy — 2% (current study), 10–15% (literature) — and is cost intensive. Costs per cured recurrent patient (current study and literature) were €6015 (\$A10,371) and €1683–5049 (\$A2902–8705) compared to minimal follow up €616–2624 (\$A1062–4524). Costs for proposed or risk-adapted follow up range from (low to high risk) €610–5910 (\$A1052–10,190).
Borie et al ⁸⁴	France	Comparison of simplified vs standard (includes CEA) follow up after curative resection (standard = 1998 French Consensus Conference)	For Dukes A, B and C, CERs were €4693, €10,068 and €1058 (\$A7898, \$A16,944, \$A1781) per QALY gained in favour of standard follow up. However, high variability (±€44,830 [\$A75,449], ±€180,195 [\$A303,268] and ±€2746 [\$A4622]) suggests no difference for the strategies. Sensitivity analysis indicates the results are robust.

^a Strategies compared in Michele, Merle, et al⁷⁹ are as follows. Strategies (S) 1–4 comprised adjuvant chemotherapy following curative resection of Stage III, plus: S1 – follow up for stage II/III patients; S2 – follow up for stage II/III younger than 75yrs; S3 – follow up for stage II/III younger than 75yrs, and for stage III patients with CEA >5 ng/ml; S4 – no follow up. Strategies 5–7 comprised adjuvant chemotherapy following curative resection of stage II/III, plus; S5 – follow up for patients stage II/III patients; S6 – follow up for stage II/III younger than 75yrs, and stage III with CEA >5 ng/ml; S7 – no follow up

22.9 Treatments

22.9.1 Surgery

Several studies investigating various surgical techniques and treatments were identified. The studies are varied in relation to disease stage investigated, techniques evaluated and comparisons made. The majority were economic analyses evaluating costs and effectiveness separately (5), or cost and consequences studies (2). Only two were cost-effectiveness/utility studies. The results are summarised in Table 22.9.

In general, the studies indicate that stenting is an effective and cost-saving procedure and that surgical resection is potentially more cost-effective than palliative chemotherapy. Findings for laparoscopic techniques vary across studies, with some indicating cost savings but others finding no cost-benefit.

Due to the variation in disease stage, techniques and treatments evaluated, comparisons made, results reported, and the studies being predominately economic analyses and cost and consequences analyses, it is not possible to recommend any one technique or treatment over another on the basis of cost-effectiveness. The studies at best provide an indication of possible cost savings for particular techniques or treatments.

Table 22.9 Results of studies investigating effectiveness, costs and cost-effectiveness of various surgical techniques and treatments

Study	Country	Study questions	Conclusion
Bouvet et al ⁸⁵	United States	Assessment of cost and outcomes for laparoscopic colon resection (LCR) vs laparoscopy converted to open colon resection (CCR) vs planned open colon resection (OCR)	LCR is an effective procedure, with costs similar to OCR but significantly less than CCR. Morbidity and mortality rates for LCR, CCR and OCR are similar, with two-year actuarial disease-free and disease-specific survival of 93%, 88%; 87%, 84%; and 88%, 84%. Costs ($\times 10^3$) were \$US12, \$US15 and \$US11 (\$A18.7, \$A23.4 and \$A17).
Janson et al ⁸⁶	Sweden	Assessment of costs to society and the health care system, of LCR compared to OCR	Within 12 weeks of surgery there is no significant difference in total cost to society (mean difference of €1846 [\$A3193]). However LCR is significantly more costly to the health care system (mean difference of €1556 [\$A2750]).
Vardulaki et al ⁸⁷	United Kingdom	Comparison of open vs laparoscopic surgery (LS)	LS costs more but the difference is relatively small (£227 [\$A607]). Short-term outcomes indicate a benefit for LS (overall conversion rate of 13% across studies, but 8% for studies with only Colorectal Cancer patients; reduction in complication rates but not significant). There was no significant difference in long-term outcomes.
Philipson et al ⁸⁸	Australia	Assessment of costs for open right hemicolectomy (ORHC) vs laparoscopically-assisted right hemicolectomy (LARHC)	LARHC results in no cost benefit. Total costs for ORHC vs LARHC were \$A7881 vs \$A9064. LAHRC is significantly more expensive.
Targarona et al ⁸⁹	Spain	Assessment of cost and outcomes of hand-assisted laparoscopic colectomy (HALS) compared to LS	HALS simplifies difficult intra-operative situations and is as effective as LS (no significant difference in clinical outcomes), with similar costs (\$US1782 vs \$US1710 [\$A2841 vs \$A2726]). HALS should be considered as a useful adjunct.

