COLORECTAL CANCER IN EUROPE AND AUSTRALIA: CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5FU/LV</td>
<td>5-Floururacil/Leucovrin</td>
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<tr>
<td>AIOM</td>
<td>Associazione Italiana di Oncologia Medica (Italy)</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost Effectiveness Analysis</td>
</tr>
<tr>
<td>COL</td>
<td>Colonoscopy</td>
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<tr>
<td>CRC</td>
<td>Colorectal Cancer</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DCO</td>
<td>Death Certificate Only</td>
</tr>
<tr>
<td>DMCG</td>
<td>Danish Multidisciplinary Cancer Groups</td>
</tr>
<tr>
<td>DRG</td>
<td>Diagnosis-Related Group</td>
</tr>
<tr>
<td>EEC</td>
<td>European Economic Community</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Evaluation Agency</td>
</tr>
<tr>
<td>ESMO</td>
<td>European Society for Medical Oncology</td>
</tr>
<tr>
<td>EUROCARE</td>
<td>Cancer Incidence, Mortality and Prevalence in the European Union</td>
</tr>
<tr>
<td>FNCLCC</td>
<td>Fédération Nationale des Centres de Lutte contre le Cancer (France)</td>
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<tr>
<td>FOBT</td>
<td>Fecal Occult Blood Test</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>Folinic Acid, Flurouracil and Oxaliplatin</td>
</tr>
<tr>
<td>FS</td>
<td>Flexible Sigmoidoscopy</td>
</tr>
<tr>
<td>HAN</td>
<td>Head and Neck (cancer)</td>
</tr>
<tr>
<td>HFA-DB</td>
<td>Health for All Database</td>
</tr>
<tr>
<td>HRG</td>
<td>Health Resource Group</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>iFOBT</td>
<td>Immunological Fecal Occult Blood Test</td>
</tr>
<tr>
<td>I/M</td>
<td>Incidence/Mortality Ratio</td>
</tr>
<tr>
<td>IARC</td>
<td>International Association of Cancer Research</td>
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<td>IDB</td>
<td>International Database</td>
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<td>IMS</td>
<td>Intercontinental Medical Statistics</td>
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<tr>
<td>LSE CRC Survey Tool</td>
<td>London School of Economics Colorectal Cancer Survey Tool</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Health and Clinical Excellence</td>
</tr>
<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
</tr>
<tr>
<td>ONS</td>
<td>Office of National Statistics (UK)</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
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<tr>
<td>QALY</td>
<td>Quality-Adjusted Life Year</td>
</tr>
<tr>
<td>SALAR</td>
<td>Swedish Association of Local Authorities and Regions</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results Database</td>
</tr>
<tr>
<td>SNGFE</td>
<td>Société Nationale Française de Gastroenterologie (France)</td>
</tr>
<tr>
<td>SOR</td>
<td>Standards, Options et Recommendations</td>
</tr>
<tr>
<td>TME</td>
<td>Total Mesorectal Excision</td>
</tr>
<tr>
<td>UFT</td>
<td>Tefafure-Uracil</td>
</tr>
<tr>
<td>UKCAR</td>
<td>United Kingdom Association of Cancer Registries</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
<tr>
<td>VIKC</td>
<td>Vereniging Integrale Kanker Centrum</td>
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Executive Summary

The issue
1. This report aims to capture current information regarding the management and funding of colorectal cancer (CRC) in Europe and Australia and is based on primary and secondary sources. Specifically, the objectives are, first, to understand the available CRC data sources, their accessibility, availability, and use in research and policy. Second, to map cancer and CRC funding and resource allocation processes. Third, to identify CRC primary and secondary (screening) prevention policies, and their encouragement, implementation and enforcement. Fourth, to discuss national and international CRC standards of care. Fifth, to examine implementation of national guidance and to examine current pathways for CRC management. Sixth, to assess access and availability of CRC diagnostic services and pharmaceutical treatments. And, finally, to investigate the appropriateness and adequacy of current funding and management of CRC services.

2. Colorectal cancer burden varies within Europe and Australia, yet remains a significant disease in all countries. In Europe, colorectal cancer is the second most diagnosed form of cancer, accounting for 13% of total cancer incidence, and is also second in cancer mortality, accounting for 12% of total cancers in 2006. Over the past decade incidence has been increasing, and is likely to continue to do so with an aging European and Australian population, while mortality has decreased somewhat but not as much as other similar high incidence, high mortality cancer. Despite this compounding problem, few countries seem to have concerned themselves with colorectal cancer, likely due to poor political and public interest, limited preventative philosophies and resource constraints.

Background
3. Incidence and mortality do differ significantly between European countries, even countries that are close to one another geographically. Southern Europe has the lowest incidence and mortality (Greece, Turkey), while Eastern Europe has the highest (Czech Republic, Hungary, Slovakia), probably due to differences in lifestyle, stage at diagnosis and treatment. Similarly, males have higher incidence and mortality than females, relating to differences in screening participation, physician seeking behaviour as well as lifestyle. These variations suggest that country policy and societal norms play a large role in colorectal cancer development and ultimately cancer burden.

4. Although survival from CRC has increased over the past decade largely due to improved treatments and standards, it still remains poor in Europe and Australia. Evidence indicates that less than 55% of Europeans and Australians achieve 5-year survival in comparison to over 75% for breast and prostate cancers and 65% for American CRC patients. These figures vary between countries from under 40% (Poland) to almost 60% (Sweden), and with women having slightly better survival than men. Part of the problem is high detection of latter stages of cancer, versus early detection found in other cancers with established screening programs, poor or irregular surveillance practices of those at increased risk, as well as limited resources or interest allocated to colorectal cancer.
Resource allocation and expenditure

5. Information regarding resources allocated to cancer is particularly scarce, even more so for colorectal cancer. Cancer expenditure adjusted for cancer population burden in the few countries collecting cancer expenditure, found large variations between countries (high of €85,116 per total cancer death in Sweden to a low of €9,528 in Russia). This continued with colorectal cancer expenditure, where the range was from €10,288 per colorectal cancer mortality (Hungary) to €122,828 (France).

6. Approximately half of surveyed countries had formal resource allocation mechanisms; fewer had disease-specific resource allocation, and only Australia reported cancer-specific resource allocation. The majority of countries perceived insufficient resources were allocated to cancer care and CRC care. Eastern European countries reported significant problems with cancer-specific funds, with persistent shortcomings and insufficient funding.

7. Many of the countries that have formal screening activities, be it for CRC or other cancers, have formal screening resource allocation. Australia, France and the UK all have governmental funding for their CRC screening programmes, ranging from €8-25 million. These values are half of what these countries allocate to their breast cancer screening programmes.

8. It appears that cancer spending displays significant variation between countries, along with the majority of countries not accounting for cancer in its resource allocation mechanisms. As cancer accounts for significant morbidity and mortality after cardiovascular disease, this seems to be an important omission. Cancer care is not an insignificant part of health care expenditure, and should be accounted and planned for appropriately.

Data quality

9. Cancer data collection, be it population statistics or spending, remains relatively poor in Europe. Not all countries have reliable cancer registries, as deemed by the International Agency for Research in Cancer (IARC), and the data that is collected varies widely between countries. One country may collect only incidence and mortality, while another may collect these plus prevalence, stage at diagnosis as well as recurrence. Furthermore, there are large variations within countries, particularly where regional cancer registries exist.

10. The existence of variations across as well as within countries implies that national coverage for all cancers may be less than 20%, raising questions in European registry reliability and validity. Even when data adheres to standards and quality control set out by the International Association of Cancer Registries (IACR), in some countries very little information is deemed of high enough quality (Greece, Romania, Turkey). Survival data appears to be of particular concern as there appears to be a time delay, and many countries have disjointed communication systems reporting mortality thus difficult to monitor disease progression to its ultimate outcome. In terms of longitudinal data, a number of countries have only begun collecting in the 1990s; Eastern European countries have collected data for decades, but their quality remains unknown.

11. Cancer expenditure data is similarly scarce, and having any cancer expenditure data, let alone CRC-specific data, seems to be the exception rather than the rule. The countries that do collect cancer spending data, usually do not collect it annually but only collect it in detail on a periodic basis (Australia, France, Germany, Hungary, Netherlands, Russia, Slovakia, Spain, Sweden, UK).
12. Both these deficiencies, in terms of population statistics and cancer, as well as CRC-related expenditure data, mean that estimating colorectal cancer requirements for the future become difficult and more prone to errors in capacity planning. Ministries of health need to collect cancer specific expenditure, including all major high incidence cancers. Cancer registries should be national, and, if regionally organised, work together under an umbrella organisation to ensure national coverage. Checks on quality, both on population statistics and on expenditure should be routinely carried out and built into the data collection system.

Screening

13. CRC is one of the few cancers amenable to cancer screening activities. If detected at its pre-cancerous adenomatous polyp stage, CRC can be prevented. As this cancer is also largely asymptomatic until latter stages, screening can detect early stage cases with much higher rates of curative treatment and longer survival. Despite these facts and in addition to rising CRC incidence, only a minority of countries participate in formal CRC screening (Finland, France, Italy, UK and Australia), yet available cost-effectiveness studies on CRC screening methods conclude that any CRC screening method is preferable to no screening. On the whole, our results do agree with the recently published 2008 Cancer Screening in the European Union with a few exceptions.

14. Poor screening partly relates to limited availability of screening tests which are easy to perform, have high test performance (sensitive, specific), high acceptability and low cost. Although several options exist for CRC screening, each has its strengths and weaknesses; most screening methods are considered cost-effective compared to no screening. There is ongoing debate between the merits of each method in addition to the arrival of several new options; however, there are limited screening trials of endoscopy, other new methods or of head-to-head trials.

15. In addition, there is limited support to actively encourage CRC screening. Few documents have been published in support of colorectal cancer screening and those that do lack the ability to enforce or follow-through with recommendations made. In 2007 an appeal was made to the European Parliament to make a stronger stance with regards to CRC screening, including formal production of guidelines. This reflects the poor public and political awareness of CRC voiced by many surveyed countries. In addition, only a limited number of countries have CRC-specific patient groups or active prevention campaigns, which furthers this disease’s poor status.

16. As a result, CRC screening activities are significantly below par compared with other cancers. Only Australia, Finland, France, Italy and the UK participate in formal screening activities, where an eligible population is invited. A few more countries in Europe have opportunistic testing, where testing is initiated by either the patient or the primary care physician (Czech Republic, Germany, Poland, Slovakia). Pilot screening is not infrequent in Europe with some formal and opportunistic screening countries also exploring other test options (Denmark, Hungary, Netherlands, Portugal, Spain, Sweden). Greece, Romania, Russia and Turkey are inactive in colorectal cancer screening.

17. Participation in CRC screening programmes is a concern. Most formal screening participation ranges from 40-60% at best, while opportunistic screening ranges from 8-50%. This poor participation may inhibit some countries from considering CRC screening implementation in any form.

18. Of further concern is endoscopy capacity, as positive screened tests must be diagnosed further with a colonoscopy. Of the countries surveyed, several reported endoscopy capacity
concerns (Denmark, Italy, Netherlands, Poland, Portugal, Russia, Spain, Sweden), including long waiting times for diagnosis even without screening inclusion in the country, as well as regions with poor endoscopy resources (Czech Republic, France, Germany, Greece, Hungary, Italy, Portugal, Romania, Russia, Slovakia, Spain, UK and Australia). Only few countries have explored policies addressing this concern, such as offering patient choice in endoscopy centres, prioritizing urgent patients or using nurse endoscopists to relieve the burden from limited physician endoscopists.

19. Overall, there appear to be large variations in screening practices throughout Europe and Australia, in addition to different levels of political support for this secondary prevention practice. Nationally, countries need to increase public awareness of colorectal cancer, such as for lung or breast cancers, and, where not available, increase political lobbying for formal screening practices. More support must be given to head-to-head screening trials using endoscopy, and endoscopy capacity must be closely examined for future needs. Nurse endoscopy could be given more support as a profession, and patient choice in endoscopy centre should be supported.

**Treatment**

20. Many countries had difficulties with delivery of CRC treatment in one way or another. Insufficient treatment facilities appear in half of surveyed countries (Czech Republic, Denmark, France, Hungary, Portugal, Romania, Russia, Spain), with Eastern Europe also indicating inadequacies in these facilities (Czech Republic, Poland, Romania, Russia). Treatment facilities or human resource distribution remains uneven in most countries, including specialty physicians with CRC training. Care may be given in surgical wards, oncology wards or gastroenterology wards.

21. All countries reported issues with access to colorectal cancer treatment in one way or another. Geographical access for many rural patients remains problematic, particularly in Australia, Greece and Russia. A few countries reported having groups in their country with poorer access to cancer treatments (Greece, Netherlands, Russia, Turkey, Australia). Many countries perceived long waiting times (Denmark, France, Greece, Netherlands, Portugal, Romania, Slovakia, UK) or had long waiting times for treatment after diagnosis, ranging from 1 week (Denmark) to 8 months (Russia), with most countries averaging between 1-2 months. Out-of-pocket payments for treatment are not uncommon, although some countries reported unofficial payments were needed to receive care (Romania, Russia, Turkey).

22. Treatment for CRC consists primarily of surgery, often supplemented by pharmaceutical therapy in CRC and radiotherapy in rectal cancer. Treatment guidelines are useful in supplying best evidence-based practice to patients, however, many countries do not have colorectal cancer treatment guidelines (Greece, Hungary, Poland, Portugal, Romania, Russia, Slovakia, Spain, Turkey). Countries with guidelines may have more than one organisation producing guidelines, while variations between countries occur in their recommendations. The breadth of discussion and guidance also differs between countries, with some having much discussion but limited recommendations (Australia, UK) while others have limited discussion and recommendations. Furthermore, only half of countries with guidelines actually have policies in place to monitor their adherence.

23. Specialty physicians and hospitals with experience and training in CRC are also often not available, particularly in some Eastern European countries. New, proven effective treatments, including laparoscopy and targeted biological treatments are also often unavailable to patients, either due to reimbursement decisions or lack of training to deliver the treatment.
This discordance within and between countries and organisations results in different standards in CRC care and is likely open to differences in quality of care.

24. Overall, there appear to be problems with colorectal cancer treatment, including availability, access and practice variations. High quality, accessible treatment guidelines should be produced in all countries. Furthermore, European-wide treatment guidelines with treatment pathways, discussion of all methods and strong recommendations would help establish a baseline level of quality. Issues of access and delivery must be addressed internally within each country – resources should be spread evenly per population base and policies in place to address rural populations.

Pharmaceutical care

25. There have been a number of advances in oncology pharmaceutical treatments: oral versions of traditional 5-fluorouracil therapy (capecitabine, UFT), additional cytotoxic chemotherapy (irinotecan, oxaliplatin), and new targeted biological treatments (cetuximab, bevacizumab). This means more choice is available for patients and oncologists for 1st to 3rd line therapies. Many of these decrease the significant risk of recurrence found with colorectal cancer, while others significantly increase survival.

26. Although the available body of clinical and cost-effectiveness evidence in relation to these therapies is increasing, there are limited high quality (economic) evaluations using both costs and effects, accounting for adverse events and presenting these in a comprehensive manner. Certain pharmaceutical treatments are under-represented in clinical cost-effectiveness analyses, including oxaliplatin and bevacizumab, and all studies focus on metastatic colorectal cancer despite significant adjuvant treatment in Stage II and III of the disease. As health technology assessment is having an increasingly important role in reimbursement decisions, high-quality clinical cost-effectiveness analyses are necessary to underpin decision making.

27. As with treatment guidelines, pharmaceutical guidelines are also few in Europe, with variations between countries in recommendations as well as breadth and depth of discussion. Many countries do not make firm recommendations of 1st or 2nd line, particularly for adjuvant treatments, offering discussion on various merits but leaving the decision making to the practitioner. These differences are most apparent for targeted treatments, one set of guidelines discussing bevacizumab but not cetuximab (Netherlands), while another offers discussion but no guidance (Australia, Germany); others have no mention of targeted treatments (Belgium). As targeted treatments are a breakthrough in oncology treatment, they are worthy of further discussion and guidance.

28. Uptake and use of targeted treatments vary widely between countries and between types of targeted treatment within a country. A number of countries have adopted these treatments, including countries with limited overall resources or income levels (Turkey, Slovakia). Adjusting for the CRC burden did change the ranking of a country’s uptake and use information, for example Germany was one of the leader in total use (measured by sales) yet adjusting for CRC burden decreased its ranking, while the opposite was true for Greece. Overall though, the evidence on uptake and use does suggest that only limited numbers of potentially Stage IV eligible patients in Europe and Australia do have access to these therapies, and the question remains as to what determines those patients’ pathway into targeted biological treatments.

29. Regional differences are likely to occur in Denmark, Germany, Hungary, Italy, Poland, Russia, Slovakia, Spain and the UK with regards to targeted treatments, either due to access to experienced cancer care or academic hospitals, regional budgetary constraints or regional
reimbursement decisions. Out-of-pocket payments are again more likely in Romania, Russia, Turkey and Australia for this type of therapy. Hospitals may or may not have flexibility in their formularies to include targeted treatments, while others have outside financial assistance for higher cost therapies. In some cases, there is greater flexibility in using targeted therapies (e.g. France Germany), but in many cases countries perceived delays in access to new treatments of proven efficacy (Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovakia, Turkey, the UK and Australia).

30. Overall, there appear to be large variations in pharmaceutical therapy in Europe and Australia, in part due to differences in the availability of treatments but also due to variations in guideline recommendations. As with treatment guidelines, pharmaceutical guidelines in Europe and Australia need to be improved, and include a mechanism for frequent updating to coincide with new treatments and evidence that emerges on them. While cost-effectiveness analysis seems to be driving decisions on inclusion of targeted therapies into reimbursement lists in several countries, consideration should also be given to equity, human dignity, and disease severity.

Surveillance

31. Surveillance of pre-cancerous adenomatous polyps in patients and post-curative surgery patients is very important to detect neoplasms at an early stage and amenable to treatment. Little research and few guidelines have been produced on this subject, despite its obvious importance for CRC outcomes. There are more guidelines available for post-curative treatment (Belgium, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Sweden, UK, Australia) than for post-adematous polyps (France, Germany, Italy, Netherlands, UK, Australia). Countries with guidelines have large differences in their recommendations on the types of tests, frequency of testing and duration of follow-up.

32. As surveillance activities are a significant portion of endoscopy practice, these discordances mean that resources may not be managed optimally and patients are receiving historically-based care versus evidence-based practice. As recurrences are common in colorectal cancer patients, this portion of colorectal cancer services must be closely examined. Greater support for research exploring best surveillance practices must be encouraged and greater agreement between countries found on guidance. Both types of patients warrant European guidelines.

Overall performance

33. Although the objective of this report is not to explicitly identify leaders and laggards, both positive and negative performance indicators were created to understand what countries do well and where they have room for improvement. Factors which improved colorectal cancer management were rewarded positive points, while factors creating barriers to evidence based CRC care management were rewarded with negative points. These scorecards show only a minority of countries score over 50% for positive points (Denmark, France, Germany, Italy, Netherlands, UK, and Australia) although none scored over 75%. For negative points, only Portugal, Romania, Russia and Slovakia score over 50%. What this shows is that although some countries perform well each does have room for (considerable) improvement, while countries performing with more barriers also do have positive aspects that others can learn from.
Shortcomings and action

34. A number of themes emerge from this survey that all countries struggle with: availability, affordability, access, quality and choice. All countries have problems with data availability to help plan for colorectal cancer services. CRC screening of any kind is not standard, and most countries have issues with capacity to diagnose and follow-up patients. In addition, many countries do not have guidelines upon which to base their clinical decision-making, and not all best evidence-based treatment is available due to resource or reimbursement constraints.

35. Not all countries have available resources to deal with the CRC burden, particularly in Eastern Europe. This means that the use of guidelines and evidence-based care given budgetary constraints is even more important. This is of particular concern for screening programs. Although each invitee is inexpensive, policy makers may decide that screening all eligible citizens may be unrealistic financially despite long-term economic benefits. Targeted biological treatments may be less likely in restricted health budgets with many demands; however, there are countries with high uptake per CRC population relative to their available resources. Specialty physicians are also of limited availability, as are endoscopists and pathologists responsible for diagnosis decisions.

36. There may be barriers in access to care, be it geographical, socio-economic, or lengthy waiting times. Regional variations are problematic, as rural patients may have lengthy travel or even no access to certain diagnostic or therapy centres. Timeliness of both diagnosis and treatment varies widely across Europe and Australia, as well as the timeliness of new treatment implementation. Regional reimbursement differences also means variety in quality of care received based on evidence, and surveillance activities may depend solely on the thoroughness of a physician.

37. These issues of availability, affordability and access cumulate into underperforming quality of care, and resulting in poorer than expected outcomes. Greater interest in CRC services must be fostered, and policies developed to ensure, at minimum, that high standard of care is given within each country. A pan-European co-operation in developing high quality guidelines for screening, treatment, pharmaceutical therapy and surveillance is required to encourage this behaviour, in addition to political support in implementing and monitoring their use. Furthermore, patient groups and politicians must work together to give CRC a greater voice within our global community in order to increase awareness, funding, support and ultimately, outcome.

38. It is important to:

1. Improve data collection procedures, internally within each country and well as promote international co-operation. This is valid for both cancer registry data as well as cancer- and CRC-specific expenditure. Both are necessary for future cancer planning, not only for CRC but also for other cancers.

2. Have greater national and international support for cancer screening activities proven to be effective and cost-effective. Continue to conduct or encourage research on the effectiveness and cost-effectiveness of new screening methods with a view to informing policy on best practice/choice available. In terms of CRC, greater effort and support for formal versus opportunistic screening programmes should be given by the European Union and national Ministries of Health.

3. Examine endoscopy capacity in each country to ensure timely diagnosis, regardless of screening activities. Patients should be given choice in endoscopy centres to manage waiting lists more effectively, and patients should be prioritized formally based on
risk. Greater support should be given to the Nurse Endoscopy profession by Ministries of Health and by physician gastroenterology associations.

4. Enhance public and political awareness as a key to improving CRC outcomes. Targeted CRC-specific campaigns need to be produced, not just campaigns that include healthy lifestyles in the hope that colorectal cancer will be addressed. Public personas affected by this disease must be encouraged to give voice, in order to raise the status of CRC.

5. Where applicable, give consideration to the principles of equity, human dignity and disease severity, among others, when deciding on diffusion of targeted treatments, rather than base decisions solely on cost-effectiveness.

6. Firm up national and European guidelines including screening, diagnosis, treatment, pharmaceutical treatments and surveillance. These guidelines must be timely, evidence-based, and freely accessible to all. They should include pathways, adequate discussion of all methods, as well as actual guidance. Non-consensus could also be included, as well as patient perspectives.
Chapter 1
Background and Objectives

1.1. Introduction

Colorectal cancer is one of the most common forms of cancer and is a substantial health burden in Europe, with high incidence and mortality in combination with moderate survival. It is often diagnosed late due to the absence of screening programmes, lack of knowledge about symptoms and/or a reluctance to seek medical help once the symptoms start. Although improvements in outcomes have been made, compared with other high incidence cancers such as breast, overall survival for CRC remains relatively poor. However, early detection is feasible and for patients with early disease, surgery alone can be curative. Chemotherapy is essential to provide a chance of cure for patients with more advanced disease, with 5-fluourouracil plus leucovorin (5-FU/LV) forming the basis of standard treatment. During the past 10 years, a number of new agents that can be used in combination with 5-FU/LV have been introduced, with a subsequent increase in life expectancy for patients with stage IV disease from 5 to >20 months. However, facilities for treatment, use and adherence to clinical management guidelines and access to new, effective agents reportedly vary widely across OECD countries. Cancer spending on colorectal cancer is difficult to disaggregate, but evidence suggests that treatment costs are high particularly for Stage III/IV. Europe also appears to have, for the most part, little concerted effort with regards to screening activities. Similarly, both public and political interest in colorectal cancer activities appears minimal to non-existent in some countries compared to public/media profile of breast cancer, for example.

1.2. Objectives

This report aims to capture current information regarding the management and funding of colorectal cancer in Europe and Australia. This allows an accurate picture of the current state of colorectal cancer management to be formulated and trends in practice to be identified. The report includes both a medical and a health economic perspective, reflecting the dual view of healthcare systems within Australia and the majority of European countries. The report also includes a patient perspective, as well as an outline of recent advances in the
management of colorectal cancer, by means of introduction. Data have been collected through both primary and secondary sources.

More specifically, the objectives of the report are, first, to understand the available data sources for CRC at national level, their accessibility, availability, and use in research and policy. Second, to map the funding and resource allocation processes on cancer in general and CRC in particular. Third, to identify the extent of primary and secondary (screening) prevention policies for CRC, and the extent to which these are actively encouraged, implemented and enforced in the study countries. Fourth, to review the differences in cancer survival between countries and to discuss the effectiveness of health care provision from a health system perspective. Fifth, to discuss the available standards of care for CRC at national and international level. Sixth, to determine ability and willingness of hospitals to implement national guidance and to examine current pathways for CRC management. Seventh, to assess the access to and the availability of diagnostic services and pharmaceutical treatments for CRC. And, finally, to investigate the appropriateness and adequacy of current funding and management of CRC services.

Chapter 2 describes the methodology followed in the data collection process. Chapter 3 examines how CRC disease burden across Europe and Australia guides resource allocation and investigates whether CRC benefits from an explicit resource allocation mechanism. Chapter 4 has a threefold objective: (a) To capture the current status of cancer registries (b) To compare recent colorectal cancer mortality-data collected from international resources with new and/or supporting mortality trends taken from case-based questionnaire information; and (c) To assess the validity of these sources of information for policy and further research. Chapter 5 presents and discusses, (a) The various CRC screening options, including their test performances; (b) The cost effectiveness of CRC screening, including limitations; (c) The organisation of CRC screening programs in Europe; (d) The participation rates in CRC screening and how these might be improved; and (e) Capacity for screening in the survey countries. Chapter 6 maps patterns across the survey countries, with regards to (a) Access to colorectal cancer treatment, including barriers to treatment, inequities of access, and waiting times; (b) Delivery of colorectal cancer services, including adequacy of human and physical resources, where treatment is given and by which specialists; (c) Guidelines for overall treatment of colorectal cancer and rectal cancer; (d) Treatment practice in surgery and radiotherapy; and (e) Clinical and cost-effectiveness of surgical and radiotherapy treatments. Chapter 7 presents the similarities and differences between countries around the use of
traditional chemotherapy regimens, as well as targeted treatments for colorectal cancer and, in particular, pays attention to: (a) The cost-effectiveness of pharmaceutical treatments; (b) Spending on novel CRC agents, bevacizumab and cetuximab; (c) Access and availability of such targeted treatments; and (d) The presence of country guidelines around the use of pharmaceutical treatments for CRC in the early and advanced settings. Chapter 8 highlights similarities and differences between the study countries for both adenoma and post-colorectal cancer surveillance with regards to (a) the effectiveness and cost-effectiveness of follow up and surveillance methods and (b) the existence of follow up and surveillance guidelines throughout participating countries, which are presented and discussed. The objective is to identify whether follow-up and surveillance are pursued with rigour or not, and highlight potential gaps in policy. Finally, Chapter 9 draws the main conclusions and debates the policy implications.
Chapter 2
Methodology

2.1. Methodological Approach

Colorectal cancer is one of the most common forms of cancer and affects large subsets of the population in developed nations and, increasingly, low-middle income countries. Due to a combination of changes in population age-structure and vast transformations in lifestyle behaviours, an increasing proportion of individuals are at increased risk for developing what is considered mostly to be an avoidable disease. Given that colorectal cancer (CRC) inflicts considerable burden on most (if not all) health systems across Europe and Australia, the main aim of this research was to capture the current status of CRC management and resource allocation within Europe and Australia. In order to achieve this goal, the research strategy involved both primary and secondary data collection. The secondary data collection relied on readily available data from national statistics, international organisations (United Nations, World Health Organisation) as well as supranational organisations (e.g. the European Union) or initiatives that collect and report cancer-related data (e.g. IARC). A literature review using sources from the peer review literature as well as published reports was also conducted. With respect to the primary data collection, a detailed Survey Tool was developed and administered to experts in the selected countries.

2.2. The LSE CRC Survey Tool© and its Objectives

The LSE CRC Survey Tool© was developed and used to collect information about national policies and practices on CRC management. This method of data collection ensured that data was collected in a structured, timely and cost- effective manner as well as benchmark these data with any publicly available sources. The LSE CRC Survey Tool©, issued to respondents late in 2007, was split into three main areas. First, it briefly looked at the current epidemiological burden of CRC reported from national and international sources. It also examined the current methods of cancer data collection. This tool was also used to determine the economic burden of CRC within the context of current health expenditure. The LSE CRC Survey Tool© went on to look at the overall health expenditure on cancer and colorectal cancer. Additionally, the survey investigated methods used to pay for CRC prevention, treatment and measures of surveillance.
The third part of the LSE CRC Survey Tool© was constructed to determine the strength of national leadership surrounding CRC management. Great attention was paid to the three main areas of the management pathway: (a) secondary prevention (screening); (b) treatment and (c) palliation. Finally, the questionnaire looked at the different methods used to accommodate national surveillance programmes. The LSE CRC Survey Tool© is presented in Appendix 1.

In particular, the objectives of the Survey Tool were:

- **First, to understand the available data sources at national level, their accessibility, availability, and use in research and policy.** In order to achieve this, questions are asked about the data sources and databases that are available in individual countries at national, regional and/or local level, to monitor cancer prevalence, incidence, mortality, etc, and evaluate the effectiveness of health policies on cancer.

- **Second, to assess the impact of colorectal cancer.** In this section data on CRC incidence, prevalence and mortality were collated; additionally, we sought to understand the societal cost of CRC.

- **Third, to understand the funding and resource allocation process on cancer in general and CRC in particular.**

- **Fourth, to identify the extent of primary and secondary (screening) prevention policies and the extent to which these are actively encouraged, implemented, and enforced.** This section attempts to understand the nature of prevention campaigns relating to cancer and its consequences and whether there are annual budget allocations for this; whether any of these campaigns are designed to specifically address risks leading to colorectal cancer; whether the study countries have screening policies and screening guidelines in place and if such screening policies exist then their key features will be studied.

- **Fifth, to assess differences in cancer survival between countries and assess efficacy of health care provision.** This section investigates the extent to which survival data (5- and 10-year) are available for colorectal cancer in the study countries.

- **Sixth, to determine level of leadership at national level, in terms of standards of care.** This section of the survey tool investigates whether there are national
standards of care for colorectal cancer and whether they differ from international best practice; and queries the current treatment guidelines for colorectal cancer.

- **Seventh, to determine ability and willingness of hospitals to implement national guidance.** (Knowledge and implementation of standards of care at local/regional level; Monitoring of standards of care implementation)

- **Eighth, to assess efficiency of health care provision.** This section seeks to examine, among others, the pathways to treatment in colorectal cancer; the time from primary physician referral to diagnosis; the access to cancer specialists; the time from diagnosis to treatment (surgery, radiotherapy, systemic therapy as appropriate); and the ability to gauge any geographical or other variations in access within the study countries.

- **Ninth, to assess the access to and the availability of diagnostic services and pharmaceutical treatments.** This section examines the availability of radiology services (CT/PET scans, etc), how is access to these services determined and whether facilities are perceived to be adequate; and whether there is sufficient access to pharmaceutical treatments or there are geographical inequities or other rationing restrictions to such treatments and where they are focused.

- **Tenth, to investigate the appropriateness and adequacy of funding and management.** This section is asking whether (a) funding is adequate to meet treatment needs in individual countries; (b) management of CRC conforms to international best practice; and (c) there are variations in the management of CRC in the study countries.

### 2.3. Country Selection and National Respondents

The Survey Tool was issued to the 21 study countries in late 2007. Twenty of the study countries are from the European region (Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, the Netherlands, Poland, Portugal, Romania, Russian Federation, Slovakia, Spain, Sweden, Switzerland, Turkey, UK); Australia is also included in the survey. Of the countries contacted, 18 returned completed surveys that enabled their inclusion into this report (Australia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, Poland, Portugal, Romania, Russian Federation,
Slovakia, Spain, Sweden, Turkey, UK). The participating countries reflect differences in the finance, organisation and delivery of health care services and an extensive array of epidemiological health profiles as well as income levels.

National respondents were senior health services researchers or clinicians and each of them was chosen to relay the present status of CRC management within their country. Their names and affiliations can be seen in Appendix 2.

A two-stage approach was used to explore the management of CRC. National respondents were instructed to collect information from both secondary and primary sources. From each of the 18 countries, literature in the form of peer reviewed journal, policy documents and grey material was used to assess the current state of CRC management. In addition to this, experts were also asked to interview key opinion leaders, policy makers and clinical professionals as means of garnering additional information where possible. The data collection process involved at least 2 iterations with the national experts, whereby upon submission of their completed Survey Tool, they received feedback and comments from the research team. This report synthesises the material received from the national experts and presents the evidence in a comparative manner. In addition to this, a series of performance indicators were created for Chapter 5 (Screening), Chapter 6 (Treatment), Chapter 7 (Pharmaceutical Treatment), and Chapter 8 (Surveillance). The purpose of compiling these was to summarise all the information collected in the relevant chapters into a simple variable, reflecting a net positive or negative situation with regards to colorectal cancer service functioning in each country. Despite the obvious limitations of doing so, the purpose of this simplification was to give an estimate of what countries may do well or what they may need to improve upon, based on the information received. Appendix 3 describes the rationale behind the indicators and presents the variables that are included.
Chapter 3
CRC Epidemiology and Resource Allocation

3.1. Introduction

Most OECD countries have implemented health care reform as a means of improving system-wide efficiency and attempting to control escalating health care costs. Despite a series of incremental changes in health system organisation, the general trend towards decentralization of the purchasing agent has been an unmistakable phenomenon. In many instances the strategic movement of the purchasing function to more localised settings, has been used to consolidate a heightened sense of financial accountability and encourage local autonomy. Such changes in health-system organisation have important implications with regard to the local purchaser ability to cater to specific population health need. Given that such arrangements have a tendency to encourage risk segmentation, resource allocation mechanisms are important when responding to population need.

In this context, this chapter examines how disease burden across Europe and Australia guides resource allocation mechanisms. The chapter focuses primarily on how CRC influences resource allocation mechanisms across the study countries and is split into two main sections: the first, assesses the current burden of CRC across Europe and Australia, introduces CRC epidemiological trends, primarily around traditional indicators such as incidence, mortality and survival, and examines variations in disease burden over the last decade. The second section examines how resources are allocated at various stages of the CRC management pathway, assesses the current context for CRC funding, by identifying explicit forms of disease-related resource allocation, and examines how various aspects of management influence funding mechanisms.

3.2. CRC Incidence and Mortality

Colorectal cancer (CRC) accounts for significant morbidity and mortality across Europe and Australia. Indeed, after breast cancer (ASR=94.3\(^1\)), CRC (ASR=55.4) is the highest diagnosed cancer in women and the third most amongst males, after prostate (ASR=86.7) and lung (ASR=75.3) cancer. As a proportion of European cancer incidence,

\(^1\) Age Standardised Rate measuring number of cases per 100,000 population.
CRC incidence accounted for 12% and 14% of total cancers in Europe in 1995, and 12.3% and 13.1% in 2006 in males and females respectively.²

The greatest cause of cancer mortality throughout Europe in men is lung cancer (ASR=64.8), followed by CRC (ASR=27.3) and prostate (ASR=22.2) cancers. In women the primary cause for cancer mortality is breast cancer (ASR=26.0), then CRC (ASR=16.6) and lung (ASR=15.1) cancers. CRC mortality as a percent of total cancers in Europe was 10% and 14% in 1995, and both 12.2% in 2006 for males and females respectively.³

In many European countries incidence has increased since 1995 while mortality has fallen (mortality ratio of 1.8 in 1995 and 2.0 in 2006). There are noted differences between European countries for incidence and mortality (Figure 3.1). Ultimately, it appears both Northern and Eastern Europe have higher CRC incidence and mortality than Southern Europe, most markedly Greece and Albania. There have been a number of hypotheses for this pattern. It may reflect greater fruit, vegetable, fiber and fish consumption and more active lifestyles in the south than elsewhere, while poorer prognosis in the east may reflect poorer treatment and advanced stage at diagnosis.⁴ There may also be genetic differences across Europe thereby creating lower proportions of high risk individuals in the south than north.

The increase in CRC incidence is likely to continue with aging populations: by 2015 the population of >65 years will have increased by 22% compared to 2000, and the population of >80 years will increase 50%.⁵ The pattern of age related CRC incidence, and lesser so mortality, is closely correlated with increasing age from around 50 years, although the proportions differ between countries.

Both incidence and mortality appear to be greater in men than in women; comparison of 1995 and 2006 cohorts found greater rises in incidence (>5% absolute difference) in men than women. There may be a number of factors accounting for this gender difference. There may be inherent biological differences in women providing added protection against CRC, such as hormonal or genetic factors. There may also be lifestyle difference between the sexes such as greater fruit and vegetable consumption in women than men, a hypothesis supported by the finding of greater plasma carotenoids in women than men in across Europe.⁶

Figure 3.1
Age standardised (number of cases per 100,000) European CRC incidence and mortality (C18-21): (1995 and 2006):

Males: Incidence

Females: Incidence
CRC Survival

Survival of patients with CRC differs markedly across countries (Figure 3.2) In comparison with other cancers, CRC survival fares marginally better than average (EUROCARE-4: CRC 53.7% 5 year relative survival versus all cancers 51.9%). When examined in comparison with other cancers with high incidence in Europe, CRC does not fare
as well. In comparison the latest European 5 year relative survival for breast cancer is 81.1%, for prostate cancer 77%, although for lung cancer survival is poor at 12.6%.\textsuperscript{7}

The recently published EUROCARE-4 survey has not published sex-specific survival figures, but previous EUROCARE studies have found sex-specific survival differences. In the majority of countries survival is better for women than men. In contrast, the American SEER data report a range of 60-65% for 5 year survival between men and women.\textsuperscript{8}

Again there appears to be regional differences in survival, with poor CRC survival particularly in Eastern Europe. Previous EUROCARE surveys also found poor survival in some Northern European countries, most notably the UK and Denmark. The latest data, however, no longer supports this trend for all Northern European countries, except for the UK and Denmark. Europe overall has improved survival by 4.2 percentage points, and certain countries have increased between 5 and 10 points (Czech Republic, Germany, Italy, Poland, Slovenia, UK). Indeed, most countries now meet moderate prognosis (40-59%) for CRC survival, except for Poland.

There are a number of hypotheses to explain these differences between countries. Early detection appears to be a significant predictor for survival, and correcting for stage at diagnosis shrinks country differences somewhat.\textsuperscript{9} Since the EUROCARE surveys began, detection of CRC has improved and (pilot) population screening programs have begun in select European countries. Additional factors affecting survival between countries are proportion of adenocarcinomas in polyps (less are associated with improved prognosis), higher proportion of tumours not microscopically verified, and access to curative surgery.\textsuperscript{10} Furthermore, treatment for CRC has also improved with the advent of better surgery, radiotherapy and combination chemotherapy.

\textsuperscript{7} Berrino F, et al. 2007.
\textsuperscript{8} Ciccolallo L, et al. 2005.
France has been consistently one of the better performing countries for CRC survival.\textsuperscript{11,12} In contrast, the UK is one of the poorer performing countries with its recent EUROCASE result ranking 10\textsuperscript{th} out 14 (many countries share the same ranking). Only Denmark fares worse for Northern and Southern European countries. This ranking has not improved with time, although there have been marked improvements since survival data begun collecting. Survival of curative resection in all stages has increased since 1974 in the UK, due to down-staging of the disease (earlier detection), improved diagnostic staging, and improvements in treatment and peri-operative care.\textsuperscript{13,14}

### 3.3. CRC Resource Allocation in Europe and Australia

The use of formal resource allocation across Europe is very patchy. Use of formal resource allocation mechanisms was reported in the Czech Republic, Romania, Greece, Italy, the Netherlands, Spain, the UK and Australia. Furthermore mechanisms of formal resource...

\begin{itemize}
  \item Mitry E, et al.  2002.
  \item Engholm G, et al.  2007.
\end{itemize}
allocation were mainly seen to be prospective. More specifically, countries tended to allocate a fixed amount of resources to ‘purchasers’ based on expected future expenditure. In the UK, semi-autonomous primary care trusts (PCTs) were allocated funds based on a set of proxy indicators used to define local population need. These were based on a series of demographic and socio-economic indicators, in addition to the current status disease burden at the local level\textsuperscript{15}. On the other hand in the Australian public healthcare-system (which uses a public-private financing mix\textsuperscript{16,17}) money was allocated from the federal to the state governments on the basis of a five-year Australian Healthcare Agreement\textsuperscript{18}. Within this arrangement, the federal government allocates a five year lump sum to state governments, ex-ante. The money is then used to fund public hospital health services within the area. The only exception to this general trend of prospective budgeting was the Netherlands, where, although use of ‘formal’ resource allocation was reported, fund distribution took the form of risk equalization rather than the distribution of funds from the source of pooling to the purchaser.

Countries that used social health insurance as a main method of financing healthcare were found to lack formal methods of resource allocation. Use of social health funds as the main collector of revenue, the locus of financial pooling as well as the purchaser of care, meant that there was an acute lack of financial distribution in the form of prospective budgeting in western and central Eastern Europe. Absence of ‘formal’ resource allocation was reported in Denmark, Germany, France, Hungary, Portugal, the Russian Federation, Slovakia, Sweden and Turkey. Out of the nine countries that reported no formal resource allocation, five used social health insurance systems as the main method of finance (France, Hungary, Turkey, Slovakia and Germany). In all instances, the main form of financial allocation took place between the purchaser of care and provider of care. In Germany, statutory care in the form of medical services was reimbursed using a DRG payment system. In addition, in Hungary a system of payment based on the American DRGs and the German fee-for-service points system was used to finance out and inpatient care. In all of these countries, central government played a critical role in sanctioning the reimbursement of services and thus coordinating the rationing of care. Although the response from Turkey stated that there was no formal method of resource distribution, data taken from secondary sources seem to

\textsuperscript{17} ‘Allocation of resources to English areas (AREA)’ http://www.dh.gov.uk/en/Policyandguidance/Organisationpolicy/Financeandplanning/Allocations/DH_076547
\textsuperscript{18} Healy, Sharman and Lonkuge, 2006
indicate that the Ministry of Health plays a significant role in the coordination of expenditure. In Germany this occurred by way of the Federal Joint Committee. Placed at a national level, this organisation has the responsibility of defining the scope of reimbursement within ambulatory care.

