ORIGINAL ARTICLE

Identification and Management of Women at High Risk for Hereditary Breast/Ovarian Cancer Syndrome

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■ **Abstract:** Despite advances in identifying genetic markers of high risk patients and the availability of genetic testing, it remains challenging to efficiently identify women who are at hereditary risk and to manage their care appropriately. HughesRiskApps, an open-source family history collection, risk assessment, and Clinical Decision Support (CDS) software package, was developed to address the shortcomings in our ability to identify and treat the high risk population. This system is designed for use in primary care clinics, breast centers, and cancer risk clinics to collect family history and risk information and provide the necessary CDS to increase quality of care and efficiency. This paper reports on the first implementation of HughesRiskApps in the community hospital setting. HughesRiskApps was implemented at the Newton-Wellesley Hospital. Between April 1, 2007 and March 31, 2008, 32,966 analyses were performed on 25,763 individuals. Within this population, 915 (3.6%) individuals were found to be eligible for risk assessment and possible genetic testing based on the 10% risk of mutation threshold. During the first year of implementation, physicians and patients have fully accepted the system, and 3.6% of patients assessed have been referred to risk assessment and consideration of genetic testing. These early results indicate that the number of patients identified for risk assessment has increased dramatically and that the care of these patients is more efficient and likely more effective. ■

Key Words: BRCA mutations, Decision Support Software, hereditary breast cancer, hereditary ovarian cancer

According to the American Cancer Society, 182,460 invasive breast cancers, 67,770 non-invasive breast cancers, and 21,650 ovarian cancers will be diagnosed in the USA during 2008 (1). The breakthrough discovery of the BRCA1 gene in 1994 (2,3) and the BRCA2 gene in 1995 (4) made it possible to identify many of the approximately 5–10% of all breast and ovarian cancer cases that are caused by a genetic predisposition (5,6) and ultimately to prevent

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them before they occur. Women with a BRCA mutation have a 40–80% lifetime risk of breast cancer and a 10–50% lifetime risk of ovarian cancer, making these mutations the most discriminating risk factors for these cancers (7,8). Mutation analysis is commercially available to identify individuals with known BRCA1 or BRCA2 mutations (Myriad Genetics, Inc., Salt lake City, UT) and multiple societies, agencies, and governing bodies suggest genetic testing for women at high risk of carrying a mutation, with a 10% or greater risk of mutation often being cited as a testing threshold (9).

Despite these advances in identifying genetic markers of high risk patients and the availability of genetic testing, it remains challenging to translate these findings into a sufficiently robust clinical program that can efficiently identify which women are at hereditary risk and to manage their care appropriately. The standard of care for women with these mutations includes increased surveillance [mammography, MRI, CA-125 testing, and transvaginal sonography (10–13)] and the consideration of preventative interventions [chemoprevention with tamoxifen or raloxifene, and surgical interventions including prophylactic bilateral mastectomy and oophorectomy (14–16)].

If identifying women with these mutations can redirect their management to cancer prevention, or identification of cancers at an earlier, more treatable stage, improved methods of identifying high risk patients early could make a significant impact on breast and ovarian cancer mortality, especially in young women. Unfortunately, of the over 1,000,000 estimated mutation carriers in the US, only about 20,000 have been identified to date and the majority of those carriers were identified after they had already been diagnosed with cancer (Myriad Genetics, Inc., personal communication). While identifying mutations in cancer patients can be helpful in the prevention and detection of second primary cancers, and may benefit the family, where a positive test can translate into testing and identifying other mutation carriers among relatives, the optimal management of hereditary breast and ovarian cancer can be accomplished only when all high risk women are identified and placed on appropriate management strategies, prior to the development of cancer.

The magnitude of this undertaking will depend on the prevalence of breast and ovarian cancer in families within the population and the proportion of these family histories that are specifically suggestive of hereditary cancer. It has been shown that approximately 6% of women in a primary care practice carry significant risk of being a mutation carrier such that further evaluation is warranted (17), and in a mammography population 3.3–5.9% of women without cancer (18) and 20.6% of women with cancer fall into this high risk category (19). Although algorithms for quantifying risk and guidelines for referring these patients for risk assessment (9) have been developed, implementing these tools to screen all women and identify those who need further evaluation is not trivial.