Study	Country	Study questions	Conclusion
Koperna ⁹⁰	Austria	Comparison of low anterior resections (LAR) with or without defunctioning stomas	Rate of defunctioning stomas should be reduced due to effect on overall costs, especially in patients with low leakage rates. Patients (without stoma) with anastomotic leakage need significantly longer hospital stay (45.3 vs 17.5 and 18 days for no stoma and stoma). Costs for LAR without stoma/no leakage, with stoma, and with leakage were €8400, €13,985 and €42,450 (\$A15,549, \$A25,888 and \$A78,580). ICER for with stoma is €158,705 (\$A293,780) and €60,915 (\$A112,760)/leakage avoided (leakage rates <3% and 6%). A 16.5% leakage rate is required to balance costs. Only duration and costs of ICU might influence the results.
Osman et al ⁹¹	United Kingdom	Assessment of costs and outcomes for stenting vs surgical decompression	Stenting is successful and cost saving. Procedure success rates, 30-day mortality and mean hospital days for stenting and surgical decompression were 94% and 100%; 0 and 1; 2.5 and 13.5. Costs/day were £1445 (\$A3866) vs £3205 (\$A8574) (mean saving of £1760 [\$A4708]/day for stenting, and at 15 procedures per year, an annual saving of £26,400 [\$A70,624]). Costs for stented proceeding to elective anterior resection vs decompression proceeding to reversal were £5035 vs £5720 (\$A13,469 vs \$A15,302 (saving of £685 [\$A1833])).
Xinopoulos et al ⁹²	Greece	Assessment of cost and outcomes for self-expanding metallic stents vs stoma for patients with inoperable malignant obstructions	Stenting is a suitable alternative, with similar costs to stoma. LOS for stenting vs stoma was 28 days vs 60 days. There was no significant difference in survival (21.4wks vs 20.9wks). Total costs were €2224 vs €2092 (\$A4265 vs \$A4011) (6.9% difference).
Binkert et al ⁹³	Switzerland	Assessment of cost and outcomes for self-expanding metallic stents as either a preoperative procedure or palliation	Metallic stent placement is a minimally invasive and less costly procedure. Average costs for stent vs no stent were 4362.11FR (\$A3211.08) vs 5538.46FR (\$A4077.03). Lower costs were due to shorter LOS, fewer surgical procedures and fewer days in ICU.

Study	Country	Study questions	Conclusion
Bissett et al ⁹⁴	New Zealand	Comparison of extrafascial excision (EFE) vs conventional surgery	EFE reduces local recurrence and appears to be associated with improved survival at costs similar to conventional surgery. For conventional vs EFE, rates for local recurrence were 21% vs 6%, 5yr actuarial local recurrence were 30% vs 10%, cancer-free survival were 63% vs 74%, and 5yr overall survival were 54% vs 60%). Average cost per local recurrence was an additional \$NZ10,471 (\$A12,468).
Beard et al ⁹⁵	United Kingdom	Comparison of hepatic liver resection vs standard non-surgical cytotoxic treatment (palliative)	Hepatic resection is cost-effective compared with non-surgical treatment. At 5yr survival, marginal benefit is 1.6LYG (undiscounted) at a marginal cost of £6742 (\$A18,435). If 17% have only palliative resections, cost is £5236 (\$A14,317)/LYG (£5985 (\$A16,365) discounted). For 20yr survival, approximate costs are £1821 (\$A4979) (£2793 (\$A7637) discounted). Sensitivity analysis shows costs/LYG are consistently less than £15,000 (\$A41,076).
Miller et al ⁹⁶	United States	Comparison of surgical resection vs diagnostic/ palliative surgery vs non-operative treatment	Diagnostic/palliative surgery is expensive and affects QALY survival adversely (1.92yr). Surgical resection may be cost-effective, particularly if calculated using patient preferences. ICER/QALY gained using health care professional preferences, and patient preferences were \$US109,777 and \$US56,698 (\$A188,124 and \$A97,163).