Furthermore within countries that described resource allocation as being ‘informal’, a more interesting phenomenon presented itself. Despite informal resource allocation characterised by retrospective payment type, certain forms of prospective budget allocation were also seen as informal. In these settings budgets were based on various transitory arrangements. A prime example of this was seen in Russia with the ‘left-over’ principle. The Russian health care system is based on many sources of revenue that are collected from federal, regional and local taxes, as well as social health insurance contributions. In the Russian case, funds from specific revenue sources are designated to specific hospital services, and therefore play an essential part framing patient care. However, in this setting, there is no clear and transparent mechanism for defining how much money should be allocated to which services. This creates problems as to which services should be provided for free and which should be paid for out of pocket.

The use of a complex allocation mechanism was a clear phenomenon with the majority of European countries and Australia which used a hybrid system of allocation to distribute funds at the national, regional and local level. These levels of distribution were found to arise from historical issues surrounding regional autonomy or, in some cases, functions of recently implemented health sector reforms. This was observed particularly in Denmark, Italy, Romania, Spain, the UK and Australia. Given the significant degree of regional autonomy in Spain and Italy, resource allocation from the federal to the state level played a significant part in determining region-specific budgets. In Denmark, on the other hand, revenue collection and the subsequent pooling of funds occurring at the regional level has caused there to be a series of risk equalization mechanisms, to avoid risk segmentation. Essentially taxes levied at the national level are reallocated based on risk. However in the UK, the relatively recent split between the purchaser and provider has lead to a series of interesting allocation processes. At this moment in time the UK government allocates an estimated 80% of the national health budget to PCTs. Although funds are simultaneously allocated to the NHS Hospital Trusts, the bulk of resource distribution occurs at the local level; in the form of PCT ‘payment’ for services conducted within the hospital setting. In the majority of cases, resource mobilization between the two organisation is based on a complex array of globalised
budgets (defined by historical analysis of past use), service lead agreements (based on cost and value agreements made between the two parties) and targeted payment by results (PbR).

Finally, risk equalization mechanisms, in their own right, seemed to play a prominent part in the overall amount of money allocated to purchasers of care. This was seen mostly within countries that presented social health insurance schemes as the main mode of healthcare finance. Indeed, this was the main way that such countries tried to safeguard against risk-segmentation. A prime example of this was seen within the Netherlands where the purchasers of care were seen to adjust budgets based on the risk profile of the specified population. Formulas used for reallocation were based on age, sex, socioeconomic deprivation, sources of income, and socioeconomic status. Equalization formulas also took into account measures of disease burden. This was seen in the form the creation of specific cost-groups for expensive drugs and DRG coding for chronic disease. These indicators were used to distribute funds accordingly; at the beginning and end of the year.

Table 3.1
Description of Resource Allocation Mechanism

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<th>Country</th>
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<th>Resources Allocated Regionally</th>
<th>Resources Allocated Locally</th>
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<th>Sufficient Resources Allocated to Colorectal Cancer Care</th>
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<td>Slovakia</td>
<td>❌</td>
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<tr>
<td>Sweden</td>
<td>❌</td>
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<tr>
<td>Switzerland</td>
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<td>❌</td>
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<tr>
<td>Turkey</td>
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<td>❌</td>
</tr>
<tr>
<td>UK</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Australia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Note: 1 Resource allocation takes place retrospectively.  
Allocation specifically to cancer was found to be extremely limited, with disease-specific allocation only in Denmark, the Russian Federation, Romania, Australia and the UK. Across the 18 countries studied, Australia was the only country to report the use of the explicit allocation process for all cancers. Denmark, the Netherlands, Romania and the UK only reported explicit mechanisms of resource allocation to cancer. Yet closer analysis of these methods of resource distribution found significant differences with regard to the distribution of funds. In Romania, funds available from the National Cancer Program were allocated to District Health Insurance Authorities on a monthly basis. In the UK money allocated to cancer was given on a yearly basis. However, in the Russian Federation oncology care is not covered by medical insurance and is exclusively funded by federal and regional budgets. Given that the majority of care is given in specialist institutions, in most cases resources were allocated on a per diem basis, with some additional cost for the consultation time. These arrangements created significant issues relating to under-funding. Particular forms of treatment tended to be financed using cost estimations. However, given that these values were defined without transparent and clear mechanisms, the costs of treatment in real terms often exceeded proposed estimates.

Many respondents indicated that the resources allocated to cancer in general and CRC in particular, were insufficient, although in the majority of cases no appropriate measure of need versus expenditure was available to substantiate this claim, but gaps in specific parts of the care delivery pattern were mentioned. Of the study countries, only the UK, Greece and the Netherlands indicated that the resources allocated to cancer and CRC care were ‘sufficient’. While countries such as the UK cited the recent levels of increased investment in cancer overall as the reasoning behind this opinion, the majority of countries highlighted lack of facilities, shortage in the clinical skill-set and poor access to pharmaceuticals, as the reasoning behind this negative response. More specifically, delays in the inclusion of important novel drugs on the Hungarian reimbursement list placed inherent barriers to pharmaceutical access. Furthermore, long diagnosis and treatment waiting times, shortages of specialized physicians and overall lack of equipment was taken to be a sign of insufficient funding within the Portuguese and Russian cancer care program.  

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Cancer and colorectal cancer spending

Only half of the surveyed countries seem to collect and report cancer expenditure and colorectal cancer expenditure, for most countries only on a periodic basis. The figures collected are reported on Table 3.2 and were adjusted for total cancer incidence and mortality, as well as colorectal cancer incidence and mortality, to reflect the population cancer burden in each country. Incidence and mortality were chosen as proxies for cancer populations, as prevalence data is less common and less reliable. In countries with poorer cancer registry data collection quality (Hungary, Slovakia, Russia) these numbers may be less accurate, however, for the remaining countries this adjustment helps estimate the cancer spending per cancer patient.

The total cancer spending per total cancer incidence and mortality shows large variations between countries. The highest spending countries appear to be France, Germany and Sweden, while the lowest spending countries appear to be Russia and the Netherlands. For colorectal cancer spending adjusted for colorectal cancer burden, the highest spending countries appear to be France, Germany and the Netherlands, while the lowest appear to be Hungary and Spain.

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cancer Exp. per Total Cancer Incidence (€)</th>
<th>Total CRC Exp. per CRC Incidence (€)</th>
<th>CRC Survival 5-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>2.16 24,985</td>
<td>174.1 14,207</td>
<td>58.5</td>
</tr>
<tr>
<td>France</td>
<td>11.20 42,047</td>
<td>60,090 122,828</td>
<td>57.5</td>
</tr>
<tr>
<td>Germany</td>
<td>15.54 38,096</td>
<td>29,776 61,562</td>
<td>57.5</td>
</tr>
<tr>
<td>Hungary</td>
<td>- - -</td>
<td>10,288 -</td>
<td>-</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2.45 9,334</td>
<td>25,362 52,024</td>
<td>57</td>
</tr>
<tr>
<td>Russia</td>
<td>1.57 8,067</td>
<td>6,721 10,288</td>
<td>-</td>
</tr>
<tr>
<td>Slovakia</td>
<td>0.155 8,300</td>
<td>1,850* 3,017*</td>
<td>-</td>
</tr>
<tr>
<td>Spain</td>
<td>4.64 28,868</td>
<td>5,490 17,610</td>
<td>52.5</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.83 42,887</td>
<td>9,138 19,863</td>
<td>58.3</td>
</tr>
<tr>
<td>UK</td>
<td>6.30 22,777</td>
<td>13,853 28,987</td>
<td>51.2</td>
</tr>
</tbody>
</table>

Notes: 1 All values have been adjusted to 2006/07 year (€); Cancer population statistics from 2002 GLOBOCAN database.

* Pharmaceutical costs only.

Resource Allocation for Screening

Although all countries have some form of pilot CRC screening, the use of national CRC screening programmes is still quite limited. Furthermore, programmes within these countries were found to be at different stages of development. National CRC screening programmes exist in the Czech Republic, France, Italy Poland, Slovakia, the UK and Australia. In terms of years in operation, Slovakia presented one of the more established programmes, with CRC screening being part of a legislated reimbursement package since 2002. Under Act No. 577 of 2004 each person over 50 was able to receive CRC screening. In the UK, however, the national screening programme is still in the early stages of implementation, with CRC screening roll-out currently taking place between the years of 2006 and 2008. The majority of the remaining countries were still within the pilot stage (Denmark, Germany, Hungary the Netherlands, Romania, Spain and Sweden). Only Greece, Poland, the Russian Federation and Turkey, reported an absence of any form of pilot CRC screening.

Unlike CRC, the existence of national breast cancer screening programmes seems to be more widespread. National programmes are running in the Czech Republic, Denmark, France, Germany, Hungary, Italy the Netherlands, Poland, Romania, the Russian Federation, Slovakia, Spain, the UK and Australia, and pilot programmes exist in Turkey. Greece and Portugal were the only countries to have no national or pilot breast screening programme. Like CRC, the presence of national cervical screening was is also quite rare, with national programmes in the Netherlands, Poland, Romania, Slovakia, Sweden and the UK. Finally, Slovakia and Poland are the only countries in which national programmes for prostate screening are run.

Explicit allocation of resources to adult screening seemed to be standard within countries offering such programmes. Of countries that participated in some form of screening, explicit funding allocation was noted in Australia, France, Netherlands, Poland, Romania and the UK. Concrete values were only reported for six countries as shown on Table 3.3. In the Netherlands, spending for the 2005 IKA pilot was reported to be €700,000; this was based on a population of 32,000. CRC screening expenditure was €4.2 million in Poland (2005-2006), while the pilot programme in Romania was allocated €185,000. Finally, although explicit CRC resource allocation was reported in Germany and the Czech Republic, no information was available regarding funding amounts.

With the exception of France and the UK, there still seems to be limited insight into the allocation methods used to finance screening initiatives. In France, programs are financed
by the state, the national insurance scheme and the departments. Prior to 2004, financing of screening programs was compulsory for the French departments. Despite the previous screening legislation, roughly half of the departments continue to finance these programmes; utilizing a 13% share of funds in 2006. On the other hand in the UK, due to the fact CRC screening was still within the Phase 1 rollout funds were held centrally within the NHS Screening Plan. Funds were then allocated to screening hubs, using demographic indicators. This calculation was based on the population composition of women, men and children. In this setting, screening hubs can use funds to respond to local health need. However such autonomy took place within the constraints of the screening protocol guideline. Eventually, it is hoped that PCTs will act as the purchaser of care, once the program has been nationalized. However it still unclear as to whether their will be a tariff, once screening is extended.

Table 3.3
Adult Screening Funding and Resource Allocation

<table>
<thead>
<tr>
<th>Country</th>
<th>Resources explicitly allocated to Adult Screening Programs</th>
<th>Resources Colorectal Cancer Screening (€)</th>
<th>Resources Breast Cancer Screening (€)</th>
<th>Resources Cervical Cancer Screening (€)</th>
<th>Resources Prostate Cancer Screening (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>✓</td>
<td>8,285,163$^1$</td>
<td>71,445,783$^2$</td>
<td>61,807,229</td>
<td>n/a</td>
</tr>
<tr>
<td>France</td>
<td>✓</td>
<td>18,644,762$^3$</td>
<td>31,451,741</td>
<td>900,000$^4$</td>
<td>n/a</td>
</tr>
<tr>
<td>Netherlands (2005)</td>
<td>✓</td>
<td>700,000$^5$</td>
<td>40,700,00</td>
<td>26,100,000</td>
<td>700,000$^7$</td>
</tr>
<tr>
<td>Poland (2005)</td>
<td>×</td>
<td>4,182,547</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>Romania</td>
<td>✓</td>
<td>185,000$^6$</td>
<td>700,000</td>
<td>1,400,000</td>
<td>55,000$^8$</td>
</tr>
<tr>
<td>England 2004)</td>
<td>✓</td>
<td>25,869,565$^9$</td>
<td>107,142,857$^{10}$</td>
<td>224,283,714$^{11}$</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Notes:
1. 43 million AUD were prospectively allocated over a period of 3 years, starting from 2005 (1 Euro:1.73 AUD. Exchange Rate on 04 Jan 2005)
4. French cervical screening is still in pilot stage. In 2008, cervical screening will begin in 4 departments. Budget was € 900,000.
5. Expenditure for pilot phase with no further information.
6. Expenditure for the Romanian CRC pilot screening programme
7. Expenditure for the Romanian prostate cancer pilot screening programme
8. According to NHS Press release £ 37.5million will be allocated to CRC screening from April 2006 for the next two years. This expenditure covers the period of national roll out which starts form 2006-2009.
9. In 2004 £ 75 million pounds (exchange rate 1 Euro: 0.70 GBP on 5 Jan 04) was spent on breast cancer screening this translated to £3000 per life year saved.
10. An estimated £157 million is spent on cervical screening per year (exchange rate 1 Euro: 0.70 GBP on 5 Jan 04)

The majority of countries in the survey did not report any amounts allocated and/or expended on breast cancer screening programmes. Only four countries reported this information. France, The Netherlands, Romania and the UK spent €31.5 million (2005), €40.7 million (2005), €700,000 (2006), and €107 million (2004), respectively. Limited information was available for other screening programmes. The Netherlands and Romania were the only countries to report a process in which explicit amounts of were given for cervical cancer screening programme. Specifically, the Netherlands allocated €26.1 million and Romania allocated €1.4 million.

**CRC Resource Allocation to Diagnosis and Treatment Programmes**

Denmark, France, Hungary, Poland, Romania, the Russian Federation, Slovakia, Sweden, the UK and Australia all had formal national management programmes for cancer. However, a considerable number of countries reported no such programmes. In Czech Republic, Germany, Greece, the Netherlands, Portugal, Spain and Turkey no formal cancer management programmes were present.

Patterns on the availability of formal CRC diagnosis and treatment programmes across countries were also polarised. Formal CRC programmes were found in the Czech Republic, Denmark, Italy, the Netherlands, Poland, the Russian Federation, Sweden and the UK. However and perhaps surprisingly a lack of these programmes was found in Germany, Greece, Hungary, Portugal, Romania, Slovakia, Spain and Turkey.

From the survey responses it is clear that a significant number of countries allocate funds specifically to cancer management programmes. Such accommodations were made in Denmark, France, Hungary, Italy, Poland, Romania, Sweden, the UK and Australia. Furthermore, it would seem, a small proportion of countries have a significant history of this activity. In 1991, Sweden allocated €623 million to cancer diagnosis and treatment programmes, while Denmark allocated more than €215 million, in the 1998-2003 period. In the UK more recent attempts to prioritize cancer diagnosis and treatment have led to the introduction of the National Cancer Plan (2000) and the Cancer Reform Strategy (2007), and these have led to an increased investment in cancer services. In 2006, some €6.24 million was spent on such programmes. Furthermore, Australia dedicated €117.4 million for the “Strengthening Cancer Care” initiative, over a five-year period. This initiative was introduced as
part of the Australian government’s attempt to fulfill its election commitment to reduce the burden of cancer.20

Given that CRC presents a significant burden of disease in the majority of the study countries, there still seems to be an acute absence of targeted diagnosis and treatment plans. Instead, the majority of countries studied tended to focus their attention on general cancer diagnosis and treatment programmes. Survey responses indicate that CRC diagnosis and treatment initiatives are present in only 7 of the countries studied (Denmark, the Czech Republic, Italy, the Netherlands, Poland, the Russian Federation, Sweden and the UK), while Germany, Greece, Hungary, Romania, Spain, Turkey and Australia reported no such programme. On the other hand, diagnosis and treatment programs for cancer overall, were used in the UK, Australia, Sweden, Slovakia, the Russian Federation, Romania, Poland, Italy, Hungary, France and Denmark.

The majority of the study countries had a serious lack of intelligence around the funding of national management programmes for CRC. The survey found data for the UK and the Netherlands only. However, even in these instances, UK data for such expenditure was not explicitly related to CRC diagnosis and treatment. In the second quarter of 2007, hospitals in the UK spent an average of €565,884 per 100,000 on all procedures based within the lower gastrointestinal canal. The Netherlands on the other hand reported CRC programme expenditure of €121,200.21

3.4. Conclusion

Although the current burden of CRC is a significant and growing burden to health systems in developed countries, resource allocation systems have yet to make appropriate accommodations for it. Given that this ‘potentially avoidable’ cancer is the second greatest cause of cancer death it is essential that funds are allocated in a way that is seen to be most effective. Indeed, the quest to lower CRC incidence through prevention initiatives, decrease rates of CRC mortality while improving CRC survival through early diagnosis and effective treatment, should be a hypothecated priority. However, the problem in achieving this goal is that for the majority of countries in this survey resource allocation mechanisms are not geared to explicitly allocate funds to individual cancers. In the majority of cases, population need is

21 Nationaal Kompas Volksgezondheid: http://www.rivm.nl/rtv/object_document/o5666n16909.html
defined by socio-economic, demographic and large composite indicators of general morbidity. This is certainly the case for tax-based systems and SHI-systems.

The only countries, within the study, to allocate hypothecated funding to CRC management programmes were Australia and the Netherlands. Yet even in these cases lessons taken from the theoretical principles of financing healthcare, indicate that there are a series of possible trade-offs that each system may have to contend with. For example, in the case of Australia, resource allocation in the form of budgets may increase financial accountability and allow policy analysts to monitor programme delivery and efficiency; however, this may hinder the resource flexibility needed to respond to changing needs of the population. Such arrangements may create budgeting silos or cause allocation of resources to be based on affordability rather than cost-effectiveness. In the case of the Netherlands, retrospective risk equalization across SHI funds using DRG costing codes may represent an effective way of constructing and responding to population need. In contrast, however, this arrangement has in some cases been seen to bolster the incentive practices of upcoding.

Furthermore, many countries lack the financial incentive structures needed to reinforce measures of diagnosis and treatment. Primarily, this stems from an acute lack of CRC-specific national management programmes in which care is delivered. Only eight of the study countries reported the existence of formal CRC diagnosis and treatment programmes. The majority of the treatment programs were organised around a general cancer plan. Yet even in these circumstances, information relating to the specific amounts allocated to the general cancer plan was rare. The exceptions being Denmark and Sweden.

In sum, while countries have tried to respond to the current and future burden of CRC, existing resource allocation mechanisms within respective healthcare systems make it difficult for funds to be allocated in such a way that reflects the population need. Having said this, however, some countries have made the attempt to allocate funds based on specific cancers. Finally, lack of formal CRC national management programmes limit the potential to incentivize methods of best practice.
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Gastroenterology department, IPOFG Lisbon.


Healy, Sharman and Lonkuge, 2006


Nationaal Kompas Volksgezondheid: http://www.rivm.nl/vtv/object_document/o5666n16909.html


Chapter 4
Cancer Registration and Data Collection

4.1. Introduction

Data from cancer registries are vital for making progress against cancer on all fronts. Indeed, the quality and accuracy of data plays an essential role in identifying and prioritizing health need. Yet issues with data validity present problems in the creation and implementation of policy agendas.

This chapter aims to briefly outline the current status of cancer registry function, coordination and positioning in the study countries, outlining the methodological issues associated with traditional indicators of disease burden. After giving brief overview of cancer registry collection practices, the chapter focuses on how countries collect vital statistics relating to CRC.

4.2 Cancer Registry Positioning, Coverage and Coordination

Cancer Registry Organisation

Cancer registries play an indispensable role in population surveillance, risk analysis, policy planning and, finally, execution. Assessment of cancer registry positioning indicates the existence of an extensive system of networks across Europe and Australia. Indeed, the number of registries found in each country range from 3 in Portugal to 40 in Romania.22 In spite of such variations, systems of organisation and coordination seem to be quite uniform. Within many of the countries, network data collection are orientated around a series of regionally-based registries and a centralised coordination centre. The UK for instance, has 11 registries (including Devolved countries) and one specialist childhood registry who are coordinated and subsequently pooled to a centralised ONS database (shortly to become part of the National Cancer Intelligence Network). Data collection practices in Germany are similar in structure, with data being centrally pooled in the Dachdokumentation Krebs.23

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22 IACR, 2002.
Cancer Registry Coverage

Acute variations with regard to cancer registry coverage still persist within and between individual countries according to this survey. Indeed, stark disparities with regard to the range of national population coverage indicate a 98% difference between the highest and lowest centres of data collection. Further analysis seems to indicate that that the capacity to confer full coverage is significantly contingent upon the countries ability to institute fully centralised national cancer registry. In contrast regional registry positioning inadvertently limits the potential to capture national burden of disease. In 1992, only 5 countries within this survey were able to confer full national population coverage (Denmark, Finland, Slovakia, Sweden and the UK). Corresponding national coverage values for France and Germany, calculated from aggregate populations monitored by regional institutions, were 2.8% and 2.9% respectively. Yet progressive analysis of national coverage changes, between countries seems to show a marked improvement in absolute levels of monitoring, albeit at a variable rate. By 2007 registries identified as collecting data of sufficient quality, had population coverage of 22% and 20% in France and Germany, respectively.

Furthermore inequalities in cancer coverage monitoring within countries have also been a consistent issue. Significant variation within countries seems to be dependent on the historical regional inequalities in resource provision in administrative regions. The extent, to which regional coverage varies, in some instances, is as much as a factor of five. In the Basque country registry coverage was measured at 5.4% while in the registries covering Tarragona and Navarra were 1.4% and 1.3%, respectively. In such cases, administrative differences between legislative states may be the reason for such low coverage; individual states are responsible for localised budgets, legislation and implementation of cancer collection policy within resident registries. Historical resource inequalities are also likely to influence the ability to collect data. In Italy substantial divergences were seen between the specific proportion that each region contributed to overall coverage. These differences were also apparent across Northern/Central Italy and the more Southern regions. More specifically, while national coverage had reached a level of 23.4%, regional coverage levels varied from 32% in Central Italy to 6% Southern Italy.

25 These percentages were calculated using reported population coverage data from ‘Cancer Incidence in Five Continents’ and the average national population between 1998-2002 taken from the International Database.
Administrative Stewardship

When looking at registry-based stewardship, there seems to be a distinct sense of independence with regards to coordination of cancer data collection across Europe and many Australian territories. Although such institutions tend to be financed explicitly by governmental funds, many of them retain their autonomy and are coordinated by independent organisations. Australia and the UK represent a prime example of such arrangements. Cancer data collection is left mainly to key independent bodies; namely Cancer Fund and Cancer Foundation in Australia and the registry conglomerate of the UKCAR in the UK. Furthermore, in Romania, the only population based registry at the regional level is funded by the Faculty of Medicine and Pharmacy of the University of Oradea.27 Despite the predominance of institutional autonomy, government financing and coordination of data collection efforts still seems to play a significant role within some of the countries in our survey. Territorial government spending and coordination is the main vehicle behind data collection within the Western and Southern states of Australia.28

All countries collect information according to standards of the International Association of Cancer Registries. This requires that all institutions collect information relating to topography (positioning of tumour) and histology (cellular morphology). Indeed, all countries seem to have tackled the need to capture valid numbers of cancer incidences within their specific populations. Notably in some cases hospital accreditation is strictly dependent on the collection of cancer statistics.29 In 1999, Hungary initiated the practice of computer-based registration of new cancer cases within all hospitals, outpatients’ centres and GP’s in the country. Furthermore, in Belgium hospital accreditation as an oncology provider is based upon confirmation of cancer data collection. In the UK, legislation allowed registries to collect patient identifiable information irrespective of consent.30 German legislation dictates that mandatory patient notification is required alongside data collection.

4.3 Aspects of Cancer Data Collection

Consistency of data collection is seen to be a prominent feature across Europe and Australia, especially when considering the different modes of data transfer and management. More specifically, with cancer registries positioned at both a regional and national level in the

majority of countries, the two-tiered stage of data collection presents itself as continent-wide phenomenon. Methods of two-tiered collection are seen across Germany, France, the Netherlands, Italy, Poland, Romania, the Russian Federation, Sweden, Spain and Australia.

Although the two-tier framework is seen to be pervasive within the European and Australian context of data collection, country-specific differences still present themselves. More specifically, issues relating to the completeness of data presents are seen. Countries such as Germany and Russia serve as key cases in point. Given the fragmentation of statutory health insurance in Germany, hospital submission to regional registries remains voluntary rather than compulsory in the majority of the country. However a clear legal obligation for data submission presides in the Rheinland Pfalz and Sachsen Lander. In Russia, on the hand, issues relating to diffusion of data causes information deemed to be unnecessary to be excluded. Indeed, while the majority of countries tend to transfer raw data from regional to central offices for interpretation purposes, the Russian centralisation process is dependent on the transfer of data which has already been interpreted at the regional level. This data makes its way centrally in the form of a series of oncological reports. Within this existing framework, a significant proportion of data excluded at regional level is not assessed and therefore not included in population risk analysis.

Further exceptions to the two-tiered method of data collection are seen within Southern, Eastern and Central Europe. While countries such as Portugal and Turkey seem to rely solely on decentralised offices of data collection at the more regional level, other countries studied rely only on national centres of cancer collection. More specifically, in these cases, centralised centres of data collation serves as the main agent of data uptake. Such practices are expressly evident within Czech Republic, Greece and Slovakia.

While it is clear that countries studied within this report collect an extensive degree of data, issues concerning their quality clearly present themselves. Problems regarding data collection seem to be disproportionately aggregated within Eastern and Central Europe (Greece, Poland, Romania and the Russian Federation and Turkey). In Greece and Turkey the problem of information based solely on regional values presents significant problems for nationwide validity. In such instances, intrinsic differences native to regions of data collection may not be representative of the whole country. Ultimately this creates problems concerning the validity of cancer statistics.

In Greece mortality data was reported to suffer from incomplete death certificate records. Problems relating to data quality span from problems related to outdated diagnostic classification tools (Turkey) to false registration in order to create the illusion of early
diagnosis (Russia). However, poor quality data countries seem to be making a concerted effort to improve standards of cancer information. As of September 2007 Romanian registries have standardised data by using EU algorithms as a quality assurance benchmark.

In contrast, however, several countries based within Western and Northern European, seem to attest high levels of data quality. Levels of data quality seem to be inextricably linked to process features associated with quality assurance and aspects of registry longevity. In the survey it was documented that countries like Spain and the UK rely on quality assurance algorithms to determine improbable combinations of data. In the case of Sweden extensive levels of data-coverage in addition to stringent regulation is also seen to be conducive to the collection of high quality data. Despite the general trend between eastern and western data quality, countries such Czech Republic and Slovakia serve as key exceptions to the rule. In both countries a system of quality assurance programs have been implemented to confer high levels of quality assurance.

Despite European and Australian consensus surrounding the prioritisation of cancer risk and the subsequent legislation in EU member states, methods of data collection vary in and around countries sampled for this study. The examination of questionnaire responses, illustrates critical differences in the collection of demographic data. In particular, information concerning the collection of incidence, mortality, survival and prevalence, present a series of interesting results.

Primary data responses seem to indicate that information regarding cancer-related incidence and mortality is universally collected. However, a clear divergence between countries is seen in the collection of survival and prevalence data. While countries such as France, Spain, Sweden, the Netherlands, and the Russian Federation collected an extensive amount of information, other countries exhibited limited activity within this area. Noticeably enough, Germany failed to collect prevalence, 10-year and 5-year survival. Lack of survival and prevalence was also seen in Greece, Slovakia and Turkey. Italy, on the other hand failed to collect survival-related data.

Cancer data collection based on essential aspects of disease progression and treatment received, present a thoroughly varied picture. Within all countries reporting patient treatment details as a standard basis of data collection (UK, Denmark, France, Germany, Hungary, Sweden, Portugal, Russian Federation, Poland, Czech Republic and Romania), chemotherapy protocols were consistently reported. Moreover countries seem to collect treatment information, beyond that of standard patient chemotherapy protocols. In Russia and Romania, comprehensive treatment data for numerous populations is collected. Amongst other things,
treatment details are collected for patients who have been cured completely or are in long-time remission in Russia. On the other hand, Romanian data collection processes have been seen to determine pathways of the cancer treatment, which include sequential reporting of oncological therapies. Additionally, while extensive information relating to methods of radiotherapy, hormonotherapy, immunotherapy and surgical treatment are collected within Germany and UK, compliance with such collection is variable across regions. Finally, unlike many of its counterparts Polish treatment details are reportedly based solely on patients who have experienced remission.

4.4. CRC Data Collection

Presented as a summary of data collection activity across the study countries, the data collection scorecard aims to capture the extent of CRC data collection activity within the study countries. Measured as a composite indicator of incidence, mortality survival and prevalence collection, each country was assigned one point for each of the 28 measures of data collection, every indicator collected. Finally, a CRC data collection performance score was calculated and countries were identified as having leading, moderate and poor CRC data performance depending on the percentage score (leading performance: 71%-100%, moderate performance: 46%- 70% and poor performance: 0-45%). Issues of data quality were not explicitly addressed, but were raised in a number of occasions. Figure 4.1 presents the aggregate results for the study countries, whereas figure 4.2 disaggregates these to their constituent components (incidence, mortality, prevalence and survival).

Collecting nearly all measures of CRC data requested, the UK and Romania emerges as the best data collection performers, although for the latter a number of questions arose in terms of completeness of records, continuity in data collection and quality. A distinct proportion of countries have poor CRC data collection performance. Poor performance is seen within Turkey (14%), Greece (25%), Slovakia (29%) and Germany (32%). However, the majority of countries studied seem to have moderate data collection activity with scores ranging from 50% (Poland) to 61% (the Netherlands).
Figure 4.1
CRC Data Collection Scorecard Results


Figure 4.2
CRC Data Collection Scorecard Disaggregated Results

Source: LSE CRC Survey, 2008
CRC data collection performance across participant countries indicates significant disparities in data collection activity. With such acute differences between the leading and poorest performers, issues concerning the development of effective CRC initiatives becomes evermore pressing. In an environment in which there is a substantial amount of contending need, lack of data collection activity, presents significant barriers to determining the population risk and burden of CRC. Ultimately, it is this lack of data activity that may lead to the incorrect prioritisation of need and the subsequent misallocation of scarce financial resources.

**CRC Incidence Data Collection**

As was shown in the previous section, there is clear divergence between leading countries of CRC data collection and those that exhibit the poorest data collection activity. In the following three sections, an in-depth examination of the current status of CRC data collection will be presented for the study countries.

Exploration of CRC data collection, across countries studied seems to indicate that the year in which incidence collection started varies from country to country. While the majority of countries have collected data continuously, the initiation of incidence collection seems to cluster into two groups, those who started collection several decades ago and others that began recently. Countries such as Denmark (communicated collection of incidence in 1943), Sweden (communicated collection of incidence in 1958); the Russian Federation (communicated collection of incidence in 1939) and the UK (communicated collection of incidence in 1948) have a clear history of early cancer incidence activity. During this relatively long period of data collection, processes’ of information uptake underwent significant development. Initially, the extent to which data was representative of the population was limited at early stages. In Russia, systems of data collection were launched in city-based oncology institutions. It was not until 1953 that data collection extended to both urban and rural areas. Furthermore in the UK, it took a system of cancer registry reformation and reorganisation to confer 100% coverage in England alone. This was finally achieved in 1962.
Table 4.1
Time span of CRC Data Collection

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence</th>
<th>Time Span: CRC Data Collection</th>
<th>Survival</th>
</tr>
</thead>
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<td></td>
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<td>Mortality</td>
<td>Prevalence</td>
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<tr>
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<td>2005</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>1943</td>
<td>1951</td>
<td>1960</td>
</tr>
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<td>✓</td>
<td>x</td>
</tr>
<tr>
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<td></td>
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<td>1999 &amp; 1963 (?)</td>
<td>2003 (?)</td>
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<td>19938</td>
<td>1957-present</td>
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<td>x</td>
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<tr>
<td></td>
<td>1948-present</td>
<td>1948-present</td>
<td>1948-present</td>
</tr>
</tbody>
</table>

Notes:
1. German prevalence data is not collected on a regular basis.
2. No national data available. Estimates from the EUCAN used
3. Mortality data is also collected for hospitalized patients.
4. No national prevalence data available. EUCAN projections are used for 1-year prevalence and 5-year prevalence.
5. No national data collected. Only regional data is presented (Amsterdam).
6. National survival data not collected. Only regionally presented
7. Years of incidence collection for all types of cancer.
8. First country-based incidence results were published for the year of 1993-1994.
9. Data collected by TURKSTAT since 1957.
10. Complete coverage achieved in 1962


The collection of European and Australian CRC incidence data is a recent phenomenon. The majority of countries studied, adopted incidence data collection at much later stages. For France, Italy, the Netherlands, Portugal and Slovakia and Australia, CRC incidence data

Detailed incidence data seems to be systematically collected across Europe. In all countries concerned incidence is collected by sex and age. Despite Greece’s lack of home-grown incidence statistics, values for these statistics have been estimated using corresponding EUCAN data. However such data is only available for 1998, 2000 and 2002.

Incidence differentiated by CRC stage seems to be widely collected according to reports from participating respondents. However, there does seem to be a certain degree of variation concerning which stages of disease warrant notification and record. While the CRC stage is recorded for all cases of new diagnosis in the majority of Europe (Denmark, France Czech Republic, Netherlands, Poland, Portugal, the Netherlands, Romania, Slovakia, Spain, the UK and Australia), Russia only records the stage of the most advanced cases of CRC. Stage-specific CRC incidence collection is absent in Germany, Greece, Italy, Sweden and Turkey.

Apart from the standard set of indicators used to describe incidence, many of the countries studied collect detailed CRC information. In Romania and the UK the histological progression of newly diagnosed CRC cases is actively recorded and collected. In addition, TNM classification is routinely used and subsequently collected to further describe CRC tumour type, lymph node progression and stage of cancer metastasis in Slovakia. Furthermore, Russian data determining the amount of newly diagnosed CRC patients resulting from medical prevention is also recorded. In an attempt to monitor inequalities in CRC burden, the geographic location of newly diagnosed CRC is routinely assessed within Slovakia, the Russian Federation, Poland and the UK.

Conclusions drawn from the current state of CRC incidence data collection illustrates key differences in length of incidence collection. From information collected, it is clear that the initiation of CRC incidence collection in the majority of countries occurred at much later stages. Detailed levels of CRC incidence are systematically collected across countries studied; with incidence differentiate by sex, age and stage being routinely collected. Despite good overall CRC incidence collection performance within the majority of countries studied, data collection in Greece is visibly poor given the lack CRC incidence collection.
Table 4.4
Aspects of CRC Incidence Data Collection

<table>
<thead>
<tr>
<th>Country</th>
<th>Gender</th>
<th>CRC Incidence Data Age</th>
<th>Stage of Diagnosis</th>
<th>Other criteria</th>
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Notes:
1. Intervals collected at < 15 years, 15-45 years, 45-65 years and > 65 years.
2. Estimates of incidence taken from EUCAN project.
3. Incidence data available by stage of diagnosis is available upon request.
4. Regional incidence values collected.
5. Histological data collected.


CRC Mortality Data Collection

Examination of the years at which CRC mortality data began, seems to suggest a divergence between countries that initiated early mortality collection and those who established it much later. The Russian Federation (1939- present) and the UK (1948- present) still exhibits early collection activity together with Turkey (1957) and Greece (1961). This occurs despite the lack of consistent incidence data collection in the later of the two counties. However, there still seems to be distinct trend of late CRC mortality data adoption in the majority of countries. The Netherlands and Spain have consistently collected mortality information since 1978 and 1989, respectively (Table 4.1). While Swedish and Romanian mortality collection began in 1995 and 1994, respectively, the rest of the countries studied
also follow suit. In Slovakia, Czech Republic and Germany, mortality data collection began in 1994, 1997 and 1998, respectively.

Mortality details concerning both sex and age of patients dying from CRC are consistently recorded in a large proportion of European countries. The only exception, however, is seen in Slovakia (CRC mortality differentiated only by age is collected) and Turkey (CRC mortality differentiated only by neither age nor sex). However, analysis of mortality differentiated by treatment depicts a varying pattern collection activity. Rates of death for CRC patients differentiated by treatment are generally absent within many countries. Of the countries participating in the study, only Denmark, the Czech Republic, Romania, Slovakia and the UK collected this information. Despite many countries reporting the collection of treatment data, it is not clear whether the regimen data collected is representative of full treatments administered throughout the duration of illness. In the UK, information does not represent complete treatment history. Patient therapy and treatment for all cases, collected at registry-level, are recorded within the first six months of diagnosis. Any treatment given to the patient past the six-month cut-off point is not recorded.

According to participating respondents, stage-specific CRC mortality rates seem to be markedly divergent. There is a distinct absence of stage-specific CRC mortality data within France, Italy, Hungary, Germany, Greece, the Russian Federation, Portugal, Spain, Sweden, Turkey and Australia. However availability of such information is seen across Denmark, Czech Republic, the Netherlands, Poland, Romania, Slovakia and the UK. Post-mortem results are subsequently used to complete death certificates in countries that collect CRC information in Germany, Italy, the Netherlands, Poland, Spain, Sweden, Russia, Switzerland, the UK and Australia. Reports of death were then reported to cancer registries and are linked to existing incidence information.

Within the framework of existing CRC mortality data, many of the countries collect information that beyond the standard indicators of mortality. Greek records report the region of residence, marriage and employment status of hospitalised patients. In addition to this mortality collection in Romania and the UK include the date and place of death.

From the results presented above it is clear that CRC mortality collection is variable. While all countries participate in some degree if data collection, the detail associated with CRC mortality collection is variable at best. Variations in the scope of CRC mortality data

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31 Exceptions to this practice were seen in Hamburg in Germany; Biella, Brescia, Genoa, Salerno, Macreata, Varese and Veneto Province and North East Registry, Italy; Warsaw City, Poland, St Petersburg in Russia; Canary Islands, Granada and Zaragoza, Spain; East of England, South and Western Regions, Trent Cancer Registries, UK; New South Wales and Capital Territory, Australia.
collection activity, present Czech Republic, the Netherlands, Romania and the UK as leading performers; Greece, Poland, Russia and Sweden as moderate performers and Germany, Slovakia, Spain and Turkey as the poorest performers.

**CRC Prevalence and Survival Data Collection**

CRC prevalence data collection within countries assessed seems to be variable at best. Although the majority of countries collect prevalence data in some form or other, collection activity seems to be limited. Prevalence data is collected irregularly in Germany while CRC projections are the only indication of prevalence for Greece. In addition to this, a divergent pattern arises when considering the dates of prevalence collection initiation. Of the fourteen countries presenting prevalence data, Denmark (1960), the Russian Federation (1939) and the UK(1948) have been seen to begin activity at much earlier points in time. The remaining four countries to give commencing dates, present data in the late 80’s and mid 90’s. Italy began its collection in 1970; The Netherlands began CRC prevalence collection in 1988 only in Amsterdam; Romania began its collection in 1994 and Sweden in 1995. Furthermore Spain began collection activity in 1998, while Poland and the Czech Republic started monitoring CRC prevalence in 2003.

Collection of CRC prevalence differentiated by sex and age remains variable. Only the Czech Republic, Denmark, Hungary, Poland, Portugal, Sweden, the UK and Australia consistently collect both. The Netherlands (Amsterdam), Greece and Spain CRC only collect prevalence differentiated by sex. Moreover, prevalence by treatment CRC patient receives is collected by Czech Republic, Romania, Poland and the UK. In addition stage related prevalence is collected in again in the Czech Republic, Romania and the UK. However there seems to be limited data collection with concerns to the prevalence of CRC patient previously identified as high- risk before the onset of disease. Only Romania and Czech Republic collect such information.

The activity of survival collection seems to be more consistent across all countries studied. It would seem the majority of countries started CRC survival collection at much later stages. While Italy, the Netherlands and Germany began survival data collection in the early 70’s to late 80’s (Italy in 1970, Australia in 1982, the Netherlands in 1988 and Germany in 1985), the majority of countries began data collection in the 90’s (Czech Republic in 1997, Romania in 1994, Portugal in 1998, Spain in 1990 and Sweden in 1995). Only Denmark the Russian Federation and the UK began survival data collection in the early 20th century – 1951, 1939 and 1948, respectively.
Detailed European CRC survival activity indicates few countries consistently monitor rates throughout the traditional 10 year period. Only the Netherlands, Sweden and the UK collect survival at the 1, 5 and 10- year survival benchmarks. Collection of survival data at the 1- year and 5- year’s active collection is seen within Romania, the Russian Federation and Spain. Finally survival rates for CRC are measured at the 1 year level for Czech Republic and 5 year- level for Germany.

Within the above CRC survival framework, details relating to patient sex, age, stage of disease and treatment tend not be consistently collected. Across the countries studied, survival differentiated by sex and stage of disease is only collected in nine instances (Denmark, France, the Netherlands, Portugal, Romania, the Netherlands, Sweden, Spain, the UK and Australia). Additionally survival collected by treatment is all the scarcer, with Romania and the UK being the only countries that collect this data. Lastly, Romania seems to be the only country that collects survival data based on with the high risk subset of the population.

In summary, the collection of CRC survival and prevalence across the given number of countries studied is variable. Although the majority of countries present some form of CRC survival and prevalence data, the scope of detailed collection activity is limited. Examination of CRC survival patterns indicate that the majority of countries fail to consistently collect data across the given 10-year period of evaluation. Furthermore, CRC survival data differentiated by sex, age and stage is variable, while survival differentiated by treatment received and surveillance is limited. Data scorecard performance for CRC prevalence is evenly distributed. The Netherlands, Romania, Spain and the UK lead in CRC survival data collection, Sweden and Russia exhibit moderate performance while the Czech Republic, Germany, Greece, Poland, Slovakia and Turkey.

