Abstract

Liebsch, Cindy Marie. Simulation Input Modeling in the Absence of Data. (Under the direction of Dr. Stephen Roberts and Dr. David Kaber.)

Simulation models provide a powerful tool for analyzing real-world systems. These models are driven by input data, so when inputs are unknown and no data exists, the development of the simulation model becomes problematic. This research addresses the problem of modeling inputs in the absence of data, with the goal being to define and verify a formal group process for developing simulation model inputs when data is lacking.

The recommended process modifies a Delphi process and employs a panel of subject-area experts to provide estimates through several rounds of web-based surveys. After each round, the panelists' responses are analyzed, and a summary of the responses and comments from the previous round, as well as any supplemental information, is provided to the panelists to help them develop estimates in the next survey round. By sharing information, the panelists gain insight into the beliefs and opinions of their colleagues, resulting in a growing consensus about the questions addressed in the study.

This process was implemented in the Colorectal Cancer Simulation Study to develop inputs for the simulation. As in this study and many other medical simulations, a number of inputs are unknown or uncertain because appropriate data does not exist or experiments cannot be performed to define the unknown inputs because of their grave nature. In this study, fifteen experts from the areas of gastroenterology, epidemiology, and microbiology were recruited to serve on the expert panel. Three rounds of web-based surveys were conducted to reach consensus on four different study objectives related to adenoma development and cancer progression. The final simulation model inputs were developed using the estimates and the VisiFit distribution-fitting software.

To examine the flexibility, usefulness, and acceptability of the process, the expert panelists and the study's Advisory Board were sent evaluation surveys asking specifically about the group process and the resulting inputs developed. The panelists felt the process was flexible, required a minimal time commitment, and the web-based surveys were easy to use. The group dynamics throughout the surveying process allowed everyone to share information without worrying about dominance or groupthink. The information available during the process to support estimate development was adequate from the perspective of the panelists. Both the panelists and the Advisory Board found the inputs developed via the process to be consistent with real-world cases of adenoma development and cancer progression. They also believed the input estimates were more accurate than what one individual or an informal group could have developed. Since the group process was fully executed and a growing consensus of the estimates produced the final simulation model inputs, the process was clearly feasible. The cost of the process was easily justified because of the limited methods currently available to otherwise gain this information for use in the Colorectal Cancer Simulation Study. Because this information represents the best estimates available to date, and considering there is limited data to support formal analysis, the inputs developed as a result of this process are extremely valuable. The method developed was therefore deemed a success and contributes a method for developing inputs in the absence of data to the field of computer simulation modeling.

Simulation Input Modeling in the Absence of Data

by

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Glossary

Distribution – a model that represents the frequency with which specific values or range of values occur. A discrete distribution is when the frequency is given in terms of specific values. A continuous distribution is when the frequency function is given for a range of value. The distribution is often referred to as a mass function for discrete distributions and as density function for continuous distributions. When the distribution is completely determined by data, it is called an empirical distribution. When it is expressed in a known, accepted mathematical form, it is called a standard distribution.

Cumulative Distribution – A cumulative distribution represents the accumulation of frequencies for a distribution so that if x is the value in the range, then the cumulative distribution is the frequency of any value less than or equal to x.

Distribution Parameter – a set of parameters that specifies each standard distribution; specific sets of parameters define specific instances of standard distributions; examples:

Exponential: [mean]
Johnson SB: [delta, gamma, lambda, xi]
Normal: [mean, standard deviation]
Triangular: [minimum, mode, maximum]
Uniform: [minimum, maximum]
Weibull: [alpha, beta]

These are just a small sampling of the many distributions and their associated parameters; whenever the word 'parameter' is used, it will be specifically associated with a distribution.

Distribution Characteristic – standard statistical properties that apply to all distributions generally describing the shape, location, and distribution of the frequencies. For example the mean, variance, skewness, and kurtosis are the first four (central) moments

and are some distribution characteristics of a standard distribution. An empirical distribution may have such values estimated from data.

Input Model/Valuation – a "value" given to a variable input to the simulation model. A constant, a distribution, or some other mathematical/stochastic model may specify this value.

Variable – component of a model that may be subject to change. For example, gender, age, and progression to cancer may be variables. Independent variables may be changed directly such as gender and age. Dependent variables may be influenced only through independent variables. For example the estimate for adenoma progression to cancer may change as a function of gender and age. Variables may be input to a simulation and are called input variables or inputs. Variables output from a simulation are called output variables or outputs.

System – a process that generates data and provides information; for example, cancer progression in human patients is a system in which cancer progression can be inferred and observed.

System Events – points in time when the state of the system changes, such as when an adenoma becoming cancerous.

Observations/Data – actual data that has been witnessed, synthesized, and numerically recorded while the system is operating, as in the number of deaths from colorectal cancer.

Information – idea of system functionality; not necessarily witnessed, but inferred by examining actions and system processes; e.g. the progression rate of medium polyps to large polyps in the colon cannot be observed because medium polyps are removed upon

discovery, but physicians may have ‘information’ on this rate through clinical experience.

Knowledge – awareness and familiarity of system information and operations, gained through direct exposure and experience with the subject matter, often accompanied by extensive reading in the field of knowledge.

Expertise – special skill and opinion gained through intense study of the system and mastery of the system operating principles; extends beyond knowledge through a comprehension beyond that gained in simple examination; usually entails practice and/or research experience.

1. INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in men and women according to the American Cancer Society (American Cancer Society 2003), and the second-leading cause of cancer death according to the National Cancer Institute (National Cancer Institute 2003). Several studies have shown that screening for and removing CRCs and pre-cancerous adenomatous polyps reduces both the incidence of and mortality due to CRC. Screenings are recommended for all patients 50 years of age and older (US Preventative Services Task Force 2002), and these screenings should follow *one* of four strategies:

1. Fecal occult blood testing (FOBT) annually
2. Flexible sigmoidoscopy every 5 years
3. Combination of annual FOBT and flexible sigmoidoscopy every five years
4. Colonoscopy every 10 years

These strategies are recommended by many organizations, including the U.S. Preventative Services Task Force (USPSTF), American Cancer Society, American College of Surgeons, American College of Obstetricians and Gynecologists, American Gastroenterological Association, and the American Academy of Physicians. The age to discontinue screenings is unspecified currently (US Preventative Services Task Force 2002).

Of particular interest to researchers is the cost-effectiveness of the different CRC screening strategies when compared to each other and when compared to no screening (Pignone et al. 2002; US Preventative Services Task Force 2002). In 2002, the National Cancer Institute awarded a grant to a group of physicians and engineers from various universities to update and augment a previously constructed computer simulation model of the natural history of CRC to improve computational efficiency, interaction with other software systems, and better simulate the healthcare systems in which the screening intervention is occurring. This particular study considers the clinical outcomes, cost, effectiveness, cost-effectiveness, and resource utilization of various CRC control strategies for patients and for complex and dynamic populations.

Simulation models allow for the approximation of complex, real-world situations, while taking into account uncertainty in both the real-world system and the computer model. These models should be much less costly than real-world testing, and, more importantly, allow for experimentation that could not be done in the real world because of ethics, cost, feasibility, etc. One of the most important tasks in developing a simulation model is identifying and valuating input variables needed to drive the simulation. A popular cliché in the simulation world is "garbage in, garbage out", which addresses the importance of properly defining model inputs. Models without appropriate and accurate data going *IN* will obviously not get dependable results coming *OUT* of the model. This study specifically addresses the development of these model inputs when data is not available.

One can easily imagine that a modeling problem with uncertain data and undefined input distributions is much harder than the same problem with known distributions and numbers (Yorke-Smith and Gervet 2001). Yet, this lack of data should not impede the development of the simulation model. Hoffman (Hoffman 2000) emphasizes the importance of accurately incorporating "data for which the mean value is not known and for which one only has range estimates of its values" into models. Input distributions combined with reliable random number generators provide the flexibility and feasibility to incorporate the data into a computer simulation.

There are several software packages that aid in the development of input models when data is scarce. These packages include PRIME, VisiFit, ExpertFit, and VIBES. All of these packages help the user develop a distribution by graphically presenting its shape, location, and dispersion, and then providing the associated distribution parameters. In order to create the graphical figure though, the user must have a general idea of the distribution's shape, location, and dispersion. In other words, the user must have a good understanding of the system generating the distribution.

Some software packages define an initial shape by asking the user to estimate certain characteristics of the distribution. However, one should note that studies have shown that humans can estimate certain distribution characteristics better than others when it comes to accurate prediction and estimation (Wickens 1992). Therefore, attention should be focused on only asking users for characteristic estimates that have been proven to be reliable. As will be presented later, the most reliable distribution characteristic estimates come when estimating modes, medians, standard deviations, and percentile points.

In the past, individuals or small, informal groups of people have participated in the development of estimates for distributions with unknown data, but better methods now exist to make group decisions. Three of these methods are the Delphi method, the Nominal Group Technique, and the Consensus Development Conference. The Delphi method in particular is very valuable to this research because it does not require that the group physically meet. Briefly, this method utilizes a panel of experts to come to consensus about an issue without physically meeting. The panelists remain anonymous and are questioned about their opinions through several rounds of surveying. During each round, panelists are given information and comments about the previous round of questioning and are asked to re-evaluate the issue with respect to the new information. Thus, a growing consensus is reached as the rounds of questioning progress.

The Delphi method is even more attractive with today's ubiquity of the Internet. Communication can be greatly enhanced in both speed and quality by using the Web to disseminate information and conduct surveys. When developing web-based applications, one must be careful to abide by the rules of usability. Usability is the idea that the development of user interfaces must incorporate design specifications that are user-centric, flexible, efficient, consistent, and accessible, while mitigating the effects of errors and providing the user with control and freedom (Dix et al. 1998).

The goal of this research was to define a process for developing simulation model inputs in the absence of data. Specifically, the CRC simulation model cited earlier has a number of

inputs for which data is nonexistent or limited. This research presents a general methodology for developing inputs when data is scarce (Chapter 3.1-3.2). This method was applied to the CRC simulation to provide inputs where information was uncertain (Chapter 3.3). The process employed the expertise of a panel of physician researchers. After the process was complete, the panelists completed one final survey that evaluated the process itself. These responses, in addition to the comments from the CRC Simulation Study Advisory Committee and the primary Research Investigators, were used to evaluate the methodology (Chapter 4). The final section of this thesis (Chapter 5) concludes the research and presents recommendations for future work.

2. LITERATURE REVIEW

Simulation studies have gained prominence and sophistication in the systems modeling arena. Computing technology has vastly improved processor speed and memory storage, allowing enthusiasts to develop more complex and more advanced models that will run in reasonable times on a desktop computer. More sophisticated computer programs have been developed, allowing modelers to work with a wider array of tools and modeling strategies. Furthermore, much work has been focused on the importance and development of several crucial activities in simulation model development (Law, McComas, and Vincent 1994):

- Formulating the problem,
- Collecting system information,
- Collecting data,
- Modeling input,
- Developing a valid and credible model,
- Selecting simulation software,
- Designing and analyzing simulation experiments, and
- Management of the simulation project.

All of the above aspects are necessary if the model is to provide significant, accurate, and truthful analysis and results of a real-world system.

2.1 Role of Input Modeling in Simulation Studies

Simulation models are composed of a multitude of random sources of information, which are meshed within the simulation project in the form of an input model. These input models can take many forms, such as probability distributions, rate processes, transition probabilities, etc. Of particular interest in this study is the role of input modeling in useful and practical simulation studies. More specifically, this research focuses on input modeling for medical simulation studies in the area of CRC. In order for this information to be useful

in a simulation model, an input model must be chosen for each source of randomness. Furthermore, the chosen input model must be in a form pliable with simulation software in use (Law and McComas 2001b). As an example, if the simulation software cannot handle a bounded Johnson distribution, referred to as a Johnson SB distribution, then an input model should not be modeled as such.

When reliable and truthful data is not available (or is not used) to drive a simulation, the model may not properly imitate real-world scenarios. Therefore, extreme attention should be focused on proper input modeling in every simulation study. It should be noted that all inputs do not carry equal weights, and consequently some inputs are simply more important than others. To illustrate, consider two inputs – X and Y. Varying X causes large shifts in the model output, while a change in Y causes only very small changes. Therefore, the simulation is more sensitive to changes in X than changes in Y, so X is a more important variable and, therefore, should be given precedence when validating and verifying model inputs. Furthermore, developing input models is not free, as it requires time and resources to gather and synthesize data and information. When deciding where to allocate resources for developing input models, one should focus on those inputs that are most sensitive and most important in the simulation.

Input modeling can be simplified if several assumptions are made (Nelson and Yamnitsky 1998):

1. The input processes should consist of independent and identically distributed observations random variables.
2. The distribution of the observations should be available in the selected simulation software.
3. Observations must be available to select and fit the distribution.
4. The standard distribution must provide a good fit to the actual process performance, according to goodness-of-fit tests and/or a visual inspection.

The above postulations are actually very hard to accept with confidence for many scenarios. While input modeling strives to obtain information to closely replicate the real world in a computer model, most modelers understand that the information will never be perfect. The probability of its accuracy is always less than 1.0 (Wickens 1992). Obtaining perfect information is many times impossible because of the high cost of obtaining fault-less information, or because of the difficulty in obtaining information from different sources. For example, in cancer studies many variables are unknown, such as the growth of an advanced-stage tumor, because the patient's life is endangered if the information is collected (i.e., an unacceptable experiment would be one where the tumor is not removed and is measured as it grows and progresses, until the eventual death of the patient).

2.2 Input Modeling in the Absence of Data

When no data exist for a certain simulation model input, it may seem impossible to fit a distribution, and if a distribution cannot be fitted to a particular input, the impact on the simulation model is negative. To resolve these problems, researchers have been working on overcoming this problem of uncertain or absent data, and several distinct areas of study have gained much attention, including (1) Bayesian updating of information and (2) distribution parameter estimation.

The first methodology, Bayesian inference, is "a formal method of injecting human opinion into an analysis" (Barton et al. 2002). Many argue that Bayesian analysis offers technical and conceptual advantages when compared to classical analyses by allowing a "more intuitive interpretation of probability" (Briggs et al. 2002). The Bayesian approach uses existing information about the estimate in question to develop a 'prior distribution.' Then, new evidence about the estimate is presented and analyzed to determine its effects on the estimates. Finally, the prior distribution is revised with respect to this new information, and the result is called the 'posterior distribution.' In this sense, analysts can incorporate past information with new information to create more reliable and acceptable distributions.

Consider, for example, an effort to estimate "X." The prior distribution developed for this estimate is referred to as *P(X)*. In Bayes' Theorem, the new information collected is in the form of a likelihood function, called *P(Y|X)*. This likelihood function simply describes the likelihood that the new information ("Y") would have occurred for any state of X. The formal method for developing the posterior distribution is as follows:

$$P(X \mid Y) = \frac{P(Y \mid X)P(X)}{P(Y)}.$$

In this equation, *P(X|Y)* is the posterior distribution and *P(Y)* is a normalizing constant. (Eddy, Hasselblad, and Shachter 1990a).

In a medical context, one approach currently being used to synthesize data using Bayesian techniques is the Confidence Profile Method (Briggs et al. 2002). This method is useful for estimating a probability distribution for a parameter when evidence from many different sources must be interpreted, adjusted, and combined. It can specifically address biases and outcome variance in the analysis. Biases exist when the new information collected refers to a related but slightly different estimate than the estimate of interest. The Confidence Profile Method corrects for the bias by defining a function that relates the two different estimates. This method also takes into account the four different types of outcomes (dichotomous, categorical, counts, and continuous) that result from the many different experimental designs, and adjusts the likelihood functions to reflect the proper outcome category. Finally, the Confidence Profile Method contains several different formulas for handling very complex problems, including estimation of distributions, incorporation of indirect evidence, and concurrent resolutions of a problem. While extremely useful, the Confidence Profile Method does require formulation of the problem in a very specific and sometimes difficult manner before Bayes' Theorem can be applied (Eddy, Hasselblad, and Shachter 1990b). Therefore, the Confidence Profile Method is somewhat less attractive because of the complexity in defining the problem in the proper form for use.

The second alternative to overcome the problem of uncertain or absent data, distribution parameter estimation, relies less on the use of prior information than Bayesian inference and perhaps simplifies the process of "problem formulation". Direct parameter estimation

allows users to create a distribution and develop its parameters via estimation of the distribution characteristics. This second alternative can take the form of either a technique that estimates the parameters of a simple distribution (Law and McComas 2001a) or a technique that employs a graph in estimating a distribution's shape, location, and dispersion (Barton et al. 2002). The parameters are obtained using specialized software that converts the graphical distribution to numerical distribution parameters. Parameter estimation will be further discussed and developed in the following paragraphs, as it is a central focus of this research.

A wide range of distributions can describe a data set; however, the proper distribution should be selected to represent the data as accurately as possible. Central moments are used to describe probability distributions, and an examination of these moments may guide the selection of the most appropriate distribution. The first central moment of a random variable y, typically denoted E(y) or μ, is simply the mean of that random variable. The variance is the second central moment, denoted $E(y^2)$ or σ^2. (Mendenhall and Sincich 1995) The third moment of a distribution characterizes its asymmetry. Denoted μ_3, the third central moment is symmetric if $\mu_3 = 0$, skewed to the left if $\mu_3 > 0$, and skewed to the right if $\mu_3 < 0$ (Kumar and Veytsman 1996). Kurtosis, which is depicted by the fourth central moment, describes both how flat or peaked a distribution is and how close the distribution is to normal (Byers 2003). Positive kurtosis indicates a peaked distribution, and negative kurtosis gives a flatter distribution with longer tails. Skewness addresses the imbalance of the distribution's tails. Kurtosis also addresses the existence of heavy tails (Cizek et al. 2001). The descriptive powers of these four moments can make a distribution more (or less) attractive by allowing it to take on various ranges of values for these moments, although kurtosis is not as useful for comparing distributions as the first three moments (Law and Kelton 2000). Triangular, beta, and Johnson SB distributions are three distributions of particular interest in this study. They will each be discussed in detail below with respect to their first four moments.

The triangular distribution is characterized by three parameters, *a*, *b*, and *c*, (or minimum, maximum, and mode) which together reflect the distribution's location, scale, and shape,

such that $a \leq c \leq b$. The first moment, the mean, is given by the equation $(a + b + c)/3$, and second moment, the variance, is given by $(a^2 + b^2 + c^2 + a\,b + a\,c + bc)/18$ (Law and Kelton 2000). The special cases where $c \rightarrow a$ and $c \rightarrow b$ are called left and right triangular distributions respectively. Subsequently, the third moment (skewness) of the triangular distribution can take on a range of values from approximately a to b. For $a = 0$ and $b = 1$, the right and left triangular distributions are special cases of the beta distribution (Anonymous 2003a). The fourth moment of the triangular distribution is fixed and should not be a point of consideration.

The beta distribution is described by two shape parameters, α and β, where $\alpha>0$ and $\beta>0$, assuming (without loss of generality) that the minimum is zero and the maximum is one. The first through fourth moments of the beta distribution are described below (Anonymous 2003a):

Beta - First Moment (Mean): $$\frac{\alpha}{\alpha+\beta}$$

Beta - Second Moment (Variance): $$\frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$$

Beta - Third Moment (Skewness): $$\frac{2(\beta-\alpha)}{(\alpha+\beta+2)}\sqrt{\frac{\alpha+\beta+1}{\alpha\beta}}$$

Beta - Fourth Moment (Kurtosis): $$\frac{3(\alpha+\beta+1)\left[\alpha+\beta(\alpha+\beta-6)+2(\alpha+\beta)^2\right]}{\alpha\beta(\alpha+\beta+2)(\alpha+\beta+3)}$$

Beta distributions are widely used because of the flexibility in the variety of shapes the beta density function can assume; however, it is not always easy and is rarely intuitive to select values for α and β (Law and Kelton 2000).

The Johnson SB distribution is a member of a set of distributions called the Johnson translation system. Distributions in the Johnson translation system can match the first four central moments (mean, variance, skewness, and kurtosis) of any feasible set of sample values (Stanfield et al. 1996). Of particular interest here is the Johnson SB distribution, which is a bounded distribution carrying four parameters – a location parameter θ, a scale

parameter σ, and shape parameters δ and γ. The Johnson SB density is continuously differentiable and the distribution is capable of matching the skewness and kurtosis of nearly all useful distributions. None of the moments of the Johnson SB distribution can be related to its parameters through any convenient equations, but estimation of the distribution's parameters allows variate generation by translating a standard normal distribution. The Johnson SB distribution can approximate normal distributions over finite ranges, can match the first four moments of all unimodal and certain bimodal beta distributions, and can serve as an alternative to some triangular distributions. (DeBrota et al. 1989).

Many times in the absence of data, modelers are tempted to use simple distributions. For example, they might try to replace a distribution by its estimated mean (Law and McComas 2001b) or use the wrong distribution simply because it is easier to handle and/or estimate. For example, the triangular distribution is easily understood and its parameters can usually be estimated fairly easily. However, the triangular distribution is not very flexible (Law, McComas, and Vincent 1994). The beta distribution, with its two shape parameters, is more accommodating than the triangular distribution; yet, beta distributions are more difficult for the modeler to specify since they require the definition of two shape parameters in addition to both of the end points. Bounded Johnson distributions are another alternative to using the triangular. Although they don't intuitively seem to have close fits to all distributions, a reasonable assumption about the distribution's spread can provide a good modeling option (DeBrota et al. 1989).

A more intuitive method of parameter estimation could yield more reliable results than adapting simple distributions. For this reason, graphical estimation is an excellent tool used by input modelers to create distributions that can be confidently used in simulation studies. Graphical estimation is a valuable method for describing and modeling input parameters in a simulation model. There are several advantages to using graphical methods of estimation, but also some associated disadvantages (NIST/SEMATECH 1999). While graphical estimation is quick and easy to use, it is typically biased by the user's knowledge, which can either be beneficial or harmful depending on the research. The visual sense and visual

testing of graphical models appeals to many input modelers as an simple check of input validity, but it is impossible to perform formal statistical tests or form confidence intervals for these graphical methods because no actual observations exist to confirm tests.

Before running a simulation model containing distributions developed via graphical estimation, the modeler must understand the distribution and have confidence in its accuracy (Barton et al. 2002). This concern brings up another valuable point – the knowledge and expertise of the estimator must be considered when using graphical estimation techniques. While seasoned statisticians may completely understand the difference between many similar statistical moments or parameters, those with less experience may be unable to make the critical distinctions between common measures such as the mode, median, and midrange (DeBrota et al. 1989).

Graphical estimation requires that the user to have a general idea about the 'look' of a distribution, but describing a distribution is certainly not an easy task. If data collection is not possible or feasible, then approximating a distribution requires an estimation of its shape, location, and dispersion. The density's outline can be specified using a combination of distribution characteristics, which may include the mean, standard deviation, skewness, kurtosis, or endpoints. Most people, even statisticians, have difficulty envisioning these characteristics for an unknown distribution with no representative data, which adds importance to the idea of a graphical software package for developing distributions. Of particular interest to many input modelers is the shape of a distribution's tails. These tails are where the extreme values of a distribution exist. If the tails are not representative of the true distribution, then any simulation that relies on system variability to influence performance measures will certainly not be representative of the real world system it is designed to depict. With all this complexity, graphical displays allowing manipulation of the graph to arrive at the desired distribution are extremely important and useful, particularly when data is lacking.

2.3 Graphical Estimation Software Used for Input Modeling

Many input modeling software packages are available for developing probability distributions for use in simulation models. Many simulation software packages, including the popular *Arena* software, contain internal distribution-fitting capabilities based on user-input data. Other simulation packages, such as *ProModel, Simul8, Extend, MedModel,* and *ServiceModel* use external packages to determine "best fits" for sets of data (Swain 2001). One of the most-used external packages is *Stat::Fit*, which fits data to one of 32 distributions. The package includes goodness-of-fit tests, graphical analysis, and random variate generation, and easily exports distributions to many simulation models (Anonymous 2002). Version 8 of SAS's *PROC UNIVARIATE* fits distributions and provides confidence limits for basic parameters and percentiles for a number of continuous distributions (Curtis 2002). XLStat fits probability distributions to continuous or discrete quantitative data (Kovach Computing Services 2002). The website www.statpoint.com offers online distribution fitting for problems with observations available (Anonymous 2003b). *Crystal Ball* distribution-fitting software fits continuous distributions for historical random data, as well as providing goodness-of-fit statistics and graphical displays (GMSL 2002).

All of these input modeling packages require the user to input data about the process being modeled, either by entering data to which a distribution can be fitted or by entering the actual distribution characteristics into the program. After putting this data into the program, a graphical representation of the distribution is displayed on the screen. Regrettably, these programs are not useful if the user does not have a representative amount of reliable observations of the system to drive the software program. Furthermore, these packages do not allow the editing of the graphical display, thus eliminating the ability to change the distribution's parameters by visually altering its shape.

Fortunately, several other programs exist that can aid an input modeler in constructing distributions in the absence of data and also allow the user to subsequently alter the graphical display to obtain the desired distribution and its parameters. Among these are

PRIME, VisiFit, ExpertFit, VIBES, and BestFit. Each of these programs is discussed in detail below.

PRIME

PRIME, which stands for **PR**obabilistic **I**nput **M**odeling **E**nvironment, is a "flexible, interactive, graphical methodology for modeling a broad range of input processes that arise in simulation input modeling" (Wagner and Wilson 1996). This graphical software program that runs on a Windows PC uses Bezier curves to represent distributional shapes, based on user input and data-driven techniques. The program aids the selection and visualization of univariate input processes needed for simulation studies. PRIME's ability to construct univariate Bezier distributions with or without observations provides an attractive means to create input distributions when data is unknown or data validity is uncertain.

PRIME was developed for easy and intuitive operation. First, a cumulative density/distribution function (cdf) is graphically constructed by incorporating user specifications of certain characteristics, such as percentiles and endpoints that should remain fixed in the redrawing of the distribution, as well as estimates of the distribution selected using menus. The cdf is displayed on the screen, with control points along the curve. Next, control points on the actual distribution line can be moved, added, and deleted to change the shape (and thus the parameters) of the distribution, with immediate graphical and numeric feedback of the changes on the computer screen. The program will also provide immediate feedback when the user specifies infeasible control point locations. After obtaining the desired shape, the user can view the probability density function, statistics, fit measures, and percentiles of the distribution (Wagner and Wilson 1996).

VisiFit

VisiFit, or the **VIS**ual **I**nteractive **FIT**ting of distributions, uses the modeler's intuition and experience in working with the system being simulated to specify a target distribution in the absence of data. In order to get an initial graphical sketch of the distribution, the input modeler must specify both the endpoints of the distribution as well as any two of the mean,

mode, median, percentile points, width of the central tendency, and standard deviation (DeBrota et al. 1989).

Once VisiFit is given the initial approximations, a preliminary graph is displayed on the screen. The user should then compare the figure to the conceptual graph of the distribution in question. If the shape is not what was expected, the modeler can use specified keystrokes to manipulate the shape of the distribution or alter the mode, width, the 2.5th and 97.5th percentile points, and the endpoints. The graphical display is automatically updated to correspond to the new inputs. Once the desired curve is displayed on the screen, the user can ask the program to find the Johnson SB distribution parameters that most closely match the graphical display (DeBrota et al. 1989).

One important advantage of VisiFit is that the modeler can adapt the display to allow him or her to estimate parameters that are most understood, and hopefully most accurate. One disadvantage to the VisiFit software is that it is a MS-DOS executable file, which makes interfacing VisiFit and other software more difficult within more recent Windows operating systems. Another limit of the software is that it only models the Johnson SB distribution. While the Johnson SB is a very flexible and adaptable distribution, modelers may like the choice of using other representations.

