The Chemoprevention of Colorectal Cancer

Background Information provided by the Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration for a Forthcoming Meeting of the Food and Drug Administration Gastrointestinal Drugs Advisory Committee that will be held on March 19, 2002.

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Executive Summary

The *Food and Drug Administration* is seeking advice from members of the *Gastrointestinal Drugs Advisory Committee* on the development of appropriate criteria to determine the efficacy and safety of chemopreventive agents (CPAs) in the US that may reduce the risk of sporadic colorectal cancer. The agency is interested in obtaining input that will lead to the elucidation of meaningful clinical benefits and establishment of acceptable standards for the design of pivotal controlled clinical studies. Consideration will be given to study inclusion/exclusion criteria based on risk for sporadic CRC, the significance of adenomatous polyps as study endpoints and the necessary duration of treatment to achieve an adequate evaluation of safety and benefit/risk. Moreover, issues surrounding the evaluation of important drug classes, such as nonsteroidal anti-inflammatory drugs, will be discussed.

An analysis of meaningful clinical *benefits* associated with CPA treatment must be made in the context of current standards for colonoscopic screening/surveillance and removal of adenomatous and malignant colorectal polyps by polypectomy. Adherence to these standards has been demonstrated to be an effective cancer prevention strategy in individuals with normal or increased risk for the development of sporadic CRC. Moreover, colonoscopy is associated with a relatively low risk for procedure-related clinical complications. Therefore, results of studies of a CPA(s) must support an indication of treatment either as an *adjunct* or as an *alternative* to colonoscopic screening/surveillance. In addition, each intended clinical benefit must be supported by appropriately crafted study designs and a body of evidence that provides a sufficient evaluation of safety to enable an informative benefit/risk analysis of long-term outcomes.

The value of using certain surrogate endpoints for CRC risk in clinical trials of CPAs, such as the incidence of recurrence of colorectal adenomas, is called into question by several findings. First, the average transition time of small adenomas to invasive CRC has been estimated to be at least 10 years. Second, the probability that a small adenoma in individuals not treated with a CPA(s) contains high grade dysplasia/malignant changes is small. Moreover, most small adenomas do not progress to malignancy. Third, in the *National Polyp Study* it was found that although one year after screening colonoscopic polypectomies to 'cleanse' the colon of polyps the percentage of patients with recurrent small or medium adenomas without advanced histopathological features exceeded 30%, the incidence of recurrent histopathologically advanced lesions or CRC was lower than the expected incidence in subjects without colonoscopy, even after 3 years of followup.

From these observations it can be concluded that a transient short-term polyp suppressive effect that disappears during long-term treatment in 'responder' patients is unlikely to be clinically useful. An important limitation of short-term treatment protocols is that a determination whether adenoma suppression in 'responders' is durable cannot be made. When extrapolated to clinical practice, CRC suppression by a CPA(s) may be compromised by poor compliance during long-term administration and/or insufficient duration of treatment. There may be instances in which CPA treatment slows the natural course of macroscopic polyp expansion but does not effectively eliminate microscopic adenomatous cell dysplasia and malignant transformation. As stated

above, in the US small polyps and microscopic adenomas not detectable by colonoscopy are unlikely to contain malignant cells. Appropriately designed long-term clinical outcome studies would determine whether the same relationship between adenoma size and likelihood of dysplasia/cancer is present in CPA treated patients.

An analysis of *risk* associated with CPA administration is impacted by the fact that the intended treatment population includes a high proportion of geriatric patients who have a high incidence of systemic diseases and are frequently exposed to multiple pharmaceutical agents. Because of these characteristics, there is a substantial potential for clinically important drug-drug interactions and drug toxicity.

In the US the life-time risk for developing sporadic CRC in the average risk population is approximately 6 percent and between twofold and fivefold higher in individuals with known risk factors. For approvability by the FDA, a *benefit/risk* analysis must demonstrate that the incidences of CPA-linked serious adverse events and mortality are substantially lower than CPA-induced reductions of morbidity/mortality caused by CRC. In addition, if a CPA is being developed as a substitute for colonoscopy, the benefit/risk profile of the agent should be more favorable than the profile associated with colonoscopy. Sufficiently powered controlled studies must be performed in order to perform this analysis. The power of studies that is required to determine rates of serious adverse events caused by a CPA is influenced both by event rates in treated patients and by background rates in untreated controls. Moreover, rates of significant drug toxicity associated with a CPA may change after continuous exposure over an extended period of time. Because of these considerations, a comprehensive benefit/risk analysis of CPA treatment depends on reliable comparisons of clinical outcomes between treatment groups in controlled studies that are adequately powered, both for numbers of enrollees and duration of treatment.

Prior to a discussion by invited members of the advisory committee, a series of short presentations will address the following topics: Mechanisms and Epidemiology of Sporadic CRC; Current Clinical Standards in Colonoscopic Screening, Surveillance and Removal of Colorectal Adenomas; An Overview of CRC Chemoprevention Trials; and Elements in the Assessment of Benefit/Risk of CPAs for the Suppression of Sporadic CRC.

TABLE OF CONTENTS

APPENDICES

1. Janne , PA and Mayer, RJ. Chemoprevention of Colorectal Cancer, N. Engl. J. Med., 342, p 1960-1968, 2000.

2. Lipkin, M.; Strategies for Intervention with Chemopreventive Agents, ***Int. J. Cancer,*** **69, p 64-67, 1996.**

3. Winawer, SJ et al. Colorectal Cancer Screening: Clinical Guidelines and Rationale ; ***Gastroenterology*****, 112, p 594-642, 1997.**

4. Winawer, SJ et al. Randomized Comparison of Surveillance Intervals After Colonoscopic Removal of Newly Diagnosed Adenomatous Polyps. ***N. Engl. J. Med*****. 328, p. 901-906, 1993.**

5. Winawer, SJ et al. Prevention of Colorectal Cancer by Colonscopic Polypectomy. ***N. Engl. J. Med*****. 329, p. 1977-1981, 1993.**

6. Steinbach, G. et al., The Effect of Celecoxib, a Cyclooxygenase-2 Inhibitor, in Familial Adenomatous Polyposis, *N. Engl. J. Med*. 342, p. 1946-1952, 2000.

7. Torrance, CJ et al. Combinatorial Chemoprevention of Intestinal Neoplasia; *Nature Medicine*, 6, p. 1024-1028.

8. Stack, E. and DuBois, R. Role of Cyclooxygenase Inhibitors for the Prevention of Colorectal Cancer, *Gastroenterology Clinics of North America,* 30, p 1001-1010; 2001.

9. Thun, MJ, NSAID Use and Decreased Risk of Gastrointestinal Cancers ; *Gastroenterology Clinics of North America*, 25, p 333-348, 1996.

10. Ladabaum, U. et al. Aspirin as an Adjunct to Screening for Prevention of Sporadic Colorectal Cancer.
***Ann. Intern. Med*. 135, p. 769-781; 2001.**

11. Bombardier C. et al. Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen Patients with Rheumatoid Arthritis. *N. Engl. J. Med*. 343, p. 1520-1528, 2000.

12. Mukherjee D., Nissen, SE and Topol EJ, Risk of Cardiovascular Events Associated with Selective Cox-2 Inhibitors. *JAMA*, 286, p 954-959, 2001.

Goals for the Advisory Committee on Chemopreventive Agents that Reduce the Risk of Sporadic Colorectal Cancer

To provide FDA with advice on:

- **Clinical trial design**
  1. **Appropriate subjects for enrollment in studies, defined by risk for the development of sporadic colorectal cancer (CRC)**
  2. **Study endpoints that would provide evidence for a benefit to the public health and in the management of patients**
  3. **Duration of treatment in sporadic CRC risk reduction studies**
- **Safety and benefit/risk evaluation of chemopreventive agents (CPAs)**
- **Approaches in the evaluation of important drug classes, such as nonsteroidal antiinflammatory drugs (NSAIDs)**

Included in this package are brief reviews of the following subjects:

- ***Mechanisms that Underlie Colorectal Carcinogenesis (Also see Appendix 1)***
- ***Current Clinical Standards in the Screening/Surveillance and Colonoscopic Removal of Colorectal Adenomas (Also see Appendix 2)***
- ***Overview of Chemoprevention Trials (Also see Appendix 3)***
- ***Common Issues in the Design(s) of Adenoma/CRC Chemoprevention studies***
- ***Points for the Advisory Committee to Consider in establishing acceptable standards of pivotal study design(s)***

BACKGROUND

Colorectal Cancer (CRC) is the 3rd most common lethal cancer in US with 130,200 new cases estimated in year 2000 and 56,300 associated deaths[1]. Approximately 6% of Americans develop CRC over their lifetime and 2.6% will die from this disease.

Typically, it takes longer than 10 years for small premalignant adenomas to become malignant carcinomas[2]. This long transition period provides the basis for current guidelines that recommend routine screening of all individuals and regular colonoscopic surveillance and endoscopic polyp removal in people at increased risk for the development of CRC. If performed optimally, these measures are relatively safe and highly effective in substantially reducing the risk of CRC.