In terms of CRC prevalence collection, a similar picture emerges i.e. variable collection differentiated by sex and age, and limited collection surrounding data differentiated by treatment and surveillance. The CRC data scorecard shows a clear divergence between countries leading in CRC prevalence collection performance and those exhibiting poorer performance. The majority of countries studied have poor CRC prevalence data collection activity. While the Czech Republic, Poland, Romania and the UK lead in CRC survival collection, poor survival performance is seen in Germany, Greece, the Netherlands, the Russian Federation, Slovakia, Spain and Sweden.
Table 4.7
Aspects of CRC Survival Data Collection

<table>
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<th>Country</th>
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<th>Age 1-year survival</th>
<th>5-year survival</th>
<th>10-year survival</th>
<th>Treatment</th>
<th>Stage of Diagnosis</th>
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<th>Other criteria</th>
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**Notes:**
1. Regional variation of survival data recorded.

**Source:** LSE CRC Survey 2008.
4.5. Conclusion

A number of problems with data collection and reporting have emerged from most study countries, which potentially disallow robust data being available for policy analysis.

First, continuous collection of standardised cancer expenditure is conspicuously lacking across all countries within Europe and Australia. With the lack of consistent and verifiable expenditure data for cancer, the quest to understand how expenditure influences national policy outcome is ultimately compromised. Indeed, it is this lack of reliable data that threatens to undermine the ability of countries to monitor and improve their performance within all areas of cancer management. However, if the values taken from 2002 are anything to go by, it is clear that national levels of cancer expenditure per capita within the lower to mid reaches, vary irrespective of geographic positioning and thus economic development. This phenomenon is apparent in countries such as Poland, Hungary, the Czech Republic, Australia, Portugal, the Netherlands and Spain, where expenditure per capita is less than €100 Euros per capita.

Second, despite the overall strength of performance in CRC incidence data collection, collection of such information at such late stage presents important implications for health policy. This is especially seen when looking at the planning and development of primary CRC prevention programmes. Longevity of incidence collection is key to differentiating legitimate epidemiological trends from coincidental artefacts. The scope of detailed CRC incidence is helpful when identifying determinants of disease, however the relative brief period of data collection may not yet be long enough to identify risk factors specific to each country. Clear identification of such behavioural determinants of health, is critical step in framing policy aims and ultimately constructing effective prevention policy.

Third, the distribution of CRC mortality data performance brings forth interesting considerations concerning the causes of inequalities of outcome within and between countries. Given the persistent phenomenon of inequalities in CRC outcome, in-depth collection of CRC mortality data is essential when trying to determine whether differences in CRC mortality are matter of behavioural selection for the disease, unequal access to treatment or due to the nature of the disease. Yet the variable data collection makes it increasingly difficult to substantiate differences in outcome. In order to construct and implement policy that effectively tackles such risk factors, detailed CRC mortality data is essential.

Finally, the acute lack of detailed CRC survival and prevalence data collection presents critical implications for the planning of nationalised initiatives. Identification of the trends of survival is instrumental in determining the overall efficacy of a number of policies.
References


Chapter 5

Colorectal Cancer Screening: A Question of Awareness and Capacity

5.1. Introduction

One of the distinguishing features of the pathophysiology of CRC is the stepwise progression from initial carcinogenic insult through to adenoma, invasion and metastasis over a long time period. The inherent stepwise progression of CRC biology makes it most amenable to secondary prevention strategies (screening). Screening is known to reduce the incidence of CRC\(^\text{32}\), as well as down-staging its presentation through enhanced awareness and early detection within the context of screening programmes. Given the importance of colorectal cancer screening in detecting - and potentially preventing - disease at an early stage, this chapter discusses:

- The various screening options, including their test performances;
- The cost effectiveness of screening, including limitations;
- The organisation of screening programs in Europe;
- The participation rates in screening;
- The awareness and interest in colorectal cancer and its screening; and
- The endoscopy capacity for screening in the survey countries.

5.2. Methods for Detecting CRC

Screening for colorectal cancer is defined as “the testing of asymptomatic individuals to determine who are likely to have adenomatous polyps or colorectal cancer”\(^\text{33}\). There are many methods of screening, each with their own strengths and weaknesses. The primary methods currently in use are fecal occult blood testing (FOBT) (3 types), flexible sigmoidoscopy (FS) and colonoscopy (CS), while newer tests such as computed tomography (CT) colonography, fecal DNA, colonic cell exfoliation and capsule endoscopy are under investigation.


\(^{33}\) Winawer, 2007.
Fecal Occult Blood Testing

There are three FOBT methods: (a) immunological (b) guaiac unhydrated, and (c) guaiac rehydrated (will not be discussed due to poorer test performance and limited use). The guaiac FOBT (gFOBT) requires dietary restrictions of red meat, as it detects general hemoglobin activity, whereas immunological FOBT (iFOBT) does not because it detects human hemoglobin. The gFOBT requires three consecutive fecal samples and iFOBT only one sample.

The FOBT is usually performed annually or biennially. Test kits are sent by post to participants with instructions for slide preparation and return posting. This does require some degree of independence, interest and literacy on behalf of the participant for success. An alternative is GP-performed screening, or test kits picked up from and delivered to the physician’s office.

Both the sensitivity and specificity of the gFOBT is low (40-50% and 2-10%, respectively). The iFOBT is fairly new and has better sensitivity (67-95%) and specificity (97%), although is more expensive than gFOBT. Both approaches have been shown in a controlled clinical trial setting to reduce mortality by 14-18%.

Endoscopy

Endoscopy is an alternate and complimentary screening tool to FOBT, and has the advantage of direct visual examination of the bowel. There are two approaches: flexible sigmoidoscopy (FS) and colonoscopy (CS).

Flexible Sigmoidoscopy

FS in population screening can be performed alone or in combination with biennial FOBT testing to improve its sensitivity, particularly to adenomas in the proximal bowel. The interval for FS-based screening programmes is usually around the 5-year mark, but there may be a case for a longer inter-screening interval in low-risk individuals.

FS has a number of advantages: it is more sensitive than FOBT, as well as being less invasive, and thus less prone to the mortality and morbidity associated with colonoscopy.

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34 Ransahoff et al, 1997
36 Fraser et al, 2006; Rubeca et al, 2006.
Further research is exploring whether once-only FS screening programme is sufficient for screening purposes.40

The sensitivity of FS depends on the part of the bowel being visualised (from 74.4% for the distil aspect of the descending bowl to 96.5% for the rectal portion). Overall mortality reduction for FS-based screening has been estimated in the order of 18-40%.41 FS has its limitations. It cannot examine the proximal bowel, which has a greater impact on screening women42 where there is an increased prevalence of proximal adenomas and frank carcinoma.43 Furthermore, a positive FS still requires a colonoscopy for diagnosis, and currently there are no guidelines as to which type and size of adenoma warrants a colonoscopy follow-up.44

Colonoscopy

Colonoscopy (COL) is considered the gold standard for diagnosis.45 Colonoscopy has a sensitivity between 75% for small adenomas and close to 100% for large adenomas.46 It may enjoy a protective effect against colorectal cancer, as individuals who have had a negative exam are less likely to test positive in the future.47 There are some drawbacks associated with colonoscopy: first, there is a small risk of bowel perforation (0.09-0.24%) and procedure-induced mortality (4.9% of perforated patients).48 Second, colonoscopy is far more time intensive for both patients and health professionals than FS, as well as more costly and resource intensive.

New Methods

There are four new methods that could be used for population screening in the future: fecal DNA, computerized tomography (CT) colonography, capsule endoscopy and colonic cell exfoliation. Fecal DNA detects alterations in DNA soughed off in the digestive tract, however, the technique to collect and measure the mutated DNA is difficult and costly. Recent new techniques have improved the methodology, resulting in approximately 85%

40 Segnan et al, 2002; UK Flexible Sigmoidoscopy Screening Trial, 2002.
42 Schoenfeld et al, 2005.
47 Brenner et al, 2006
48 Misra et al, 2004
sensitivity and 80% specificity for colorectal cancer.\textsuperscript{49} It is still in the early stages of development,\textsuperscript{50} however, may offer an alternative to FOBT if its performance proves superior at lower costs.\textsuperscript{51}

CT colonography, otherwise known as virtual colonoscopy, may be an alternative to colonoscopy screening, delivered by imaging departments. It has a reported high sensitivity (61-85\%) and specificity (84-86\%)\textsuperscript{52}, and may have the potential for greater adherence,\textsuperscript{53} however, is expensive and positive test still requires a full colonoscopy. To date, no population screening trials have been performed using this method, although trials of high-risk patients have been completed with mixed results.\textsuperscript{54}

Most CT units already struggle to meet screening demand without the addition of asymptomatic, low-risk patients. A UK survey found 64\% of CT departments did not offer CT colonography primarily due to competing clinical demands, and of those offering the service only 12\% performed it daily.\textsuperscript{55} Recent modelling of colorectal cancer screening on current CT capacity in Europe, assuming a CT colonography once per decade and 30\% screening adherence, found capacity could meet some of the demand for screening\textsuperscript{56}, particularly if patients were risk stratified\textsuperscript{57}. Overall, more clinical trials and pilots studies need to be performed before this method becomes clinically acceptable for screening purposes.

Capsule endoscopy and cell exfoliation are two other promising methods in colorectal cancer screening. The former requires subjects to have a number of days with dietary changes, including two days of only clear liquids, while the detection results for polyps are similar to colonoscopy\textsuperscript{58}. Cell exfoliation involves the insertion of a small balloon into the rectum to collect colonic epithelial cells that increase production and turnover with neoplasia, and can be performed by a nurse or primary care physician\textsuperscript{59}. Both methods are still in their infancy and require extensive research prior to its recognition as an acceptable screening method with comparable costs to FOBT.

\begin{flushright}
\textsuperscript{49} Itzkowitz et a, 2007; Lees et al, 2007.
\textsuperscript{50} Indeed, mcm2-based assays may improve this approach.
\textsuperscript{51} Half et al, 2006.
\textsuperscript{52} Heitman et al, 2005; Pickhardt et al, 2007.
\textsuperscript{53} Angtuaco et al, 2001.
\textsuperscript{54} White et al, 2008; Roberts-Thomson et al, 2008; Pickhardt et al, 2007
\textsuperscript{55} Burling et al, 2004.
\textsuperscript{56} Hassan et al, 2008.
\textsuperscript{57} Lin et al, 2006.
\textsuperscript{58} Eliakim et al, 2006
\textsuperscript{59} Lektionov et al, 2007
\end{flushright}
5.3. Are Colorectal Cancer Screening Methods Cost-Effective?

The use of cost effectiveness models in cancer screening is advantageous in many ways. It models various screening methods (important where no head to head clinical trial exists), screening intervals, age groups, and adherence levels in addition to biological hypotheses of disease development. It can be used to explore conflicting evidence produced by various clinical trials, expand to include population mortality and incidence trends, and help develop screening policies.

Relevant Costs

Available evidence on colorectal cancer screening costs

Published costs of colorectal cancer screening programmes are few, due to greater use of opportunistic screening rather than invitational screening in Europe. The budget for the French screening pilot in 2005 was €1.3 million with €29.3 per screened individual, comprising a fixed cost of €4.9 and a variable cost of €7.5 per year per 50-74 year old invitee.60 In 2007, France spent €41.4 million on screening prior to the 2008 nation-wide screening implementation. The Netherlands spent €700,000 for a FOBT pilot soon to be completed. Australia spent $43.4 million during the first 3 years of their national screening program. All these data relate to FOBT testing on a biennial basis.

Available evidence on colorectal cancer treatment costs vs. screening costs

The importance of screening is highlighted by the significant treatment costs for a patient developing colorectal cancer, and the available figures are compelling. In France, the mean 2004 costs during first year after diagnosis for Stage I were €17,596, increasing in Stage IV to €35,059 per patient.61 In Switzerland, Stage I median costs were $19,638 and Stage IV costs were $39,298 in patients followed for 3 years after 1997-98 diagnosis.62 In the UK, the screen-detected lifetime costs for Stage I were £8,299, Stage II £12,441, Stage III £19,076 and Stage IV £11,945.63 In screened patients, costs per neoplasia was €2,163, per advanced neoplasia €3,645, and per cancer €13,466.64

60 Denis et al, 2007.
63 UK Colorectal Cancer Screening Pilot Group, 2004.
64 Denis et al, 2007, op. cit.
Effects

Primary goals of colorectal screening are to detect early asymptomatic colorectal cancers as well as to detect polyps prior to carcinoma development, preventing cancer development and promoting early, less-costly treatment. Various FOBT screening programs, primarily pilots, have found 2.5-15.3 polyps and 0.6-0.9 colorectal cancers per 1,000 screening invitations.\(^6^5\) It is hoped screening will also detect more carcinomas in earlier rather than latter stages. The FOBT screening programs and pilots have found 24-55% of carcinomas were at Stage I, 17-24% Stage II and 20-30% at Stage III/IV, and 19% unstaged polyp adenomas.\(^6^6\) These Stage at Diagnosis results were obtained with colonoscopy, required for diagnosis, which is not risk-free. Screening programs and pilots have reported complications (2-7 per 1,000 colonoscopies) and, rarely, fatalities.\(^6^7\)

Cost Effectiveness in the context of CRC screening

Colorectal cancer screening is more cost-effective than no screening, and all methods are under an acceptable threshold\(^6^8\). The method primarily investigated has been FOBT (Table 5.1), although other methods such as FS, colonoscopy and CT colonography (Table 5.2) have also been explored. A few publications explore variations in methodology rather than only comparing to no screening. Most present results per life years gained (LYG) rather than in quality adjusted life years (QALY).

Cost-effectiveness analysis of the UK Nottingham trial found gFOBT more cost effective than breast cancer screening\(^6^9\) (Table 5.1). Examination of Danish and French gFOBT screening pilots found both annual and biennial testing to be cost-effective.\(^7^0\) The iFOBT is more effective and more expensive than gFOBT, however, an analysis using French data found it a viable option to gFOBT.\(^7^1\)

There are limited cost-effectiveness analyses dealing with endoscopy in Europe (Table 5.2). Both American and European studies have found FS a cost-effective screening option,

\(^{65}\) Weller et al, 2007 ; Australia’s Bowel Cancer Screening Pilot, 2005; Santvirta et al, 2002
\(^{67}\) Evaluation of UK Colorectal Cancer Screening Pilot, 2003; Altenhofen et al, 2005; Denis et al, 2007
\(^{68}\) The UK’ National Institute of Clinical Excellence sets threshold at £30,000/quality adjusted life year
\(^{71}\) Berchi et al, 2004.
with or without biennial FOBT,\(^\text{72}\) while colonoscopy once a decade or even only once is also seen feasible in America.\(^\text{73}\)

Few explorations of other newer colorectal cancer screening methods have been performed, particularly in Europe. To date, cost-effectiveness analysis of CT colonography has not found it superior to traditional colonoscopy,\(^\text{74}\) although it may be if polyps <5mm are not reported.\(^\text{75}\) A recent cost-effectiveness analysis of capsule endoscopy found it only became a viable option if adherence was greater than colonoscopy\(^\text{76}\), perhaps unlikely with 2 days of clear fluids. No cost-effectiveness analyses have been published yet on cell exfoliation. The opportunity costs of implementing new screening methods must be heavily considered, particularly for CT colonography with costs of CT equipment and capacity constraints in many European CT units.

There are a number of problems in Europe and Australia with these cost effectiveness analyses. First, there is a scarcity of analyses meeting minimum cost-effectiveness requirements. Second, only a minority perform head to head comparisons between screening methods.\(^\text{77}\) Third, only two studies explore endoscopy using FS\(^\text{78}\) while only non-American analysis exists for colonoscopy\(^\text{79}\). These issues are all worrying, in light of increasing interest in colorectal cancer screening, as decision making regarding screening implementation in individual countries will have little scientific basis.

As reimbursement and resource allocation decisions are increasingly based on effectiveness and cost-effectiveness of different interventions, including diagnostic procedures, it appears that the evidence base needs to be reinforced for decisions to be made on sound evidence. In addition, appropriate measures also need to be taken at insurance level in order for the diagnostic method of choice to be implemented robustly, thus ensuring a high level of compliance by the target population.

\(^{73}\) Khandker et al, 2000; Sonnenberg et al, 2000; Sonnenberg et al, 2002.
\(^{75}\) Pickhardt et al, 2007; Heitman et al, 2005; Hassan et al, 2007
\(^{76}\) Hassan et al, 2008
\(^{79}\) Hassan et al, 2007, \textit{op. cit.}
Table 5.1

Synopsis of European and Australian cost-effectiveness publications on colorectal cancer FOBT screening (1998-2008)

All figures presented are discounted at rates presented in the publication, costs presented in 2006 €.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Screening</td>
<td>45-74y for 36y</td>
<td>50-74y for 20y</td>
<td>50-74y for 20y</td>
<td>45-74y</td>
<td>45-74y</td>
<td>55-74y</td>
</tr>
<tr>
<td>FOBT:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(a) q2y (65-74y); (b) q2y (60-74y); (c) q2y (55-74y); (d) q1y (55-74y); (e) q1y (50-74y) (f) no screening</td>
<td>(a) iFOBT q2y</td>
<td>(a) FOBT q2y (b) no screening (per 153,000 invitees)</td>
<td>(a) FOBT q2y (b) no screening (per 100,000 invitees)</td>
<td>(a) FOBT qXy (b) no screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LYG</td>
<td>(a) 974 total (b) 1425</td>
<td>(a) 9.8-16.7 (b) 9.8-16.7</td>
<td>(a) 788 total</td>
<td>-</td>
<td>(a) 250/y</td>
<td></td>
</tr>
<tr>
<td>(c) 1831 (d) 2607 (e) 3081</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>QALY Costs</td>
<td>(a) €2,686,068 total</td>
<td>€7,396,232 total</td>
<td>(a) €222-271 targeted screen;</td>
<td>€2,006,979 total;</td>
<td>€9,003,249-18,040790 total</td>
<td>€46,128,331/y</td>
</tr>
<tr>
<td>(b) €5,574,029 (c) €5,574,029 (d) €9,709,390 (e) €12,971,438</td>
<td></td>
<td>(b) €172-204</td>
<td>€8504/cancer detected;</td>
<td>€14.79/screen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICER</td>
<td>(a) €2,572DKK/LYG; (b) €3,059; (c) €3,726; (d) €5,743; (e) €6,881</td>
<td>(a) €3,619²⁰₀/LYG; 5,072- e¹⁰⁵⁻</td>
<td>(a) €3317²⁰₀/LYG - €8463¹⁰⁻</td>
<td>(a) €2,546/LYG</td>
<td>(a) €2,446-10,143/QALY</td>
<td>(a) €14,257/ DALY</td>
</tr>
</tbody>
</table>

Notes: LYG = life years gained; QALY = quality adjusted life years; ICER = incremental cost effectiveness ratio; q = every;
## Table 5.2

### Synopsis of European and Australian cost-effectiveness publications on colorectal cancer endoscopy screening (1998-2008)

All figures presented are discounted at rates presented in the publication, cost presented in 2006 €.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Screening</td>
<td>50-80y for 30y (a) FS q10y; (b) COL q10y; (c) CT q10y (d) no screening (per 100,000)</td>
<td>50-70y (a) FOBT q2y (50-69y); (b) FOBT q2y (60-69y); (c) FS once-only (55y); (d) FS once-only (60y); (e) FS once-only (60y) + FOBT q2y (61-70y) (f) no screening</td>
<td>60y for 7y (a) FS once-only (b) no screening (per 100,000 invitees)</td>
<td>(a) FOBT q1y; (b) FOBT q2y; (c) FS q10y; (d) COL q10y; (e) no screening</td>
</tr>
<tr>
<td>LYG</td>
<td>(a) 2,945; (b) 3,821; (c) 3,589</td>
<td>(a) 0.026; (b) 0.0126; (c) 0.0237; (d) 0.0197; (e) 0.0271</td>
<td>1,194 total</td>
<td>-</td>
</tr>
<tr>
<td>QALY</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total costs</td>
<td>(a) €49,728,410; (b) €50,360,402; (c) €46,862,560</td>
<td>(a) €106.15; (b) €38.89; (c) -€45.61; (d) -€45.20 (e) -€3.04*</td>
<td>€6,625,596 total</td>
<td>No screen vs (a) €36,644/LYG; (b) €32,177; (c) €13,127; (d) €15,046</td>
</tr>
<tr>
<td>ICER</td>
<td>No screen vs (a) -€579/LYG; (b) -€281; (c) -1274 (a) vs (b) €721; (c) dominated (c) vs (b) €15,091</td>
<td>LYG: No screen vs (a) €4,085/LYG; (b) €3,092; (c), (d), (e) dominant; No screen vs QALY: (a) €4675/QALY; (b) €3749; (c), (d), (e) dominant</td>
<td>€5,548/LYG</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** LYG = life years gained; QALY = quality adjusted life years; ICER = incremental cost effectiveness ratio; q = every; * marginal costs compared to no screening

**Source:** LSE CRC Survey 2008.
5.4. The Impetus for Screening Policy

The first document coming from the European scientific community setting colorectal cancer screening guidance was published in 1999, the one page document simply recommending “repeated, FOBT screening for asymptomatic adults aged 50 and over, with colonoscopy done in those screening positive”. In contrast, the first American guidelines were published earlier in 1997, with details of various test performance, screening interval, ages and recommendations.

This guidance was replaced in 2000, by new European guidelines for all cancers, outlining general screening principles, and briefly describing gFOBT test performance with little to no acknowledgement of other methods. The document recommended annual or biennial FOBT screening for 50-74 years with colonoscopy as follow-up. A following editorial rebutted the absence of other methods, particularly the iFOBT. Since then, there have been no European guidelines for colorectal cancer screening coming from the scientific community.

In 2003, the European Union Council formally supported cancer screening, specifically for breast, cervical and colorectal cancer, and specifically “FOBT screening for CRC in men and women aged 50 to 74 years”. In 2007, an appeal was made to the European Parliament to combat colorectal cancer with the Declaration of Brussels. Among its requests is that the European Commission provides European health ministers with colorectal cancer screening guidelines as soon as possible, and that these guidelines should include high-risk group management, quality assurance, formal invitations as well as adequate training. In Australia, in the 2000-1 budget, the federal government announced funds for a colorectal cancer screening pilot, which ran from 2002 to 2004 in three locations, and upon completion a national screening programme was implemented.

Recently, a report has been produced on the implementation of European Council recommendations on cancer screening made in 2003, including CRC screening. It found overall that although some progress had been made to include cancer screening as part of population health, there is considerable room for improvement, including opportunistic versus

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80 European Group for Colorectal Screening, 1999.
82 Advisory Committee on Cancer Prevention, 2000.
85 Europe against Colorectal Cancer, 2007.
formal screening, slow implementation of screening, variability in ages and screening methods. Greater support of screening implementation is recognized as a major barrier to universal access to cancer screening in Europe.

It appears as though the impetus for national screening policies has increased significantly in some countries and at EU level over the past decade, as has the awareness that CRC screening is essential to prevent and/or cure disease with increasing chances of survival. The rest of this chapter presents the implementation to-date of screening policies and the difficulties encountered in their implementation.

5.5. National Screening Programmes

There are currently a number of European countries with colorectal cancer screening, which can be distinguished by formal (invitational), opportunistic, pilot and inactive screening programs (Table 5.3). There are other screening programs also operating in each country, and a minority of countries have screening guidelines. The specific methodology of each screening program varies throughout Europe, as does the funder.

There is also much variation in screening methodology, including delivery, age, intervals, tests and funders. Delivery may be via mailed tests, picked up from primary care, or via endoscopy (Table 5.3). The age of initiation ranges from 50 to 60 years, while completion ranges from 69 to indeterminate. The tests may be guaiac FOBT or immunological FOBT or both, or FS, or colonoscopy.

Opportunistic Screening

Opportunistic screening is defined as screening initiated by either the physician or the patient. It is reliant upon action taken by the physician or patient, and thus falls prey to physician/patient pro-activism and confidence in testing method. Only patients who visit their physician and have a rapport with them will likely have the opportunity to participate in screening. These programs have notoriously poor adherence rates, and, usually, are poorly advertised.

The majority of European countries with colorectal cancer screening have opportunistic screening (Table 5.3). There are some similarities between these opportunistic countries: first, no end age of screening is given, and, second, colonoscopy appears more frequently than FOBT. When participation is explored in these programmes, it appears less than national, regional or most pilot programs (See 5.6 Participation).
Germany deserves special note as the longest running provider of colorectal cancer screening in Europe (1971), using primarily gFOBT, iFOBT and colonoscopy. The recent addition in 2002 of colonoscopy to g/iFOBT has not improved participation, as less than 10% of eligible inhabitants partook in colonoscopy screening and FOBT participation decreased from 8.2 million (2001) to 4.5 million (2005).\textsuperscript{87}

\textsuperscript{87} Altenhoven et al, 2005.
<table>
<thead>
<tr>
<th>Country</th>
<th>Program</th>
<th>Other Screening</th>
<th>Screening Guidelines</th>
<th>Delivery</th>
<th>Age</th>
<th>Method and Interval</th>
<th>Funder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>O$^{2000}$</td>
<td>BC$^{1992, R}$, CC</td>
<td></td>
<td>N</td>
<td>E</td>
<td>50+y</td>
<td>gFOBT, iFOBT every 2y</td>
</tr>
<tr>
<td>Czech Rep</td>
<td>P</td>
<td>BC$^{1991-1994, R}$, CC</td>
<td>n/a</td>
<td>M</td>
<td>50-74y</td>
<td>FOBT</td>
<td>G</td>
</tr>
<tr>
<td>Denmark</td>
<td>F</td>
<td>BC$^{1989, F}$</td>
<td></td>
<td>M</td>
<td>60-69y</td>
<td>gFOBT every 2y</td>
<td>G</td>
</tr>
<tr>
<td>Finland</td>
<td>F$^{2004-08}$</td>
<td>BC$^{1990-1995, F}$, CC$^{F}$</td>
<td>Y</td>
<td>M</td>
<td>50-74y</td>
<td>gFOBT every 2y</td>
<td>G</td>
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<tr>
<td>Greece</td>
<td>I</td>
<td>BC$^{1989-1991, R}$</td>
<td>n/a</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hungary</td>
<td>P</td>
<td>BC$^{2002, F}$, CC$^{F}$</td>
<td>n/a</td>
<td>M</td>
<td>50-70y</td>
<td>gFOBT, iFOBT annually</td>
<td>G</td>
</tr>
<tr>
<td>Italy</td>
<td>F, R$^{2000}$</td>
<td>BC$^{1990, R}$, CC$^{F}$</td>
<td>Y</td>
<td>E, GP</td>
<td>50+y</td>
<td>50-55y: gFOBT annually; 55+y: COL every 10y OR gFOBT every 2y</td>
<td>SHI</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2 P$^{2006-8}$</td>
<td>BC$^{1998, F}$</td>
<td>n/a</td>
<td>E, M</td>
<td>50-74y</td>
<td>gFOBT, iFOBT every 2y</td>
<td>G</td>
</tr>
<tr>
<td>Norway</td>
<td>P$^{2008-09}$</td>
<td>BC$^{1995}$</td>
<td>n/a</td>
<td>E</td>
<td>-</td>
<td>COL</td>
<td>G</td>
</tr>
<tr>
<td>Poland</td>
<td>O$^{2000}$, P</td>
<td>BC$^{F}$, CC$^{F}$, PC$^{F}$</td>
<td>-</td>
<td>E</td>
<td>50+y</td>
<td>FOBT annually; OR FS every 5y; OR FOBT annually + FS every 5y; OR COL every 10y</td>
<td>NCP</td>
</tr>
<tr>
<td>Portugal</td>
<td>P</td>
<td>BC$^{1990, R}$</td>
<td>n/a</td>
<td>M</td>
<td>50-74y</td>
<td>gFOBT every 2y OR COL every 10y</td>
<td>G</td>
</tr>
<tr>
<td>Romania</td>
<td>I</td>
<td>BC$^{F}$, CC$^{F}$, PC$^{P}$</td>
<td>n/a</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Russia</td>
<td>I</td>
<td>BC, PC</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Slovakia</td>
<td>O</td>
<td>BC$^{1998, O}$</td>
<td>Y</td>
<td>GP</td>
<td>50+y</td>
<td>FOBT annually</td>
<td>SHI</td>
</tr>
<tr>
<td>Spain</td>
<td>P</td>
<td>BC$^{1989-1993, R}$</td>
<td>n/a</td>
<td>M</td>
<td>50-69y</td>
<td>iFOBT, gFOBT every 2y</td>
<td>G</td>
</tr>
<tr>
<td>Sweden</td>
<td>P$^{2008}$</td>
<td>BC$^{1986-1990, F}$, CC</td>
<td>n/a</td>
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<td>60-69y</td>
<td>FOBT</td>
<td>G</td>
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<td></td>
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<td>50+</td>
<td>COL q10y</td>
<td>PHI</td>
</tr>
<tr>
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<td>I</td>
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<td>n/a</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>UK: England</td>
<td>F$^{2007}$</td>
<td>BC$^{1998, F}$</td>
<td>Y</td>
<td>M</td>
<td>60-69y</td>
<td>gFOBT every 2y</td>
<td>G</td>
</tr>
<tr>
<td>UK: Scotland</td>
<td>N$^{2007}$</td>
<td>BC$^{1998, F}$</td>
<td>Y</td>
<td>M</td>
<td>50-74y</td>
<td>gFOBT every 2y</td>
<td>G</td>
</tr>
<tr>
<td>Australia</td>
<td>N$^{2006-08}$</td>
<td>BC$^{F}$, CC</td>
<td>Y</td>
<td>M</td>
<td>55-74y</td>
<td>iFOBT every 2y</td>
<td>G</td>
</tr>
</tbody>
</table>

**Notes:** F Formal; R Regional; O Opportunistic; I Inactive; N National; P Pilot
BC Breast Cancer; CC Cervical Cancer; PC Prostate Cancer
M = Mailed; GP = primary care; E = Endoscopy
gFOBT guaiac unrehydrated FOBT; iFOBT immunological FOBT; COL colonoscopy; FS flexible sigmoidoscopy
G Government; PHI Private Health Insurance; SHI Social Health Insurance; NCP National Cancer Program; GP must buy the FOBT kits to distribute to their patients and are reimbursed when patient returns test

**Source:** LSE CRC Survey 2008.
Formal Screening

Formal screening is defined as screening initiated by an outside health body, usually as part of the public health services. Invitation is given formally to the patient, inviting the patient to complete the accompanying FOBT kit or arrange appointments for endoscopy, depending on the method chosen by the screening program. The advantage of formal screening is that adherence rates are greater than by opportunistic screening and usually formal record keeping is maintained.

Formal screening has few participant countries in Europe, limited to Finland, France, regions of Italy, UK and Australia. These countries are similar to the Cancer Screening in the EU report, with the exception of Poland whom the latter classifies as formal rather than opportunistic screening, although both agree on colonoscopy as a method. It is primarily limited to g/iFOBT screening, although regions of Italy also use FS (Table 5.3). None use colonoscopy as a screening method.

In Australia, the National Bowel Cancer Screening Programme commenced in August 2006. The programme is being phased in gradually to help ensure that health services, such as colonoscopy and treatment services, are able to meet any increased demand. An invitation with iFOBT test kit arrives in the post, to return at no personal costs. Positive results are referred on by primary care to colonoscopy for diagnosis.

In the UK, the NHS Bowel Screening Programme is currently in phase one of implementation and is being rolled-out nationally in England (Scotland, Wales and N. Ireland are in charge of their own screening initiatives). By 2009, it is thought that the implementation of the national screening programme will be complete. Screening is offered to individuals between the age of 60-69 every two years, however it is hoped that once the program reaches the third phase the initiative will be extended to those 50 or above. Individuals 70 years and over have the freedom to request FOBT kits. In this current set of arrangements patients between the ages of 60-69 are sent gFOBT kit by post and, subsequently, returned by post. Once the FOBT tests positive, patients are automatically registered for an endoscopy appointment at a local endoscopy unit. Given the patient accepts the appointment, all positive FOBTs should be referred to an endoscopy centre within two weeks. For patients with a positive test who fail to respond, a month’s waiting period is given. After this the patient is contacted again to schedule an appointment.

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In Italy, screening programs are regional, with variations in methods between regions ranging from FOBT to FS. Screening is not yet national, yet the majority of regions do have formal screening. Once sufficient inhabitants have been screened, it will be interesting to compare regions on their methodology and participation rates.

**Pilot Screening**

A number of countries are exploring or have explored CRC screening using pilot programmes. Pilot screening consists of one or more methods being used in a smaller subpopulation of a country or in a specific region. An advantage of completing pilot screening is to aid in decision making on whether to have formal colorectal cancer screening, to identify potential problems with national implementation (such as diagnostic and treatment capacity) and to determine which screening method best suits the majority of the population.

There are and have been a number of pilot CRC screening programmes throughout Europe (Table 5.3). These countries are similar to the Cancer Screening in the EU report\(^\text{89}\) although in the Netherlands two pilot programmes have been omitted. The International Colorectal Cancer Screening Network recently published a list of all colorectal cancer screening trials up to 2004, finding 23 organised activities in Europe (Australia, Belgium, Czech Republic, France, Italy, Norway, Poland, Spain, Switzerland, and the UK). They identified the FOBT as the most popular screening method (gFOBT 11, iFOBT 6), FS was also explored (12) as well as colonoscopy (4). Only a minority explored more than one method (5), and these were all research projects.\(^\text{90}\)

Since 2004, there have been a number of new pilot initiatives in Europe according to our survey. Encouragingly, these pilots often test more than one method, although colonoscopy pilots are still not supported in Europe. For example, in Portugal (Administração Regional de Saúde do Centro), a pilot screening campaign is being developed, likely FOBT testing in 50-74 year olds. However, the completion of a pilot does not necessarily mean that national colorectal cancer screening will be implemented. Box 5.1 provides the feedback received from individual countries.

\(^\text{89}\) European Commission, 2008, *op. cit.*

\(^\text{90}\) Bensen et al, 2007.
Box 5.1

Pilot screening programmes

- **Denmark**: The Pilot in Vejle and Copenhagen counties commenced in 2005 as part of Cancer Plan. The pilots have been evaluated, but no political action has yet been taken, as the evidence on participation and organisation is ambiguous” and the target of 60% was not reached.
- **Hungary**: A small pilot project with 3500 inhabitants has been conducted using immunological FOBT. No policy decisions about colorectal cancer screening yet, and the pilot program might not be followed by national screening in any form.

Non-Participant Screening Countries

There are a number of countries reporting no CRC screening activities: Greece, Romania, Russia and Turkey (Table 5.3). This may be due to prioritisation of scarce resources, although CRC screening is likely to be occurring in an unofficial or/and opportunistic way. These countries often do have other national cancer screening programmes, such as breast and cervical cancer, thus there may be opportunity in the future for CRC screening if resources appear (Box 5.2).

Box 5.2

Non-participant screening countries

- **Russia**: The screening program is aimed at preventive medical examination of certain population groups (those who work at state and municipal institutions exposed to professional hazards). It is not aimed at the early detection of certain diseases (particularly cancer), but includes a number of tests and examinations by several specialists. There may be some screening programmes at regional level or in certain groups of patients, but there is little information about them; nobody makes systematic analysis.
- **Turkey**: Screening has to be considered as a priority area as diagnoses of cancer at late stages is an important problem in Turkey.

Overall, colorectal cancer screening appears to be still in its infancy: all formal colorectal cancer programs have just been initiated, while opportunistic screening appears slightly older. In contrast, breast cancer screening is in many countries almost two decades old with more formal screening.
5.6. Participation in screening activities

Most CRC screening methods are either invasive or personally awkward, thus participation may not be optimal. The term participation, rather than adherence or compliance, is used due to the plethora of opportunistic rather than formal screening programs in Europe. Participation is complex, and there are factors affecting participation such as invitations that are discussed in depth elsewhere\(^{91}\); this discussion reports the actual participation rates of various programs and pilots.

Participation depends on the type of method. The FOBT participation rate ranges from 14.6 to 57.5% across screening programs and pilots\(^{92}\). The participation of iFOBT ranges from 55-60%, perhaps due to no dietary restrictions and only one collection day compared to gFOBT. The participation rate for endoscopy is also quite variable, FS reports 7-73%, while colonoscopy ranges from 8-26% for screening purposes but higher (75-91%) for follow-up after a positive screen.\(^{93}\) The results of a Eurobarometer survey on general health of European citizens found only 15% of eligible EU residents surveyed participated in FOBT screening during the previous 12 months.\(^{94}\)

Participation may vary within society. In Germany, women participate more in colonoscopy screening than men\(^{95}\). Australia also found women participating more than men (by 4%), while Aboriginal and Torres Strait Islander people had lower participation. To combat this poor performance, Australia is translating information in multiple languages, with a targeted screening campaign and working group created for Aboriginal and Torres Strait Islander people. Germany has information translated in other languages (e.g. Turkish) and tries to raise awareness through media campaigns.

The participation in FOBT screening declines in each subsequent round,\(^{96}\) which is unfortunate for a method relying on annual or biennial testing over a period of two decades. Endoscopy serial participation may be higher than FOBT, however, insufficient evidence is available at this point.

It is unfortunate that participation rates for colorectal cancer screening are so poor, whether it is due to insufficient screening campaigns to raise awareness, insufficient political or financial support, or due to poor acceptability of test method. If a pilot occurs with poor

\(^{91}\) Stone et al, 2002


\(^{94}\) Eurobarometer, Health in the European Union, 2007

\(^{95}\) Altenhofen et al, 2005

participation, the implication is whether implementation of national screening will occur, particularly if public and political support are not on hand. In Denmark, this is precisely what occurred with results of less than 50% participation. In addition, individuals declining participation may be at higher risk of colorectal cancer, thus undermining the social and financial benefit of colorectal cancer prevention and early stage diagnosis.

5.7. Colorectal Cancer Awareness

Awareness of colorectal cancer can also affect participation in colorectal cancer screening. A Europe-wide study of CRC awareness found only half of respondents were aware of CRC screening and a number of countries unwilling to discuss bowel issues. Our survey examined a number of factors linked to awareness, including perception of country awareness, awareness campaigns and cancer organisations.

Approximately half of the countries indicated the perception of poor public or political awareness of colorectal cancer (Table 5.4), and only a minority of countries produced CRC-specific campaigns, be it for prevention or screening purposes. Examples of prevention campaigns are shown in Box 5.3.

Box 5.3

Examples of screening prevention campaigns

- **Australia**: “Avoid the Cure” campaign, which promotes healthy lifestyle to prevent bowel cancer”.
- **Germany**: In 2006 and 2007 nationwide patient symposia were organised in select major cities to raise awareness about CRC and screening.
- **Greece**: Advertising spots such as ’Colon Cancer appears in 1 in every 20 persons – coming across it is a matter of chance. Overcoming it is not.’ Also included lifestyle factors associated with colorectal cancer risks.

Reflecting the scarcity of formal national screening in Europe, only a few counties had screening campaigns. These are shown in Box 5.4.

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Box 5.4

National screening campaigns

- **Australia**: “Cancer Institute NSW Bowel Cancer Awareness”
- **France**: “National week for colorectal cancer screening, with green pins (similar to pink breast cancer pins) to promote colorectal cancer awareness and screening. Timing is synchronous with national colorectal cancer screening implementation.”
- **Germany**: “Screening campaign from 2003-2005 to evaluate implementation of colonoscopy to screening arsenal.”
- **UK**: “National Bowel Cancer Screening Program has used a series of music concerts such as the ‘Be Loud Campaign’ to reach out to the community and break down taboos surrounding CRC. In addition to this a nationwide poster campaign entitled ‘Do your bit, Use your kit’ has been initiated to inform people of their risk status.”

Most countries have umbrella cancer organisations that cover all cancers, including colorectal cancer (Table 5.4). The UK has a plethora of cancer organisations, from Cancer Research UK to Marie Curie Cancer Care, often with some replication of activities. A minority of countries have CRC-specific organisations.

The UK has two colorectal cancer groups, Bowel Cancer UK and Beating Bowel Cancer. Germany also has two colorectal cancer groups, the Felix Burda Stiftung and Deutsche Patientenvereinigung Leben mit Darmkrebs. Hungary has the “You Can Recover” organisation. In Portugal, the colorectal cancer group is europacolon Portugal, while in Slovakia the group is europacolon Slovakia. All these organisations have a similar goal: to raise awareness of and improve survival.

A minority of countries have separate professional organisations for colorectal cancer (Table 5.4), the remainder having special working groups with gastrointestinal and oncology physician groups. Denmark has the Danish Colorectal Cancer Group and the Netherlands has the Dutch Colorectal Cancer Group, which independently maintain a clinical database on treatment practice and outcomes. As surgeons and oncologists have diverse practice, the creation of working groups within umbrella organisations creates the opportunity to foster this practice diversity.

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98 Meggyógyulhatsz” Egyesület a Vastag- és Végbérlákos Betegek Élhetőbb Életéért.
## Table 5.4
Awareness of colorectal cancer (CRC), publicly, politically and organisationally.

<table>
<thead>
<tr>
<th>Country</th>
<th>Perceived Poor Public Awareness</th>
<th>Perceived Poor Political Awareness</th>
<th>Cancer Prevention Campaigns</th>
<th>CRC Prevention Campaigns</th>
<th>CRC Screening Campaigns</th>
<th>Patient-Led Cancer Groups</th>
<th>Patient-Led CRC Groups</th>
<th>CRC Physician Groups</th>
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<td>Y</td>
<td>Y</td>
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<td>B, LS, S</td>
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<td>Y U</td>
<td>N U</td>
<td>Y S</td>
</tr>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y WG</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y U</td>
</tr>
</tbody>
</table>

**Notes:**
- NGO = only some pilot and small awareness increasing campaigns by NGO and industry
- WG = colorectal cancer working groups within gastrointestinal or oncology organisations; S = specialty CRC organisation
- B = breast cancer; C = cervical cancer; L = lung cancer; P = prostate cancer; O = overall cancer; OT = other cancers; R = regional groups; S = skin cancer; LS = lifestyle related cancers; U = umbrella cancer organisation which also encompasses some CRC activity; GI = Gastrointestinal support group

**Source:** LSE CRC Survey 2008.
5.8. Screening Impact on Endoscopy Capacity

A common thread running through these discussions is the ability of health systems to meet increased demand, not only for screening but also for diagnosis. Without the addition of formal screening, endoscopy demand has already increased 25-20% over the past decade,\(^9\) a requirement for diagnosis. Pilot screening programs have shown colonoscopy demand increased by 20-30%, which resulted unacceptable waiting times for symptomatic patients due to insufficient endoscopy staff.\(^1\) Thus the access, management and delivery of endoscopy services is key to screening success. The results presented here largely do not account for screening impact, due to limited participation in opportunistic screening and only quite recent formal screening implementation.