22.9.2 Chemotherapy

Numerous studies have investigated the effectiveness and cost-effectiveness of various chemotherapy regimes or agents, methods of delivery, timing and setting. Methodologies used and comparisons made varied considerably across studies. The majority of the studies have conducted cost-effectiveness, cost-utility, cost-benefit or cost-minimisation analyses. There have also been several cost and consequences, economic, and cost analyses, as well as a few reviews. The results of studies conducting analyses are summarised in Table 22.10. Reviews are summarised in Table 22.11.

Although these studies indicate some regimes or agents, delivery methods, timing or setting appear to be relatively more cost-effective or cost saving than others, there is insufficient evidence at this stage to recommend one over others on the basis of cost-effectiveness. It should also be noted that extrapolating these results to the Australian context is not appropriate, as relative cost-effectiveness is largely driven by the costs of the different chemotherapy regimes and modes of delivery, which can vary internationally. The studies at best provide an indication of possible cost-effectiveness or cost savings for particular regimes or agents, delivery methods, timing or setting.

Table 22.10 Results of studies investigating effectiveness, costs and cost-effectiveness of alternative chemotherapy regimes

Study	Country	Study questions	Conclusion
Durand-Zaleski et al ⁹⁷	France/United States	Comparison of HAI vs intravenous chemotherapy vs symptom palliation	Cost-effectiveness of HAI is within the range of accepted treatment for serious conditions, but may be borderline in some countries. Mean discounted survival HAI vs intravenous chemotherapy was 16.3mths vs 13.1mth). ICERs/LYG for Paris and Canada were \$US73,635 and \$US72,300 (\$A137,491 and \$A134,998). Sensitivity analysis indicates variations in survival and costs result in ICER ranges of \$US63,717–73,680 (\$A118,972–137,574) (Paris) and \$US65,867–87,012 (\$A122,986–162,468) (Canada).
Vidal-Jove et al ⁹⁸	Spain	Comparison of intra-arterial chemotherapy vs IV chemotherapy for advanced malignancies	Intra-arterial chemotherapy results in improved median survival (13mths vs 6mths) and overall response rates (80% vs 20%) and is cost-effective compared to IV chemotherapy (cost per response-for each month of survival month of \$US919 vs \$US662 [\$A1843 vs \$A1327]).
Tampellini et al ⁹⁹	Italy	Assessment of cost of chronochemotherapy vs FOLFOX (de Gramont)	Direct costs for a single cycle of chronochemotherapy appear to be comparable to single course FOLFOX (€337 (\$A543) or €356 (\$A574) (rented pump) vs €346 (\$A558). Major material cost is balanced out by lower toxicity costs (€144 vs €288 [\$A232 vs \$A464]).
Messori et al ¹⁰⁰	Italy	Comparison of adjuvant intraportal chemotherapy vs none	Adjuvant intraportal chemotherapy is cost-effective with an ICER/ LYG of \$US1210 (\$A2171)/discounted (\$US494 (\$A888) undiscounted). Sensitivity analysis shows results are robust for drug costs and still cost-effective for variation in LOS and survival.
Jansman et al ¹⁰¹	Netherlands	Analysis of the cost benefit of capecitabine vs 5-FU+LV	Treatment with oral capecitabine is cost-saving compared to 5-FU+LV. Baseline savings for palliative and adjuvant treatment estimated at €1610 (\$A2946) and €934 (\$A1709). Sensitivity analysis shows results are robust.