ExpertFit

ExpertFit is a Windows-based distribution-fitting software that specifies probability distributions from among its 40 built-in standard distributions. It can display them in a proper format for input into 26 different simulation packages. When no observations are present, ExpertFit offers two options to the analyst. If the unknown distribution is a general distribution for task time, ExpertFit will model it using a triangular or beta distribution using the analyst's estimates of minimum, maximum, and most likely times. If the unknown estimate is a time-to-failure or time-to-repair distribution, for example for a machine that breaks down, then the analyst may provide estimates for the percentage of uptime or the mean repair time (Law and McComas 2001b). ExpertFit also allows the analyst to view and

change distributions without entering any observations. When the "distribution viewer" window is open, the analyst can move a 'slider bar' to change any of the distribution characteristics, and the display is interactively changed (Barton et al. 2002). This manipulation allows the user to experiment with different characteristics of ExpertFit's many distributions, which also makes this software a good learning tool.

VIBES

VIBES, the **VIS**ual **I**nteractive **B**eta **E**stimation **S**ystem, is very similar to VisiFit except it fits distributions to a beta distribution, as opposed to a Johnson SB distribution in VisiFit. The user must specify the end points of the envisioned distribution as well as two other characteristics, including the mode, mean, variance, or selected percentile points of the envisioned distribution. VIBES then displays a graph of the generalized beta distribution that most closely matches the input characteristics. The user then varies the characteristics entered until the desired shape is obtained. Next, VIBES displays the probability density function (PDF) resulting from the graph of the desired shape. The user can alter the PDF using the arrow keys until the distribution graph is finalized. Finally, the user is presented with the parameters of the beta distribution that correspond to the graph of the distribution (AbouRizk, Halpin, and Wilson 1991).

BestFit 4.5

BestFit software from Palisade Corporation is a component of their @Risk risk-analysis and simulation add-in for Microsoft Excel. BestFit is typically used to fit distributions to data, as it includes distribution fitting for 27 different distributions, graphical displays, and goodness-of-fit tests. The program can accept data in sample, density, or cumulative formats. However, BestFit also allows users to preview and edit 37 different distributions in two different ways. The first method involves the user selecting a distribution from a drop-down menu and then either defining initial distribution parameter estimates or using general parameter estimates. After BestFit quickly displays the graph on the screen, the user can alter the shape of the graph using buttons to systematically change parameters. Another method for previewing and editing distributions is to specify endpoints and then draw the

distribution freehand with a mouse. Using the figure drawn, BestFit fits the estimate to different distributions, and shows an overlay of the best-fitting distributions against what was drawn as well as providing goodness-of-fit measurements for each fitted distribution. This process gives the user the opportunity to either select a chosen distribution or further modify one of the distributions by making changes to its shape, thus changing the distribution's parameters (Palisade Corporation 2002).

Interfacing Input Modeling Packages with Simulation Software

The input modeling packages described above are not stand-alone products because they are used in conjunction with a simulation model and its associated software. The inputs generated by input modeling software must be among those the chosen simulation software is capable of processing. Furthermore, the simulation software must have a capable random number generator to allow proper sampling from a distribution. As Law and Kelton (Law and Kelton 2000) describe, "A simulation of any system or process in which there are inherently random components requires a method of generating or obtaining numbers that are random, in some sense." Simulation inputs represent the randomness in the system, and random number generators initiate this randomness by causing the random selection, or sampling, of a distinct value from the distribution each time the input is called. Hence, there is great importance in having a reliable and accurate random number generator. The random numbers are generated from a continuous uniform distribution bounded between zero and one. For example, a generated random number of 0.01 would represent some value in the left tail of a distribution. Similarly, a distribution's right tail will be used when a random number close to 1 is generated. Simulations models must strive to sample in a way that is unbiased but still reproducible between experiments. Since this random number defines the values used in the simulation model, a good random number generator must be employed in conjunction with accurate input distributions (Law and Kelton 2000).

2.4 Human Reliability in Data Estimation

While the input modeling packages discussed above are all quite different, they do share several commonalities. They all rely on the use of a random number generator and appropriate random variate generators to be properly incorporated into a simulation model. In addition, PRIME, VisiFit, ExpertFit, VIBES, and BestFit have one additional aspect in common – they require some type of input that creates an initial drawing of the distribution. In this sense, the user must employ all his or her knowledge of the real system, draw out information, many times gained over a long period of time, and synthesize this information into meaningful representations. As an example, consider a medical doctor who is being asked to estimate a specific distribution for a medical system which he or she has no actual data available. This doctor would have to think about hundreds, maybe thousands, of patients and their conditions and the progression and type of condition. The doctor would then have to mentally separate the relevant cases from the irrelevant cases, gather notions about the specific variable being estimated, and then finally the doctor can provide an intellectual estimate of relevant distribution characteristics.

One can see from this example that the process of estimation requires extensive mental digestion of information. Can these mental processes be trusted? Research shows that the capability of humans when processing information is very limited because of the boundaries of human memory, attention, and logic (Wickens 1992). The accuracy in human estimation of statistical parameters is an issue to consider because of the human limitations stated above. The degree of imprecision can be affected by factors such as experience, exposure to the system, and the limitations on compiling and summarizing observations.

Humans are fallible and susceptible to errors in judgment, particularly when estimating descriptive statistics (Wickens 1992). Furthermore, as Lathrop (1967) states, this may be due to the fact that "events do not normally occur as distributions with a mean and a standard deviation." While we cannot create perfect simulation input models, we must strive to increase the accuracy of the estimations by extracting the proper information from

experts on the subject matter. Therefore, to retrieve the most accurate information in distribution characteristic estimation, developers of these graphical estimation techniques must be aware of the human limitations in estimating and attempt to extract input from humans in such a way that the estimations can be used with confidence. The best approach in determining which types of information that humans can reliably estimate is to examine previous research. Numerous studies show that certain types of information can indeed be estimated with more confidence and reliability than other types of data. This topic will be discussed in the following section.

Peterson and Beach (1967) support the idea that, when estimating under uncertain situations where human inference is imperfect, descriptive theory provides models for making inferences. On the other hand, statistical estimation by humans is limited by both "a person's ability to perceive and store probabilistic data accurately and the ability to draw inferences (and thereby make decisions) on the basis of those data" (Wickens 1992). Statistical estimation can also be influenced by limitations on the type of information humans can process as well as the problem solving strategy each estimator uses (Pitz 1980).

The understanding of distributions and probabilistic information is critical to the successful acquisition of reliable distribution parameter estimates (Pitz 1980). Without a background in probability and statistics, one might have a difficult time creating an estimate. However, as (Kahneman and Tversky 1982) point out, fundamental intuitions about uncertainty will not change with statistical training alone. Regressions are still hard to observe, sequences are still hard to ignore, and background information may not always be completely accurate or representative.

Particular types of statistical information are more difficult for most people to visualize, and thus estimate. In the context of building input modeling software, a programmer should attempt to avoid asking persons providing the input distributions to offer estimates of statistical characteristics that typically cannot be given with reliance. Important and widely-

used descriptive statistics will be discussed in this section with respect to their reliability, ease of estimation, and bias.

2.4.1 Measures of Central Tendency

➔ *Estimating the Mean*

According to Wickens (1992), the mean value can be estimated reasonably well. Peterson and Beach (1967) found that human estimation of the mean does not tend to be biased higher or lower, and the authors report that estimations of the mean are fairly accurate. However, estimates of mode and median are better than that of the mean when the distribution in question is skewed (Peterson and Miller 1964). The mean is quite often the chosen measure of central tendency; however, the mean can be skewed by very large or very small observations (Mendenhall and Sincich 1995). In support of these observations, testing done by Beach and Swenson (Beach and Swenson 1966) show that estimation of the mean is weakest and least reliable when a large amount of data is present, when the distribution has a large variance, or when the distribution is skewed.

➔ *Estimating the Mode*

The mode, which is the value in a distribution with the greatest frequency, is easy to envision in an estimated distribution. Accordingly, "A target's mode is more easily specified than any other measure of central tendency" (DeBrota et al. 1989). The mode is also a 'stand-alone' measure of the distribution because it does not reflect any information about its tails or asymmetry. So, estimations of the mode should not be influenced by other aspects of the distribution such as skewness or kurtosis (DeBrota et al. 1989).

➔ *Estimating the Median*

The median is a much better representation of the "center" of a skewed distribution because it is resistant to extreme behaviors (Mendenhall and Sincich 1995). Therefore, medians can likely be estimated with a higher degree of confidence for skewed distributions.

2.4.2 Estimating Variability and Spread

➔ *Estimating Variance*

The concept of variance is much more complex than that of many other statistical characteristics. Consequently, variance estimations have not performed as well as other simpler descriptive statistics. Variance estimates also tend to be correlated with the mean, which is certainly an error in estimation (Lathrop 1967). In this manner, as the mean increases, the estimated variability also increases. Several studies have shown that the sequence of information presentation alters the estimated variability (Lathrop 1967), so one must ignore sequencing affects when making estimates in order to produce an accurate estimate of variance. Variability estimates are also influenced by the salient, most recognizable features of a distribution (Pitz 1980). When no concrete data is available, one might focus on considering only observations and information relevant to the estimate at hand. Thus, when presenting data to decision makers, only information directly relevant to the decision should be offered (Kahneman, Slovic, and Tversky 1982).

➔ *Estimating Standard Deviation*

When estimating standard deviation or variance, one must ensure to keep the two types of estimates separate. Standard deviation is the square root of variance, but standard deviations and variability are often times estimated interchangeably although they are not the same. When estimates are hard to develop, one might choose to define the standard deviation as one-sixth of the range. This method, known as the PERT method, assumes that the standard deviation is (b-a)/6, where a and b are the endpoints of the range (Wilson, Naylor, and Voss 1982).

2.4.3 Other Estimates

➔ *Estimating Future Growth*

Research has proven a distinct bias when predicting future trends. Both naïve estimators and expert predictors show noticeable conservatism by consistently underestimating growth

patterns (Wagenaar and Sagaria 1975). The conservatism can be attributed to the complex nature of growth functions and an inadequate understanding of future growth, to a resistance to acknowledging extreme values, or to confusion between the estimation task and real-life experiences where change is controlled. Regardless of the cause of the underestimation, humans do not follow mathematical laws when extrapolating and predicting growth functions (Wickens 1992).

➔ *Estimating Proportions*

Proportion estimates have an unfortunate tendency to be biased. While estimates that are actually toward the midrange can be estimated with less bias, small biases appear when the proportion estimate reaches out toward the extreme values (Wickens 1992). This bias could stem from human reaction to be cautious, or it could reflect the increased attention that is given to more prominent outcomes. Accuracy of proportion estimates increases when the estimator has had more exposure to the distribution in question (i.e., when the estimator is an expert) (Peterson and Beach 1967).

➔ *Estimating Percentile Points*

Percentile points can be estimated with accuracy (DeBrota et al. 1989). The research supporting this statement is based on a study showing that the evaluation and predication of percentiles are highly correlated (Kahneman and Tversky 1982).

➔ *Estimating Moments*

For practical purposes, moments of a distribution cannot be estimated with accuracy. These should only be calculated when data is present. (DeBrota et al. 1989)

The following is a brief summary of reliability and accuracy for particular distribution characteristics when making estimates based on experience with little or no data:

- Mean – questionable reliability when the distribution is skewed or has a large variance;
- Mode – acceptable accuracy;
- Median – acceptable accuracy;

- Variance – not as reliable as other estimates;
- Standard Deviation – can be estimated as 1/6 of the range;
- Future Growth – shows bias, so not very reliable;
- Proportions – shows bias, so not very reliable; better estimates of proportions are given if the estimator is an expert;
- Percentile Points – acceptable accuracy;
- Moments – estimations are not reliable;

2.5 Group Methods for Eliciting Information

A majority of decisions in healthcare policy and practices over the past 40 years have been based on mostly unstructured group meetings with few formal rules or procedures (Murphy et al. 1998). Group meetings typically bring people together with the aim of reaching an agreement on the problem being discussed. Several problems arise with this sort of group interaction. First, instructions are rarely given on how to reach the desired consensus. Second, domination by one member of the group may sway results to be in that member's favor. This occurrence relates to another unfortunate group dynamic called 'groupthink.' Groupthink is "a phenomenon wherein people seek unanimous agreement in spite of contrary facts pointing to another conclusion" (Janis 1986). Group members may have such a strong desire for agreement that they unconsciously fail to evaluate alternative courses of action. In this sense, unanimous or majority decisions threaten the group goals (Janis 1986). Groupthink also relates to the third negative issue in group decision making. People tend to conform to the judgment of others because of social pressures. This conformance can thwart the group's decision-making process and reduce their ability to find the best agreement on the issue. As Murphy, et al. (1998) states, "The desire to reach agreement may override concerns about the accuracy of the result to the extent that there is premature closure on a particular solution without consideration of the alternatives."

In view of these potential problems with group decision-making, one might question whether group decisions are better than individual decisions. However, one should consider

the benefits of groups. The saying "safety in numbers" portrays how multiple people together are less likely to develop a wrong conclusion than an individual. Groups of people can enlighten each other, thereby increasing understanding within the group as a whole. Decisions may be improved when others' notions are challenged and members must defend their perceptions (Murphy et al. 1998).

Several formal methods of consensus development have emerged that aim to lessen the problems of groupthink and social pressure. These formal methods provide a more controlled and structured process that aid positive group decision-making. Three of the most popular formal methods are discussed below, including the Delphi method, the nominal group technique, and the consensus development conference.

2.5.1 The Delphi Process

The Delphi technique has been in use since the late 1960's, when it was developed by the RAND Corporation (Cline 2002). One significant advantage of this method is that groups do not have to physically meet, making it an excellent approach for eliciting information and opinions from individuals with expert knowledge, but who may not be able to meet (Nehiley 2002). The approach of a Delphi study is a cyclic process that occurs in waves. It starts by selecting a group of experts with the necessary knowledge to address the issues at hand. Next, a series of questions, often open-ended, is presented to the panel, via mail, fax, email, or telephone. The responses are collected and summarized, and then the next wave starts by sending out a summary of the anonymous responses from the first phase. The panel is then requested to analyze the information. At this stage, panel members may be swayed to revise estimates toward consensus, or alternatively panel members may stick with the original estimate. Members are instructed to provide support for the original estimate and provide justifying information when keeping an original estimate. Responses are again collated and the third wave begins by sending panelists yet more information and clarification on the issue. The process continues in this manner until consensus is reached. Three waves are typically enough to develop a final agreement on the issue, at which time a final report is

distributed to all members. Each wave typically takes around two weeks to conduct, so the entire Delphi process can be expected to take a month or longer to complete.

Throughout the process, Delphi team members become increasingly aware of the opinions of other experts, thus facilitating a growing consensus as the situation is analyzed (Nehiley 2002). In this manner, the Delphi process allows members to identify and exchange information, which may persuade them to similar points of view (Dick 2000). Disagreements are used to increase comprehension of others views and gain additional information. Decisions are consequently made on the basis of more information than one person alone would possess. Furthermore, Delphi panelists are motivated to participate to increase understanding and knowledge in their area of expertise.

Delphi is particularly useful when the group must come to some consensus of opinion about subjective rather than factual information, when decision-makers have strongly opposing preferences, when the environment is emotional, or when the process must be insulated from limitations of group decision processes as discussed above. Delphi is also advantageous for busy professionals, as they are given ample time to contemplate a problem and collect information, as well as an equal opportunity to contribute to the group (Dick 2000). Thus, panelists are not pressured into consensus and no one member of the group can dominate, since the only communication is done through a facilitator. Furthermore, all opinions and estimates are anonymous, so panelists should not be apprehensive about sharing ideas and information because they will not be judged. As Cline (2002) states, Delphi can work as an "informal, subjective model when the decisions are based on opinion, and can be directly converted to a formal model, when the data is more knowledge-based."

2.5.2 Nominal Group Technique

The nominal group technique (NGT) was developed by Andrew Van de Ven and Andre Delbeq at the University of Wisconsin in the 1971 (Martens 2002). This method uses a structured meeting and a group facilitator to elicit opinions from the group in attendance.

Specifically, formal NGT develops a panel of experts, similar to the Delphi method. However, NGT brings these experts (about 9-12 of them) together to gather information. While NGT provides more immediate feedback and responses than the Delphi method, NGT requires a bit of upfront work, for both facilitators and panelists. The facilitator should compile a packet of relevant literature on the issues, and the panelists should review the literature prior to attending the group meeting. NGT has been used in many areas of healthcare, for example when examining education and training, practice development, measures of clinical trials, components of research studies, and priorities in cancer care (Jones and Hunter 1999). NGT is typically used when expert opinion is needed in addition to a body of evidence that panelists should use to make their decisions (Jones and Hunter 1999).

The NGT starts by convening the experts. Individually and anonymously, each member records his or her ideas about the issue at hand. Then, either the facilitator collects and summarizes the responses, or all the responses are presented in a round-robin fashion. Once all ideas have been listed, each idea is addressed and discussed in turn. At the end of round one, each participant privately ranks each idea. The rankings typically occur on a scale from 0 (inappropriate/irrelevant/incorrect) to 9 (appropriate/relevant/correct). The facilitator then tabulates the rankings and presents them to the group. This overall ranking is discussed and debated, bringing out further information about the topic. Round 2 concludes with all members re-ranking the issues. The facilitator again tabulates the ranking, and presents it to the panel as the 'group judgment.'

The NGT promotes the generation, elaboration, and evaluation of ideas during the private brainstorming phase. Since this is done individually and often presented anonymously, panel members may be less inhibited and present a broader range of ideas. Also, sufficient time should be allowed for thought and reflection. Since the idea generation and discussion phases are separate, more ideas will be developed, and the facilitator should ensure that every idea generated is given ample time for discussion (Murphy et al. 1998). Furthermore,

the facilitator should control interaction, allowing all participants a chance to express his or her views and reducing the dominance effect of one group member (Murphy et al. 1998).

2.5.3 Consensus Development Conference

The U.S. National Institute of Health introduced the consensus development conference in 1977 (Murphy et al. 1998). This method calls for a select group of people to reach consensus about an issue in an open meeting. The meeting, which may take place over the course of several days, begins by having interest groups and other panel members who are not on the panel present information and evidence about the questions at hand. The panel members, as well as others in the audience, are allowed to ask questions and have discussions in the presence of the public. The panel as a whole then departs to contemplate the evidence and the issues with regard to this new information. They strive to reach consensus about the issues. If consensus is not reached, panelists are allowed to include minority or alternative views in their final evaluations and recommendations rather than providing one definitive response (Murphy et al. 1998).

2.5.4 Discussion of group methods

Murphy, et al. (1998) have shown that formal methods of group consensus generally perform equal to or better than informal methods. One can think of formal methods of group decision making as a win/win situation, where panelists can make better decisions by expanding their base of information, and ultimately arriving at a response that everyone in the group is typically more satisfied with than the initial response (Dick 2000). It should be noted that no one specific formal group method can definitively outperform other methods. This conclusion is clearly due to the different applications for each method. As stated earlier, the Delphi method is most appropriate when opinions are requested in the absence of evidence, and the NGT works best when responses are based on expert opinions infused

with external evidence. Other aspects of group methods, such as panel characteristics, group size, and consensus, are discussed below.

Panel Characteristics

Group composition is an extremely important consideration when using group decision-making methods. Many situations, especially those concerning medical research, involve the use of expert panels. These panelists are chosen based on both their extensive knowledge of and exposure to the subject and their willingness to share information (competitors should not be on a panel) (Nehiley 2002). Participant status should not affect group dynamics. For example one should not include a boss and his or her employee, for the employee may fail to be impartial in sharing ideas, information, and opinions. Clinical specialty may also influence judgment (Murphy et al. 1998). Consider the case where an expert physician works mainly with pediatric cancer patients. If a panel is addressing colon cancer, which predominantly occurs in adults, the expert physician may not provide a result consistent with the actual prevalence of colon cancer since this physician does not see colon cancer regularly, although he or she may treat other types of cancer regularly. Another example is the case where a physician has expertise in diagnosing CRC; however, this same doctor refers patients to another physician to treat the cancer, so he or she is not versed in cancer progression or cancer treatment.

Group Size

Since groups vary in purpose and situation, no average, minimum, or maximum group size can be determined for all circumstances. The group size should be large enough to mitigate any effects of panelists' personal characteristics. However, despite the reduced amount of error (or increased validity of responses) with more participants, there are decreasing returns with increasing size as communication, facilitation, and the time required for each round increases as sample size increases.

A popular statistical method for determining appropriate sample size in order to ensure the statistical reliability of results is to use the standard statistical measure for calculating sample size, as given in the equation below (Mendenhall and Sincich 1995):

$$n = \left(\frac{Z_{\alpha/2}\sigma}{H} \right).$$

In this equation, n is the sample size assuming each subject represents one observation, σ is the population standard deviation, H is the desired half-width of the confidence interval, and $Z_{\alpha/2}$ is a tabled z-value with an area of α/2 on each side of the mean. The tabled z-values are applicable only when the sample size is large, say n > 30. If enough samples are not available, the student t-tabled values can be used. These z- and t-values are available in most statistical books.

Many researchers use less formal methods of determining sample size, particularly when expert opinion is required or when a limited number of participants are eligible to participate. Some researchers using the Delphi technique believe that there are a limited number of new ideas, and therefore 30 participants is the upper bound that the process can adequately handle (Gould 2000). These researchers feel that three or four participants are not enough to sufficiently examine the problem, and between 10 and 20 people are typically reasonable for Delphi panels (Gould 2000). Researchers at the Rand Corporation, where the Delphi method was developed, and the University of California at Los Angeles found that seven-member groups showed around a 50% reduction in error over individual estimations, but groups larger than that did not reduce error as quickly. As proof, 27-member groups showed just a 60% reduction in error over individual estimations (Dalkey 2003). The expertise of the respondents should also be considered when defining group size, as Linstone and Turoff (Linstone and Turoff 2002) explain that accuracy of responses can be improved not only by increasing the number of responses but also by selecting a more-expert subgroup.

What is consensus?

As Jones and Hunter (1999) assert, two forms of agreement exist in group decision making. The first form is a numeric or scaled rating of the extent one concurs with an issue or statement. The second form is the level of agreement the participants have with each other. When consensus within a group has not been reached, participants should expect to defend, justify, and face questions about their individual views. In any manner, participants should clearly understand that they do not need to have identical views to have consensus, as this helps impede groupthink, which has been identified as a negative outcome of group processes (Jones and Hunter 1999).

Clearly, consensus (or agreement) is not easily determined or calculated. Often times, the final response from a group process is actually an average of all participants' responses. Delphi group processes usually report the median of the responses as the group approximation. Nominal Group Techniques frequently ask participants to rank their agreement with a particular response using a pre-specified scale, and then the distribution of the rankings helps describe the group consensus. Upper and lower quartiles of the estimate can also help identify group uncertainty around the estimate (Jones and Hunter 1999).

Consensus Development Activities

All consensus development models involve three activities – planning, individual judgment, and group interaction(Murphy et al. 1998). These actions successively represent a generic outline for any group decision-making approach, and they involve the following actions:

- Planning includes selecting the proper formal method to use, determining what information is to be determined, developing the expert panel, establishing rules of interaction, and gathering literature and research materials if necessary.
- Individual judgment is both what the participants might do to prepare themselves to make a decision as well as making observations and forming opinions.
- Group interaction refers to the sharing of information among group members, whether it is through a moderator or in direct contact.

2.5.5 Use of surveys for eliciting responses from groups of people

In addition to consensus methods, surveys are an excellent medium for obtaining specific information from large numbers of people. While surveys appear easy to develop, users must be aware of potential complications of using this tool. Surveys can be considered biased for many reasons, including when they ask leading questions, when the sample population selected is biased, when the questions are unclear, and when the respondents are influenced by the researcher (Brown 1999). Other complications include logistical and hardware problems, issues with a lack of responses, challenges in analyzing qualitative data, etc.

Since almost every person living in the United States has access to the Internet due to its widespread availability, using the web to conduct surveys is a growing trend. Web use greatly reduces the time and effort in distributing surveys, and it typically eliminates the tedious task of inputting responses. Furthermore, many software packages for developing web surveys simplify the analysis process by automatically collecting, grouping, graphing, and doing numerical calculations on the responses. Unfortunately, a bias may exist within people using the web, as studies show that the socio-economic and educational level of typical web users is above that of the general population (Schmidt 1997). Developers should be aware of these potential biases when developing surveys.

2.6 Designing Usability into a Process

From the advent of the computer-programmer interaction in the 1960s, to the rise of personal computing in the 1970s, through the emergence of the World Wide Web in the early 1990s, and up to the present time, researchers have considered the interaction of humans and computers in a plethora of studies whose goal is to determine how best to apply this technology to accommodate and augment the knowledge, skills, and creativity of humans (Dix et al. 1998). The overall concept, known as "usability," addresses the design of useful and accessible people-computer or people-process interfaces. Additionally,

usability engineering prescribes a process for "defining, measuring, and thereby improving, the usability of products," and transforms the concept of usability into a measurable characteristic (Wixon and Wilson 1997). For example, IBM considers usability in their 'user engineering' process by defining user-centered design principles for their products and services, such as understanding users, assessing competitiveness, evaluating designs via user feedback, and continually monitoring the total user experience (IBM 2003). Microsoft employed usability concepts when designing their new home page in 1998, and its success lead to an additional step in their design process that considers usability as well as to a Microsoft Usability Group for research (Nordgaard and Richardson 1999).

The National Cancer Institute (NCI) has also realized the importance of usability and they have dedicated a branch within their Office of Communications focusing on usability (National Cancer Institute 2002). In fact, this Communication Technology Branch offers assistance to other government agencies with integrating usability into their work. They focus the concept of usability toward "improving the communication of cancer research." The NCI defines usability as "the measure of the quality of a user's experience when interacting with a product or system – whether a Web site, a software application, mobile technology, or any user-operated device." The factors affecting usability include ease of learning, efficiency of use, memorability, error frequency and severity, and subjective satisfaction (Dix et al. 1998). When developing a design, one must consider both the purpose of the design (what are the goals?) as well as these usability factors. Collecting data from users via feedback forms, system metrics, and usability testing can help determine the users' needs. After developing a baseline prototype, the content of the design must be revised with respect to its format and the information included. The information included should be valuable and understandable, and it must be in a location and format that is quick and easy to use. The iterative process of usability testing will shed more light on the true user expectations of the design, and alterations to the design should be made accordingly (Wixon and Wilson 1997). Finally, after the design is 'completed', its performance should be continuously monitored through reports, usage logs, user feedback, and other data sources. A usable design can have a great impact in multiple ways – saving time and effort

for the user, having satisfied users return, decreasing lost users, and decreasing the time spent in the re-design phase (National Cancer Institute 2002).

Jakob Nielsen, a usability expert, developed a heuristic evaluation technique for assessing interactive system usability in the early 1990s, and it is still widely used today. He recommends ten usability heuristics, which are summarized below (Nielsen 2003):

1. Visibility of system status – design for appropriate feedback within reasonable time.
2. Match between system and the real world – present information in an accepted and logical order.
3. User control and freedom – allow users to easily move forward and backward in the process with clearly marked 'entrances' and 'exits.'
4. Consistency and standards – follow a convention.
5. Error prevention – try to prevent problems from occurring, but when they do provide a good error explanation.
6. Recognition rather than recall – instructions should be visible or easily attainable; do not make the user remember information.
7. Flexibility and efficiency of use – allow the system to easily operate for both experienced and inexperienced users.
8. Aesthetic and minimalist design – bring relevant information forward and reduce/eliminate unneeded or rarely-needed information.
9. Help users recognize, diagnose, and recover from errors – not only present the error encountered, but also provide a solution.
10. Help and documentation – provide a convenient way to reference the system, search for answers, and find step-by-step solutions.

