The Global Paradigm Shift in Screening for Colorectal Cancer

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Abbreviations: CRC – colorectal cancer; PBOS – population-based organized screening; SOS – structured organized screening; ASR – age-standardized rate; OMED – Organization Mondial d'Endoscopy Digestive; WEO – World Endoscopy Organization; FIT – fecal immunochemical test for hemoglobin; gFOBT – guaiac fecal occult blood test; IARC – International Agency for Research on Cancer; RCT - randomized controlled trial; FS -flexible sigmoidoscopy.

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Introduction

In the last 20 years screening for colorectal cancer (CRC) has undergone a paradigm shift once its prevention potential was recognized. It has progressed from parochial "*ad hoc* opportunistic" activities, led by clinical champions, to a structured, organized public health priority tailored to specific health-care environments in population-based settings. 2018 marks the 20th anniversary of a global initiative established by the Organisation Mondiale d'Endoscopie Digestive (OMED, now World Endoscopy Organization, WEO) that was charged "to promote the international implementation of CRC screening programs".[1] This commentary evaluates this remarkable healthcare transformation and the reasons for its success.

CRC is a major worldwide public health issue ranked in the top ten diseases for health burden by the World Bank.[2] While there is wide geographic variation in CRC incidence (Figure 1A),[3] being higher in developed than developing countries, incidence is increasing in those with growing affluence (Figure 1B).[4] It is predicted that by 2040, the number of cases will have risen from 1.850 million now to 3.093 million in 2040 (http://gco.iarc.fr/tomorrow/home). This huge burden remains a challenge despite the expert consensus view that CRC is one of the most preventable cancers.[5] [6] Secondary prevention is effective in reducing incidence and mortality without regard to lifestyle changes.

Establishment of a global expert network

Five decades ago, WHO developed criteria for a public health approach to screening providing that evidence and health burden justified it and it was feasible[7]. Two decades ago the evidence emerged. Guaiac-based fecal occult blood tests (gFOBT) had been proven to reduce mortality through early detection of neoplastic lesions.[8-11] Colonoscopy had been shown to reduce incidence and CRC mortality following polypectomy,[12] subsequently supported by flexible sigmoidoscopic screening.[13-17] Fecal immunochemical tests for hemoglobin[18] (FIT) had been shown to reduce CRC mortality,[19] and then promised to replace gFOBT.[20] Guidelines for screening had emerged even before definitive supporting evidence in Australia[21] and soon after in the USA. [22, 23]

It was in this environment in 1997 that colleagues, led by Massimo Crespi and Glaciomar Machado, proposed the establishment of a global network. OMED endorsed this approach by convening a CRC Screening Committee (SC) to provide "a forum for international interaction" and "promote innovation" and collaboration "with fellow professional associations".[1, 24] It was felt that this would facilitate translation of the evidence into clinical practice and reduce the CRC burden. The initial committee of 12 members (see Acknowledgements) first met in Vienna in 1998, under the chairmanship of Paul Rozen.[24]

Style of the network

From the outset the committee did not deviate from its mission. Where evidence was inadequate or new solutions necessary, committee members conceptualized, discovered and critically evaluated likely solutions. The meeting style adopted was of short focused talks and uninhibited critical discussion that included early- and mid-career colleagues. An atmosphere of collaboration and mutual respect prevailed, thus stimulating innovation and a thirst for understanding. Members lead or contributed to the development of guidelines, interacted with policy-makers, funders and governments and debated challenging dichotomies, which included:

- one-step screening (colonoscopy) *versus* two-step screening (a simple test selecting who gets colonoscopy),
- the importance of technology (accuracy) *versus* behavior (acceptability and feasibility),
- structured opportunistic screening in a clinical setting *versus* organized population-based public health programs,
- CRC and advanced adenomas *versus* only CRC as the crucial screening target,
- Classical colorectal adenomas *versus* serrated lesions, their prevalence, nature and how best to detect them.

What emerged from this network

The global network grew from 12 individuals from eight countries in 1998 to 1,180 from 78 countries in 2018 (Figure 2). Graeme Young became Chair in 2005 and Linda Rabeneck in 2013. Network activities grew from one to at least four regional meetings annually, led by regional chairs, held in Europe, Asia-Pacific, North and South America. Annual meeting attendance increased exponentially (Figure 2).

