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Discussion paper 2010/07

March 2010

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Abstract

Colorectal cancer (CRC) is one of the most common forms of cancer in western countries and represents the second leading cause of cancer mortality in Europe. Early detection and removal of cancerous lesions can reduce the incidence of CRC, its mortality and improve patients' quality of life. The main literature on this topic refers to USA and few studies have been conducted in Italy to date.

Aim of the paper is to shed some light on the effectiveness and costs of CRC screening programs in the Italian health care system.

We use as case-study a Regional CRC screening program to determine the full costs and the effectiveness of the adopted techniques, FOBT combined with colonoscopy.

The costs involved in each phase of the program are valued using a micro-costing analysis. Effectiveness is valued in terms of early detected lesions and years of life gained. A MISCAN-COLON Model© is used to simulate and compare two alternative scenarios, with or without the screening program, and estimate the costs for year of life gained.

The preliminary results show that the screening will prevent almost 1.700 deaths in 30 years with an incremental cost effectiveness ratio of € 2.388,63 for life year gained. The results outpace those of previous studies, signalling an increasing effectiveness of CRC screening programme. Besides, the paper highlights the importance of implementing a screening not only for the effects that prevention can have in clinical terms, but also for the economic impact of such a policy in relation to the long-term sustainability of healthcare systems.

Key words: cost-effectiveness, colorectal cancer, screening, MISCAN-COLON Model
JEL codes: C13, H51, I10, I18

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1. Introduction

Colorectal cancer (CRC) is one of the most common forms of cancer in western countries, and represents the second leading cause of cancer mortality in Europe (AIRTUM 2009). Early detection and removal of cancerous lesions can reduce the incidence of CRC, its mortality (Mandel, Bond et al. 1993; Selby, Friedman et al. 1993; Lieberman 1995; Mandel, Church et al. 1999; Sonnenberg, Delco et al. 2000) and improve patients' quality of life (Ramsey, Andersen et al. 2000; Ramsey, Berry et al. 2002; Rauch, Miny et al. 2004; Miles and Wardle 2006; Taupin, Chambers et al. 2006).

The main literature on this topic refers to USA and few studies have been conducted in Italy so far (Lazovich, Weiss et al. 1995; Lieberman 1995; Kronborg, Fenger et al. 1996; Zappa, Castiglione et al. 1997; Declan Fleming 1998; Tappenden, Chilcott et al. 2007).

For this reason, the development of a specific study referring to a particular setting has been considered appropriate and relevant to shed some light on the effectiveness and the costs of screening programs in the Italian framework.

Aim of the paper is to present the results of a cost-effectiveness analysis of a screening program for the colorectal cancer prevention in Italy.

We use as case-study the experience of a Regional CRC screening program started in 2005 in the Province of Ferrara to determine the full cost of the screening program, compare the costs and the effectiveness of the adopted techniques (FOBT- faecal occult blood test- and colonoscopy). A micro-costing analysis is used to identify and evaluate all the costs involved in each phase of the screening program considering all the activities carried out during the patient pathway.

We present the results for the first two years (2005-2007) of screening activity in terms of set up costs, development, implementation and management of the prevention program and the costs of all the activities of diagnosis (FOBT and colonoscopy), surgery, oncological therapies and follow-up of the patients involved in the program. The effectiveness of the screening is valued in terms of early detected lesions, avoided deaths and years of life gained.

The preliminary results show that, after the screening implementation, a huge number of new cases of hyperplastic polyps, dysplastic adenomas and carcinomas are detected. Moreover, early diagnosis allows the diagnosis of colorectal cancer at the earliest Dukes' stages (Dukes 1932).

Finally, we use the cost and effectiveness data collected to estimate the costs for year of life gained, using a MISCAN-COLON Model © to simulate and compare two alternative scenarios with or without the screening program (Habbema, van Oortmarssen et al. 1985; Loeve, Boer et al. 1999).