Chemopreventive Agents (CPAs) may suppress the appearance and/or growth of colorectal polyps and inhibit progression to sporadic CRC. From a regulatory standpoint, in order to gain FDA approval, administration of a CPA must be associated with a tangible clinical benefit(s) (e.g., reduction of CRC incidence) that is demonstrated by controlled clinical trials and a favorable benefit/risk assessment. Reduction of the incidence of recurrent premalignant adenomatous lesions or other

[1] Ries, LAG et al. The Annual Report to the Nation on the Status of Cancer, 1973-1997, with a Special Section on Colorectal Cancer; *Cancer*, 88, p. 2398-2424; 2000.
[2] Winawer SJ Natural History of Colorectal Cancer; *Am. J. Med*., 106 (1A); p 3S-6S; 1999.

markers of CRC risk may be permissible as a primary endpoint if the suppressive effect can be validated as a surrogate of a clinical benefit. Because of the likelihood of both wide scale and long-term administration of a FDA approved CPA to older patients, there is a high stringency of safety that is required for approval. This is especially true since the current standard of care guidelines using colonoscopic screening/surveillance are highly effective for CRC prevention. It is likely that partial suppression of cancer risk in a percentage of individuals administered a CPA may not effectively erase the need for current screening/colonoscopic surveillance strategies. Taking this possibility into account, studies of a CPA(s) must support one or more of the following:

- *An additive clinical benefit when combined with colonoscopic colorectal polyp screening/surveillance (using current guidelines)*
- *An alternative to current colonoscopic screening/surveillance guidelines*
- *Improvement in the overall risk profile for the development of serious adverse events or death that are linked to colonoscopy and polypectomy*
- *An improvement in CRC rates in individuals who do not/are unable to comply with standard screening/surveillance recommendations*

TOPIC HIGHLIGHTS

Mechanisms that Underlie Colorectal Carcinogenesis

As described in Appendix 1 the genetic abnormalities which accumulate during the premalignant and malignant phases of CRC highlight the complexity and interdigitating pathways that govern growth regulation of colonocytes. Given that multiple mechanisms confer a growth selective advantage to cells, an effective CPA would be expected to possess the following characteristics:

- Effective inhibition of one or more critical steps of adenoma formation, growth, transformation or invasion in lesions destined to develop 'advanced' characteristics ('Advanced' lesions are defined as those >1cm, with tubulovillous or villous histopathologic characteristics, dyslasia, and/or carcinomas. These have a significant likelihood of progression to invasive malignancies). Rapid compensatory growth selection events that evade this inhibitory effect defeat the rationale for CPA administration.

- Suppressive responses of neoplastic progression should be observed in a significant proportion of 'normal risk' subjects or a well defined subset(s) of 'increased risk' individuals destined to develop histopathologically 'advanced' lesions.

- A durable suppressive effect in 'responder' individuals should be present. The duration of suppression must be of sufficient magnitude to meaningfully expand the adenoma-carcinoma transition interval or block carcinogenesis altogether.

Current Clinical Standards in Colonoscopic Screening, Surveillance and Removal of Colorectal Adenomas

As described in Appendix 2, colonoscopic screening/surveillance guidelines for the detection, removal and prevention of sporadic polyps/CRC have been advocated by the American Cancer Society, the United States Preventive Service Task Force and a consortium encompassing the American Gastroenterology Association, the American Society of Gastrointestinal Endoscopy, the American College of Gastroenterology, the American Society of Colon and Rectal Surgeons and the Society of American Gastrointestinal Endoscopy Surgeons[3].

Recommendations for 3 to 5 year intervals for colonoscopic surveillance in patients at increased risk for sporadic CRC (see Appendix 2) have been influenced by the finding that after colonoscopic excision new sporadic adenomas with advanced pathological features (lesions >1cm in diameter and those with high-grade dysplasia or malignant transformation) are unlikely to occur within 3 years after baseline colonoscopic excision of polyps[4]. The 'safe' maximal interval during which most new adenomas with advanced pathological features and CRC are unlikely to develop is considerably longer but has not been defined.

Overview of Chemoprevention Trials (see Appendix 3)

REGULATORY HISTORY OF CRC CHEMOPREVENTION

- No agents have been approved by FDA for the chemoprevention of sporadic colorectal polyps/CRC.

- Based on the Federal Food, Drug and Cosmetic Act (Section 505) approval of a drug for a new indication requires the presence of substantial evidence of effectiveness consisting of adequate and well controlled investigations. *Accelerated approval* applies only to treatments for serious or life-threatening illnesses that provide a meaningful therapeutic benefit to patients over existing treatments (21 CFR 314 Subpart H). Studies submitted for accelerated approval that measure a surrogate endpoint may be approved if the effect is reasonably likely to predict clinical benefit. After approval the sponsor must verify the benefit where there is '*uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate ou*tcome.'

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[3] Winawer, SJ et al. Colorectal Cancer Screening: Clinical Guidelines and Rationale; *Gastroenterology*, 112, p 594-642, 1997; (Copy included in Appendix 4).

[4] Winawer, SJ et al. Randomized Comparison of Surveillance Intervals After Colonoscopic Removal of Newly Diagnosed Adenomatous Polyps. *N. Engl. J. Med*. 328, p. 901-906, 1993; (Copy included in Appendix 4).

Winawer, SJ et al. Prevention of Colorectal Cancer by Colonscopic Polypectomy. *N. Engl. J. Med*. 329, p. 1977-1981, 1993; (Copy included in Appendix 4).

Celecoxib has been granted accelerated approval status (21 CFR Subpart H) for the reduction of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (eg endoscopic surveillance, surgery) [5]. Colorectal polyps at sites in the rectum and colon were counted at baseline and following 6 months of treatment with celecoxib or placebo, and the mean reductions in numbers of polyps were measured[6]. As stated in the labeling, it is not known whether there is a clinical benefit from the statistically superior reduction in the number of colorectal polyps in FAP patients treated with celecoxib 400 mg bid for 6 months or whether celecoxib treatment beyond six months is effective/safe. The approval is contingent upon performance of post-approval studies to verify and assess clinical benefit and measure long-term safety outcomes. The decision of accelerated approval for this indication has taken into account the very high likelihood of development of CRC in young adult patients with FAP. Management of FAP patients includes prophylactic procto-colectomy whose timing might be influenced by treatment with a chemopreventative agent (CPA). It is self evident that both the rationale and risk/benefit analysis which are linked to administration of a CPA in the management of FAP patients are very different from considerations that underlie treatments in the prevention of sporadic CRC.

COMMON ISSUES IN THE DESIGN(S) OF CRC CHEMOPREVENTION STUDIES

Although common in adults over the age of 50, a large majority of sporadic adenomas do not progress to invasive malignancy, even in the absence of colonoscopic surveillance. As a corollary, most individuals with adenomas are healthy and have a normal life expectancy. Because of the distinction that can be drawn between *prevention* of sporadic CRC and required *treatment* of an ongoing disease there is an obligation to apply more stringent standards of safety for treatment with a CPA(s).

In many CRC chemoprevention trials adenoma recurrence has been employed as an endpoint. So far, markers to reliably identify the subset of small tubular adenomas which are destined to become histopathologically advanced have not been identified. The risk that a small sporadic adenoma will become malignant in the lifetime of the patient is determined by both hereditary and environmental lesions or CRC factors and is influenced by whether there is a prior history of advanced adenomas/CRC (see above). Therefore, although phenotypically indistinguishable from other similar lesions, it is not possible to accurately gauge the actual CRC risk attached to any particular small colorectal polyp.

Significance of Adenomas as Endpoint Biomarkers

Conceptually, the enumeration of adenomas or incidence of patients with recurrence of adenomas as *surrogate endpoint biomarkers (SEBs)* of CRC relies on a number of assumptions:

[5] *Physician's Desk Reference*, 2002

[6] Steinbach, G. et al., The Effect of Celecoxib, a Cyclooxyenase-2 Inhibitor, in Familial Adenomatous Polyposis, *N. Engl. J. Med*. 342, p. 1946-1952, 2000; (Copy included in Appendix 4).

- ***A predictable relationship between each SEB that is scored and CRC risk is required.***

  This must be reconciled with the fact that in study subjects with different risks to develop sporadic CRC there may be corollary differences in the CRC risk that can be assigned to individual small adenomas. Even when the study population is narrowed (to include for example only subjects who are at increased risk for the development of CRC) there are differences in the long-term malignant potential of each small polyp that is scored as a SEB.

  As described in Appendix 1, populations which are at increased risk for the development of sporadic CRC are heterogenous and are linked to different levels of increased risk. Appropriate study designs must reconcile boundaries of statistical significance that surround the finite number of enrollees and the advantage of ensuring an even distribution of subsets, each characterized by a defined CRC risk, into each study arm.

- ***Detection and characterization of SEBs must be reliable and consistent****.*

  The miss rate in colonoscopic detection of small adenomas (<0.5 cm in diameter) is approximately 25%. Therefore, it is not unexpected that some polyps detected colonoscopically after treatment with a CPA were already present at the time of enrollment. The cumulative incidences of study subjects with recurrent adenomas randomized to treatment with a CPA(s) or placebo has been measured as an endpoint in some studies. With this type of measure, the presence of missed polyps during baseline colonoscopy (prior to treatment) in a significant proportion of study subjects may cause an underestimation/masking of real adenoma suppressive effects linked to the CPA.