**Adequacy of Endoscopy Resources**

A number of countries in our survey indicated that diagnostic facilities were inadequate (Table 5.5), reflecting a belief possessed by many endoscopy units that they are placed on low budgeting priority, with insufficient funds for staff, equipment and space.\(^1\) A number of countries explicitly commented on this, as shown in Box 5.5.

<table>
<thead>
<tr>
<th>Box 5.5</th>
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</table>

**Adequacy of endoscopy services**

- **Czech Republic**: “Common opinion of low funding of endoscopy”
- **France**: “In some areas there are demographic shortages of endoscopists”
- **Greece**: “In general, the delivery of NHS services is underfunded, since there is a gap between the amount reimbursed and the actual cost and this also applies to endoscopy”
- **Hungary**: “The budget for endoscopy is lower than the budget available in developed countries, although not disproportionately low compared to other services”
- **Portugal**: “The long waiting times for diagnosis and treatment show that resources are insufficient. The lack of equipment and specialized physicians are examples of shortcomings”
- **Romania**: “Few centers, low budget for colonoscopy, equipment is old” “Few and inadequate disposables, more physician expertise/experience is needed”
- **Russia**: “it seems that there are enough specialists and equipment to satisfy the current needs in examining patients referred to endoscopy, BUT there may be not enough if screening for CRC is implemented, besides physicians get low salaries and do not have financial incentives to do extra work or even routine one”
- **Spain**: “They do not allocate enough resources for endoscopy”
- **UK**: “Although endoscopy within the screening program costs more than ones that are practiced within GP referral, they are given less money per head”

Furthermore, regional differences in endoscopy services are also a problem in the majority of countries (Table 5.5), due to either geographical inequities or due to resource allocation issues; several countries expressed concern about this, as shown on Box 5.6.

**Box 5.6**  
**Regional differences in endoscopy services**

- **Czech Republic:** “Different density of endoscopic units” “All border regional of Czech Republic are poorly served with endoscopy”
- **Australia:** “Rural and remote regions have particular problems with capacity of facilities to meet demands and reduced availability of colonoscopists and nurses” “Difficulty with postal contact for Aboriginal and Torres Strait Islander people”
- **Greece:** “Mainly the small Aegean and Ionian islands as well as mountainous remote areas have poor access to endoscopy”
- **Romania:** “Uneven distribution of endoscopy specialists in the country, variable number of endoscopes per center” “Large cities are better served than small towns or rural areas”
- **Spain:** “Regional differences according to endoscopy services, organisation and management”

These endoscopy insufficiencies can result in long waiting times for endoscopy services; many countries indicated this perception of long waiting times from referral to endoscopy to diagnosis (Table 5.5). The actual waiting time from referral to diagnosis ranges from 5 days to 2 months, frequently reflecting bottlenecks in diagnostic services where the gap between referral and diagnosis is longest (Box 5.7).

**Box 5.7**  
**Time gap between referral and diagnosis**

- **Denmark:** “Since 2006 colorectal cancer is treated as acute disease: first hospital consultation within 48 hours from the GP’s referral for suspected cancer. Maximal waiting time for diagnosis is 5 days from referral”
- **Portugal:** “Differences in length of time are due to different availability of facilities and specialized health care professionals in health care units and to the distance between those units”
- **Sweden:** “The doctor delay for colorectal cancer is on average a few months”
- **UK:** “Within the second round of the bowel screening initiative, selected endoscopy centers experienced an increased workload, resulting in increased waiting times”
Management of Endoscopy Resources

Policies affecting waiting lists and quality, as well as health insurance, are important aspects of endoscopy management. One method to ensure shorter waiting times as well as positively affect quality is to offer choice of endoscopy centers. This allows patients to find centers with the shortest waiting times. A limited number of countries offer choice in endoscopy centers (Table 5.5). A greater number of countries offer patients an endoscopy appointment at the first available center.

Most countries with perceived long waiting times offer either choice of endoscopy center or endoscopy at first available center; the Netherlands offers both options, and health insurance companies have patient advocates to help find the fastest care throughout the country. There are a number of countries who perceive long waiting times yet offer neither option as a potential solution to their waiting list problem.

A minority of countries have private facilities bypassing waiting lists for patients with private health insurance (Table 5.5). Furthermore, there are a number of private diagnostic companies operating within Europe, offering all types of services from imaging to endoscopy, which circumvent waiting lists. These facilities operate as fee-for-service, with some health insurance companies providing reimbursement in some cases. For instance, in Greece, colonoscopy in public hospital costs €82, while in private hospital €250-300; reimbursement depends on Social Insurance Fund’s policy and existence of private insurance on behalf of the patient.
Table 5.5
Factors affecting Endoscopy (E) Capacity, including Resources, Delivery and Policies

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HI health insurance; E endoscopy; Ref = referral to another region; P = private health insurance; R regional N national
Source: LSE CRC Survey 2008
Another aspect of managing endoscopy services is appropriateness of referral and prioritisation of patients. Studies comparing colonoscopy referrals to referral guidelines or national referral guidelines find 14.8% to 36% are inappropriate.102 There seems to be concern that colonoscopies are being diverted from high-risk to low-risk patients, placing both sets of patients at undue risks of untimely colonoscopy.103 Thus, if there is an element of inappropriate colonoscopies, these must be decreased in order to better manage a constrained service in the absence of an increase in resources available to perform more.

Patient prioritisation is also important in managing this limited resource. Only a minority of countries report having policies which place urgent patients in priority on the waiting list (Table 5.5). Of great concern during the UK Screening Pilot, waiting times for symptomatic patients was twice as long as for screening subjects during the pilot.104 The management of symptomatic patients in conjunction with screening participants is a valid concern.

**Delivery of Endoscopy Services**

Delivery of the endoscopy and what quality measures are in place to ensure completeness of procedures are also important in endoscopy management. Endoscopy can be performed by physicians and trained nurse endoscopists, this training, however, must be sufficient to ensure good quality of services are provided.

In most countries, endoscopy is the sole domain of gastroenterologists and internists, however, it can be performed by personnel other than gastroenterologists. In the UK, GPs successfully and safely perform both flexible endoscopy and colonoscopy; unfortunately, primary care endoscopy units are less likely to offer colonoscopy and do not receive the funding to increase capacity.105 Nurse endoscopists have been successfully trained in a minority of countries (Table 5.5) to meeting increased endoscopy demand. In the UK, there are currently over 200 formally trained nurse endoscopists to screen FOBT-positive patients, freeing gastroenterologists to perform high-risk and treatment colonoscopies. Sweden also has similar formal training of nurse endoscopists, while Denmark and the Netherlands have regional pilot initiatives, although the Netherlands recently decided not to support nurse endoscopy despite long endoscopy waiting times. Where sufficient facilities are in place but insufficient endoscopists exist, the use of nurse endoscopists as a proxy is very useful particularly in screening endoscopy.

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105 Galloway et al, 2002; personal communication.
Sufficient endoscopists are important to meet endoscopy demand, but adequate training to ensure colonoscopy completion is just as important. Poor training is attributed to poor colonoscopy completion rates. This is not a rare problem, various hospital audits throughout Europe and Australia have found incomplete colonoscopies ranging from 4-30%. These incomplete colonoscopies place strain both on the limited endoscopy services as well as on patients who must undergo the procedure again or be referred onto other imaging services. Although there may be alternatives to endoscopy, such as CT colonography, capsule endoscopy and barium enemas, none of these methods can actually take tissue samples for firm diagnosis. In the case of adenomatous polyps, these methods are able to detect their presence, however, their removal must be achieved with the colonoscopy.

**Impact on Pathology and Other Health Services**

Other services are also affected by endoscopy, primarily pathology but also primary and emergency care. An often neglected area of colorectal cancer care is pressure on pathology services. There has been a significant decrease in the small numbers of physician trainees choosing pathology as a career choice in Europe as well as large variations in practicing pathologists per million population. This is cause for concern, as even if endoscopy resources are managed well with reasonable waiting times, if pathology services are inadequate the waiting time for diagnosis could become long.

Screening for colorectal cancer also places greater pressure on primary care, with particular stress on administrative duties including checking notification lists, filing, responding to enquiries, and corresponding with pathology and endoscopy units. In fact, more than half of GPs polled during the UK Colorectal Cancer Screening Pilot felt they should be remunerated for the extra workload pertaining to screening, and the GI consultants also felt the impact of greater administrative duties.

On the other hand emergency care and priority endoscopy patients may decrease with screening implementation, as patients detected may be more likely to be in the early, asymptomatic stages. During the UK Colorectal Cancer Screening Pilot, emergency admissions decreased significantly over the pilot period by 46.6%, with further reductions by

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107 Cremers et al, 2006 ; Bowles et al, 2004 ; Adler et al, 2007 ; Canard et al, 2005 ; Integraal Kankeercentrum West, 2007; Australian Bowel Cancer Screening Pilot, 2005
108 Lambert et al, 2006 ; Ruiter et al, 2004
47.1% for emergency surgery. As these emergency admissions and surgery are likely more costly with poorer outcomes, this provides a good argument for colorectal cancer screening.

5.9. Colorectal Cancer Performance Indicators and Implication for Patients

A country performance indicator for colorectal cancer screening was developed using the data collected above. The following positive indicators were selected:

- Publication of cost-effectiveness analyses
- Colorectal cancer screening: 3 points for national (invitational), 2 points for opportunistic, 1 for pilot and 0 points for no screening
- Greater than 40% participation in screening
- Colorectal cancer prevention campaigns, screening campaigns, patient-led groups and physician groups
- Endoscopy: choice of center, endoscopy at 1st available center, priority policy and nurse endoscopy, average waiting times <4 weeks

In addition, the following negative indicators were selected:

- Poor public or poor political awareness
- Perceived inadequate diagnostic facilities,
- Long diagnosis waiting times, actual diagnosis waiting times ≥4 weeks, and
- Regions with poor endoscopy resources

No positive or negative points were given to the actual methods themselves, including test methods, intervals and age ranges, as each has its positive and negative aspects. The performance ranking show that the UK ranks the highest, then Germany, Italy, Australia and France, which reflects their mostly national screening programs and good endoscopy management (Figure 5.1). Countries with low positive rankings are those primarily without screening programs of any kind, although the inclusion of Hungary is due to poor participation and awareness. Likewise, high negative rankings are in countries without screening, or with poor endoscopy management (Netherlands, Portugal).

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From a patient and a broader societal perspective, it is imperative that awareness is increased both on the disease itself and the benefits that screening for CRC can bestow. Many diverse groups need better information and education on the disease, its development, prevention, diagnosis, treatment and survival possibilities. Understanding and education of all aspects of CRC and its positioning relative to other cancers needs to be created and communicated to (a) Politicians; (b) Healthcare administrators; (c) Healthcare professionals, in particular, physicians and nurses, GPs, family doctors and health system “Gatekeepers”; (d) High risk groups – those with a family history and the 50 years group; (e) Schoolchildren; and (f) the public at large. Different methods of screening and examination need explaining; the life-saving value of having to discuss problems associated with bowel functions, undergo the embarrassment of stool collection, invasive examination via a “taboo” area of the body, needs promoting. The risk and discomfort factors associated with endoscopic examination should not be overstated, as technology improves and patient preparation regimes become simpler.
5.10. Conclusions

Colorectal cancer screening is complex and multivariable. First, there are many issues with the screening tests. All are invasive or socially sensitive to some degree, and although only colonoscopy and CT colonography at this point have high test performance, the former carries risk of perforation and - in rare cases - mortality while the latter carries high costs and limited availability for screening asymptomatic individuals.

Second, cost effectiveness analysis shows that any CRC screening is more cost effective than no screening. However, limited analyses have been performed comparing methods, and even fewer analyses have taken place on endoscopy. This reflects the scarcity of screening research and pilots using more than one method, and even more so for flexible sigmoidoscopy and/or colonoscopy. Only a few European and Australian analyses have been performed on FS and COL.

Third, despite increasing awareness in recent years, overall support for CRC screening has been poor, particularly in Europe, with the exception of very few cases. Europe-wide mechanisms, otherwise a very positive step in the development of awareness and policy initiation, have not been timely, and their publication has not been enthusiastic in their exploration of methods. In fact, since 1999 there have been no European CRC-specific recommendations on screening, whereas European breast cancer guidelines are now in their fourth edition (and comprising 12 chapters). This reflects a general lack of interest in CRC population screening, which is unfortunate for a cancer responsible for significant morbidity and mortality.

Fourth, CRC screening in Europe is not standard with great variations between countries in organisation, intervals, ages and test methods. The recent Cancer Screening in the EU Report also made this observation, with the addition that colorectal cancer support and implementation in many countries was hindered. Most countries participate in opportunistic screening and only Australia, France, Finland, Italy and the UK participate in national screening. Although a number of pilot screening projects are currently underway, comparison of methodology is scarce as with the lack of endoscopy screening. Furthermore, countries vary in their methods, age of initiation and completion, as well as testing intervals. This reflects mediocre understanding of CRC disease development and best practice to reduce risk and disease progression, which is not a problem only for colorectal cancer but also for other cancers such as breast and cervical cancers.

Fifth, participation in CRC screening remains a major barrier to implementation. Most programmes and projects do not exceed much over 50% participation, and serial participation is worse. It is unfortunate that minimal research has been performed on patient choice in this matter, as perhaps choice will encourage discussion and may improve uptake. In addition, this lack of support for exploration of CRC screening methods with greater test performance could lead to poor confidence in FOBT screening, in combination with already poor population participation. Poor participation also reflects a poor overall awareness of CRC and a lack of formal support for CRC in most countries.

Sixth, capacity for CRC screening, in particular endoscopy capacity is a problem for many countries. Only two countries have broadened the medical personnel to include Nurse Endoscopists to address capacity issues and there is still a need for appropriate prioritisation of patients, given capacity constraints. Still, available resources are limited as is funding and improvements are needed in most countries on this front. There also appears to be a number of endoscopy inefficiencies with poor completion rates in some countries and inappropriate endoscopy referrals.

In conclusion, CRC screening in has been somewhat neglected in comparison with other high incidence and high mortality diseases. Colorectal cancer awareness is poor publicly and professionally, resulting in poor participation where screening exists and minimal resources allocated to CRC. Endoscopy, in particular, is neglected, and capacity is a problem in many countries. Overall, CRC screening is more opportunistic than formally organised; this is highly problematic as screening can identify cancers early in the asymptomatic stage and perhaps lead to changes in cancer incidence and survival. Addressing these issues could greatly change the ultimate incidence and mortality if tackled properly.
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Chapter 6
Colorectal Cancer Treatment: Access, Availability and Cost-Effectiveness

6.1. Introduction
Colorectal cancer treatments have made significant improvements over the past decade. For instance, 5-year survival has increased over the past decade from 50% to 56%. Some of the primary factors responsible for this increase are treatment improvements, tumour-specific protocols, multidisciplinary management and use of evidence-based guidelines. Patients must however also have access to treatments, newer more effective treatments should be introduced and adopted in a timely manner, and barriers to access should be recognized and addressed. Otherwise the finance and time spent in research will not have the maximum impact on colorectal cancer outcomes.

This chapter discusses non-pharmaceutical treatment options in CRC, highlighting similarities and differences between countries, as well as identifies patterns across the survey countries with regards to:

- Access to CRC treatment, including barriers to treatment, inequities of access, and waiting times;
- Delivery of CRC treatment, including adequacy of human and physical resources, where treatment is given and by which specialists;
- Guidelines available and outlined for overall treatment of CRC and rectal cancer;
- Treatment practice in surgery and radiotherapy;
- Clinical and cost-effectiveness of surgical and radiotherapy treatments

6.2. Colorectal Cancer Overview
Management pathways give a good summary of various options available in treatment delivery, as well as provide decision points and major factors to be aware of during the treatment process (Figure 6.1). Stage I is defined as a small tumour that has no invasion of surrounding muscle and has not spread to nearby or distant sites. This is usually treated with surgery alone and no adjuvant treatment is needed.

Stage II can be divided into low-risk and high-risk. Low-risk Stage II disease which has invaded the bowel wall but has not spread to nearby or distant sites, has no abnormalities, and can also be treated with surgery alone. High-risk Stage II tumours are those which have invaded the bowel wall, display some abnormalities, but not spread to nearby or distant sites. The treatment options in this case include surgery, adjuvant chemotherapy with / without radiotherapy.

Stage III is defined as having spread to local lymph nodes but not distant sites, treated with surgery and adjuvant chemotherapy. In Stage IV CRC there is distant metastasis, usually in the liver or lungs. The majority of patients who die of colorectal cancer have liver metastases at the time of death. Rectal cancer must be differentiated from colon cancer, as prognosis and treatment are significantly different. Colorectal cancer is treated with surgery and chemotherapy, while rectal cancer following surgery is treated with chemoradiotherapy.

6.3. Access to Colorectal Cancer Treatment

Access to treatment is complex and multi-faceted and our survey addressed the following issues:

- Is treatment of proven efficacy available and are there any barriers, such as geography, in receiving care?
- Are there specific social groups that, implicitly or explicitly, seek out or receive less care? How long must patients wait for treatment?
- How lengthy is the adoption of new treatments or technologies?

Every country surveyed indicated problems with access to colorectal cancer treatment (Table 6.1). The most common problem appears to be geographical barriers to optimal access to treatments. In Greece, cancer patients from many of the islands must travel to urban centers...
to receive treatment, often staying away from home for the duration of their treatment. In Portugal, rural areas have less access to diagnostic services. In Australia, rural patients also travel long distances and stay away from home for the duration of their treatment, this coupled with difficulties accessing travel support to do so.

It appears only few countries perceive groups within their territory as having difficulties accessing (colorectal) cancer treatment (Table 6.1), interesting as literature suggests inequities in health and cancer care are ubiquitous, particularly for minority groups.\textsuperscript{118} This omission of group inequities may be due to respondent and interviewee perception, or prioritisation of cancer care priorities. In the Netherlands, it is recognized that new immigrant and minority groups use less cancer care, perhaps due to language barriers, poor communication, cultural differences and religious beliefs. In Australia, aboriginal groups and Torres Strait Islander people are recognized as having poor access to health care, including cancer care. In Greece, mainly lower socio-economic groups in both rural and urban areas are recognized as having difficulty with accessing cancer services in their immediate geographical vicinity. Likewise, no country reported denying care to elderly (75+ years) patients (Table 6.1), although literature suggests elderly patients are less likely to undergo curative resection and adjuvant chemotherapy than younger patients.\textsuperscript{119}

Lengthy waiting times for treatment after diagnosis are difficult from a psychology perspective and after a certain time (greater than three month wait) detrimental to CRC outcomes. Our survey found that the perception of waiting time and its actual waiting time for treatment differs enormously between countries (Table 6.1). It appears a number of countries have waiting times of 3 months or more from diagnosis to treatment, but do not perceive this as a major issue in their country. Other countries reported problems of waiting times for treatment, yet actual waiting time was less than one month. This dichotomous perception could be due to the prioritisation of issues. For instance, Russia reports it has large regional variations in care, potentially large out-of-pocket payments by patients, and poor treatment availability, thus waiting time for treatment is a minor issue in comparison to the actual existence and delivery of treatment. Perhaps elsewhere lengthy waiting times for treatment is the norm for all diseases, and may not be seen as a problem, perhaps more so for in diseases affecting the elderly. Only Portugal indicated the perception of long waiting times and actual long waiting times (8 months), due to insufficient specialized staff and equipment.

\textsuperscript{118} McCollum et al, 2002; Mayberry et al, 1995; Akerley et al, 1993.
\textsuperscript{119} Lemmons et al, 2006; Gatta et al, 1996;
Few countries reported guidelines for maximum waiting times for treatment after diagnosis (the exceptions being Denmark at 2 weeks; Greece at 3 weeks; France, The Netherlands and the UK all at 4 weeks; and Sweden at 12 weeks), however, most of these countries admit to exceeding these maximums in select regions. Sweden reported that their ‘doctor delay’ is a greater issue in waiting time for diagnosis than for treatment: colorectal cancer experiences a few months’ diagnosis delay while prostate cancer on average a 15-month delay.

Only a minority of countries reported guidelines on prioritisation of patients based on urgency of care. In the UK, the maximum waiting time from GP to specialist referral for urgent care is two weeks. In Australia, patients are classified as Category 1 (30 days) if the patient is likely to deteriorate quickly or become an emergency, or Category 2 (90 days) if the patient is in pain, dysfunction or disability. In the Netherlands, patients may be classified ‘met spoed’ (with haste) thereby coming to the top of waiting lists; in addition, health insurance companies in the Netherlands have patient advocates to help find the fastest care route for both urgent and non-urgent patients.

Only Russia and Romania indicated they had problems with poor quality treatment in their country. The Russian survey reported strong suspicion of large variations in quality of care between institutions. Many countries reported patients had choice in where they received their treatment, including a number of Eastern European countries. This is encouraging, as patient choice is viewed as a policy improving quality of care where patients may choose care based on perceived quality. Russia indicated that choice of treatment centre was only available to patients who paid out-of-pocket or were persistent and lucky enough in getting the best care available.

Our survey reported that out-of-pocket payments occur in Western and in Eastern Europe. All payments, except the private markets of some countries (Greece, Portugal, UK, Australia), are capped (Sweden Skr 900/yr, Germany 10% co-payment with €10 maximum, ambulatory care capped at 2% annual after-tax income) and reimbursed for low-income patients. In Eastern Europe, out-of-pocket payments may be more frequent, and perhaps in an unofficial manner as stated by the survey respondents. For example, the Russian survey reported several sources (articles and reports) indicating patients were increasingly spending more of their personal income on out-patient and in-patient diagnostic and treatment services. Official payments are needed for physician or institution choice, jumping diagnostic waiting queue, modern treatment methods (e.g. laparoscopy), or sedation during colonoscopy, while informal payments are suspect. In Turkey, patients are faced with out-of-pocket payments
when there are reimbursement restrictions. In Portugal, many patients are forced into the private market due to excessive waiting times, where they face many out-of-pocket payments.

Access to treatment depends to a certain extent on citizenship, particularly for newer treatments both surgical and pharmaceutical. Our survey respondents from primarily Eastern European countries perceived limited, poor or delayed access to new treatments of proven efficacy (Table 6.2), in addition to the UK and Australia. The inclusion of the UK onto this list is due to the perception of the National Institute of Health and Clinical Excellence (NICE) as “an additional, untimely fourth hurdle to the introduction of new treatments”. Eastern European countries indicate poor new treatment access, reflected partially by their poorer colorectal cancer statistics, due to resource constraints and multiple shortcomings in service provision.
Table 6.1
Perceived access to colorectal cancer treatment throughout Europe

<table>
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<th>Perceived Long Waiting Times</th>
<th>Actual Waiting Time</th>
<th>Patient Priority Policy</th>
<th>Choice in Treatment Center</th>
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Notes: † for new treatments ∞ all treatments * private sector § capped ‡ unofficial
C = treatment with curative intent, P = palliative treatment, L = less likely to be offered curative treatment
Likewise, the survey indicated that a number of Eastern European countries perceive *the timeliness of new treatments to be behind other countries*, with the addition of the UK again in this perception; this is shown in Box 6.1.

**Box 6.1**

*Is the timeliness of new treatments perceived to be behind other countries?*

- **Hungary**: ‘There are delays of new technology being included into the coverage scheme. Urban patients and academic hospitals are more likely to have access to new treatments.’
- **Poland**: ‘There seems to be longer treatment approval for colorectal cancer than breast cancer; reportedly, the availability of new treatments is dependent on the discretion of health insurance.’
- **Romania**: ‘Access to new treatments is limited and use in clinical practice is delayed’; there are severe regional differences in access to treatment.’
- **Russia**: ‘Access to modern treatment is limited’
- **UK**: ‘Adoption of new treatments can be delayed due to the fourth hurdle of Health Technology Assessment.’

Most study countries feel *the timeliness of new treatments to be on par in comparison with other countries*. This included the Czech Republic, Greece and Slovakia who indicated problems with limited, poor or delayed access to treatments by patients (Table 6.2), reflected by bureaucratic delays, regulatory structures and regional decision-making processes, as shown in Box 6.2:

**Box 6.2**

*Is the timeliness of new treatments perceived to be on a par with other countries?*

- **Denmark**: ‘New treatments are adopted relatively quickly.’
- **France**: ‘New treatments are introduced quickly and often have temporary authorisation prior to official authorisation.’
- **Greece**: ‘There are significant market delays for new drugs due to bureaucracy, and the nature of the pricing and reimbursement system.’
- **Italy**: ‘New treatments are introduced by the state but regions can decide timing of introduction.’
- **Netherlands**: ‘Academic hospitals are likely to adopt new technology more quickly than regional hospitals.’
- **Portugal**: ‘The introduction of new cancer treatments into the formulary is often delayed due to economics issues.’
- **Slovakia**: ‘Expensive treatments are covered outside hospital budget.’
- **Spain**: ‘New treatments are incorporated quickly into the National Health Service.’
- **Turkey**: ‘Currently, delays are experienced in the acceptance of new cancer treatments mainly because of general cost containment measures in the public sector.’
No country indicated *leadership in timeliness of new treatments*, even France with their temporary authorisation scheme for new drugs. On the other hand, when asked to compare their country to international best practice in colorectal cancer, a number of countries indicated they were *leaders in colorectal cancer practice and standards* or that they were *meeting international standards* (Table 6.2). A number of areas were indicated for improvement in these countries (see Box 6.3).

**Box 6.3**

*Areas for improvement in the provision of CRC treatment*

(a) *Leaders in CRC practice and standards*
- **Czech Republic**: ‘Almost all areas can be improved upon.’
- **France**: ‘None specifically.’
- **Italy**: ‘Colorectal cancer prevention activities.’
- **The Netherlands**: ‘Increase quota for gastroenterologist and oncologist residents.’
- **Portugal**: ‘There should be earlier diagnosis and treatment (less waiting times).’
- **Spain**: ‘National screening.’
- **UK**: ‘Uniform adoption of approved and desirable standards of practice. Due to their financial status, institutional ethos and endeavour for clinical exploration, some hospitals have an increased capacity to provide higher levels of care. On the other hand, other institutions simply do not have the capability to provide this level of care.’

(b) *Meeting international standards*
- **Germany**: ‘Co-ordination between ambulatory and secondary care, poor communication between specialties in multi-disciplinary care.’
- **Greece**: ‘(a) screening b) official implementation of standards and guidelines c) registry d) disease specific resource allocation system;’
- **Slovakia**: ‘Screening, research, standards.’
- **Sweden**: ‘Specialised surgeons, development of treatment and diagnosis.’
- **Turkey**: ‘Screening, research, earlier access to new drugs and therapies.’

The survey respondents reported many Eastern European countries and Denmark *in need of improvement*, and the areas indicated for improvement are shown in Box 6.4.

**Box 6.4**

*Countries in need of improvement*

- **Denmark**: ‘Surgeon expertise, increase surgeon output, early detection of metastasis by systematic surveillance.’
- **Hungary**: ‘(a) screening b) centralised surgery c) management and organisation of data, pathology, registry;’
- **Poland**: ‘National treatment and surveillance guidelines, cancer registry, clinical trial registry.’
- **Romania**: ‘Increased funding for treatment and equipment, modern radiation therapy facilities, more training and staff, national screening and prevention, national standards, center accreditation.’
- **Russia**: ‘Modern treatment approaches, screening policies and participation therein, quality of care variations, systematic training of physicians, diagnostic and treatment standards, financing of new treatments.’
Almost all countries indicated screening and prevention activities as areas for improvement, reflecting the prevalence of countries participating in colorectal cancer pilot screening research. All countries participated in colorectal cancer research, primarily in pharmaceutical clinical trials, although other activities such as surgical techniques and screening were also included.

### Table 6.2

**Access to new treatments of proven efficacy, perceived timeliness of adoption of new treatments, as well as treatment standards in comparison to international best practice**

<table>
<thead>
<tr>
<th>Limited, poor, or delayed access to New Treatment</th>
<th>No access to New Treatment</th>
<th>Perceived Timeliness of New Cancer Treatment</th>
<th>Treatment Compared to International Best Practice</th>
<th>Colorectal Cancer Research</th>
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**Notes:** ° For surgery, staging and treatment only; * International clinical trials; ^ = monoclonal antibodies; surgery; Sc = screening; T = Treatment; R = radiotherapy; P = polyp; M = prognosis markers; L = leaders compared to other countries; P = on par with other countries; B = behind other countries; R = regional; HI = depends on health insurance. LL = leading colorectal cancer practice and standards for other countries to follow; M = meeting international standards; I = colorectal cancer practice and standards improved; D = international practice does not apply. 

**Source:** LSE CRC Survey 2008.

### 6.4. Delivery of Colorectal Cancer Treatment

Colorectal cancer treatment delivery can also be exposed to difficulties. Both physical and human resources may be insufficient or in poor condition, and may be poorly distributed within a country. The type of physician specialists as well as specialty department providing care may also vary between countries.
Our survey found that insufficient facilities appear to be a problem in nearly half the surveyed countries (Czech Republic, Denmark, France, Hungary, Portugal, Romania, Russia and Spain), while inadequate diagnostic and treatment facilities appear to be limited to Eastern European countries (Table 6.3). The Russian survey reported many problems with their facilities, including old buildings in need of renovation and lack of modern equipment in many oncology departments. In Turkey, the respondent indicated that modern equipment is a shortcoming in some regions. Australia indicated insufficient availability of radiation services, in addition to particular problems in remote areas where insufficient endoscopy resources limit national screening and surveillance activities. At the time of the survey, patients in the Australian Northern Territory had no access to radiation oncology.

There appears to be great diversity to where treatment is given. Some colorectal cancer patients are treated in oncology wards, others in the surgery wards, or both. Many countries indicate specialist cancer centres for colorectal cancer treatment, more likely situated in urban areas with academic hospitals.

A number of countries indicated problems with poor distribution of resources across their territory. Sweden expressed regional differences in colorectal cancer survival and mortality statistics were likely due to regional health care structuring and variations in the systematic use of new surgical techniques. The Romanian survey indicated both human and physical resources are unevenly distributed, with significant variability in the quantity and quality of equipment per centre (maximum of two centres/district and only few districts have radiation therapy).

Our survey found that many countries indicated insufficient human resources as a problem, and some highlighted specific areas. Denmark, Romania and Russia coupled poor physician oncology training to insufficient numbers in this area. The Portuguese survey stated that ‘there was insufficient investment in cancer treatment services, insufficient health care units to deliver care, and insufficient specialized health care professionals all over the country’.

In some countries, the care of colorectal cancer patients appears to be given by limited physician specialities, while in others it is quite diverse. This means that the burden of colorectal cancer care can be diversified across many physician specialities rather than few. Furthermore, this means that some countries may have greater colorectal cancer specialty training and delivery than others.

The Russian survey reported that lack of physician awareness regarding signs and symptoms for cancer leading to failure in appropriate referrals was one of the primary reasons
for lengthy waiting times for treatment. In addition, Russia indicated many physician barriers to providing care, including financial deficiencies, lack of time and low salaries, thus lacking incentive to perform extra or even routine work. The Romanian survey reported that their Ministry of Health delegate indicated poor physician training as a problem, while physicians interviewed felt poor political interest in cancer care was the root of Romania’s state in cancer care. Greece indicated continued education of physicians as well as difficulty accessing and using international databases remains a barrier to optimal colorectal cancer care.

6.5. The Existence and Monitoring of Treatment Guidelines for Colorectal Cancer

Treatment guidelines

Treatment guidelines are important to determine, implement and monitor treatment of proven efficacy in any disease. Our survey found that approximately half of the countries have treatment guidelines in Europe, with addition of Australia. Many countries without treatment guidelines adopt other international or American guidelines. Countries with treatment guidelines do not necessarily monitor physician practice against them. Guidelines appear primarily in Western Europe, although there are a number of Western European countries that do not have their own treatment guidelines (Table 6.4). In countries without colorectal cancer treatment guidelines, our survey recorded a number of different methods in planning treatment. In Spain, treatment is determined by a multidisciplinary group, no other country’s treatment guidelines are adopted, and our Spanish respondent could find no reports of regional differences in colorectal cancer treatment. In Greece and Portugal, treatment is determined by international guidelines, none specifically noted as different physicians will follow different guidelines. The Russian survey indicated that there are no national treatment guidelines, however regional guidelines from PA Gertzen Research Oncology Institute do exist, and occasionally adopted. Romania reported minimal ESMO guidelines followed, yet treatment in many cases was determined by availability of funds. Turkey reported using both local committee-based and international guidelines to guide treatment.

A number of Eastern European countries do not have treatment guidelines (Poland, Russia, Slovakia, and Romania), in addition to their severe access and delivery problems. These countries then rely on other country’s guidelines or umbrella organisation guidelines, such as ESMO and NCCN guidance, described below. It is questionable whether these guidelines are appropriate across such settings, given resource differences, therapy
availability and knowledge, as well as pharmaceutical approvals. On the other hand, guidelines with discussion of each method along with appropriate treatment pathways are useful in these situations as a guide and example of ideal practice. The creation of native guidelines would be helpful in these countries to provide a framework for ideal and realistic practice given commonly encountered practice restraints, as well as help establish discussion between health care professionals to create the guidelines.
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</table>

*Notes:* * radiologists; ‡ oncologists; ° gastroenterologists; ∞ MRI, PET scan; ° between palliative cancer care; S = general surgeon; S<sup>CRC</sup> = general surgeon with colorectal cancer training; G = gastroenterology surgeon; O = general oncologist; O<sup>G</sup> = gastroenterology oncologist; O<sup>R</sup> = radiation oncologist.

G<sup>0</sup> = general hospital; oncology department; G<sup>G</sup> = general hospital, gastroenterology department; G<sup>S</sup> = general hospital, surgery department; C = specialist cancer hospital.

Standards of care monitoring

Our survey found a number of countries that monitor their standards in care. In the UK, the National Bowel Cancer Audit collects data from regional cancer networks to ensure that treatment guidelines are being followed. In Sweden, there are 56 regional quality registers reporting to the Swedish Association of Local Authorities and Regions (SALAR) who collect information on how well hospitals follow the guidelines as well as results from various treatments. In Denmark, the Danish Multidisciplinary Cancer Groups (DMCG) monitors quality of cancer care, and in 2008 is expected to implement a national monitoring system. In the Netherlands, the Vereniging Integrale Kanker Centrum (VIKC) has special periodic committees who monitor the treatment guidelines via physician questionnaires, care indicators and discussion groups.

The Australian survey reported not monitoring their standards of care; however, it also reported regular public hospital monitoring, and that the 2006 National Priority Actions for Change listed this as one of their recommendations. Other countries who also reported having guidelines but not monitoring them are Czech Republic, France and Italy.

<table>
<thead>
<tr>
<th>National Treatment Guidelines</th>
<th>Year</th>
<th>Perceived Problem: Poor or No Practice Guidelines</th>
<th>Monitor Guidelines</th>
<th>Management with No Treatment Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Y</td>
<td>2006</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Czech Rep</td>
<td>Y</td>
<td>1996</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Denmark</td>
<td>Y</td>
<td>2005</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Y</td>
<td>2007</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Germany</td>
<td>Y</td>
<td>2005</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Greece</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Hungary</td>
<td>N</td>
<td>-</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Italy</td>
<td>Y</td>
<td>2004</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Y</td>
<td>2008</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Poland</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Portugal</td>
<td>N</td>
<td>-</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Romania</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Russia</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Slovakia</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Spain</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Sweden</td>
<td>Y</td>
<td>2007</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Switzerland</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>UK</td>
<td>Y</td>
<td>2004-7</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Australia</td>
<td>Y</td>
<td>2005</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Notes: C = committee; O = other country’s treatment guidelines adopted; OESMO = adoption of ESMO guidelines; OASCO = adoption of ASCO guidelines; O^NCCN = adoption of NCCN guidelines; R = regional guidelines are available; NO = no adoption of other country’s treatment guidelines; * not officially.

6.6. The Content of Colorectal Cancer Treatment Guidelines

Treatment guidelines can take many forms and often reflect the underlying philosophies of physician organisations. They may be available openly and freely, or limited to those with professional memberships. They may provide strong recommendations in a ‘how-to’ manual, or provide guidance on outcomes of various options but leave decision making to the clinician. There may be differences between countries due to their interpretation of the evidence, as well as limits to prescribing certain chemotherapeutic agents and / or using certain procedures.

Guideline content and access

Most countries have two sets of publicly available guidelines: one for colorectal cancer and one for rectal cancer, although some countries attempt to integrate the two into one document (Australia, Germany, UK). Metastatic colorectal cancer may also be treated in a separate guideline (ESMO, France), however, most countries integrate metastases within their document under separate sections.

There are a few countries with visual treatment pathways (Belgium, France, Italy). In some cases the entire process is outlined from beginning to end (National Comprehensive Cancer Network), while in other cases only part of the treatment is addressed. The French Standards, Options et Recommendations (SOR) outlines pathways only for metastatic colorectal cancer, while the French Société Nationale Française de Gastroenterologie (SNFGE) shows the pathway for adjuvant chemotherapy treatment for non-metastatic colorectal cancer. The Italian Associazione Italiana di Oncologia Medica (AIOM) has 3 treatment pathways: colorectal cancer, rectal cancer, and metastatic colorectal cancer. Likewise, in Belgium, the College of Oncology provides 2 pathways, one for colorectal cancer and one for rectal cancer.

The European Society for Medical Oncology (ESMO) produces treatment guidelines for many cancers. Their guidelines offer ‘requirements for a basic standard of cancer care that ESMO considers necessary’ and their goals are to achieve and maintain high common standards in medical practice, to help clinicians offer best care, to support policy, political and insurance negotiations, and to sustain treatment by qualified oncologists. The guidelines are offered online, although a subscription to the Annals of Oncology is required to view the document.
ESMO has produced treatment guidelines for colorectal, metastatic colorectal and rectal cancer. These guidelines are meant to be the European guidelines for physicians treating colorectal cancer patients. The brevity of these guidelines (2 pages each) means no discussion or little evidence (6-10 references) can be provided to base guidance upon, although strength of evidence is sometimes supplied. Only the coordinating author is given and no pathways are provided. For physicians operating without national guidelines, these guidelines may offer little help. Even within European countries with national treatment guidelines, the usefulness of these guidelines as supplemental guidance may be very limited.

In contrast, the most recent guidelines for colorectal and rectal cancer produced by the American National Comprehensive Cancer Network (NCCN) are very lengthy (60 pg) and thorough (169 references); even potentially too comprehensive. Their definition of guidelines in oncology is the ‘systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances’. Its purpose is to assist in clinical decision making, to develop treatment pathways with main decision points, to provide information regarding appropriate care, and to produce guidelines under systematic conditions.

The NCCN guidelines describe the panel members, summarize changes from the previous guidelines, and encourage active participation in clinical trials. Detailed flow charts are given with primary recommendations and discussion is offered on the relevant literature. There are even separate guidelines for patients produced by the NCCN written by the American Cancer Society. The patient guidelines are very thorough, covering all aspects of colorectal cancer pathology, diagnosis, staging, and treatment (86 pages), as well as offer guidance for patients on which questions to ask and how to become active in their care. Pathways are also available for patients for all possible scenarios (early stage, liver metastasis, palliative care) with space for patients to make notes while meeting with health care professionals.

Many countries produce their own guidelines and occasionally, more than one organisation will produce guidelines in a country, which is repetitive in content as well as in time and resources, and may perhaps contradict each other. For example, guidelines in France for colorectal cancer can be found in two places: the SNFGE and the Féderation Nationale

120 ESMO, 2007a, 2007b, and 2007c.
121 NCCN, 2008.
122 Field et al, 1990.
des Centres de Lutte contre le Cancer (FNCLCC) under the auspices of SOR.\(^{124}\) The former covers colon cancer, rectal cancer and metastatic colorectal cancer, while the latter covers only rectal cancer and metastatic colorectal cancer. The National Institute for Health and Clinical Excellence (NICE) in the UK produces guidelines for colorectal cancer treatment, as does the Association of Coloproctology of Great Britain and Ireland. Germany also has two sets of guidelines, one produced by the Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS), and the other by the Duetsche Krebsgesellschaft and Informationszentrum für Standards in der Onkologie (ISTO), both published in 2004.

Access to these guidelines is usually through the physician organisation for oncology or gastroenterology. All country guidelines are freely available online as downloadable files. In the Netherlands, a central organisation for oncology guidelines is published, under the auspices of the VIKC, on an online database (www.oncoline.nl), with regional variations added into the database as well as English translation.\(^{125}\) In France, the SNFGE (www.snfge.org) has an online Thésaurus Cancérologie, produced in conjunction with the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR), FNCLCC and the Fédération Francophone de Cancérolgie Digestive (FFCD). Sections are updated annually when new evidence or treatments emerge, the date of revision can be seen in each document section.

**Strengths and weaknesses of different guidelines**

All guidelines offer strength of evidence upon which their guidelines are based. Many countries use their own method for appraising the strength of clinical evidence, some of which are detailed in their methodology (ESMO, Belgium, Germany, France, Netherlands, UK, Australia) and some are not (Italy). All countries have plans set up when their guidelines will be next reviewed.

Our survey revealed variations in philosophies underpinning treatment guidelines. The UK guidelines are based on health technology assessment, thus although a treatment may be more effective it may not be endorsed if costs are deemed excessive. The overall UK NICE guidelines (2004) do not offer strong guidance or much discussion on treatments, while the supplemental NICE guidance does. Furthermore, the UK 2004 guidelines provide little to no discussion on emerging new treatments. For example, laparoscopic surgery is given one paragraph and not recommended with substantive evidence appraisal, while many European

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\(^{125}\) VIKC, 2008a and 2008b.
countries had already been using this technique for years by 2004. Laparoscopic surgery was eventually approved by NICE in 2006, although it is difficult to distinguish between recommendations and evidence in the text.