In fact, there are numerous barriers to the large-scale identification and management of high-risk women. First, the clinician must take a family history in sufficient detail to see any patterns, yet most clinicians do not have time to collect a thorough family history (20). Second, because of deficiencies in Electronic Health Records Systems, this family history is not commonly stored in an easily updatable format leading clinicians to duplicate family history collection efforts during subsequent patient visits, rather than simply adding to and editing existing information. Third, the clinician must understand hereditary cancer and the patterns that denote risk in a family history. Most clinicians do not have the knowledge base to identify the hereditary chronic disease syndromes seen in adults (20). If the clinician does not know every pattern, the family history needs to be analyzed by a risk assessment program that can identify these patterns. Yet, few such systems exist and use of these systems is often time consuming or difficult. Finally, when high risk women are identified, they need to be successfully directed to the appropriate resources, including risk assessment and often genetic testing. Finding effective ways to communicate risk and awareness of what resources are available to high risk patients is still a barrier.

There are a number of methods used with varying success to overcome these barriers. The problem of data collection has been addressed in a number of ways. Clinicians have long used self-administered questionnaires in clinic waiting rooms in an effort to streamline the intake of patient family histories. While paper forms allow physicians to quickly collect necessary information, they introduce other inefficiencies and inaccuracies into the workflow. This paper form, stored in the patient's chart, is neither easily updated nor is the data collected available for Clinical Decision Support (CDS). To store and use this information, a staff member must manually enter this data into a structured database, thus adding staff or clinician

work and introducing opportunities for inaccuracy. Forms that can be scanned into electronic databases have also been used in an attempt to eliminate some of this inefficiency. While this innovation was a great step in enhancing data storage, there was still room for improvement. These forms cannot incorporate branching logic and are difficult to modify as new information about risk factors becomes available.

Myriad Genetics, Inc has sought to increase awareness about hereditary cancers and increase genetic testing through direct to consumer advertizing. While this may be successful in increasing patient interest in genetic testing, it does not insure that the appropriate patients will seek genetic testing. Because this effort is not targeted specifically at the high-risk population, some patients may be missed and some resources misallocated. Even if direct to consumer advertizing were successful, the burden of collecting, analyzing, and using the information contained in family history remains.

To address the shortcomings in our ability to identify and treat the high risk population, HughesRiskApps, an open-source family history collection, risk assessment, and CDS software package, was developed. This system is designed for use in breast centers, primary care offices, and in the risk assessment clinic. It collects family history and risk information with minimal added workload for the staff by using either tablet PC's, or direct entry computer screens, and provides the necessary CDS to increase quality of care and efficiency. This paper reports on the implementation of HughesRiskApps in an existing work flow at a busy community hospital. Our objective was to show that this system would facilitate efficient screening for hereditary cancer and allow the benefits of genetic advances to be accessible on a public health level.

METHODS

HughesRiskApps was designed to efficiently and accurately collect the necessary elements of family history and other risk factor information, to store this data in an easily updated format, to provide clinicians with the information necessary to identify and manage risk, and to streamline the identification and counseling process. To accomplish these goals Hughes RiskApps integrates innovative data collection methods with risk assessment and CDS tools. This system can be used in primary care, breast imaging centers, or similar settings to identify patients who should be referred for risk assessment (which often takes place in a specialized cancer risk clinic). In these types of cancer risk clinics, HughesRiskApps uses the same techniques to refine the patient's risk assessment, determine if genetic testing is appropriate, and recommend a treatment plan. To accomplish this twofold mission of identifying and managing high risk patients, HughesRiskApps is equipped with two tiers of patient surveys: the "Standard Survey," designed to efficiently identify potentially high risk patients in a mammography imaging center or the primary care setting; and the "Risk Clinic Survey," designed to fine-tune the risk assessment and develop a management plan for patients seen at cancer risk clinics.