  Size is an important determinant of the potential for malignant transformation of an adenoma. The possibility of observer variation in the interpretation of polyp size during colonoscopy has often not been addressed by many study protocols. The absence of an appropriate objective morphometric measurement(s) may lead to inconsistencies in the enrollment and distribution of suitable patients into each of the treatment arms.

  In large double-blind clinical trials bias linked to some of the deficiencies in the detection and characterization of SEBs may be minimized by a balanced distribution of the study subjects into each of the treatment arms.

- ***Measurement of relevant clinical outcomes (e.g., the incidences of advanced adenomas/CRC/CRC mortality) must be performed, in order to validate each SEB.***

  In the case of typical CRC chemoprevention trials that measure adenoma recurrence rates a SEB validation procedure is not possible since all small polyps are excised during each colonoscopic surveillance procedure. A recent study of the effects of combination treatment with EKI-785 (an EGF receptor antagonist) and sulindac (a

non-selective NSAID) in mice with a genetic 'hit' in the APC locus demonstrated a strong suppressive effect on the development of naturally occurring intestinal adenomatous polyps[7]*. Despite the significant reduction of macroscopic lesions associated with the combined administration of these agents, under high-power magnification numerous microscopic adenomatous lesions in the CPA-treated mice were observed. This finding underlines the possibility that some chemoprevention treatments may alter the natural course of polyp expansion but not fully eliminate adenomatous/dysplastic cells which over time could acquire the features of malignant transformation. In the US small polyps and microscopic adenomas (not detected by colonoscopic inspection) are very unlikely to contain malignant cells. However, after CPA treatment the probability of malignancy associated with small lesions has not been fully elucidated. Although adenoma expansion and size may have been suppressed by exposure to certain CPAs it is not inconceivable that the lack of colonoscopic detection of such lesions may result in a higher risk for malignant transformation.*

Other Biomarkers

- Other potential SEBs are being studied for their predictive values as measures of increased CRC risk[8]. These include markers which reflect perturbations of cellular, biochemical, cell cycle regulation and genetic functions that occur at one (or more) of a number of steps during the course of initiation and transition of adenomas to malignancy from the normal state. The detection of markers linked to early stages of polyp formation do not necessarily imply the inevitability of transition to more advanced stages that are associated with high grade dysplasia and cancer; Moreover, the detection of late stage perturbations are often limited in sensitivity/specificity in the detection of all histopathologically advanced adenomas. In addition, assuming performance of routine colonoscopic surveillance, the presence/absence of such SEBs often does not add to the clinical management of adenomas, since advanced adenomas/CRCs are detected endoscopically and characterized histologically in an effective manner. Further studies to determine the predictive values of SEBs and their added benefit to histopathological analysis in the determination of CRC risk are necessary.

- To date, none of the listed potential SEBs have been validated in humans as reliable surrogate measures of effective outcome response(s) to chemoprevention treatment(s) of sporadic CRC, comparable to cholesterol blood level lowering responses to HMG CO-A reductase inhibitors for the reduction of cardiovascular risk. Until there is such validation, it appears that clinical trials cannot rely on these SEBs as primary clinical endpoints in pivotal trials of CPAs.

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[7] Torrance, CJ et al. Combinatorial Chemoprevention of Intestinal Neoplasia; *Nature Medicine*, 6, p. 1024-1028; (Copy included in Appendix 4).

[8] Srivastava, S, Verma, M and Henson, DE; Biomarkers of Early Detection of Colon Cancer (Minireview), *Clinical Cancer Res.*, 7, p 1118-1126; 2001;

Syngal S, Clarke, G and Bandipalliam, P; Potential Roles of Genetic Biomarkers in Colorectal Cancer Chemoprevention; *J Cell. Biochem.* 34 (Supplement), p 28-34; 2000;

Benefit/Risk Evaluation of Chemopreventive Agents

Since the time span of transition from initiation of adenomas to carcinoma in untreated individuals is longer than 10 years the benefit of a CPA(s) is likely to depend on long-term treatment. A benefit/risk evaluation of CPAs may take into consideration some of the following issues as assessed over an extended period of time:

- Determination whether adenoma suppression is consistently maintained over an extended period of time in individuals who are determined to be 'responders' at the time of the first colonoscopic analysis performed a few years after CPA treatment has commenced. A transient polyp suppressive effect that is not maintained over the long-term in 'responder' individuals might not be considered clinically meaningful, especially since the natural course of polyp progression occurs over a long period of time.

- Determination what is the therapeutic gain (percentage of responders) in a population administered the CPA. On a population basis, a CPA associated therapeutic gain could be measured in relative terms to that achieved by the colonoscopy screening/surveillance paradigm.

- Determination whether other modalities of cancer prevention including colonoscopic surveillance are necessary in treated subjects. This is important in order to provide adequate instructions to physicians and patients regarding the interplay between CPA treatment and appropriate patient care. Ambiguities surrounding this point may present an important unresolved safety issue since patient consumers may inappropriately assume that approval of a CPA implies that self-administration of the product is an acceptable alternative to following regular colonoscopic surveillance guidelines (outlined above). On the other hand, stipulation that colonoscopic surveillance should not be altered despite concomitant use of the CPA may profoundly undercut the rationale for chemoprevention, particularly if there are clinically significant adverse events and cost/compliance concerns linked to the product.

- Determination whether drug toxicity is cumulative in a population of treated individuals after a substantial period of administration. It is expected that for the indication of sporadic CRC chemoprevention (in the context of current standards of care in the US) the safety profile of a CPA should be characterized by negligible incidences of serious adverse events and mortality (particularly in geriatric subjects who would be targeted for treatment). The statistical power for safety endpoint measurements is a function of both the number of treated study subjects and the duration(s) of treatment. Therefore, CRC CPA studies must contain adequate numbers of patients treated for a sufficient period of time. An adequate analysis of subsets of patients who due to their underlying medical conditions are at increased risk for the development of specific drug-related adverse events (e.g., cardiovascular events) must be performed. This is especially important in light of the high

proportion of undifferentiated geriatric patients that would be administered a CPA for the prevention of sporadic CRC. To further maximize the power of the safety outcomes/mortality analysis, similar patients treated with the product for other indications should be analyzed.

- Determination whether significant drug-drug interactions occur. There are three areas of concern. First, the potential for CPAs to enhance the toxicity of concomitant medications. This is especially important since a large bulk of the targeted geriatric patient population is exposed to multiple pharmaceutical agents that have significant toxicity profiles. Second, that latent toxic effects associated with the CPA may be enhanced and become clinically significant due to concomitant administration of other drugs. Third, the putative adenoma/CRC suppressive effect linked to the CPA may be diminished/reversed by concomitant administration of another agent(s).

- Determination whether microadenomas and small adenomas occur during CPA treatment and whether these lesions progress towards malignant transformation.

Issues for the Advisory Committee to consider in establishing acceptable standards of pivotal study designs for efficacy and safety

Significance of CPA Clinical Benefits

- Determination of which the following are meaningful clinical benefits of CPA treatment that should be demonstrated/supported in clinical studies.
  - *A reduction in the incidence of CRC in all patients or in those who do not comply with colorectal polyp screening/colonoscopic screening guidelines.*
  - *A reduction of premalignant lesions with 'advanced' histopathologic characteristics and/or invasive CRC and/or CRC mortality.*
  - *A lengthening of the 'safe' interval of surveillance colonoscopy for the removal of premalignant polyps.*
  - *An elimination of the need for colonoscopic screening/surveillance.*
  - *A reduction in the number of procedural complications associated with polypectomies with a concomitant reduction in the overall risk for a serious adverse event or death.*
  - *Other benefits.*

- Evaluation of possible benefits of CPA treatment in the context of colonscopic screening/surveillance procedures
  - *The added benefit that a CPA should provide(s) to individuals who undergo regular surveillance colonoscopy.*
  - *The levels of response (duration and percentage of treated subjects) that a CPA(s) should provide to justify relaxation/reduced compliance with adenoma screening and colonoscopy surveillance guidelines. The information that would be required*

to change the current recommendations of colonoscopic surveillance for chemoprevention agent 'responders'.