The Australian guidelines (2005) produced by the National Health and Medical Research Council (NHMRC) provide much discussion of the literature (>300 pages) including many new techniques. Guidelines are clearly denoted in boxes with level of evidence, practice recommendation and references given. It is peculiar, however, that despite the introduction and discussion of many treatments, often no guidance is given. For example, in metastatic colorectal cancer, a page discussion is given on hepatic arterial infusion, although no official guideline is given on this topic.

The German guidelines provide much discussion and evidence (611 references, half of the document is the reference list), each discussion followed by treatment recommendations, strength of evidence as well as alternative options. The French and Belgian guidelines also are arranged in this manner. Dutch guidelines present discussion in addition to recommendations of the options with their pros and cons, but appear to leave the actual decision making up to the clinician.

The ESMO guidelines do not discuss surgery except for rectal cancer, however, all other country guidelines do discuss surgery in both colorectal and rectal cancers. It appears the European Colorectal Metastases Group has attempted to fill this gap by providing guidance and discussion on liver metastases resection and treatment. The discussion of colorectal surgery is quite varied between the countries, the Netherlands discussing surgical techniques (ie laparoscopy) while France discusses which procedure should occur.

In staging colorectal cancer, ESMO and all countries except the Netherlands and the UK recommend testing CEA pre-operatively. ESMO recommends examining a minimum of twelve nodes, mirrored by most other countries except the Netherlands which recommends a minimum of 9 nodes. A MRI or PET scan is not discussed by the ESMO guidelines, however, the MRI is recommended in Belgium in the metastatic setting and in Germany as an additional useful test, while PET scans are discussed in a limited manner in the UK and as an option in metastases in the Netherlands.

For rectal cancer, all guidelines frequently recommended chemo-radiotherapy in the neoadjuvant setting. The ESMO guidelines, in addition to France and the Netherlands, discuss radiation details. With regards to surgery, the ESMO guidelines are limited, while the

\[126\text{ van Cutsem et al, 2006.}\]
Netherlands provides much discussion and evaluation of evidence of various surgical procedures. Specific chemotherapy regimens are discussed by ESMO, Belgium, France (only SNFGE) and the Netherlands.

The UK and Australia provide limited guidance for rectal cancer. In Australia only 5 official recommendations are made, although two chapters are devoted to rectal cancer in their guidelines. The UK also has limited recommendations for rectal cancer compared to other countries; this may be because rectal cancer is interdispersed throughout the document diluting its importance as a separate entity in colorectal cancer treatment.

Our survey could not compare colorectal cancer practice to treatment guidelines; however, the literature suggests that variations in practice do occur. A review of Italian practice found 93% of breast and 80% of colorectal cancer patients received recommended care.\(^{127}\) An audit of Australian practice found 67% of patients were treated according to national guidelines.\(^{128}\) Other publications have found similar variations in practice throughout Europe.\(^{129}\)

### 6.7. Practice

The primary treatment method for colorectal cancer is surgery, supported by chemotherapy in colorectal cancer and (chemo-) radiotherapy in rectal cancer. Historically, surgery involved open resection; however the advent of laparoscopy has made it possible for colorectal cancer in its early stages to be a candidate for this type of surgery. This technique has spread throughout most of Europe (Table 6.5), in some countries earlier than in others. The advantages of laparoscopy is that it is less invasive than open surgery and has shorter recovery time, however, is associated with longer operating time and mortality in patients who convert from laparoscopic to open surgery mid-surgery.\(^{130}\) It is well known that laparoscopic surgery in colorectal cancer has a very high learning curve and requires high expertise by the surgeon;\(^{131}\) this relegates this technique to hospitals that have higher CRC volume, usually academic or urban hospitals.

Although timing of radiotherapy by ESMO and many other country guidelines is preferentially prior to surgery, a few countries state that radiotherapy is given post-operatively in their country (Table 6.5). In some cases this is explained by case dependency, for example

\(^{127}\) Barni et al, 2007  
\(^{128}\) Young et al, 2007  
\(^{129}\) Lemmers, 2006; Jestin et al, 2004; Duxbury et al, 2003  
\(^{130}\) Jayne et al, 2007.  
\(^{131}\) Reichenbach et al, 2006
when radiotherapy was unable to be delivered pre-operatively due to emergency surgery. In the case of Poland and Romania, however, only post-operative radiotherapy is reported by our survey respondents, which is worrisome as it is contrary to all evidence and guidelines.

Two treatment practices that our survey did not address are total mesorectal excision (TME) in rectal cancer and radio frequency ablation in metastatic colorectal cancer with liver metastases. The former is a surgical technique associated with much lower rates of recurrence, with a number of trials underway examining the combination of radiotherapy with TME and its effect on survival and other outcomes.132 The latter involves local hepatic therapy to reduce the metastases, and some promising initial results have emerged in patients not eligible for resection.133

### Table 6.5

**Colorectal treatment general practices**

<table>
<thead>
<tr>
<th>Country</th>
<th>Open Surgery</th>
<th>Laparoscopic Surgery</th>
<th>Year of Laparoscopic Introduction</th>
<th>Radiotherapy Timing with Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Y</td>
<td></td>
<td></td>
<td>Pre</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Y</td>
<td>Y</td>
<td>2002</td>
<td>Pre °, Post</td>
</tr>
<tr>
<td>Denmark</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Pre °, Post</td>
</tr>
<tr>
<td>Finland</td>
<td>Y</td>
<td></td>
<td></td>
<td>Pre °</td>
</tr>
<tr>
<td>France</td>
<td>Y</td>
<td>Y</td>
<td>1990s</td>
<td>Pre °</td>
</tr>
<tr>
<td>Germany</td>
<td>Y</td>
<td>Y</td>
<td>1990s</td>
<td>Pre, Post</td>
</tr>
<tr>
<td>Greece</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Pre, Post</td>
</tr>
<tr>
<td>Hungary</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Pre, Post</td>
</tr>
<tr>
<td>Italy</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Pre §, Post §</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Y</td>
<td>Y</td>
<td>1990s</td>
<td>Pre °</td>
</tr>
<tr>
<td>Poland</td>
<td>Y</td>
<td>N</td>
<td></td>
<td>Post</td>
</tr>
<tr>
<td>Portugal</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Pre, Post</td>
</tr>
<tr>
<td>Romania</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Post</td>
</tr>
<tr>
<td>Russia</td>
<td>Y</td>
<td>Rarely</td>
<td>-</td>
<td>Pre</td>
</tr>
<tr>
<td>Slovakia</td>
<td>Y</td>
<td>N</td>
<td>-</td>
<td>Pre</td>
</tr>
<tr>
<td>Spain</td>
<td>Y</td>
<td>Y</td>
<td>2005</td>
<td>Pre, Post</td>
</tr>
<tr>
<td>Sweden</td>
<td>Y</td>
<td>Y</td>
<td>1991</td>
<td>Pre</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Y</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Turkey</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Pre</td>
</tr>
<tr>
<td>UK</td>
<td>Y</td>
<td>Y</td>
<td>2006</td>
<td>Pre</td>
</tr>
<tr>
<td>Australia</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Pre, Post *</td>
</tr>
</tbody>
</table>

*Nos:** ° rectal cancers, * Post-operatively only if not given pre-operatively, § depending on circumstance, *Source*: LSE CRC Survey 2008.

### 6.8. Is Colorectal Cancer Treatment Cost-Effective?

Cost-effectiveness analyses are helpful in estimating the worthiness of new treatments in comparison to established treatments, with regards to both costs and effectiveness.

133 Ruers et al, 2007; Abitabile et al, 2007
Furthermore, where no head-to-head clinical trials exist, cost-effectiveness analyses can model the treatments against each other. There have been few publications on cost-effectiveness of colorectal cancer treatments, specifically surgery and radiotherapy.

One such area where cost-effectiveness analysis has been helpful is in new surgical techniques, such as laparoscopic resections (Table 6.6) and hepatic resections (Table 6.7). The former has been shown to be as effective in the short-term as open resection and with shorter recover time, although long-term survival is yet to be known.\(^{134}\) There is the risk of conversion to open resection associated with higher mortality risk, as well as longer operating times and high surgeon learning curve. Meta-analysis found post-operative mortality and 3-year survival similar between laparoscopy (1.4%; 75.8%) and open (1.6%; 75.3%), not uncommon risk of conversion (19%), and similar rate and location of recurrence.\(^{135}\)

The two UK cost-effectiveness analyses found open resection to be dominant over laparoscopic surgery, while the New Zealand analyses found laparoscopic surgery to be perhaps under an acceptable cost-effectiveness threshold (Table 6.6). What these studies illustrate is that although laparoscopy has short-term benefits in recovery time, less tissue trauma and shorter hospital stays, these do not tally into significant QALY gained or costs saved. There is significant risk of conversion associated with higher mortality, risks and costs associated with a high surgeon learning curve, and no gain in survival. Essentially, the adoption of laparoscopic surgery is related to opportunity costs; i.e. could the money that is needed for introduction of this type of resection be used more worthwhile in other colorectal cancer treatments.

Of interest is that many countries have already adopted laparoscopic resection in colorectal cancer prior to these clinical trials and untimely cost-effectiveness analyses. Our survey shows many countries began using laparoscopy in colorectal cancer surgery from the mid-1990’s (Table 6.5), albeit primarily in academic and high volume hospitals. This is an example of how new technology can occasionally surpass evidence, and how research should be integrated into new practice to ensure timely evidence.

\(^{134}\) Lacy et al, 2002; COST Study Group, 2004; Veldkamp et al, 2005; Guillou et al, 2005
\(^{135}\) Bonjer et al, 2007.
Table 6.6
Synopsis of cost-effectiveness analysis in laparoscopic versus open surgery in colorectal cancer
(All costs are presented in 2004 €)

<table>
<thead>
<tr>
<th>Country</th>
<th>Model</th>
<th>Perspective</th>
<th>Timeline</th>
<th>Stage</th>
<th>Treatment</th>
<th>LYG</th>
<th>QALY</th>
<th>Total Costs/ Patient</th>
<th>Sensitivity</th>
<th>Analysis</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>UK¹</td>
<td></td>
<td></td>
<td>(1) laparoscopic (2) open resection</td>
<td>(1) 15.30 (2) 15.35</td>
<td>(1) 14.63 (2) 14.68</td>
<td>(1) €14,961 (2) €14,562</td>
<td>Survival, disease-free</td>
<td>survival</td>
<td>(2) dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UK²</td>
<td></td>
<td></td>
<td>(1) laparoscopic (2) open resection</td>
<td>(1) 15.298 (2) 15.351</td>
<td>(1) 14.630 (2) 14.679</td>
<td>(1) €15,850 (2) €15,412</td>
<td>survival</td>
<td>(2) dominant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>New Zealand</td>
<td></td>
<td></td>
<td>(1) laparoscopic (2) open resection</td>
<td>N/A</td>
<td>(1) 0.018-0.049*</td>
<td>(1) €654*</td>
<td>Recovery time</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: LYG: Life Years Gained; QALY: Quality Adjusted Life Years; ICER: Incremental Cost Effectiveness Ratio; * marginal costs and QALYs in relation to open surgery.

Liver metastases are a significant problem in advanced CRC, with approximately 50% either presenting with or latter developing of liver metastases. Although chemotherapy can prolong survival, overall survival in these cases remains poor. Surgery of liver metastases (hepatic metastasectomy) appears to be a primary method for significant prolongation of survival. However, there remain a number of unresolved questions which cost-effectiveness analysis can bring clarity to.

The first question is how to determine which patients are appropriate for hepatic metastatic resection. The use of laparoscopy prior to liver resection can help determine whether patients are indeed candidates for resection of their hepatic lesions, but are the additional costs and procedure worthwhile? A recent decision analysis found the addition of pre-surgical laparoscopy is cheaper with greater quality adjust life years, as candidates who have unresectable metastases are spared unnecessary surgery (Table 6.7). This is, however, in a select risk-stratified rather than total surgical group, likely affecting the outcome.

The second question is to determine whether curative resection in liver metastasis is cost-effective compared to best practice with chemotherapy. Both analyses (Table 6.7) show

137 Karuna et al, 2008
hepatic metastasectomy is cost-effective compared to best non-surgical treatment, under acceptable cost-effectiveness thresholds and with significant increases in survival.

The third question is how to cost-effectively manage the number of metastases and number of resections allowable. An analysis concluded that less than 6 metastases with one repeat hepatic resection remains within an acceptable cost-effectiveness threshold (Table 6.7). The interval for repeating resection of hepatic metastasis appears to be problematic, as shorter interval times (4 months) is more costly and only minimally more effective than longer intervals (12 months).

Both studies examining cost-effectiveness of curative surgery itself are quite old with respects to aspects of their chemotherapy. Neither used newer cytotoxic agents or targeted treatments discussed in Chapter 9. The addition of these newer treatments could create a more complete picture and lead to improved cost-effective combinations.

<table>
<thead>
<tr>
<th>Table 6.7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synopsis of cost-effectiveness analysis in hepatic resection of colorectal cancer liver metastases</strong></td>
</tr>
<tr>
<td>(All costs are presented in 2005 €)</td>
</tr>
<tr>
<td><strong>Country</strong></td>
</tr>
<tr>
<td>Model</td>
</tr>
<tr>
<td>Perspective</td>
</tr>
<tr>
<td>Timeline</td>
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<tr>
<td>Stage</td>
</tr>
<tr>
<td>Treatment</td>
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<tr>
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<tr>
<td>QALY</td>
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<tr>
<td>Total Costs/Patient</td>
</tr>
<tr>
<td>Sensitivity Analysis</td>
</tr>
<tr>
<td>ICER</td>
</tr>
</tbody>
</table>

*Notes: LYG: Life Years Gained; QALY: Quality Adjusted Life Years; ICER: Incremental Cost Effectiveness Ratio. Source: LSE CRC Survey 2008, based on Beard et al, 2000 (UK); Gazelle et al, 2003 (USA); Karuna et al, 2008 (USA).¹²*

¹ Gazelle et al, 2003
² Gazelle et al, 2003; Beard et al, 2000
Radiotherapy in rectal cancer is another area of treatment where cost-effectiveness analyses have been applied, specifically the addition of radiotherapy prior to surgery to reduce recurrences and improve surgical outcomes. All analyses reported acceptable incremental cost-effectiveness ratios within threshold limits (Table 6.8). The figures do differ, most likely due to differences in surgery and model perspectives, and differences in denominator used.

The previous section on guidelines demonstrated that pre-operative radiotherapy has been largely adopted and implemented. What is lacking in comparison to the guidelines is the inclusion of chemo-radiotherapy; to date no cost-effectiveness or decision analyses have addressed this aspect of rectal cancer treatment that appears to have entered standard practice, particularly as chemotherapy may be costly but with significant benefits.

Table 6.8
Synopsis of cost-effectiveness analysis of adjuvant radiotherapy in rectal cancer
(All costs are presented in 2002, €)

<table>
<thead>
<tr>
<th>Country</th>
<th>Netherlands</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
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<td>CEA</td>
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<td>Health care</td>
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<td>Unknown</td>
</tr>
<tr>
<td>Stage</td>
<td>Potentially resectable rectal cancer</td>
<td>Potentially resectable rectal cancer</td>
</tr>
<tr>
<td>Treatment</td>
<td>Total Mesorectal Excision with (1) pre-surgical radiotherapy (2) without pre-surgical radiotherapy</td>
<td>Surgery with (1) pre-surgical radiotherapy (2) without pre-surgical radiotherapy</td>
</tr>
<tr>
<td>LYG</td>
<td>(1) 13.59 years (2) 12.92 years</td>
<td>(1) 81 months (2) 60 months</td>
</tr>
<tr>
<td>QALY</td>
<td>(1) 8.34 (2) 7.95</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Costs/Patient</td>
<td>(1) €120,129 (2) €109,981</td>
<td>(1) €35,930 (2) €30,644</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Age, recurrence, survival benefits, radiotherapy costs</td>
<td>Survival benefits, complications costs, recurrence rate</td>
</tr>
<tr>
<td>ICER</td>
<td>(1) €26,219/QALY</td>
<td>(1) €3,722/LYG</td>
</tr>
</tbody>
</table>

Notes: LYG: Life Years Gained; QALY: Quality Adjusted Life Years; ICER: Incremental Cost Effectiveness Ratio.
Source: LSE CRC Survey 2008, based on van den Brink et al, 2004 (Netherlands); Dahlberg et al, 2002 (Sweden).

6.9. Performance Indicators, Country Ranking and Implications for Patients

A performance indicator was created based on the responses received to a number of questions, using the variables listed above. There are two sets of indicators, positive indicators facilitating treatment access and availability, and negative indicators creating barriers to treatment access and availability.
Positive indicators include the following 14 variables:

- Waiting time (diagnosis to treatment) ≤ 2 months
- Treatment elderly, curative
- Leader in timeliness in new cancer treatments
- Leading colorectal cancer practice and standards for other countries to follow
- Patient priority policy
- Patient choice in treatment center
- Participation in colorectal cancer research
- Specialist cancer hospitals
- Specialist physicians (gastroenterology surgeon, gastroenterology oncologist)
- Country specific colorectal cancer guidelines
- Country specific rectal cancer guidelines
- Published cost-effectiveness analysis
- Laparoscopic surgery
- Pre-surgical radiotherapy

A total of 20 negative indicators were included, notably:

- Geographical inequity
- Groups with access difficulty
- Treatment elderly, less likely
- Perceived long waiting times
- Poor quality treatment
- Out-of-pocket payment, informal
- Actual waiting time >2 months
- Limited, poor, or delayed access to new treatment
- No access to treatment
- Behind other countries in timeliness of new treatments
- Improvement of practice and standards compared to international best practice
- Insufficient facility resources
- Poor distribution of resources
- Inadequate diagnostic facilities
- Inadequate treatment facilities
- Insufficient human resources
- Poor physician resources or networks
- Poor physician oncology training
- Post only surgical radiotherapy
- No treatment guidelines

The purpose of the performance indicators and country rankings is to summarise all the information presented above into a simple variable, reflecting a net positive or negative situation with regards to treatment access, availability and delivery. There are naturally limitations to this simplification, some countries provided much more information than others. In some cases surveys were incomplete, thus no positive or negative points could be given. Much of the information gathered is derived from concrete sources such as government publications, interviews with health policy makers and physicians, however there is room for interpretation bias, opinion and perception which can affect the results.
With these caveats in mind Figure 6.2 outlines the country rankings for the performance indicators described above. The maximum positive or negative score a country can receive is 100 percent. These rankings are a guide only and give an overview of which countries have significant problems in access, availability and delivery of CRC treatment. Most countries have a positive balance of performance indicators, yet there are a number of countries with net negative balance (Poland, Portugal, Romania, Russia, Turkey). Few countries have positive indicator over 60% (Czech Republic, France, Netherlands, UK) while two countries have negative indicators over 60% (Romania, Russia).

Australia fares well in comparison to Europe, by scoring 57 positive points to the European average of 45, and 20 negative points to the average of 28. Its positive ranking is 5th, while its negative is 12th. Other countries with similar rankings, both positive and negative, include France, Germany, Italy, Netherlands and the UK.

**Figure 6.2**

*Country rankings of positive and negative performance indicators*

![Bar chart showing the country rankings of positive and negative performance indicators.](chart)

*Source:* The authors.

From a patient and a broader societal perspective, access to treatment is particularly sensitive. Four points raised in this chapter are particularly relevant to patient scrutiny. First, patients will contest that it is unacceptable for citizens in some countries to be waiting up to 8
months for treatment of CRC, as this is an unnecessary psychological burden to themselves and their families beyond the likelihood of worsening their prospects. Second, it is also not acceptable that the quality of treatment received relates to geographical location; where geographical inequity exists, it can be overcome with careful planning and investment. Third, access to innovations in CRC medical treatment – laparoscopic surgery being one example – is a human right. And fourth, when faced with a potentially life threatening disease, patients and their families have a basic human right to expect high quality care and facilities that deliver this.

6.10. Conclusions

There appear to be a number of serious access and availability issues relating to colorectal cancer treatment across Europe. Geographical barriers to access appear almost universal in Europe and Australia, bar Denmark, the Netherlands, and, to a lesser extent, the UK. Only a minority of countries indicated perceived problems with access inequities with regards to specific population groups. Approximately half of European countries reported the perception of long waiting times and only a minority of countries have high quality guidelines. Poor quality treatment was reported only in Russia and Romania, while a number of Western and Eastern European countries reported patient choice of treatment centre. Out-of-pocket payments are not uncommon in Europe for treatment, although in most cases reimbursable or capped. Informal payments were also reported in a number of cases, particularly in Eastern and South-eastern Europe.

Approximately half of European countries perceived access to new treatment modalities, both surgical and pharmaceutical, to be limited, poor or delayed. In addition, perceived timeliness of access to new treatments was found to be roughly on par compared to other countries, with the exception of a few countries. On the other hand, when respondents were asked to rate their country treatment practices in comparison with international best practice, a number of countries indicated leadership.

Colorectal cancer delivery was also not without perceived problems. A number of countries indicated insufficient facilities, be it for diagnosis or treatment, while the majority of study countries indicated difficulties with insufficient human resources, including oncology training.

Approximately half of surveyed countries reported national treatment guidelines, the majority published in the last five years. Unfortunately a number of these countries do not
monitor the use of their treatment guidelines, thus making it difficult to monitor overall quality of colorectal cancer care, or the implementation and / or appropriateness of treatments. In countries with no guidelines the NCCN and ESMO guidelines are most likely to be adopted. 

The philosophy and content of colorectal cancer treatment guidelines varies between countries, partly due to reimbursement and partly due to practice philosophy. Some guidelines are very explicit and make strong recommendations, thus making it easy to develop and monitor quality indicators, while others may have long or short discussion but offer little guidance. Access to these guidelines is fairly ubiquitous although publication is generally in the native language only, making it difficult for countries without guidelines to adopt others and for cross referencing purposes.

A number of cost-effectiveness analyses have been published on a variety of colorectal cancer treatments, including surgery and radiotherapy. Analysis of laparoscopy questions its implementation and opportunity costs in practice, after many countries have adopted the technique in large hospitals. Other more timely analyses have determined that hepatic resection for liver metastases and pre-surgical radiotherapy in rectal cancer are cost-effective treatments. Overall, these cost-effectiveness analyses show that new treatments should be analysed in a timely manner prior to general adoption, and that these analyses should become more prevalent as guideline-based practice becomes the norm across Europe.

The country rankings created by using positive and negative performance indicators give a reflection of the overall issues discussed throughout this chapter. Most countries fare well for net positive indicators, while not surprisingly Romania and Russia fare especially poorly. These indicators show the complexity of the issues involved in colorectal cancer treatment access and delivery, and how a country may fare well in some parts yet poorly in others.

Australia compares well to other Western European countries with regards to access, availability and delivery of its colorectal cancer care. Its main problems with access are related to the geographical vastness and isolation of many parts of the country, which make delivery of cancer care challenging. It may often be more cost effective for patients to travel to main centres rather than specialists travel and there is often difficulty in the recruitment of staff to rural areas even with financial incentives. Furthermore, it recognizes there are problems in accessibility for its aboriginal groups, official recognition of this has been a large part of the solution. The development of colorectal cancer treatment guidelines is on par, despite the guidelines’ overwhelming focus on discussion with limited direct advice. The use
of cost-effectiveness analysis appears to be limited; however, this is a comment that could also be directed to many European countries.

There appear to be large differences between Western and Eastern European countries, although there are a number of countries with considerable development, notably the oldest Eastern entrants to the European Union. Turkey has a low positive ranking and a high negative ranking, its net ranking is slightly more negative than positive which is encouraging in comparison to Russia and Romania.

Overall, many country appear to be facing challenges with CRC access and delivery. In part, this may be a functioning of the health system as a whole, however the lack of treatment guidelines, long (perceived) waiting times, lack of specific colorectal cancer care structures, delayed access to new treatments and limited cost-effectiveness analyses points to directional issues in colorectal cancer management.
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127
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Chapter 7
Pharmaceutical Treatments in Colorectal Cancer: Access, Availability and Cost-Effectiveness

7.1. Introduction

Medicines (chemotherapy) play an increasingly important role in colorectal cancer treatment. In the past, the options for chemotherapy were limited in colorectal cancer and almost exclusively devoted to fluorouracil-based regimens post-surgery. During the past decade, many advances have been made in developing new chemotherapeutic agents and new regimens for CRC (Box 7.1), many of which have led to significant increases in survival.

Furthermore, oral analogues of fluorouracil were approved in the last five years as an alternative to intravenous fluorouracil delivery. Adjuvant chemotherapy has also been added to treatment for Stage III and occasional high risk Stage II patients, outside their use in traditional realm of metastatic and palliative CRC. Thirdly, new cytotoxic agents have been approved, improving survival and opening up 2nd and 3rd line chemotherapy choices. Lastly, biologically targeted treatments have now been approved in metastatic colorectal cancer, lengthening survival which in the past was less than one year in the metastatic setting.

This chapter highlights similarities and differences between countries with regards to traditional fluorouracil-based regimens, adjuvant chemotherapy and targeted treatments, with particular attention paid to:

- The effectiveness and cost-effectiveness of pharmaceutical treatments;
- Spending on targeted pharmaceutical treatments;
- Access and availability of targeted treatments;
- Presence of country guidelines in the use of pharmaceutical treatments for colorectal cancer and metastatic colorectal cancer.

<table>
<thead>
<tr>
<th>Box 7.1 Pharmaceutical Treatments and Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU/LV</td>
</tr>
<tr>
<td>Xeloda</td>
</tr>
<tr>
<td>UFT</td>
</tr>
<tr>
<td>Eloxatin</td>
</tr>
<tr>
<td>Campo</td>
</tr>
<tr>
<td>Erbitux</td>
</tr>
<tr>
<td>Avastin</td>
</tr>
</tbody>
</table>
7.2. Effectiveness and Cost-Effectiveness of Colorectal Cancer Pharmaceutical Treatments

Cost-effectiveness analysis has become essential for pharmaceutical (and many non-pharmaceutical) treatments in recent years. New treatments are reaching the market at costs that must be weighed against their proven effectiveness under health system constraints. Frequently, thresholds are used in some countries to define the range of acceptable costs for the offered effectiveness (or in many cases simply efficacy). For example, in the UK the National Institute of Clinical Excellence (NICE) has defined a notional ‘threshold’ of £30,000 per quality adjusted life year (QALY), above which the probability of rejection increases significantly. In the case of cancer treatments, costs must be weighed against the effects of toxicity, quality of life, overall survival, and progression-free survival, although no cancer-specific threshold has been set in any country.

Australia and a number of European countries now require cost-effectiveness analysis as part of new treatment applications for reimbursement (Australia, Finland, Netherlands, Sweden, UK, Netherlands), however, its weight in the decision making process may differ resulting in different conclusions from one country to another. Other factors, such as patient advocacy groups and politics also have significant effects on reimbursement decisions.

There is a scarcity of acceptable colorectal cancer pharmaceutical cost effectiveness analyses. A number of publications investigate costs plus survival benefits but do not combine the two into a meaningful Incremental Cost Effectiveness Ratio (ICER). A few neglect to address costs and incidences of adverse events such as toxicity that greatly impact patient treatment. Only a handful expresses effectiveness as QALYs, although many discuss the impact of treatment on patient quality of life. The majority of studies take the health system perspective, neglecting societal and indirect costs. The UK appears to be the primary producer of published cost effectiveness analysis, with France producing the remainder over the past decade (Tables 7.1-7.3).

Traditional 5-fluorouracil based regimens: Capecitabine and UFT

Recently two new oral 5-fluorouracil medicines have been introduced, capecitabine and tegafur + uracil (UFT). These new therapies have many benefits, however, they are more expensive than traditional iv 5-FU-based regimens, which have been off-patent for many years. They increase patient freedom as intravenous delivery is no longer necessary, and
decrease in-patient hospital costs. They satisfy patient preferences for oral over intravenous therapy\textsuperscript{140} in addition to improved safety profiles.\textsuperscript{141}

Only two cost-effectiveness studies were found for these drugs, one for Stage III and one in the metastatic setting (Table 7.1). Neither compared capecitabine to UFT, while both compared to various traditional fluorouracil delivery regimens. This reflects an absence of head to head clinical trials comparing the two oral analogues.

Both studies found capecitabine to be a dominant\textsuperscript{142} therapy over intravenous fluorouracil delivery (Table 7.1). Higher drug costs associated with oral fluorouracil agents were adequately recouped by lower hospital costs, and in some cases fewer adverse events were found. Drug costs were universally an issue in sensitivity analyses, as well as administration costs of the traditional hospital-based treatments of intravenous 5-FU. A comparison of intravenous 5-FU regimens found higher costs associated with inpatient de Gramont approach than for quicker MdG schedule.\textsuperscript{143} It appears that oral fluorouracil agents are an acceptable replacement for intravenous 5FU therapy, and in fact may be cost-saving for the health system as therapy can be delivered in a community-setting.

Despite the potential cost-savings of oral fluorouracil regimens, a number of our survey respondents reported minimal uptake due to difficulties in monitoring patient adherence and toxicity, as well as poor physician adoption (The Netherlands, UK).

Table 7.1
Cost effectiveness analysis of oral 5-fluorouracil based CRC treatments
(All costs are in 2004, €)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Dukes Stage C</td>
<td>Metastatic</td>
</tr>
<tr>
<td>Survival Analysis</td>
<td>(1) 81.3% (2) 77.6%, at 36m</td>
<td>(1) 4.3-5.2m (2) 3.4-3.5m (3) 3.3-4.7m</td>
</tr>
<tr>
<td>Total Costs</td>
<td>€5,335 (2) €12,792</td>
<td>€3,284 (2) €5,215 (3) Mayo €5,535, de Gramont €9,637, MdG €5,369</td>
</tr>
<tr>
<td>ICER</td>
<td>(1) dominant</td>
<td>(3) MdG: €20,909/LYG; de Gramont: €63,701/LYG compared to (1)</td>
</tr>
<tr>
<td>Health System Cost Savings</td>
<td>(1) €5,412/patient</td>
<td>(1) €2251-6,352/patient (2) €155-4422/patient</td>
</tr>
</tbody>
</table>

Notes: ICER: incremental cost effectiveness ratio; QALY: quality adjusted life years; LYG: life years gained.


\textsuperscript{140} Borner et al, 2002.
\textsuperscript{141} Twelves et al, 2001; Twelves et al, 2005.
\textsuperscript{142} Dominant refers to a treatment being more effective and less costly than another, thus dominating the other choice.
\textsuperscript{143} Ward et al, 2006.
New cytotoxic agents: Irinotecan and Oxaliplatin

A number of cost effectiveness studies address cytotoxic agents: irinotecan (4 studies) and oxaliplatin (1 study) (Table 7.2), both used in combination with 5FU chemotherapy in metastatic setting. These analyses evaluated irinotecan in combination for both 1st and 2nd line treatments, while oxaliplatin in combination was evaluated only for 1st line.

The effects of life years gained (LYG) and quality adjusted progression free (QAPF) survival were taken from other clinical trials reported in the literature. Irinotecan + 5FU increases overall survival by 2-3 months in metastatic colorectal cancer, while oxaliplatin + 5FU increases overall survival by more than 6 months in comparison with irinotecan and QAPF by 3 months (Table 7.2).

The range of costs for irinotecan are very similar to its comparator fluorouracil-based treatments (Table 7.2). However, this conclusion depends heavily on whether follow-up costs are included,\textsuperscript{144} as well as which iv 5-FU-based regimen was used as a comparator. Many cost effectiveness analyses accounted for differences in fluorouracil regimens,\textsuperscript{145} as these appear to make a large difference in administration costs.

Irinotecan + 5FU was found to be cost-effective in both first and second line treatments.\textsuperscript{146} There is only one oxaliplatin study, which found it to be acceptable, depending on its survival benefits and administration method with 5FU. Sensitivity analysis in most studies found the type of fluorouracil regimen to be significant factor (in addition to survival).

As the treatment guidelines in the following section show, oxaliplatin is recommended in Stage III and metastatic colorectal cancer settings in most countries while irinotecan is only recommended in the metastatic setting. It appears that all of the cost-effectiveness analyses address the metastatic setting, and none deal with the Stage III adjuvant setting. As approximately 20% of colorectal cancer patients are Stage III,\textsuperscript{147} not to include this patient group is an unfortunate omission.

Targeted Biological Agents: Bevacizumab and Cetuximab

After decades of conventional 5-FU based cytotoxic regimens bevacizumab and cetuximab have been hailed as major breakthroughs for the treatment of colorectal cancer. Although these agents are both antibodies, and have applications in other cancers

\textsuperscript{144} Cunningham et al, 2002; Levy-Piedbois et al, 2000.
\textsuperscript{146} i.e. under the cost effectiveness threshold of £30,000/QALY.
\textsuperscript{147} Ciccolallo et al, 2005.
(bevacizumab: advanced non-small lung cancer, metastatic breast cancer, renal cell cancer; cetuximab: head and neck cancer), their specific action and effects on CRC survival are very different.

Bevacizumab was approved for use in Europe in March 2005 and Australia in 2005 in metastatic colorectal cancer patients, in combination with fluoropyrimidine-based chemotherapy (i.e. 5FU/LV, FOLFOX, FOLFIRI, XELOX, XELIRI). It is a humanised monoclonal antibody that binds to and inhibits vascular endothelial growth factor (VEGF). VEGF stimulates tumour angiogenesis and this is important in the formation of tumour angiogenesis.

Significant improvement in progression-free and overall survival were demonstrated with the addition of bevacizumab to standard first- and second-line chemotherapy regimens. These results led to the broad approval by the European Medicines Evaluation Agency (EMEA) for the use of bavacizumab in combination with chemotherapy for patients with metastatic carcinoma of the colon or rectum.

Cetuximab is a chimeric (mouse) antibody that binds to epidermal growth factor receptor (EGFR) that is responsible for cell replication, and only effective in patients expressing EGFR. It was approved for use in Europe in June 2004 and Australia in 2005 in metastatic colorectal cancer, alone or in combination with irinotecan for patients expressing EGFR who have failed previous irinotecan-containing therapy.

Significant improvements in progression-free but not overall survival have been demonstrated with the addition of cetuximab to chemotherapy in first- and second-line. Only in third-line, cetuximab has proven to extend survival versus best supportive care. Cetuximab is currently indicated in combination therapy for the treatment of patients with metastatic colorectal cancer expressing EGFR after failure of irinotecan.

There are currently three published cost-effectiveness analyses for cetuximab, while only one for bevacizumab (Table 7.3). These analyses range from 1st line (bevacizumab) to 2nd and 3rd line (cetuximab) in metastatic colorectal cancer treatment. The use of QALY is more prevalent here than with other analyses presented here previously.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Regimen</th>
<th>Survival Analysis</th>
<th>QAPF Survival</th>
<th>Total Costs/Patient</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(1) 10.8m, 44.8% at 1y</td>
<td>(1) 16.8m (2) 14.0m</td>
<td>(1) 19.55-26.65m (2) 16.12-19.52m (3) 6.89-12.28m</td>
<td>(1) Dominant - €19,577/LYG</td>
</tr>
<tr>
<td>Metastatic 2nd line</td>
<td>(1) Irinotecan (2) 5FU infusional</td>
<td>(1) 16.8m (2) 14.0m</td>
<td>NR</td>
<td>€15,760 (2) €21,148</td>
<td>(1) €23,371/LYG</td>
</tr>
<tr>
<td>Metastatic 1st line</td>
<td>(1) Irinotecan + de Gramont or AIO (2) 5FU/FA de Gramont or AIO</td>
<td>(1) 19.55-26.65m (2) 16.12-19.52m (3) 6.89-12.28m</td>
<td>NR</td>
<td>€15,760 (2) €21,148</td>
<td>(1) €23,371/LYG</td>
</tr>
<tr>
<td>Advanced 1st, 2nd line</td>
<td>(1) Oxaliplatin + de Gramont OR 5FU/FA 1st line (2) Irinotecan + de Gramont OR 5FU/FA 1st line</td>
<td>(1) 19.55-26.65m (2) 16.12-19.52m (3) 6.89-12.28m</td>
<td>NR</td>
<td>€15,760 (2) €21,148</td>
<td>(1) €23,371/LYG</td>
</tr>
<tr>
<td>Metastatic 2nd line</td>
<td>(1) Irinotecan; 5FU infusion with (2) Lokich (3) AIO (4) LV5FU2</td>
<td>(1) 10.8m (2) 8.5m</td>
<td>NR</td>
<td>€13,523 (2) €9,803-16,355</td>
<td>(1) Dominant - €19,577/LYG</td>
</tr>
<tr>
<td>(1) Irinotecan (2) 5FU infusional</td>
<td>(1) 10.8m, 44.8% at 1y</td>
<td>(1) 16.8m (2) 14.0m</td>
<td>(1) 8.66-9.11 (2) 6.24-6.93 (3) NR</td>
<td>€13,523 (2) €9,803-16,355</td>
<td>(1) Dominant - €19,577/LYG</td>
</tr>
<tr>
<td>(1) Irinotecan (2) 5FU infusional</td>
<td>(1) 10.8m, 44.8% at 1y</td>
<td>(1) 16.8m (2) 14.0m</td>
<td>(1) 8.66-9.11 (2) 6.24-6.93 (3) NR</td>
<td>€13,523 (2) €9,803-16,355</td>
<td>(1) Dominant - €19,577/LYG</td>
</tr>
<tr>
<td>(1) Irinotecan (2) 5FU infusional</td>
<td>(1) 10.8m, 44.8% at 1y</td>
<td>(1) 16.8m (2) 14.0m</td>
<td>(1) 8.66-9.11 (2) 6.24-6.93 (3) NR</td>
<td>€13,523 (2) €9,803-16,355</td>
<td>(1) Dominant - €19,577/LYG</td>
</tr>
</tbody>
</table>

**Notes:** QAPF - Quality Adjusted Progression Free; ICER - Incremental Cost Effectiveness Ratio; LYG – life years gained

**Source:** LSE CRC Survey 2008.
Due to an absence of head-to-head clinical trials, survival data (effects) is modelled from various clinical trials, which is often the case in cost-effectiveness analysis. In the case of cetuximab, survival data was primarily gathered from the then only published clinical trial\textsuperscript{148}, reporting on 329 patients comparing monotherapy to irinotecan combination therapy. Active best practice was gathered from other trials. In the case of bevacizumab, a variety of trials were used, some of which compared bevacizumab to active best practice and found significant increases in survival from 4-8 months.\textsuperscript{149}

Despite costs being inflated to the same year the estimated costs differ between countries for cetuximab in combination with irinotecan treatment (£17,602 to £31,119). As only one study was found for bevacizumab, no comparison could be found. The sensitivity analyses for both cetuximab and bevacizumab both show that drug costs and survival length are the largest influences on results for both drugs. There have been a number of suggestions to reduce costs: smaller units to reduce waste, using other symptoms (ie skin rash) as surrogate marker for treatment response, and a change to shorter schedules.\textsuperscript{150}

Both cetuximab and bevacizumab analyses found their ICER to have large ranges depending on the assumptions made in the model (Table 7.3). Often the lower end of the ICER is just above the UK acceptable threshold set out by NICE at £30,000/QALY. In countries where health technology assessment plays a significant role in reimbursement of new treatments (UK, Sweden), these treatments are at best relegated to 2\textsuperscript{nd} or 3\textsuperscript{rd} lines. On the other hand, this is a group of patients where it is most difficult to show survival benefits due to their metastatic status, as found in sensitivity analyses. It has been suggested that these thresholds should not apply or should be adjusted for individuals with terminal illnesses, as there are limited patient population who require this annually and hopefully less so once national screening programs are in place. Furthermore, the additional length in survival, of a lifespan usually less than one year, could also be taken into account, as well as the degree of innovation of a new drug in a disease that has had few significant breakthroughs in treatment.

Most countries in Western Europe have added targeted biological agents as part of their treatment arsenal against metastatic colorectal cancer (e.g. France, Germany, Netherlands, Spain), while there is only limited use in others (e.g. UK, Australia).

\textsuperscript{148} Cunningham et al, 2004  
\textsuperscript{149} Hurwitz et al, 2004; Kabbinavor et al, 2003; Kabbinavar et al, 2005  
\textsuperscript{150} Norum, 2006.
7.3. Spending on Targeted Treatments for Metastatic CRC

The purpose of this section is to provide comparative evidence on the uptake and use of targeted treatments in CRC in the study countries, taking into account the number of eligible metastatic colorectal cancer patients per country. Sales data was obtained from Intercontinental Medical Statistics (IMS) for the year 2007, while the cancer population statistics was obtained from 2002 GLOBOCAN database (the latest available).

The sales data was adjusted for the number of colorectal cancer patients in each country. As little to no data exists on the actual number of Stage IV metastatic colorectal cancer patients in each country, three different proxies were chosen: incidence, mortality which likely has large numbers of Stage IV patients prior to death, and Stage IV at diagnosis. The country specific 2002 (incidence and mortality) data was obtained from GLOBOCAN, which maintains a quality controlled global cancer registry. Incidence reports the number of new individuals diagnosed with colorectal cancer each year, while mortality data likely reflects large numbers of Stage IV metastatic during the last year of life and when targeted biologicals are most likely to be used.

The proportion of Stage IV patients at diagnosis was obtained from 4 studies presenting stage at diagnosis from 5 different European countries. Where possible country-specific Stage IV data was used (France 19.5%, Italy 20%, Netherlands 18%, Spain 19% and the UK 21%) and an average of these data (19.5%) was used as an estimate in the remaining countries. The data upon which these calculations are based on cancer registry data from 1990 to 2004, there may be changes over time due to greater awareness and opportunistic screening programs in place in some countries. National screening has yet to be implemented or is in the process of implementation, thus it is unlikely these stages at diagnosis ratios will be significantly different. This stage at diagnosis does not capture all the patients who progress to Stage IV at a latter date or who have Stage IV recurrence. Results are presented using all three proxies, as each reflects different segments of what may be the real situation.