Clearly, the usability of designs is extremely important. While many concepts for usability are currently focused on web page design, usability concepts have been applied to a vast array of systems and functions (Dix et al. 1998). The key methodology in usability is to be customer-centered and keep clear objectives and goals in mind.

3. DEVELOPMENT OF A METHOD FOR ELICITING INFORMATION

For this CRC Simulation Study, numerous model inputs are unknown. For example, one element of the model of cancer development is the conversion time between a colorectal adenoma and cancer. Developing this conversion time distribution from data would involve monitoring patients with adenomas and measuring the time from when the adenoma developed until the time it became cancerous. Clearly this information cannot be determined by analyzing data or by conventional experimentation because testing would be detrimental to the health of the patient. This data is necessary in the development of the simulation model, and therefore a process must be developed for acquiring this information. To reiterate, the goal of the research is to define a process for defining simulation model inputs when data is absent or scarce.

3.1 Requirements of the Formal Group Process

A formal group method for eliciting knowledge needs to be defined to facilitate the process of eliciting input estimates from experts. The literature review in Chapter 2 uncovered numerous aspects to consider when developing these estimates. Several important considerations are summarized below.

- The cost of developing the input models should be weighed against their relative importance and the levels of accuracy required. (Chapter 2.1)
- While Bayesian updating of information is often times useful, it also requires the careful formulation of both prior and likelihood distributions, which would create additional challenges in the model development. (Chapter 2.2)
- Johnson SB distributions offer increased modeling flexibility in the variety of shapes the distribution can hold, allowing it to closely model many real-world distributions. (Chapter 2.2)

- The study could make excellent use of graphical estimation software. In particular, the VisiFit program and its use of the Johnson SB distribution are quite appropriate for modeling medical uncertainty, as in this simulation study. (Chapter 2.3)
- Statistical information can be estimated with varying degrees of confidence. In general, experts can estimate statistical modes, medians, percentile points, and proportions with confidence, while means, variances, and moments should not be estimated because of their inaccuracy. Standard deviations can be estimated with the PERT method, utilizing the distribution's endpoints. (Chapter 2.4)
- Formal group methods for eliciting information are preferred over both informal group methods and methods using only individual judgment. Popular formal group methods include the Delphi Method, Nominal Group Technique, and Consensus Development Conference. (Chapter 2.5)
- The formal group method should mitigate negative group effects such as groupthink, domination, and conformance, should provide anonymity, should develop a platform for increasing understanding within the group, and should offer a means for both challenging and defending ideas. (Chapter 2.5)
- The expert panel chosen to participate in formal group decision-making should consist of 10-20 members, who are all chosen based on their expertise and willingness to share information. (Chapter 2.5)
- Web-based surveys may provide an excellent medium for eliciting information from experts that eliminates physical meetings and the need to travel. (Chapter 2.5)
- This process should be developed with usability features in mind, including the user's requirements and the goals/purpose of the research. The process should be flexible to account for many potential applications while still being simple and efficient. (Chapter 2.6)

Formal methods for eliciting information from groups are discussed in Chapter 2.5. Several of the most widely known and widely used formal group methods are the Delphi Process, Nominal Group Technique (NGT), and Consensus Development Conference. Unfortunately, a 'cookie cutter' approach for eliciting information from groups is not

suitable for every circumstance. A hybrid group method may be most appropriate for our goal of developing input representations for the CRC Simulation Model.

While the three group methods are similar in some aspects, they each have their own defining characteristics. All three processes use a facilitator to aid in communication, but the facilitator has varying levels of control in the different processes. In Delphi, each individual member communicates solely with the facilitator. NGT relies heavily on the facilitator to prepare upfront literature, collect and summarize responses, and control group interaction (discussions, debates, and etc.). Consensus development uses the facilitator to organize the group, arrange for outside presentations, and oversee the questioning and discussion phases. Consensus development does not use the facilitator to diminish negative group effects like Delphi and NGT attempt to do. All three processes allow each group member to expand his or her knowledge by questioning and challenging others' ideas and defending personal notions. However, the NGT and Consensus Development require face-to-face interaction while Delphi relies only on indirect communication, such as mail, fax, and email. Delphi can accommodate large expert panels whereas NGT and Consensus Development are more appropriate for smaller groups, perhaps less than a dozen participants, because of the effort to draw the expert panel together. The Delphi method is most appropriate when opinions are requested and evidence is scarce, such as in the case of many input models for the CRC Simulation Study. NGT and Consensus Development both work well when both expert opinion and external evidence are available.

In the absence of sufficient data, subject area experts must be available to offer their knowledge to develop the input estimates. Often times, particularly in the case of medical simulations, these experts are incredibly busy individuals and it may be difficult to ensure their participation. One tactic to gain expert participation is to minimize their commitment – require little or no travel, minimize the time they spend providing estimates, design an intuitive process that does not require preparation time to learn software or background information, present background information and instructions as needed, etc. The Delphi method is the preferred formal group method in terms of minimal time commitment.

With all this in mind, the formal group process of eliciting estimates in this research closely resembled a Delphi method, with a panel of experts providing input estimates to be used in the simulation model. Additionally, the Delphi method was used in conjunction with web-based surveys to further decrease the amount of time required since experts were expected to be quite familiar with using the Internet. These experts, especially those in medicine and medical research, guard their time and the process was designed to be as easy for them as possible.

3.2 Formal Group Process Methodology

Before surveying panelists, the structure of the information being collected must be defined. Questions must be carefully developed that address the simulation objectives and they should request information that an expert can reliably estimate. For example, if the objective is to determine a distribution for the conversion time between asymptomatic and symptomatic cancer, the final result of the process should provide a distribution and its parameters. However, people cannot be expected to provide a distribution and parameters directly (Barton et al. 2002). They must be asked other information that will in turn help develop these parameter estimates. Furthermore, the input model structure must be considered prior to developing distributions.

The model structure is the method for representing the system in the computer simulation model, or more simply the model structure is how the inputs will be used in the simulation model. If the time it takes an adenoma to convert to cancer is dependent upon patient factors such as gender or age, how do these covariates affect the distribution? Should multiple distributions be defined? Can one distribution be 'transformed' to account for all different patient characteristics? These structure issues must be resolved prior to developing any questions and surveying any panelists. Structuring the problem requires knowledge of computer simulation modeling techniques. The chief investigators working on the research, who are familiar with both the process being examined and the modeling aspect of the

problem, should determine the structure. This structure can be verified by considering the simulation model as a whole and ensuring that the combinatorial use of inputs will allow the computer simulation to model real-world phenomena.

The process of developing estimates can begin after the structure has been verified and the objectives of the process are clear. The process for developing inputs in the absence of data mimics a Delphi method. Like traditional Delphi processes, the method occurs in rounds, with new information and a growing consensus resulting in each round, but this new process differs from traditional Delphi because it is an evolutionary process. While the objectives of the process remain the same throughout the rounds, the questions are allowed to change to target different information about the same objective or to clarify or restate questions to increase comprehension among the panelists. The process is outlined in Table 1:

Table 1: Formal Group Method for Estimating Inputs

Preliminary Activities:	
0a.	Define the simulation model structure.
0b.	Define the objectives of the study.
0c.	Develop questions to use in the surveying. Keep in mind that the questions may change as surveying progresses.
0d.	Contact participants requesting their participation in the expert panel.
Round One:	
1a.	Panelists receive background information addressing the purpose of the study, study objectives, and the web address of the first survey via email.
1b.	Each expert panelist independently estimates the inputs using a web-based survey. Proportions are given as percentages and distributions are valuated by describing their distribution characteristics. Comments about the estimates are encouraged and can be submitted as part of the survey.
1c.	The facilitator collects all responses and summarizes them for ease of comparison and analysis. Summary data must be prepared for both

	individual responses and for the group responses. Summary data may include simple averages, graphical data analysis, distribution characteristics extracted from the raw data, etc.
Round Two:	
2a.	The facilitator prepares the survey for Round Two. Survey questions may be added to elicit additional information or altered to elicit more specific information, but the objectives remain the same.
2b.	The facilitator distributes the summary of the group estimates and comments from Round One, as well as individual Round One response summaries. The web address of the second survey is also distributed. All information is sent via email.
2c.	Each panelist should analyze the information. In light of this information, panelists should again use a web-based survey to estimate the inputs. Panel members may be swayed to revise their estimates toward consensus or to provide additional information in support of original responses.
2d.	The facilitator collects all responses and summarizes them for ease of comparison and analysis. Summary data must be prepared for both individual responses and for the group responses. Summary data may include simple averages, graphical data analysis, distribution characteristics extracted from the raw data, etc.
Subsequent Rounds:	
Subsequent rounds continue as in Round Two, with facilitators carefully developing the surveys and panelists responding to the survey with respect to new information provided from the previous rounds. Survey questions may be altered or added to gain further information about the estimates. Questions may be omitted from the survey as consensus is developed. The rounds conclude when the responses for all questions converge to a final group estimate.	
Final Activity:	

For objectives targeting proportions or other rote estimates, the process is complete after consensus has been reached on the final estimate during the surveying rounds. For objectives requiring the development of distributions, use a software package for graphical input modeling to determine the final distribution parameters.

From a facilitator's standpoint, each round consists of developing questions for that round, distributing information and the link for the web-based survey to the panelists, and then collecting and analyzing the panelists' responses. From a panelist's standpoint, each round consists of receiving information from the facilitator, reviewing this information, and then submitting responses to questions on a web-based survey. The survey questions asked may vary as rounds progress. Questions may become more specific to target very precise and detailed information, and questions may be excluded as consensus is reached. In this way, the panelists are not simply coming to consensus about an original set of questions. Rather, they are continuously providing information to develop estimates for specified study objectives. Panelists should note that consensus occurs when the entire group is in an acceptable range of agreement.

Consensus does not insinuate that every member of the group has given an *identical* response for every objective. Instead, the facilitator should decide when the group has reached a high level of understanding and accord. Then he/she should choose a representative estimate that is in an acceptable range of agreement with all panelists' responses, and this is submitted as the group's final estimate.

The facilitator must be greatly involved in the dissemination of information to the panelists. Before the process begins, the panelists should receive an explanation of the study, a set of clearly stated objectives, and an approximate timeline with deadlines and milestones marked. At the end of each round, the facilitator analyzes the survey data received and prepares information to distribute to the panelists in the next round (unless consensus is reached). Each panelist receives a summary of the group responses and an outline of his/her individual responses from the previous round.

The summaries of group and individual responses will rely heavily on the work of the facilitator to prepare meaningful and accurate summaries of information. Throughout the summary activities, all responses should remain anonymous. Different types of information, for example a summary of comments versus an estimate of proportions or distributions, will be summarized in varying ways. All comments given for the previous survey should be included in the summary information. Comments should remain anonymous, and comments may need to be summarized to eliminate identifying information and restrict writing style identification. Even though they are being summarized, no comments should be omitted from the group summary. For proportions and constants, the group summary is simply the average of all the responses, and the individual response may show the panelists where his/her response falls in relation to the rest of the group's responses.

Analyzing distributions is difficult because methods of collecting information are complex. For all objectives of the survey that require specification of distributions, the ultimate goal is to develop a Johnson SB distribution by using VisiFit to provide the Johnson SB parameters for a specified graphical distribution. During the course of this research project, a revised VisiFit was developed but has not yet been published. This revised software enhances the capability of the original package by using windows-based programming that simplifies the display of the graphical distributions, eases the altering of distribution characteristics and parameters, and allows enhanced printing capabilities. The revised VisiFit also allows modeling of Beta distributions in addition to the original modeling of Johnson SB distributions. As in the original program, the revised VisiFit uses distribution characteristics to create graphical probability density functions for the Johnson SB distribution. The user can alter these graphs with simple keystrokes, and he or she can easily acquire the parameters of the Johnson SB distribution when satisfied with the graphical display of the distribution. As stated earlier, panelists should not be asked to provide the parameters of a distribution for a given objective. Instead they should be asked information about a distribution's characteristics that can later be used in VisiFit. From this point forward, references to the VisiFit software actually address the revised VisiFit.

The characteristics elicited from the group process may come as percentages, cumulative density functions, modes, endpoints, etc. The summary of these characteristics may be the average mode, the average endpoints, a graphical display of all the CDF plots overlaid on one graph, a graphical display of the Johnson SB distribution for the average distribution characteristics, etc. These summaries should focus on what type of information panelists will be able to incorporate into their decision-making. For example, if a particular group of panelists may not be able to relate to data from a Johnson SB probability density function, then alternative summary information should be provided.

Along with the group response, participants should receive a summary of their own responses, both to remind them of their previous thoughts and responses and to aid the comparison with the group response. This individual summary may include raw data, distribution characteristics drawn from raw data, such as the mode and endpoints, a graph of the CDF from raw data, and/or a graph of the Johnson SB distribution generated from participant responses.

Consensus in Delphi methods is typically achieved after three rounds of surveys (Martens 2002;Nehiley 2002), and likewise a minimum of three rounds of surveying should be expected to acquire input estimates for a simulation model.

3.3 Implementation of the Formal Group Process

The process explained in Chapter 3.2 was used to develop four inputs for the CRC Simulation Study. This section steps through the complete process, including the development of the questions and surveys, gathering of participants, analysis of the survey responses from each round, and the arrival at the final group estimate for each objective of the survey study. In addition to presenting the group responses from each round, this section also follows one individual's responses (Panelist XYZ) through the entire process and provides an idea of the process from the user's perspective.

The objectives of this study were to develop model inputs for the following four topics:

1. Estimate the proportion of CRCs that cannot be prevented through conventional screening (i.e. the cancers that cannot be detected because they develop from normal tissue without passing through a visible polyp intermediary).
2. Genetic predisposition posed by an affected first-degree family member can be evidenced by an increased rate of adenoma incidence or an increased progression rate from adenoma to cancer. Estimate the relative proportion of these two factors in affecting a person's underlying risk of developing cancer based on family history.
3. Estimate the distribution for conversion time to CRC among the existing adenomas that are going to become cancerous.
4. For incident CRCs, estimate the distribution for the conversion time period between incident asymptomatic and symptomatic cancers.

The first two objectives are simple proportions, while the third and fourth objectives require the development of Johnson SB distributions for use in the CRC simulation model.

These objectives were developed after a careful scrutiny of the available inputs needed for the CRC Simulation Study as well as an analysis of the model structure. These steps were accomplished with the heavy reliance on the knowledge of the CRC experts among this study's principal investigators. The model structure is particularly important to understand because it prescribes how information will be utilized in the computer simulation. For example, in this model adenomas are considered to have three different progression rates – *non-progressing adenomas* (adenomas that do not progress to CRC), *progressing adenomas* (which will progress to cancer after enduring an adenomatous growth phase), and *immediate-progressing adenomas* (which become cancerous immediately without passing through a visible polyp intermediary detectable by conventional screening techniques). The first objective, examining the proportion of all CRC cases that stem from immediate-progressing adenomas, is a direct progression from the model structure. This aspect of the model structure is also incorporated in the third objective as it estimates a distribution for the duration of adenomatous growth phase for both progressing and immediate-progressing

adenomas. Clearly the model structure is quite important in this third objective because without it, an inadequate distribution for the time from adenoma to cancer would be developed. The distribution would potentially include the slow-progressing adenomas in the growth estimation, thus challenging the simulation modeler to incorporate growth times for all adenomas, including those slow-progressing adenomas, into one distribution. It would be extremely difficult, if not impossible, to find a distribution to properly model such a long-range time frame with extremes in both tails of the distribution.

This example illustrates the importance of defining the model structure before defining objectives. Without an established model structure, unnecessary or inadequate information may be estimated, thus lengthening the time to develop model inputs and/or increasing the modeling complexity by requiring the use of more complex and less efficient information. The importance of the model structure also compounds the necessitates the inclusion of both simulation modeling experts as well as experts in the area of interest, CRC experts in this instance, on the primary investigation team for the study.

The surveys were developed using survey software and services provided by WebSurveyor (www.websurveyor.com). The software is freely available through the Internet, and WebSurveyor hosted each survey at an educational price of $49/survey. The fee included hosting the web-based survey on the website and storing responses. The software allowed development of the survey as well as tools for analyzing survey data. While this particular process utilized the WebSurveyor software and services, there are many companies offering web-based surveying software, hosting, and support for varying prices, ranging from simple, free versions to complex packages designed for surveys with high-volume responses. The WebSurveyor services were elicited in this instance because of the simplicity in survey development, ability to add non-standard functionality to surveys through the use of HTML snippets, superior technical support during the survey development and response phases, and reasonable price.

Initially, 30 participants were selected by the study's principal investigators from among distinguished CRC researchers in the areas of molecular biology, epidemiology, and gastroenterology. Eighteen panelists responded to the first survey; however, only 15 of the original 18 completed the remainder of the surveys. Throughout the process, the identity of the panelists remained confidential and was known only to the study's facilitator and principal investigators. These panelists were physically dispersed throughout the United States, but may be associated through professional societies, as members of committees, or as affiliates on research teams. In accordance with Federal law and North Carolina State University's policy for research involving human subjects, review and approval from the University's Internal Review Board (IRB) was required to protect the human subjects, the researchers, and the institution. The approved IRB protocol is presented in Appendix 7.1.

Several methods were used to persuade the CRC experts to participate in the research process. Two senior-level researchers at Vanderbilt University, Dr. Robert Coffey and Dr. Raymond DuBois, endorsed this study and signed an initial letter to all 30 researchers encouraging their participation in this study. This letter, presented in Appendix 7.2, introduces Dr. Reid Ness as the primary investigator in this study and relays the importance of the study. Furthermore, each participant was offered $300 compensation in exchange for their full participation in the process, i.e. if they completed all three surveys as well as the evaluation survey.

Dr. Ness sent a second letter, shown in Appendix 7.3, to these initial 30 experts. This letter provided a brief overview of the objectives of the study, gave a general timeline for the process, explained the compensation available, and provided the web link for the first survey.

Once the preliminary group of expert panelists was composed, the surveying process began. The process followed the below timeline:

Monday, March 3	Introductory Letter Sent from Senior Researchers
Tuesday, March 11	Round One Survey distributed to Panelists

Tuesday, March 18	Reminder Email/Round One Survey Concluded
Monday, March 24	Round Two Survey distributed to Panelists
Monday, March 31	Reminder Email sent to Panelists for Round Two Survey
Monday, April 7	Round Two Survey Concluded
Tuesday, April 15	Round Three Survey distributed to Panelists
Tuesday, April 22	Reminder Email sent to Panelists for Round Three Survey
Tuesday, May 6	Round Three Survey Concluded

Because of the schedules of the expert panelists, ample time had to be given between survey distribution and survey conclusion to allow an acceptable number of panelists to respond. One week after each survey was distributed, a reminder email was sent to panelists. Further reminders were given to non-responding panelists as needed. Approximately one week was needed between each survey round to allow time to analyze results and prepare the survey for the next round.

The first survey is shown in Appendix 7.4. The survey gives a brief introduction to the study on Page 1, covers the Informed Consent (as required by the IRB) on Page 2, and then asks for responses to questions targeting the four study objectives on Pages 3 – 6. Finally, page seven asks for the participants email address for tracking purposes.

The responses for this first survey are summarized in Appendix 7.5. Objectives 3 and 4 asked panelists to provide cumulative density functions; however the ultimate goal was to determine endpoints and percentile points to develop distributions using VisiFit. Therefore, the 50^{th} percentile point was determined from the given data using simple linear interpolations to provide initial estimates of percentiles for this first round.

After creating the survey and analyzing the results, a Second Round survey was created. Recall that the goal of this process was to develop inputs for the CRC simulation model by eliciting information from experts via several rounds of surveying, with additional information and a growing consensus resulting in each round. The Second Round survey

was developed with this goal in mind. In the Second Round of surveying, each panelist received the web link for the second survey accompanied by a summary of the group responses from Round One as well as a reminder of his responses from the previous round. To show what was sent to the panelists, "Panelist XYZ's" summary information is presented in Appendix 7.6.

Appendix 7.7 shows the Round Two survey for the CRC Simulation Study. This survey targets the same objectives as the Round One survey, but asks some questions differently. The questions for Objectives 1 and 2 remain the same; however, questions for Objectives 3 and 4 have significantly changed. In the first round, the questions for the latter two objectives asked panelists to provide a cumulative density function, but in the second round panelists are asked to provide responses based on percentiles. Fifteen participants responded to the Round Two survey, and a summary of their responses is shown in Appendix 7.8.

The development of the third survey relied heavily on the analysis of the Round Two responses. The comments provided by the panelists indicated there was some confusion about the terminology used in the questions for the first objective, addressing the proportion of CRCs that go through a non-adenomatous state. Therefore these questions were modified to be more specific. Panelists' responses for the second objective, the affects of genetic predisposition on the development and progression of CRC, seemed to have converged on a group response after the second round of surveying. The mean response changed only slightly from the first round to the second round. Further analysis, however, showed that while the mean changed slightly, panelists' responses were changing. Therefore, the questions for the second objective remained in the Round Three survey. Several clarifying words were added to the third objective to be as specific as possible and ensure that all panelists were considering only certain cases of CRCs when providing responses. The third question is meant to target only progressing adenomas and not 'immediate progressing' adenomas, so the phrase "excluding flat adenomas" was added to each question in the third objective. The questions for Objective 4 were unchanged in this third round of surveying.

After developing the Round Three survey, panelists were sent information gathered from the second round survey as well as a link to the Round Three survey. This information was tailored for each panelist to remind him of his second round responses and show how his responses compared with the mean and median responses from the group. For further analysis, graphs were provided where appropriate to graphically show where each panelists' responses fit in the distribution of the other panelists' responses. To show what was sent to the panelists, "Panelist XYZ's" summary information from Round Two is presented in Appendix 7.9. Appendix 7.10 presents the Round Three survey.

The Round Three survey was the final estimation survey sent to the expert panel. Fifteen panelists also responded to this survey, and a summary of their responses is presented in Appendix 7.11. Once all the responses were received, the inputs for the simulation model were developed.

The development of inputs for the first two study objectives was quite simple because they concerned proportions and, as discussed in Chapter 2.4, experts in a subject area can estimate proportions reliably. The first study objective was to estimate the proportion of CRCs that fail to pass through a visible polyp intermediary, given that all CRCs develop from preexisting adenomas, and thus these cancers cannot be prevented through conventional screening because they are not detected by a standard colonoscopy. Since this objective is simply a proportion, the mean response from the surveys is the final simulation model input for this objective. The mean response indicated that 15% of CRCs could not be prevented through traditional screening because they develop from flat adenomas that are never polypoid and thus cannot be seen by a standard colonoscopy.

The second study objective addressed how genetic predisposition posed by an affected first-degree family member affects a person's underlying risk of developing CRC. This genetic predisposition can be evidenced by an increased adenoma incidence, an increased progression rate from adenoma to cancer, or some combination of the two. The specific objective was to estimate the relative proportion of these two factors in affecting a person's

underlying risk of developing cancer based on family history. The median responses from the surveys indicated that, for the population of people with an affected first-degree relative, 50% are only affected by an increased rate of adenoma incidence, 25% are only affected by an increased progression rate from adenoma to cancer, and 25% are affected by both an increased incidence rate and an increased progression rate at equal rates (50% due to an increased incidence rate and 50% due to an increased progression rate).

The third and fourth study objectives were more difficult to develop because they both addressed distributions required for the simulation model. Our expert panelists were not asked to estimate distributions because humans cannot reliably estimate many parameters of a distribution. Instead, panelists were asked to estimate endpoints, proportions, etc., and then this information was entered into the VisiFit distribution fitting software (discussed in Chapter 2.3) to develop the final simulation model inputs.

The third study objective sought an estimate for the distribution for conversion time to cancer among adenomas that are going to become cancer. The endpoints of this distribution can be estimated using the responses from the Round 1 Survey, when panelists provided CDFs for this question. Of course, the left endpoint is 0 years. The right endpoint was assumed to be a maximum of 100 years during the first round because the structure of the simulation study limits a patient's life to 100 years. Endpoints ranged from 30 to 100 years during the surveying, with a median endpoint of 55 years and a mean of 58.33 years. During the other two rounds of surveying, panelists were asked to estimate the time when 50% of adenomas that are going to become cancerous have done so and the percentage that would become cancerous after 10 years. The data from these two questions provided two percentile points that were used to fit a distribution with the VisiFit distribution-fitting package. At the conclusion of three survey rounds, the panel came to consensus on both of these questions. For the 50th percentile point, the mean response was 18.667 years and the median response was 20 years, with a minimum response of 5 years, a maximum response of 30 years, and a standard deviation of 7.19 years. After 10 years, the mean response for the percentage of adenomas to become cancerous was 31.53% and the median response was

25%. The minimum response was 10%, the maximum response was 80%, and the standard deviation of the responses was of 19.5%. Using these responses, the following distribution characteristics can be used in VisiFit to develop an appropriate distribution:

Endpoints: [0, 55] years

50th Percentile: 18.667 years

31.533th Percentile: 10 years

Figure 1 shows the bounded unimodal Johnson distribution that most closely fits those characteristics. The parameters for this JohnsonSB distribution are $\chi = 0$, $\lambda = 55$, $\gamma = 0.382$, and $\delta = 0.574$.

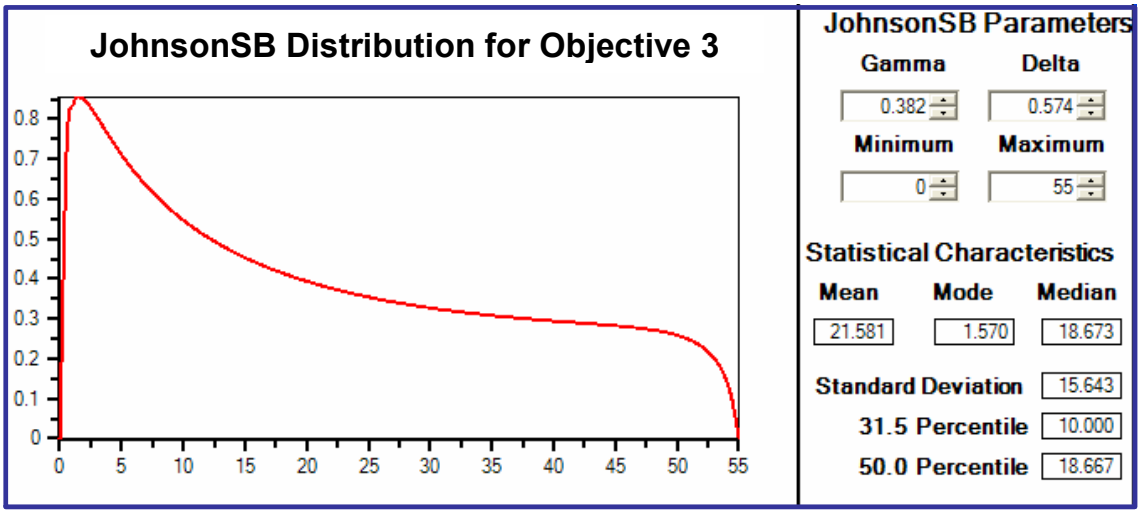

Figure 1: Johnson SB Distribution for Objective 3

VisiFit also allows the fitting of a unimodal Beta distribution. For the same distribution characteristics as above, the Beta distribution is given in Figure 2 and has the parameters $\alpha = 1$ and $\beta = 1.733$, with endpoints [0,55] years. Comparing the graphs for these two distributions shows that the Johnson SB distribution is a better fit in this case. It has a more appropriate curve in the left tail that closely mimics the way expert physicians believe adenomas convert to cancer over time.