DATA COLLECTION

The process of identifying high risk patients using the HughesRiskApps system begins when the patient enters the mammography or primary care setting. HughesRiskApps employs tablet PCs in patient waiting rooms and exam rooms, which allows the patient to enter her own family history, medical history, and risk factor data by using a touch screen and stylus to answer a series of questions. The application can also be implemented on desktop or laptop PCs or a kiosk depending on clinic infrastructure. The patient survey was designed to be easily customizable for different clinics and to use branching logic, skipping over questions that are excluded by previous answers. Once the data is collected, it is stored in a structured, HL7 compliant database and is available for the clinician to view or modify through the management application. Some clinicians choose to enter patient data directly into the management application during the patient consultation. To facilitate accessibility and transparency of data, HughesRiskApps includes auditing features that records changes to patient data over time.

When the patient completes the standard screening survey, her data is immediately evaluated by CaGene (UT Southwestern, http://www8.utsouthwestern.edu/utsw/cda/dept47829/files/65844.html) where BRCAPRO and the Myriad models are used to estimate her risk of carrying a BRCA1 or BRCA2 mutation (21–23). This data transfer and risk analysis is accomplished through translators that enable communication with outside data sources and datasets. The risk factors and family history, the risk of mutation, and the lifetime risk of breast cancer are presented to the clinician. For all patients with a 10% or greater risk

of BRCA1 or BRCA2 mutation, an information sheet explaining hereditary breast and ovarian cancer and a letter suggesting she make an appointment at the risk assessment clinic is printed and given to or mailed to the patient. In this way, HughesRiskApps allows clinicians to provide high-volume risk screening with very little effort. This system insures that the patient is informed of her potential risk of carrying a BRCA1 or BRCA2 mutation and is encouraged to make an appointment at the risk clinic. At the end of each week, letters are automatically sent both to all patients with a 10% or greater risk of mutation and also to their physicians reminding them of the results of the risk assessment and encouraging them to seek counseling in the risk clinic.

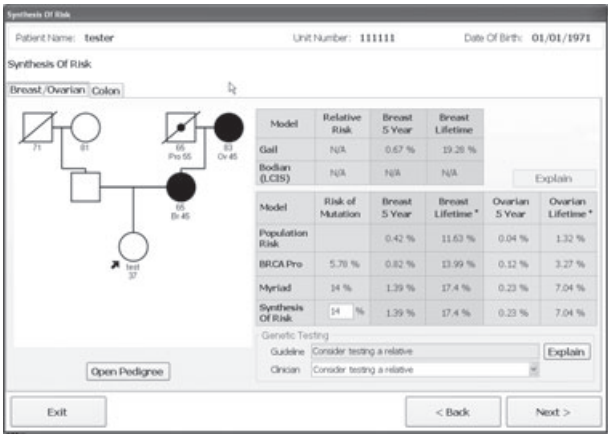

Figure 1. Synthesis of risk screen.

RISK ANALYSIS

Patients seen in a cancer risk clinic are asked to provide a more detailed family history to refine the risk analysis by a self administered questionnaire using the risk clinic Tablet Survey, which collects the name of all relatives, their ages and their vital status. As patient data is stored in a structured central database, all clinicians involved in patient care (i.e., mammography techs, nurse practitioners, genetic counselors, radiologist, surgeons, oncologists, etc.) have access to the patient data. A nurse practitioner or genetic counselor in the risk clinic can therefore prepopulate the tablet application with a patient's previous responses during each subsequent visit, giving the patient the opportunity to modify or simply accept her previous responses. This system serves to increase continuity of patient care and save clinic staff time by eliminating redundant data entry. At each level of care, clinicians may enhance a patient's data, adding for example, pathology reports from a biopsy or genetic testing results. With this more complete patient data CaGene will automatically re-run BRCAPRO and Myriad. Using the results of these models, HughesRiskApps displays the patient's risk of being a BRCA1 or BRCA2 carrier and her lifetime risk of breast and ovarian cancer. To help the clinician communicate the patient's level of risk, the risk estimates are presented with the general population's lifetime risk of breast and ovarian cancers, and the patient's pedigree (Fig. 1). This presentation was designed to help clinicians quickly get a sense of the patient's risk relative to the general population and to give them the tools to convey this information to their patients.