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Table 7.3
Cost effectiveness analysis of monoclonal antibody based colorectal cancer treatments
(All costs are in 2004, €)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Metastatic 3rd line</td>
<td>Metastatic 3rd line</td>
<td>Metastatic 1st line</td>
<td>Metastatic 2nd line</td>
</tr>
<tr>
<td></td>
<td>(1) Cetuximab, irinotecan (2) Cetuximab monotherapy (3) Active best treatment</td>
<td>(1) Cetuximab, irinotecan (2) Active best treatment</td>
<td>(1) Bevacizumab + irinotecan + 5FU/FA (2) Irinotecan + 5FU/FA; AND (3) Bevacizumab + 5FU/FA (4) 5FU/FA</td>
<td>(1) Cetuximab + irinotecan (2) Active best treatment</td>
</tr>
<tr>
<td>LYG</td>
<td>0.91 (2) 0.80 (3) 0.47</td>
<td>1.7-2.0</td>
<td>1.98 (2) 1.57 (3) 1.59 (4) 1.41</td>
<td>0.79 (2) 0.60</td>
</tr>
<tr>
<td>QALY</td>
<td>0.68 (2) 0.35</td>
<td>-</td>
<td>1.44; (2) 1.13; (3) 1.19; (4) 1.01</td>
<td>0.55 (2) 0.41</td>
</tr>
<tr>
<td>Overall</td>
<td>8.4-8.6 (2) 6.4-6.9 (3) 5.64m</td>
<td>6.4-8.6m</td>
<td>20.3m (2) 15.6m (3) 16.1-21.5m (4) 12.9-13.8m</td>
<td>8.6-9.7m</td>
</tr>
<tr>
<td>Survival</td>
<td>Total Costs</td>
<td>€33,736 (2) €28,293 (3) €5,102</td>
<td>€34,256-45,764</td>
<td>€26,663-34,218</td>
</tr>
</tbody>
</table>

Notes: QALY – quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; LYG – life years gained.
The proportion of colorectal cancers must be separated from the other cancers in whom the drug is prescribed. In the case of cetuximab, these cancers include head and neck (HAN) cancers. The proportion of colorectal cancer to head and neck cancer was calculated from GLOBOCAN 2002 data. The countries with highest incidence in proportion of colorectal cancer to colorectal plus head and neck cancers were Norway (86%), Sweden (84%), UK (82%) and Czech Republic (82%) while the lowest were France (63%) and Spain (65%). The countries with the highest mortality proportion were Norway (88%), Sweden (87%) and UK (85%) while the lowest were Spain (62%) and France (70%). To present an estimation of potential spending per eligible Stage IV colorectal cancer patient, the following was calculated:

\[
\frac{\text{total cetuximab sales}}{\text{proportion CRC to HAN incidence or mortality}} \times \frac{1}{\text{CRC Stage IV diagnosis cases}}
\]

In the case of bevacizumab the majority of sales are for colorectal cancer, as lung cancer and breast cancer approvals did not occur until end 2007, and thus all sales were considered to be a result of colorectal cancer purposes:

\[
\frac{\text{total bevacimab sales}}{\text{CRC incidence or mortality}} \times \frac{1}{\text{CRC Stage IV diagnosis cases}}
\]

Sales data also includes the differences in pricing systems in different countries and if system-wide variables are included in this analysis, some of the variations shown below may be exacerbated.

(a) Cetuximab

Cetuximab is approved as a second- or third-line treatment of metastatic colorectal cancer in 2004 as well as head and neck cancer in 2006, the latter which is accounted for by the aforementioned calculations. The total 2007 sales data are presented in Figure 7.1. The highest sales were found in France, Germany, Spain and Italy, while the lowest in Greece, Poland and Australia.

\[\text{Due to lack for lack of precise prescribing data an equal prescribing split of 50/50 was made between CRC and HAN.}\]
Figure 7.1
Total 2007 cetuximab sales data for Europe and Australia

![Graph showing cetuximab sales per country](image)

**Source:** Authors’ compilations based on IMS sales data, 2007.

Colorectal cancer population was then accounted for in total sales, using the aforementioned proxies for CRC incidence, mortality and Stage IV at diagnosis, accounting for the prescriptions for head and neck cancer (Figure 7.2). The first column represents cetuximab sales per CRC incidence, as incidence is higher than mortality or Stage IV at diagnosis this column represents the least amount of sales per eligible patient. Further adjustment using the proxies of mortality and Stage IV at diagnosis show higher amounts of sales per potential eligible Stage IV metastatic CRC patients.

The highest sales per colorectal cancer incidence were France (€1,172), Spain (€910), Denmark (€898) and Belgium (€846), while the lowest were Poland (€23), Greece (€60) and Australia (€76). The countries with highest sales per mortality were France (€2,981), Spain (€2,613) and Belgium (€1,815), while the lowest were Poland (€47), Greece (€122) and Australia (€221). Correcting colorectal cancer incidence for only Stage IV at diagnosis found highest sales countries were France (€9,509), Spain (€7,304) and Belgium (€5,959), while the lowest were Poland (€177), Australia (€503) and UK (€559).
Adjusting for colorectal cancer incidence, mortality and Stage IV at diagnosis resulted in Germany and Italy disappearing from the top 4 sales places, and being replaced by Belgium and Denmark. This adjustment also resulted in Greece moving up the ranking, due to its relatively low colorectal incidence and mortality. Countries such as Poland and Czech Republic may have poor sales due to overall lower cancer resources and allocation to cancer treatments, regardless of colorectal cancer disease burden. Other countries such as Australia and the UK with relatively high colorectal cancer disease burden have poor sales due to limited colorectal cancer reimbursement decisions.

**(b) Bevacizumab**

As discussed previously, bevacizumab is approved for 4 different solid tumors: metastatic colorectal cancer (**1st** and **2nd** line therapy), **1st** line treatment for advanced non-small cell lung cancer, as well as for metastatic breast cancer and renal cell cancer. As the European approvals for other oncology patients were quite recent (lung cancer **Q3** 2007;
breast cancer Q2 2007), the focus will be to compare countries on 2007 colorectal cancer sales per eligible metastatic patient.

The total bevacizumab sales results for 2007 are presented in Figure 7.3, showing the highest sales in France, Germany and Spain and the lowest in Belgium, Poland and Australia. In fact, Belgium’s sales were so low, it appeared to be the result of a single patient use (€3,107).

**Figure 7.3**

Total 2007 bevacizumab sales data in Europe and Australia

Source: Authors’ compilations based on IMS sales data, 2007.

Bevacizumab sales per colorectal cancer incidence, per mortality and per Stage IV at diagnosis are presented in Figure 7.4. The highest sales per colorectal cancer incidence were Turkey (€3,541), France (€3,285), Netherlands (€2,257) and Spain (€2,253), while the lowest were Belgium (€0), Poland (€46), UK (€188) and Australia (€262). The inclusion of Turkey is likely due to the low incidence of colorectal cancer reported to the cancer registry, while Slovakia also show relatively high sales likely due to low incidence and mortality. The highest sales per colorectal cancer mortality were Spain (€7,225), France (€6,715) and the Netherlands (€4,629), while the lowest were Belgium (€1), Poland (€83), UK (€393) and Australia (€662). When incidence was accounted for the proportion of Stage IV at diagnosis,
the highest sales were Turkey (€18,140), France (€16,890), Netherlands (€12,538) and Spain (€11,856) while the lowest were Belgium (€2), Poland (€234), UK (€893) and Australia (€1,342).

Figure 7.4
Bevacizumab sales data (2007) corrected for colorectal cancer incidence, mortality and Stage IV at diagnosis

What is clearly shown is that a minority of countries appear to be regularly using bevacizumab with their patients in metastatic colorectal cancer. When the amount of colorectal cancer, and specifically stage IV at diagnosis, adjusts total sales data Germany and Italy disappear as front-runners, while Greece increases its ranking due to low relatively lower incidence and mortality. The rank of the UK is lowered due to higher incidence and mortality, while both the UK and Australian sales are low due to severe limitations on reimbursement.

The overall conclusion that seems to be emerging from this data is that countries with high CRC incidence and mortality are making less use of newer monoclonal antibodies, relative to countries having lower CRC incidence and mortality.
7.4. Access to Targeted Treatments

As shown in the preceding section, spending on targeted treatments varies widely across the survey countries. Our survey examined accessibility targeted treatments (Table 7.4) with regards to health insurance influence, health technology assessment, out-of-pocket payments, regional differences and formulary flexibility.

Table 7.4
Access to targeted CRC treatments in surveyed countries
Effect of different factors on access

<table>
<thead>
<tr>
<th>Effect of different factors on access</th>
<th>Health Technology Assessment</th>
<th>Out-of-Pocket Payment</th>
<th>Regional Differences</th>
<th>Formulary Flexibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>N</td>
<td>-</td>
<td>N</td>
<td>N°</td>
</tr>
<tr>
<td>Czech Rep</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Denmark</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Finland</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>France</td>
<td>Y ‡</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Germany</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Greece</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Hungary</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Italy</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Netherlands</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Poland</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N*</td>
</tr>
<tr>
<td>Portugal</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Romania</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Russia</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Slovakia</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y §</td>
</tr>
<tr>
<td>Spain</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Sweden</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Switzerland</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Turkey</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>UK</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Australia</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

Notes: HTA – Health technology assessment required in country for reimbursement or practice approval; OPP – out-of-pocket payment for patients who would like targeted treatments
° dictated by health insurance; * dictated by hospital directors; ‡ HTA but not cost-effectiveness; § innovative oncology drugs covered outside hospital budget

A number of countries discussed the influence of health insurance on the accessibility of targeted treatments. Many countries felt their health insurance had little effect on accessibility of targeted treatments (Denmark, Netherlands, Sweden, UK) and other surveys reported that insurance did have some effect (Czech Republic, Germany, Romania). This is reported in Box 7.2. In particular, specific highlights of the survey included:
Box 7.2

Impact of health insurance on accessibility of targeted treatments

- **Denmark**: ‘expenses are held by hospitals and not by health insurance’; as a consequence, hospitals are responsible for making allocations.
- **Czech Republic**: ‘health insurance is dominant’, implying that health insurance has monopsony power and, therefore, dominates the decision as to what treatments are included in the reimbursement process and what are not.
- **Germany**: ‘All registered cancer drugs can be reimbursed, unless their use is forbidden by the Federal Joint Committee (which has not yet been exercised in oncology drugs). However, physicians can get exceptions from that, if they can prove that the specific patient has a higher morbidity than the average which in oncology regularly will be the case’.
- **Netherlands**: ‘Care is given regardless of health insurance provider; health insurance does not have ability to dictate treatment, or prescriptions’.
- **Romania**: ‘The health insurance budget can cover the costs of new treatments only for a small number of patients, based on strict fulfilment of indications for such treatments’.
- **Russia**: ‘There is no effect: expenditures for cancer are not covered by insurance’.
- **Sweden**: ‘The Swedish patients have the same access to novel (targeted) cancer treatments as they have to other treatments.’
- **UK**: ‘There is no specific effect on novel drugs. Drugs are introduced and funded based on their ability to improve health of the patient within the given context. In the case of colorectal cancer, the use of irinotecan and oxaliplatin are in ready use.’

Health technology assessments are currently in use in a number of countries. Countries discussed the role these assessments play in their process of new treatment approvals. In Australia, once the Pharmaceutical Benefits Advisory Committee (PBAC) has recommended a drug for listing on the PBS, the Pharmaceutical Benefits Pricing Authority (PBPA) negotiates the price with the sponsor company. The PBPA consists of government, industry and consumer representatives. After agreement is reached, the Australian Government considers the advice of both the PBAC and the PBPA and makes a decision on whether the drug will be listed on the PBS. In Denmark, a mini-Health Technology Assessment analysis is normally required for new cancer drugs. The model is designed to give a quick overview to be used as decision tool for the health authorities. In Hungary, due to the EU accession according to the 89/105/EEC transparency Directive, the country has to insure a transparent, accountable coverage process applied by the National Health Insurance Fund (NHIF) for pharmaceuticals based on the strict deadlines and forms required by the Directive. In Portugal, an economic evaluation study is required as part of acceptance of all new pharmaceuticals to hospital and out-patient provision. In Russia, according to the existing normative documents evidence of clinical efficacy and cost-effectiveness should be taken into account when standards of care, formularies and Essential Drug List are made. But there are

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problems with interpretation of evidence because decision makers do not have enough knowledge on the field. That’s why HTA and cost-effectiveness studies are carried out but they are not of high quality and they are not taken into account in practice. Finally, in the UK it would seem that there are two main health technology assessment processes. Nationally, formulary inclusion in all NHS hospitals is dependent on NICE health technology assessments. Locally, hospitals are able to define their formulary based on their own internal health technology assessment process (however, funding for approved cancer drugs through the NICE process should carry mandated funding). Although this is not as formal as the national NICE HTA, it will be based on a wealth of supporting evidence in addition to existing HTA information. However, there is a certain element of professional trust ‘it is assumed that if doctors have requested such treatment there is a valid clinical need.’

Out-of-pocket payments are required in a number of Eastern European countries for targeted treatments, often placing such treatment out of reach for most CRC patients. In Romania, if they have indications for treatment but the local/national cancer expenditure is exceeded at the time given, patients who can afford it may buy the novel medication in question directly from the supplier. In Russia there is no official data about out-of-pocket payments in general and for cancer treatment particularly. It is, however, mentioned in several sources (articles, reports) that patients spend more and more money for needed medicines. In Turkey, when there are restrictions on reimbursement, patients are faced with out-of-pocket payments.

A number of countries indicate regional differences in their access to targeted treatments (Box 7.3). In some cases this is due to regional control over introduction and reimbursement (Italy, UK, Spain), while in others this is due to specialisation of services (Germany, Hungary) or regional resource constraints (Russia).
Box 7.3
Regional differences in access to targeted treatments

- **Denmark**: ‘There might be minor differences between the regions but this is not considered to have impacted mortality rates;’
- **Germany**: ‘theoretically not, but it can be assumed due to inequalities in specialty care institutions might influence access to novel treatments;’
- **Hungary**: ‘According to Hungarian regulation there cannot be any differences in access to novel cancer drugs. However, in real life we can see some differences. People living in large cities or close to medical schools have greater chance to get access to novel drugs;’
- **Italy**: ‘these are introduced by the State but then each region can decide on the timing of such an introduction;’
- **Russia**: ‘we do not know for certain, but most probable there are regional differences in access to (targeted) treatments;’
- **UK**: ‘There are differences in access to novel drugs, but not specific to novel drugs only. The introduction of drugs is generally variable due to the region- specific role of commissioners.’

Hospitals may or may not have flexibility in their formularies to include targeted treatments (Table 7.4). The inclusion of targeted drugs depends to a large extent on hospital budgets and who is responsible for paying. In some cases, the hospital shares such cost with other health departments (The Netherlands), or is solely responsible for the drug costs (UK). In many cases, these novel treatments are beyond the hospital budget and thus have limited inclusion, particularly in Eastern European countries. Box 7.4 summarises the key factors determining the inclusion of targeted treatments into hospital formularies.

Box 7.4
Factors determining the inclusion of targeted treatments in hospital formularies

- **Australia**: ‘inclusion depends on the hospital, that controls the budget, whether there is reimbursement, Access Programs, PBS,’ ‘PBS is decided by the government, except in Western Australia and private hospitals. Access Programs are run by companies – and are generally accepted by all centers. Reimbursement can be decided locally, but this is rare under special access schemes run within a state’
- **Denmark**: ‘Standard regimes are normally decided at the local level while decisions about treatment with the new drugs are decided at national level.’
- **France**: ‘Doctors can use novel treatments cancer as long as these last have a market authorisation or a temporary authorisation for use (ATU) for the case of clinical situation that doctors have to treat or as long as doctors follow référentiels de bon usage (RBU) (good clinical practice guidelines);’
- **Germany**: ‘drug costs are included in the DRG payment, which can be adapted when new technologies are introduced’
- **Hungary**: ‘The list of reimbursed pharmaceuticals is determined at central level, thus hospitals are not allowed to broaden the list of reimbursed drugs. Hospitals have no influence on pricing and reimbursement, they can use drugs accepted by the Technology Appraisal Committee’
Netherlands: ‘although hospitals could include different treatments in their formularies, they choose not to compete with each other in this aspect believing it is unethical (and likely protested against by strong patient groups). Many of these new treatments fall under "dure geneesmiddelen" (expensive drugs) - hospitals are compensated for 80% of these costs, with the remainder coming from their regular budget;’

Russia: ‘The hospitals have to provide drugs from the Essential Drug List for all patients; they can include more drugs into the formulary but they cannot decrease the list. In practice not all essential drugs are available at all hospitals.

Spain: ‘Novel treatments are incorporated without (significant) delay, but may be subject to prescribing control and only senior specialists may have authorisation to prescribe these;’

Turkey: ‘Drugs can only be used for the indication registered by the Ministry of Health. In cases of demands for using such drugs outside the scope of licensed indications, the doctor has to submit a form to the MoH with detailed information about the patient, indications, consent of the patient, prognosis etc. However, as this poses legal responsibilities on the doctor, in practice, doctors are reluctant to use drugs out of indication.

UK: ‘Drugs may be implemented before or without NICE approval. Doctors have to submit a form to a committee in which the cost effectiveness and the benefit are considered by the hospital trust, however, the hospital not the system has to fund the treatment’

7.5. Pharmaceutical Treatment Guidelines

All treatment guidelines include discussion of pharmaceutical treatments. Each country has separate guidelines for adjuvant colorectal cancer treatment and metastatic colorectal cancer treatment. These guidelines all offer strength of evidence upon which their guidance is based (Table 7.5-7.6), although there are differences between countries in their actual guidance.

The publication date of treatment guidelines ranges from 1996 (Czech Republic) to 2008 (Netherlands). As treatments can change quite rapidly with newer and advanced treatments entering the market, timely updating of colorectal cancer guidelines is important. The Société Nationale Française de Gastroenterologie (SNFGE) guidelines are revisited yearly, with changes made to the online document noting the date of revision to the appropriate section. The European Society for Medical Oncology (ESMO) guidelines appear to be revisited every 2 to 4 years, as previous guidelines were published in 2001 and 2005.

Few countries state preferences in regimens (ESMO, France, Netherlands). In adjuvant treatment, only France recommends which therapies are 1st versus 2nd line. In metastatic treatment, all countries except for the Netherlands explicitly state 1st line treatment, however, 2nd line or 3rd line treatments are given in France, Germany, UK and Australia.

In adjuvant colorectal cancer treatment guidelines, all countries give guidance on 5FU/LV as a historically standard treatment, as well as for capecitabine for oral treatment (Table 7.5). Fewer discuss or give guidance on UFT as additional oral treatment. The
FOLFOX regimen is accepted by all countries as treatment with improved outcomes, except for in the UK where it is accepted but its line of treatment unclear. Interestingly, a few countries give specifics on some or all types of regimens (Belgium, France, Germany, Netherlands), such as Mayo infusion for 5FU/LV or FOLFOX 4, while others give no specific details (ESMO, UK). Australia is particularly poor in its guidance, discussing many options at length but limiting actual recommendations.

It appears all countries agree that high risk Stage II patients qualify for adjuvant treatment, although the definition of high risk varies between countries. ESMO guidelines are quite explicit, while other countries do not discuss number of lymph nodes examined (Belgium, Germany, Netherlands, UK, Australia), poor differentiation (Germany, UK) or vascular invasion (Germany). The Netherlands gives no criteria at all on the definition of high risk Stage II patients.

In metastatic treatment guidelines, France appears to have two sets of guidelines, one from the SNFGE and the other from the Standards, Options et Recommendations (SOR), the latter more concerned with metastatic and palliative treatment (Table 7.6). The two do appear to agree with each other for the most part, although the SOR guidelines have more liberal pharmaceutical treatment qualifiers and offer more options for 2nd line treatments.

The 5FU/LV treatment in the metastatic setting appears to be standard 1st line treatment across all countries, with infusion or oral preferred over bolus. Likewise, FOLFOX and FOLFIRI also appear as 1st line treatments, except for Australia, where FOLFOX is discussed but no guidance given and FOLFIRI is deemed 2nd line according to the guidelines. No guidelines state preference of one cytotoxic agent over the other.

Targeted treatments in metastatic colorectal cancer are discussed but given no explicit guidance from ESMO (Table 7.6). Cetuximab in the ESMO guidelines is ‘active in patients with irinotecan-refractory metastatic colorectal cancer’ and is to 2nd line in France, Germany and the UK, but not discussed in Belgium and the Netherlands. Bevacizumab in the ESMO guidance states ‘increases the survival and progression-free survival in 1st line treatment…’ and is 1st line treatment in France and the Netherlands, while not approved in the UK due to cost and only discussed guidelines from Germany and Australia.

There are a number of countries without guidelines (Greece, Poland, Romania, Russia, Slovakia, Spain and Turkey) and they frequently rely on other countries’ guidelines reported by our survey respondents (Table 7.5-7.6).
<table>
<thead>
<tr>
<th>Country</th>
<th>Guidelines Details</th>
<th>5FU/LV Details</th>
<th>Capecitabine Details</th>
<th>UFT Details</th>
<th>FOLFOX Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO: colon cancer (2007)</td>
<td>Yes</td>
<td>Stages T1-4, N1-2, M0, or high risk node-negative Stage II T4</td>
<td>Standard</td>
<td>‘at least as effective and less toxic as bolus 5FU/LV</td>
<td>NNG</td>
</tr>
<tr>
<td>Belgium153</td>
<td>Yes</td>
<td>Stage III, high risk Stage II</td>
<td>Yes</td>
<td>Yes</td>
<td>NNG</td>
</tr>
<tr>
<td>Czech Rep (1996)</td>
<td>Yes</td>
<td>Translation</td>
<td>Yes</td>
<td>No details on other guidelines used</td>
<td></td>
</tr>
<tr>
<td>Denmark (2005)</td>
<td>Yes</td>
<td>Translation</td>
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<td>Yes: 2nd choice to FOLFOX</td>
<td>Yes: 2nd choice to FOLFOX</td>
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<tr>
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<td>Yes</td>
<td>Stage III, high risk Stage II</td>
<td>Yes: 2nd choice to FOLFOX</td>
<td>Yes: 2nd choice to FOLFOX</td>
<td>Yes: 2nd choice to FOLFOX</td>
</tr>
<tr>
<td>France (SNFGE 2007)</td>
<td>Yes</td>
<td>Stage III, high risk Stage II</td>
<td>Yes: 2nd choice to FOLFOX</td>
<td>Yes: 2nd choice to FOLFOX</td>
<td>Yes: 2nd choice to FOLFOX</td>
</tr>
<tr>
<td>Germany154</td>
<td>Yes</td>
<td>Stage III, high risk Stage II</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: &gt; survival over 5FU/LV</td>
</tr>
<tr>
<td>Greece</td>
<td>No</td>
<td>Based on ESMO, NCCN guidelines</td>
<td>Yes</td>
<td>Yes: &gt; survival over 5FU/LV</td>
<td>Yes: &gt; survival 5FU/LV; Stage III only</td>
</tr>
<tr>
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<td>?</td>
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<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>Translation</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes</td>
<td>Stage III, high risk Stage II</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
</tr>
<tr>
<td>Poland</td>
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<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
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<tr>
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<td>No details on other guidelines used</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
</tr>
<tr>
<td>Romania</td>
<td>No</td>
<td>Based on ESMO guidelines</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
</tr>
<tr>
<td>Russia</td>
<td>?</td>
<td>No details on other guidelines used</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
</tr>
<tr>
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<td>No</td>
<td>No details on other guidelines used</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
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<td>No</td>
<td>No details on other guidelines used</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
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<td>Sweden (2007)</td>
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<td>Yes</td>
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<td>Switzerland</td>
<td>Yes</td>
<td>Translation</td>
<td>Yes</td>
<td>Yes: &gt; survival, &lt; toxicity than 5FU/LV</td>
<td>Yes: similar survival 5FU/LV</td>
</tr>
<tr>
<td>Turkey</td>
<td>No</td>
<td>Dukes Stage C, high risk Stage B</td>
<td>Yes</td>
<td>Yes: 1st line2006</td>
<td>Yes: 1st line2003</td>
</tr>
<tr>
<td>UK NICE 2003-7</td>
<td>Yes</td>
<td>Dukes Stage C, high risk Stage B</td>
<td>Yes</td>
<td>Yes: 1st line2006</td>
<td>Yes: 1st line2003</td>
</tr>
<tr>
<td>Australia155</td>
<td>Yes</td>
<td>Stage III, perhaps high risk Stage II</td>
<td>DNG</td>
<td>DNG</td>
<td>DNG</td>
</tr>
</tbody>
</table>

**Notes:** DNG: discussed, no guideline given; NR: not recommended; NNG: not discussed, no guideline given; Y=Year
* high risk only § metastatic colorectal cancer
[-] refers to strength of evidence, where supplied, based on internal guidelines

**Source:** LSE CRC Survey 2008.

153 College of Oncology, 2006.
154 Deutsche Krebsgesellschaft, 2005.
155 Cancer Council Australia, 2005.
### Table 7.6
**Country guidelines for pharmaceutical treatments in metastatic colorectal cancer**

<table>
<thead>
<tr>
<th>GL Details</th>
<th>5FU/LV</th>
<th>FOLFOX</th>
<th>FOLFIRI</th>
<th>Cetuximab</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Colorectal Metastases Group 2006</td>
<td>Yes</td>
<td>Role: Preoperative neoadjuvant in unresectable to make resectable OR neoadjuvant in resectable to decrease recurrence</td>
<td>DNG</td>
<td>DNG</td>
<td>DNG</td>
</tr>
<tr>
<td>ESMO: advanced colorectal cancer 2007</td>
<td>Yes</td>
<td>1st line palliative (infusion &gt; bolus); oral</td>
<td>&gt; survival than 5FU/LV</td>
<td>&gt; survival than 5FU/LV</td>
<td>Active in irinotecan cancer</td>
</tr>
<tr>
<td>Belgium College of Oncology 2006</td>
<td>Yes</td>
<td>Surgery primary + metastatic tumour; or Surgery primary then metastatic OR chemotherapy then metastatic surgery</td>
<td>1st line</td>
<td>1st line</td>
<td>1st line</td>
</tr>
<tr>
<td>Czech Rep 1996</td>
<td>Yes</td>
<td>Translation</td>
<td>1st line: LV5FU2, oral</td>
<td>1st line</td>
<td>1st line</td>
</tr>
<tr>
<td>Denmark 2005</td>
<td>Yes</td>
<td>Translation</td>
<td>Non-resectable metastatic: in good state; OR +75y without comorbidities and independent OR 1-2 comorbidities</td>
<td>1st line: LV5FU2; Oral for patients refusing IV oxaliplatin mono</td>
<td>1st line, 2nd line: irinotecan mono</td>
</tr>
<tr>
<td>Finland 2006</td>
<td>Yes</td>
<td>Translation</td>
<td>Limited resectable: reassess after 4-6 chemotherapy; Non-resectable: patient in good state</td>
<td>1st line: 5FU/LV, oral mono</td>
<td>1st; 2nd line: FOLFIRI, irinotecan mono</td>
</tr>
<tr>
<td>France SNFCCG 2007</td>
<td>Yes</td>
<td>LV5FU2, oral</td>
<td>1st line</td>
<td>1st line</td>
<td>2nd line: with FOLFIRI</td>
</tr>
<tr>
<td>France FNCLCC/SOR 2003-5</td>
<td>Yes</td>
<td>1st line: LV5FU2; Oral for patients refusing IV oxaliplatin mono</td>
<td>1st line, 2nd line</td>
<td>1st line, 2nd line</td>
<td>NNG</td>
</tr>
<tr>
<td>Germany Deutsche Krebsgesellschaft 2005</td>
<td>Yes</td>
<td>Translation</td>
<td>1st line: 5FU/LV, oral mono</td>
<td>1st; 2nd line: FOLFIRI, irinotecan mono</td>
<td>Yes: infusion, oral</td>
</tr>
<tr>
<td>Greece</td>
<td>No</td>
<td>?</td>
<td>Based on ESMO, NCCN guidelines</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Hungary</td>
<td>Yes</td>
<td>Translation</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Italy AIO, 2004</td>
<td>Yes</td>
<td>Translation</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Netherlands VIKC 2006-8</td>
<td>Yes</td>
<td>Chemotherapy improves survival</td>
<td>Yes: infusion, oral</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Poland</td>
<td>No</td>
<td>?</td>
<td>No details on other guidelines used</td>
<td>?</td>
<td>?</td>
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<td>Portugal</td>
<td>Yes</td>
<td>Translation</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Romania</td>
<td>No</td>
<td>?</td>
<td>Based on ESMO guidelines</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Russia</td>
<td>No</td>
<td>?</td>
<td>?</td>
<td>?</td>
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<td>GL</td>
<td>Details</td>
<td>5FU/LV</td>
<td>FOLFOX</td>
<td>FOLFIRI</td>
<td>Cetuximab</td>
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<tr>
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<td>-----------</td>
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<tr>
<td>Slovakia</td>
<td>No</td>
<td>No details on other guidelines used</td>
<td></td>
<td></td>
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<tr>
<td>Spain</td>
<td>No</td>
<td>No details on other guidelines used</td>
<td></td>
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<tr>
<td>Sweden</td>
<td>Yes</td>
<td>Translation</td>
<td></td>
<td></td>
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<td>Switzerland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>No</td>
<td>Based on NCCN, ASCO, ESMO guidelines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>2007&lt;br&gt;NICE&lt;br&gt;2003-7</td>
<td>Yes&lt;br&gt;Chemotherapy early &gt; survival; Pre-operative chemotherapy &gt; chance of resection</td>
<td>Yes: Infusion or oral</td>
<td>1st line</td>
<td>1st line; 2nd line irinotecan alone</td>
</tr>
<tr>
<td>Australia</td>
<td>2005&lt;br&gt;Cancer Council Australia, 2005</td>
<td>Optimal timing in asymptomatic patients unclear; Adjuvant given post-resection liver metastases</td>
<td>1st line: infusion &gt; bolus), oral</td>
<td>DNG</td>
<td>2nd line</td>
</tr>
</tbody>
</table>

**Notes:** DNG: discussed, no guideline given; NR: not recommended; NNG: not discussed, no guideline given; Y=Year  
* currently under appraisal  
[-] refers to strength of evidence, where supplied, based on internal guidelines  
**Source:** LSE CRC Survey 2008.
7.6. Pharmaceutical Performance Indicator and Implications for Patients

Performance indicators were created to give an overview of country performance on access and availability to pharmaceutical treatments for CRC.

The following indicators were chosen as positive indicators:

- Publication of cost-effectiveness analyses
- Sales over €4,000 for cetuximab and €5,000 for bevacizumab, reflecting an estimate of over 25% of Stage IV eligible patients receiving targeted biological treatments (assuming €16,500 drug costs/patient for cetuximab, and €21,000 1st line acquisition costs for bevacizumab)\(^{156}\)
- Formal use of health technology assessment in drug reimbursement decisions
- Use of additional criteria in reimbursement decision-making process, in conjunction with or in lieu of cost-effectiveness analysis
- Pharmaceutical guidelines for the treatment of CRC in the adjuvant and metastatic settings
- Formulary flexibility to allow the use of targeted treatments

The following indicators were chosen as negative indicators:

- Un-official out-of-pocket payments for pharmaceutical treatments
- Regional differences in pharmaceutical treatment access
- Health insurance affecting accessibility to targeted biological treatments
- No pharmaceutical guidelines
- No guidance on more than one adjuvant or metastatic treatment, given approval of drug prior to guidelines

A few countries have no negative indicators for pharmaceutical treatments (France, Netherlands, Sweden), while only Romania has no positive indicators. France has a perfect score which reflects its completely open door pharmaceutical policies. Higher negative scores are found in countries with greater financial limitations; however, Germany also has a high negative score relating to regional differences in targeted biological access and poor pharmaceutical guidelines although it does have a net positive performance.

\(^{156}\) Starling et al, 2007; Tappenden et al, 2007
This chapter has highlighted some of the challenges countries face in terms of pharmaceutical treatments for CRC. Patients and their organisations are often very vocal about access to and availability of new medicines for their condition. In particular, it is very difficult to explain decisions often based on cost effectiveness thresholds, as they would perceive these as having total disregard to the value of human life. Beyond that, regional disparities in access to medicines raise significant concerns, as does the timeliness of introducing life-saving therapies and their subsequent uptake by health systems and prescribing clinicians.

7.7. Conclusions

There appear to be wide variations within Europe and Australia around pharmaceutical treatments for colorectal cancer. Access to appropriate chemotherapy for CRC is not universal, as reimbursement decisions and available budgets differ substantially between countries. Sales data of targeted biological treatments reflect this accessibility, as well as reimbursement decisions and guideline recommendations. Cost-effectiveness analyses
are limited to metastatic pharmaceutical treatments, which account for less than a quarter of the colorectal cancer population.

Only a few countries produce peer-reviewed published cost-effectiveness analyses (UK, France) despite numerous countries stating they use health technology assessments in making reimbursement decisions. Very few actually compare competing treatments for similar situations. Similarly, very few use quality adjusted life years reflecting effectiveness, patients are largely ignored in these analysis with the focus on metastatic CRC. Both oxaliplatin and bevacizumab are also under-represented in cost-effectiveness analyses.

Access to treatment, particularly targeted biological therapies, is not standard in Europe and Australia. Previous chapters discussed regional and group variations, which include pharmaceutical treatments. It appears that there are also variations between hospitals in some countries, particularly when budgetary decisions are made locally. In some countries a separate national budget for expensive drugs relieves the pressure from hospitals and allows greater access to novel treatments. Still, certain countries have un-official out-of-pocket payments for targeted biological treatments, while other countries have budgets so limited that these treatments are simply not available.

Spending on targeted biological treatments is very interesting. As total sales data does not account for the number of patients who might be prescribed biological therapy, the figures were adjusted for incidence, stage IV at diagnosis, and mortality, the latter two most likely to reflect the actual number of eligible patients. The results show that by making this adjustment, countries who may have very high or very low total sales (ie Germany, Greece), slip or climb in the ranking due to the actual burden of colorectal cancer in the country.

There are a few countries of particular note with regards to sales. Turkey appears to have particularly low incidence and mortality from colorectal cancer, perhaps reflecting poor registration, with high bevacizumab sales regardless of adjustment, a reflection of the wealthier portion of the population having access to this treatment. Another country of note is Slovakia, which has higher unadjusted bevacizumab sales than many other richer European countries in addition to its relatively higher incidence and mortality. Along with regional variations in access, innovative drugs being covered outside hospital budgets, and a relatively small total population.

There also appears to be differences between countries with which targeted treatments are supported. For example, Belgium has almost no bevacizumab sales, yet reports one of the higher unadjusted cetuximab sales. For Turkey and Slovakia this is exactly the opposite. Other countries rank equally low, reflecting overall restricted reimbursement decisions.
(Denmark, Sweden, UK, Australia). The question for these countries is whether their lack of support for innovative treatment will result in poor technology diffusion in relation to other countries, and in the long-run, overall differences in colorectal cancer survival and mortality (particularly when screening activities are not supported, such as Denmark and Sweden).

Treatment guidelines also reflect reimbursement and approval decisions; unfortunately not all countries have native guidelines, an additional barrier to evidence-based practice, and forcing physicians to become regional or historic decision makers. Pharmaceutical guidelines from other countries may be adapted; however, as reimbursement and budgetary constraints may be significantly different, this may not be appropriate. For countries with guidelines there are differences between countries with regards to their recommendations, with a number of countries discussing but not recommending treatments, resulting in regional variations in care.

In Australia, no firm guidance is given on adjuvant or metastatic CRC treatments despite lengthy discussion. There appears to be no regional variations in access to targeted treatment, probably a reflection of overall poor access due to reimbursement decisions and low sales, despite known regional variations in overall cancer diagnosis and treatment.

In conclusion, pharmaceutical treatment access and availability is not standard throughout Europe and Australia. This reflects differences in the weight of cost-effectiveness analyses in reimbursement decisions, as well as the overall country wealth, politics, and colorectal cancer care budget. The use of targeted biological treatments in particular appears to have huge variations between countries, often regardless of overall country wealth, resulting in poor support for innovative treatments and in poor survival statistics, as well as sending a message that colorectal cancer patients count less than other similar patients with metastatic cancer.
References


Deutsche Krebsgesellschaft EV. Leitlinienkonferenz “Kolorectales Karzinom”. Informationalszentrum fur Standards in der Oncologie. 2004


Chemotherapy Guidelines


Deutsche Krebsgesellschaft EV. Leitlinienkonferenz “Kolorectales Karzinom”. Informationalszentrum fur Standards in der Oncologie. 2004


National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. V.1.2008

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. V.1.2008


NICE. Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. 2005.


NICE. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. 2007.


Chapter 8
Colorectal Cancer Follow-up and Surveillance

8.1. Introduction

There are two groups of patients to whom surveillance or follow-up applies: those with adenomas at colonoscopy who have undergone polypectomy (removal of pre-cancerous adenomas) and those with colorectal cancer who have undergone treatment with curative intent. In the former group the goal of surveillance is early diagnosis of primary CRC, while for the latter the goal is to diagnose recurrences early. In both cases, early detection results in better outcomes.

Proper management of colorectal cancer surveillance is important in many different ways. First, surveillance at regular timely intervals may prevent adenomas from developing into carcinomas\(^{157}\), and detect recurrences at early stages in post-colorectal cancer patients, thus increasing the likelihood for curative treatment.\(^{158}\) Second, proper surveillance will ensure that patients are not subject to unnecessary testing. Third, surveillance accounts for significant proportion of colonoscopy practice, and optimal management ensures that this pressured service is not over-burdened.

This chapter highlights similarities and differences between the study countries for both adenoma and post-colorectal cancer surveillance with regards to (a) the effectiveness and cost-effectiveness of follow up and surveillance methods and (b) the existence of follow up and surveillance guidelines in participating countries.

8.2. Adenomas and Post-Polypectomy Surveillance

The removal of adenomas via polypectomy using a colonoscopy may prevent the development of colorectal cancer, however, the precise development and timing of adenoma transformation into neoplasms is not well understood. It appears there may be different types of adenomas, some more likely to develop into neoplasms than others. The serrated adenoma grows more quickly and is now known to be responsible for a portion of colorectal cancer cases.\(^{159}\) Other adenomas may be less aggressive but more plentiful, thus increasing the risk

\(^{158}\) Guyot et al, 2005.
\(^{159}\) Lazarus et al, 2005.
of CRC developing. On the whole however, many of the steps from adenoma to frank CRC are not yet fully mapped.160

By removing these adenomas it is estimated that 90% of colorectal cancers could be prevented,161 however colorectal cancer risk still remains higher in adenoma patients than in the general population warranting on-going surveillance.162 There are a number of risk factors that increase the likelihood of finding advanced adenomas at follow-up surveillance colonoscopy: (a) having greater than 3 adenomas, (b) having large adenomas, (c) having villous adenomas, and (d) having high grade dysplasia at initial colonoscopy.163

8.3. Effectiveness and Cost-Effectiveness of Surveillance Post-Polypectomy

There have been no cost-effectiveness analyses of surveillance methods post-polypectomy. The sole method of post-polypectomy surveillance is colonoscopy and no other methods have been explored for surveillance purposes. The flexible sigmoidoscopy or CT colonography may also be candidates for surveillance; however no research has been performed on variations of surveillance methodology except for the double-contrast barium enema (found to be less effective than colonoscopy). It is estimated that 259-320 surveillance colonoscopies are needed to detect one colorectal cancer case, while 100 colonoscopies are needed to detect one colorectal cancer case in screening an asymptomatic population.164

As shown in the following section, there is also little understanding of timing of colonoscopies in post-polypectomy surveillance. Recent evidence points to an interval length of three to five years,165 although longer extensions such a six to eight or even ten years based on risk factors of patient have not been investigated. Furthermore, less is known about adherence to surveillance protocols. It is estimated that 85% of adenoma patients adhere to colonoscopy – although this percentage decreases significantly over time - while more than 50% of surveillance endoscopies are thought to be performed too early or too late.166

A decision analysis model has been put forward evaluating surveillance of two classifications of post-polypectomy patients based on risk analysis: one static by only initially classifying patients into risk groups, and the other dynamic by classifying patients depending on their last surveillance colonoscopy findings. In comparison with no surveillance, any

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surveillance method gained 10.2 years, while better outcomes were found in patients following dynamic surveillance, although 30% more colonoscopies were required. Adherence and colonoscopy complications were both significant factors in sensitivity analysis.\textsuperscript{167}

It is unfortunate that no cost-effectiveness analyses have been performed in surveillance of post-polypectomy patients, as this would enhance our understanding of both costs and benefits and would further inform the decision-making process. Published evidence suggests that surveillance colonoscopies accounted for 18\% of practice in France,\textsuperscript{168} 19\% in Portugal,\textsuperscript{169} and 25\% in Italy,\textsuperscript{170} thus it is responsible for a significant portion of endoscopy practice and cost. Through cost-effectiveness analysis the above limitations could be explored with regards to surveillance methods, timing, adherence, additional risk factors and variations in practice, without having to perform further clinical trials.

**8.4. Guidelines for Surveillance Post-Polypectomy**

There are fewer country guidelines for surveillance post-polypectomy than there are for colorectal cancer treatment and surveillance guidelines (Table 8.1). In addition, the organisations responsible for this segment of care are more diverse than for colorectal cancer. Accessibility appears to be an issue, and there are a number of differences between countries.

The location in which post-polypectomy surveillance guidelines are found differs between countries. The guidelines may be found with colorectal cancer guidelines (Australia, Italy), with gastroenterology cancer guidelines (Germany, France), with medical journal publications (UK), or with central government health departments (The Netherlands). The accessibility of the guidelines is similar to that of colorectal cancer guidelines, all documents are available online except for the UK which needs a subscription, however, due to the diversity of organisations responsible for these guidelines they are more difficult to find.

Strength of evidence for recommendations is found in all surveillance guidelines. Most countries have poorer strength of evidence guidance, reflecting the little research performed in this field. All documents are written in their native tongue, none are translated into English. As our survey found so few countries with post-polypectomy guidelines, accessibility issues mean that practice variations are likely to be greatest in countries without guidelines.