2. Methods

This study aimed at calculating the cost-effectiveness of the CRC screening. In so doing, two separate, but interconnected phases were undertaken. Firstly, the actual cost of the CRC screening had to be determined, given that in the Italian context there are not robust proxies to estimate the cost of treatments. In so doing, the screening program was analysed in its macro-activities: adoption of the Regional project and provincial organization and coordination; community communication and information; management of the invitation and the FOBT; colonoscopy; surgery; oncology; radio-therapy; and follow-up treatments. In order to measure the resource consumption of each activity, a micro-costing methodology was adopted. This methodology, although more time-consuming, provides more detailed and reliable cost data in comparison to the gross-costing analysis (Brouwer, Rutten et al. 2001; Drummond and McGuire 2001).

The detection and measurement of the cost-item and their value were made through direct observation and in collaboration with the hospital and/or local health authority's staff and information system. The only exception was made for the anatomo-pathology laboratory costs, given the impossibility to calculate them, the limited relevance to the overall cost of the CRC screening and the availability of a Regional tariff system.

The effectiveness analysis was made adopting a general model for evaluation of the CRC screening in the micro-simulation program MISCAN-COLON (Loeve, Boer et al. 1999; Loeve, van Ballegooijen et al. 2005). The model is an adapted version of the model MISCAN (Habbema, van Oortmarssen et al. 1985), which was originally built and used for the evaluation of the breast cancer and cervical cancer.

The Model is based on a statistical structure as Markov, but it allows a lesser simplification and a greater flexibility to explore and analyse the different assumptions. It can be adapted, thus, to different type of tests used in performing a screening program.

Two parts of the program can be distinguished, a natural history part and a screening part. In the natural history part of the program, life histories are generated during which colorectal polyps and cancer may develop and sometimes cause death and in which no screening takes place. In the second part of the program, screening for colorectal cancer is simulated. Screening will change some life histories. The aggregated changes in life histories constitute the effectiveness of the screening. The effects of different screening policies can be compared by applying them to identical life histories. If one is solely interested in modelling the natural history of the disease, the screening part is not necessary. The stochastic model underlying

the simulation is specified in the input of the program. The input relates to demographic characteristics (e.g., the life table), the epidemiology and the natural history of the disease (e.g., the duration of preclinical cancer), and the characteristics of screening (e.g., the sensitivity of the screening test).

The total MISCAN-COLON package consists of two programs: (1) the actual simulation program, and (2) a post-processing program for processing simulation output. The random number generator is divided into two disjoint random number sub-sequences and requires two initial seeds. For each source of randomness the number of the random number subsequence can be specified, which can be used to reduce variance between simulation runs. For each new person in a simulation, the starting points of the random number generators are calculated. In this way, as long as the same initial seeds are used in simulations, in every simulation the same random number sequence is assigned to a life history. This reduces the variance between simulation runs. The output of the actual simulation program consists of two files, a file for post-processing and a standard output file. The post-processing file contains all important outcomes for the evaluation of a screening policy. It contains results per year, useful for detailed analysis, and aggregated totals over time that can be used directly by the post-processing program. The output in this file can be subdivided into maximally three groups of strata. The preclinical stage assigned to a positive screening or surveillance test is defined by the most advanced stage found by the test or during its diagnostic follow-up. The preclinical stage assigned to a negative test is the most developed stage within reach of the screening test. The age groups into which the output is divided, the reference year for discounting and the discount rates can be specified.

For any clinical stage, the annual number of entries and the number life-years can be tabulated in the output file on demand. The standard output file contains a summary of the input specifications and additional output data if desired, such as incidence and prevalence per age group. Extra output can easily be added to both output files.

The post-processing program uses the discounted totals over time in the post-processing output file to calculate the costs and effects of a screening policy. Costs are assigned to screening tests, diagnostic tests, surveillance tests, and cancer treatment based on the previous described micro-costing analysis. The post-processing program calculates costs per life-year gained and costs per prevented death using three discount percentages.

3. Results

In this section we first present the results of the micro-costing analysis for each screening phase, then the effectiveness data and, finally, the cost-effectiveness results of the MISCAN model simulation.

3.1 Costs results

In tab.1 we provide a synthesis of the actual costs of each macro-activity of the screening program for the biennium 2005-2007.

The total costs of the first level phase, which includes the set-up, the development, implementation and management of the prevention program is some € 393.639,62.

The unitary cost for a FOBT is € 5,59 per person, for a total cost of € 271.654,71. Individuals with a positive FOBT result are invited for a consultation with a physician, to evaluate the possibility to have a second level diagnostic exam. The cost of the visit is almost € 11,00 for patient, for a total cost of almost € 34.081,00 in the biennium.