Study	Country	Study questions	Conclusion
Hieke et al ¹⁰²	Germany	Assessment of costs for 5-FU regimens (Mayo, AIO/Ardalan) vs oral capecitabine as inpatient vs outpatient/day clinic vs office-based oncologist treatment	Most expensive treatments were AIO/Ardalan for office-based, and Mayo for hospital setting. The least costly in office-based was capecitabine. Overall, the least expensive option was AIO/Ardalan in municipal hospital settings. Hospitals are unlikely to cover costs in this situation. Substantial cost savings (without incurring loss to the provider) possible with office-based capecitabine treatment.
Iveson et al ¹⁰³	United Kingdom	Comparison of irinotecan vs infusional 5-FU	Irinotecan is cost-effective compared to 5-FU, with an ICER/LYG of £7696 (\$A20,089) (de Gramont) and £11,947 (\$A31,185) (Lokich). Sensitivity analysis shows that using lifetime estimates instead of median survival changes ICERs to £10,104 and £14,942 (\$A26,583 and \$A39,003).
Levy-Piedbois et al ¹⁰⁴	France	Comparison of irinotecan vs intrafusional 5-FU (Lokich) vs intrafusional 5-FU (AIO) vs intrafusional 5-FU (de Gramont [LV5-FU2]) for 2nd-line treatment	Least expensive treatment is 5-FU, but the additional cost of irinotecan is balanced by additional survival (2.3 mths). ICERs range from \$US9344 to \$US10,137 (\$A16,445–17,840)/LYG. Sensitivity analysis shows that with variation in survival, ICERs range from \$US3000–45,000 (\$A5280–79,196), and adding irinotecan to intrafusional 5-FU (de Gramont [LV5-FU2]) results in an ICER of \$US29,373 (\$A42,190)/LYG.
Norum et al ¹⁰⁵	Norway	Assessment of cost and outcomes for raltitrexed vs Nordic-FLv in metastatic cancer	No difference in overall survival (median survival of 14.7mths vs 15.4 mths) and costs (€6800 vs €6881 [\$A1235 vs \$A1249]). Raltitrexed is the most toxic in terms of diarrhoea, nausea/vomiting, appetite loss, but more patients receiving raltitrexed preferred the treatment schedule and frequency of hospital visits (87% and 75%) than did those having Nordic Fly (55% and 45%).
Groener et al ¹⁰⁶	Netherlands	Comparison of 5-FU+LV vs raltitrexed	There was no significant difference in survival benefits, but raltitrexed resulted in fewer side effects (rate of 57.07% vs 72.97%). The ICERs/additional survivor post 6mths and 12mths of raltitrexed were \$US16,086 and \$US154,611 (\$A29,894 and \$A272,102). ICER/additional side-effect-free patient was \$US3936 (\$A6927).

Study	Country	Study questions	Conclusion
Kerr and O'Connor ¹⁰⁷	United Kingdom	Assessment of cost and outcomes for raltitrexed vs 5-FU (Mayo regimen)	There is no difference in response rate and survival, but raltitrexed reduces demand on clinic and pharmacy resources (reduced toxicity (12.4 vs 16.7) and administration (6 vs 22 days) without increasing cost of monthly treatment (£781 [\$A2039] [raltitrexed] vs £834 [\$A2177] [5-FU]).
Maroun et al ¹⁰⁸	Canada	Comparison of UFT/FA vs parenteral FU/FA	Cost of treatment per patient and per cycle using UFT/FA is less than using FU/FA. Total cost savings per patient per cycle and per treatment were \$CAN826 and \$CAN3221 (\$A1217 and \$A4745).
Ward et al ¹⁰⁹	United Kingdom	Assessment of cost and outcomes for capecitabine vs UFT/LV vs three 5-FU regimens — (Mayo, modified de Gramont and inpatient de Gramont), as 1st-line treatment	Oral therapies are associated with cost-benefits but have no proven survival benefit. There is no proven survival difference for the 5-FU regimens. Cost savings for capecitabine and UFT/LV vs Mayo, modified de Gramont and de Gramont were £1461, £1353 and £4123; £209, £101 and £2870 (\$A3696, \$A3422, \$A10,429, \$A529, \$A255 and \$A7260). Sensitivity analysis indicates savings for capecitabine could range from £483 (\$A1222) vs modified de Gramont to £4123 (\$A10,429) vs de Gramont; Results for UFT/LV could range from saving of £101 (\$A255) vs modified de Gramont to an additional cost of £445 (\$A1126) vs Mayo.
Smith et al ¹¹⁰	Australia	Comparison of 5-FU + levamisole vs no chemotherapy after full resection for Dukes C patients	Inclusion of 5-FU results in incremental cost of \$A7000 with ICER of \$A2916/LYG and \$A17,500/QALY gained. Sensitivity analysis shows results may vary from \$A12,000–\$A31,900.
Glimelius et al ¹¹¹	Sweden	Comparison of 5-FU+LV (palliative chemotherapy) + best supportive care vs best supportive care	Palliative chemotherapy is cost-effective with an ICER/LYG of 102,000–204,000SEK (\$A25,166–50,332). Results are sensitive to changes in survival differences.
Bonistalli et al ¹¹²	Italy	Comparison of adjuvant FU+ levamisole vs no chemotherapy for stage III cancer	Adjuvant therapy with FU + levamisole has favourable economic benefits (ICERs = \$US1422 (\$A3239)/LYG, \$US1501 (\$A3419)/QALY gained. Sensitivity analysis confirms the results robust.

