Clinical Results Using Informatics to Evaluate Hereditary Cancer Risk

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A 12-year medical informatics project is described whose goal was to create a distributable computer-based service to support the identification of hereditary cancer patterns and recommend concomitant protocols of patient care surveillance. Key elements of the successful implementation strategy are described as the service has been successfully utilized at more than a dozen other cancer centers. Multi-year clinical results are presented from the implementation of this service.

INTRODUCTION

Recognition of the expanded role of heredity in cancer has increased steadily over time.[1-3] For example, it is estimated that approximately 9% of carcinoma of the breast is consistent with hereditary breast cancer, and an additional 15-20% will be clearly familial.[4] In addition, the potential for gene testing to confirm hereditary cancer has escalated in recent years, with the discovery of genes that cause breast cancer, colon cancer, and several other cancer syndromes. However mass testing of the population with dozens of extremely expensive gene tests is not viable. The most effective way to identify hereditary cancer families has been with a detailed and accurate cancer family tree.[5] From such a family tree, the patterns of hereditary cancer can be detected by expert clinical oncologists. Subsequently proper surveillance and management may then be ascertained in concert with judicious gene testing, if and when available, to confirm the risk evaluation. Unfortunately physicians generally do not take a detailed cancer family history. One study found that in most cases, "the family history of cancer had either been omitted altogether or reported as negative, despite substantial evidence to the contrary.[6] Documentation of the failure to apply proper genetic principles or to obtain necessary family cancer histories has been repeatedly obtained.[7-8]

METHODS

Background

The Hereditary Cancer Institute (HCI) at Creighton University's School of Medicine analyzes cancer family histories from individual patients obtained through physician referrals or client-initiated contacts in the USA and sites world-wide (e.g., Italy, Sweden, Israel, Japan, Germany, etc.). Hereditary cancer pattern recognition can be quite challenging, given that there are now over 200 types of hereditary cancer, the family history relayed from the patient can be "fuzzy" and imprecise, and the variation in the patterns may have billions of different presentations. With over 100,000 individuals reviewed during the last 30 years, HCI has aggregated what is believed to be the world's largest database of hereditary, familial, and sporadic cancer cases. Unfortunately patient analysis by HCI is labor-intensive, costly per patient, and is limited by the availability of HCI staffing and its serendipitous contact with other oncologists. Thus we undertook the development of an *informatics-based* approach that could distribute the services of HCI by (1) significantly automating as much as possible the risk evaluation process, (2) increasing its range of availability, (3) reducing the cost to provide the analysis, while (4) evaluating a much larger number of individuals in a shorter period of time.

The HCCS Service

To address this problem, the entire HCI process was analyzed and codified so that the constituent processing steps were explicitly articulated. The results of our efforts is the Hereditary Cancer Consulting Service (HCCS) which provides a service regarding hereditary cancer risk assessment, surveillance, and management for the spectrum of over 200 hereditary cancers. This multi-million dollar 12-year developmental effort required over seventeen person years of effort and has been evaluated in over a dozen individual clinical settings in the USA. A client (i.e., any concerned individual with a cancer family history) may learn of the service from the advertising a cancer center undertakes regarding available community risk assessment programs. Based on their own self-selection, clients call to participate in the screening. Alternatively some cancer centers present the screening program to affiliated physicians, encouraging them to refer a patient if they determine there is a basis of concern that the client might be at elevated risk. With either strategy, there is a selection bias. Only motivated clients take the initiative to use the service.

Clients are given an initial 10-question screen to identify suitable candidates for further cancer history-taking. These questions may be answered on a computer or by paper and graded by hand. If a full history is needed, the HCCS computer-guided history-taking process is broad enough to capture data that would indicate hereditary patterns but is constrained enough to be practical, time-

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limited, and commensurate with most clients' knowledge about their family histories. The entire interview process at a site takes approximately 45 minutes and is accomplished by an on-site nurse in conjunction with the client. All the information is then integrated into a cancer family tree for quick and accurate evaluation. An example of a typical computer-generated tree is given in Figure 1. The collected history and cancer family tree are automatically telecommunicated back to HCI for review.