For the second level of diagnosis, the cost of each endoscopic exam (partial or complete colonoscopy, with or without biopsy and polypectomy) has been calculated separately, in order to take into account the different resources consumption in each case (tab. 2).

The costs for endoscopic exams done in the first wave are almost € 465.000,00 (tab.1).

In the second level of diagnosis we also included the cost of complications, as blooding or perforation that required further interventions such as haemostasis or tattoos.

The cost of the surgical intervention includes the preparation activities, the operation and the post-surgery activities and it takes into account the differences in terms of times and material used in each type or intervention (ascendant or descendent colon, transverse colon or sigma). On average a single surgical intervention costs between € 2.060,00 and € 2.608,00.

The cost of the hospitalisation after the intervention has been calculated assuming an average length of stay of 7 days and a standard pharmacological therapy. For each treated patient a week of hospitalisation costs on average € 2.097,00.

For the first two years of screening, the total cost for the surgical treatment of all the 186 patients, including the costs of hospital in-stay, was almost € 823.000,00 (tab.1).

After an endoscopic exam or a surgical operation, part of the area detected during the investigation is sent to the anatomo-pathologic laboratory for a morphological biopsy.

The total cost of the anatomo-pathologic exams for the first wave is € 27.000,00 (tab.1).

Patients with lesions or cancer are sent to an oncologist to define the most appropriate therapy with respect to the cancer localization (colon or rectus), the cancer stage and their general health conditions.

Table 3 provides a summary of the costs of each type of oncological therapy according to the cancer stage. The total cost for the oncologic treatment of all the patients with cancer is almost € 312.139,00. This includes also the radiotherapy treatments (25 cycles), which costs on average € 875,00 per patient (at present, only one patient has been treated with radio-therapy).

In rare cases patients require a nutritional therapy of support if they have had an abdominal failure at the peritoneum: metastasis can cause an intestinal block and the patient is not able to feed anymore. The cost for the treatment of a single patient with an average expected life of 3 months is almost € 1.636,70.

In figure 1 we show the total costs for each macro-activity: the cost for the first two years of screening program is almost € 2.326.000.

3.2 Effectiveness results

The first effectiveness data referred to the screening program have been provided by the Tumours Register of the Province. The data show that since 2005, year in which the program started, the incidence of all lesions is increased. In particular, hyperplastic polyps are increased from 368 new cases in 2005 to 451 in 2006 (versus the 230 of the previous years), adenomas are increased from 1.043 new cases in 2005 and 1.242 in 2006 (versus the almost 800 in the previous years), but especially adenomas with dysplasia are increased from 300 before the 2005 to 444 and 655 in 2005 and 2006 respectively. Finally, in 2006 have been detected 492 new cases of cancer versus the 455 new cases in 2005.

An important result of the screening program concerns the stage of the detected tumours: since 2005 the cases of cancer in Dukes'stage A are increased from 10% to 14% with respect to 2004, whereas the cases of cancer in the worst stages are decreased, from 9,4% to 8,1% in stage B, from 53,2% to 50,6% in stage C and form 17,1% to 16,5% in stage D.

In the biennium 2005-2007 the incidence was of 12,6% for polyps, 47,6% for adenomas, 29% for dysplastic adenomas and 10,8% for cancers. Comparing these data with the incidence percentage registered before the screening program implementation (13,1% of polyps, 46% of adenomas, 18,2% of dysplastic adenomas and 22% of cancers) we can see how an early diagnosis of dysplastic adenomas can reduce the incidence of colorectal cancer in the future.

Adenomas, if early detected and removed can increase the possibility of a total eradication without metastasis diffusion (Mandel, Bond et al. 1993; Winawer, Zauber et al. 1993). This confirms the importance of the screening program, which not only can reduce the incidence of cancer and save human lives, but also can save future costs due to avoided surgical and oncologic treatments for the most advanced disease stages.

3.3 Cost-effectiveness results - MISCAN model simulation

The simulation program provides two outputs: a file containing all the outcomes for the evaluation of the screening policy (post-proceeding file) and a standard output file.

Results are reported per year and aggregated over time.