\textsuperscript{167} Becker et al, 2007.  
\textsuperscript{168} Canard et al, 2003.  
\textsuperscript{169} Cremers et al, 2006.  
\textsuperscript{170} Grassini et al, 2007.
There are a number of differences between countries within the guidelines (Table 8.1). Only two countries state age of discontinuation (The Netherlands, UK). The UK guidelines appear very dynamic with patients moving in between risk and surveillance categories depending on the last colonoscopy finding. It appears that surveillance colonoscopy at year 3 post-polypectomy is the “optimal” standard of care, although for lower risk patients in the Netherlands and the UK surveillance colonoscopy is extended to 6 and 5 years respectively. The definition of high risk also appears to differ between countries: France considers (a) the type, (b) number and (c) size of polyps; Germany examines the type of polyps; The Netherlands take into consideration the number of polyps; the UK considers both the number and size of polyps; and Australia examines the size and type of polyps.

The use of aspirin in chemoprevention of colorectal cancer warrants brief discussion in conjunction with surveillance methods. Aspirin may slow the development of colorectal adenomas in the general population, although at higher doses and longer duration as required for cardiovascular disease benefits. They may also benefit patients diagnosed with colorectal cancer and adenomas, although dosage and treatment length vary between studies. More research is needed to explore this avenue, particularly as lengthy high dosages can be risky and as such no guidelines have explicitly supported their use in adenoma patients.

### Table 8.1

<table>
<thead>
<tr>
<th>Country</th>
<th>Guideline</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Czech Rep</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Yes</td>
<td>Y3, then Y3 if positive findings (&gt;1 cm, villous, &gt;2 polyps) OR q5Y if negative findings</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>Y3, then Y3 if positive findings (metachronous adenomas) OR Y5 if negative findings [A, 1b]</td>
</tr>
<tr>
<td>Greece</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>If multiple adenomas, then Y1, then Y3 then every 5y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If single adenoma, then Y3 then every 5y</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes</td>
<td>Y3 if positive findings (≥3 polyps) OR Y6 if &lt;3 polyps [3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stop: after 3 negative colonoscopies OR after 65y if cumulative testing shows only 1 adenoma OR after 75 if cumulative testing shows only 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>Guidelines</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland</td>
<td>No</td>
<td>Double contrast barium enema if COL not possible [4]</td>
</tr>
<tr>
<td>Portugal</td>
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<td>Romania</td>
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<tr>
<td>Turkey</td>
<td>No</td>
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</tbody>
</table>
| UK [177]       | Yes        | (A) If baseline low risk (1-2 <1cm adenomas) then no surveillance or at Y5: if negative then stop, if low risk then (A), if intermediate then (B), if high then (C)  
                 |            | (B) If baseline intermediate risk (3-4 <1cm or 1 ≥1 cm adenomas) then Y3: if negative then (B), if 2 consecutive negative then (B), if low/intermediate then (B), if high then (C)  
                 |            | (C) If baseline high risk (≥5 <1cm or ≥2 of ≥1cm) then at Y1: if negative/low/intermediate then (B), if high then (C) [B]  
                 |            | Stop after age 75 unless patient willing. [C]  
| Australia [178]| Yes        | Colonoscopy surveillance as followed: Y1 in patients with incomplete or inadequate colonoscopy (ie multiple adenomas) [II]; Y3 in patients with adenomas >1cm, high-grade dysplasia, villous changes, 60+ years of age, or with a 1st degree relative with colorectal cancer [II]; Y4-6 in patients without above risk factors [III-3] |

Y – year after polypectomy  M = month after polypectomy  
[-] indicates the strength of evidence upon which these guidelines were given in the document  
Source: LSE CRC Survey 2008 and various published sources.

### 8.5. Colorectal Cancer Recurrence

**Epidemiology of Colorectal Cancer Recurrence**

Following treatment with curative intent in colorectal patients, there remains a risk that approximately 30% may develop either colorectal or metachronous recurrence, regardless of initial staging. Until 20 years ago most of these patients would not have received additional treatment with curative intent, however 25% now receive curative resection with distant metastases and 60% curative resection with local recurrence. Survival of patients with recurrent disease is approximately 35-50% at 1 year and 5-15% at 5 years, with lower survival belonging to those with distant metastases. Survival appears to be longer in younger patients and those undergoing curative resection.

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177 Atkin et al, 2002.  
178 Cancer Council Australia, 2005.  
Recurrences are difficult to identify and monitor across countries. Very few cancer registries collect details on which patients have recurrences despite the high recurrence risk in colorectal cancer. Furthermore, even fewer registries collect data on where recurrence occurred (site of primary tumour, metachronous tumours), whether treatment of curative intent was given, or details of treatment regimen. Many registries do not collect survival data past five years, when patients are statistically considered as “cured”. Hospital-based data cannot apply as little records are kept on “cured” patients. As a reflection of the published literature, France appears to be one of the few countries interested in cancer recurrence. This does not only appear to be a problem for colorectal cancer, but all cancers. As a significant number of patients develop colorectal cancer recurrences, it is important to have better data collection methods.

Overall, the active surveillance of cancer patients is not standard throughout Europe (Table 8.2). In many countries, post-treatment surveillance is collected only by specific regions, however this appears more complete in France, Italy, and Switzerland. In some countries surveillance data collection is nationally performed (Czech Republic, Denmark, Finland, Slovakia, Sweden). As recurrence risk in colorectal cancer is high, this surveillance activity is very important to prioritize resources for colorectal cancer surveillance.

Table 8.2

| Active surveillance of live cases by cancer registries with sufficient standards of quality |
|---|---|
| **Cancer Registry with sufficient quality** | **Surveillance** |
| Belgium (Flanders) * | Y |
| Czech Republic | Y |
| Denmark | Y |
| Finland | Y |
| France (Bas-Rhin, Calvados, Doubs, Haut-Rhin, Loire Atlantique, Manche, Somme, Tarn, Vendée) ° | Y |
| Germany (Hamburg, Munich) ∞ | Y |
| Italy (Biella Province, Brescia, Ferrara, Florence and Prato, Genoa, Milan, Modena, Naples, Parma, Ragusa, Reggio Emilia, Romagna, Salerno, Sassari, Sondrio, Syracuse, Torino, Umbria, Varese, Veneto) § | Y |
| Netherlands (Eindhoven, Maastricht) | Y |
| Poland (Cracow) | Y |
| Portugal (Porto, South Regional) | Y |
| Russia (St. Petersburg) | Y |
| Slovak Republic | Y |
| Spain (Basque County, Girona, Granada, Murcia, Navarra, Tarragona, Zaragoza) * | Y |
| Sweden | Y |
| Switzerland (Geneva, Graubünden, Glarus, Neuchatel, St Gall-Appensell, Ticino, Valais, Vaud) | Y |
| Turkey (Antalya, Izmir) | N |
| UK (East England, Oxford, South & Western, Northern Ireland) ~ | |
| Australia (Tasmania, South Australia) ‡ | |

**Notes:**

Insufficient quality: * Antwerp; ° Hérault, Isere; ∞ Brandenburg, Free State Saxony, Mecklenburg-Western Pomerania, Northrhine-Westphalia Münster, Saarland; § Macerata, North-East; ‡ Cielce, Warsaw City; ~
8.6. Surveillance Cost Effectiveness

The definition of what constitutes best surveillance practices in colorectal cancer patients is not empirically based but contains many differences in opinion and practice. Recent meta-analyses found only 8 randomized trials globally which had examined surveillance programmes.\(^{183}\) CRC mortality was significantly less in patients following intensive follow-up, although no difference was found for all cause mortality. Lower mortality was found in patients with regular chest X-rays, colonoscopy and particular regular CEA monitoring. No difference in recurrence was found, however, there were higher asymptomatic recurrence and early recurrence detection by 6 months with intensive follow-up, as a result greater likelihood of curative resection. Due to the method heterogeneity between studies, optimum methodology and timing of surveillance were impossible to identify.\(^{184}\)

Our survey highlights cost-effectiveness models for surveillance of colorectal cancer post-curative treatment. The terms “colorectal cancer”, “surveillance” OR “follow-up”, and “cost effectiveness” with limits of English language were entered into PubMed, and 46 articles were found between 1995 to 2008. A number of articles were related to cost-effectiveness of screening (10) or treatment (4), or were editorials (2), colorectal cancer trials (10), meta-analysis or review (12). The remainder were examined for methodology, only 5 were found to be true cost-effectiveness studies,\(^{185}\) the remainder relating to other economic evaluations (3).

A small number of cost-effectiveness studies in Europe have been published on colorectal cancer surveillance (Table 8.3). Intensive follow-up appears to be more cost-effective than no or standard follow-up,\(^{186}\) although perhaps stratifying patients on their disease stage may be even more cost-effective.\(^{187}\) Unfortunately, the majority of the studies

\(^{185}\) Drummond et al, 2005.
did not specify in detail what constituted standard surveillance\textsuperscript{188} and none addressed adherence to surveillance protocol.

Adherence to surveillance protocols found 28% - 93% adherence for colonoscopy on time, 52% with delayed timing, and 18% who did not undergo surveillance.\textsuperscript{189} These relatively poor figures for adherence highlight the gap in policy and the potential cost implications of non-adherence. Methodologically, these figures also highlight the importance of including this factor in cost-effectiveness models to inform policy decisions.

It is interesting that many chemotherapy cost-effectiveness studies found during their sensitivity analysis that follow-up costs were significant in affecting the results.\textsuperscript{190} Within the surveillance costs themselves, it appears disease stage, length of survival and costs of examination may be significant in affecting cost-effectiveness outcomes.

\textsuperscript{189} Cardella et al, 2008; McFall et al, 2003; Mulder et al, 2007.
\textsuperscript{190} Cassidy et al, 2006; Levy-Piedbois et al, 2000.
Table 8.3
Synopsis of cost-effectiveness analysis in surveillance of colorectal cancer treatment post-treatment with curative intent
(Costs are presented in 2002, €)

<table>
<thead>
<tr>
<th>Country</th>
<th>France</th>
<th>Norway</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Markov</td>
<td>CEA</td>
<td>CEA: ICER</td>
</tr>
<tr>
<td>Perspective</td>
<td>Appears health service</td>
<td>Health service</td>
<td>Health service</td>
</tr>
<tr>
<td>Timeline</td>
<td>7 years</td>
<td>4 years</td>
<td>5 years</td>
</tr>
<tr>
<td>Stage</td>
<td>Stages A, B, C</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Regimen</td>
<td>(1) Standard: CEA q3m 2y then q6m 3y; colonoscopy q3y; CT q4-6m 3y then q1y for 2y; chest radiography q1y (2) Simplified: greater intervals</td>
<td>(1) CEA q3m 4y; colonoscopy year 1 and 4; rectoscopy q3m (LAR, TME); chest Xray q6m; liver ultrasound q6m 2y then q3m 2y (2) no follow-up</td>
<td>(1) Intensive follow-up (2) Standard follow-up</td>
</tr>
<tr>
<td>Life Years Gained</td>
<td>NR</td>
<td>(1) 12y in 2% of patients OR 3y in 10% of patients</td>
<td>(1) 0.73-0.82</td>
</tr>
<tr>
<td>Quality Adjusted Life Years</td>
<td>(1) 5.36 (2) 5.05; Stage A (1) 5.36 (2) 5.48; Stage B (1) 5.36 (2) 5.23; Stage C (1) 5.36 (2) 4.21</td>
<td>(1) 0.83 (2) 0.83</td>
<td>NR</td>
</tr>
<tr>
<td>Total Costs/ patient</td>
<td>(1) €1,591 (2) €558; Stage A (1) €1,340 (2) €317; Stage B (1) €1,900 (2) €739; Stage C (1) €1,631 (2) €632</td>
<td>(1) €3,366 (2) €60 (1996)</td>
<td>(1) €7,411 (2) €3,549</td>
</tr>
<tr>
<td>Sensitivity Analysis</td>
<td>Cancer Stage</td>
<td>Survival of patients after salvage surgery</td>
<td>Surveillance costs</td>
</tr>
<tr>
<td>Incremental Cost Effectiveness Ratio</td>
<td>(1) €3.315/QALY; Stage A (1) €4.965/QALY; Stage B (1) €10,653/QALY; Stage C (1) €1,119/QALY</td>
<td>(1) €16,502-28,054/LYG OR €19,883-33,799/QALY</td>
<td>(1) €4,792-5,298/LYG</td>
</tr>
</tbody>
</table>

Source: LSE CRC Survey 2008, based on Borie et al, 2004 (France); Norum et al, 1997 (Norway); and Renehan et al, 2004 (UK).
Of all recurrent colorectal cancer patients, approximately 25-35% will develop metachronous liver metastases, of which one-third will be eligible for curative resection.\(^{191}\) This risk increases significantly with higher stages at diagnosis; five year survival is improved from all stage of 6% to 29% with recurrences with curative resection.\(^{192}\) Recently a new method of follow-up diagnosis in patients with suspected liver metastases has been developed which appears more sensitive than traditional CT follow-up.\(^{193}\) This new imaging technique called [\(^{18}\)F]2-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) can detect the increased glucose found in malignant cells.

Only two studies were found that examined the cost-effectiveness of introducing this new technology into metachronous liver metastases detection in comparison to traditional CT technology (Table 8.4). Both found that the PET was more cost-effective than CT, likely due to its enhanced detection and staging capabilities. Both authors conjectured that the introduction of FDG PET in liver metastases management could save 2.5-6.1% of patients from unnecessary exploratory surgery, in addition to having greater sensitivity in staging the disease, in comparison to CT.\(^{194}\) By detecting recurrence early and staging disease correctly, the likelihood of curative resection increases.

### Table 8.4

**Results of cost-effectiveness analyses for the use of FDG PET in the diagnosis of liver metastases in recurrent colorectal cancer patients**

<table>
<thead>
<tr>
<th>Country</th>
<th>USA</th>
<th>France</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>CEA: ICER</td>
<td>Decision analysis</td>
</tr>
<tr>
<td>Perspective</td>
<td>Health service</td>
<td>Health service</td>
</tr>
<tr>
<td>Timeline</td>
<td>5 years</td>
<td>Not stated</td>
</tr>
<tr>
<td>Stage</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Regimen</td>
<td>Elevated CEA followed by either: (1) CT (2) CT + FDG PET</td>
<td>Positive abdominal ultrasound followed by: (1) CT (2) CT + FDG PET</td>
</tr>
<tr>
<td>Life Years Gained</td>
<td>(1) 3.5634 (2) 3.5896</td>
<td>(1) 1.88 (2) 1.88</td>
</tr>
<tr>
<td>Quality Adjusted Life Years</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Total Costs/ patient</td>
<td>(1) US$8,354 (2) US$8,783</td>
<td>(1) €19,735 (2) €17,064 (2004)</td>
</tr>
<tr>
<td>Sensitivity Analysis</td>
<td>CT sensitivity, recurrence prevalence, FDG PET costs, life expectancy</td>
<td>Cost of FDG PET</td>
</tr>
<tr>
<td>Incremental Cost Effectiveness Ratio</td>
<td>(2) US$16,437</td>
<td>(2) dominant</td>
</tr>
</tbody>
</table>

Source: LSE CRC Survey 2008, based on Park et al, 2001 (USA); and Lejeune et al, 2005 (France).

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8.7. Surveillance Guidelines Post-Colorectal Cancer Treatment

There are more countries with post-treatment colorectal cancer guidelines than for post-polypectomy (Table 8.5). As with treatment guidelines, there are also a number of countries who do not have surveillance guidance. This is understandable, as surveillance guidelines for all countries are linked to colorectal treatment guidelines, thus if a country does not have its own treatment guidelines it is even more unlikely that they have post-treatment surveillance guidelines. Our survey respondents indicated which treatment guidelines were adopted in such cases, usually ESMO or NCCN guidelines; in the case of surveillance, even fewer were used.

Strength of evidence is given less frequently in surveillance than for treatment, guidelines, and appears to vary between countries (Table 8.5). For example, France gives no strength of evidence for any of surveillance guidelines despite giving its conviction for previous diagnosis and treatment guidance in the same document. Belgium rates all its guidance as level C while others such as ESMO give stronger or weaker strength. This likely reflects poor or limited research supporting recommendations, as seen by strength of evidence.

When present, guidelines varied between countries to an even greater extent than was found with treatment guidelines (Table 8.5). Physical history is not discussed in the ESMO guidelines except for rectal cancer, while it is recommended regularly by a number of countries (Belgium, France, The Netherlands, UK and Australia). The first colonoscopy recommendation after curative treatment appears to range from 6 months (France, Germany) to 1 year (ESMO, Italy) to 3 years (Belgium, UK, Australia) or based on Stage of Disease (Netherlands). Carcinoembryonic antigen (CEA) is recommended by ESMO, discussed but no guidance given in Denmark, the UK and Australia, while timing differs between Belgium, France Germany and the Netherlands.

Imaging by radiographs, ultrasound, PET and CT scan also varies between countries, and guidance is given on all these methods by ESMO. In contrast, a number of countries offer no discussion or guidance on some or all of these methods (Belgium: X-rays, ultrasound; France: CT scan; Netherlands: X-rays, PET; UK: PET), or offer discussion but no guidance (UK, Australia: X-rays, ultrasound). Recto-sigmoidoscopy is recommended in rectal cancer follow-up, however it is only discussed and guided in Germany and Australia.

This heterogeneity in surveillance guidelines reflects the scarcity of research performed on this topic. The outcome of such heterogeneity is potentially poor outcomes for
colorectal cancer patients, potential sub-optimal management of diagnostic resources, and patients placed at undue risk.
Table 8.5
Presence and content of post-colorectal cancer surveillance guidelines in various countries

<table>
<thead>
<tr>
<th>GL</th>
<th>COL</th>
<th>Physical History</th>
<th>CEA</th>
<th>X-rays</th>
<th>Liver Ultrasound</th>
<th>PET</th>
<th>Rectosigmoidoscopy</th>
<th>CT scan</th>
<th>Digital Rectal Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO: colon cancer(^{195})</td>
<td>Yes</td>
<td>Y1, 3 [I, B]</td>
<td>Y0-3 q3-6m; Y4-5 q6-12m if initially high</td>
<td>Y0-5 q1y</td>
<td>Y0-3 q6m; Y4-5 q1y</td>
<td>NNG</td>
<td>N/A</td>
<td>Y0-3 q6m*</td>
<td>NNG</td>
</tr>
<tr>
<td>ESMO: advanced Belgium(^{197})</td>
<td>Yes</td>
<td>Symptom driven visits only [V, D]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESMO: advanced (^{198})</td>
<td>Yes</td>
<td>Y3 then q5y [C]</td>
<td>Y0-3 q3-6m; Y4-5 q6m; Y5+ q1y [C]</td>
<td>Y0-3: q3m [C]</td>
<td>NNG</td>
<td>NNG</td>
<td>Only rising CEA*</td>
<td>NNG</td>
<td>m3 post surgery, Y0-3 q1y* [C]</td>
</tr>
<tr>
<td>Czech Rep, 1996</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark, 2005</td>
<td>Yes</td>
<td>DNG</td>
<td>DNG</td>
<td>DNG</td>
<td>DNG</td>
<td>DNG</td>
<td>DNG</td>
<td>MRI?</td>
<td>NNG</td>
</tr>
<tr>
<td>Finland, 1996</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France(^{199})</td>
<td>Yes</td>
<td>6m post-op; Y2/3, then q5y; If adenoma q3y then q5y; If adenoma q1y(^3)</td>
<td>Y0-3: q3m; Y4-5: q6m</td>
<td>Y0-3 q2-3m; If elevated postT, q3m(^3)</td>
<td>Y0-5 q1y; If pulmonary Y0-3 q6m(^3)</td>
<td>Y0-3: q3-6m; Y3-4: q1y(^3)</td>
<td>Only if suspect recurrence</td>
<td>NNG</td>
<td>NNG</td>
</tr>
</tbody>
</table>

\(^{195}\) ESMO, 2007a.
\(^{196}\) ESMO, 2007c.
\(^{197}\) ESMO, 2007b.
\(^{198}\) Peeters et al, 2006.
\(^{199}\) SNFGE, 2007.
<table>
<thead>
<tr>
<th>GL</th>
<th>COL</th>
<th>Physical History</th>
<th>CEA</th>
<th>X-rays</th>
<th>Liver Ultrasound</th>
<th>PET</th>
<th>Rectosigmoidoscopy</th>
<th>CT scan</th>
<th>Digital Rectal Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece</td>
<td>No</td>
<td>Based on ESMO, NCCN guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>Yes</td>
<td>Y1, Y3, then q5y Stage I: q6y</td>
<td>?</td>
<td>?</td>
<td>Stage II+: Y0-2 q6m; Y3-5 q1y</td>
<td>?</td>
<td>NNG</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>Y1, Y3, then q5y Stage I: q6y</td>
<td>?</td>
<td>?</td>
<td>Stage II+: Y0-2 q6m; Y3-5 q1y</td>
<td>Y4-5: q6m</td>
<td>NNG</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes</td>
<td>Stage II+: Y2-3; Then q6y if 0-2 polyps of q3y if 2+ polyps</td>
<td>Liver Met: Y0-2 q3m; Y3-5 q6m [2, B]</td>
<td></td>
<td>Stage II+: Y0-1 q6m Y2-5 q1y</td>
<td>?</td>
<td>NNG</td>
<td>?</td>
<td>? Stage II+: only if U/S not complete Liver Met: Y0-2 q3m Y3-5 q6m</td>
</tr>
<tr>
<td>Poland</td>
<td>No</td>
<td>No details on other guidelines used</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>No</td>
<td>Based on ESMO guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>No</td>
<td>No details on other guidelines used</td>
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<tr>
<td>Slovakia</td>
<td>No</td>
<td>No details on other guidelines used</td>
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<tr>
<td>Spain</td>
<td>No</td>
<td>No details on other guidelines used</td>
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<tr>
<td>Sweden</td>
<td>Yes</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>2007</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>No</td>
<td>Based on NCCN, ASCO, ESMO guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>No</td>
<td>Y3 post surgery</td>
<td>Y0-2 monitor</td>
<td>DNG</td>
<td>DNG</td>
<td>DNG</td>
<td>NNG</td>
<td>N/A</td>
<td>6m post surgery</td>
</tr>
<tr>
<td>UK</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

200 Deutsche Krebsgesellschaft, 2005.
<table>
<thead>
<tr>
<th>GL</th>
<th>COL</th>
<th>Physical History</th>
<th>CEA</th>
<th>X-rays</th>
<th>Liver Ultrasound</th>
<th>PET</th>
<th>Rectosigmoidoscopy</th>
<th>CT scan</th>
<th>Digital Rectal Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia&lt;sup&gt;204&lt;/sup&gt;</td>
<td>Yes</td>
<td>Y3 post surgery then q3-5y (q3y 5+ adenomas)</td>
<td>Y0-2 q3-6m; Y3+ q6-12m</td>
<td>Regular</td>
<td>DNG</td>
<td>DNG</td>
<td>DNG</td>
<td>Y0-2 q3-6m; Y3+ q6-12m</td>
<td>Regular</td>
</tr>
</tbody>
</table>

Y: Year post-curative treatment; q: every DNG: discussed, no guideline given; NR: not recommended; NNG: not discussed, no guideline given

* high risk only § metastatic colorectal cancer

8.8. Surveillance Performance Indicator and Implications for Patients

A performance indicator was created for surveillance activities. Positive indicators were chosen that facilitate surveillance, as follows:

- Effectiveness and cost-effectiveness analysis for post-curative treatment and for post-polypectomy
- Surveillance guidelines for post-curative treatment and for post-polypectomy
- Cancer registry monitoring of recurrence

Negative indicators were chosen that hinder surveillance activities, as follows:

- No guidelines for post-curative treatment and for post-polypectomy
- Poor quality guidelines: more than one method was not given recommendations

The surveillance performance indicator shows a net negative balance in most countries. Denmark, Germany, Italy, and Sweden have no negative indicators, while Greece, Hungary, Romania, and Turkey have no positive indicators. These scores reflect the scarcity and quality of guidelines, as well as overall interest in surveillance activities including research. As surveillance activities account for a considerable amount of resources, this situation must be improved upon.

Scores were poor for most countries, relating back to the scarcity and quality of guidelines. This in turn reflects the scarcity of available interest. As surveillance activities account for a considerable amount of resources, this status must be resolved.
Patients who undergo treatment for CRC need to be vigilant and aware of surveillance. It is not uncommon that patients have little idea as to what they should do after polypectomy or CRC treatment. Patient organisations admit that their members are very rarely informed about the risks, the need of colonoscopy or any other necessary examinations. This should be taken into consideration and perhaps lead to campaigns aiming at this group of patients.

8.9. Conclusions

It appears there is limited interest in surveillance activities in comparison to other CRC services in Europe and Australia. Sparse research underpins the few recommendations that are presented in the few countries with guidelines. This is unfortunate, as surveillance activities do account for a significant portion of endoscopy services as well as other diagnostic services.

Despite approximately one-third of CRC patients experiencing recurrence, and improved outlook if caught in the early stages, limited interest is placed in surveillance after curative surgery. Research is scarce on surveillance practices with
regards to outcomes, resulting in large variations between countries’ treatment
guidelines and likely large variations in practice. A similar situation is present for
adenoma patients, where again guidance is limited and practice is varied.

Few comments were directed towards post-polypectomy or colorectal cancer
surveillance in the LSE CRC Survey. Only Denmark indicated ‘early detection of
metastases by systematic surveillance’ as an area for improvement in their country.
Poland also indicated ‘national treatment and surveillance guidelines’ as an
improvement area. This lack of focus on surveillance is likely due to prioritisation of
colorectal cancer care. Perhaps most countries feel that other activities, such as
screening and treatment, have priority in attention and resources at this time. This
case is particularly true and just for Eastern European countries, as shown throughout
Chapters 4 to 6. On the other hand, as a number of countries indicate issues with their
cancer registries (Greece, Hungary, Poland), standard monitoring and recording of
recurrences may increase surveillance importance.

Surveillance accounts for up to a quarter of colonoscopy practice, and thus
makes up a significant portion of financial, human and physical resources. As shown
in Chapter 5 on colorectal cancer screening, endoscopy resources are currently under
strain in Europe and Australia. As surveillance also contributes to endoscopy practice
alternative methods, optimal timing and intervals and adherence need to be explored
further through clinical trials and cost-effectiveness analyses in order to produce the
body of evidence needed. Although this research may not be as exciting as research
focusing on cure and treatment, it is still important part of colorectal cancer care.

In order to ensure best chance for curative treatment and prolonged survival, it
is important to detect recurrences in a timely and accurate fashion. In addition, proper
surveillance of adenoma patients detects early stages of colorectal cancer, also
improving outcomes. Unfortunately, this area of colorectal cancer care appears to be
based primarily on best “usual practice”, rather than “best evidence-based practice”,
as the quantity of good surveillance research is scarce.
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Chapter 9
Conclusions

9.1. The Present

Colorectal cancer is the second most diagnosed form of cancer as well as the second cause of cancer mortality, making it a cancer that warrants interest and attention. Colorectal cancer 5-year survival in 2002 is far less than other high-incidence high-mortality cancers at less than 55% versus over 75% for breast and prostate cancers. Although survival has increased from under 45% in 1985, incidence is increasing and large variations in these figures occur within and between countries.

What do these survival figures reflect? First of all, these figures are very sensitive to many different factors, from societal interest to clinical treatments to health policies. The significant variations between countries, as well as the slow improvements in survival, suggest that improvements in colorectal cancer outcomes are definitely within reach using many different means. Part of the purpose of this survey was to examine differences in policies and practices across the study countries in order to share information and knowledge that may improve disease management and outcomes. The survey has highlighted significant variations in policy and practice across different themes of the CRC treatment pathway.

A simplified method of viewing these variations between countries is our composite performance indicator (Figures 9.1 and 9.2). The use of both positive and negative indicators reflects that each country may have positive and negative aspects to colorectal cancer services. For example, both France and the UK have high aggregate positive scores, however they also have several negative points, indicating room for improvement. Also telling is that few countries scored 50% as total of all positive indicators (equalling score over 200) (Denmark, France, Germany, Italy, Netherlands, UK, Australia) and none over 75%. These countries may have policies facilitating colorectal cancer care, however their low overall score suggests they could do better.

High negative scores appear to be concentrated in countries with problems in availability, affordability, access and quality of colorectal cancer services provided. Many of these countries appear to be Eastern European countries, although Portugal
and Spain are also included primarily due to longer waiting times and lack of care standards. Screening and treatment appear to make a large influence on the overall score, underscoring the obvious importance of these activities to colorectal cancer services.
Figure 9.1

Total positive performance indicators for screening, treatment, pharmaceutical treatment and surveillance activities in each country*

Note: * Maximum score is 400%.
Source: The authors.

Figure 9.2

Total negative performance indicators for screening, treatment, pharmaceutical treatment in each country*

Note: * Maximum score is 400%.
Source: The authors.
9.2. The Future: Addressing Current Shortcomings

The results of this survey raise several policy questions and points for action with regards to screening, treatment, pharmaceutical care, surveillance and data collection.

The first policy and practice that can have significant influence on CRC outcomes is population screening. Colorectal cancer is largely an asymptomatic disease until latter stages but is a potentially preventable disease if diagnosed in the pre-cancerous stage, making it an ideal candidate for screening. Cost-effectiveness analysis proves that colorectal cancer screening is more cost-effective than no screening and perhaps more so than breast cancer screening.

Despite these arguments, colorectal cancer screening has not become standard policy or practice in Europe. Only five of the surveyed countries have recently initiated formal screening programs, with the rest dabbling in pilots and opportunistic screening. There are a number of explanations for this. Foremost, there is limited political or public awareness of colorectal cancer resulting in minimal pressure to introduce screening into public health. In addition, all of the tests used in colorectal cancer screening have imperfections. The combination of poor societal interest plus test imperfections creates an ideal environment for poor participation, which in turn affects whether countries are willing to adopt colorectal cancer screening.

Linked to screening is endoscopy capacity, as it is necessary for diagnosis and used in a minority of countries for screening. The proper management of this resource is vital, poor management can result in long waiting times for diagnosis in both asymptomatic and high-risk symptomatic patients, as well as can undermine population screening if diagnostic services are not available. Although some countries profess to having policies such as choice and patient prioritisation to encourage short waiting times, use of nurse endoscopists as substitutes are not supported in the vast majority of European countries or Australia despite their successes elsewhere. These policies, in combination with concerns of endoscopy quality, suggest that endoscopy management could be considerably improved.

The second most important influence in CRC outcomes is treatment and pharmaceutical practices and policies. Only half of surveyed countries have treatment and pharmaceutical guidelines, countries that do have guidelines frequently have
mixed quality with no or minimal monitoring. Some countries have more than one organisation producing guidelines and other countries offer much discussion but little guidance. For pharmaceutical treatments, 1\textsuperscript{st} and 2\textsuperscript{nd} line are often not given, and large variations between countries are present, particularly for targeted treatments. These factors result in variations between countries with regards to guidance, and in the end likely variations in practice within and between countries concluding in mixed quality care.

There appears to be several barriers to treatment, ranging from geographical barriers to the necessity of out-of-pocket payments. Long waiting times from diagnosis to treatment are not uncommon in Europe and Australia, and minority groups may be less likely to partake in cancer care. There are problems with delivery including insufficient facilities and physicians, not only isolated to Eastern Europe, and resources unevenly spread within countries based on population and demand. There appear to be many physician specialties to provide care in many different hospital wards, however physician training and the level of colorectal cancer specialisation appears to be an issue in a number of countries.

Pharmaceutical treatments have special note in this document, as a few new advances have been made during the past decade, including targeted biological treatments in metastatic CRC. On the whole the quantity and quality of cost-effectiveness analysis is minimal, particularly in comparing competing therapies and for adjuvant treatments, while health technology assessments are becoming important in reimbursement decision-making. Many country respondents felt the timeliness of new treatments were par or below par, and untimely health technology assessments can potentially worsen this state.

The use of pharmaceutical treatments varies between countries, as reflected by the discordances in guidance as well as uptake. Uptake and use of targeted biological treatments range from none to a significant portion of metastatic CRC patients. Country wealth does not necessarily play a deciding role in this respect, as uptake adjusted for eligible CRC populations in some Eastern European countries is higher than Western European countries and Australia. Within countries there are often regional variations, as hospitals with flexibility in their formularies choose to adopt these treatments, while in other countries out-of-pocket payments are necessary.
Weaving these factors together paints a highly unequal access to targeted biological treatments, within and between countries.

The third influence relates to surveillance; this is an often neglected aspect but of vital importance to CRC management and outcomes. Follow-up of colorectal cancer and high-risk pre-cancerous adenoma patients is where the most variations in practice and quality of care are seen. Limited research and minimal cost-effectiveness analyses result in large divisions in guidelines, practice and formal monitoring of these patients who have a one-third chance of recurrence. As endoscopy entails a significant portion of surveillance activities, again endoscopy capacity and proper management are key to providing timely, high-quality care.

Common themes emerge from each of these colorectal cancer practices and standards: availability, affordability, access and quality. First, the availability of political and public interest in colorectal cancer is still limited, including limited interest in screening activities, continuous Europe-wide discussion or documentation, awareness campaigns and colorectal cancer-specific interest groups, despite the good intentions of European institutions which have ongoing research, and at times voice their concern about these matters. Screening activities are not always available, particularly formal screening, in addition to highly acceptable tests by both the public and public health departments.

There are limited data available on cancer and CRC expenditure and population data. Clinical cost-effectiveness analyses, of high standard, are also not ubiquitous. These limitations in available data for decision-makers and health planners result in many difficulties with regards to reaching funding decisions and/or evaluating the effectiveness of individual policies.

Guidelines for treatment, for pharmaceutical treatment and for surveillance, are simply not present in many countries, perpetuating historical-based practice instead of updated evidence-based practice. Specialty physicians and hospitals with experience and training in CRC are also often not available, particularly in some Eastern European countries. New, proven effective treatments, including laparoscopy and targeted biological treatments are also often unavailable to patients, either due to reimbursement decisions or lack of training to deliver the treatment. Furthermore, variations in hospital formulary flexibility may exacerbate this lack of availability.
Affordability emerges as a second theme in this survey, notably for Eastern European countries such as Romania and Russia. Limited public resources result in limited health budgets, in turn difficult decisions are made about how to allocate scarce resources. New treatments may not be made available, in part due to their cost but also due to the opportunity costs of replacing old treatments. Untimely replacement of equipment results in greater frequency of non-performance resulting in longer waiting times, as well as its less liberal usage. Screening becomes less likely due to implementation costs, regardless that it is likely to be cost saving due to prevention and decreased high-cost Stage III and IV patients.

Targeted treatments are of particular note in this discussion of affordability. These treatments are more costly than previous treatments for metastatic colorectal cancer, however, bevacizumab in particular does present with significantly longer progression-free survival and overall survival. Of interest, it was unexpected to find Turkey and Slovakia having higher uptake per estimated metastatic colorectal cancer patient than many other Western European countries, suggesting these countries are interested in investing in new technology.

This discussion would not be complete without the mention of cost-effectiveness analysis and thresholds, given the fast uptake of clinical cost-effectiveness in the decision-making process. While it is understandable that some countries may want to place a lot of emphasis on cost effectiveness, there are other factors such as innovation, equity, and disease severity which also should be considered in this context.

The third theme arising is access to colorectal cancer services. Almost all countries reported regional differences within their country with regard to diagnostics, treatment and pharmaceuticals. Out-of-pocket payments place an additional barrier to receiving care, particularly if unofficial. Lengthy waiting times for diagnosis or treatment are not unusual, and only a minority of countries have policies in place to facilitate prompt delivery, such as patient choice, patient prioritisation, and nurse endoscopy substitutes. There are greater barriers to opportunistic screening than formal screening as patients and physicians must be motivated. Timeliness of new treatments appears to be a universal concern, with only France having a policy in place to facilitate implementation. On the whole, access to colorectal cancer services
is not unhindered, and it appears most countries, particularly those where the problem appears more acute, do not have policies or practices in place to facilitate access.

The final theme is the quality of CRC services and of data. Due to variations in treatment and pharmaceutical guidelines as well as minimal monitoring, it is likely that variations in quality occur and perhaps delivery of potentially inappropriate care. This, coupled with restrictions in resource allocation in some countries, may affect quality of screening (opportunistic versus formal), treatment, pharmaceutical treatment and also surveillance. Part of the problem in some areas is insufficient research underpinning policy and practice. In furtherance of this is often poor quality data, both of (CRC) cancer expenditure and of (CRC) cancer populations. Both areas have significant problems, the former having minimal collection throughout Europe while the latter has greater collection yet length and depth of collection are variable. Without good quality data, decision-making, policy creation and future health planning remain difficult and dark processes.

Overall, in the future, it is important to: (a) Improve data collection procedures, internally within each country and well as promote international co-operation. This is valid for both cancer registry data as well as cancer- and CRC-specific expenditure. Both are necessary for future cancer planning, not only for CRC but also for other cancers; (b) Have greater national and international support for cancer screening activities proven to be effective and cost-effective. Continue to conduct or encourage research on the effectiveness and cost-effectiveness of new screening methods with a view to informing policy on best practice/choice available. In terms of CRC, greater effort and support for formal versus opportunistic screening programmes should be given by the European Union and national Ministries of Health; (c) Examine endoscopy capacity in each country to ensure timely diagnosis, regardless of screening activities. Patients should be given choice in endoscopy centres to manage waiting lists more effectively, and patients should be prioritized formally based on risk. Greater support should be given to the Nurse Endoscopy profession by Ministries of Health and by physician gastroenterology associations; (d) Enhance public and political awareness as a key to improving CRC outcomes. Targeted CRC-specific campaigns need to be produced, not just campaigns that include healthy lifestyles in the hope that colorectal cancer will be addressed. Public personas affected by this disease must be encouraged to give voice, in order to raise
the status of CRC; (e) Where applicable, give consideration to the principles of 
equity, human dignity and disease severity, among others, when deciding on diffusion 
of targeted treatments, rather than base decisions solely on cost-effectiveness; and (f) 
Firm up national and European guidelines including screening, diagnosis, treatment, 
pharmaceutical treatments and surveillance. These guidelines must be timely, 
evidence-based, and freely accessible to all. They should include pathways, adequate 
discussion of all methods, as well as actual guidance. Non-consensus could also be 
included, as well as patient perspectives.

The above sets out a long and strenuous agenda for action and change by 
national as well as regional governments. In this environment, the role of supra-
national organisations, such as the European Union and the European Parliament, is 
important to initiate as well as support the debate for change. Arguably, positive steps 
have already been undertaken to raise awareness\textsuperscript{205}, but it is important that the 
impetus is maintained over time and translated into concrete policy action. Patients 
rightly request and demand the best available treatment for their condition. Where 
geographical disparities or inequities in access have been found, it is justifiable that 
they cause concern.

\textsuperscript{205} Coleman et al, 2008; European Commission, 2008.
Dear Project Participant

Thank you for helping us with this project exploring colorectal cancer (CRC) services in Europe. Our main objective is to capture the current information regarding the management of resources and funding of CRC in different European countries, as well as assess the effectiveness of policies implemented. This will allow an accurate picture of the current state of CRC management to be formulated and trends in practice to be identified.

Please complete this questionnaire to the best of your ability and in as much detail as possible, including individuals interviewed (and contact details) as well as literature used. If resources are published or online, please give complete reference to them. If possible, please complete the questionnaire via your computer, rather than hand writing your responses, this will avoid transcription errors. The questions can be answered in the fields, denoted by the grey boxes. Please remember, any additional information is always welcome.

Kind Regards,

The CRC research team
### Objective 1: To catalogue the available cancer data sources within each European country, as well as their accessibility, availability, and use in research and policy.

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1.1. Does your country collect data on cancer?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Yes</td>
<td>□ No</td>
<td>□ Not sure, explain:</td>
</tr>
<tr>
<td>1.2. Does your country collect data on CRC?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Yes</td>
<td>□ No</td>
<td>□ Not sure, explain:</td>
</tr>
<tr>
<td>1.3. Are data collected on a national or regional level?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ National, details:</td>
<td>□ Regional, details:</td>
<td>□ Other (please describe), details:</td>
</tr>
<tr>
<td>1.4. What data is collected?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Incidence</td>
<td>□ Mortality</td>
<td>□ 5 year survival</td>
</tr>
<tr>
<td>□ Mortality</td>
<td>□ Prevalence</td>
<td>□ 10 year survival</td>
</tr>
<tr>
<td>□ Incidence</td>
<td>□ Prevalence</td>
<td>□ Stage at diagnosis</td>
</tr>
<tr>
<td>□ 1 year survival</td>
<td>□ Treatment details, describe:</td>
<td>□ Other:</td>
</tr>
<tr>
<td>□ Other:</td>
<td>□ Other:</td>
<td>□ Other:</td>
</tr>
<tr>
<td>1.5. Do you believe the data to be of good quality, accurately reflecting its population?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Yes, because:</td>
<td>□ No, because:</td>
<td></td>
</tr>
<tr>
<td>1.6. Is data on all types of cancer collected?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Yes</td>
<td>□ No, only:</td>
<td></td>
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<tr>
<td>1.7. Is data freely accessible?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Yes</td>
<td>□ No, access only to:</td>
<td></td>
</tr>
<tr>
<td>1.8. Is data available for research use?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Yes</td>
<td>□ No, give explanation if available:</td>
<td></td>
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</tbody>
</table>
Objective 2: To assess the impact of CRC within each European country with regards to incidence, prevalence, mortality, survival as well as economic burden.