An artificial-intelligence-based approach was developed to rapidly and accurately identify all but the most obscure, new, or extremely subtle cancer patterns and to correlate these patterns to "previously solved problems" (that is, patterns which HCI had already recognized as hereditary, familial, or sporadic for that combination of cancers). We created an expert rule-based system that modelled the pattern recognition capabilities of Dr. Lynch and his HCI colleagues. The expert system makes a preliminary evaluation of the risk assessment and then uses this assessment to correlate cancer risk management protocols corresponding to the mix of cancer patterns and conditions presented by the client. All the computer-based responses are reviewed by professional health care personnel to insure that no medical evaluations are conveyed (whether involving no risk or the highest risks) without a prior ***human*** review and confirmation. Hence users of the service are assured that no assessment is made strictly by a computer, reducing any heightened anxiety such machine dependence might entail for some. This ***man-machine*** strategy successfully obviated the reluctance physicians might otherwise have exhibited if an exclusively computer-based strategy were provided.

Information and report summary software integrates all pertinent information which is conveyed by the site coordinator to the client. Several key aspects of the implementation strategy are noted. First, the clients' surveillance and management protocols are provided as recommendations, to be reviewed and discussed by the clients and their physicians, recognizing the patients' physicians as the integrator of all the information. HCI (through the commercial arm that provides the service)[9] returns the evaluation to the sites providing the service to the clients, so that there is no prospect for the service coming between the physician providers and their clients.

Second, a personal letter is developed for the client, recounting all the specific cancer family history information the client provided, and summarizing the results of the assessment for the client. If the client has provided the name of his or her own physician, (and consented to have the information sent), a copy of all results are also sent to the client's physician, along with a very telegraphic Physician's Executive Summary of the analysis. All pertinent protocols of surveillance and American Cancer Society guidelines are included. All materials are mailed to the site for re-distribution to the client (and any specified physician(s) as noted above). If the evaluation uncovers a hereditary or putative hereditary cancer pattern based on the information provided, a one-on-one counseling session with a genetic counselor is arranged for the client.

RESULTS

To present statistics most representative of current experiences, we focused on results of the past few years, particularly sites on the west coast and in the southwest, at medium and large clinical cancer centers as typical implementation examples. Some sites primarily relied on advertisements and concomitant patients' self-selection to be assessed. Other sites primarily relied on physicians' referrals where physicians determined there might be a hereditary pattern. In this report, we shall give a composite picture by pooling results over multiple client identification strategies to present a picture of what a typical multi-level approach might yield. To represent up-to-date results, we elected to examine the last 300 consecutive presenting cases irrespective of which site they represented or the client selection strategy that brought them to that site. It is imperative that one recalls a key selection factor in this patient cohort, namely most of the patients using the service were ones positive for family histories of cancer.

Results in Table 1 summarize those who presented with high risk (hereditary patterns in which the individual may be at approximately 50% risk for a specific cancer over their lifetime) and elevated risk (familial patterns in which the individual has a higher risk than the general population such as familial breast cancer where there risk may approach 25% over their life times).