The file specifies the age groups into which the output is divided, the reference year for discounting and the discount rates. The annual number of entries and the number life-years are reported for each clinical stage. The discounted totals over time contained in the post-processing output file are used to calculate the costs and effects of the screening program.

Predicted effects and costs are calculated assuming a population of one million individuals, for a whole period of 30 years and in the two different scenarios, the one presence of biennial FOBT screening, and the one without screening. Effects and costs are discounted according to three discount rates: 1.5%, 3% and 4%[1].

In table 4 we report the predicted effects in terms of number of deaths and years of life lost for CRC. The results show that the screening allows a reduction of more than 1.770 deaths from CRC and a reduction of almost 17.000 life years lost (at 3% discount rate).

Costs are assigned to screening tests, diagnostic tests, cancer treatment and follow-up. The incremental costs of the screening program compared to the situation in absence of screening are almost € 40.983.000 (at 3% discount rate) as reported in table 5.

The cost effectiveness of the screening program is given by the ratio between the total screening costs and the prevented deaths or life-years gained.

The incremental cost effectiveness ratio (ICER) of the screening program compared to the situation in absence of screening is given by the ratio between the incremental costs of the program and its incremental effects (Drummond and McGuire 2001):

$$ICER = \frac{COSTS_{SCREENING} - COSTS_{NO\_SCREENING}}{EFFECTS_{SCREENING} - EFFECTS_{NO\_SCREENING}}$$

[1] We use a 3% discount rate according to the NICE guidelines.

The final results (tab. 6) show that the ICER (Incremental Cost Effectiveness Ratio) of the program, compared with no screening, for a 3% discount rate, is € 2.388,63 for life year gained and € 23.082,64 for avoided death.

4. Discussion

The results presented in this work show that a colorectal cancer screening program has certainly a great impact in terms of costs borne by the local health organization and the society. In presence of screening new cases of lesions and cancers can be detected, increasing the cost for the following treatments that would not have been borne in absence of screening. Nevertheless the effectiveness of the screening program cannot be valued only in clinical terms (number of lesions diagnosed, number of lives saved) but also in economic terms: the screening allows an early detection of adenomas and lesions at the first stages, with consequent savings of money due to avoided future treatments.

From an economic point of view, also the compliance rate has a strong impact in the program effects, as the fixed costs born to adopt and implement the program can be highly spread, reducing the unitary cost of the screening for single patient. A high compliance can increase the costs due to further diagnostic exams and treatments for the people found positives, but can also avoid the future costs of treatments, especially for the latest and worst stages of the disease.

The preliminary results of the MISCAN-COLON Model simulation show that the screening program will prevent almost 1.700 deaths, with 17.158 years of life gained in a period of time of 30 years (at a discount rate of 3%). Comparing the costs borne in the first wave of the screening with the number of years potentially saved, the model show that the incremental cost effectiveness ratio of the program is almost € 2.388,63 for life year gained.

The results of this study confirm the results of similar studies conducted in other countries (Sonnenberg, Delco et al. 2000; Sonnenberg and Delco 2002) and highlight the importance of implementing a screening program not only for the importance that prevention can have in clinical terms, but also for the economic impact of such a policy to save future avoidable expenses.

The different results obtained in our analysis, compared to Sonnenberg's, can be explained by four main factors. First of all, the rate of participation of the target population to the screening

is one of the factors that can impact on the effectiveness of any prevention program. Secondly, the epidemiologic characteristics of the target population that has above the average rates of CCR prevalence and mortality. Thirdly, the medical advancement in the treatment of cancer may have increased also the cost of therapy given the time lag between the Sonnenberg's study and our own. Finally, we adopted a micro-costing analysis that provided the study with more reliable data, than proxies like DRGs. However, these preliminary considerations needs to be further studied through technique such as the sensitivity analysis.

Some limitations of the study need to be considered. From a wider societal and economic perspective, we neglected the indirect costs of the screening program, such as the time off work for the subjects and their caregivers, travel costs, production losses, out of pocket expenses and intangible costs (Heitman, Au et al. 2008).