CLINICAL DECISION SUPPORT

The first step of CDS is presented to the clinician on the screen next to the results of the risk analysis and the patient pedigree. Using the output from the risk models as a guideline, the clinicians are encouraged to enter the best estimate of risk for a patient using their own judgment. This composite risk assessment, coupled with some relevant patient responses, is then used in decision support, which generates recommendations regarding genetic testing, surveillance options (clinical breast exam, mammography, MRI, pelvic exam, CA-125, transvaginal sonography), and prevention interventions (prophylactic mastectomy and oophorectomy, chemoprevention). These recommendations are presented for both breast (Fig. 2) and ovarian cancer (Fig. 3) risk management.

These recommendations are the results of decision paths, which reflect current practice guidelines and take into account patient responses (24,25). For example, prophylactic oophorectomy should be "considered" (not "recommended") for patients with known mutations if they report that they have not completed childbearing and chemoprevention is "not recommended" if the patient reports that she is a smoker even if she meets other criteria for recommending treatment. In the latter case, HughesRiskApps will provide the clinician with additional support by automatically printing smoking cessation information to help address the smoking barrier before chemoprevention may be recommended. The clinician has an opportunity to accept or modify each of these recommendations and to enter information about the patient's willingness to comply with the recommendation.

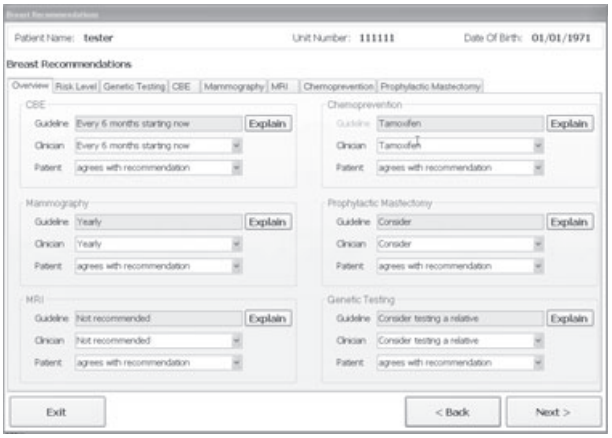

Figure 2. Breast recommendations screen.

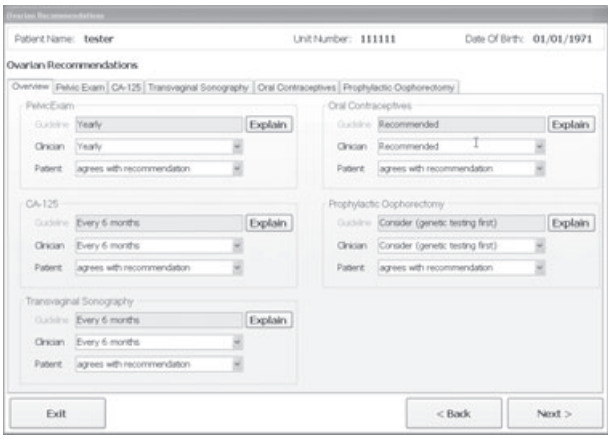

Figure 3. Ovarian recommendations screen.

If after this refined analysis, the patient maintains a 10% or greater risk of mutation the CDS will help the clinician determine which relative or patient to test for a BRCA1 or BRCA2 mutation by providing a prioritized list of relatives to test. After discussing these options with the patient, there is an opportunity for the clinician to enter information about each relative's willingness to be tested and their location (Fig. 4). From this reprioritized list, letters are automatically generated for the patient to send to each relative who might be willing to be tested. These letters explain hereditary risk of breast and ovarian cancer and the patient's risk assessment and then recommend clinics in the relatives' area where they should consider being tested for BRCA1 or BRCA2 mutation.