Table 1. Site Results of 300 Consecutive Cases

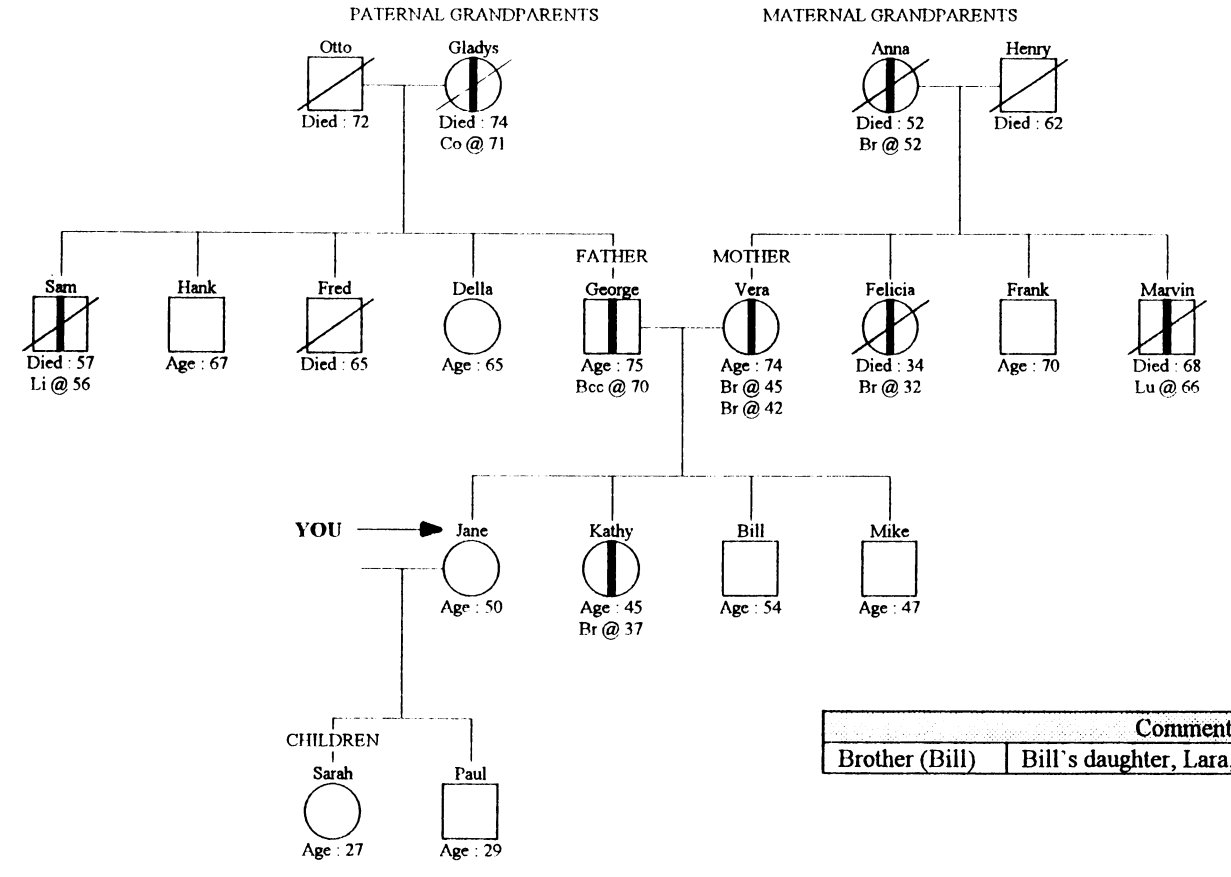
Findings and Characteristics	# of Cases
Hereditary Breast & Breast-Ovarian Risk	68
Other Hereditary Cancer Risks	16
Familial (non-hereditary) risks	165
No elevated risk	51
Women (men)	237 (63)
Clients under 40 years old	102
Clients between 40 and 50 years old	99
Clients 50 years old or older	99

Doe, Jane
123-45-6789
Thursday 7/28/94
Interviewed by John Doe

The Hereditary Cancer Consulting Service

Provided by Mercy General

Explanation of Abbreviations	
Bcc	Basal Cell Carcinoma
Br	Breast Cancer
Co	Colon Cancer
Li	Liver Cancer
Lu	Lung Cancer



Comments	
Brother (Bill)	Bill's daughter, Lara, had breast cancer at age 30

Figure 1: Computer-Display of a Hypothetical Cancer Family Tree

DISCUSSION

Among the 300 cases, 28% had confirmed hereditary cancer history patterns (this is approximately an order of magnitude greater than would otherwise be expected) while another 55% had validated familial (elevated risk) cancer histories. Thus 83% or five of every six participants benefitted from the assessment provided. Clients who come but who have no significant cancer family histories (17%) may also benefit since their anxieties are usually reduced by learning from an independent, reliable source that there is no known cancer pattern associated with their particular constellation of cancers in their families. These clients with no significant cancer family histories are also advised of screening recommendations based upon general population risks as provided by the American Cancer Society.

A significantly larger proportion of clients were women (79%). Not surprisingly, the predominant hereditary cancer identified in the 300 cases was breast cancer or breast-ovarian cancer (81%). Heavy participation by women has consistently been the case for reasons one may easily speculate. The extensive publicity about breast cancer, its continued increase in frequency (now one in eight women), and the prospects for gene testing for the newly discovered BRCA1 and BRCA2 genes associated with hereditary breast and breast-ovarian cancers. As gene testing becomes widely available (although this is decidedly not the case at this time), the interest in such risk assessment such as this service provides can be predicted to increase significantly.