While initially championed by gastrointestinal experts promoting the adoption of an effective test with little involvement of public health professionals, it grew to be a truly multidisciplinary professional network – including

gastroenterologists, epidemiologists, surgeons, bench scientists, pathologists, imaging specialists, public health experts, behavioral scientists, sociologists, nurses, statisticians, plus representatives from governmental, patient, and cancer organizations. The strategy that emerged – provision of an effective evidence-based screening test in an organized, high quality, tightly-monitored, structured program directed at an informed and responsive population, that was feasible within the relevant health care environment – reflected the WHO principles for screening[7] and IARC definition of an organized program.[25]

It took time to engage public health experts, with their expertise and focus on sustainable, cost-effective, population-based interventions. Some saw CRC screening ~~was~~ to be ~~seen to be~~ more challenging than breast and cervical cancer screening, in part ~~because of the complex risk groups for CRC and the characteristics of the screening test options.~~ due to complexity of the screening program, multiplicity of risk groups needing personalized approaches, multiple test options, high-volume invasive diagnostic testing (colonoscopy) and risks inherent in removal of the precancer lesions.

CRC screening was seen as a multi-phase organized process (Figure 3) in which failure in any step would compromise mortality reduction.[25, 26] Monitoring of each phase for service quality, especially colonoscopy withdrawal time and adenoma detection rate,{Meester, 2015 #586} was important to population benefit and credibility with funders, policy makers and the public.[27] The wide variation in health-service environments meant that no single program design could be applied globally.

By sharing experiences and providing practical examples, new standards and expectations were developed. Those new to screening implementation were able to scrutinize earlier experiences, choose the right protocol, process and test for their environment, accept the challenge to do it even better and to avoid the pitfalls others encountered. Members were energized and became powerful advocates for CRC screening in their respective environments.

To address issues that were perceived to be either neglected or challenging, Expert Working Groups (EWG) were established in 2012 and 22 peer-reviewed consensus documents have so far emerged from these (see { HYPERLINK "http://www.worldendo.org/about-us/committees/colorectal-cancer-screening/ccs-testpage2-level4/" }).

Industry involvement was encouraged with a beneficial impact on technology development. Industry was exposed to the issues facing the public and health professionals. As a result, major advances were made in the steps leading to diagnosis. For example, qualitative gFOBTs have been replaced by quantitative FIT,[6, 20, 28] and the introduction of molecular tests presents new opportunities.[29]

Detection of neoplasia was seen in a public health framework as being the product of access, participation, and test sensitivity, together with program principles of feasibility, acceptability and equity. The test options for CRC screening differ greatly in terms of access, simplicity, acceptability and cost; studies now show that these differences affect participation. For example, better participation is achieved with FIT compared to gFOBT.[30] Increasing awareness of the benefit of screening[31] and developing processes that facilitate easy participation[30] all serve to improve screening.

Global explosion in screening activities

The nature and coverage of CRC screening increased across the globe (Table 1) in these two decades.[1, 24, 28, 32-35] Given the need to be feasible within the local health-care environment, two types of public health, WHO and IARC principle-consistent programs emerged (in contrast to *ad hoc* opportunistic screening): population-based organized screening (PBOS) and structured opportunistic screening (SOS)[6, 25, 33].

PBOS has an explicit policy, a team responsible for organization, invitation and health care, processes to monitor and improve quality and outcomes. In 1999, the only PBOS (including pilots) were in Japan (which started in 1992), Uruguay and Italy.[24] By 2002, Australia, Taiwan, France and UK had started pilot programs to assess their feasibility.[1] By 2015, 22 countries had commenced and by 2018 this has grown to at least 30 countries with an additional 19 in the pilot phase (Figure 4).[35] Almost all countries with a PBOS have chosen two-step screening with FIT as the first step (see Table 1). Only Italy and the UK now include flexible sigmoidoscopy (FS) as an initial screening test and few have adopted colonoscopy. Insufficient endoscopy workforce capacity and skill is the major factor, and for colonoscopy the lack of RCT-evidence (although these are now underway) and equity of access.