HughesRiskApps also eliminates dictation time by employing automatic letter generation to create letters to the patient and referring physician summarizing the

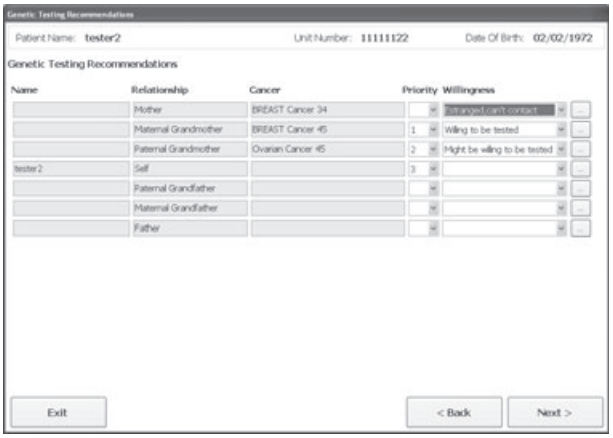

Figure 4. Genetic testing recommendations screen.

patient's risk level, treatment plan, and genetic testing recommendations, as well as letters of medical necessity for genetic testing. In future versions, we plan to implement auto-printing of requisitions, and follow-up reminders.

RESULTS

HughesRiskApps was recently implemented at the Newton-Wellesley Hospital (NWH) where data has been collected in both the Manton Breast Imaging Center and the Auerbach Breast Care Center. In the Breast Imaging Center, mammography technicians enter patient data directly into the management application during the patient interview. Previously, the mammography technicians entered patient data into a proprietary Electronic Health Record (Picis) that lacked the capability to analyze the data. The data entry screen of HughesRiskApps was designed to have an updated but similar look and feel to the previous method, but with the full functionality of HughesRiskApps. The Breast Care Center, on the other hand, has chosen to allow patients to enter their own data into the tablet PCs. In both cases, the data is automatically transferred to the central database where it is analyzed and accessible to clinicians although the management application. The primary care physicians at NWH were told about the implementation of HughesRiskApps and agreed to allow their patients to be contacted through the automatic letter generation.

With Institutional Review Board (IRB) approval, a retrospective review of the data collected at NWH between April 1, 2007 and March 31, 2008 was per-

formed. During this time, we performed 32,966 analyses in 25,763 individuals. Within this population, we identified 915 (3.6%) individuals eligible for genetic testing based on the 10% risk of mutation threshold. The number of patients seen for consultation has increased from approximately 1–2/month to 5–6/week, with a significant backlog. There has also been a marked increase in genetic testing during the first year of implementation; full analysis of these data will be presented in future manuscripts.

The system, which uses Open Source software, has been relatively inexpensive to implement. The implementation at NHW used the standard version of the software, which is freely available, while enhancements and customizations to the software may be licensed for a fee. Implementation of the system as described required involvement from the Information Systems department for installation, training, and periodic maintenance of the software. As the system replaced an existing family history collection system there was no significant change in workflow. The radiologists accepted the task of discussing hereditary cancer risk levels with the additional patients who were identified as high-risk each day without significant strain. No additional personnel were hired to implement HughesRiskApps at NWH.

While the system did not increase costs in any meaningful way at NWH, the system holds significant financial benefit for both the Radiology Department and the Auerbach Breast Care Center. Use of the system identifies a high-risk population who have previously gone unidentified that is eligible for increased surveillance with MRI and transvaginal sonograms. Therefore, we expect an increase in use of these services. In addition, because HughesRiskApps more appropriately selects these women for services, coverage by insurance companies is expected to be easier and more complete, which will further increase the use of these services.