- *The relative benefit attached to increasing the recommended interval of colonoscopic surveillance. The type of study design which would provide requisite information for such a change.*
- *The relative benefit of a partial reduction in the number of polypectomies. The relative benefit of a reduction of polypectomy complications (see risk/benefit criteria below).*

Clinical Trial Design

- Patient enrollment in pivotal studies
  - *Determination of what subsets of subjects (e.g. patients with normal vs increased risk for the development of sporadic CRC) should be studied in randomized, double-blind, placebo-controlled pivotal CPA trials. Determination of what risk criteria should be used to determine which individuals should be studied/treated with a chemoprevention agent. The incidence of sporadic CRC increases significantly with age and is more common in geriatric subjects.*
  - *Determination what other demographic characteristics must be considered in enrollment (e.g. age, gender,race).*
  - *Determination whether individuals treated with NSAIDs for other indications should be studied. Determination whether study designs should stratify by NSAID usage, age, other variables.*
  - *Determination whether individuals who do not comply with screening/surveillance guidelines should be studied separately.*

- Significance of adenomatous polyps as study endpoints
  - *Suitability of sporadic colorectal adenomatous polyps as surrogate markers for colorectal cancer risk. (The incidence of sporadic colorectal adenomatous polyps is approximately 50% in the over age 60 US population.) Determination of whether small sporadic adenomatous polyps are lesions that are intrinsically harmful (disease) or merely surrogates of cancer risk (since only a small percentage are destined to become malignant in a subset of patients).*
  - *Suitability of consideration of adenomatous polyps (detected during colonoscopic surveillance) as surrogates for colorectal cancer in patients with/without an increased risk for the development of sporadic CRC.*
  - *Significance of recurrence of small tubular adenomas as a meaningful endpoint. Patient subsets in which this measure is valid (e.g. patients with/without an increased risk for the development of CRC). Determination whether the polyps (as surrogates of CRC risk) should be of a predefined size/stage of dysplasia/malignancy.*
  - *Suitability of other study endpoints including rates of histopathologically advanced adenomas, CRC, invasive CRC, CRC mortality, overall serious adverse events and overall mortality.*

- Duration of polyp suppression
  - *Determination of what minimal duration of polyp suppression should be studied. (The natural course of sporadic carcinogenesis is identified with a time line in excess of 10 years and the current recommended interval of surveillance colonoscopy with polyp excision is 3-5 years.) Determination whether consistency of response (durability) to a CPA(s) in individual patients is a critical endpoint for clinical studies.*
  - *Determination of what minimal study duration is required to exclude the possibility of an increase in cancers in small lesions in CPA treated individuals. (Adenoma expansion and size may be suppressed by a CPA(s) without eradication of dysplastic cellular foci. Therefore, the risk for malignant transformation in microscopic adenomas of treated subjects may be different than in untreated individuals.)*

- Power of study to ensure safety
  - *Establishment of criteria for safety endpoints.*
  - *Establishment of requirements for statistical power of safety measurements. Definitions of sample size and treatment duration that are required to adequately assess CPA safety.*
  - *Determination whether the safety analysis should be pre-specified.*
  - *Determination how factors such as age, gender, underlying diseases and other medications (including aspirin), which confound the risk of drug toxicity, should be factored into the protocol of safety measurements.*

Data Analysis Issues

- Analysis of study dropouts/censored patients.
  - *Establishment of criteria to guide the measurements of efficacy and safety outcomes in patients who have dropped out of studies.*

- Role of uncontrolled safety data in overall safety analysis.
  - *Determination whether there are necessary characteristics of treated patients, controls and duration of CPA(s) exposure to permit incorporation of ancillary study results into the safety analysis.*

- Analysis of surrogate endpoints.
  - *Issues surrounding surrogate endpoints in the absence of results which directly demonstrate a clinical benefit.*

Benefit/Risk Assessment

- Determination whether sufficient efficacy and safety evidence is present to support a clinically meaningful benefit.
  - *Determination how an analysis of risk vs benefit of treatment with CPAs should be planned.*
  - *Determination of the magnitude(s) of specific clinical benefits of CPA treatment, measured in clinical trials, that is required to offset safety risks and costs associated with chronic treatment. (This must take into account the current*

standard of care that includes endoscopic screening of all risk groups and colonoscopic surveillance and polypectomy of individuals who are at an increased risk to develop sporadic CRC).

- *Based on clinical benefit, determination of upper limits of CPA-related serious adverse event and mortality rates which are acceptable.*
- *Determination how significant toxicity of drugs that are administered for non-CPA indications should be incorporated into the benefit/safety analysis for a CRC chemoprevention indication.*
- *Determination of an acceptable level of cumulative toxicity in patients who may have other medical conditions and who are treated with multiple pharmaceutical agents.*
- *Determination of which subsets of vulnerable patients should be further studied to assess CPA safety.*
- *Determination how measurements of compliance with the long-term self administration of a CPA and with adherence to guidelines for colonoscopic screening/surveillance affect the benefit/risk analysis. Definitions of which measurements and analyses of compliance should be performed. Definitions of acceptable absolute and relative levels of compliance for each of these functions.*
- *Determination how cost and compliance measurements should be considered in the benefit/risk analysis of a CPA.*

APPENDIX 1

Mechanisms that Underlie Colorectal Carcinogenesis

In the US the incidence of CRC has increased until 1985[1]. Since then, there has been a slow (1.6%) but not dramatic decrease (See Figure 1). Not surprisingly, the incidence of CRC-related mortality has followed this trend. The gradual decline in incidence of CRC in the general US population is mirrored by a decline in deaths. Between 1978 and 1986 there has been a 0.6% decline/year in deaths of white males from CRC and since 1986 the rate of this decline has accelerated. This decline may be related to screening and colonoscopic polypectomy procedures. It is less likely that this downward trend is related to changes in behavior, diet or other causes.

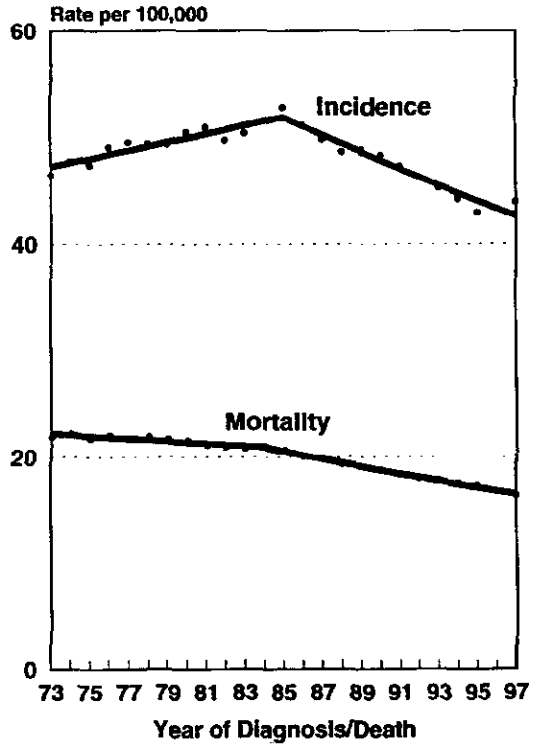

Figure 1. CRC incidence and death rates 1973-1997 (figure obtained from reference 1). CRC incidence data are from 9 Surveillance, Epidemiology and End Result (SEER) program areas and represent all races and both genders. Death rates are from the National Center for Health Statistics.

Milestones in the understanding/Diagnosis/treatment of Colorectal cancer that have an impact on public health

- Recognition that enviromental/dietary factors play an important role in risk
- Discovery of a common set of somatically acquired or inherited genetic perturbations which accumulate during progression of adenomas between premalignant and malignant phases
- Development of fiberoptic/digital endoscopic technology that has enabled routinized colonoscopic polypectomy of premalignant colorectal adenomas to *effectively* prevent colorectal cancer. This has culminated in effective 'standard of care' guidelines by the medical community that include:
  - Routine screening of low risk individuals
  - Preemptive screening/surveillance of individuals at high risk to facilitate identification and colonoscopic removal of premaligant adenomatous polyps

Epidemiology of Colorectal Cancer (CRC)

- The collection of patients with CRC represents a heterogeneous group of patients with inheritable or sporadically acquired forms of disease (See Figure 2).

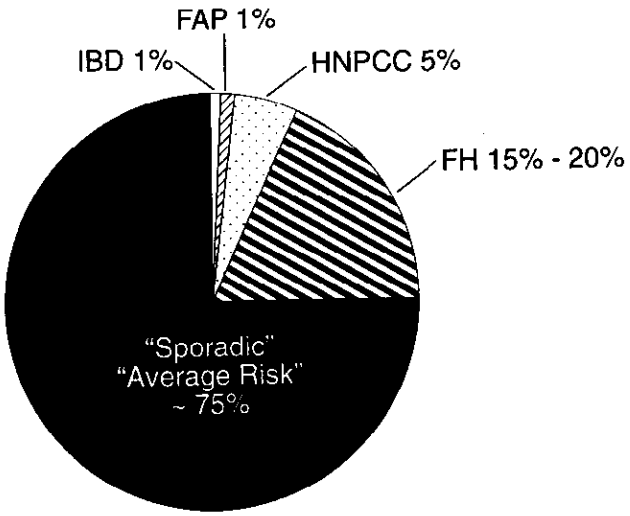

Figure 2. Factors associated with CRC[9] (figure obtained from indicated reference). 'Sporadic', 'Average Risk', men and women age 50 and older with no risk factors associated with a positive family history, hereditary condition or disease; FH, family history positive for colorectal neoplasms; HNPCC, hereditary non-polyposis colorectal cancer; FAP, familial adenomatous polyposis; IBD, inflammatory bowel disease.

[9] Winawer, SJ, Schottenfeld, D and Flehinger BJ. Colorectal Cancer Screening. J. Natl Cancer Inst. 83, 243-253, 1991.