SOS had already gathered momentum in the USA in 1999, with Germany just underway (Table 1).[1, 24] By 2018 this had grown to nine countries promoting SOS (Figure 4). Colonoscopy is somewhat more likely as the screening test in SOS. In reality, many countries have some degree of *ad hoc* opportunistic screening which may run in parallel with PBOS depending on the health care environment and its funding.

All but two of the 30 countries with an age-standardized CRC incidence rate (ASR, 0-85 years) of 30 per 100,000 or greater[3] have PBOS or SOS underway (data not shown). Thirty-six with incidence rate ≥25/100,000 are beyond the pilot phase (data not shown). Pilot screening programs (see Table 1 for concept explanation) are highly desirable before committing to PBOS. Besides determining feasibility, they enable calculation of cost-effectiveness based on actual local observations rather than modelling. Such have proved useful in convincing authorities to proceed in many countries but as is evident in Figure 4 and Table 1, some jurisdictions are slow in advancing from pilot to PBOS.

Screening programs are heterogeneous.

While the highest level of evidence (multiple RCTs) supports implementation of FOBT screening for the general population 50 years and older,[8-10] many countries have constrained their PBOS programs in various ways so as to manage the resultant colonoscopy workload in an equitable, timely and high-quality manner. For instance, countries such as England and Australia have initially constrained the age-range of those offered screening while settings such as the Netherlands and Scotland have tailored the sensitivity of FIT (using a higher quantitative FIT threshold) to reduce colonoscopy workloads. Whilst many countries have a PBOS in place, most have scope for further adjusting FIT thresholds for positivity (using quantitative FIT), increasing coverage, and improving participation rates and/or colonoscopy quality.

Since CRC screening is a multiphase process (Figure 3)[26] that must be feasible within a health-care environment, remarkable diversity in processes, summarized in Table 2, is seen across jurisdictions.

The new screening tools

The impact of gFOBTs on CRC mortality in the RCTs was modest[8-10] as they missed cancers and many adenomas.[36] Quantitative FIT have proved superior to gFOBT: increased participation rates (single stool sample and simpler collection technique), automated analyzer for objective and consistent measurement, increased sensitivity for cancer and adenomas, no significant drug or dietary interference and an objective adjustable endpoint that can be tailored to available colonoscopy capacity and expectations of test performance.[20] FIT eventually replaced gFOBT and became a game-changer for two-step screening.

Biomarkers other than hemoglobin are now under investigation, including those in stool relating to neoplastic tissue and the microbiome[37] and in blood. Blood tests for circulating tumor-derived DNA (ctDNA) are emerging but lack sensitivity for adenomas.[38 39] The multi-target stool test based on an algorithm including stool hemoglobin and certain genetic events (somatic and epigenetic) is the most sensitive of the available non-invasive screening tests.[29]

What comes next for screening?

Despite the explosion in screening programs, there is much more to be done as emphasized in a recent report from Asia.{Chiu, 2017 #588}

Commitment to an adequate *infrastructure* (Figure 3) can be lacking. Jurisdictions vary greatly in their commitment to training the workforce needed to conduct a full program. The desired outcomes of a program must be set, every important measurable event monitored and actual performance relative to goals reported on a regular basis. Monitoring identifies underperforming areas and facilitates improvement. Health system data access including cancer registries are vital infrastructure components.

Population reach remains a concern for all countries. Reported participation uncommonly exceeds 65% and can be as low as 9%.[28, 35] Inequities are frequently seen according to age, sex, education, ethnicity, language and socioeconomic status. Obstacles to participation need to be addressed by considering lessons learned from higher-participation programs. Solutions are required for failure to progress to diagnostic colonoscopy following a positive test in two-step screening with uptake in most programs less than 90%.

The *quality* of colonoscopy is emerging as a fundamental challenge and attention to quality measures will improve screening.{Meester, 2015 #586} The processes for monitoring performance and taking remedial action are not

always well-defined and tend to be under-resourced. Image-enhanced endoscopic methods are being developed for difficult-to-detect lesions such as sessile serrated adenoma but have not proved to be superior to white light endoscopy in experienced hands. Two of the Expert Working Groups (Interval Cancers and Image-enhanced Endoscopy) have emphasized the importance of high-quality procedures to detect flat and/or sessile lesions so as to avoid interval cancers.{Rutter, 2018 #585}