Study	Country	Study questions	Conclusion
Cunningham et al ¹¹³	United Kingdom	Comparison of irinotecan + 5-FU+FA vs 5-FU+FA alone as 1st-line treatment	Irinotecan + 5-FU/FA is cost-effective compared to FU/FA alone, with ICER = £14,794 (\$A40,452)/LYG. Sensitivity analysis confirms the results are robust.
Poston et al ¹¹⁴	United Kingdom	Comparison of oxaliplatin + 5-FUFA vs 5-FU/FA alone	Oxaliplatin + 5-FU/FA increases resection rates compared to 5-FU/FA at an acceptable cost (ICER = £11,985 [\$A31,182]/LYG). Sensitivity analysis indicates an ICER range of £5489–15,624 (\$A14,560–41,471), with variations to resection rates, survival rates and discounting.
Kopera and Semmler ¹¹⁵	Austria	Comparison of oxaliplatin + FU/LV vs FU/LV alone for stage III patients	Oxaliplatin + FU/LV is cost-effective for stage III patients. Even under the most conservative scenario, (20% increase in mortality and recurrence reduction rates), compared to best supportive care, LYG (undiscounted and discounted) for FU/LV and for oxaliplatin + FU/LV was 51 vs 62; 41.8 vs 50.8. Undiscounted and discounted ICERs/LYG were \$US5352, \$US6503 (\$A7907, \$A9608); \$US7425, \$US8865 (\$A10,970, \$A13,098); \$US9920, \$US10,956 (\$A14,656, \$A16,187); and \$US10,609, \$US12,485 (\$A15,674 \$A18,446).
Focan ¹¹⁶	Belgium	Comparison of 5-FU/FA + oxaliplatin administered either as standard (flat arm A) or chronomodulated (arm B) drug infusions	Costs are basically equivalent. Higher treatment costs for chronomodulated drug infusion are counterbalanced by fewer complications and shorter LOS. Costs are also less for melodie pump. For flat arm A and arm B (intelliject and melodie pump), costs/course were 131,340BEF, 107,176 BEF, 134,668 BEF and 110,592 BEF (\$A246,129, \$A200,846, \$A252,366, \$A207,248).