- All CRCs develop because of the accumulation of multiple genetic abnormalities including somatic mutations, deletions, translocations and duplications of DNA sequences in individual colonic epithelial cells that lead to their transformation (loss of contact inhibition, loss of normal cellular adhesion, change in cellular morphology, etc.)[10]. There is significant overlap in the group of genes which are targeted by inherited and sporadic forms of CRC. Disruption of these common genetic targets leads to loss/change of function of their associated gene products (proteins) with a resultant loss of normal growth control of cells.
- Less than 10% of patients with CRC have classical hereditary syndromes due to an inherited germline mutation of a critical target gene which is present in all cells. These germline mutations confer a high probability for the development of CRC since all affected individuals begin life with at least one critical genetic 'hit' present in all cells; The hereditary diseases include Hereditary Nonpolyposis Coli (HNPCC), Familial Adenomatous Polyposis (FAP) and Peutz-Jeughers Syndrome (PJS). Critical classes of target genes that are targeted in the hereditary diseases include genes which regulate repair of errors of DNA replication (HNPCC), the APC gene and its associated pathways (FAP) and pathways linked to TGF-β (PJS). Based on the specific type of mutation and typical age during which CRC develops all of these diseases are managed by a combination of endoscopic / colonoscopic surveillance strategies in conjunction with either polyp removal or, in the case of FAP, prophylactic procto-colectomy / colectomy.
- Patients with inflammatory bowel disease (IBD; both Ulcerative Colitis and Chrohn's disease) are at increased risk for the development of CRC. CRC in these patients share common target genes with other etiologies. Genetic alterations in CRC associated with IBD are somatically acquired during the inflammatory process. The increase in risk is dependent on both extent and duration of disease.
- The majority of patients with CRC have *sporadically* acquired tumors in which all of the genetic perturbations are somatically acquired. The probabilities that an individual will incrementally accumulate combinations of genetic 'hits' that will sequentially cause proliferative, adenomatous, dysplastic and malignant changes in at least one mucosal site are influenced by both environmental and hereditary factors.

***Factors that Influence the Risk for Sporadic CRC*[11]**

- Age (the probability begins to significantly rise after age 50);
- Diet/Environment (the risk for disease is strongly influenced by diet. The disease is 10X more prevalent in First World Countries compared to many Third World Countries. This is thought to be mainly a manifestation of differences in diet. The important contribution of an environmental/dietary component to risk for CAC is underlined by the observation of increasing rates in some low incidence areas and studies of migrants who move from CRC low risk to high risk areas. The precise

[10] Fearon, ER and Vogelstein, B. A Genetic Model of Colorectal Tumorigenesis; *Cell*, 61, p 759-767; 1990; Dumont, N. Genetic and Epigenetic Contributions to Colorectal Cancer, *APMIS*, 107, p 711-722; 1999. Ilyas, M, et al. Genetic Pathways in Colorectal and Other Cancers, *Eur.. J. Cancer*; 35, p 335-351; 1999.

[11] Bresalier RS and Kim, YS. Malignant Neoplasms of the Large Intestine, In*: Sleisenger & Fordtran's Gastrointestinal and Liver Disease*, Feldman, M, Scharschmidt, BF and Sleisenger, MH (eds.), WB Saunders Co., 6th Ed., 1998; p 1906-1942.

interplay between diet and CRC risk has not been elucidated. However, a number of dietary constituents have been extensively studied. These include:

- *Fat* containing foods. Fat soluble products may have carcinogenic activity mediated by the following pathways.
- Presence of dietary genotoxins
- Stimulation of ornithine decarboxylase activity in cells and induction of synthesis of primary and secondary bile acids which provoke colonocyte proliferation.
- Induction of colonic bacterial enzymes which convert certain precursor compounds to mutagens (eg fecapentaenes)
- *Fiber* which contains complex carbohydrates (cellulose, hemicellulose and pectin) and noncarbohydrates (eg lignin). These constituents may be protective of CRC by enhancing the dilution and elimination of exogenous/endogenous carcinogenic substances altering bacterial flora and associating with protective nonfiber vegetable components, nutrients and micronutrients
- *Micronutrients/Antioxidants* such as carotene, vitamin C, selenium salts, and folic acid which have anticarcinogenic activity
- *Calcium* promotes antiproliferative and differentiative changes in colonocytes. In addition the cation binds to ionized fatty acids/bile acids.

  The exact roles of each/defined combinations of these dietary agents in sporadic CRC has been difficult to define because of the complexity of diets and the long interim period between the normal and malignant states.

- Family history (increased risk caused by hereditary influences with partial penetrance of undefined germline genetic perturbation(s)/common environmental influences). Separate from patients with classical colorectal cancer syndromes which are transmitted in a Mendelian fashion, individuals with a positive family history for CRC are at increased risk to develop sporadic CRC. The risk is:
    - 3-fold with one first degree relative (FDR) who has developed CRC
    - 8-fold with one FDR under age 40
    - 5-fold with 2 FDRs

Pathogenesis of Colorectal Cancer (CRC)

All CRCs develop because of a time-dependent accumulation of genetic alterations ('hits') in a select group of growth regulating genes within target colonocytes. These growth selective alterations include somatic mutations, DNA deletions, translocations and duplications. With successive 'hits' cells undergo sequential proliferative, dysplastic and malignant changes. In hereditary syndromes the critical germline hit is present in all cells, by-passing a rate limiting step with the subsequent sequential accumulation of a combination of somatically acquired hits that cause malignancy.

The underlying mechanism of sporadic CRC is linked to somatically acquired hits in many of the same growth regulating genes in colonocytes throughout life. However, the

probability of accumulating the threshold number of synergistic 'hits' required to develop malignancy is much lower than in the hereditary forms of the disease.

Based on the concept of a multistep growth selective process in transformed colonocytes originally proposed by Foulds[12] a schematic model of successive genetic changes in CRC was described by Fearon and Vogelstein in 1990[7] which correlate with the pathogenesis of CRC (see Figure 3). Although common in sporadic CRC, the temporal order or precise combination of specific events that occur at different stages of the adenoma - carcinoma sequence which are shown in the figure is not uniform in all patients. The model has been expanded to include the discovery of additional target genes/mechanisms that synergize with or increase the rate of these steps. These play a role in the pathogenesis of CRC in certain patients. Defects in a number of genes which control repair of DNA replication errors, normal DNA segregation, DNA stability during mitosis and physiological apoptosis (programmed cell death) have also been discovered in colorectal tumors.

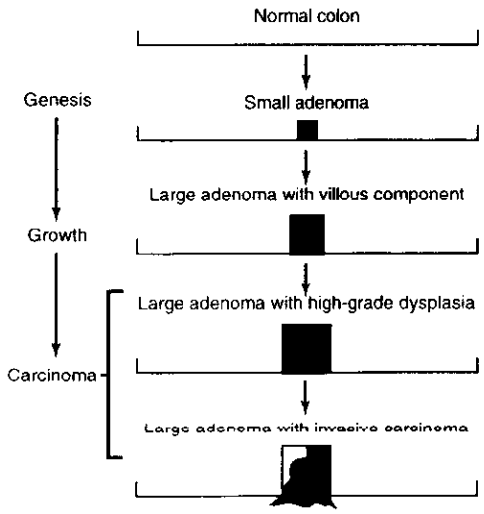

Figure 3. Pathogenesis of CRC[13] (figure obtained from indicated reference).

Examples of genes which are targets for genetic alteration in CRC include:

Oncogenes which stimulate cell growth when genetically altered in CRC.

- Kirsten ras; Mutations occur in approximately 50% sporadic CRCs and cause unbridled adenyl cyclase activity and increased cell cycle activity by the inhibition of other tumor suppressor genes

[12] Foulds, L. The Natural History of Cancer. *J. Chronic Dis.* 8, p 2-37, 1958.
[13] O'Brien, MJ, Winawer, SJ, and Waye, JB. Colorectal polyps. In: Management of Gastrointestinal Diseases, Gower Medical, NY (ed. Winnawer, SJ), 1992

Tumor Suppressor genes which are disrupted in CRC.

- Adenomatous Polyposis Coli (APC) gene. Product blocks β-catenin induced transcription of cell cycle and proliferation genes (stimulated by WNT signaling pathway). Mutations which occur in 60-80% of sporadic CRC and in most early adenomas lead to loss of transcriptional inhibition. Germline mutations are inherited in FAP. Effects of mutations on APC protein function (products with/without partial function) are influenced by the site/type of each mutation and presence/absence of other modifier gene products (eg PLA2g2a linked gene)

- SMAD-2; SMAD-4; These are components of the TGF-β signaling pathway which inhibits the cell cycle and tumor progression.

- p53 - regulates a) cell cycle arrest which occurs after DNA damage in cycling cells, b) DNA repair and c) apoptosis. Frequently, p53 is disrupted in histopathologically advanced adenomas and invasive carcinomas. This gene is also disrupted in approximately 70% of sporadic CRCs.

- DNA Mismatch Repair; Replication error repair (RER) genes. These are disrupted in HNPCC (germline defects) and 10-15% of sporadic CRC (somatically acquired defects). RER genes include hMSH2, hMLH1, hPMS1, hPMS2, hMSH3, hMSH6 - Normally, they control the repair of DNA mismatches which occur more commonly in sites with nucleotide repeat sequences which are prone to DNA replication slippage. Tumors which are RER+ are associated with the rapid accumulation of other genetic 'hits' involving growth selective target genes and are not associated with abnormal karyotypes. Not surprisingly, HNPCC is characterized by shortening of the adenoma-carcinoma transition time.