Greater *personalization* of screening that adjusts age to start screening, screening intervals and choice of screening test according to an individual's risk would enable us to move on from the standardized somewhat impersonal approach characteristic of PBOS. Personalization is possible using data held by health-care systems but better access to such data at each phase together with processes to deal with privacy concerns will be needed. Age, sex, family history, diet, BMI, lifestyle (including alcohol and smoking), ethnicity, socioeconomic history, genetic polymorphisms, past screening behavior and colonoscopic investigations as well as past FIT stool concentration levels (even when negative),[40] can potentially be used to create algorithms and make decisions about when to screen, how often to screen and whether to undertake two-step or one step screening. This is particularly attractive for resource-limited countries or those where subpopulations have widely differing risks.[41] Artificial intelligence might facilitate this. Given the evidence for increasing CRC incidence at a younger age, consideration to expand the target age-range is required.[42]

Integration of *research*, whether basic, applied or health delivery in nature is proving increasingly difficult as countries commit to mandated programs and monitored outcomes. Very few countries have structurally incorporated such research into their program and this is essential if we are to further improve delivery and fully evaluate potentially better tests.[43]

Although huge gains in screening programs have been achieved, the SC continues to strive to conduct the necessary research and support appropriate translation into good evidence-based screening practice.

Conclusions

CRC screening is unique amongst cancer screening programs due to its complexity, multiple test options that can be adapted to suit local circumstances, and capacity to detect and *easily* remove the precancer lesion and hence prevent the cancer.

Huge progress has been made in providing evidence and translating this into screening practice as demonstrated by the documented increase in organized programs. Screening programs that are feasible within the resources of the local health care environments and include explicit policy, monitoring of outcomes and mechanisms to achieve quality assurance – all essential WHO and IARC principles – are now widespread (Table1).{European Colorectal Cancer Screening Guidelines Working Group, 2013 #558;Ponti, 2017 #569} It is remarkable to see the diverse ways in which such complex programs have been implemented across the globe and adapted to suit relevant circumstances (Table 2). Despite the advances made, however, provision of structured organized screening in most countries still falls short of what is justified by the evidence base{Altobelli, 2014 #556;IARC, 2018 #575;Schreuders, 2015 #555}{Chiu, 2017 #588} and jurisdictions can be slow to commit to rolling out screening beyond pilots as deomonstrated by the failure in some countries to move from pilots to expanded and organized programs.

It is no longer considered that CRC screening is a simple clinical exercise in detection but rather a multiphase public health initiative requiring multidisciplinary support and integration into the relevant health-care system. If one step fails, the whole process fails.

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Figure legends

Figure 1. Current status and trends in the worldwide incidence of colorectal cancer.

A: Geographical variation in the estimated age-standardized incidence rates of colorectal cancer (both sexes, ages 0-85 years).[3] The ASR for Hong Kong and Taiwan are shown separately because of their very different rates to adjacent areas. [Data sources: Hong Kong Cancer Registry (online calculator: http://www3.ha.org.hk/cancereg/allages.asp) and Taiwan Cancer Registry (http://tcr.cph.ntu.edu.tw/uploadimages/Top%2010%20cancer%20in%20Taiwan%202008-2014.pdf).

B: Trends in age-standardized incidence rates (both sexes, ages 0-69 years) of colorectal cancer, from 1977 to 2014 shown as the three-year moving average. Data are shown for selected countries to show contrasting trends in countries from different regions.[4] Data for Brazil, China, India, Philippines, Thailand and Uganda are available only for specific regions in those countries and so may provide an incomplete picture.

Figure 2. Growth in World Endoscopy Organization Colorectal Cancer Screening Committee (SC) membership (which is open to anyone who is interested) and SC meeting attendances, 1998-2017.
Data for membership for 2001-2005 are unclear. Attendances have not been corrected to allow for changes in attendances at the adjacent regional meetings (i.e., Digestive Diseases Week – DDW, Asia-Pacific Digestive Week – APDW and United European Gastroenterology Week – UEGW). The first two "main" SC meetings were held as part of the World Congress of Gastroenterology and thereafter adjacent to DDW. The first Asian meeting was held in 2007 (at Kobe, APDW) and the first European meeting in 2008 (at Vienna, UEGW). Annual Latin American meetings began with SOBED (Brazilian Society of Digestive Endoscopy) and SIED (Pan American Digestive Disease Week) conferences in 2016.