Study	Country	Study questions	Conclusion
Murad et al ¹¹⁷	Brazil	Assessment of costs of UFT/LV compared to 5-FU	UFT/LV has an economic advantage over 5-FU and is therefore a useful and economic alternative. Costs for UFT/LV vs 5-FU (Brazil; Argentina) as adjuvant therapy were \$US9624 vs \$US9654 (\$A15,672 vs \$A15,721); \$US12,295 vs \$US13,077 (\$A20,022 vs \$A21,296). For treatment of metastatic disease, costs were \$US10,178 vs \$US10,491 (\$A16,575 vs \$A17,084); \$US12,369 vs \$US13,558 (\$A20,143 vs \$A22,079). Sensitivity analysis indicates the results are robust.
Monz et al ¹¹⁸	Germany	Comparison of FU/FA + levamisole vs FU + levamisole alone	Adding FA results in clinical benefits and costs that may be acceptable to decision makers in the long term. The 5yr trial mean overall and disease-free survival (5% discounted) for FA vs none was 3.72yrs, 3.27yrs vs 3.52yrs vs 2.90yrs. Survival for beyond the trial was 9.38yrs, 8.11yrs vs 8.13yrs, 7.06yrs. For the trial, ICERs/LYG and disease free LYG (5% discounted) were €51,225 and €33,008 (\$A88,324 and \$A56,913). Beyond the trial, ICERs were €11,020 and €11,176 (\$A19,001 and \$A19,270). Sensitivity analysis confirmed the results are robust.
Nicholls et al ¹¹⁹	United Kingdom	Comparison of 5-FU/FA + oxaliplatin vs 5-FU/FA + irinotecan vs 5-FU/FA alone	Both combinations offer comparable benefits in terms of effectiveness and cost-effectiveness over 5-FU/FA alone. The addition of oxaliplatin is more cost-effective than the addition of irinotecan. Compared to 5-FU/FA, the ICERs per progression-free year were £26,665 and £30,171 (\$A70,877 and \$A80,102). Sensitivity analysis indicated ICERs could range from £21,421–31,909 (\$A56,863–84696) and £23,692–36,651 (\$A62,886–97,284).

Study	Country	Study questions	Conclusion
Lloyd Jones et al ¹²⁰	United Kingdom	Comparison of irinotecan vs oxaliplatin vs raltitrexed vs (all either alone or in combination with 5-FU/FA) vs 5-FU/FA in 1st- and 2nd-line treatment for advanced patients	For 1st-line treatment, a combination of either irinotecan or oxaliplatin with infusional FU/FA appears to extend progression-free survival by 2–3mths compared to 5-FU/FA alone. Marginal costs per progression-free survival year for oxaliplatin and irinotecan are £23,000 and £58,400 (\$A61,049 and \$A155,012). If it is assumed all treatment is conducted as outpatients, ICER per progression-free year is unchanged for oxaliplatin, £49,000 (\$A130,061) for irinotecan, and £26,400 (\$A70,074) for 2nd irinotecan. For 2nd-line treatment ICER/LYG for irinotecan vs outpatient 5-FU/FA and best supportive care are £11,180 and £17,700–28,200 (\$A29,675 and \$A46,981–74,852).
Hale et al ¹²¹	United Kingdom	Assessment of costs and outcomes of de Gramont regimen vs Lokich regimen vs raltitrexed	Lokich, with comparable clinical benefit at only ½ the cost of de Gramont, offers best value for money. Total societal costs for de Gramont, Lokich and raltitrexed were £5050 vs £2616 vs £2435 (\$A13,807 vs \$A7,153 vs \$A6,658). From the hospital perspective, Lokich was the least costly (£1699 vs £666 vs £814 (\$A4646 vs \$A1821 vs \$A2226). Although cost differences for treatment of side effects and serious adverse events were not significant, raltitrexed resulted in higher toxicity and impaired QoL vs de Gramont and Lokich. Sensitivity analysis confirmed the results are robust.
Rowe et al ¹²²	United Kingdom	Assessment of outpatient de Gramont (using elastomeric infusional device) vs inpatient treatment	Outpatient administration is acceptable to patients who chose it, shows better QoL scores (improved overall health and QoL scores), and results in considerable cost saving (£3800 vs £1735 [\$A9612 vs \$A4389]).

Only a few reviews have been published, predominately concerning evidence about the cost-effectiveness of newer agents such as capecitabine, raltitrexed, irinotecan, oxaliplatin and oral tegafur compared to 5-FU-based regimens. The findings, summarised in Table 22.11, suggest that the newer agents may be more cost-effective than the 5-FU-based regimens, but further research is required and an optimal agent is difficult to determine. The reviews confirm the findings of this current evaluation. There is insufficient evidence at this stage to recommend one chemotherapy regime or agent over others on the basis of cost-effectiveness. The studies at best provide an indication of possible cost-effectiveness or cost savings for particular regimes or agents.