In terms of ages, 34% of clients were under 40 years old, 33% were between 40 and 50, and 33% were 50 or older. Since approximately 43% of breast cancer among those with the inherited BRCA1 hereditary breast cancer gene is expressed between the ages of 40 and 50, there are thus excellent opportunities among the at-risk cohorts utilizing the service to discover breast cancer through intense surveillance while it may be at its earliest stages, hence potentially permitting statistically much higher rates of cure at lower cost. In addition, without a family history, there is little justification to undertake the substantial expense of gene testing. With a hereditary cancer family history, it will hardly be prudent not to offer the prospects for gene testing once this actually can be made available (with tightly coupled genetic counseling and carefully accomplished informed consent) if the client wishes to undergo such testing.

From a cost point of view, our initial goal was to be able to provide this service at approximately 10% of what we estimated a client would easily spend on a similar personal consultation with a genetic oncologist. We have made substantial progress toward accomplishing this goal through the incorporation of informatics approaches (expert systems, neural nets, and data mining combined with automated administrative processing). We have expedited the experts' decision-making process by partitioning the cases into easily addressed, fully "solved" cases for which all recommendations have been formulated and prepared. With typically more than 98% fidelity of pre-processing of cases with informatics tools, expert medical reviewers can then in approximately a minute or less confirm the "draft" recommendations for a particular client. Total processing time between the onset of the project 12 years ago to today has yielded nearly two orders of magnitude reduction in the total case processing time.

As one of many benefits to a cancer center and its clients, the risk management recommendations provided by the service help insure that there is neither an excess in unnecessary risk management (e.g., unwarranted hysterectomies) nor mismanagement of increased cancer risk (e.g., use of flexible sigmoidoscopy when a colonoscopy is necessary). The prospects for early detection and hence much lower intervention costs with concomitantly significantly higher cure rates are consistent with the cost control policies for health care. This systematic capture and analysis of cancer family histories minimize omissions of preventive surveillance or early detection evaluations, which can reduce the potential for future patient-physician legal confrontations. Finally, with the forthcoming availability of gene testing for numerous hereditary cancers, the service provides a gatekeeper function to identify those individuals who could legitimately benefit from testing versus the wholesale indiscriminate application of such new technology. Such a service as described here offers a reliable, cost-controlling gatekeeper to the gene testing domain.

FURTHER INFORMATICS DEVELOPMENTS

It is of interest that the expert system used to determine hereditary cancer patterns became so internalized by the case processors that the actual expert system's use became completely superfluous. All experienced case processors totally inculcated the rule-based system; quality control experiments demonstrated no difference between our expert system performance and the experienced case processors.

We have initiated more advanced methodologies to be automatically integrated into the case processing in anticipation for exponentially increasing volume. We have begun data mining applications [10] to derive expert

system rules that would optimally recognize and categorize cases into appropriate risk levels. Efforts are underway to apply this process to substantial sections of the vast HCI electronically-based case histories (127,000 cases) which may more subtlety refine the expert decision-making of both the system and even the human experts themselves. The rules derived with such data mining techniques in turn are linked to specific cases that substantiate the rule. By reviewing the subset of applicable cases, a matched pattern can be obtained that permits the substantiated reduction of the present case unambiguously to a previously solved problem. We have also created neural network recognizers that further improve the efficiency of the pattern recognition task of the case processing staff. These recognizers have used the vast HCI database to refine their capabilities. Potentially both strategies will significantly increase the rate and accuracy of the preliminary analysis and classification of cases, thus further optimizing the final ***human*** review that provides the assurance to both cancer centers and physicians alike.

SUMMARY

Over the course of 12 years, a practical composite of medical informatics strategies have been molded into a dedicated service focusing on the evolving area of hereditary cancers. This service for insuring the capture and analysis of a client's cancer family tree assures that one of the most beneficial components of the client's workup will not get omitted. With recent breakthroughs in the availability of gene testing (and the very high associated costs), it becomes imperative to implement a gatekeeper function such as this service which can be widely disseminated, reliable, and engenders the trust of both the clients and the physicians. With its combination of informatics coupled with expert medical review, this strategy has enabled the HCCS to accomplish its goals in a physician-accepted, efficient, and cost-effective manner.

AFFILIATIONS

Steven Evans, Senior Research Scientist for the Hereditary Cancer Institute since 1983, has been the Director for the HCCS service for OncorMed, Inc., Gaithersburg, Maryland (the commercial firm that makes the service available in collaboration with HCI) since 1993. Dr. Henry T. Lynch has been a scientific advisor to OncorMed, Inc. We are indebted to Carolyn Deters, R. N., for her invaluable assistance in case processing informatics design and analysis, client analysis, and the aggregation of site data.

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