Figure 3. Conceptual model for processes and options applicable to structured organized screening for colorectal cancer that ensure coordination across phases in the screening process. Note infrastructure and other requirements including attention to quality of care, transition between providers, monitoring of outcomes and incorporation into policy and health care environment. Adapted from the PROSPR model.[26]

Figure 4. Growth in structured and/or organized screening activities since 1999 according to their nature and implementation.
See Table 1 for sources of information and definitions of the nature of such activities. *Ad hoc* opportunistic screening is not included.

Tables

Table 1. Global status of structured and organized CRC screening by world region and country or place, showing growth in activities and the number and nature of the predominant program over the last 20 years.

World Region	Predominant style of program[a]	1999	2002	2015	2018
Europe	Population-based organized			13 (Belgium, Croatia, Czech Republic, Denmark, France, Ireland, Italy, Lithuania, Malta, Netherlands, Slovenia, Spain, United Kingdom.)	19 (Belgium[c], Croatia [b], Czech Republic[c], Denmark[c], Estonia[c], France[c], Hungary*[c], Ireland[c], Italy[c,d], Lithuania[c], Luxembourg[c,e], Malta[c], Montenegro[c], Netherlands[c], Norway*[c], Poland*[e], Slovenia[c], Spain[c], United Kingdom[c,d].)
	Population-based organized pilot	1 (Italy, regional)	3 (underway: France, Italy, UK) 3 (agreed to undertake: Netherlands, Spain, Austria)	7 (Finland, Norway, Montenegro, Poland, Portugal, Serbia and Sweden)	7 (Austria[c], Cyprus[c], Georgia[c], Portugal[c], Serbia[c], Sweden[c], Switzerland[c,e,f],)
	Structured opportunistic	1 (Germany)	2 (Germany, Czech Republic)	5 (Austria, Germany, Greece, Latvia, Switzerland)	4 (Austria[e], Germany[e], Greece[e], Latvia[b])
North America	Population-based organized	0		1 (Canada)	1 (Canada[c,f])
	Structured opportunistic	1 (USA)	1 (USA)	1 (USA)	1 (USA[c,d,e])
Latin America	Population-based organized			1 (Uruguay)	1 (Uruguay[c])
	Population-based organized pilot	1 (Uruguay)	1 (Uruguay)	3 (Argentina, Brazil, Chile)	3 (Argentina, Brazil, Chile)
	Structured opportunistic			1 (Colombia)	1 (Colombia)

World Region	Predominant style of program[a]	1999	2002	2015	2018
Africa	Population-based organized pilot				1 (Morocco)
Central, west, south Asia	Population-based organized			2 (Israel, UAE)	2 (Israel[c], UAE)
	Population-based organized pilot	1 (agreed to undertake, Israel)	1 (pending commencement, Israel)	2 (Bahrain, Kuwait)	6 (Bahrain, Kuwait, Kazakhstan, Lebanon, Qatar, Saudi Arabia)
	Structured opportunistic			2 (Saudi Arabia, Iran)	1 (Iran)
East and south-east Asia	Population-based organized	1 (Japan, regional)	1 (Japan, regional)	4 (Japan, Taiwan, Korea and Singapore)	5 (Japan[c], Taiwan[c], Korea[c], Hong Kong[c] and Singapore[c])
	Population-based organized pilot		1 (Taiwan) 2 (being considered, Korea, Hong Kong)	3 (PR China, Hong Kong, Thailand)	2 (PR China, Thailand)
	Structured opportunistic		1 (Japan)	2 (Japan, Malaysia)	2 (Japan[e], Malaysia)
Oceania	Population-based organized	0		1 (Australia)	2 (Australia[c], NZ*[c])
	Population-based organized pilot	1 (agreed to undertake, Australia)	1 (underway, Australia)	1 (NZ, pilot complete)	

* The roll-out of population-based organized screening (PBOS) programs from pilot to population program takes some years with variation between jurisdictions as to whether this is implemented locally, regionally or nationally. For example, some pilot regions just continue as the early stage of a more wide-spread program. No effort has been made to identify whether programs are at an early or more mature stage except where they are formally transitioning from a pilot in which case they are identified as PBOS and marked "*". More detail may be obtainable from the cited sources.