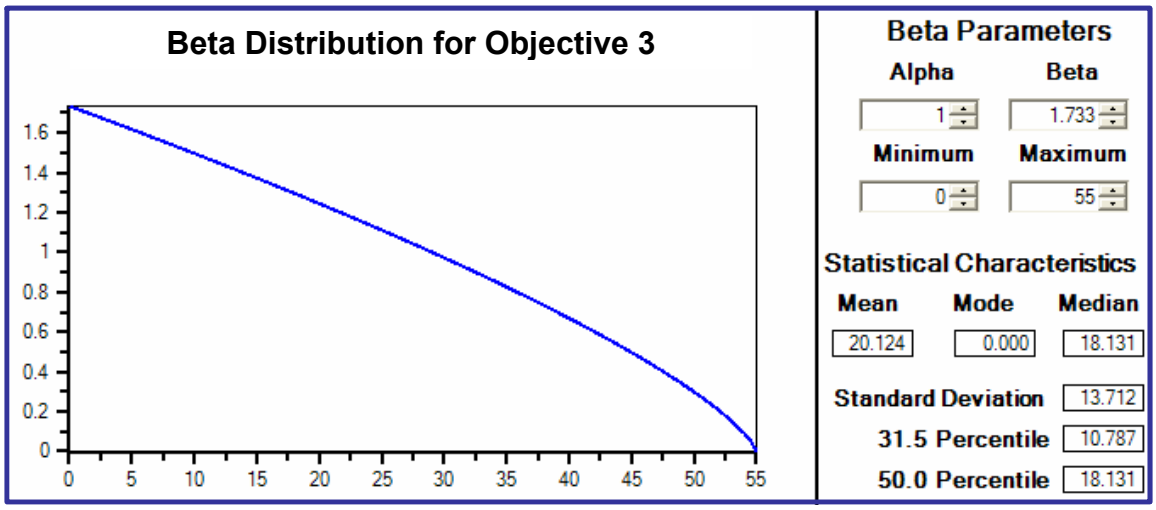

Figure 2: Beta Distribution for Objective 3

Objective 4 sought an estimate of a distribution for the conversion time period between incident asymptomatic and symptomatic cancers. The endpoints of this distribution can be estimated using the responses from the Round 1 Survey, when panelists provided CDFs for this question. Similar to Objective 3, the left endpoint is 0 years. The right endpoint was assumed to be a maximum of 10 years during the first round. Endpoints ranged from 3 to 10 years during the surveying, with a median endpoint of 5 years and a mean of 5.778 years. During the other two rounds of surveying, panelists were asked to estimate the time when 50% of incident CRC will have become symptomatic and the percentage that would be symptomatic by 1 year. The data from these two questions provide two percentile points that can be used to fit a distribution using the VisiFit distribution fitting package. At the conclusion of three survey rounds, the panel came to consensus on both of these questions. For the 50th percentile point, the mean response was 2.567 years and the median response was 2 years, with a minimum response of 1 year, a maximum response of 7 years, and a standard deviation of 1.57 years. After 1 year, both the mean and median responses for the percentage of incident CRCs to become symptomatic were 30%, with a minimum response of 15%, a maximum response of 50%, and a standard deviation of 9.97%. Using these responses, the following distribution characteristics can be used in VisiFit to develop an appropriate distribution:

Endpoints: [0,5] years

50th Percentile: 2.567 years

30th Percentile: 1 year

The Johnson SB distribution that most closely fits these characteristics is presented in Figure 3. Since the bounded Johnson distribution cannot fit all graphs, this is the closest approximation, with parameters $\chi = 0$, $\lambda = 5$, $\gamma = 0.124$, and $\delta = 0.621$.

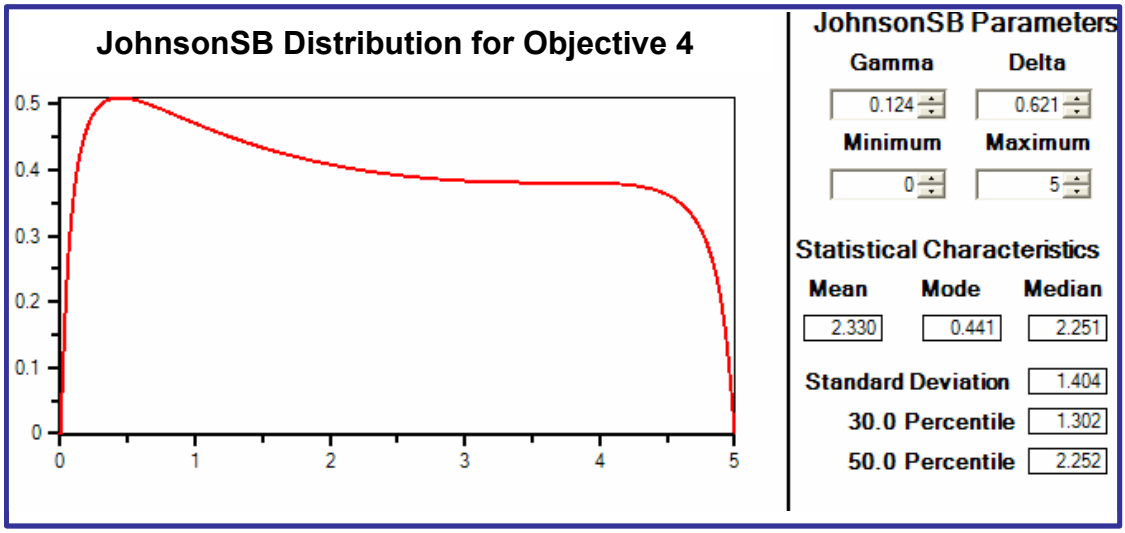

Figure 3: Johnson SB Distribution for Objective 4

Again, VisitFit was used to also examine a Beta distribution for this same set of distribution characteristics. The best-fit unimodal Beta distribution is presented in Figure 4 and has the parameters $\alpha = 1$ and $\beta = 1.164$, with endpoints [0,5] years. The Johnson SB distribution

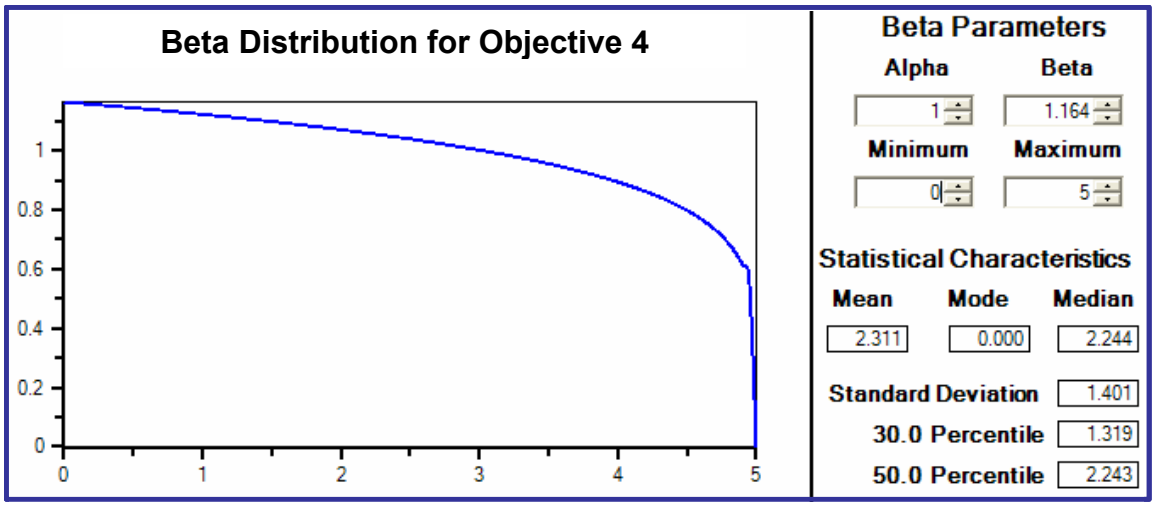

Figure 4: Beta Distribution for Objective 4

again proves to be the more appropriate choice for a distribution in this instance, as it more closely follows the researchers' perceptions of the conversion time between cancer formation and symptomatic cancer.

4. EVALUATION OF THE METHOD FOR ELICITING INFORMATION

The group process described in Chapter 3.2 was used in the medical simulation model development, as detailed in Chapter 3.3. While this implementation has proven that the process is capable of developing inputs for a simulation model, why is this process better than other processes? Why should this process be used? What did the panelists think of the process? Do the investigators who will use the inputs developed using the formal group process think the process results are useful? Do the project advisors think the inputs produced are valid? These concerns and others are addressed in the following sections in an attempt to evaluate the recommended process.

4.1 Feasibility of the Group Process

The overarching goal of this process is to develop simulation model inputs when data are scarce or non-existent. A motivation to using this iterative process is to increase the information available to the panel over the course of several rounds of surveys, and as the level of information increases panelists can make more informed estimates. Also, over the rounds of surveys the estimates should be converging on a 'best' estimate. One useful way to indicate feasibility of the group process is to show convergence of the responses over the course of surveying.

A conventional way of examining convergence is to compare the standard deviation of responses in different surveying rounds. Appendix 7.12 includes the standard deviation of responses for each round of surveying, and Figure 5 provides a graphical analysis of these standard deviations. For Objective 1, the standard deviation of responses decreased between the first two rounds, but then increased slightly in the last round. The standard deviations for Objective 2 steadily decreased over all three rounds of surveying. Similar to Objective 1, the standard deviation for Objective 3 – estimation of the percentile at 10 years – increased between the first two rounds, but then it drastically decreased in the third round of

surveying. The 50th percentile estimation for the third objective gave the most impressive decrease of standard deviation over the three rounds, starting at 22.58 years of standard deviation in the responses and then decreasing to a standard deviation among responses of only 7.19 years in the third round. While the standard deviation for the percentile at 1 year in Objective 4 decreased over each of the three rounds, the estimation of the 50th percentile

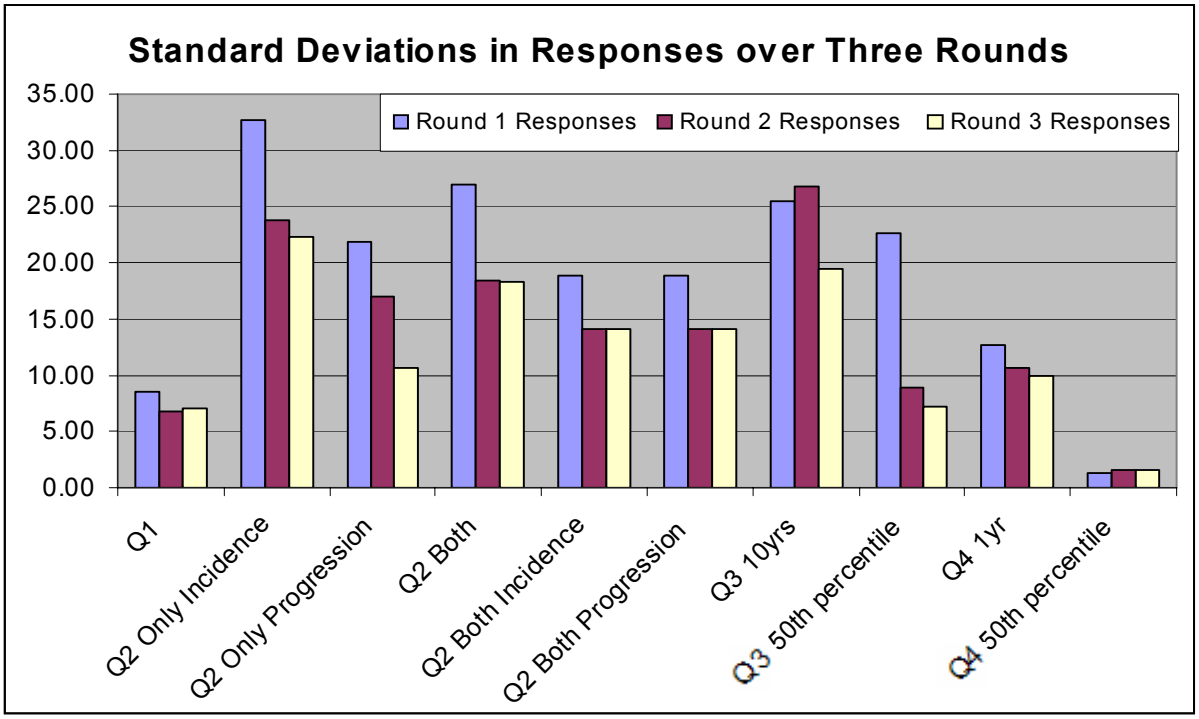

Figure 5: Standard Deviations of Responses throughout the Survey Rounds

increased in each round. This inconsistency has no attributable causes, but the increases in standard deviation are small (1.33 years in the first round, 1.53 years in the second round, and 1.57 years in the third round) and can perhaps be considered inconsequential. These reductions in standard deviation and convergences on the final group estimates are due to three factors:

1. Increasing improvement in panelists' knowledge as a result of the sharing of information during the survey process.
2. Clarification of survey questions as the rounds progressed.
3. Possible slight peer pressure among the panelists to alter responses.

Another method for examining the feasibility is to pair the responses from each individual over all three rounds and investigate if those responses converge to the final group response. The responses paired by participant are given in Appendix 7.12, and a summary of selected panelists' responses is given in Table 2. The questions asked for Objective 1 changed significantly during the rounds of surveying, so convergence for this objective cannot be

Table 2: Summary of Selected Panelists' Responses Paired by Round

	Means			Panelist 1			Panelist 7			Panelist 12			Panelist 14		
	Round 1	Round 2	Round 3	R1	R2	R3	R1	R2	R3	R1	R2	R3	R1	R2	R3
Q1	10.40%	11.333	13.867	25	15		2	10		5	5		2	3	
Q2 Only Incidence	50.78%	52.000	54.000	25	25	25	100	65	65	25	40	50	80	80	80
Q2 Only Progression	22.39%	25.333	22.143	25	25	25	0	35	25	50	20	25	15	20	15
Q2 Both	26.83%	22.667	25.333	50	50	50	0	0	10	25	40	25	5	0	5
Q2 Both Incidence	50.69%	42.917	49.643	50	50	50			50	25	50	50	60		80
Q2 Both Progression	49.31%	57.083	50.357	50	50	50			50	75	50	50	40		20
Q3 50%	31.78	20.567	18.667	20	20	20	8.3	3	5	67	20	15	60	20	15
Q3 10yrs	23%	33.200	31.533	10	33	33	60	95	80	0	20	10	5	25	30
Q4 50%	2.66	2.787	2.567	3	2.5	2	1.5	2	2	2	3	2	4	2	1
Q4 1yr	21%	29.533	30.067	10	50	33	30	35	35	20	30	30	20	25	50

analyzed. Objective 2, however, can be examined and does in fact show convergence.

While some panelists altered their response very little during the three survey rounds, others seemed to use the information and opinions of other panelists to influence their responses. For example, Panelist 7 initially believed genetic predisposition solely affected one's adenoma incidence rate, but during Round Two this panelist allocated 65% of the effect of genetic predisposition to an increased adenoma incidence rate and 35% to an increased rate of adenoma progression to cancer. Finally, in Round Three Panelist 7 showed even more convergence to the group response, and allocated a portion to incidence, a portion to progression, and a portion to both. Panelist 12 provides another good example of convergence for Objective 2.

Objective 3 considered the conversion time between adenoma formation and cancer, asking questions about the 50th percentile for conversion time and requesting a percentile for the number of adenomas that have converted to cancer within 10 years. Panelist 14 converged

well for both questions. For the 50th percentile, this panelist began the first round with a response in the 60-year range and concluded the final round with a response of 15 years, when the mean response from the entire group was 18.667 years. Panelist 14 also converged to the group response for the percentile of adenomas that had converted after 10 years, with a response of 31.53%. This panelist started the surveys with an opinion that only 5% had converted after 10 years and then increased the responses to 25% and 30% in the second and third rounds, respectively.

Objective 4 addresses the time between cancer formation and the development of symptoms. The group response estimated that after 1 year, 30% of CRC will be symptomatic, and that 50% of CRCs become symptomatic by 2.6 years. Panelist 1's responses provide an excellent example of convergence on both of these questions. Looking at the percentile of symptomatic cancers after one year, this panelist first responded with 10%, which was much lower than the average response, but then in the second round the panelist responded with 50%, which was much higher than the average response. Finally, in Round Three the panelist responded with 33%, which approached the final group response. For the 50th percentile, the panelist responded 3 years, 2.5 years, and then 2 years in the first, second, and third round respectively. These three responses all hovered around the group response.

The convergence on the group responses for all objectives indicates that, as the process was designed and as expected, panelists did converge on a group response. Moreover, the extreme lack of information on the four objectives in this study is a dominant factor in the difficultly in seeking convergence and reaching consensus on these issues.

4.2 Users' Opinions of the Group Process

The implementation of the group process, as discussed in Chapter 3.3, provides several good avenues for evaluating the methodology of the group process, finding its strengths and weaknesses, and providing suggestions for its future uses. The evaluation of this formal

group process occurs on two levels. The first level is the evaluation of the process from the perspective of the expert panel, which directly participated in the survey rounds. The second level of evaluation is from the perspective of those who will be using the inputs developed as a result of this method, namely the Advisory Board for the research project.

4.2.1 Evaluation of the Process by Expert Panelists

The evaluation of this iterative group process for eliciting information via surveys focuses on four main areas of interest – (1) feasibility of the process, (2) the group dynamics throughout the course of surveying, (3) the acceptability of the responses developed by the process, and (4) the information awareness the panel had during the rounds of surveying. The evaluation survey sent to the panelists is presented in Appendix 7.13, and the resulting responses and comments to the survey are presented in Appendix 7.14.

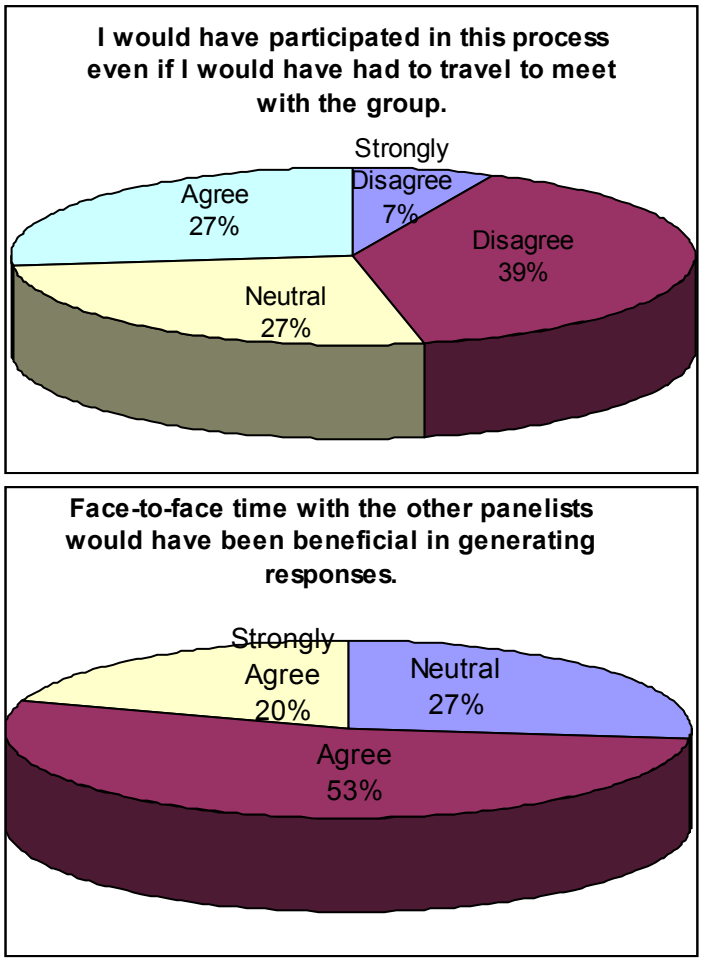

Figure 6: Comparison of Responses Concerning Face-To-Face Meetings

In terms of flexibility, the process should consider the time limitations of the expert panel, and evidence should show that iterative web-based surveys are an appropriate technique for eliciting information. Only one-fourth of the panel said they would participate if travel was required. However, the comparison in Figure 6 shows that 75% thought that face-to-face time would have been beneficial in developing estimates for the CRC Simulation Study. The trade-off between the benefit of face-to-face time and the cost of travel is very

hard to define, and of course this trade-off may have a greater (or lesser) impact depending on the project. For this CRC Simulation Study, if travel was required it would have severely limited the number of expert panelists, which in turn would have negatively affected the reliability of the estimates. Conversely, if participants had traveled it would have allowed additional sharing of information as well as a reduced cycle time to complete the whole process. Also in evaluating flexibility of the surveying process, the large majority (93%) of the panelists found the web surveys were easy and convenient to use. Less than 15% of the panel felt the web surveys made it more difficult to share their beliefs and opinions.

As discussed in Chapter 2.5, one of the deficiencies of group processes is negative group interactions (groupthink, dominance, and conformance) that often result. One of the goals when designing this group process was to eliminate (or minimize) these incidents. Through the evaluations, it seems clear that the group process did in fact minimize the negative group interactions, as depicted in the graphs in Figure 7. Only 20% of the panel felt pressured to alter their responses throughout the iterations of surveying. This was perhaps caused by asking similar (or identical) questions multiple times over the three rounds of surveying, causing the panelists to feel pressured to alter their responses toward consensus. Fortunately, the panel fully agreed that there was no domination by any members of the

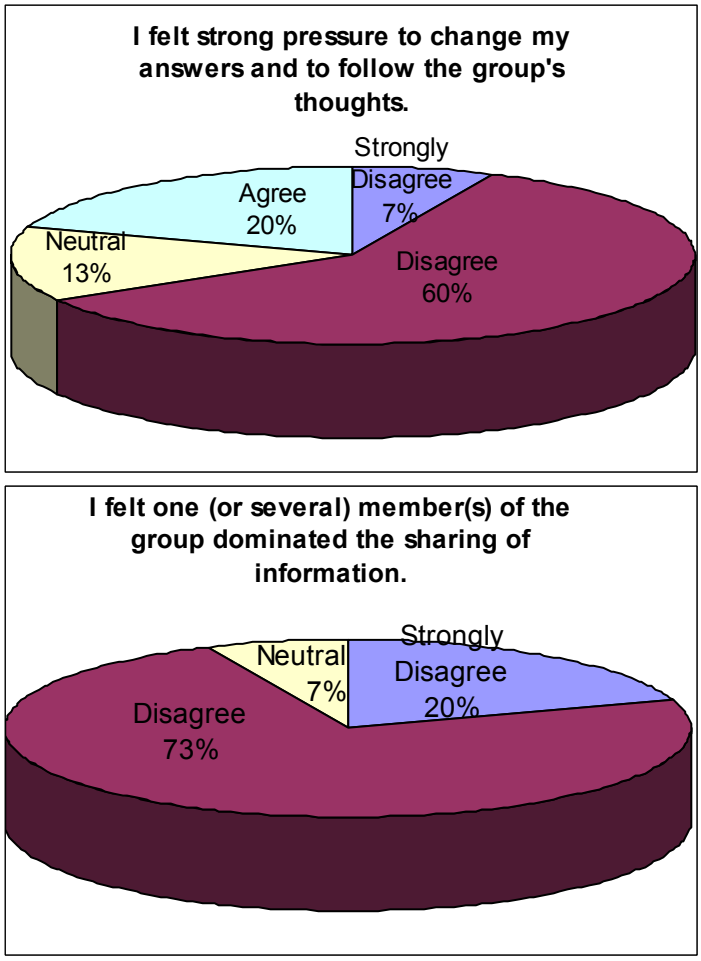

Figure 7: Evaluation of Attempts to Mitigate Negative Group Effects

group. Since the panelists' identities remained anonymous, it was very unlikely that dominance could have been exhibited in this study because of its design. The comments would have provided a means for exuding dominance, but individual responses were not associated with particular comments, so dominance was also eliminated in this sense.

The information provided by the expert panel should be consistent with real-world phenomena, and the information must be managed in a satisfactory manner that does not skew its interpretation. The process' acceptability addresses these concerns and also supports the use of this formal group process rather than an informal group process or individual estimates. This value is mainly due to the increased understanding within the panel over the course of the surveying rounds. Over 50% of the panel agreed that the group process allowed others in the group to understand their own beliefs and opinions about the questions asked, while 26% disagreed, indicating the group process did not allow them a good avenue for expressing and getting others to understand their beliefs. Over 50% of the panelists indicated their own understanding of the subject area was improved as a result of this study, perhaps showing that the sharing of information was beneficial for the participants in additional to being beneficial for the study. Figure 8 presents the evaluation responses on how this process compares with other methods. The panel was divided on the question asking if this formal group process provided better estimates than an informal group meeting. Since all panelists have been involved in group decision-making in the past, they had a valid basis to make this comparison of formal versus informal group methods.

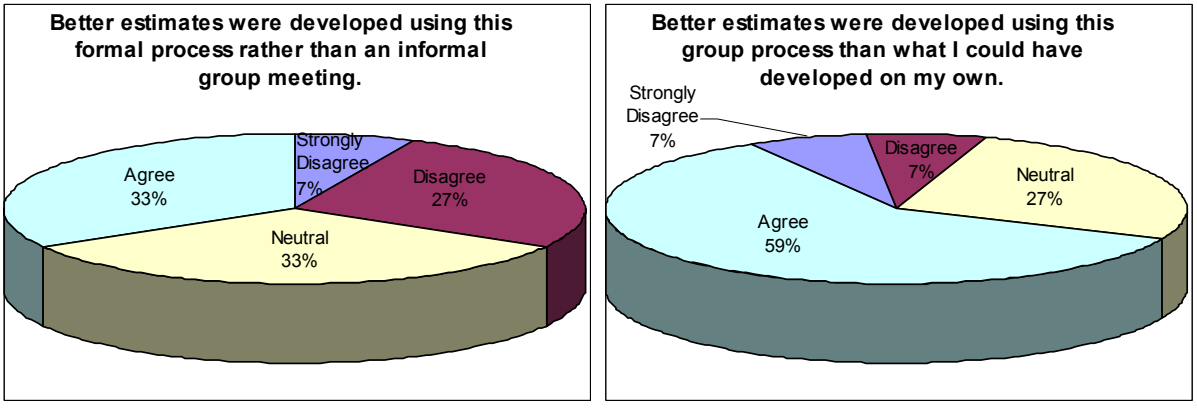

Figure 8: Evaluation of Estimate Development as Compared to Alternative Methods

One-third of the panel agreed that better estimates were developed, the same percentage of the panel disagreed and thought an informal group meeting would have been more beneficial, and the rest were neutral on the topic. In spite of this, almost two-thirds of the panelists were convinced that the inputs developed were better than what they could have developed on their own.

The final evaluation area of interest is the level of information awareness among the panel during the group process. The group process required a significant amount of information from panelists to base decisions, and the increasing information acquired in subsequent rounds should help guide the group responses toward convergence on the 'most acceptable' answer. Recall that the panelists were sent an initial letter explaining the process (Appendix 7.3), and after each round they were sent a summary of group responses and a reminder of their responses from the previous round (Appendices 7.6 and 7.9) along with any additional information that might help them make decisions. This additional information involved abstracts and links to articles mentioned in comments from previous rounds. Instructions relating to the surveys were also given on the first page of each survey. A summary of the panelists' responses concerning information awareness is given in Table 3. Over 50% of the panel indicated they were provided enough information to clearly understand the goals and objectives of the survey process. As for the information provided between rounds, 80% agreed that this information was useful and relevant, while only 60% said this information actually influenced their decision-making.