HughesRiskApps has also produced a significant increase in the number of patients referred to the risk clinic at the Breast Center and a significant increase in the number of genetic tests ordered. In the risk clinic, the workload for the counselor is decreased by sharing data from the screening center, reducing duplicate data entry, and by shifting much data entry to the patient. Newer versions of the software will also decrease the genetic counselors' workload by automatically generating what are now dictated letters and notes.

DISCUSSION

The advance of the genomic age brings the promise of significant improvement in patient care while simultaneously highlighting deficiencies in the systems required to make use of genetic information. The identification and management of individuals with genetic markers requires innovative approaches to data collection, risk assessment, and clinical decision support. Unfortunately, current approaches to family history collection and risk identification are inadequate and do not take advantage of current genomic developments. In the community hospital setting, we successfully implemented HughesRiskApps, a software system designed to identify and manage individuals at risk for carrying genetic mutations by collecting family history, analyzing hereditary risk, and providing the necessary CDS to increase efficiency and quality of care.

While HughesRiskApps continues to be refined and improved, the system has addressed many of the barriers to identifying and treating patients at high risk of hereditary breast and ovarian cancer. The improved efficiency of this system was achieved using multiple approaches. First, the system was able to decrease data entry by making use of existing data from multiple sources. Second, the system successfully allowed for data entry and maintenance by the patient via the tablet PC, which decreased staff workload while enhancing quality by making the patient a partner in data integrity. In addition, patient data is automatically stored in a structured, central database that is easily accessible for all clinicians to view or modify, helping to avoid redundant data entry. Third, the system performed automated risk analysis, thus facilitating referral of high risk patient for risk assessment and testing. This risk information is clearly presented to clinicians in easily understandable printouts and screens allowing high-volume risk identification and facilitating communication between clinician and patient. Fourth, the CDS helps clinicians manage and communicate a treatment plan; letter generation increases efficiency and helps clinicians communicate risk and insure that patients are reminded of referrals. The automatically created consultation letters using merge techniques decreases dictation time and editing time and also allows these letters to be created while the patient is still at her appointment, rather than over a period of a few weeks. Finally, the system can further automate administrative tasks, such as patient reminders and generation of requisitions.

The improved efficiency of this system was accomplished without significant increase in staff workload (no full-time equivalents [FTE's] were added) and enabled improved clinical management. Identifying women at high risk for hereditary breast ovarian cancer using this system makes the counseling approach more efficient, thereby, helping to manage the increased workload. Commonly, risk counseling requires 1–3 hours per patient, which often includes redundant data entry, and dictation and editing of notes and letters. HughesRiskApps shortens this time significantly, and markedly increases efficiency. This efficiency allows risk clinics to be more efficient and see the large number of women who can be identified in the breast imaging department without significant increases in staff. Making the system cost-effective can increase interest in implementation at hospitals, thus increasing the quality of medical care throughout the US.

In addition, one of the major issues in identifying individuals at increased risk of hereditary breast/ovarian cancer is the ability to reach relatives who may be affected. Past experience has shown that it is often difficult to reach family members of mutation carriers, and/or to test living affected relatives who live in distant locations. Typically, patients are merely told to encourage their relatives to get genetic testing; however, this practice did not often result in a family member being tested. It is our belief that the letters generated through HughesRiskApps will help increase the number of relatives who seek risk assessment, thereby, increasing quality of care for all members of the family.

The system has been installed and is currently being used in 10 additional clinics. Given the success of this study, we anticipate similar results in these clinics. The approach this system uses can be extended to the identification and management of other hereditary diseases, both malignant and benign. Currently, software for hereditary colorectal cancer and cardiovascular disease is in development.

In summary, over the first year, physicians and patients have fully accepted the system, and there appears to be a major increase in referrals and genetic testing. As this system enters its second year at NWH, we look forward to assessing practical and psychological barriers that might interfere with follow-up. The early results indicate that the number of patients seeking risk assessment has increased dramatically and that the care of these patients is more efficient and likely more effective, suggesting promise for this innovative system to significantly improve the process of identifying and managing high risk patients.

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