[a] Nature of program - Definitions:

Population-based organized screening (PBOS): The definition is adapted from that applied by IARC.[25] These programs aim to operate at a population level and target an 'age defined' population. They follow an explicit policy, with structures responsible for organization, including invitation, primary (e.g. FIT) and secondary testing (e.g. colonoscopy), service monitoring including outcomes and quality assurance.

Population-based pilot programs: These population programs are undertaken on a limited scope, usually at a regional level and with intent to roll out if successful. The usual goals are to test feasibility, test procedural options, gain experience and gain support for progressing to a PBOS program. Elements such as an explicit policy, structures responsible for organization, including invitation, primary (e.g. FIT) and secondary testing (e.g. colonoscopy), service monitoring including outcomes and a structure for quality assurance may not be fully determined or need testing.

Structured Opportunistic screening (SOS): This is screening supported by official policy (not merely professional guidelines) with support at a public health level and by funders such that it aims to achieve extensive coverage of the target population. Attention to quality and monitoring of outcomes must be included. This does not include *ad hoc* opportunistic screening either in the absence of or outside an organized screening program that relies on recommendation from individual health-care providers or individual self-referral.

[b] screening test is gFOBT.
[c] screening test is FIT.
[d] screening test is sigmoidoscopy.
[e] screening test is colonoscopy
[f] status of most active jurisdictions within this country where a national policy is not feasible at present.

Methodology: The predominant style of program and principle screening test have been determined using information sourced from selected authoritative publications[1, 24, 28, 32-35] supported by documented presentations to the World Endoscopy Organization Colorectal Cancer Screening Committee and a survey of WEO members in 2018 with responses from 46 countries or places. The latter was used to clarify conflicting information. Definitions for Population-based organized screening (PBOS), structured opportunistic screening (SOS) and pilot PBOS are given above.

Ad hoc opportunistic screening occurs in many countries, sometimes as the only form of screening but also as an alternative and alongside organized programs. This *ad hoc* activity is generally practitioner-based and is not included in the category termed SOS even when supported by professional guidelines.

Table 2. Diversity of approaches around the world determined by the health-care environment and according to the phase of CRC screening. Remarkable diversity is apparent regardless of whether the approach is as a population based organized screening program or structured organized screening.

Phase of screening process	Examples
Screening test distribution -	1. Distribution to the home (e.g. by post or courier) from a central coordinating location. This can occur with or without advance notification. 2. Available from local non-physician site such as pharmacies. 3. Available from primary care physicians or specialists. 4. Available through request by internet, phone or mail.
Site for analysis of non-endoscopic screening test.	1. Centralized and dedicated laboratory determined by contract for the mandated manufacturer's test. 2. Approved pathology service laboratory for tests in use. 3. In-office testing.
Notification of test result	1. By letter to invitee and/or nominated/requesting physician. 2. By telephone call from screening facility, physician's office or central facility. 3. In person by physician. Note: Such notification may or may not also include immediate scheduling of follow-up investigation as needed.
Colonoscopy provision (as screening test or simple-test follow-up)	1. By coordination through mandated screening process using approved dedicated screening colonoscopy facilities. 2. By designated and accredited screening colonoscopists (physicians/internists/surgeons, nurses, technicians etc.). 3. By "usual care" processes available to participants through their chosen accessible options. Note: Data reporting obligations and processes vary considerably between these options.
Histopathology	1. By pathologists dedicated and accredited for CRC screening pathology (including regular audit review of service quality, quality assessment program for screening pathologists). 2. By "usual care" processes available to colonoscopists.
Monitored data and managed quality assurance	1. Monitoring might be by centralized computer monitoring of all service activities and results reported to it, especially for designated outcomes of interest. How this operates depends on data reporting obligations and processes in place. 2. Monitoring of quality is often devolved to local facilities which might or might not be required to report regularly to a governing authority. 3. Regional or national cancer registries are crucial measurement for impact. Note: regular service audits and data review vary considerably between these options.
Navigation between phases	1. By centralised coordinating staff with real-time access to data and authority to manage processes such as notification of results and coordination of appointments (such as for colonoscopy). 2. By "usual care" processes determined by choice of participant and according to advice from their chosen physicians.