Table 3: Panelists' Evaluation of Information Awareness

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I was provided enough information to clearly understand the goals and objectives of the survey process.	0%	13%	27%	53%	7%
The information provided between rounds was useful and relevant.	0%	7%	13%	80%	0%
The information provided between rounds influenced my responses.	0%	7%	33%	60%	0%

Overall, the panelists seemed very receptive to this process of developing estimates using iterative rounds of web-based surveys. Roughly one-fourth of the panel had participated on a panel like this before, and an impressive 100% of the panel said they would participate in a group process like this again in the future. Finally, 85% of the panel thought that the $300 compensation they were given was adequate.

The comments, given along with the raw data in Appendix 7.14, bring up some interesting points about the group process. Several panelists commented that the questions asked in the surveys were completely opinion-based and that no data exists to support their responses, and hence the 'correctness' of the group estimates should be questioned. These panelists may not have fully reviewed the background material provided prior to surveying and recalled that the motivation behind this process was the lack of data available to develop estimates for the CRC Simulation Study. It is true that the accurateness of these estimates should be taken into account when using them, but since there is no real-world data available, these estimates are the best available for use in the simulation study. It may also be true that the panelists did not understand fully that the information was being measured statistically rather than by analyzing individual responses. Two other panelists commented that face-to-face discussions may have revealed more information than this group process allowed, which is simply a limitation of the web-based surveys used to facilitate this estimation method. Finally, one panelist made a comment that the first survey was a bit confusing, and that the clarity improved in subsequent rounds. Great effort was put into the surveys to ensure the questions were targeting the correct information, were straightforward, and eliminated confusion for those being surveyed. As the rounds progressed, using very direct and specific language in the questions and stating all assumptions to eliminate confusion addressed the misunderstandings.

4.2.2 Evaluation of the Process by the Advisory Board

The Advisory Board for the CRC Simulation Study is comprised of a broad group of people with interest in research methodology and medical decisions. Several members of the Advisory Board also participated as expert panelists. While most of the Advisory Board did

not directly participate in the surveys and cannot directly comment on the procedures used in this group elicitation method, they offered their opinions on the accuracy, validity, and usefulness of the simulation model inputs developed as a result of the group process. Therefore, the Advisory Board was given an overview of the process and its outcomes, and then they were asked to complete a short survey about this process. Six members of this board responded to the survey. These documents are shown in Appendix 7.15, and the results of this survey are given in Appendix 7.16.

A summary of these evaluation responses is provided in Table 4. The Advisory Board overwhelmingly agreed that the inputs developed will be useful in the simulation model, but they were more hesitant to comment on the validity and accuracy of the inputs because of their limited knowledge of CRC development and progression. Over 80% of the Advisory Board respondents agreed that the inputs developed are an improvement over what could have been developed both by an individual and an informal group. They believed the participation rate for this process was better than it could have been if travel was required.

Table 4: Summary of Evaluation Responses from the Advisory Board

	Strongly Agree	Agree	Neutral
The inputs developed using this process are useful in the CRC Health Policy Model.	33%	67%	0%
The inputs developed using this process are valid.	0%	33%	67%
The final inputs developed are similar to what I believe are the true values.	0%	40%	60%
The outcomes of the process seemed to be an improvement over what could have been developed by one person.	50%	33%	17%
The outcomes of the process seemed to be better than what could have been developed in an informal group meeting.	33%	50%	17%
The process was conducted solely using internet technologies, and therefore it led to an increased participation rate among the experts (i.e. because it eliminates the need for travel).	50%	33%	17%
The process is a reasonable way to develop simulation model inputs when data are scarce.	33%	33%	33%
The process cost $147 to conduct the surveys and $4500 to pay the panelists. This was a reasonable cost for developing these simulation model inputs.	33%	50%	17%

When asked if the process was a reasonable method for developing simulation model inputs when data are scarce, one-third of the group strongly agreed, one-third of the group agreed, and one-third of the group was neutral. They also indicated that the cost of the study ($147 to conduct the surveys and $4500 to pay the expert panelists) were reasonable, with over an 80% agreement on the issue.

The comments offered by the Advisory Board showed some concern that the process may have ended abruptly and that further surveying rounds may have yielded better estimates as consensus grew. The time limitations of this surveying process did not allow additional surveying rounds, so the outcome of more surveys cannot be known. The panelists also seemed to be settling in their answers and additional rounds may not have had any influence in changing opinions. Another comment also indicated that this type of process is used frequently in the 'greater quality of care arena' and that it works well in those instances. Perhaps this is an indication that the process also works well in this instance.

4.3 Motivations for Using This Group Process

Chapter 3.1 presents requirements of the group process. In the development of the process, these requirements, which are based on research presented in the Literature Review in Chapter 2, were considered carefully. Additionally, the purpose of the group process (the development of inputs when data is scarce) was considered as the methodology for the process was developed. The largest motivation for using this process was that it met all the requirements of the group process and is very tailored to the specific purpose of developing simulation model inputs when data is unavailable.

The process implemented as discussed in Chapter 3.3 cost $4,647, made up of $49 per survey for three survey rounds and $100 per participant per round. Clearly this cost could vary widely depending on the study, they type of survey hosting and survey software utilized, the level of expertise of the panelists, and the number of panelists participating.

The process was well worth the cost for the CRC Simulation Study because without these inputs, the simulation would be hampered by the quality of the input. Furthermore, it is impossible to gather direct observations for some of these inputs because of the risk to the patients, so a process such as this is extremely valuable and the cost-benefit ratio is quite low.

The lack of concrete data on simulation model inputs, addressed during the process implementation, presents many challenges to researchers that finding a simple way to derive information is essential. Eliminating the need to develop prior and likelihood distributions, necessary when using Bayesian processes, removed much complication from the study. By carefully formulating the questions asked, the researchers were able to develop reliable estimates in a rather straightforward manner. The questions, in particular, were developed so that they elicited information about distribution characteristics and data types that can be estimated with the highest degree of reliability and accuracy. After eliciting estimates for the distribution characteristics, the VisiFit software used to develop the inputs was quite helpful because it allowed the study investigators to examine the inputs as both Beta and Johnson SB distributions.

The formality of this group process guided group interactions and eliminated negative group interactions such as groupthink and dominance, possibly providing better estimates from which to develop the inputs. Using a group to develop the estimates perhaps allowed better estimates to be developed than an individual could have defined. An expert panel of 15 participants was an acceptable size, in terms of being small enough to be manageable yet being large enough to represent most of the beliefs about CRC progression to develop the best estimates possible. The expert panelists' responses remained anonymous, and for the most part the panelists did not know who else was serving on the panel. This anonymity fostered an environment where panelists were free to share their opinions and beliefs.

One large advantage to this method is its use of the Internet. The ubiquity of the Internet in the United States facilitates quicker exchanges of information and improved mediums to

elicit information, which are certainly advantageous to this study. Despite the Internet's omnipresence, not everyone is comfortable using computers or the World Wide Web. The 'type' of users in a particular study may dictate whether or not the Internet is a viable means of communication. For the CRC simulation study, the panelists were experts in the fields of epidemiology and molecular biology, and all work with computers and the Internet on a daily basis, so for this study the Internet is a proper medium, but that may not always be the case. Furthermore, the use of the Internet helped maintain the 'anonymous' environment desired, and it also provided a great benefit to this group process because it allowed the panelists to participate in the process at their leisure without the pressures of an overly strict time schedule.

4.4 Development of Objectives and Survey Questions

One drawback of the group process is that it does not prescribe a manner of identifying study objectives, nor does it aid in development of the model structure or survey questions. The study objectives must first be identified before the group process can even begin. Without clearly stated objectives, the remainder of the process is fruitless. The question structure, discussed in the beginning of Chapter 3.2, is another difficult issue because it involves technical knowledge of the simulation development and the use of the study/survey objective in the simulation model. Developing questions for which the experts can provide reliable responses is also an intricate task because it required an understanding of the expert panelist's depth of knowledge and the type of information they are able to recall and mentally summarize. For example, consider the conversion time between incident asymptomatic and symptomatic CRCs. An epidemiologist specializing in this area may be able to estimate that at one year, *A%* of asymptomatic cancers have progressed to symptomatic cancer, and that by two years, *B%* have progressed. However, it may be more difficult for this same person to estimate the most likely (modal) time period between asymptomatic and symptomatic cancer. Furthermore, the questions should be developed while keeping in mind that the most specific information does not necessarily need to be

targeted in the first round of surveys. Questions in subsequent rounds can build upon each other and become more specific and more detailed as necessary.

This research did not focus on the development of a method for posing the structure and questions. Since every situation is quite different, it becomes difficult to impose a process that will overcome these weaknesses. Perhaps a set of guidelines would lessen the burden of objective, structure, and question development. Below is a series of steps that should be followed in the development of the objectives, structure, and questions for the group process.

1. Search for any existing data and identify data deficiencies.
2. Define objectives by considering the critical inputs that lack data.
3. Define the simulation input model structure for each objective.
4. Determine panel composition – what specific subject areas should be invited to join the panel? How will these experts be motivated to participate?
5. Develop a question set by considering the knowledge area and expertise of the panel as a whole. Take into account the multiple rounds of questioning and consider the levels of detail targeted in each round.
6. "Field test" the structure and questions with other project investigators and researchers in the subject area. Ask for advice and opinions, and then revise the questions as necessary. The question development itself may be an iterative process.
7. Develop the survey.

Following these sequential steps will not only save considerable time and effort in the completion of the process, but also enable that the final results of the process to be meaningful, accurate, useful, and valuable in the simulation model.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Input modeling in the absence of data is a critical problem when building simulation models. Fortunately, the group process developed through this research allows the development of inputs when scientifically founded data is unavailable. The process follows the route of a Delphi process, allowing researchers to question experts in the subject area via several rounds of web-based surveys. Between each round, the information from the previous round is analyzed and summarized and the survey for the following round is created and fine-tuned. By providing feedback to the panelists after each round, a growing amount of information becomes available and panelists gain insight into the opinions of their colleagues. This information sharing leads to a growing consensus in responses in subsequent surveying rounds.

This process was implemented within the CRC Simulation Model to create inputs for four different objectives where data was lacking. After three rounds of surveying, the final simulation model inputs were developed and both the expert panelists and the study's Advisory Board evaluated the process. The majority of panelists felt the process was flexible and required minimal time commitment. The ease of use of the web-based surveys and the group dynamics throughout the surveying process allowed everyone to share information without worrying about dominance or groupthink. The information available during the process to support estimate development was adequate from the perspective of the panelists. A majority of both the panelists and the Advisory Board found the inputs developed via the process to be consistent with real-world cases of adenoma development and cancer progression. They also believed the input estimates were more accurate than what one individual or an informal group could have developed. Since the group process was carried out and a growing consensus of the estimates produced the final simulation

model inputs, the process is clearly feasible. The cost of the process was easily justified because of the limited methods currently available to otherwise gain this information for use in the CRC Simulation Study. Because this information represents the best estimates available to date and considering there is limited data to support formal analysis, the inputs developed as a result of this process are extremely valuable.

Overall, this method for developing simulation model inputs in the absence of data using a web-based group process is a very viable alternative. There are limited methods for developing these types of inputs, and this method provides an excellent alternative for several reasons:

- Minimal Cost – the cost is extremely low when compared to the high cost of performing medical experiments involving humans; the cost is variable and can be decreased by using less expensive survey software and hosting, by decreasing the number of participants, and by altering the payment to participants based on expertise and time required;
- Ease of Participation – web-based surveys allow the participants to respond at their leisure; the web-based surveys are extremely easy and quick to distribute to the panelists and they allow instantaneous receipt of panelists' responses;
- Small Time Frame – the rounds of surveying can be constructed to fit a specified time frame; when compared to many medical experiments, the 2.5 months this method required to carry out is a relatively short time span;
- Better Estimates from Groups – evaluation of this process' implementation indicated that the inputs developed were potentially better than what could have been developed in an informal and unstructured group or by an individual;
- Generalized Process – the process, while implemented in one specific instance, is generic and can be implemented for many different types of simulation studies where data is scarce; the process is well documented and can be replicated;

5.2 Recommendations for Future Study

Future research could focus upon creating a method to define objectives and input model structure along with the development of proper questions. As discussed in Chapter 4.4, this process is quite complex and requires the appropriate mix of experts. Expertise in simulation modeling is needed to understand how real-world phenomena are mimicked in computer models. Expertise in the area of study (in this case CRC experts) are needed who can interpret information given by expert panelists and who can understand what types of information this expert panel can reliably estimate given their backgrounds. Therefore, the primary investigators must ensure the proper combination of technical simulation specialists and subject-area experts are available to assist the study efforts before, during, and after the surveying rounds to ensure the proper interpretation of results, development of survey questions, and formulation of the final simulation model inputs.

Another shortcoming defined when implementing the process was the clarity of the questions used in the surveys. More time in question construction would certainly have been beneficial in reducing confusion among the panelists during the survey rounds. Instead of requesting responses in the first round of surveying, the first round of surveying could instead ask for objective clarification and questions clarification. The panelists could provide comments on their understanding of what information the objectives and questions target. This additional step would ensure that the panelists, facilitator, and principal investigators are all focused on the same information. Thereby, the panelists will be considering the same set of information when responding to questions, and the facilitator and principal investigators will not have to decipher responses and guess at the meanings and implications of the estimates, which will ease the analysis of the responses.

An alternative method for implementing the process could employ the surveys as originally prescribed, but then gather the expert panel at the conclusion of the surveying rounds for face-to-face meetings. These meetings could provide immediate feedback about the process and allow the panelists to finalize the inputs used rather than allowing the facilitator and

primary investigators to develop the model inputs. The panelists could explain their rationale and ensure their opinions were heard and understood by the other group members. While this may further increase consensus and confidence in the inputs developed, it may also harbor negative group effects that the original group process was attempting to mitigate. The concept of face-to-face meetings may be quite difficult to arrange given the busy schedules of the panelists, and it might be overly expensive since experts' time is highly valued, but the results might be extremely beneficial in developing the best possible estimates for the simulation inputs.

Another area of future research could address the timeline maintained during the study. This particular study took approximately four months to completely accomplish. This included one-and-a-half months to develop the simulation input model structure, surveying objectives, and associated questions. Another two-and-a-half months were necessary to carry out the three survey rounds, allowing around 2 weeks to collect responses for each survey and about one week between each surveying round to analyze responses and configure the survey and questions for the next round. For participants who responded to the survey shortly after receiving it, they would not have any contact with the process for three weeks. Perhaps if the time allowed to collect responses was shortened and the turnaround time between surveys was reduced, then the panelists would have improved recollection of the surveying process and their thoughts and concerns when providing responses during previous surveying rounds. However, shortening the time per round may also limit the number of responses received because of panelists' time limitations and travel obligations.

One final area of research could reconsider the idea of consensus in a process such as this. It is very hard to define an appropriate level of consensus when data are scarce. When panelists have varying ideas of the "correct" answer, it may be difficult to sway their opinions without direct conversations. Fostering more comments to support responses, perhaps making them mandatory, may help participants gain a higher level of insight into what others believe, thus improving the consensus level. For this study, three rounds of

surveys seemed to provide adequate consensus for the purpose of this study and its accuracy requirements. Additional survey rounds may have fostered more agreement among the group, but it would have come with monetary and time costs. Defining consensus against cost may prove to be a very beneficial research area.

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7. APPENDICES

7.1 IRB Application and Approval Documentation

North Carolina State University
Institutional Review Board for the Use of Human Subjects in Research
SUBMISSION FOR NEW STUDIES

Title of Project: *Input Modeling for the Simulation Modeling of Colorectal Cancer*

Principal Investigator *Cindy M. Liebsch* Department *IE/OR*

Source of Funding (**required** information): *Simulation Modeling of Colorectal Cancer - R01CA92653 (at Vanderbilt University)*

(if externally funded include sponsor name and university account number)

Campus Address (Box Number)*7906*

Email: *cmliebsch@ncsu.edu* Phone: *9192478486* Fax: *N/A*

RANK: Student – Masters

If rank is other than faculty, name of faculty sponsor overseeing the research: *Dr. David B. Kaber*

Faculty Sponsor's Email *dbkaber@eos.ncsu.edu* Campus Box *7906* Phone 515-3086

As the principal investigator, my signature testifies that I have read and understood the University Policy and Procedures for the Use of Human Subjects in Research. I assure the Committee that all procedures performed under this project will be conducted exactly as outlined in the Proposal Narrative and that any modification to this protocol will be submitted to the Committee in the form of an amendment for its approval prior to implementation.

Principal Investigator:

Cindy M. Liebsch

As the faculty sponsor, my signature testifies that I have reviewed this application thoroughly and will oversee the research in its entirety. I hereby acknowledge my role as the principal investigator of record.

Faculty Sponsor:

Dr. David B. Kaber

North Carolina State University
Institutional Review Board for the Use of Human Subjects in Research
PRELIMINARY QUESTIONS

1) Is this a taste and food quality evaluation and consumer acceptance study, where (i) wholesome foods without additives are consumed or (ii) food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture ?

Yes X No

2) Will the subjects remain completely anonymous (i.e. no identifiers which can link an individual subject to their data – projects using coded data sheets with a "key" linking code numbers to subjects are not anonymous)?

Yes X No

3) Will anyone other than the PI or the research team have access to the data (including any completed surveys) from the moment they are collected until they are destroyed?

Yes X No

4) Is your subject population going to consist of only elected or appointed public officials?

Yes X No

5) Does your research involve the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior?

X Yes No

6) Does your research involve the analysis of existing data, documents, records, pathological specimens or diagnostic specimens?

Yes X No

7) In your estimation does the study involve no more than minimal risk to the subjects (see definition of minimal risk in the Policies and Procedures page)

Yes X No

North Carolina State University
Institutional Review Board for the Use of Human Subjects in Research
GUIDELINES FOR A PROPOSAL NARRATIVE

In your narrative, address each of the topics outlined below. Failure to follow these directions will result in delays in reviewing/processing the protocol.

A. INTRODUCTION

1. Briefly describe in lay language the purpose of the proposed research and why it is important.
   This research supports work being done for a grant from the National Cancer Institute between Vanderbilt University's School of Medicine, Indiana University's School of Medicine, and North Carolina State University's Industrial Engineering Department. The overall goal of the research is to analyze clinical outcomes, effectiveness, cost, cost-efectiveness, and resource utilization of various colorectal cancer (CRC) control strategies (i.e. primary prevention, screening, surveillance, and treatment) for patients and for complex and dynamic populations. This analysis will be conducted using a discrete-event simulation model.

   The colorectal cancer (CRC) simulation model requires inputs to drive the simulation. While many inputs for the model have already been developed from data, observations, and past research, there are several areas of the model where no data is available. For example, one input in the simulation is the distribution of time from when an adenoma develops in the colon until it becomes cancerous. As you might tell, it is impossible to 'experiment' to develop a distribution for this input. Adenomas are typically removed as they are discovered, and allowing one to grow and develop into cancer would obviously be unethical.

   Unfortunately this 'unknown' information is still needed for the simulation model. While we cannot test to develop these model inputs, other researchers (such as epidemiologists, molecular biologists, etc.) have 'ideas' or 'information' about what this distribution might look like. In order to elicit this information from these experts, we are using a process similar to a Delphi method to survey expert panelists and ask them very specific questions about modeling parameters of interest.

   This information is important because without it, the simulation model will not properly model real-world scenarios.

2. If student research, indicate whether for a course, thesis, dissertation, or independent research.
   The research is thesis work for Cindy Liebsch.

B. SUBJECT POPULATION

1. How many subjects will be involved in the research? *30 subjects*

2. Describe how subjects will be recruited. *Subjects will be sent an initial recruiting letter from Dr. Robert Coffee and Dr. Raymond DuBois, senior researchers at Vanderbilt University's School of Medicine. This letter introduces them to the study and relays its importance. Dr. Reid Ness, one of the primary investigators for this research, will then send a follow-up letter introducing himself, telling more about the study, and providing the web link to the first survey.*

3. If applicable, please provide the IRB office with a copy of any advertisement to be used in recruiting subjects. This includes print ads as well as scripts for radio and television ads. If this is not applicable, please check here

4. List specific eligibility requirements for subjects (or describe screening procedures), including those criteria that would exclude otherwise acceptable subjects.
   Participants will be recruited to participate based on their levels of expertise in the area of CRC carcinogenesis or prevention. All participants are in the fields of molecular biology and gastroentorology.

5. Explain any sampling procedure that might exclude specific populations (women, minorities, elderly).
   N/A
6. Disclose any relationship between researcher and subjects - such as, teacher/student; employer/employee.
   There are no relationships betweeen the researchers and the subjects.

7. Check any vulnerable populations included in study:

   minors (under age 18) - if so, have you included a line on the consent form for the parent/guardian signature

   fetuses

   pregnant women

   persons with mental, psychiatric or emotional disabilities

   persons with physical disabilities

   economically or educationally disadvantaged

   prisoners

   elderly

   students from a class taught by principal investigator

   other vulnerable population.

   If any of the above are used, state the necessity for doing so. Please indicate the approximate age range of the minors to be involved. *N/A*

C. PROCEDURES TO BE FOLLOWED

1. In lay language, describe completely all procedures to be followed during the course of the experimentation. Provide sufficient detail so that the Committee is able to assess potential risks to human subjects. *Round One: (1a.)Panelists receive background information, study objectives, and the web address of the first survey via email. (1b.)Each expert panelist independently provides responses to questions about the inputs using a web-based survey. Comments about the estimates are encouraged and can be submitted as part of the survey. (1c.)The facilitator collects all responses and summarizes them for ease of comparison and analysis. Summary data must be prepared for both individual responses and for the group responses. Summary data may include simple averages, graphical data analysis, distribution characteristics extracted from the raw data, etc. Comments will be summarized as well. No identifying information will be included in the summaries. Round Two: (2a.)The facilitator prepares the survey for Round Two. Survey questions may be added to elicit additional information or altered to elicit more specific information, but the objectives remain the*

same. (2b.)The facilitator distributes the summaries of both the group estimates and the comments from Round One, as well as their individual Round One response summary. The web address of the second survey is also distributed. All information is sent via email. (2c.)Each panelist should analyze the information. In light of this information, panelists should again use a web-based survey to estimate the inputs. Panel members may be swayed to revise their estimates toward consensus or to provide additional information in support of original responses. (2d.) The facilitator collects all responses and summarizes them using a similar method as that used in Round One, with all responses being kept confidential.
Round Three: Round Three continues as in Round Two, with facilitators carefully developing the surveys and panelists responding to the survey with respect to new information provided from the previous rounds. Survey questions may be altered or added to gain further information about the estimates. Questions may be omitted from the survey as consensus is developed. After Round Three is over, researchers will examine the final responses and develop the inputs to use in the Colorectal Cancer Simulation Study. No further feedback will be distributed to the panelists after Round Three. Evaluation Questionnaire: After completion of the round-three survey, each participant will be sent a questionnaire evaluting the process used to elicit this information.

2. What will subjects be asked to do? *The subjects will be asked to complete three web-based surveys and a follow-up questionnaire. The surveys will ask for their opinions and comments on four aspects of colorectal cancer risk and progression. The questionnaire evaluates the process used to elicit these estimates.*

3. How much time will be required of each subject? *35 minutes over the course of 4 weeks*

D. POTENTIAL RISKS

1. State the potential risks (physical, psychological, financial, social, legal or other) connected with the proposed procedures and explain the steps taken to minimize these risks.
N/A

2. Will there be a request for information which subjects might consider to be personal or sensitive (e.g. private behavior, economic status, sexual issues, religious beliefs, or other matters that if made public might impair their self-esteem or reputation or could reasonably place the subjects at risk of criminal or civil liability)? If yes, please describe and explain the steps taken to minimize these risks.
Yes. Participants will be asked to provide comments supporting their survey responses. Since participants may be colleagues, may sit on boards and committees together, or may be in a boss-employee relationship, there exists a risk that a participant may be judged because of responses or comments she/he made. This risk is minimized because of two reasons. First, this risk has been mitigated because participants identities will be kept confidential. All comments provided in the surveys will be summarized prior to distribution, and no identifying informtion will be associated with any comment or response. No personal information will be used in any written or unwritten reports. Second, of the 30 participants, 5 are from Vanderbilt University and the remaining 25 are distributed throughout the United States. It is unlikely that any two participants might have personal knowledge of each other to the extent that comments or responses could be associated with a particular person.

3. Could any of the study procedures be considered as offensive, threatening, degrading, or could study procedures produce stress or anxiety? If yes, please describe why they are important and what arrangements have been made for psychological counseling.
No

4. Describe methods for preserving confidentiality. How will data be recorded and stored? How will identifiers be used? How will reports will be written, in aggregate terms, or will individual responses be described?

Participants in these surveys will never be in contact with each other. All communication is conducted via web-based surveys through Cindy Liebsch. Any potential identifying comments will be summarized to remove any identity distinction. All data recorded on subjects during the experiments will be kept confidential. No subject names, Social Security Numbers or other forms of identification will be used on any reports (of research results), written or verbal. (See attached copy of Informed Consent form.)

5. If audio or videotaping is done how will the tapes be stored and how/when will the tapes be destroyed at the conclusion of the study.

N/A

6. Is there any deception of the human subjects involved in this study? If yes, please describe why it is necessary and describe the debriefing procedures that have been arranged.

N/A

E. POTENTIAL BENEFITS

Please address benefits expected from the research (this does not include compensation for participation, in any form). Specifically, what, if any, direct benefit is to be gained by the subject? If no direct benefit is expected, but indirect benefit may be expected (knowledge may be gained that could help others), please explain.

Since the survey is conducted in rounds, each round of surveying will provide new/additional information to the panelists to use in completing the survey is subsequent rounds. Indirectly, subjects may gain knowledge and insight from other panelists about various aspects of colorectal cancer presence and progression.

F. COMPENSATION

1. Explain compensation provisions if the subject withdraws prior to completion of the study.

Panelists will receive no compensation if withdrawling early from the study.

2. If class credit will be given, list the amount and alternative ways to earn the same amount of credit.

N/A

G. COLLABORATORS

If you anticipate that additional investigators (other than those named on **Cover Page**) may be involved in this research, list them here indicating their institution, department and phone number.

Dr. Stephen Roberts, NCSU, Industrial Engineering Department, 515.6400

Dr. Reid Ness, Vanderbilt University, Health Services Research, 615-936-0773

H. ADDITIONAL INFORMATION

1. If a questionnaire, survey or interview instrument is to be used, attach a copy to this proposal.
2. Attach to this proposal a copy of the informed consent document that you will use.
3. Please provide any additional materials or information that may aid the IRB in making its decision.

The informed consent document is the second page of the round-one survey, which is attached.

North Carolina State University
INFORMED CONSENT FORM

Input Modeling for the Simulation Modeling of Colorectal Cancer

Principal Investigator: Cindy M. Liebsch Faculty Sponsor: Dr. David B. Kaber

You are invited to participate in a research study. The purpose of this study is to develop inputs for the Colorectal Cancer Health Policy Model.

INFORMATION

1. BACKGROUND: This process involves three rounds of surveys plus an evaluation questionnaire. The surveys will ask questions pertaining to the four objectives of the study. Comments are encouraged to support your responses. Throughout the entire process, your identity will remain confidential. No identifying comments will be disclosed to other participants or used in any written or verbal reports.
2. PROCEDURE: After all panelists have completed the first round of surveys, the data and comments will be summarized and emailed to you. With respect to this additional information, you will respond to the questions on the second-round survey. Again, after all panelists have completed the second round of surveys, the data and comments will be summarized and emailed to you. This process will repeat for a third round. After completing the third survey, you will be sent a questionnaire for evaluating the process used to elicit your responses.
2. TIME COMMITMENT: Each survey will take approximately 7-10 minutes, with three rounds of surveying. Additionally, a follow-up survey will evaluate the process used, and this survey should take no more than 5 minutes. The total time commitment is approximately 30 minutes.