Besides, we did not considered any measure for the psychosocial consequences of the screening in terms of quality of life for the patients (Whynes, Neilson et al. 1994; Brodersen, McKenna et al. 2007) and mental health (Taupin, Chambers et al. 2006). Participation in screening programs for malignant disease may have psychological health effects that could outweigh the beneficial effects of the screening itself (Wardle, Williamson et al. 2003; Wardle, Williamson et al. 2003) and increase the anxiety in case of positive results (Miles and Wardle 2006). Attendance to screening program may results from individual risk aversion, patients'preferences (Pignone, Bucholtz et al. 1999) and psychosocial impacts (Tymstra and Bieleman 1987; Ling, Moskowitz et al. 2001).

Italy, as other countries world-wide, is going towards a national screening program, giving autonomy to the Regions to organise and manage the activities. In many Regions, like in the Emilia-Romagna, we have a large-scale data base with results from a real-world setting. Despite the limitations, the results strongly suggest that the screening program, through FOBT test, is likely to be cost-effective in the long-run. These data represent a relevant and strong argument to continue with, in the specific case of the Emilia-Romagna Region, and spread the program also in those areas still not covered.

Tables

Tab. 1 Cost for each activity, volumes and unitary cost for patient

Activity	Total Cost	Overall activity	Unitary costs*
Adoption and coordination	€ 122.729,30	99.207 invited	€ 2,53
Information activity	€ 38.362,20	99.207 invited	€ 0,79
Management	€ 232.548,12	99.207 invited	€ 4,79
FOBT	€ 271.654,71	48.596 tests	€ 5,59
Second Level-Colonoscopy	€ 498.724,41	2.362 exams	€ 211,14
Surgery	€ 823.127,52	186 patients	€ 4.425,42
Anatomo pathology	€ 26.787,61		
Chemo-radio therapy	€ 312.138,94	198 patients	€ 1.576,46

*the unitary cost has been calculated over the total number of patients entering the screening
Source: our elaboration

Tab. 2 Cost for each type of endoscopic examination

Endoscopic examination	Unitary cost
Complete colonoscopy (explorative)	€ 171,00
Complete colonoscopy with biopsy	€ 179,53
Complete colonoscopy with polypectomy	€ 232,10
Partial colonoscopy (explorative)	€ 140,54
Partial colonoscopy with biopsy	€ 171,64
Partial colonoscopy with polypectomy	€ 149,07

Source: our elaboration

Tab. 3 Costs of oncological therapies for each Dukes' stage of CRC

Colon treatments	Nr. of patients	Cost per patient*	Total costs
Polyps		€ 23,62	
A and B not at risk	112	€ 23,62	€ 2.644,97
B at risk and C, without comorbidities			
Folfox (6 cycles)	33	€ 4.496,42	€ 148.381,87
B at risk and C, with comorbidities			
Capecitabine (8 cycles)	42	€ 3.383,16	€ 142.092,84
D I line			
Folfiri+Bevaciz. (3 months)	6	€ 2.882,81	€ 17.296,83
D II line			
Folfiri+Cetuximab (3 months)		€ 11.082,03	
CPT-CET (3 months)		€ 13.949,69	
Folfox (3 months)		€ 4.496,42	
D III line			
Fumit-Mitomicina (3 months)		€ 772,95	
D with comorbidities			
Capox (3 months)		€ 5.023,81	
Fufaset (3 months)		€ 863,92	
Rectum treatments	**Nr .of patients**	**Cost per patient***	**Total costs**
A and B not at risk	4	€ 23,62	€ 94,46
not surgically treateed, without comorbidities			
Fluoruroracil + RT (35 days)	1	€ 752,84	€ 752,84
not surgically operated,			
with comorbidites (refuses infuser)			
Capecitabine + RT (5 weeks)		€ 864,46	
B surgically treated			
DeGramont+5FU+RT+DeGramont			
C stage			
Folfox+FU-IC+RT+Folfox		€ 4.496,42	
Radiotherapy (25 cycles)	1	€ 875,00	€ 875,00
*The unitary cost has been calculated assuming a patient with an average body mass of 70 kilos of weight and 170 cm of height.			