- DNA Stability (DS) Genes. These regulate normal sister chromatid separation and the integrity of the mitotic spindle apparatus. Their disruption leads to aneuploidy. DS genes include HSecurin - In experimental cell culture disruption of this gene that regulates the mitotic spindle in CRC cells causes chromosomal instability with loss of a normal karyotype.

APPENDIX 2

Current Clinical Standards in Colonoscopic Screening, Surveillance and Removal of Colorectal Adenomas

Clinical Practice recommendations for screening and colonoscopic surveillance for the detection, excision and prevention of sporadic adenomas/CRC[3,14] are based on the following observations:

- The average age difference between people with early stage adenomas and those with invasive CRC has been observed to be 18 years.

- Small adenomatous polyps (<1cm in diameter) are common and occur in more than 25% of individuals by age 50 (One autopsy series demonstrated that by age 50 the prevalence is 60% in men and 40% in women, respectively). This prevalence of all adenomas increases with age. Therefore, in the aggregate, the probability of a small adenoma evolving into a CRC over the lifetime of an individual is small. The prevalence of adenomas > 1cm in diameter which are more predisposed towards malignant transformation than smaller lesions (see below) has been observed in an autopsy series to be 4.6% at age 54 and 15.6% at age 75.

- The probability that an adenoma contains high grade dysplasia/malignant changes correlates with its size. Less than 1% of lesions <1cm in diameter are malignant compared to >10% of larger polyps. In one study adenomas <0.5, 0.5-0.9 and $\geq$1.0cm in diameter had incidences of high grade dysplasia of 1.1%, 4.6% and 20.6%, respectively. At this time it is unknown whether the same size – probability of dysplasia relationship can be applied to a population of individuals chronically treated with a polyp suppressive agent(s). In such treated individuals it remains to be determined whether nests of dysplastic cells continue to form in lesions which grow at a slower rate and are more difficult to detect colonoscopically).

- Individuals with one or more tubulovillous, villous or large adenomatous polyps of any type (>1cm in diameter) that are excised during baseline colonoscopy are at increased risk (more than 3-fold higher than people in the general population) for the development of synchronous and metachronous CRC (separate lesions separated by site and/or time of onset).

- Individuals with small tubular adenomas (< 1cm in diameter), whether single or mutliple, are not at increased risk for the subsequent development of CRC, in the absence of other risk factors.

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[14] Eisen, GM et al. Guidelines for Colorectal Cancer Screening and Surveillance, 51, p. 777-782; 2000; Byers, T et al. American Cancer Society Guidelines for Screening and Surveillance for Early Detection of Colorectal Polyps and Cancer: Update 1997. *Ca Cancer J. Clin*., 47: p 154-160, 1997
Guide to Clinical Preventive Services, 2nd ed., Report to the US Preventive Services Task Force, Washington, DC; DHHS, 1995.

- The average transition time from small adenoma to invasive cancer has been estimated to be at least 10 years. A shorter duration of transition is likely in the case of polyps in patients with HNPCC.

- Colonoscopic screening is the most effective method of detection of colorectal adenomas. In addition, it provides the only means of polyp excision, compared to other screening methods. The impact on CRC prevention by colonoscopic screening and surveillance in a target population is influenced by measures taken to enhance compliance and optimize overall cost (eg cost per CRC death prevented). It is predicted that public education programs and interventions by health care providers to increase voluntary adherence to screening programs in conjunction with reductions in colonoscopy cost and appropriate upward adjustments in the intervals of effective polyp surveillance (which do not compromise patient safety) will lead to substantial improvement in the overall compliance and cost effectiveness of colonoscopic screening/surveillance in the US population.

- By anatomical location the frequency of CRC is as follows: rectosigmoid – 55%; descending colon – 6%; transverse colon – 11%; ascending colon – 9%; cecum – 13%. Complete examination to the cecum depends on the experience of the endoscopist and the adequacy of the cathartic/enema preparation. In a general population of patients, the cecum is reached in 95% of examinations, when performed by adequately trained colonoscopists. Although the approximate 'miss' rate of small adenomas < 0.5 cm in diameter after colonoscopic examination has been reported to be as high as 25%, it is low for adenomas $\geq$ 1 cm (6-10%) and very low for CRC. This has been determined both by back-to-back colonoscopy studies as well as by retrospective correlations with pathological specimens in patients who underwent colorectal resections. It can be inferred that a substantial proportion of adenomas detected at first followup examination were already present but missed during initial screening colonoscopy. It is expected that miss rates will diminish as more improvements in colonoscopic technology are made.

- Colonoscopic polypectomy almost always cures early stage Dukes A CRC lesions which are 1) limited to the mucosa; 2) non-sessile; 3) associated with differentiated histopathological features and 4) not invading the polyp stalk

- Colonoscopy and polypectomy are generally safe procedures. Nonetheless, they are rarely complicated by perforation, hemorrhage and respiratory depression due to sedation. Such complications occur in approximately 0.1% - 0.3% of patients. Older individuals are not at substantially greater risk for these complications. Mortality associated with colonoscopy has been reported in a range of 0.01%-0.03% and includes patients with confounding medical conditions who have undergone the procedure in a variety of health care settings. Data on compliance with screening colonoscopy is sparse. Compliance is variable and depends on multiple factors, including the procedure for recruitment, demographic characteristics of patients and health care provider/ physician interactions.

Current recommendations for the colonoscopic screening of sporadic adenomatous polyps/colorectal cancer in the US can be summarized as follows:

People at Average Risk, asymptomatic, age ≥ 50 years:

- Annual occult blood screening and sigmoidoscopy every 5 years. *A positive finding for occult blood or sigmoidoscopic detection of a polyp >1cm should prompt colonoscopy or, if not possible, double contrast barium enema. Patients with tubular adenomas <1cm should decide with their doctor whether to undergo colonoscopy.*
- An alternative screening program is colonoscopy every 10 years. *In the future this approach may be most cost effective.*

People at Increased Risk, asymptomatic, age ≥ 50 years:

- *Family History of CRC/polyps (First degree relatives)*
  - Initiation of screening is recommended at age 40. If relative was diagnosed with CRC before the age of 55 years or with an adenoma before age 60 colonoscopic screening is recommended every 3-5 years beginning at an age that is 10 years younger than the age of the youngest affected relative.

- *Personal History of Adenomatous Polyps*
  - Finding of villous, tubulovillous or large (>1cm in diameter) adenomas or multiple adenomas that are removed colonoscopically should have a colonscopic examination 3 years after the initial examination. If the first followup examination is normal or only a single, small, tubular adenoma is found, the subsequent interval for colonoscopies can be increased to 5 years. In special circumstances (eg finding of large sessile lesions, malignancy or multiple lesions at baseline examination) a shorter interval may be necessary.

- *Personal History of Colorectal Cancer*
  - After resection with curative intent, if the baseline colonoscopic examination was incomplete an examination should be performed within 1 year. If the findings of this followup colonoscopy are normal, subsequent examinations should be performed after 3 years and subsequently every 5 years (with normal findings or identification of a single small tubular adenoma).

APPENDIX 3

Overview of Chemoprevention Trials

CPAs – Modeling a Mechanism(s) of Action and Observation of Chemopreventive Effects[15]

One or more critical steps in the transitions from normal mucosa to adenoma to malignancy are hypothesized to be blocked by a CPA. Observation of these effects must take a number of considerations into account.

- Carcinogenesis is the culmination of multiple genetic and growth selective events (see above and below). Therefore, the observation of suppression of adenoma or CRC formation/growth by a CPA does not infer any particular mechanism of action.
- In animal models of carcinogen or transgenically induced colorectal polyps, the ratio of duration of treatment with a CPA to the duration of polyp development is high. In contrast, because of the long transition time of naturally occurring polyps in humans this ratio is much lower.
- The power to detect the effectiveness and safety of a CPA in a study population depends on the size of the treatment arm, the duration of treatment and the CPA mechanism(s) of action. Sporadic polyp development (from normal mucosa) may be longer than 10 years. Moreover, late stage blockade is not predicted to inhibit growth of early and mid stage adenomas (and vice versa). Therefore, in some instances the duration of treatment that is required to detect an effect on polyp formation in a large population of study subjects (after baseline colonoscopic screening and polypectomy) may be considerably longer than 3 years. Shorter duration studies of treatment related change in progression rates might be informative in subjects with uniformly staged lesions that are not excised. However, from an ethical perspective these are difficult to justify.
- Regulatory pathways linked to discrete steps of initiation, neoplastic growth and malignant transformation are frequently redundant. Theoretically, CPA induced pinpoint blockades in some cases could be overcome by stimulation of alternate (redundant) pathways, leading to further growth selection. Therefore, CPA targeted blockade may have a modest and only temporary suppressive effect on the adenoma-carcinoma transition process.

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[15] Krishnana, K., Ruffin, MT IV, and Brenner, DE; Clinical Models of Chemoprevention of Colon Cancer, *Hematology/Oncology Clinics of North America*, 12, p 1079-1113; 1998.
Lipkin, M.; Strategies for Intervention with Chemopreventive Agents, *Int. J. Cancer*, 69, p 64-67, 1996; (Copy included in Appendix 4).
Kelloff, GJ, et al. Progress in Clinical Chemoprevention, *Seminars in Oncology*, 24, p 241-252.
Sharma, RA et al. Colorectal Cancer Chemoprevention, Biochemical Targets and Clinical Development of Promising Agents; Eur. J. Cancer, 37, p 12-22, 2001.