RISKS

There are no foreseeable risks or discomforts associated with this study.

BENEFITS

The outcome of this study will be simulation model inputs, which will directly be used in the Colorectal Cancer Simulation Study to analyze the clinical outcomes, effectiveness, costs, cost-effectiveness, and resource utilization of various colorectal cancer control strategies. As a result of participating in this study, panelists may have an increased understanding of the study objectives.

CONFIDENTIALITY

The information in the study records will be kept strictly confidential. Data will be stored securely and will be made available only to persons conducting the study unless you specifically give permission in writing to do otherwise. No reference will be made in oral or written reports which could link you to the study.

COMPENSATION

For fully participating in this study you will receive $300. **If you withdraw from the study prior to its completion, you will receive no compensation**. Compensation will only be distributed after completing all THREE surveys AND the evaluation questionnaire.

CONTACT

If you have questions at any time about the study or the procedures, you may contact the researcher, Dr. Reid Ness**, at reid.ness@vanderbilt.edu, or (**615)936.0773**, or coinvestigator,** Cindy Liebsch**, at cmliebsch@ncsu.edu, or** (919)515.8614**. If you feel you have not been treated according to the descriptions in this form, or your rights as a participant in research have been violated during the course of this project, you may contact Dr. Matthew Zingraff, Chair of the NCSU IRB for the Use of Human Subjects in Research Committee, Box 7514, NCSU Campus (919/513-1834) or Mr. Matthew Ronning, Assistant Vice Chancellor, Research Administration, Box 7514, NCSU Campus (919/513-2148)**

PARTICIPATION

Your participation in this study is voluntary; you may decline to participate without penalty. If you decide to participate, you may withdraw from the study at any time without penalty and without loss of benefits to which you are otherwise entitled. If you withdraw from the study before data collection is completed your data will be returned to you or destroyed.

North Carolina State University is a land-grant university and a constituent institution of The University of North Carolina

Office of Research and Graduate Studies

NC STATE UNIVERSITY

Sponsored Programs and
Regulatory Compliance
Campus Box 7514
1 Leazar Hall
Raleigh, NC 27695-7514

919.515.7200
919.515.7721 (fax)

From: Debra A. Paxton, Regulatory Compliance Administrator
North Carolina State University
Institutional Review Board

Date: March 11, 2003

Project Title: Input Modeling for the Simulation Modeling of Colorectal Cancer

IRB#: 050-03-3

Dear Ms. Liebsch:

The research proposal named above has received administrative review and has been approved as exempt from the policy as outlined in the Code of Federal Regulations (Exemption: 46.101.b.2). Provided that the only participation of the subjects is as described in the proposal narrative, this project is exempt from further review.

NOTE:

1. This committee complies with requirements found in Title 45 part 46 of The Code of Federal Regulations.
   For NCSU projects, the Assurance Number is: FWA00003429; the IRB Number is: IRB00000330

2. Review de novo of this proposal is necessary if any significant alterations/additions are made.

Please provide a copy of this letter to your faculty sponsor. Thank you.

Sincerely,

7.2 Initial Correspondence from Senior Researchers

Greetings,

We are sending this letter to introduce to you Dr. Reid Ness, one of our junior faculty here at Vanderbilt. His area of research involves the delivery of colorectal cancer preventative services. As part of a more comprehensive effort to improve upon an existing computer model of the natural history of CRC, Reid and his colleagues are looking to garner expert opinion concerning some of the basic processes underlying CRC carcinogenesis. To accomplish this objective, they have devised a short web-based survey that should require little of your time.

We feel that this project is important to furthering our understanding of the issues surrounding the delivery of CRC preventative services and would encourage you to take part in this effort. Reid will be sending mail and email in a few days to elicit your participation on this project.

Thank-you for your consideration,

Robert J. Coffey, Jr., M.D.
Ingram Professor of Medicine and Cell Biology
Director, GI Cancer Program
Director, Epithelial Biology Program

Raymond N. DuBois, M.D., Ph.D.
Mina C. Wallace Professor
Chief of Gastroenterology, Hepatology & Nutrition

7.3 Email Eliciting Survey Participation

Dear Sirs,

Thank you for considering participation in this formal group process for developing model estimates for the Colorectal Cancer Health Policy Model! The objectives of this study will be met through three rounds of web-based surveys. Please respond to the survey questions based on your beliefs, as there is little data available to analyze some survey questions. Each survey should take you no more than 10 minutes to complete, and your responses will remain confidential. Between each survey round you will receive additional information to help you develop estimates for the next survey. We also ask that you complete one follow-up survey at the conclusion of the study that will evaluate the methods used to elicit this information. In exchange for your time, you will be paid $300 for your participation in all three survey rounds and the follow-up survey.

The timeline is as follows:

Tuesday, March 11	Round 1 Survey distributed
Monday, March 17	Round 1 Survey answers due date
Wednesday, March 19	Round 2 Survey distributed
Tuesday, March 25	Round 2 Survey answers due date
Thursday, March 27	Round 3 Survey distributed
Wednesday, April 2	Round 3 Survey answers due date
Friday, April 4	Follow-up Survey (due a.s.a.p.)

Much of the survey correspondence will be sent via Cindy Liebsch, a co-investigator on this project, from the address cmliebsch@ncsu.edu, and all emails will begin with the subject: CRC Simulation Study.

Please complete the first survey by going to:

http://websurveyor.net/wsb.dll/11331/CRCValuationSurvey1.htm

Again, your participation in this expert panel is highly valued. If you do not wish to participate as part of this expert panel, please email your regrets to me at reid.ness@vanderbilt.edu .

Warmest regards,
Reid M. Ness, M.D., M. P.H.
Assistant Professor of Medicine
Division of Gastroenterology, Hepatology, and Nutrition
Department of Medicine
Vanderbilt University Medical Center

7.4 Round One Survey

Page 1

Colorectal Cancer Health Policy Model

Thank you for agreeing to serve as an expert on this panel to develop estimates of model inputs for the Colorectal Cancer Health Policy Model.

This survey asks four specific questions concerning colorectal cancer carcinogenesis. Your estimates should be based on your beliefs, which include both personal and professional experience and understanding of the related issues. Some questions have very little or no data on which to base your repsonses, so please respond with your best estimate. Comments supporting your estimates are encouraged in order to provide other panelists with insight into your opinions.

Your responses will be automatically collected and will remain confidential. Your identity will never be revealed or associated with your responses in any publication.

If you are having technical problems with the survey, please contact Cindy Liebsch (coinvestigator) at cmliebsch@ncsu.edu.

Thank You,
Dr. Reid Ness

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Colorectal Cancer Health Policy Model

The INFORMED CONSENT for this study on Input Modeling for the Simulation Modeling of Colorectal Cancer is given on the following webpage:

http://www4.ncsu.edu/~cmliebsc/InformedConsent.doc

Briefly, the document states that this study will occur over the course of four rounds web-based surveys, with a total time commitment of approximately 30 minutes. You will be compensted $300 for completing ALL FOUR surveys. No compensation will be given for partial participation. All responses and comments will remain confidential and your identity will not be revealed in any publication, written or unwritten.

☐ I understand the INFORMED CONSENT given on the webpage above. I agree to participate in this study.

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Colorectal Cancer Health Policy Model

Objective 1:

What percentage of incident colorectal cancers develop from normal tissue without passing through a visible polyp intermediary?" (Responses can range from 0-100.)

[ ] %

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

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Colorectal Cancer Health Policy Model

Objective 2:
Genetic predisposition to colorectal cancer posed by an affected first-degree family member can be due to two factors:
*An increase in the rate of adenoma incidence
*An increased progression rate from adenoma to cancer.

For the population of people with an affected first-degree relative, what percentage of this population are at an increased risk due to each of the following:
(Please note that your responses must total 100%.)

[ ] % due to ONLY an increased rate of adenoma incidence

[ ] % due to ONLY an increased adenoma progression rate to cancer

[ ] % due to BOTH an increased incidence rate and increased progression rate

Answer the following question only if you responded in the "BOTH" choice above with a proportion GREATER THAN 0%.
What percentage of the "BOTH" population's increased risk for colorectal cancer is due to the following two factors?
(Please note that your responses must total 100%)

[ ] % due to an increased rate of adenoma incidence

[ ] % due to an increased adenoma progression rate to cancer

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

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Colorectal Cancer Health Policy Model

Objective 3:

For all adenomas that are going to become cancer, what percentage will become cancer by each of the following years? These are cumulative values, so each response must be equal to or greater than the previous response.

We assume that by 100 years, 100% of progressing adenomas will become cancerous, however this can happen before 100 years. For example, if you believe 100% of adenomas will become cancer in 60 years, then your response for 60 years will be 100%, with decreasing percentages for each interval leading up to 60 years.

10 years: [ ] %

20 years: [ ] %

30 years: [ ] %

40 years: [ ] %

50 years: [ ] %

60 years: [ ] %

70 years: [ ] %

80 years: [ ] %

90 years: [ ] %

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

[ ]

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Colorectal Cancer Health Policy Model

Objective 4:

What percentage of incident cancers will become symptomatic by each of the following years? As in the previous question, these are cumulative values, so each response must be equal to or greater than the previous response.

We assume that by 10 years, 100% of incident cancers will become symptomatic, however this may happen before 10 years. For example, if you believe 100% of colorectal cancers will become symptomatic in 8 years, then your response for 8 years will be 100%, with decreasing percentages for each year leading up to 8 years..

1 year: [ ] %

2 years: [ ] %

3 years: [ ] %

4 years: [ ] %

5 years: [ ] %

6 years: [ ] %

7 years: [ ] %

8 years: [ ] %

9 years: [ ] %

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

[ ]

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Colorectal Cancer Health Policy Model

We request your email for tracking purposes only. Please be assured that your responses will remain confidential, and your responses will never be associated with your name in any publication.

email address:

Thank you for participating in this round! You will receive information about the Round 2 Survey no later than Wednesday, March 19. If you have any questions or comments concerning this survey, please contact Cindy Liebsch at cmliebsch@ncsu.edu.

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7.5 Round One Survey Summary

Colorectal Cancer Health Policy Model
Round One Survey Summary

Objective 1: Estimate the proportion of colorectal cancers that cannot be prevented through conventional screening (i.e. the cancers that cannot be detected because they develop from normal tissue without passing through a visible polyp intermediary).

Question: What percentage of incident colorectal cancers develop from normal tissue without passing through a visible polyp intermediary?

Response Summary:

Mean – 10.4%
Minimum Response – 0%
Maximum Response – 25%

Raw Data: *All numbers are given as percentages*

0	0	2	2	3	5	5	5	10	10	10	10	15	20	20	20	25	25

Comments:

a. Interval cancers occur in every screening program, even in the distal colon among people screened with sigmoidoscopy.
b. Profound reduction in colorectal cancer mortality following adenoma polypectomy
c. A visible polyp intermediary may not be observed among microsatellite unstable colorectal cancers due to its rapid transgression into cancer. It is possible that a polyp actually does form, but that it is so quick that endoscopists do not observe it.
d. Based on current data it is felt that at least 85% of incident colorectal cancers develop via the polyp intermediary.....however, these numbers may depend on the genetic background of the population being evaluated.
e. There are no absolute data or studies to prove this, but there are strong studies showing that removal of adenomas prevents the vast majority of colorectal cancers. The molecular biology supports the adenoma-carcinoma sequence as well.
f. It is my belief that all adenocarcinomas of the colorectum start out as adenomas, but there is no question that some neoplasms can begin as flat adenomas and become flat adenocarcinomas. It is anyone's guess what percentage of neoplasms are flat from start to finish, but let me guess about 10-15%. I don't think that any colorectal cancers develop from normal tissue without first going through a stage in which they are adenomatous, i.e., are unable to invade or metastasize. What percentage of humans do you think develop from germ cells without going through the embryo stage? I cannot prove that a colorectal adenocarcinoma has never developed without having been adenomatous tissue,

but it violates what I think I know about multistep carcinogenesis. It is however reasonably certain that some adenocarcinomas grow from flat adenomatous tissue.

g. There are data from the 1970's that suggest a "de novo" genesis of CRC but this is believed to be quite unusual.

Objective 2: Genetic predisposition posed by an affected first-degree family member can be due to an increased rate of adenoma incidence or an increased progression rate from adenoma to cancer. Estimate the relative proportion of these two factors in affecting a person's underlying risk of developing cancer based on family history.

Question: For the population of people with an affected first-degree relative, what percentage of this population are at an increased risk due to each of the following:

2a. % due to ONLY an increased rate of adenoma incidence

2b. % due to ONLY an increased adenoma progression rate to cancer

2c. % due to BOTH an increased incidence rate and increased progression rate

(If allocating a portion in BOTH above, answer below)

What percentage of the "BOTH" population's increased risk for colorectal cancer is due to the following two factors?

2d. % due to an increased rate of adenoma incidence

2e. % due to an increased adenoma progression rate to cancer

Response Summary:

Question	Average	Minimum	Maximum
2a.	50.70%	0%	100%
2b.	22.40%	0%	90%
2c.	28.40%	0%	100%
2d.	47.70%	1%	80%
2e.	46.40%	20%	99%

* 6% of respondents allocated 100% to only an increased rate of adenoma incidence (2a)
* 6% of respondents allocated 100% to both an increased incidence rate and progression rate. (2c)

Raw Data:

Q2 Only Incidence	85	60	34	25	90	20	25	0	85
Q2 Only Progression	10	20	33	50	0	20	25	0	0
Q2 Both	5	20	33	25	10	60	50	100	15
Q2 Both Incidence	80	50	50	25	80	50	50	50	1
Q2 Both Progression	20	50	50	75	20	50	50	50	99
Q2 Only Incidence	80	30	15	80	45	5	85	50	100
Q2 Only Progression	15	40	20	15	25	90	15	25	0
Q2 Both	5	30	65	5	30	5	0	25	0
Q2 Both Incidence	60	70	50	50	45	50		50	
Q2 Both Progression	40	30	50	50	55	50		50	

Comments:

a. Early age of cancers in this category, often without more than a few synchronous adenomas, argues for increased rate of progression being the predominant factor

b. Based on our current understanding, there are some patients that develop microsatellite unstable tumors that seem to progress at a faster rate than non microsatellite unstable tumors.
c. Previous studies have strongly suggested that adenoma formation may be a stochastic process and that progression factors appear to be heritable. There are rare syndromes in which tumor suppressor gene germline mutations predispose to initiation events evidenced by polyposis.

Objective 3: Estimate the distribution for conversion time to cancer among adenomas that are going to become cancerous.

Question: For all adenomas that are going to become cancer, what percentage will become cancer by each of the following years?

Response Summary:
**Average 50th percentile (year when 50% of adenomas become cancerous): 32.2 years

Year	Average Response	Minimum (years)	Maximum (years)
10 years	24%	0	80
20 years	44%	1	90
30 years	66%	3	100
40 years	71%	5	100
50 years	77%	8	100
60 years	82%	30	100
70 years	88%	50	100
80 years	93%	70	100
90 years	97%	80	100

Raw Data:

Q3 10yrs	5	75	25	0	50	0	10	80	10	5	5	25	10	15	5	15	20	60
Q3 20Yrs	75	80	50	1	80	0	50	90	30	10	8	50	20	30	10	50	30	80
Q3 30yrs	100	100	100	3	90	0	100	100	75	20	12	75	50	60	20	75	35	100
Q3 40yrs	100	100	100	5	100	10	100	100	90	30	17	100	80	80	30	90	40	100
Q3 50yrs	100	100	100	8	100	20	100	100	95	40	22	100	100	90	60	95	50	100
Q3 60yrs	100	100	100	30	100	30	100	100	100	50	30	100	100	100	80	100	60	100
Q3 70yrs	100	100	100	60	100	50	100	100	100	60	50	100	100	100	100	100	70	100
Q3 80yrs	100	100	100	70	100	80	100	100	100	70	70	100	100	100	100	100	80	100
Q3 90yrs	100	100	100	80	100	100	100	100	100	80	90	100	100	100	100	100	90	100
50th %ile	16.43	6.67	20.00	66.67	10	70	20	6.25	24.4	60	70	20	30	26.67	46.67	20	50	8.33

Comments:
a. I am assuming that the values above represent years after adenoma formation.
b. I assume that the 10 years is 10 years after the polyp first appears, and so on.

c. I assume that the author meant all polyps of any size or histology at the beginning of the 90 year span.
d. It is not clear what you mean by "adenomas that are going to become cancer". I assume you mean any adenoma, but to me, an adenoma that is going to become cancer is already large or villous or HGD and this takes less time to turn cancerous.

Objective 4: For incident cancers, estimate the distribution for the conversion time period between incident asymptomatic and symptomatic cancers.

Question: What percentage of incident cancers will become symptomatic by each of the following years?

Response Summary:

**Average 50th percentile (year when 50% of adenomas become symptomatic): 2.6 years

Year	Average Response	Minimum (years)	Maximum (years)
1 year	21%	2	50
2 years	43%	5	80
3 years	66%	10	100
4 years	79%	25	100
5 years	88%	40	100
6 years	92%	60	100
7 years	95%	70	100
8 years	97%	80	100
9 years	99%	90	100

Raw Data:

Q4 1yr	30	15	25	20	30	2	10	50	35	20	15	10	10	3	25	10	35	30
Q4 2Yrs	60	30	50	50	70	5	25	75	80	30	20	25	30	5	50	50	45	70
Q4 3yrs	90	60	75	70	90	10	50	100	100	40	30	75	50	10	85	90	55	100
Q4 4yrs	100	90	85	90	100	25	75	100	100	50	40	100	80	35	90	99	70	100
Q4 5yrs	100	95	90	100	100	40	100	100	100	75	50	100	100	55	100	100	80	100
Q4 6yrs	100	100	91	100	100	60	100	100	100	100	60	100	100	60	100	100	90	100
Q4 7yrs	100	100	92	100	100	70	100	100	100	100	70	100	100	75	100	100	100	100
Q4 8yrs	100	100	93	100	100	80	100	100	100	100	80	100	100	90	100	100	100	100
Q4 9yrs	100	100	94	100	100	90	100	100	100	100	90	100	100	100	100	100	100	100
50th %ile	1.67	2.67	2	2	2	6	3	1	1.33	4	5	2.5	3	4.75	2	2	2.5	1.5

Comments:

a. Not all incident cancers will become symptomatic
b. I will assume symptomatic means patient symptoms, and not signs from hemoccult tests, etc. I am also assuming that the cancer just formed at time zero.
c. It will obviously depend on the initial stage of cancer, but I based my estimates on an adenoma that just turns cancerous at time "zero".

7.6 Example of Round Two Information Sent to Panelist XYZ

Dear Dr. XYZ,
Thank you for participating in the first round of surveying for the Colorectal Cancer Health Policy Model. The information you provide as part of this expert panel is highly valued.

The summary of responses from the previous round of surveying is given below, with your responses paired side-by-side with the average group responses. You may use this information to help guide your decision-making during this second round of surveying. On the other hand, you may provide additional information in the comments sections to support your original responses. Your responses to this second survey are needed by **Monday, March 31.** The link for the second survey is:

http://websurveyor.net/wsb.dll/11925/CRC_Survey2.htm

Summary of Responses from Round One:

Question 1: What percentage of incident colorectal cancers develop from normal tissue without passing through a visible polyp intermediary?

Average Response:	Your Response:
10.4 %	20%

Supporting Comments:

a. Interval cancers occur in every screening program, even in the distal colon among people screened with sigmoidoscopy.
b. Profound reduction in colorectal cancer mortality following adenoma polypectomy
c. A visible polyp intermediary may not be observed among microsatellite unstable colorectal cancers due to its rapid transgression into cancer. It is possible that a polyp actually does form, but that it is so quick that endoscopists do not observe it.
d. Based on current data it is felt that at least 85% of incident colorectal cancers develop via the polyp intermediary.....however, these numbers may depend on the genetic background of the population being evaluated.
e. There are no absolute data or studies to prove this, but there are strong studies showing that removal of adenomas prevents the vast majority of colorectal cancers. The molecular biology supports the adenoma-carcinoma sequence as well.
f. It is my belief that all adenocarcinomas of the colorectum start out as adenomas, but there is no question that some neoplasms can begin as flat adenomas and become flat adenocarcinomas. It is anyone's guess what percentage of neoplasms are flat from start to finish, but let me guess about 10-15%. I don't think that any colorectal cancers develop from normal tissue without first going through a stage in which they are adenomatous, i.e., are unable to invade or metastasize. What percentage of humans do you think develop from germ cells without going through the embryo stage? I cannot prove that a colorectal adenocarcinoma has never developed without having been adenomatous tissue,

but it violates what I think I know about multistep carcinogenesis. It is however reasonably certain that some adenocarcinomas grow from flat adenomatous tissue.

g. There are data from the 1970's that suggest a "de novo" genesis of CRC but this is believed to be quite unusual.

Question 2: For the population of people with an affected first-degree relative, what percentage of this population are at an increased risk due to each of the following:

	Average Response:	Your Response:
Q2 Only Increased Incidence	51%	50
Q2 Only Increased Rate of Progression	22%	25
Q2 Both Increased Incidence and Rate of Progression	27%	25
Q2 If Both: What proportion caused by increased Incidence	51%	50
Q2 If Both: What proportion caused by increased rate of Progression	49%	50

Supporting Comments:

a. Early age of cancers in this category, often without more than a few synchronous adenomas, argues for increased rate of progression being the predominant factor

b. Based on our current understanding, there are some patients that develop microsatellite unstable tumors that seem to progress at a faster rate than non microsatellite unstable tumors.

c. Previous studies have strongly suggested that adenoma formation may be a stochastic process and that progression factors appear to be heritable. There are rare syndromes in which tumor suppressor gene germline mutations predispose to initiation events evidenced by polyposis.

Question 3: For all adenomas that are going to become cancer, what percentage will become cancer by each of the following years?

	Average Response:	Your Response:
Q3 10yrs	23%	20
Q3 20Yrs	41%	30
Q3 30yrs	62%	35
Q3 40yrs	71%	40
Q3 50yrs	77%	50
Q3 60yrs	82%	60
Q3 70yrs	88%	70

Q3 80yrs	93%	80
Q3 90yrs	97%	90
50th percentile	31.78 years	50

Supporting Comments:

a. I am assuming that the values above represent years after adenoma formation.
b. I assume that the 10 years is 10 years after the polyp first appears, and so on.
c. I assume that the author meant all polyps of any size or histology at the beginning of the 90 year span.
d. It is not clear what you mean by "adenomas that are going to become cancer". I assume you mean any adenoma, but to me, an adenoma that is going to become cancer is already large or villous or HGD and this takes less time to turn cancerous.

Question 4: What percentage of incident cancers will become symptomatic by each of the following years?

	Average Response:	**Your Response:**
Q4 1yr	21%	35
Q4 2Yrs	43%	45
Q4 3yrs	66%	55
Q4 4yrs	79%	70
Q4 5yrs	88%	80
Q4 6yrs	92%	90
Q4 7yrs	95%	100
Q4 8yrs	97%	100
Q4 9yrs	99%	100
50th percentile	2.66 years	2.5

Supporting Comments:

a. Not all incident cancers will become symptomatic
b. I will assume symptomatic means patient symptoms, and not signs from hemoccult tests, etc. I am also assuming that the cancer just formed at time zero.
c. It will obviously depend on the initial stage of cancer, but I based my estimates on an adenoma that just turns cancerous at time "zero".

Thank you for your participation.

Sincerely,
Cindy Liebsch
Co-Investigator for the CRC Health Policy Model

7.7 Round Two Survey

Page 1

Colorectal Cancer Health Policy Model

Thank you again for serving as an expert on this panel for developing estimates for the Colorectal Cancer Health Policy Model.

You have received summaries of both your responses and the group responses and comments from ROUND ONE. With respect to this new information, please answer the questions on this survey. You may be convinced, using this new information, to revise your thinking, or you may want to provide comments to support your personal views. Again, estimates should be based on your beliefs, which include both personal experience and understanding of the issues. Some questions have very little or no data on which to base your repsonses, so please respond with your best estimate. Comments supporting your estimates are encouraged to provide other panelists insight about your beliefs.

Your responses will be automatically collected and will remain confidential. Your identity will never be revealed or associated with your responses in any publication.

If you are having technical problems with the survey, please contact Cindy Liebsch at cmliebsch@ncsu.edu.

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Colorectal Cancer Health Policy Model

Objective 1:

What percentage of incident colorectal cancers develop from normal tissue without passing through a visible polyp intermediary? "Normal" may include flat adenomas that are not detectable by endoscopic or conventional screening methods.

In the previous round, the mean response for this question was 10.4%, and responses ranged from 0%-25%.

[ ]%

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

[ ]

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Colorectal Cancer Health Policy Model

Objective 2:

Genetic predisposition posed by an affected first-degree family member can be due to two factors:
*An increase in the rate of adenoma incidence
*An increased progression rate from adenoma to cancer.

For the population of people with an affected first-degree relative, what percentage of this population are at an increased risk due to each of the following:

In Round 1 the average responses were 51%, 22%, and 27%, respectively, and 89% of the panel allocated some portion to the "both" response. (Please note that answers must sum to 100%.)

[ ] % due to ONLY an increased rate of adenoma incidence

[ ] % due to ONLY an increased adenoma progression rate to cancer

[ ] % due to BOTH an increased incidence rate and increased progression rate

Answer the following question only if you responded a proportion GREATER THAN ZERO in the "BOTH" choice above.

What percentage of the "BOTH" population's increased risk because of an affected first-degree family member is due to the following two factors?

In Round 1 the average responses were 51% and 49%, respectively. (Please note that answers must sum to 100%.)

[ ] % due to an increased rate of adenoma incidence

[ ] % due to an increased adenoma progression rate to cancer

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please do not include identifying information.

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Colorectal Cancer Health Policy Model

Objective 3:

You received a summary of responses from Round 1 concerning the progression time from adenoma to cancer. *The average time when 50% of adenomas become cancerous was 31.8 years. The average percentage of adenomas that had progressed to cancer by 10 years was 23%.*

In light of this information, please evaluate the following questions considering ONLY adenomas that will progress. (While some adenomas may regress or have no chance of becoming cancer, this question deals with only those that will progress.)

50% of progressing colorectal adenomas will become cancerous by _____ years from the time of adenoma formation.

At 10 years from the time of adenoma formation, _____ % of progressing colorectal adenomas will become cancerous.

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

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Colorectal Cancer Health Policy Model

Objective 4:

The summary responses from Round 1 concerning the time between asymptomatic and symptomatic colorectal cancers indicated that *50% of colorectal cancers will become symptomatic after 2.66 years, and that after 1 year 21% of cancers will become symptomatic.* With respect to this new information, please answer these questions, assuming that (1) the patient survives, (2) there is an absence of screening, and that (3) symptomatic means any symptoms leading to a diagnosis of colorectal cancer:

50% of incident colorectal cancers will have become symptomatic by _____ years.

After 1 year, _____ % of incident colorectal cancers will have become symptomatic.

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

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Page 6

Colorectal Cancer Health Policy Model

We request your email for tracking purposes only. Please be assured that your responses will remain confidential, and your responses will never be associated with your name in any publication.

email address: _____

Thank you for participating in this round! You will receive information about the Round 3 Survey no later than Friday, April 4. If you have any questions or comments concerning this survey, please contact Cindy Liebsch at cmliebsch@ncsu.edu.