Source: our elaboration

Tab. 4 Predicted discounted effects of the screening compared to the situation in absence of screening

Number of patients invited and screened			
Discount rate	0.03		
	screening	no screening	difference
Nr. First Invited	450.297	0	450.297
Nr. rep inv.	2.033.153	0	2.033.153
Tot. invited	2.483.450	0	2.483.450
Nr. first screened	225.235	0	225.235
Nr. repeated s creen.	894.035	0	894.035
Nr. positives	54.366	0	54.366
Nr. negatives	1.064.904	0	1.064.904
Total screenings	1.119.270	0	1.119.270
Tot. Tests surv.	124.714	0	124.714

Effects			
Discount rate	0.03		
	screening	no screening	difference
Death for disease	**14.137**	**15.913**	**-1.776**
Life Years lost for CRC	**173.830**	**190.988**	**-17,158**

Source: our elaboration of MISCAN simulation results

Tab. 5 Predicted discounted costs of the screening compared to the situation in absence of screening

Costs			
Discount rate	0.03		
	screening	no screening	difference
Screenings	15.620.900	0	15.620.900
Surveillance tests	28.582.958	0	28.582.958
Diagnost. screening	11.442.978	0	11.442.978
Clinic. Diagnost.	8.002.901	9.437.482	-1.434.581
Screen Complications	0	0	0
Surv. Complications	374,142	0	374.142
Compl. diag. in scr. pr	124,749	0	124.749
Compl. clin. diag.	77,198	91,037	-13.838
Total treatment	213.193.340	226.907.420	-13.714.080
Total costs	**277.419.166**	**236.435.938**	**40.983.228**

Source: our elaboration of MISCAN simulation results

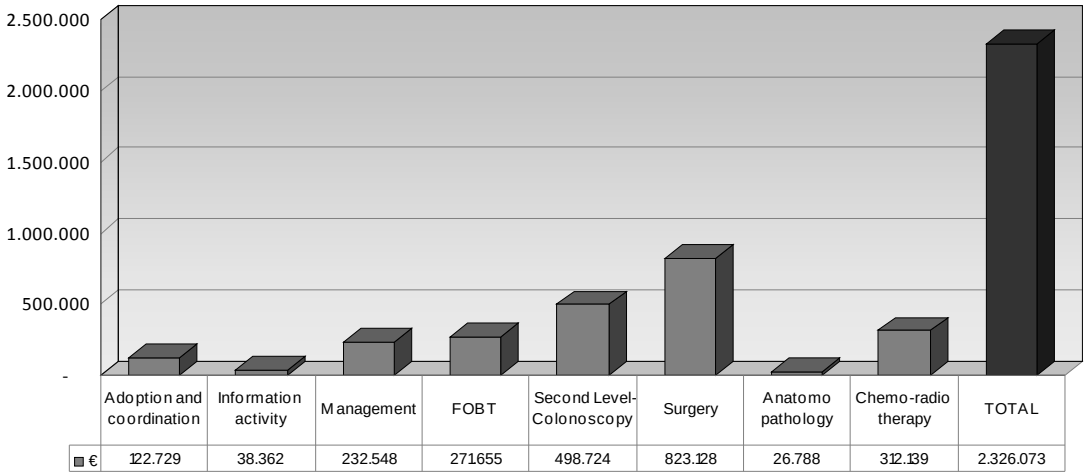
Tab. 6 Incremental cost-effectiveness ratio of CRC screening program

Discount factor	0.00	0.03	0.015
Incremental Costs			
Screening costs	€ 23.375.393	€ 15.620.899	€ 18.923.186
Surveill. costs	€ 63.272.752	€ 28.582.957	€ 41.689.740
Diagnostic costs	€ 16.817.046	€ 11.442.978	€ 13.734.907
Clinic diagnostic costs	-€ 2.980.002	-€ 1.434. 580	-€ 2.022.712
Complic costs	€ 988.443	€ 485.052	€ 677.713
Treatment costs	-€ 38.660.000	-€ 13.714.080	-€ 22.878.570
Total costs	€ 62.813.632	€ 40.983.227	€ 50.124.264
Effectiveness			
Lives gained	4.214	1.776	2.674
Life years gained	46.863	17.158	27.746
Incremental Cost-Effectiveness ratio			
Cost per avoided death	€ 14.905	**€ 23.082**	€ 18.742
Cost per life year	€ 1.340	**€ 2.388**	€ 1.806

Source: our elaboration of MISCAN simulation results

Figures

Fig. 1 Total cost of each level of activity



Source: our elaboration

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This paper has been produced by the Healthcare Management Group
at Imperial College Business School

ISSN: 1744-6783

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