<table>
<thead>
<tr>
<th>2.1. Over what time span has your country collated CRC incidence data?</th>
<th>Please give years collected:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2. Please attach all the CRC incidence data you are able to access. What additional information is collected?</td>
<td>Please check all that apply.</td>
</tr>
<tr>
<td>☐ Sex</td>
<td>☐ Age</td>
</tr>
<tr>
<td>☐ Stage at diagnosis</td>
<td>☐ Other:</td>
</tr>
<tr>
<td>2.3. Over what time span has your country collated CRC mortality data?</td>
<td>Please give years collected:</td>
</tr>
<tr>
<td>2.4. Please attach all the CRC mortality data you are able to access. What additional information is collected?</td>
<td>Please check all that apply.</td>
</tr>
<tr>
<td>☐ Sex</td>
<td>☐ Stage at diagnosis</td>
</tr>
<tr>
<td>☐ Age</td>
<td>☐ Treatment received</td>
</tr>
<tr>
<td>☐ Other:</td>
<td></td>
</tr>
<tr>
<td>2.5. Over what time span has your country collated CRC prevalence data?</td>
<td>Please give years collected:</td>
</tr>
<tr>
<td>2.6. Please attach all the CRC prevalence data you are able to access. What additional information is collected?</td>
<td>Please check all that apply.</td>
</tr>
<tr>
<td>☐ Sex</td>
<td>☐ Treatment received</td>
</tr>
<tr>
<td>☐ Age</td>
<td>☐ Under surveillance</td>
</tr>
<tr>
<td>☐ Stage at diagnosis</td>
<td>☐ Other:</td>
</tr>
<tr>
<td>2.7. Over what time span has your country collated CRC survival data?</td>
<td>Please give years collected:</td>
</tr>
<tr>
<td>2.8. Please attach all the CRC survival data you are able to access. What additional information is collected?</td>
<td>Please check all that apply.</td>
</tr>
<tr>
<td>☐ 1 year survival</td>
<td>☐ Age</td>
</tr>
<tr>
<td>☐ 5 year survival</td>
<td>☐ Stage at diagnosis</td>
</tr>
<tr>
<td>☐ 10 year survival</td>
<td>☐ Treatment received</td>
</tr>
<tr>
<td>☐ Sex</td>
<td>☐ Under surveillance</td>
</tr>
<tr>
<td>☐ Other:</td>
<td></td>
</tr>
<tr>
<td>2.9. Has there been an exploration of CRC’s burden of disease on your country?</td>
<td></td>
</tr>
<tr>
<td>Burden of disease is defined at the measurement of financial costs, mortality, morbidity, relative risks and other indicators to assess the impact of a health problem (please see <a href="http://www.who.int/healthinfo/bodproject/en/">http://www.who.int/healthinfo/bodproject/en/</a> for examples)</td>
<td></td>
</tr>
<tr>
<td>☐ Yes, please give weblink: or attach hardcopy</td>
<td>☐ No</td>
</tr>
<tr>
<td>2.10. Has there been an exploration of other cancers’ burden of disease in your country?</td>
<td></td>
</tr>
<tr>
<td>☐ Yes, please give weblink: or attach hardcopy</td>
<td>☐ No</td>
</tr>
</tbody>
</table>
Objective 3: To understand the funding and resource allocation process in each European country, as well as the measurement of resources allocated and expended on cancer in general and CRC in particular.

3.1. What is your country’s expenditure on health care over the past decade?

<table>
<thead>
<tr>
<th>Year</th>
<th>Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007: €</td>
<td>201: €</td>
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<tr>
<td>2006: €</td>
<td>2000: €</td>
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<td>2005: €</td>
<td>1999: €</td>
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<td>2004: €</td>
<td>1998: €</td>
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<td>2003: €</td>
<td>1997: €</td>
</tr>
<tr>
<td>2002: €</td>
<td>1996: €</td>
</tr>
</tbody>
</table>

(Best Estimates:  Yes  No)

3.2. What is your country’s expenditure on cancer care over the past decade?

<table>
<thead>
<tr>
<th>Year</th>
<th>Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007: €</td>
<td>201: €</td>
</tr>
<tr>
<td>2006: €</td>
<td>2000: €</td>
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<tr>
<td>2005: €</td>
<td>1999: €</td>
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<td>2004: €</td>
<td>1998: €</td>
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<td>2003: €</td>
<td>1997: €</td>
</tr>
<tr>
<td>2002: €</td>
<td>1996: €</td>
</tr>
</tbody>
</table>

(Best Estimates:  Yes  No)

3.3. What proportion is spent on CRC care?

*If you are unaware of the exact proportion, please tell us so and give us your best estimate based on your research and interviews.*

Best Estimate:  Yes  No

3.4. What proportion is spent on breast cancer care?

*If you are unaware of the exact proportion, please give your best estimate based on your research and interviews.*

Best Estimate:  Yes  No

3.5. What proportion is spent on prostate cancer care?

*If you are unaware of the exact proportion, please give your best estimate based on your research and interviews.*

Best Estimate:  Yes  No
3.6 Does your country have a formal resource allocation mechanism?

☐ NO:
   1. How are resources allocated in your country?
   2. How are resources allocated for CRC care?

*Please proceed now to Question 3.7.*

☐ YES, our country does have a formal resource allocation mechanism.

Please proceed to answer the following:

3. Are resources allocated at a national or regional level?

☐ National  ☐ Local
☐ Regional  ☐ Other:

4. Is disease type included in the resource allocation method?

☐ Yes, including:
   ☐ Cancer overall
   ☐ CRC
   ☐ Breast cancer
   ☐ Prostate cancer
   ☐ Other specific cancer(s):

☐ No

5. Please give an overview of your country’s resource allocation method:

---

3.7. Are there any resources allocated for any adult screening programs in your country?

☐ None formally but adult screening does exist in my country

What are the perceived barriers to allocating resources for screening programs in your country?

*Please list all and any sources (individuals and literature) for your rationale.*

Please proceed now to Question 3.8.

☐ No, our country does not participate in screening of adults.

What are the perceived barriers to allocating resources for screening programs in your country?

*Please list all and any sources (individuals and literature) for your rationale.*

Please proceed now to Question 3.8.

☐ Yes our country does have resources allocated to screening adults in my country: €

*Best Estimate: ☐ Yes  ☐ No*

Please proceed to answer the following:

1. What adult screening programs exist in your country? Please check all that apply.

   **National** Screening Program
   ☐ CRC
   ☐ Breast cancer
   ☐ Cervical cancer
   ☐ Prostate cancer
   ☐ Other:

   **Pilot** Screening Program
   ☐ CRC
   ☐ Breast cancer
   ☐ Cervical cancer
   ☐ Prostate cancer
   ☐ Other:

   ☐ Other:

   ☐ Other:

   ☐ Other:
2. What funding is allocated to each for the purpose of screening?

- CRC: €
- Breast cancer: €
- Cervical cancer: €
- Prostate cancer: €
- Other: €

(Best Estimates: Yes No)

3.8. Are there any resources allocated specifically for diagnosing and treating cancer in your country?

☐ None formally but diagnosis and treatment does exist in my country

What are the perceived barriers to allocating resources for cancer diagnosis and treatment in your country?

*Please list all and any sources (individuals and literature) for your rationale.*

Please proceed now to Question 3.9.

☐ No, please explain:

What are the perceived barriers to allocating resources for cancer diagnosis and treatment in your country?

*Please list all and any sources (individuals and literature) for your rationale.*

Please proceed now to Question 3.9.

☐ Yes, my country does formally allocate resources specifically for cancer diagnosis and treatment:

€

(Best Estimate: Yes No)

Please proceed now to answer the following:

1. What formal cancer diagnosis and treatment programs exist in your country? Please check all that apply.

- CRC:
- Breast Cancer:
- Prostate Cancer:
- Lung Cancer:
- Stomach Cancer:
- Uterine cancer:
- Other:

Please give name of program(s) or organization(s).

2. How much funding is allocated to each of the following for the purpose of diagnosis and treatment? Please check all that apply.

- CRC: €
- Breast Cancer: €
- Prostate Cancer: €
- Lung Cancer: €
- Stomach Cancer: €
- Uterine cancer: €
- Other: €

(Best Estimates: Yes No)
3.9. Are there specific resources allocated for cancer surveillance of high risk patients in your country?

High risk patients defined as those being at increased risk due to prior cancer, prior risk factors, strong family history or genetic susceptibility.

- None formally but surveillance does exist in my country

What are the perceived barriers to allocating resources for cancer surveillance in your country? Please list all and any sources (individuals and literature) for your rationale.

Please proceed now to Question 3.10.

- No, please explain:

What are the perceived barriers to allocating resources for cancer surveillance in your country? Please list all and any sources (individuals and literature) for your rationale.

Please proceed now to Question 3.10.

- Yes, my country does formally allocate resources specifically for cancer surveillance.

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>CRC:</td>
<td>€</td>
</tr>
<tr>
<td>Breast Cancer:</td>
<td>€</td>
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<tr>
<td>Prostate Cancer:</td>
<td>€</td>
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<td>Lung Cancer:</td>
<td>€</td>
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<td>Stomach Cancer:</td>
<td>€</td>
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<tr>
<td>Uterine cancer:</td>
<td>€</td>
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<tr>
<td>Other:</td>
<td>€</td>
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</tbody>
</table>

Best Estimate: [ ] Yes [ ] No

Please proceed now to answer the following:

1. What formal cancer surveillance of high risk patients exist in your country? Please check all that apply.

Please give name of program(s) or organization(s).

- CRC: [ ]
- Breast Cancer: [ ]
- Prostate Cancer: [ ]
- Lung Cancer: [ ]
- Stomach Cancer: [ ]
- Uterine cancer: [ ]
- Other: [ ]

2. How much funding is allocated to cancer surveillance of high risk patients for each of the following? Please check all that apply.

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>CRC: €</td>
<td>Stomach Cancer: €</td>
</tr>
<tr>
<td>Breast Cancer: €</td>
<td>Uterine cancer: €</td>
</tr>
<tr>
<td>Prostate Cancer: €</td>
<td>Other: , €</td>
</tr>
<tr>
<td>Lung Cancer: €</td>
<td>Other: , €</td>
</tr>
</tbody>
</table>

(Best Estimate: [ ] Yes [ ] No)
3.10. What has been the total expenditure on pharmaceuticals in your country?

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>(€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>€</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>€</td>
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<tr>
<td>1997</td>
<td>€</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>€</td>
<td></td>
</tr>
</tbody>
</table>

(Best Estimates: [ ] Yes [ ] No)

3.11. What proportion of pharmaceutical expenditure has been in the following:

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Cancer Pharmaceuticals</th>
<th>Novel (Targeted) Cancer Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>2006</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>2005</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>2004</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>2003</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>2002</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>2001</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>2000</td>
<td>€</td>
<td>€</td>
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<tr>
<td>1999</td>
<td>€</td>
<td>€</td>
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<tr>
<td>1998</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>1997</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>1996</td>
<td>€</td>
<td>€</td>
</tr>
</tbody>
</table>

(Best Estimates: [ ] Yes [ ] No)

3.12. What is your perception of timeliness of new treatments for cancer introduced into the formulary?

3.13. What effect does your country’s health insurance have on access to novel (targeted) cancer treatments?

1. Does your country have out of pocket payments for patients who would like novel (targeted) cancer treatments?
   - [ ] Yes, please explain:
   - [ ] No, please explain:

3.14. Are there regional differences in access to novel (targeted) treatments for cancer?
   - [ ] Yes, please describe:
   - [ ] No

3.15. Are hospitals allowed flexibility in their formulary to include novel (targeted) treatments for cancer?
   - [ ] Yes, please describe:
   - [ ] No, dictated by:

3.16. Does your country require Health Technology Assessments and cost effectiveness analysis as part of acceptance of cancer treatments to formulary or practice?
   - [ ] Yes, please describe:
   - [ ] No

3.17. In your opinion, are sufficient resources allocated to cancer care?
   - [ ] Yes, please describe:
   - [ ] No, please describe shortcomings:
3.18. In your opinion, are sufficient resources allocated to CRC care?

- Yes, please describe:
- No, please describe shortcomings:

3.19. What are the main problems surrounding the delivery of cancer care in your country? Please check all that apply.

- Insufficient human resources
- Insufficient facility resources
- Poor distribution of resources
- Inadequate diagnostic facilities
- Long waiting times for diagnosis
- Limited access to facilities due to geographical inequities
- Inadequate treatment facilities
- Long waiting times for treatment
- Poor quality treatment
- Poor practice guidelines
- No practice guidelines
- Poor physician cancer resources/network
- Poor physician cancer training
- Poor political interest in cancer care
- Poor press coverage of cancer care
- Limited or poor access to new treatments of proven efficacy
- Delayed access to new treatments of proven efficacy
- No access to new treatments of proven efficacy
- High out-of-pocket cost to patient
- Other:
- Other:
- Other:

Objective 4: To identify the extent of screening policies and prevention in each European country, as well as the extent to which these are actively encouraged, implemented, monitored and enforced.

4.1. Has your country ever had a campaign regarding cancer prevention?

- Yes, please describe its/their name(s) and key feature(s):
  1. Their website(s):
  2. What was the impact of the campaign(s):
  3. What were its cost(s):
  4. Who was responsible for the campaign(s):
- No

4.2. Has your country ever had a CRC prevention campaign?

- Yes, please describe its/their name(s) and key feature(s):
  1. Their website(s):
  2. What was the impact of the campaign(s):
  3. What were its cost(s):
  4. Who was responsible for the campaign(s):
- No

4.3. Has your country ever had a CRC screening campaign?

- Yes, please describe its/their name(s) and key feature(s):
  1. Their website(s):
  2. What was the impact of the campaign(s):
  3. What were its cost(s):
  4. Who was responsible for the campaign(s):
- No
4.4. Are there official patient led groups for **cancer**?

<table>
<thead>
<tr>
<th>Yes, please give the group name(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is their purpose(s):</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

4.5. Are there official patient led groups for **CRC**?

<table>
<thead>
<tr>
<th>Yes, the organization is called:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Their website:</td>
</tr>
<tr>
<td>2. What is their purpose(s):</td>
</tr>
<tr>
<td>3. What is their annual budget:</td>
</tr>
<tr>
<td>4. What is their main source of funding:</td>
</tr>
<tr>
<td>5. What are their main activities:</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

4.6. Are there official physician led groups for **CRC**?

<table>
<thead>
<tr>
<th>Yes, the organization is called:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Their website:</td>
</tr>
<tr>
<td>2. What is their purpose(s):</td>
</tr>
<tr>
<td>3. What is their annual budget:</td>
</tr>
<tr>
<td>4. What is their main source of funding:</td>
</tr>
<tr>
<td>6. What are their main activities:</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

4.6. Has your country adopted a **national CRC screening policy**?

| NO, please proceed to Question 4.7 |
| NO, but we are currently in the piloting stage of national CRC screening |
| Yes, please give weblink: |
| or attach hard copy |

If ‘YES’ or ‘NO, piloting stage’ to Question 4.6:

| 1. What are the guidelines: |

2. Which of the following specific groups do the screening guidelines or pilot include. Please check all that apply.

- Average risk individuals
- Familial adenomatous polyposis
- Family history of CRC
- Hereditary non-polyposis CRC
- History of adenomatous polyps
- All adults over the age of ___ years
- Personal history of CRC
- Other:

3. If there is a choice of methods, please indicate the most common method. Please check all that apply.

- Fecal occult blood test (FOBT) every ___ years
- Flexible sigmoidoscopy (FS) every ___ years
- FOBT every ___ years + FS every ___ years
- Colonoscopy every ___ years
- Barium enema every ___ years
- Digital rectal examination every ___ years
- Other:
4. What are the ages of screening:

<table>
<thead>
<tr>
<th>Begin:</th>
<th>years of age</th>
<th>End:</th>
<th>years of age</th>
</tr>
</thead>
</table>

5. What is the adherence rate of all invitees:

percent

6. Are there specific groups in society where adherence is lower than average? Please check all that apply.

- [ ] Men
- [ ] Women
- [ ] Over 70 years
- [ ] Geographically remote
- [ ] Low socioeconomic status
- [ ] Ethnic groups: Other:

7. Are there any policies/plans in place to address these groups with poorer adherence?

- [ ] Yes, please describe:
- [ ] No

8. Is the screening invitation formal (e.g. invitation via letter) or opportunistic (e.g. suggested at routine doctor’s visit)?

- [ ] Formal, describe:
- [ ] Opportunistic, describe:
- [ ] Other, describe:

4.7. Which of the following screening methods used in screening individuals?

Please check all that apply.

- [ ] FOBT, guaiac, unrehydrated
- [ ] FOBT, guaiac, rehydrated
- [ ] FOBT, immunological
- [ ] Fecal DNA
- [ ] FS
- [ ] COL
- [ ] Barium enema
- [ ] Digital rectal examination
- [ ] Computerized tomography
- [ ] Other:

4.8. Please indicate the most common methods (choose maximum of 3):

- [ ] FOBT, guaiac, unrehydrated
- [ ] FOBT, guaiac, rehydrated
- [ ] FOBT, immunological
- [ ] Fecal DNA
- [ ] FS
- [ ] COL
- [ ] Barium enema
- [ ] Digital rectal examination
- [ ] Computerized tomography
- [ ] Other:
### Objective 5: To determine the level of leadership on a national level in each European country for CRC services.

<table>
<thead>
<tr>
<th>5.1. Has your country adopted a national standards of care for CRC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ NO Please proceed to Question 5.3.</td>
</tr>
<tr>
<td>☐ Yes, please answer the following:</td>
</tr>
<tr>
<td>When were they created/established?</td>
</tr>
</tbody>
</table>

2. Does this include CRC treatment guidelines?  
   - ☐ Yes  
   - ☐ No  

3. Does this include CRC post treatment surveillance guidelines?  
   - ☐ Yes  
   - ☐ No  

4. What else do they contain? Please check all that apply.  
   - ☐ Minimum waiting times for diagnosis, define:  
   - ☐ Minimum waiting times for treatment, define:  
   - ☐ Chemotherapy as outpatient  
   - ☐ Chemotherapy as inpatient  
   - ☐ Radiotherapy as outpatient  
   - ☐ Radiotherapy as inpatient  
   - ☐ Choice of endoscopy centers  
   - ☐ Endoscopy at first available centre  
   - ☐ Access to endoscopy center depends on health insurance  
   - ☐ Choice of treatment centers  
   - ☐ Treatment at first available centre  
   - ☐ Access to treatment center depends on health insurance  
   - ☐ Other:  
   - ☐ Other:  

5. Please attach national standards of care for CRC:  
   - ☐ Weblink:  
   - ☐ Attached document (document or summary in English)  

5.2. If your country has national standards of care which include CRC treatment guidelines:  
   - ☐ No, please proceed to Question 5.3.  

1. Which of the following specific groups do the treatment guidelines include (Please check all that apply):  
   - ☐ Average risk individuals  
   - ☐ Family history of CRC  
   - ☐ History of adenomatous polyps  
   - ☐ Personal history of CRC  
   - ☐ Familial adenomatous polyposis  
   - ☐ Hereditary non-polyposis CRC  
   - ☐ Other:  

2. What are the treatment guidelines?  
   - ☐ Weblink:  
   - ☐ Attached document (English document or summary)  

3. Briefly describe how the treatment guidelines were determined.
5.3. What are the most common procedures for CRC care in your country? Please check all that apply.

- Minimum waiting times for diagnosis, define:
- Minimum waiting times for treatment, define:
- Chemotherapy as outpatient
- Chemotherapy as inpatient
- Radiotherapy as outpatient
- Radiotherapy as inpatient
- Choice of endoscopy centers
- Endoscopy at first available centre
- Access to endoscopy center depends on health insurance
- Choice of treatment centers
- Treatment at first available centre
- Access to treatment center depends on health insurance
- Other:
- Other:

5.4. Which of the following methods are most commonly advocated? Please check all that apply.

- Laparoscopic surgery, early stage
- Laparoscopic surgery, early and middle stages
- Laparoscopic surgery, all stages
- Open surgery
- Chemotherapy pre surgery
- Chemotherapy post surgery
- Other:

5.6. What is your country’s current metastasectomy rate?

5.7. If your country has national standards of care which includes post treatment surveillance guidelines:

   - No, please proceed to Question 5.8.

1. Which of the following specific groups do the post treatment surveillance guidelines include (Please check all that apply):

- Average risk individuals
- Family history of CRC
- History of adenomatous polyps
- Personal history of CRC
- Familial adenomatous polyposis
- Hereditary non-polyposis CRC
- Other:

2. What are the post treatment surveillance guidelines?

   - Weblink:
   - Attached document

3. Briefly describe how they were determined.
5.8. If your country has **NO** national standards of care for CRC:
(☐ No, my country **has** national standards of care outlined above. Go to Question 6.1.)

<table>
<thead>
<tr>
<th>Question</th>
<th>Response Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does your country have an official organization of physicians treating CRC? (For example a physician oncology group)</td>
<td>☐ Yes, describe: ☐ No</td>
</tr>
<tr>
<td>2. Are official physician groups organized primarily regionally or nationally in your country?</td>
<td>☐ Regionally ☐ Nationally ☐ Other:</td>
</tr>
<tr>
<td>3. How is treatment for the large part determined?</td>
<td></td>
</tr>
<tr>
<td>4. Are there large regional (geographical) variations in CRC treatment?</td>
<td>☐ Yes, describe: ☐ No</td>
</tr>
<tr>
<td>5. Are other country’s treatment guidelines adopted?</td>
<td>☐ Yes, describe whose: ☐ No</td>
</tr>
<tr>
<td>6. Are other country’s post treatment surveillance guidelines adopted?</td>
<td>☐ Yes, describe whose: ☐ No</td>
</tr>
<tr>
<td>7. Please give any other important information pertaining to treatment and post treatment surveillance in your country.</td>
<td></td>
</tr>
</tbody>
</table>

**Objective 6.** To determine the ability and willingness of hospitals throughout Europe to implement national standards of care.

6.1. Are the national standards of care for CRC monitored?

☐ No, our country does NOT have national standards of CRC care.

Please proceed to Question 7.1.

☐ No, our country has national standards of care for CRC but they are **not** monitored.

Please proceed to Question 6.2.

☐ Yes:

1. Who monitors the national standards of care for CRC?
2. Are the national standards of care for CRC monitored regionally or nationally?
   ☐ Regionally ☐ Nationally ☐ Other:
3. How are the national standards of care for CRC monitored?
4. Have there been any significant issues or problems relating to monitoring of CRC care?
   ☐ Yes, please describe:
   ☐ No
6.2. **When** were the national standards of care for CRC implemented?

6.3. **How** were the national standards of care for CRC implemented?

6.4 Were there any significant issues or problems relating to implementing these national standards of care for CRC?

**Objective 7: To assess the efficiency of healthcare provision, specifically CRC services, throughout Europe.**

7.1. Please outline the treatment pathway for patients with colorectal cancer:

7.2. What is the average length of time from referral for endoscopy services to diagnosis by endoscopy?

7.3. Are there regional differences in this length of time?
- [ ] Yes, please explain:
- [ ] No

7.4. Are some regions poorly served geographically with endoscopy services (e.g., must travel long distances to endoscopy services)?
- [ ] Yes, please explain which regions:
- [ ] No

7.5. Do certain groups in your country have difficulty with access to endoscopy services?
- [ ] Yes, please describe which groups:
- [ ] No

7.6. Are there formal policies in place to determine priorities in receiving endoscopy services?
- [ ] Yes, please describe:
- [ ] No

7.7. In your opinion, do endoscopy services receive adequate funding?
- [ ] Yes, please describe:
- [ ] No, please describe:

7.8. Are there any other additional issues relating to endoscopy services that are significant?
- [ ] Yes, please describe:
- [ ] No

7.9. What is the average length of time from diagnosis with CRC to treatment for CRC?

7.10. Are there regional differences in this length of time?
- [ ] Yes, please describe:
- [ ] No

7.11. Are some regions poorly served geographically with cancer treatment centers (long distance from home to treatment center)?
- [ ] Yes, please describe which regions:
- [ ] No

7.12. Do certain groups in your country have difficulty with access to treatment for CRC services?
- [ ] Yes, please describe which groups:
- [ ] No
7.13. Are there formal policies in place to determine priorities in receiving CRC treatment?

☐ Yes, please describe:
☐ No

7.14. In your opinion, do cancer treatment centers receive adequate funding?

☐ Yes, please describe:
☐ No, please describe:

7.15. Are there any other additional issues relating to cancer treatment services that are significant?

☐ Yes, please describe:
☐ No

7.16. Please indicate if any of the following targeted treatments are used in your country:

<table>
<thead>
<tr>
<th>Brand</th>
<th>Molecule</th>
<th>Access: All</th>
<th>Access: Limited (describe process to attain access to the drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eloxatin</td>
<td>Oxaliplatin</td>
<td>☐</td>
<td>☐ procedure:</td>
</tr>
<tr>
<td>5-FU</td>
<td>5-Fluorouracil</td>
<td>☐</td>
<td>☐ procedure:</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>Folinic Acid</td>
<td>☐</td>
<td>☐ procedure:</td>
</tr>
<tr>
<td>Erbitux</td>
<td>Cetuximab</td>
<td>☐</td>
<td>☐ procedure:</td>
</tr>
<tr>
<td>Campto/Camtosar</td>
<td>Irinotecan</td>
<td>☐</td>
<td>☐ procedure:</td>
</tr>
<tr>
<td>Avastin</td>
<td>Bevacizumab</td>
<td>☐</td>
<td>☐ procedure:</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td>☐</td>
<td>☐ procedure:</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td>☐</td>
<td>☐ procedure:</td>
</tr>
</tbody>
</table>

7.18. Is there any other information regarding novel/targeted treatments you feel is important to tell us?

Objective 8: To measure the appropriateness and adequacy of funding and management for CRC services throughout Europe.

8.1. In comparison to international best practice, how do you feel your country stands? Please only choose one that best fits your country’s status.

☐ Leading CRC practice and standards for other countries to follow
☐ Meeting international standards
☐ Believe CRC practice and standards could be improved upon, explain:
☐ Don’t believe that international practice applies to my country because:
☐ Other:

8.2. In what areas do you feel CRC care in your country could be improved upon?

8.3 Does your country have active participation in cancer research?

☐ Yes:
   1. Does your country have active participation in CRC research?
      ☐ Yes, in particular (describe focus):
      ☐ No
      ☐ No

8.4. Does your country have governmental funding of cancer research?

☐ Yes (please elaborate):
   1. Does your country have governmental funding of CRC research?
      ☐ Yes, in particular (describe focus):
      ☐ No
      ☐ No
Objective 9. To determine the usual methods of CRC care delivery.

9.1. Who performs the endoscopy services:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Endoscopist</th>
<th>Trained Nurse</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexible sigmoidoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy, diagnostic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9.2. What types of physicians provide care for CRC patients? Please check all that apply.

- General surgeon
- General surgeon with special training in CRC
- Digestive or gastroenterology surgeon
- General oncologist
- Digestive or gastroenterology oncologist
- Other:

9.3. What are the costs of the following services:

<table>
<thead>
<tr>
<th>Service</th>
<th>Cost borne by insurance</th>
<th>Out of pocket cost for patient</th>
<th>Other details relating to payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal occult blood test</td>
<td>€</td>
<td>€</td>
<td></td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>€</td>
<td>€</td>
<td></td>
</tr>
<tr>
<td>Colonoscopy, diagnostic</td>
<td>€</td>
<td>€</td>
<td></td>
</tr>
<tr>
<td>Colonoscopy, polypectomy</td>
<td>€</td>
<td>€</td>
<td></td>
</tr>
<tr>
<td>Average chemotherapy</td>
<td>€</td>
<td>€</td>
<td></td>
</tr>
<tr>
<td>Average surgical</td>
<td>€</td>
<td>€</td>
<td></td>
</tr>
<tr>
<td>Average radiotherapy</td>
<td>€</td>
<td>€</td>
<td></td>
</tr>
</tbody>
</table>

9.4. What is your perception of timeliness of new treatments for cancer?

- We are leaders in access to new treatments compared to other countries
- We are on par with other countries
- We are behind other countries
- Timeliness of new treatments differs in different regions within the country
- Timeliness of new treatments depends on health insurance
- Other:

9.5. Do CRC patients have out of pocket treatment costs?

- Yes, for:
  - endoscopy services: describe
  - standard treatment: describe
  - new treatment: describe
  - other:

- No

9.6. Is laparoscopic surgery offered to CRC patients?

- Yes, since (insert year):
- No
7. When radiotherapy is given, it is delivered:
- [ ] Pre-operative
- [ ] Post-operative

8. Elderly patients (80+ years) diagnosed with CRC, are offered:
- [ ] Palliative treatment
- [ ] No treatment
- [ ] Treatment with curative intent
- [ ] Other:

10. Where is CRC treatment generally delivered?
- [ ] General hospital, oncology department
- [ ] General hospital, gastroenterology department
- [ ] General hospital, department
- [ ] Specialist Cancer Hospital or Center
- [ ] Other, describe:
9. Which of the following chemotherapy regimens are most commonly advocated?

<table>
<thead>
<tr>
<th>Drug Combinations</th>
<th>Bolus</th>
<th>Delivery</th>
<th>Oral</th>
<th>In-patient</th>
<th>Out-patient</th>
<th>Home</th>
<th>Treatment Line 1st line</th>
<th>Treatment Line 2nd line</th>
<th>Stage I/A</th>
<th>Stage II/B</th>
<th>Stage III/C</th>
<th>Stage IV/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/FA</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<td>☐</td>
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<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5-FU + Oxaliplatin</td>
<td>☐</td>
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<td>(FOLFOX )</td>
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<tr>
<td>5-FU + Irinotecan</td>
<td>☐</td>
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<td>(FOLFIRI )</td>
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<tr>
<td>Uracil+Tegafur (UFT)</td>
<td>☐</td>
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<tr>
<td>Oxaliplatin+Irinotecan</td>
<td>☐</td>
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<tr>
<td>Oxaliplatin+Capecitabine</td>
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<td>Bevacizumab+</td>
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<tr>
<td>Other:</td>
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</tbody>
</table>
Thank you very much for your help in this matter. This report will help improve the standard of CRC services in Europe, and provide direction to future policies.
## Appendix 2

### List of national respondents

<table>
<thead>
<tr>
<th>Country</th>
<th>CRC respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Australia</td>
<td>Dr Debbie Gum, Research Associate Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, University of South Australia</td>
</tr>
<tr>
<td>2. The Czech Republic</td>
<td>Dr Tomas Sechser, Department of Infectious Diseases, Hospital of Masaryk Ústí nad Labem, and Ministry of Health</td>
</tr>
<tr>
<td>3. Denmark</td>
<td>Dr Karsten Vraenbeck, University of Copenhagen, Institute of Political Science, Copenhagen</td>
</tr>
<tr>
<td>5. Germany</td>
<td>Professor Matthias Graf von der Schulenburg, University of Hannover</td>
</tr>
<tr>
<td>6. Greece</td>
<td>Professor Mary Geitona, University of Thessaly and National School of Public Health, Athens</td>
</tr>
<tr>
<td>7. Hungary</td>
<td>Professor Laszlo Gulasci, Corvinus University, Budapest</td>
</tr>
<tr>
<td>8. Italy</td>
<td>Ms Cristina Masseria, LSE</td>
</tr>
<tr>
<td>9. The Netherlands</td>
<td>Ms Willemien Schurer, LSE</td>
</tr>
<tr>
<td>10. Poland</td>
<td>Professor Jacek Ruszkowski, Leon Kosminski Academy, Warsaw</td>
</tr>
<tr>
<td>11. Portugal</td>
<td>Professor Carlos Gouveia Pinto, Universidade Técnica de Lisboa - Instituto Superior de Economia e Gestão, Lisbon</td>
</tr>
<tr>
<td>12. Romania</td>
<td>Ms Irina Haivas, LSE</td>
</tr>
<tr>
<td>13. The Russian Federation</td>
<td>Professor Maria Avxentieva and Professor Pavel Vorobiev, Moscow Medical Academy, Moscow</td>
</tr>
<tr>
<td>14. Slovakia</td>
<td>Mr Dominik Tomek, Advisor, MoH Bratislava</td>
</tr>
<tr>
<td>15. Spain</td>
<td>Dr Julio Lopez-Bastida, Spanish Ministry of Health, Servicio Saluz Canario, Santa Cruz de Tenerife</td>
</tr>
<tr>
<td>16. Sweden</td>
<td>Dr Ulf Persson, Institute of Health Economics, Lund</td>
</tr>
<tr>
<td>17. Turkey</td>
<td>Professor Mehtap Tatar, Hacettepe University, Ankara</td>
</tr>
<tr>
<td>18. United Kingdom</td>
<td>Ms Candida Owusu-Apenten &amp; Dr Panos Kanavos, LSE</td>
</tr>
</tbody>
</table>
Appendix 3
Performance indicators

Performance indicators were created for Chapter 5 (Screening), Chapter 6 (Treatment), Chapter 7 (Pharmaceutical Treatment), and Chapter 8 (Surveillance). The purpose of the performance indicators and country rankings is to summarise all the information collected in the relevant chapters into a simple variable, reflecting a net positive or negative situation with regards to colorectal cancer service functioning in each country. The purpose of this simplification is to give an estimate of what countries may do well or what they may need to improve upon, based on the information received.

There are naturally limitations, some countries provided much more information than others, giving a good overview of what is occurring in their country, compared with other counties. In a small number of cases, survey questions could not be answered, thus no positive or negative points could be given. Much of the information gathered is derived from concrete, reliable sources, such as government publications, interviews with health policy makers and physicians, however, there is room for interpretation bias, opinion and perception which can affect the results. Additional peer-reviewed data was compared to survey answers for further substantiation, and queries were sent to respondents for further clarification when discordances occurred.

These indicators are positive or negative, depending on whether the survey question was a positive query (i.e. ‘Are there formal policies in place to determine priorities in receiving endoscopy services?’ with a yes or no response) or negative query (i.e. ‘What are the main problems surrounding the delivery of cancer care in your country?’ with a list of possible situations to acknowledge). Where there is a judgement on positive or negative nature of a point, the rationale is explained (Tables A1, A2). No judgement is made on screening methods, interval or ages, as each method has strengths are weaknesses. The maximum positive or negative score a country can receive is 100 percent. These rankings are a guide only, and show the country balance as a comparison of positive and negative indicators.
### Table A1

**Explanation of positive variables used in performance indicators**

(Indicators with judgement attached (J) are given additional explanation)

<table>
<thead>
<tr>
<th>Positive Indicators</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Cost-effectiveness analysis</td>
<td>Countries with peer-reviewed publications</td>
</tr>
<tr>
<td>2. Colorectal cancer screening</td>
<td>Formal screening 3 points (all eligible are invited with record keeping and monitoring), opportunistic screening 2 points (better than no screening but less population coverage), pilot screening 1 point (country indicates interest in activity), 0 points for no screening</td>
</tr>
<tr>
<td>3. Participation</td>
<td>Greater than 40% participation, reflecting base-case scenario where screening is cost-effective</td>
</tr>
<tr>
<td>4. Prevention campaigns</td>
<td>Only colorectal cancer prevention campaigns are rewarded</td>
</tr>
<tr>
<td>5. Screening campaigns</td>
<td>Only colorectal cancer screening campaigns are rewarded</td>
</tr>
<tr>
<td>6. Patient groups</td>
<td>Colorectal cancer groups within a national cancer group 1 point, separate colorectal cancer group 2 points</td>
</tr>
<tr>
<td>7. Physician groups</td>
<td>Colorectal cancer groups within a national cancer group 1 point, separate colorectal cancer group 2 points</td>
</tr>
<tr>
<td>8. Endoscopy delivery policy</td>
<td>Choice of centre</td>
</tr>
<tr>
<td>9. Endoscopy delivery policy</td>
<td>Endoscopy at 1st available center</td>
</tr>
<tr>
<td>10. Endoscopy delivery policy</td>
<td>Urgent patient priority</td>
</tr>
<tr>
<td>11. Endoscopy delivery policy</td>
<td>Nurse endoscopy</td>
</tr>
<tr>
<td>12. Endoscopy waiting times</td>
<td>&lt; 4 weeks, as less than 4 weeks is seen as target level for UK waiting times for diagnosis</td>
</tr>
<tr>
<td><strong>Treatment:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Treatment waiting time</td>
<td>≤ 8 weeks, as less than 8 weeks is seen as target level for UK waiting times for treatment</td>
</tr>
<tr>
<td>2. Treatment elderly</td>
<td>Curative, when applicable</td>
</tr>
<tr>
<td>3. Timeliness new treatment</td>
<td>Leader, perception by survey respondent</td>
</tr>
<tr>
<td>4. Practice and standards</td>
<td>Leader in colorectal cancer practice and standards for other countries to follow, perception by survey respondent</td>
</tr>
<tr>
<td>5. Treatment delivery policy</td>
<td>Patient priority</td>
</tr>
<tr>
<td>6. Treatment delivery</td>
<td>Cancer specialist hospitals</td>
</tr>
<tr>
<td>7. Treatment delivery</td>
<td>Specialist physicians: gastroenterology surgeon, gastroenterology oncologist</td>
</tr>
<tr>
<td>8. Treatment guidelines</td>
<td>Colorectal, rectal cancer</td>
</tr>
<tr>
<td>9. Treatment guidelines</td>
<td>Monitoring of treatment guidelines</td>
</tr>
<tr>
<td>10. Colorectal cancer research</td>
<td>Participant</td>
</tr>
<tr>
<td>11. Cost-effectiveness analysis</td>
<td>Peer-reviewed publications</td>
</tr>
<tr>
<td>12. Surgery</td>
<td>Choice of laparoscopic surgery for eligible patients</td>
</tr>
<tr>
<td>13. Radiotherapy</td>
<td>Pre-surgical in rectal cancer patients</td>
</tr>
<tr>
<td><strong>Pharmaceutical Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>1. Cost-effectiveness analysis</td>
<td>Peer-reviewed publications</td>
</tr>
</tbody>
</table>

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206 Berchi et al, 2004

207 Colorectal Cancer Collaborative Group, 2001
2. Targeted biological therapy 1 point for having sales, 2 points for having sales over €4,000 for cetuximab and €5,000 for bevacizumab, reflecting an estimate of over 25% of Stage IV eligible patients receiving targeted biological treatments (assuming €16,500 drug costs/patient for cetuximab, and €21,000 1st line acquisition costs for bevacizumab) J *  

3. Health technology assessment Part of reimbursement decisions  
4. Pharmaceutical guidelines Adjuvant, metastatic treatment  
5. Hospital formulary Flexibility to allow targeted treatments  
6. Other criteria applying Principles of equity, human dignity, and disease severity in addition to cost-effectiveness  

**Surveillance**  
1. Cost-effectiveness analysis Peer-reviewed publications on post-curative treatment surveillance  
2. Cost-effectiveness analysis Peer-reviewed publications on post-polypectomy (adenomas) treatment surveillance  
3. Surveillance guidelines Post-curative treatment surveillance  
4. Surveillance guidelines Post-polypectomy treatment surveillance  
5. Cancer registry Monitoring of recurrence  

**Notes:**  
1 Unless otherwise noted, each indicator receives 1 point.  
* Tappenden et al, 2007
Table A2

Explanation of the negative variables used in performance indicators \(^1\)
(Indicators with judgement attached \(^J\) are given additional explanation)

<table>
<thead>
<tr>
<th>Negative Indicators</th>
<th>Explanation</th>
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</thead>
<tbody>
<tr>
<td><strong>Screening:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Public awareness</td>
<td>Poor public awareness perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>2. Political awareness</td>
<td>Poor political awareness perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>3. Diagnostic delivery</td>
<td>Inadequate facilities, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>4. Diagnostic waiting time</td>
<td>Long, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>5. Actual waiting time</td>
<td>≥4 weeks, as greater than 4 weeks is seen as negative (^J)</td>
</tr>
<tr>
<td>6. Regional endoscopy resources</td>
<td>Poor, regions with poor endoscopy services</td>
</tr>
<tr>
<td><strong>Treatment:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Regional treatment facilities</td>
<td>Geographical inequities, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>2. Minority groups</td>
<td>Inequities of access, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>3. Treatment elderly</td>
<td>Curative treatment less likely</td>
</tr>
<tr>
<td>4. Quality of treatment</td>
<td>Poor, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>5. Out-of-pocket payment</td>
<td>Informal, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>6. Access to new treatments</td>
<td>Limited or poor, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>7. Access to new treatments</td>
<td>Delayed, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>8. Access to new treatments</td>
<td>None, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>9. Timeliness new treatments</td>
<td>Behind other countries, as perceived by the survey respondent</td>
</tr>
<tr>
<td>10. Practice and standards</td>
<td>Improvement of practice and standards compared to best international practice</td>
</tr>
<tr>
<td>11. Treatment waiting times</td>
<td>Long, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>12. Actual treatment waiting time</td>
<td>&gt; 8 weeks, as greater than 8 weeks is seen negative (^J)</td>
</tr>
<tr>
<td>13. Treatment delivery</td>
<td>Insufficient facility resources, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>14. Treatment delivery</td>
<td>Poor distribution of resources, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>15. Treatment delivery</td>
<td>Inadequate treatment facilities, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td>16. Treatment delivery</td>
<td>Insufficient human resources, perceived as major problem in colorectal cancer service delivery</td>
</tr>
<tr>
<td></td>
<td>Description</td>
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<tr>
<td>17</td>
<td>Treatment support</td>
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<tr>
<td>18</td>
<td>Treatment support</td>
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<td>19</td>
<td>Radiotherapy</td>
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<td>Treatment guidelines</td>
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**Pharmaceutical Therapy**

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<th>Description</th>
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<tr>
<td>1</td>
<td>Out-of-pocket payments</td>
</tr>
<tr>
<td>2</td>
<td>Regional treatments</td>
</tr>
<tr>
<td>3</td>
<td>Health insurance</td>
</tr>
<tr>
<td>4</td>
<td>Pharmaceutical guidelines</td>
</tr>
<tr>
<td>5</td>
<td>Pharmaceutical guidelines</td>
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<tr>
<td>6</td>
<td>Pharmaceutical guidelines</td>
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</table>

**Surveillance:**

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<td>1</td>
<td>Surveillance guidelines</td>
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<tr>
<td>2</td>
<td>Surveillance guidelines</td>
</tr>
<tr>
<td>3</td>
<td>Surveillance guidelines</td>
</tr>
</tbody>
</table>

**Note:** Unless otherwise noted, each indicator receives 1 point.

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208 Colorectal Cancer Collaborative Group, 2001.
References