Submit Survey (6 of 6)

7.8 Round Two Survey Results

Colorectal Cancer Health Policy Model
Round Two Survey Summary

Objective 1: Estimate the proportion of colorectal cancers that cannot be prevented through conventional screening (i.e. the cancers that cannot be detected because they develop from normal tissue without passing through a visible polyp intermediary).

Question: What percentage of incident colorectal cancers develop from normal tissue without passing through a visible polyp intermediary?

Response Summary:

Mean	Median	Min	Max
11.333	10	2	25

Raw Data:

2	3	3	5	10	10	10	10	10	12	15	15	20	20	25

Comments:

a. Cancer is the result of genetic changes with adenoma being a passer by. Some of these changes likely accelerated with little or no time spent in the adenoma stage.
b. I still believe that all colon cancers develop from an antecedant polyp whether it can be detected or not is another question. A flat adenoma even if not detected is still an adenomatous process and not "normal" tissue. But if you want to include a flat adenoma as normal tissue, then a few cancers may develop without detection of a "polyp" stage.
c. There is simply no way to know this quantitatively. The Rembacken data are a bit worrisome. In the K-P case conrol study of sig, why were many CRCs NOT prevented (RR reduction was about 60%); were some cancers fast-growing. In a model you will need to have a wide range in sensitivity analysis.
d. This is probably rare.
e. I have a strong belief, which is not entirely data-based, but is based upon modelling, and what I know about the biology and genetic basis of neoplasia, that no cancer ever emerges from "normal" tissue without going through an adenomatous stage. The question is phrased in a way that will confuse the answerer, because the term "polyp" is a morphological descriptor, whereas adenoma and carcinoma are pathological descriptors.
f. This is a bit confusing. I believe that the percentage of cancers arising from truly normal mucosa is less than 3-5%. However, it is possible that as many as 20% of cancers may arise from flat adenomas.

Objective 2: Genetic predisposition posed by an affected first-degree family member can be due to an increased rate of adenoma incidence or an increased progression rate from

adenoma to cancer. Estimate the relative proportion of these two factors in affecting a person's underlying risk of developing cancer based on family history.

Question: For the population of people with an affected first-degree relative, what percentage of this population are at an increased risk due to each of the following:

2a. % due to ONLY an increased rate of adenoma incidence

2b. % due to ONLY an increased adenoma progression rate to cancer

2c. % due to BOTH an increased incidence rate and increased progression rate

(If allocating a portion in BOTH above, answer below)

What percentage of the "BOTH" population's increased risk for colorectal cancer is due to the following two factors?

2d. % due to an increased rate of adenoma incidence

2e. % due to an increased adenoma progression rate to cancer

Response Summary:

	Average Response:	Median Response:	Minimum Response:	Maximum Response:
Q2 Only Incidence	52	50	10	85
Q2 Only Progression	25.33333333	25	0	80
Q2 Both	22.66666667	20	0	50
Q2 Both Incidence	42.91666667	50	15	55
Q2 Both Progression	57.08333333	50	45	85

Raw Data:

Q2 Only Incidence	25	50	45	25	75	80	50	10	85	60	85	60	40	65	25
Q2 Only Progression	25	25	25	25	15	20	20	80	0	30	15	20	20	35	25
Q2 Both	50	25	30	50	10	0	30	10	15	10	0	20	40	0	50
Q2 Both Incidence	50	50	55	50	50		50	15	20	50		50	50		25
Q2 Both Progression	50	50	45	50	50		50	85	80	50		50	50		75

Comments:

a. There is evidence to support that pts with 1st degree relatives with CRC have a higher incidence of CRC formation. Evidence also supports that early age pts with CRC have a increased rate of progression of their tumors.
b. Familiality puts people at increased risk for developing polyps. The genetics of individual polyps, as well as their background, may influence the speed of progression. However, the polyp has to form initially before progression can take place.

Objective 3: Estimate the distribution for conversion time to cancer among adenomas that are going to become cancerous.

Questions:

a. 50% of progressing colorectal adenomas will become cancerous by ____ years from the time of adenoma formation.

b. At 10 years from the time of adenoma formation, _____ % of progressing colorectal adenomas will become cancerous.

Response Summary:

	Mean	Median	Min	Max
Q3 50%	20.567	20	3	30
Q3 10yrs	33.2	20	10	95

Raw Data:

Q3 50%	20	25	28	7.5	30	20	20	20	25	30	30	25	20	3	5
Q3 10yrs	33	20	25	75	10	25	20	25	20	20	10	20	20	95	80

Comments:

a. I do not believe it will take an average of 30 years for polyps that are destined to become cancers to do so. Clearly not all polyps will become cancers, but those destined to do so will usually do so within a decade. The adenoma to carcinoma sequence generally takes 7-10 years.

Objective 4: For incident cancers, estimate the distribution for the conversion time period between incident asymptomatic and symptomatic cancers.

Questions:

a. 50% of incident colorectal cancers will have become symptomatic by _____years.
b. After 1 year, _____% of incident colorectal cancers will have become symptomatic.

Response Summary:

	Mean	Median	Min	Max
Q4 50%	2.787	2	1	7
Q4 1yr	29.533	30	10	50

Raw Data:

Q4 50%	2.5	5	2.8	1.5	2	2	7	2	2	4	1	3	3	2	2
Q4 1yr	50	20	25	33	30	25	10	30	35	20	50	20	30	35	30

Comments:

a. In the Stryker study, many of the over-1-cm "polyps" may have already been cancer, and they "progressed" to become clinical cancer at a rate of only 1% per year. Perhaps some (many?) cancers progress slowly.

7.9 Example of Round Three Information Sent to Panelist XYZ

Email:
Dear Dr. XYZ,
Thank you for participating in the first and second rounds of surveying for the Colorectal Cancer Health Policy Model. The information you provide as part of this expert panel is highly valued. This third survey is the last research survey, and this study will conclude with one brief evaluation survey.

The summary of responses from the second round of surveying is attached to this email, with your responses paired side-by-side with the group responses. You may use this information to help guide your decision-making during this third round of surveying. On the other hand, you may provide additional information in the comments sections to support your original responses. Your responses to this second survey are needed by **Monday, April 21.** The link for the third survey is:

http://websurveyor.net/wsb.dll/11928/CRC_Survey3.htm

Sincerely,
Dr. Reid Ness

Attachment:

Colorectal Cancer Health Policy Model
Round Two Survey Summary

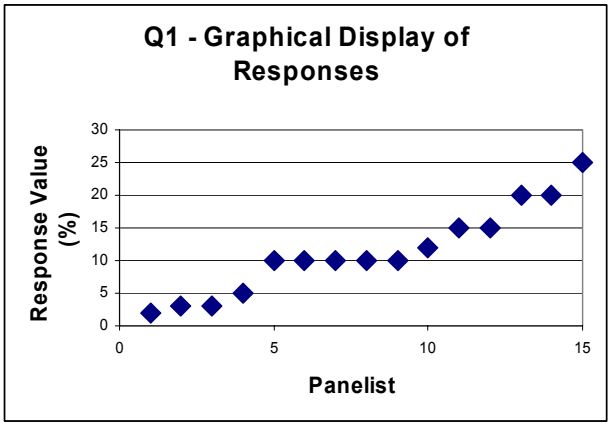
Articles cited by panelists have abstracts at the end of this summary.

Objective 1: Estimate the proportion of colorectal cancers that cannot be prevented through conventional screening (i.e. the cancers that cannot be detected because they develop from normal tissue without passing through a visible polyp intermediary).

Question: What percentage of incident colorectal cancers develop from normal tissue without passing through a visible polyp intermediary?

Response Summary:

Median Response:	Your Response:
10	20



**The graph to the left allows you to compare your response against those of the other panelists.*

Comments:

a. Cancer is the result of genetic changes with adenoma being a passer by. Some of these changes likely accelerated with little or no time spent in the adenoma stage.
b. I still believe that all colon cancers develop from an antecedant polyp whether it can be detected or not is another question. A flat adenoma even if not detected is still an adenomatous process and not "normal" tissue. But if you want to include a flat adenoma as normal tissue, then a few cancers may develop without detection of a "polyp" stage.
c. There is simply no way to know this quantitatively. The Rembacken data are a bit worrisome. In the K-P *(Kaiser Permanente)* case control study of sigmoidoscopy, why were many CRCs NOT prevented (RR reduction was about 60%); were some cancers fast-growing. In a model you will need to have a wide range in sensitivity analysis.
d. This is probably rare.
e. I have a strong belief, which is not entirely data-based, but is based upon modeling, and what I know about the biology and genetic basis of neoplasia, that no cancer ever emerges from "normal" tissue without going through an adenomatous stage. The question is phrased in a way that will confuse the answerer, because the term "polyp" is a morphological descriptor, whereas adenoma and carcinoma are pathological descriptors.
f. This is a bit confusing. I believe that the percentage of cancers arising from truly normal mucosa is less than 3-5%. However, it is possible that as many as 20% of cancers may arise from flat adenomas.

Objective 2: Genetic predisposition posed by an affected first-degree family member can be due to an increased rate of adenoma incidence or an increased progression rate from adenoma to cancer. Estimate the relative proportion of these two factors in affecting a person's underlying risk of developing cancer based on family history.

Question: For the population of people with an affected first-degree relative, what percentage of this population are at an increased risk due to each of the following:

2a. % due to ONLY an increased rate of adenoma incidence
2b. % due to ONLY an increased adenoma progression rate to cancer
2c. % due to BOTH an increased incidence rate and increased progression rate

(If allocating a portion in BOTH above, answer below)
What percentage of the "BOTH" population's increased risk for colorectal cancer is due to the following two factors?

2d. % due to an increased rate of adenoma incidence
2e. % due to an increased adenoma progression rate to cancer

Response Summary:

	Average Response:	Median Response:	Minimum Response:	Maximum Response:	Your Response:
Q2 Only Incidence	52	50	10	85	25

Q2 Only Progression	25.33333333	25	0	80	25
Q2 Both	22.66666667	20	0	50	50
Q2 Both Incidence	42.91666667	50	15	55	25
Q2 Both Progression	57.08333333	50	45	85	75

* 20% (3/15) of respondents allocated 0% to "BOTH"

Comments:

a. There is evidence to support that pts with 1st degree relatives with CRC have a higher incidence of CRC formation. Evidence also supports that early age pts with CRC have an increased rate of progression of their tumors.
b. Familiality puts people at increased risk for developing polyps. The genetics of individual polyps, as well as their background, may influence the speed of progression. However, the polyp has to form initially before progression can take place.

Objective 3: Estimate the distribution for conversion time to cancer among adenomas that are going to become cancerous.

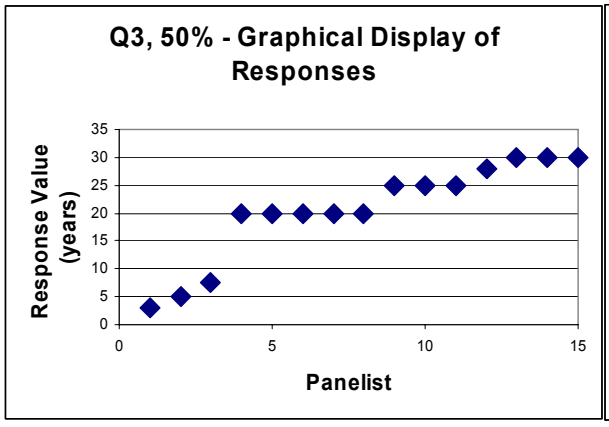
Questions:

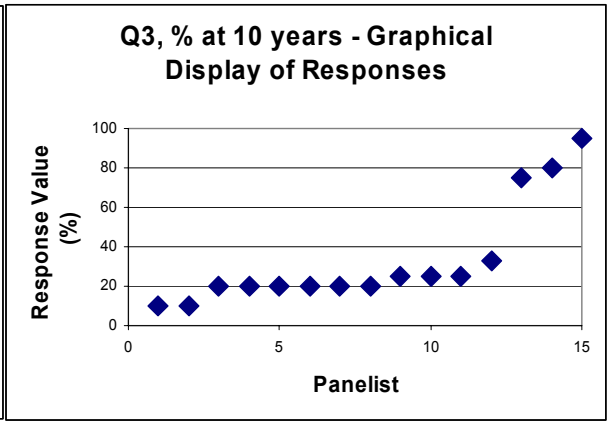
a. 50% of progressing colorectal adenomas will become cancerous by ____ years from the time of adenoma formation.
b. At 10 years from the time of adenoma formation, _____ % of progressing colorectal adenomas will become cancerous.

Response Summary:

	Median Response:	Your Response:
Q3 50%	20	5
Q3 10yrs	20	80

**The graphs below allow comparison of your response with the other panelists' responses.*





Comments:

a. I do not believe it will take an average of 30 years for polyps that are destined to become cancers to do so. Clearly not all polyps will become cancers, but those destined to do so

will usually do so within a decade. The adenoma to carcinoma sequence generally takes 7-10 years.

Objective 4: For incident cancers, estimate the distribution for the conversion time period between incident asymptomatic and symptomatic cancers.

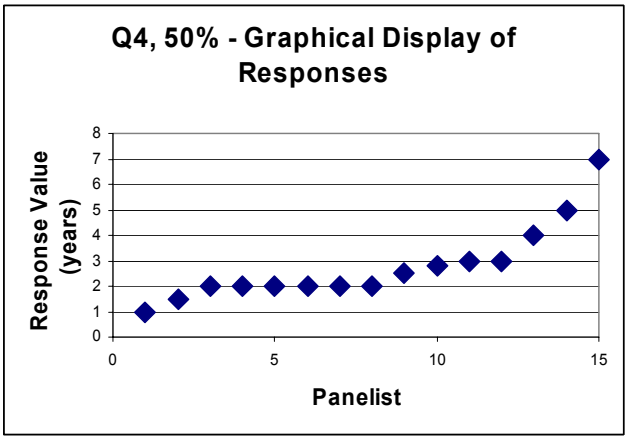
Questions:

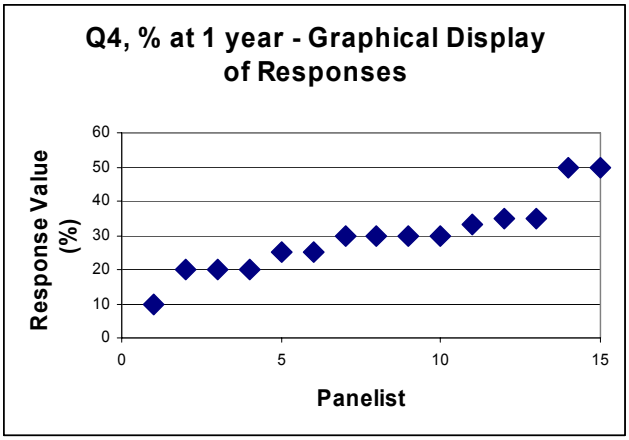
a. *50% of incident colorectal cancers will have become symptomatic by _____years.*
b. *After 1 year, _____% of incident colorectal cancers will have become symptomatic.*

Response Summary:

	Median Response:	Your Response:
Q4 50%	2	2
Q4 1yr	30	30

**The graphs below allow comparison of your response with the other panelists' responses.*





Comments:

a. In the Stryker study, many of the over-1-cm "polyps" may have already been cancer, and they "progressed" to become clinical cancer at a rate of only 1% per year. Perhaps some (many?) cancers progress slowly.

Related Articles:

Lancet 2000 Apr 8;355(9211):1211-4 Related Articles, Links

Comment in:

- Lancet. 2000 Jul 15;356(9225):255.

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Flat and depressed colonic neoplasms: a prospective study of 1000

colonoscopies in the UK.

Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM, Axon AT.

Centre for Digestive Diseases, The General Infirmary, Leeds. BJR@firstnet.co.uk

BACKGROUND: Flat and depressed colorectal tumours were originally thought to be unique to the Japanese population. Recently there have been reports of flat and depressed lesions in western countries but they have been thought to be uncommon. METHODS: In this prospective study, 1000 consecutive patients attending for routine colonoscopy were examined for flat or depressed lesions. The examinations were done by one European colonoscopist using methods developed in Japan. FINDINGS: 321 adenomas were found: 202 (63%) were polypoid, 36% (117) were flat and 2 (0.6%) appeared depressed. Most adenomas contained areas of mild or moderate dysplasia but 10% (31) were severely dysplastic. Six Dukes' A adenocarcinomas were identified together with 25 more advanced adenocarcinomas. The likelihood of Dukes' A cancer or severe dysplasia increased from 4% (3/70) in small flat lesions, to 6% (9/154) in small polyps, 16% (8/50) in larger polyps, 29% (14/49) in large flat lesions, and 75% (3/4) in depressed lesions. 54% (20/37) lesions containing severe dysplasia or Dukes' A carcinoma were flat or depressed. INTERPRETATION: The polyp-carcinoma hypothesis prompts colonoscopists to search only for polypoid lesions when screening for cancer, and many early colorectal neoplasms may therefore be missed. Colonoscopists require training in the recognition of flat and depressed lesions to detect colorectal tumours in the early stages.

PMID: 10770302 [PubMed - indexed for MEDLINE]

N Engl J Med 1992 Mar 5;326(10):653-7 Related Articles, Links

Comment in:

- N Engl J Med. 1992 Aug 6;327(6):435.
- N Engl J Med. 1992 Mar 5;326(10):700-2.

A case-control study of screening sigmoidoscopy and mortality from colorectal cancer.

Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS.

Division of Research, Kaiser Permanente Medical Care Program, Oakland, Calif.

BACKGROUND. The efficacy of sigmoidoscopic screening in reducing mortality from colorectal cancer remains uncertain. A randomized trial would be ideal for clarifying this issue but is very difficult to conduct. Case-control studies provide an alternative method of estimating the efficacy of screening sigmoidoscopy. METHODS. Using data on the 261 members of the Kaiser Permanente Medical Care Program who died of cancer of the rectum or distal colon from 1971 to 1988, we examined the use of screening by rigid sigmoidoscopy during the 10 years before the diagnosis and compared it with the use of screening in 868 control subjects matched with the case subjects for age and sex. RESULTS. Only 8.8 percent of the case subjects had undergone screening by sigmoidoscopy, as compared with 24.2 percent of the controls (matched odds ratio, 0.30; 95 percent confidence interval, 0.19 to 0.48). Adjustment for potential confounding factors increased the odds ratio to 0.41 (95 percent confidence interval, 0.25 to 0.69). The negative association was as strong when the most recent sigmoidoscopy was 9 to 10 years before diagnosis as it was when examinations were more recent. By contrast, for 268 subjects with fatal colon cancer above the reach of the sigmoidoscope and for 268 controls, the adjusted odds ratio was 0.96 (95 percent confidence interval, 0.61 to 1.50). The specificity of the negative association for cancer within the reach of the sigmoidoscope is consistent with a true efficacy of screening rather than a confounding by unmeasured selection factors. CONCLUSIONS. Screening by sigmoidoscopy can reduce mortality from cancer of the rectum and distal colon. A screening once every 10 years may be nearly as efficacious as more frequent screening.

PMID: 1736103 [PubMed - indexed for MEDLINE]

Related Articles, Links

Gastroenterology 1987 Nov;93(5):1009-13

Gastroenterology

Natural history of untreated colonic polyps.

Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL.

Section of Colon and Rectal Surgery, Mayo Clinic, Rochester, Minnesota 55905.

The natural history of untreated colonic polyps is uncertain. A retrospective review of Mayo Clinic records from a 6-yr period just before the advent of colonoscopy identified 226 patients with colonic polyps greater than or equal to 10 mm in diameter in whom periodic radiographic examination of the colon was elected over excisional therapy. In all patients, follow-up of polyps spanned at least 12 mo (mean, 68 mo; range, 12-229 mo) and included at least two barium enema examinations (mean, 5.2; range, 2-17). During the follow-up period, 83 polyps (37%) enlarged. Twenty-one invasive carcinomas were identified at the site of the index polyp at a mean follow-up of 108 mo (range, 24-225 mo). Actuarial analysis revealed that the cumulative risk of diagnosis of cancer at the polyp site at 5, 10, and 20 yr was 2.5%,

8%, and 24%, respectively. In addition, 11 invasive cancers were found at a site remote from the index polyp during the same follow-up period. These data further support the recommendation for excision of all colonic polyps greater than or equal to 10 mm in diameter. Periodic examination of the entire colon is recommended in this group of patients to identify neoplasms arising at a site remote from the index polyp. Although this study has limitations inherent to any retrospective analysis, comparable prospective data are unlikely to be available in the future because of the current widespread availability of colonoscopy.

PMID: 3653628 [PubMed - indexed for MEDLINE]

7.10 Round Three Survey

Page 1

Colorectal Cancer Health Policy Model

Thank you again for serving as an expert on this panel for developing estimates for the Colorectal Cancer Health Policy Model. This survey will be the last research survey addressing these questions, and there will be one short (<3 minute) evaluation survey to conclude this study.

You have received summaries of both your responses and the group responses and comments from ROUND TWO. Additionally, article abstracts mentioned in comments from Round Two were also sent with the summaries. With respect to this new information, please answer the questions on this survey. You may be convinced, using this new information, to revise your thinking, or you may want to provide comments to support your personal views. Some questions have very little or no data on which to base your repsonses, so please respond with your best estimate.

Your responses will be automatically collected and will remain confidential. Your identity will never be revealed or associated with your responses in any publication.

If you are having technical problems with the survey, please contact Cindy Liebsch at cmliebsch@ncsu.edu.

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Colorectal Cancer Health Policy Model

Objective 1:

What percentage of colorectal adenocarcinomas develop from adenomas that are flat, so that the adenoma itself is never polypoid (i.e. lesions that cannot be seen by standard colonoscopy)?

[ ] %

Do any colorectal cancer develop without going through an adenoma intermediary - either flat or polypoid?

[ ] Yes [ ] No

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

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Colorectal Cancer Health Policy Model

Objective 2: This question has been asked in previous rounds, and we ask that you respond with respect to the summary information provided from Round 2.

Genetic predisposition posed by an affected first-degree family member can be due to two factors:
*An increase in the rate of adenoma incidence
*An increased progression rate from adenoma to cancer.

For the population of people with an affected first-degree relative, what percentage of this population are at an increased risk due to each of the following:
In Round 2 the median responses were 50%, 25%, and 20%, respectively, and 80% of the panel allocated some portion to the "both" response. (Please note that answers must sum to 100%.)

[ ] % due to ONLY an increased rate of adenoma incidence

[ ] % due to ONLY an increased adenoma progression rate to cancer

[ ] % due to BOTH an increased incidence rate and increased progression rate

Answer the following question only if you responded a proportion GREATER THAN ZERO in the "BOTH" choice above.
What percentage of the "BOTH" population's increased risk because of an affected first-degree family member is due to the following two factors?
In Round 2 the median responses were 50% and 50%, respectively. (Please note that answers must sum to 100%.)

[ ] % due to an increased rate of adenoma incidence

[ ] % due to an increased adenoma progression rate to cancer

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please do not include identifying information.

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Colorectal Cancer Health Policy Model

Objective 3:

You received a summary of responses from Round 2 concerning the progression time from adenoma to cancer. *The median time when 50% of adenomas become cancerous was 20 years. The median percentage of adenomas that had progressed to cancer by 10 years was 20%.*

In light of this information, please evaluate the following questions considering ONLY adenomas that will progress. (While some adenomas may regress or have no chance of becoming cancer, this question deals with only those that will progress.)

50% of progressing colorectal adenomas, excluding flat adenomas, will become cancerous by _____ years from the time of adenoma formation.

At 10 years from the time of adenoma formation, _____ % of progressing colorectal adenomas, excluding flat adenomas, will become cancerous.

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

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Page 5

Colorectal Cancer Health Policy Model

Objective 4:

The median responses from Round 2 concerning the time between initial colorectal cancer formation and the occurrence of symptoms indicated that *50% of colorectal cancers will become symptomatic after 2 years, and that after 1 year 30% of cancers will become symptomatic.* With respect to this new information, please answer these questions, assuming that (1) the patient survives, (2) there is an absence of screening, and that (3) symptomatic means any symptoms leading to a diagnosis of colorectal cancer:

50% of incident colorectal cancers will have become symptomatic by [ ] years.

After 1 year, [ ] % of incident colorectal cancers will have become symptomatic.

Please provide any comments you wish to add supporting your above response. Comments will remain anonymous, so please *do not* include identifying information.

[ ]

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Page 6

Colorectal Cancer Health Policy Model

We request your email for tracking purposes only. Please be assured that your responses will remain confidential, and your responses will never be associated with your name in any publication.

email address: [ ]

Thank you for participating in this round! You will receive information about the final survey in this process, the Evaluation Survey, in several days. If you have any questions or comments concerning this survey, please contact Cindy Liebsch at cmliebsch@ncsu.edu.

Previous Page | Submit Survey (6 of 6)

7.11 Round Three Survey Results

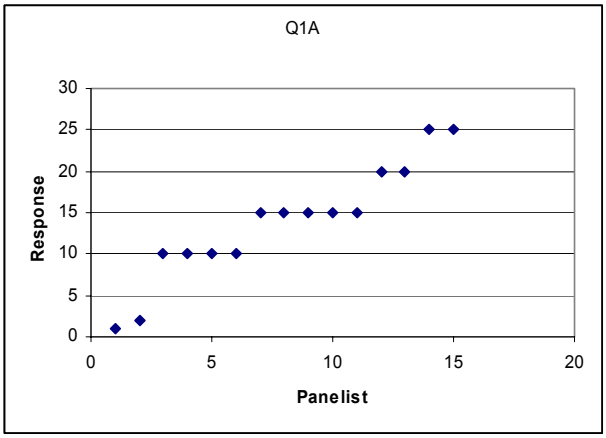
Colorectal Cancer Health Policy Model
Round Three Survey Summary

Objective 1: Estimate the proportion of colorectal cancers that cannot be prevented through conventional screening (i.e. the cancers that cannot be detected because they develop from normal tissue without passing through a visible polyp intermediary).

Question: What percentage of colorectal adenocarcinomas develop from adenomas that are flat, so that the adenoma itself is never polypoid (i.e. lesions that cannot be seen by standard colonoscopy)?

Response Summary:

Median	Mean	Min	Max
15	13.867	1	25



Question: Do any colorectal cancer develop without going through an adenoma intermediary - either flat or polypoid?

Response Summary:
*60% (9/15) responded *YES*.
*40% responded *NO*.

Comments:

a. The best evidence to answer this question comes from the Selby case-control study, in which sigmoidoscopy was associated with 60-70% reduced colorectal cancer mortality for distal cancers (within reach of the sigmoidoscopy). This was done with any exposure to rigid sigmoidoscopy--whether the prep was good or not, whether the exam was complete or not. So as many as 20-30% of lesions may not be detectable by colonoscopy. Modern day colonoscopy is done differently than the rigid sigmoidoscopy of the '70s and '80s used in the Selby study, and right sided colon cancers may have a different biology and natural history, so 25% is a reasonable guess. In reality it may be as high as 50% or as low as 5%. The proportion here will also vary depending on the age of the screening population, in ways that are also not well understood.

b. Not all cancers follow the same genetic paradigm as previously established.

c. The question is poorly constructed. Just because an adenoma is flat (not polypoid) does not mean that "lesions cannot be seen by standard colonoscopy". The lesions might be seen more easily with chromoendoscopy or magnifying endoscopy, but a careful examiner might detect them with a standard colonoscope.

d. I do believe that flat adenomas exist, but the incidence is much lower in the USA than in Japan (even considering Rembacken's data). I also believe that very few cancers arise from truly normal mucosa. Since the question was a YES/NO format, I answered NO.
e. Probably, such as in chronic ulcerative colitis. The percentage would be small in my mind.
f. The above is possible, but just not observed. Large studies, such as the National Polyp Study, simply did not find such lesions or new cancers without residual adenoma tissue. GI experience is the same. GI's screening lots of patients just don't see small cancers unless there is residual adenoma tissue. Similarly depressed lesion would either be seen, or many patients that get screening would come up with unexpected cancers if these lesions occurred with any frequency. They just don't.
g. This is opinion, but I think that in the evolution of what we know as multistep carcinogenesis, there is a benign phase. The fact that it may be very brief in the case of MSI makes this almost a semantic issue, but I think that conceptually, there is always a benign stage.