Examples of Agents which have been linked to Putative Mechanisms of Chemoprevention Activity[16]

- Reduction of endogenous carcinogen synthesis
  - Ascorbate, α-tocopherol (Nitrosamine synthesis inhibitors)
  - Dehydroepiandrosterone (G-6PD inhibitor)
- Reduction of carcinogen absorption
  - Dietary fiber
- Enhancers of Carcinogen detoxification
  - Isothionates, dithiolthiones, oltipraz (enhancers of Glutathione-S-transferase activity)
- Modulation of metabolism leading to a reduction in carcinogens or free radicals
  - flavones, sulfur compounds, indoles, Perillyl Alchohol
- Inhibition of formation or eradication of electrophilic intermediate compounds,
  - Antioxidants eg tocopherols, carotenes, Se, ascorbate
- Reduction of arachdonic acid metabolism with effects on apoptosis and angiogenesis
  - NSAIDs, Cox-2 Inhibitors
- Modulation of oxidative reactions
  - plant phenolic compounds, flavonoids, omega-3 fatty acids
- Blockade of covalent binding between mutagens and target DNA in cells
- Inhibition of tumor promotion/cell proliferation (Epigenetic Expansion of cells)
  - Bile acid, fatty acid sequestration agents (eg calcium)
  - Bile acid synthesis modifiers (eg ursodeoxycholic acid)
  - Difluoromethylornithine (inhibitor of ornithine decarboxylase)
  - Tamoxifen (anti-estrogen)
- Induction of epithelial cell differentiation
  - Calcium, vitamin D, Retinoids
- Reduction of oncogene isoprenylation (eg c-ras activation)
  - Terpenes, Perillyl Alchohol
  - HMG-CoA Reductase Inhibitors
- Enhancer of DNA methylation
  - Folate
- Inhibition of gene transcription with effects on apoptosis (e.g. blockade of NF-κb activation and DNA binding by PPARδ)
  - NSAIDs

[16] Janne, PA and Mayer, RJ. Chemoprevention of Colorectal Cancer, N.Engl. J.Med., 342, p 1960-1968, 2000; (Copy included in Appendix 4).
Kelloff G et al. Chemoprevention of Colorectal Cancer. In*: Prevention and Early Detection of Colorectal Cancer*. Young G. Rozen, P. and Levin, B. (eds.) W.B. Saunders; 1996, p 116-139.

Examples of Preclinical/Clinical Studies of CPAs *(The categories of agents and studies listed below are representative and do not represent a comprehensive listing)*

ASA and other NSAIDs, including COX-2 inhibitors[17]

- Mechanisms of action may include perturbation of both COX dependent and independent pathways. Increased production of PGE-2 and other related compounds by cyclooxygenases in CRC has been hypothesized to play a role in promoting neoplastic cell expansion. Whereas COX-1 is constitutively expressed in a wide variety of normal tissues, COX-2 expression is negligible in normal colorectal mucosa but is induced in 90% and 40% of CRC and colorectal adenomas, respectively. The inhibition of COX-2 by nonselective inhibitors such as ASA, sulindac, piroxicam and indomethacin or by COX-2 selective inhibitors such as celecoxib or rofecoxib appears to play a role in the chemopreventive activity associated with these agents. It is likely that some NSAIDS inhibit neoplastic cell growth or stimulate apoptosis by effects not mediated by blockade of cyclooxygenases. For example, inhibition of NFκb activation and PPARδ binding to DNA by certain NSAIDs or their metabolites may suppress neoplastic cells. The effects of NSAIDs have been tested in a number of preclinical and clinical models linked to neoplasia. It should be emphasized that there are important mechanistic/pathological differences between each model. These must be taken into account when an evidence based rationale for treatments for the chemoprevention of specific human populations is being considered.

- CRC or adenomas are inhibited by NSAIDs in a number of rodent models.
  - In azoxymethane (AOM) treated rats, administration of certain NSAIDs (ASA, piroxicam and sulindac) has been observed to cause a reduction in the incidence, multiplicity and size of CRC induced by the carcinogen.
  - In $Apc^{\delta 716}$ mice with a genetically altered APC locus that leads to formation of colorectal adenomas (this phenotype is similar to humans with FAP), treatment with NSAIDs including a COX-2 inhibitor or introduction of a null COX-2 genetic background (through crossbreeding with a COX-2 'knockout' mouse strain) resulted in a reduction in number and size of polyps. Similarly, treatment of the $Min^{+/-}$ mice (heterozygotes with deletion of the APC locus) with sulindac suppressed polyp formation. In the latter instance, at the dose of drug that was administered, inhibition of prostaglandin biosynthesis was not evident.

- The results of several retrospective case control studies have been consistent with a protective effect conferred by ASA exposure on the subsequent risk for the

[17] Thun, MJ, NSAID Use and Decreased Risk of Gastrointestinal Cancers; *Gastroenterology Clinics of North America*, 25, p 333-348, 1996; (Copy included in Appendix 4).
Smalley, WE and DuBois RN., Colorectal Cancer and Nonsteroidal Anti-inflammatory Drugs, *Advances in Pharmacology*, 39, p 1-20, 1997;
Stack, E. and DuBois, R. Role of Cyclooxygenase Inhibitors for the Prevention of Colorectal Cancer, *Gastroenterology Clinics of North America*, 30, p 1001-1010; 2001; (Copy included in Appendix 4).

development of sporadic CRC (In addition, a study by Logan et al measured the effect of NSAIDs on colorectal adenomas[18]). Most of these studies have relied on interviews of study subjects to determine NSAID exposure history. Because of their designs, the outcomes of these studies were subject to a number of confounding variables and biases.

- Among a number of prospective cohort studies, using survey techniques prior to the measurements of outcomes, most have demonstrated a protective effect on CRC risk and CRC mortality associated with NSAID use. However, a study by Paganini-Hill et al of retirees (67,000 person years) to determine the relationship between ASA use and chronic diseases did not reveal such an effect[19]. In the Cancer Prevention Study II (3.9 million person years), even infrequent ASA use (once/month) was associated with a reduction in the relative risk of CRC death[20]. Since mortality was the endpoint, the influence of ASA on CRC incidence was not assessed. In the Nurses' Health Study (540,00 patient years) the relative risk reduction was significant only in a group exposed to ASA for longer than 20 years[21].
- The only large randomized controlled trial of the effect of ASA on CRC, the Physician's Health Study of 22,071 male subjects that has been performed, (designed with the primary intention of assessing the effect of ASA on coronary artery disease) did not reveal a trend towards reduction of self-reported CRC and polyp incidence, even after 12 years of followup[22,23]. The study, which also measured the effect of β-carotene treatment, was limited in that the dose of ASA was 325 mg every other day (low-dose). Moreover, because of the beneficial effect of ASA on decreasing the incidence of MIs, the study was terminated only after 5 years of continuous treatment.
- In patients with FAP colorectal adenomas have been reported to be reduced in size and number after administration of Sulindac. In addition, regression of polyps in patients with FAP has been reported after administration of celecoxib, a selective COX-2 inhibitor[3] (see above; *Regulatory History of CRC Chemoprevention*). It is important to emphasize that these responses are only partial and not observed in all treated individuals. Moreover, long-term studies to determine duration of response have not been performed. The development of a new colorectal carcinoma in a patient with FAP being treated with sulindac has emphasized the importance of continued surveillance and prophylactic proctocolectomy in these patients.

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[18] Logan, RF et al. Effect of aspirin and nonsteroidal anti-inflammatory drugs on colorectal adenomas: Case-control study of subjects participating in the Nottingham faecal occult blood screening programme. *B.M.J.* 307, p. 285-289, 1993.

[19] Paganini-Hill, A. et al., Aspirin Use and Chronic Diseases: A Cohort Study of the Elderly. *B.M.J.* 299, p 1247-1250.

[20] Thun, MJ, Namboodiri, MM, and Heath, CW Jr. Aspirin Use and Reduced Risk of Fatal Colon Cancer, *N Engl. J. Med*., 325, p 1593-1596, 1991.

[21] Giovannucci, E. et al., Aspirin and the Risk of Colorectal Cancer in Women. *N. Engl. J. Med*., 333, p. 609-614; 1995.

[22] Gann, PH et al. Low -dose Aspirin and Incidence of Colorectal tumors in a Randomized Trial. *J. Natl. Cancer Inst*., 85, p. 1220-1224, 1993.

[23] Sturmer, T. et al. Aspirin Use and Colorectal Cancer: Post-trial Follow-up Data from the Physician's Health Study. *Ann. Intern. Med*., 128, p. 713-720, 1998.