Table 22.11 Summary of findings from reviews of cost-effectiveness of chemotherapy agents and regimes

Study	Country	Study questions	Conclusion
Redaelli et al ⁴⁷	United States	Review cost-effectiveness evidence for alternative chemotherapy regimens	New treatments (particularly oral tegafur) appear to be more cost-effective than 5-FU-based therapies for advanced and metastatic cancer. Depending on country, setting (1st-line, 2nd-line or rescue therapy) and comparative treatments, ICERs of irinotecan and raltitrexed are generally within the threshold of \$US30–50,000 (\$A44,323–73,872)/LYG. Both have significant and consistent economic advantage over 5-FU. There is a limited evidence for adjuvant therapy. It appears FU + levamisole or FA are cost-effective (if 5% improvement in 5yr survival rate), with possible ICERs of \$US2094–6500 (\$A3094–9,603)/LYG. More research is needed.
Scott and Twelves ¹²³	United Kingdom	Review cost-effectiveness of new chemotherapy drugs vs FU (concentrating on drug costs)	Capecitabine, raltitrexed, irinotecan and oxaliplatin alone, or in combination with 5-FU or FU/FA, are cost-effective compared to FU or FU/FA alone. Cost savings range from \$US626–5000 (\$A925–7387) per patient, ICERs/LYG range from \$US21,591–59,403 (\$A31,899–87,764) (1st-line treatment) and \$US9344–10,137 (\$A13,805–14,977) (2nd-line treatment). Comparisons between newer agents is difficult due to non standardised methods, and judgments may differ between countries, tumour type, available treatments, etc.
Matasar et al ⁷⁷	United States	Review cost-effectiveness of chemo regimens in elderly patients	ICER of fluorouracil-based regimens, depending on delivery strategy, use of model agents and stage of cancer, vary from \$US2000–20,000 (\$A2790–27,897) per QALY gained. Reported ICER of \$US10,000 (\$A13,949) per QALY gained for irinotecan is likely to be an underestimate and requires further research. Raltitrexed, capecitabine and oxaliplatin also require further research. UFT appears to be potentially cost saving. HAL cannot be recommended for elderly patients

22.9.3 Other

A small number of studies have investigated other treatment alternatives such as preoperative radiotherapy and radiofrequency ablation.

In the Netherlands, van den Brink et al¹²⁴ evaluated the cost utility of preoperative radiotherapy (PRT) and found that, in the short term, PRT is effective and cost-effective, with a cost/QALY gained of \$US25,100 (\$A40,015). Sensitivity analysis confirmed the results are robust. In a Swedish study, Dahlberg et al¹²⁵ investigated the cost-effectiveness of PRT in the primary treatment of resectable rectal cancer and found it to be cost-effective with a cost/LYG of \$US3654 (\$A6134). Even in the most pessimistic scenario, the cost/LYG was US15,228 (\$A25,562). These studies provide some evidence that PRT is cost-effective, but additional evidence from further research is needed before a definitive recommendation can be made.

Radiofrequency (RF) ablation for the treatment of liver metastases was evaluated in a cost-effectiveness study by Shetty et al.¹²⁶ Results of the study indicate RF ablation is a cost-effective strategy compared to palliative care. Incremental cost-effectiveness ratios per life year gained at six months, one-, two-, three- and five-year median survival were \$US20,424, \$US11,407, \$US6731, \$US5034 and \$US3492 (\$A31,895, \$A17,814, \$A10,512, \$A7861 and \$A5453). Sensitivity analysis shows that the results, though sensitive to observation hours, number of lifetime treatments, frequency of follow up, and cost of abdominal CT and outpatient treatment, remain cost-effective. While these results suggest that RF is cost-effective, recommendations cannot be based on the findings of only one study. These results indicate that RF is potentially cost-effective with further research required.

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