Objective 2: Genetic predisposition posed by an affected first-degree family member can be due to an increased rate of adenoma incidence or an increased progression rate from adenoma to cancer. Estimate the relative proportion of these two factors in affecting a person's underlying risk of developing cancer based on family history.

Question: For the population of people with an affected first-degree relative, what percentage of this population are at an increased risk due to each of the following:

2a. % due to ONLY an increased rate of adenoma incidence

2b. % due to ONLY an increased adenoma progression rate to cancer

2c. % due to BOTH an increased incidence rate and increased progression rate

(If allocating a portion in BOTH above, answer below)

What percentage of the "BOTH" population's increased risk for colorectal cancer is due to the following two factors?

2d. % due to an increased rate of adenoma incidence

2e. % due to an increased adenoma progression rate to cancer

Response Summary:

	Median Response:	Average Response:	Minimum Response:	Maximum Response:
Q2 Only Incidence	50	54	25	85
Q2 Only Progression	25	22.14286	0	50
Q2 Both	25	25.33333	0	55
Q2 Both Incidence	50	49.64286	25	80
Q2 Both Progression	50	50.35714	20	75

* 6.6%% (1/15) of respondents allocated 0% to "BOTH"

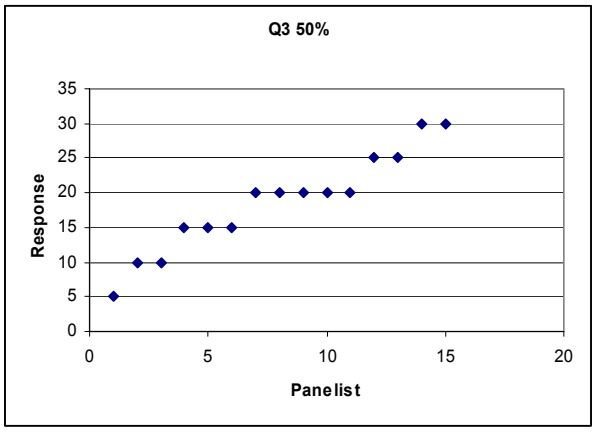
Comments:

a. I don't know of any data that can guide this estimate, so I conclude we are only guessing.
b. Using HNPCC as an example of hereditary colon cancer syndrome, I believe both the rate of incidence and progression are increased due to the genetic changes.
c. The population of people who fall into this group is likely to be very heterogeneous, and currently there is very little clinical trial data to base answers on. The key pieces of missing data here are studies that use colonoscopy in common familial colon cancer patients and assess whether the polyps do start earlier, occur in higher number, and/or progress more rapidly.
d. Again, just guessing. I would like to have data.

Objective 3: Estimate the distribution for conversion time to cancer among adenomas that are going to become cancerous.

Questions:

a. *50% of progressing colorectal adenomas will become cancerous by ____ years from the time of adenoma formation.*
b. *At 10 years from the time of adenoma formation, _____ % of progressing colorectal adenomas will become cancerous.*

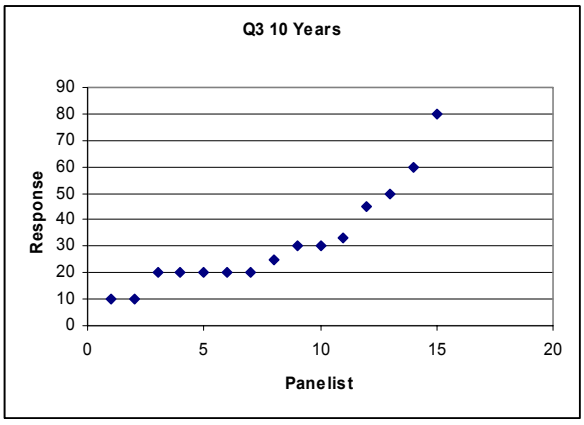


Response Summary:

	Mean	Median	Min	Max
Q3 50%	20	18.66667	5	30
Q3 10yrs	25	31.53333	10	80

Comments:

a. With respect to the first item, I differ from the group's summary response. I believe that for adenomas which are progressing (i.e. destined to become cancerous), it should not take as long as 20 years to do so. I also feel that for adenomas that are destined to become cancerous, most should do so by 10 years.



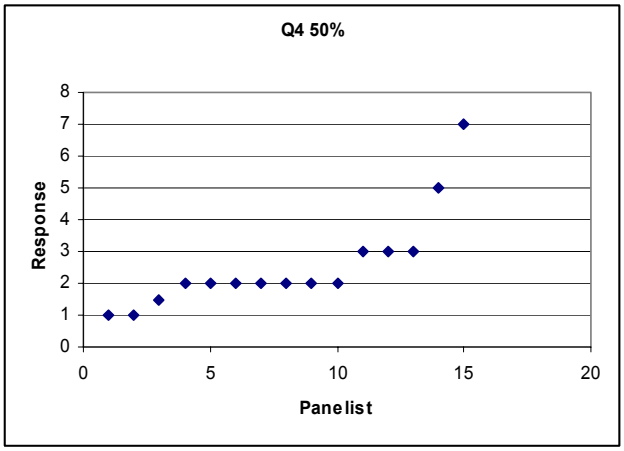
Objective 4: For incident cancers, estimate the distribution for the conversion time period between incident asymptomatic and symptomatic cancers.

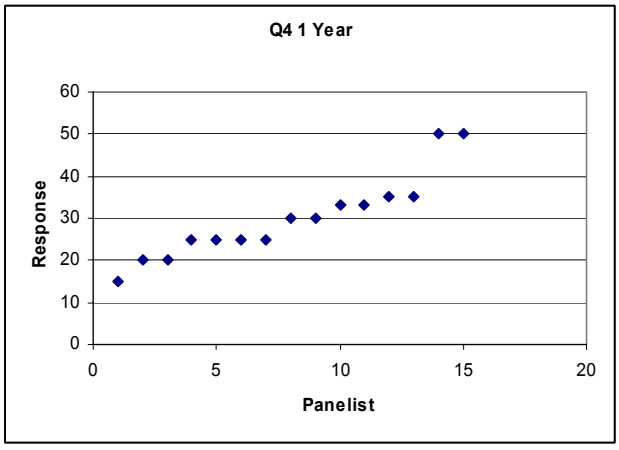
Questions:

a. *50% of incident colorectal cancers will have become symptomatic by _____years.*
b. *After 1 year, _____% of incident colorectal cancers will have become symptomatic.*

Response Summary:

	Median	Mean	Min	Max
Q4 50%	2	2.566667	1	7
Q4 1yr	30	30.06667	15	50





7.12 Raw Data From Surveys, Paired by Panelist

	Round 1					Round 2				
	Mean	**Median**	**Min**	**Max**	**StDev**	**Mean**	**Median**	**Min**	**Max**	**StDev**
Q1	10.40%	10	0	25	8.49	11.333	10	2	25	6.76
	Mean	**Median**	**Min**	**Max**	**StDev**	**Mean**	**Median**	**Min**	**Max**	**StDev**
Q2 Only Incidence	50.78%	47.5	0	100	32.76	52	50	10	85	23.81
Q2 Only Progression	22.39%	20	0	90	21.85	25.333	25	0	80	17.06
Q2 Both	26.83%	22.5	0	100	26.93	22.667	20	0	50	18.41
Q2 Both Incidence	50.69%	50	1	80	18.87	42.917	50	15	55	14.05
Q2 Both Progression	49.31%	50	20	99	18.87	57.083	50	45	85	14.05
	Mean	**Median**	**Min**	**Max**	**StDev**	**Mean**	**Median**	**Min**	**Max**	**StDev**
Q3 50%	31.78	22.2222	6.3	70	25.50	20.567	20	3	30	26.83
Q3 10yrs	23%	12.5	0	80	22.58	33.2	20	10	95	8.88
	Mean	**Median**	**Min**	**Max**	**StDev**	**Mean**	**Median**	**Min**	**Max**	**StDev**
Q4 50%	2.66	2.25	1	5.5	12.72	2.787	2	1	7	10.71
Q4 1yr	21%	20	2	50	1.33	29.533	30	10	50	1.53

	Round 3				
	Mean	**Median**	**Min**	**Max**	**StDev**
Q1	13.867	15	1	25	7.05
	Mean	**Median**	**Min**	**Max**	**StDev**
Q2 Only Incidence	54	50	25	85	22.30
Q2 Only Progression	22.143	25	0	50	10.69
Q2 Both	25.333	25	0	55	18.27
Q2 Both Incidence	49.643	50	25	80	14.07
Q2 Both Progression	50.357	50	20	75	14.07
	Mean	**Median**	**Min**	**Max**	**StDev**
Q3 50%	18.667	20	5	30	19.50
Q3 10yrs	31.533	25	10	80	7.19
	Mean	**Median**	**Min**	**Max**	**StDev**
Q4 50%	2.567	2	1	7	9.97
Q4 1yr	30.067	30	15	50	1.57

	Panelist 1			Panelist 2			Panelist 3			Panelist 4			Panelist 5			Panelist 6		
	R1	**R2**	**R3**	**R1**	**R2**	**R3**	**R1**	**R2**	**R3**	**R1**	**R2**	**R3**	**R1**	**R2**	**R3**	**R1**	**R2**	**R3**
Q1	25	15		25	25		10	12		20	20		15	2		20	15	
Q2 Only Incidence	25	25	25	34	50	50	45	45	45	20	50	50	85	85	85	60	60	60
Q2 Only Progression	25	25	25	33	25	25	25	25		20	20	20	0	0	0	20	30	25
Q2 Both	50	50	50	33	25	25	30	30	55	60	30	30	15	15	15	20	10	15
Q2 Both Incidence	50	50	50	50	50	50	45	55	45	50	50	50	1	20	25	50	50	50
Q2 Both Progression	50	50	50	50	50	50	55	45	55	50	50	50	99	80	75	50	50	50
Q3 50%	20	20	20	20	25	20	26.7	28	25	70	20	30	24.4	25	20	6.7	30	20
Q3 10yrs	10	33	33	25	20	20	15	25	45	0	20	20	10	20	20	75	20	20
Q4 50%	3	2.5	2	2	5	2	4.75	2.8	5	5.5	7	7	1.33	2	2	2.67	4	3
Q4 1yr	10	50	33	25	20	30	3	25	25	2	10	15	35	35	35	15	20	25

	Panelist 7			Panelist 8			Panelist 9			Panelist 10			Panelist 11			Panelist 12		
	R1	R2	R3	R1	R2	R3	R1	R2	R3	R1	R2		R1	R2		R1	R2	
Q1	2	10		20	20		10	10		0	10		10	10		5	5	
Q2 Only Incidence	100	65	65	50	25	25	5	10	25	0	25	25	85	60	60	25	40	50
Q2 Only Progression	0	35	25	25	25	25	90	80	50	0	25	25	10	20	20	50	20	25
Q2 Both	0	0	10	25	50	50	5	10	25	100	50	50	5	20	20	25	40	25
Q2 Both Incidence			50	50	25	50	50	15	25	50	50	50	80	50	50	25	50	50
Q2 Both Progression			50	50	75	50	50	85	75	50	50	50	20	50	50	75	50	50
Q3 50%	8.3	3	5	50	5	20	46.7	20	15	6.25	8	10	16	25	25	67	20	15
Q3 10yrs	60	95	80	20	80	25	5	25	20	80	75	60	5	20	30	0	20	10
Q4 50%	1.5	2	2	2	2	2	2	2	2	1	2	2	2	3	3	2	3	2
Q4 1yr	30	35	35	30	30	25	25	30	25	50	33	33	30	20	20	20	30	30

	Panelist 13			Panelist 14			Panelist 15		
	R1	R2		R1	R2	R3	R1	R2	R3
Q1	3	3		2	3		0	10	
Q2 Only Incidence	80	75	80	80	80	80	85	85	85
Q2 Only Progression	15	15	15	15	20	15	15	15	15
Q2 Both	5	10	5	5	0	5	0	0	0
Q2 Both Incidence	50	50	70	60		80			
Q2 Both Progression	50	50	30	40		20			
Q3 50%	30	30	30	60	20	15	20	30	10
Q3 10yrs	10	10	10	5	25	30	15	10	50
Q4 50%	3	2	3	4	2	1	2	1	1
Q4 1yr	10	30	20	20	25	50	10	50	50

7.13 Evaluation Survey for Expert Panelists

Dear Panelist,
Those of us working on the Colorectal Cancer Health Policy Model are very grateful for the information you provided over the past 3 rounds of surveys to allow us to create inputs for our computer simulation model studying colorectal cancer. As a last step in this process, we would like to evaluate the *process* used to create these inputs, namely the usefulness and applicability of these iterative surveying rounds. The final survey, which will take no more than 5 minutes of your time, can be found at the following web address:

http://websurveyor.net/wsb.dll/11926/PanelistEvaluationSurvey.htm

Upon completion of this evaluation survey, you will receive $300 compensation for your participation in this study. For your reference, the inputs developed as a result of this surveying are given below.

Objective 1: Estimate the proportion of colorectal cancers that cannot be prevented through conventional screening (i.e. the cancers that cannot be detected because they develop from normal tissue without passing through a visible polyp intermediary).

> ***13.867%*** *of colorectal cancers cannot be prevented through traditional screening because they develop from flat adenomas that are never polypoid and thus cannot be seen by a standard colonoscopy.*

Objective 2: Genetic predisposition posed by an affected first-degree family member can be due to an increased rate of adenoma incidence or an increased progression rate from adenoma to cancer. Estimate the relative proportion of these two factors in affecting a person's underlying risk of developing cancer based on family history.

> ***50%*** *are only affected by an increased rate of adenoma incidence,* ***25%*** *are only affected by an increased progression rate from adenoma to cancer, and* ***25%*** *are affected by BOTH an increased incidence rate and an increased progression rate at* ***equal rates (50%*** *due to an increased incidence rate and* ***50%*** *due to an increased progression rate).*

Objective 3: Estimate the distribution for conversion time to cancer among adenomas that are going to become cancerous.

> *50% of progressing adenomas will become cancerous after* ***20 years****. At 10 years,* ***20%*** *of progressing adenomas will become cancerous. (These percentile points will be used to develop a Johnson SB distribution using the VisiFit distribution fitting software, and this distribution will be used in the simulation model.)*

Objective 4: For incident cancers, estimate the distribution for the conversion time period between incident asymptomatic and symptomatic cancers.

> *50% of incident colorectal cancers will become symptomatic after* ***2.567 years****. After 1 year,* ***30%*** *of incident colorectal cancers will become symptomatic. (Similar to Objective Three, these percentile points will be used to develop a Johnson SB distribution using the VisiFit distribution fitting software, and this distribution will be used in the simulation model.)*

Thank you again for the time and expertise you provided to this study!

Sincerely,
Dr. Reid Ness

Colorectal Cancer Simulation Study - Process Evaluation

Thank you again for participating in the expert panel for developing input estimates for the colorectal cancer simulation study. We would like to get your opinions, observations, and comments on the process used to develop these estimates.

---

1) Please provide your opinions to the following statements about the FLEXIBILITY of this process.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1.1) I would have participated in this process even if I would have had to travel to meet with the group.	☐	☐	☐	☐	☐
1.2) Face-to-face time with the other panelists would have been beneficial in generating responses.	☐	☐	☐	☐	☐
1.3) The web surveys were easy to use and convenient.	☐	☐	☐	☐	☐
1.4) I felt that I was easily able to share my beliefs and opinions through the web surveys.	☐	☐	☐	☐	☐

2) Please provide your opinions to the following statements about the GROUP DYNAMICS during this process.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
2.1) I felt strong pressure to change my answers and to follow the group's thoughts.	☐	☐	☐	☐	☐
2.2) I felt one (or several) member(s) of the group dominated the sharing of information.	☐	☐	☐	☐	☐

3) Please provide your opinions to the following statements about the ACCEPTABILITY of this process.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

3.1) The group process allowed increased understanding in the group.					
3.2) The group process allowed increased understanding of the subject area for me personally.					
3.3) Better estimates were developed using this formal process rather than an informal group meeting.					
3.4) Better estimates were developed using this group process than what I could have developed on my own.					

4) Please provide your opinions to the following statements about INFORMATION AWARENESS during this process.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
4.1) I had ample information about the process used to develop the estimates.					
4.2) The information provided between rounds was useful and relevant.					
4.3) The information provided between rounds influenced my responses.					

5) Please answer yes or no to the following GENERAL questions:

	Yes	No
Have you ever participated in a group process similar to this?		
If asked, would you participate in a process like this again?		
Do you feel the $300 compensation is adequate?		

6) Please provide any comments or suggestions you have about the process.

7) You will be compensated $300 for your participation in this survey. To issue you the check, we must collect some personal information from you. This information will be separated from your responses and will remain strictly confidential.

Social Security Number:
Format: 999-99-9999

Name:

Address 1:

Address 2:

City, State, Zip Code

Submit Survey (1 of 1)

7.14 Results of Evaluation Survey for Expert Panelists

KEY:
SA = Strongly Agree
A = Agree
N = Neutral
D = Disagree
SD = Strongly Disagree

FLEXIBILITY															
I would have participated in this process even if I would have had to travel to meet with the group.	D	A	D	SD	N	N	D	D	N	D	D	A	N	A	A
Face-to-face time with the other panelists would have been beneficial in generating responses.	N	A	A	A	N	A	N	A	SA	SA	A	SA	A	N	A
The web surveys were easy to use and convenient.	SA	A	A	A	A	N	A	SA	N	SA	D	N	SA	A	SA
I felt that I was easily able to share my beliefs and opinions through the web surveys.	SA	A	A	A	A	N	A	SA	D	A	A	D	A	A	N
GROUP DYNAMIC															
I felt strong pressure to change my answers and to follow the group's thoughts.	A	D	D	D	D	N	D	D	A	D	D	D	A	SD	N
I felt one (or several) member(s) of the group dominated the sharing of information.	D	D	D	D	D	D	D	D	D	SD	D	SD	N	SD	D
ACCEPTABILITY															
The group process allowed other group members to understand my beliefs about the questions asked.	A	N	A	A	N	N	A	A	D	D	A	D	A	A	D
The group process allowed increased understanding of the subject area for me personally.	SA	A	D	N	A	A	A	A	N	D	N	A	N	A	N
Better estimates were developed using this formal process rather than an informal group meeting.	A	N	D	D	A	D	A	N	SD	N	D	A	N	A	N
Better estimates were developed using this group process than what I could have developed on my own.	A	A	D	A	A	N	A	A	SD	N	N	A	N	A	A

INFORMATION AWARENESS															
I was provided enough information to clearly understand the goals and objectives of the survey process.	A	A	A	A	N	A	A	A	D	N	D	N	A	SA	N
The information provided between rounds was useful and relevant.	N	A	A	A	A	N	A	A	D	A	A	A	A	A	A
The information provided between rounds influenced my responses.	A	A	D	A	A	N	A	A	N	N	N	A	A	N	A
GENERAL															
Participated Before	No	No	No	Yes	No	No	Yes	No	Yes	No	No	No	No	Yes	No
Participate again	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adequate Compensation	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

Comments:

a. The answers to the issues discussed are really science based, although not completely known. Collecting opinions is interesting in reviewing how others feel about the questions, but gives no information or comfort as to what the real answers are. When data are lacking, opinion dominates, but is not necessarily correct.
b. I have a problem with the fundamental premise of the whole thing. For many of these items there is no information. So the estimates are just a guess. Sharing information between rounds does not make the information better it just reduces the standard deviation.
c. Undue importance should not be attributed to the group guesses of "experts" on subjects for which scientifically validated data are lacking.
d. Face to face discussion of details, and about what the information will be used for, would be useful. I wonder if the 'precision' arrived at may be a bit artificial.
e. I was unaware of the compensation when I started. I did it just to help out, but it is nice that you have done this. I didn't feel any pressure to modify my answers, since the feedback was pretty much limited to the estimates that the others made. It may have been more useful if others had actually given rationale; that would have made a face-to-face meeting more useful. But, the bottom line is that I don't care what the estimates are, I much prefer data, and I will stick to my idiosyncratic estimates until I see real data. Good luck.
f. This was an interesting exercise, but I found the first round of questions to be somewhat confusing. This was improved somewhat with the additional rounds.
g. Please keep the $300 for study costs.

7.15 Evaluation Survey for Advisory Board

Dear Advisory Board Members,

As part of the Colorectal Cancer Simulation Project whose goal is to produce a Colorectal Health Policy Model, we recently conducted a study to develop inputs for the simulation model in areas where the data are absent or sparse. The four model inputs examined were as follows:

1. If all colorectal cancers develop from preexisting adenomas, what proportion fail to pass through a visible polyp intermediary (i.e. cannot be detected by standard endoscopy)?

2. The genetic predisposition posed by an affected first-degree family member can be due to an increased rate of adenoma incidence, an increased progression rate from adenoma to cancer or some combination of the two. Estimate the relative proportion of these two factors in affecting a person's underlying risk of developing cancer based on family history.

3. Estimate the mean conversion time to colorectal cancer among adenomas that will become cancerous (given sufficient lifespan). Also, estimate what percentage of these adenomas will have converted to colorectal cancer by 10 years.

4. Estimate the mean conversion time from asymptomatic to symptomatic colorectal cancer among all incident colorectal cancers (given sufficient lifespan). Also, estimate what percentage of these adenomas will have converted from asymptomatic to symptomatic over 1 year.

A modified Delphi process was used to elicit opinions and beliefs from 15 experts in the areas of molecular biology, epidemiology, and gastroenterology. The process occurred in three rounds, with a growing consensus regarding the input characteristics as the process progressed and more information became available through questions and comments. In the first round, participants responded to a web-based survey asking initial questions about each of the objectives stated above. Their responses and comments were summarized and returned to them. In light of the new information, the panelists responded to a second web-based survey. Again, their responses and comments were summarized and returned to the panelists, and a third and final survey was distributed to develop the final model inputs. Given the information gained from this group process, the following simulation model inputs have been developed:

*1. **13.867%** of colorectal cancers cannot be prevented through traditional screening because they develop from flat adenomas that are never polypoid and thus cannot be seen by a standard colonoscopy.*

*2. For the population of people with an affected first-degree relative, **50%** are only affected by an increased rate of adenoma incidence only, **25%** are only affected by an increased*

*progression rate from adenoma to cancer only, and **25%** are affected by BOTH an increased incidence rate and an increased progression rate at **equal rates (50%** due to an increased incidence rate and **50%** due to an increased progression rate).*

*3. **50%** of progressing adenomas will become cancerous within **20 years**. At 10 years, **20%** of progressing adenomas will have become cancerous. (These percentile points will be used to develop a Johnson SB distribution using the VisiFit distribution fitting software, and this distribution will be used in the simulation model.)*

*4. **50%** of incident colorectal cancers will become symptomatic within **2.567 years**. After 1 year, **30%** of incident colorectal cancers will have become symptomatic. (Similar to Objective Three, these percentile points will be used to develop a Johnson SB distribution using the VisiFit distribution fitting software, and this distribution will be used in the simulation model.)*

The formation of these inputs is significant because either little or no direct scientific data are available to support their development in traditional avenues, such as data analysis or experimentation. Furthermore, the level of expertise within this participant panel was profound.

As a member of the advisory board for the study project entitled "Simulation Modeling of Colorectal Cancer", we would ask that you could give *5 minutes* of your time to evaluate this methodology using a web-based survey. The link for the survey is:

http://websurveyor.net/wsb.dll/11927/AdvisoryBoardEvaluationSurvey.htm

An example copy of the summary sheet sent to the expert panel members between rounds two and three is also attached for your perusal.

Thank you for your continued support during this project.

Sincerely,

Dr. Reid Ness

Colorectal Cancer Health Policy Model - Process Evaluation

The following survey will ask you general questions about the development of model inputs for the Colorectal Cancer Health Policy Model. Your responses will be used to evaluate the *formal group process* used to develop these inputs. Your responses will be kept confidential.

---

1) Please provide your opinions to the following statements about the formal group process used to develop inputs for the Colorectal Cancer Health Policy Model.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1.1) The inputs developed using this process are useful in the CRC Health Policy Model.	☐	☐	☐	☐	☐
1.2) The inputs developed using this process are valid.	☐	☐	☐	☐	☐
1.3) The final inputs developed seem to fit my idea of the "real world".	☐	☐	☐	☐	☐
1.4) The outcomes of the process seemed to be an improvement over what could have been developed by one person.	☐	☐	☐	☐	☐
1.5) The outcomes of the process seemed to be better than what could have been developed in an informal group meeting.	☐	☐	☐	☐	☐
1.6) The process was conducted solely in the realm of cyber-space. The use of internet technologies allowed the study to be more successful by eliminating the need for participants to travel.	☐	☐	☐	☐	☐
1.7) The process is a reasonable way to develop simulation model inputs when data are scarce.	☐	☐	☐	☐	☐
1.8) The process cost $147 to conduct the surveys and $4500 to pay the panelists. This was a reasonable cost for developing these simulation model inputs.	☐	☐	☐	☐	☐

2) Please provide any comments or suggestions you have about the process.

Submit Survey (1 of 1)

This survey was created with WebSurveyor

7.16 Results of Evaluation Survey for Advisory Board

Raw Data:

	Strongly Agree	Agree	Neutral	Raw Data					
The inputs developed using this process are useful in the CRC Health Policy Model.	2	4	0	A	SA	A	A	A	SA
The inputs developed using this process are valid.	0	2	4	N	N	N	N	A	A
The final inputs developed are similar to what I believe are the true values.	0	2	3	N		N	A	A	N
The outcomes of the process seemed to be an improvement over what could have been developed by one person.	3	2	1	SA	SA	N	A	SA	A
The outcomes of the process seemed to be better than what could have been developed in an informal group meeting.	2	3	1	A	SA	A	N	SA	A
The process was conducted solely using internet technologies, and therefore it led to an increased participation rate among the experts (i.e. because it eliminates the need for travel).	3	2	1	N	A	SA	A	SA	SA
The process is a reasonable way to develop simulation model inputs when data are scarce.	2	2	2	SA	SA	N	A	N	A
The process cost $147 to conduct the surveys and $4500 to pay the panelists. This was a reasonable cost for developing these simulation model inputs.	2	3	1	SA	SA	A	A	N	A

Comments:

a. It seems to me that evaluation question 1.6 is a matter reasonably more subject to data than opinion. The question that gets substituted in my mind is "would I be more likely to participate if it is web-based versus mail-out?" Regarding the process and the resulting estimates themselves, I wonder whether it has come to a conclusion too soon. What provokes this thought is the comments. It appears that several experts felt the *model* of the process they were asked to provide parameters for was wrong in that they just did not believe cancer could develop from normal tissue without going through

the adenomatous phase. I wonder if clarifying this further and perhaps changing the questions/model some might accommodate this (clarifying, for instance, that the critical thing was ability to be detected and not necessarily the transition from normal to cancer directly? Several groups have been fitting transition models to CRC data. How well do the results of the Delphi survey correspond to sojourn times estimated by these more traditional methods?

b. The process is often used in the greater quality of care arena and works pretty well. I couldn't answer some of the questions because I am not familiar enough with cholorectal epidemiology--I am a non physician and non epidemiologist.