- Both non-selective NSAIDs and COX-2 inhibitors are associated with potential advantages and disadvantages regarding their safety profiles. These may have a strong impact on their benefit as CPAs. Using computer simulation models, a number of investigators have estimated the clinical and economic consequences of aspirin chemoprevention of sporadic CRC, either as an adjunct or substitute for endoscopic screening/surveillance strategies[24]. Taking into account age-related adenoma and CRC incidences and rates of aspirin-related complications, and testing a range of assumptions of compliance with CRC screening/surveillance guidelines and levels of aspirin-linked reduction of CRC risk, these simulations have concluded that aspirin cannot be considered a substitute for screening/surveillance and that screening/surveillance should be advocated in patients already treated with aspirin. Moreover, the studies have concluded that aspirin treatment of a population that adheres to screening/surveillance guidelines may not be highly cost effective. In these models, the overall benefit of aspirin is strongly affected by the rate of screening adherence, the magnitude of the CRC chemoprevention effect, the rate/consequences of aspirin-related complications and the presence/absence of a significant impact on the prevention of cardiovascular events. Although COX-2 inhibitors are associated with a lower incidence of both clinical and complicated upper GI events compared to some non-selective NSAIDs, chronic administration of certain members of the class may be linked to a significantly higher incidence of serious cardiovascular thrombotic events, including cardiac events (e.g. myocardial infarctions). At this time, the full scope and clinical impact of this problem is not known and is undergoing further review and study. Nonetheless, concern has been raised by studies such as the randomized double-blind VIOXX GI Clinical Outcomes Research (VIGOR) study of 8076 patients with RA who required chronic NSAID treatment (mean age 58 yrs; median duration of treatment 9 months)[25]. In this large study it was demonstrated that daily treatment with 50 mg doses of rofecoxib was linked to a statistically significant increased rate of serious cardiovascular events compared to naproxen 500 mg twice daily (rate 1.67 vs 0.70 per 100 patient years; p=0.0016). Moreover, the incidence of MI in the VIGOR study was fivefold higher in patients treated with rofecoxib 50 mg compared to naproxen (cumulative rate 0.74 vs 0.15 per 100 patient year; p=0.03). In addition, rofecoxib was not free of both clinical and complicated upper GI side effects (rates of 2.08 and 0.59 per 100 patient years, respectively). Other studies are underway that will determine whether the measured increases in rates of cardiovascular adverse events that have been linked to rofecoxib are reproducible at lower doses and whether they are related to a toxic effect of the COX-2 inhibitor rather than a protective effect of the comparator non-selective NSAID.

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[24] Ladabaum, U. et al. Aspirin as an Adjunct to Screening for Prevention of Sporadic Colorectal Cancer. *Ann. Intern. Med*. 135, p. 769-781; 2001; (Copy included in Appendix 4).
Suleiman, S. Rex, DK and Sonnenberg, A., Chemoprevention of Colorectal Cancer by Aspirin; A Cost Effective Analysis. *Gastroenterology*, 122, p. 78-84, 2002.

[25] Bombardier C. et al. Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis. *N.Engl. J. Med*. 343, p. 1520-1528, 2000; (Copy included in Appendix 4).
Simon LS, Cox-2 Inhibitors, Are they Nonsteroidal Anti-Inflammatory Drugs with a Better Safety Profile? *Gastroenterology Clinics of North America,* 30, p. 1011-1025, 2001.
Mukherjee D., Nissen, SE and Topol EJ, Risk of Cardiovascular Events Associated with Selective Cox-2 Inhibitors. *JAMA*, 286, p. 954-959, 2001; (Copy included in Appendix 4).
FitzGerald GA, and Patrono, C., The Coxibs, Selective Inhibitors of Cyclooxygenase-2, *N. Engl. J. Med*., 345, p. 433-442, 2001.

Calcium

- Oral calcium binds luminal bile acids and fatty acids which are believed to participate in the promotion of neoplastic cells. In addition, calcium has a stimulating effect on differentiation of epithelila cells. Addition of calcium to the diet has been observed to reduce the colonocyte proliferation index and inhibits the formation of tumors in carcinogen treated rodents.
- A number of case-control and cohort studies in humans have demonstrated trends towards high calcium in the diet and a reduction in the risk of CRC or colorectal adenomas (Statistical significance was achieved in only a few of these). In some cases these studies have been marked by difficulties in excluding effects of other dietary constituents and imprecise quantitation of calcium intake. In a study by the Calcium Polyp Prevention Study Group of 930 randomized subjects with a history of colorectal adenomas, those treated with 1200 mg of elemental calcium demonstrated a modest reduction in polyp incidence during followup colonoscopies after 1 and 4 years.

Folate

- As a methyl donor that is required for thymidine and methionine synthesis folate and its products play an critical role in producing adequate levels of essential DNA and protein building blocks. Administration of folate has been observed to reverse the increased risk for the development of CRC in individuals who are homozygotes with a methylenetetrahydrofolate reductase polymorphism. A number of case control and cohort studies have provided evidence that the incidence of sporadic CRC and colorectal adenomas is lower among individuals with high dietary folate intake. In contrast, individuals with diets low in folate content may be at increased risk for CRC. In the Nurse's Health Study, supplementation with folate (typically contained in a multivitamin) was associated with CRC risk reduction, particularly in women. This effect became statistically significant only after 15 years of treatment.

Antioxidants and Vitamins

- Vitamins have been hypothesized to possess chemopreventive qualities through a variety of mechanisms. Vitamins C and E manifest physiologically significant anti-oxidant activities. Vitamins A and D are known to be important factors in stimulating the differentiation of different cellular lineages, including gastrointestinal epithelial cells. There is a paucity of information that would support a protective role of vitamins and antioxidants in the development of CRC. Large prospective cohort studies including the Physician's Health Study, the Nurse's Health Study and the α-Tocopheral, β-carotene Cancer Prevention Study have found no significant effects associated with administration of vitamins A, C, D or E or β-carotene. A randomized study of 864 subjects by the Polyp Prevention Study Group assessing the individual and combinatorial protective effects of the antioxidants β-carotene, vitamin

C and vitamin E differences in the rates of adenoma formation after 1 and 4 years were not found.

Fiber

- Fiber is comprised of a heterogenous group of plant derived nonstarch polysaccharides and noncarbohydrates. These products act as sequestration agents of luminal toxins, promoters of gastrointestinal transit and precursors of colorectal fermentative products, including short -chain fatty acids which stimulate colonocyte differentiation. Although combined analyses of retrospective epidemiological and case-control studies have suggested a protective effect of dietary fiber against CRC, a number of prospective studies have not demonstrated a significant effect both against the development of adenomas and CRC. In the Polyp Prevention Trial, of 2079 subjects with a history of colorectal adenomas, those who were randomized to receive dietary counseling together with a low fat, high-fiber diet did not manifest a reduction in incidence of recurrent adenomas after 1 and 4 years. In the Phoenix Colon Cancer Prevention Physicians' Network, in which 1429 patients were randomized to receive on a daily basis either 2.0 g or 13.5 g of supplemental wheat bran, a difference in the incidence of recurrent adenomas was not apparent after approximately 3 years. Similarly, no substantial differences in polyp recurrence were observed in 2 smaller randomized trials - the Australian Polyp Prevention Project and the Toronto Polyp Prevention Group. It is evident that most of the aforementioned studies were limited by the relatively short duration of treatment with fiber.

APPENDIX 4

Published Literature

1. Janne, PA and Mayer, RJ. Chemoprevention of Colorectal Cancer, N. Engl. J. Med., 342, p 1960-1968, 2000.

2. Lipkin, M.; Strategies for Intervention with Chemopreventive Agents, *Int. J. Cancer*, 69, p 64-67, 1996.

3. Winawer, SJ et al. Colorectal Cancer Screening: Clinical Guidelines and Rationale; *Gastroenterology*, 112, p 594-642, 1997.

4. Winawer, SJ et al. Randomized Comparison of Surveillance Intervals After Colonoscopic Removal of Newly Diagnosed Adenomatous Polyps. *N. Engl. J. Med*. 328, p. 901-906, 1993.

5. Winawer, SJ et al. Prevention of Colorectal Cancer by Colonscopic Polypectomy. *N. Engl. J. Med*. 329, p. 1977-1981, 1993.

6. Steinbach, G. et al., The Effect of Celecoxib, a Cyclooxygenase-2 Inhibitor, in Familial Adenomatous Polyposis, *N. Engl. J. Med*. 342, p. 1946-1952, 2000.

7. Torrance, CJ et al. Combinatorial Chemoprevention of Intestinal Neoplasia; *Nature Medicine,* 6, p. 1024-1028.

8. Stack, E. and DuBois, R. Role of Cyclooxygenase Inhibitors for the Prevention of Colorectal Cancer, *Gastroenterology Clinics of North America*, 30, p 1001-1010; 2001.

9. Thun, MJ, NSAID Use and Decreased Risk of Gastrointestinal Cancers; *Gastroenterology Clinics of North America*, 25, p 333-348, 1996.

10. Ladabaum, U. et al. Aspirin as an Adjunct to Screening for Prevention of Sporadic Colorectal Cancer.
Ann. Intern. Med. 135, p. 769-781; 2001.

11. Bombardier C. et al. Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen Patients with Rheumatoid Arthritis. *N. Engl. J. Med*. 343, p. 1520-1528, 2000.

12. Mukherjee D., Nissen, SE and Topol EJ, Risk of Cardiovascular Events Associated with Selective Cox-2 Inhibitors. *JAMA*, 286, p 954-959, 2001.