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Hereditary Breast and Ovarian Cancer and Other Hereditary Syndromes: Using Technology to Identify Carriers

Brian Drohan, PhD[1], Constance A. Roche, MSN, RN[1], James C. Cusack Jr., MD[1], and Kevin S. Hughes, MD[1,2]

[1]Division of Surgical Oncology, Department of Surgery, Avon Comprehensive Breast Evaluation Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]Bermuda Cancer Genetics and Risk Assessment Clinic, Massachusetts General Hospital, Harvard Medical School, Boston, MA

ABSTRACT

Purpose and Methods. Most patients who harbor a genetic mutation for hereditary breast cancer have not been identified, despite the availability of genetic testing. Developing an effective approach to the identification of high-risk individuals is the key to preventing and/or providing early diagnosis of cancer in this patient population. This educational review addresses these issues.

Results and Discussion. Using data available on the internet, and making assumptions regarding the types and results of genetic testing, we have estimated the number of mutation carriers in the country and the number who have been tested and identified as such. Overall, our ability to fund and more effectively manage carriers is weak. A technological solution is discussed.

The rapid growth of genetic science could lead to improved public health if individuals susceptible to a hereditary syndrome were adequately identified before disease occurred. In reviewing 2,592 syndromes described in the Online Mendelian Inheritance in Man (OMIM) database, Scheuner et al.[1] found 188 syndromes that included at least one major adult disease (coronary artery disease, myocardial infarction, stroke, sudden death, arrhythmia, aneurysm, arteriovenous malformation, cardiomyopathy, thrombosis, diabetes, and cancers of the breast, ovary, uterus, prostate, colon, kidney, and thyroid) and occurred in more than 2 families in the world. Thus, there are 188 adult hereditary syndromes that a primary care provider could identify in the course of daily practice. Identification of these syndromes is likely an impossible task with continued reliance on what Crane and Raymond have called memory-based medicine,[2] stating, "Current medical practice relies heavily on the unaided mind to recall a great amount of detailed knowledge."

Here, we examine the charge of identifying patients with hereditary breast ovarian cancer syndrome (HBOC), determine the scope of this charge, and offer a technology-based solution. We examine HBOC in depth, but our conclusions and approaches can likely be applied to any adult hereditary syndrome.

BACKGROUND

The breast and ovarian cancer susceptibility genes, *BRCA1* and *BRCA2*, were cloned in 1994 and 1995, respectively, and testing for these genes became commercially available in 1996. *BRCA1/2* mutations account for a large proportion of hereditary breast and ovarian cancer caused by major cancer susceptibility genes.[3]

To find all *BRCA* mutation carriers, one approach would be to follow the newborn screening model and test all individuals in the population, regardless of risk level. However, the cost of testing and concerns regarding privacy and freedom of choice have currently limited the viability of population level testing. The prevailing approach has therefore been to identify a high-risk population and then offer testing for those individuals. It is also

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J. C. Cusack Jr., MD
e-mail: jcusack@partners.org

K. S. Hughes, MD
e-mail: kshughes@partners.org

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common to expand testing to blood relatives of those individuals who test positive. Extensive efforts have been made to educate clinicians about this highly nuanced process since testing has become widely available. Identification of individuals at highest risk requires attention to family history and knowledge of features suggestive of HBOC: number of relatives affected, young age at diagnosis, multiple primary cancers in a single individual, or male breast cancer. These features require more knowledge, time, and expertise than most clinicians possess today.[4] To facilitate the identification of high-risk individuals, numerous guidelines and algorithms have been developed to provide both quantitative and semiquantitative approaches for risk assessment and testing.[5] Some are complicated mathematical models, while others are simple checklists of conditions.

There are algorithms, such as BRCAPro, BOADICIA, Tyrer-Cuzick, and the Myriad tables, that use family history data to produce an actual probability that the proband carries a *BRCA1* or *BRCA2* mutation.[6–9] For the unaffected individual, this probability can then form the basis for further calculations estimating the subsequent risk of developing cancer, sometimes bringing in additional risk information beyond family history.

For example, let us assume you have an unaffected non-Jewish patient with a family history including the mother diagnosed with breast cancer at age 40 and a maternal aunt with ovarian cancer diagnosed at age 50. It is not obvious that genetic testing is appropriate, although the patient does look to be at high risk for hereditary breast cancer.

You can go to the Myriad risk tables (https://www.myriadpro.com/brca-risk-calculator), plug the family history into the matrix, and identify a 7.2% risk of a *BRCA1/2* mutation for the patient. You can also download the Tyrer-Cuzick model software (http://www.ems-trials.org/riskevaluator), enter the family history, and find that the patient has a 5.8% risk of mutation. The BOADICEA model is available to registered members of their Web site (http://www.srl.cam.ac.uk/genepi/boadicea/boadicea_home.10.08.10.html), which can be used to enter the data and obtain another risk model score. In terms of BRCAPro, for this patient, calculation of risk based on this model yields a 16% chance of being a *BRCA1/2* carrier, although there is no simple way to perform this calculation. To access the BRCAPro model, the BayesMendel group publishes an R script (R is a language and environment for statistical computing and graphics that includes an integrated suite of software facilities for data manipulation, calculation, and graphical display) that is available for download (http://www.cancerbiostats.onc.jhmi.edu/BayesMendel/). Utilization of this model in the clinic often requires redundant data entry into disparate data stores. However, there are a few choices for software packages that include many models accompanied by a database application component: one is CancerGene (http://www4.utsouthwestern.edu/breasthealth/cagene), written by a contributing author in this series, David Euhus; another is HughesRiskApps (http://www.hughesriskapps.com). Although more user-friendly, CancerGene does not manage a high-risk clinic, maintain extensive clinical decision support (CDS), or generate documents. HughesRiskApps is medical-grade software and thus requires IT support to install, but it does integrate the identification and management of high-risk patients throughout screening, counseling, and surgery.

With these models, a threshold can be set to guide the selection of individuals who warrant testing according to risk level. An arbitrary threshold of 10% has been used for some time, although this cutoff has no scientific basis.[10] Defining this threshold effectively establishes a cost-benefit relationship for testing. At a 10% threshold, 10 tests will find 1 carrier, at a cost of $2750 per test, with an overall cost of $27,500 per carrier. Third-party payers and our medical system have accepted a 10% threshold and thus accepted a per-mutation found cost, excluding the cost of counseling. It should be noted that if cost is the determining factor, the 10% threshold may not be appropriate for all groups. For instance, in subpopulations with founder mutations, there is a less expensive style of testing. For example, an Ashkenazi Jewish individual can be tested for $415 for the three founder mutations. Working with an estimate that 1 in 40 Ashkenazi individuals carry mutations, population-level testing in this group would cost $16,600 per mutation carrier found.[11] This is well below the cost in the non-Ashkenazi population of $27,500 per mutation carrier found. Yet the 10% threshold is commonly applied, even for the Ashkenazi population, suggesting an inconsistency that should be addressed.

An alternative to quantitative algorithms is the use of guidelines or protocols created by professional societies, government agencies, or those with an academic or financial interest. Rather than a complex mathematical model that can unify a variety of heterogeneous data, guidelines provide examples of minimum family history requirements that should be met or exceeded in order for testing to be considered. Palomaki et al. applied six well-accepted HBOC family history screening protocols to a population-based cohort of women.[12] They found that of 321 women evaluated, 39 met the testing criteria of one or more of these 6 guidelines, but only 6 patients met the criteria for all 6 guidelines. The challenge of such guideline development is to be comprehensive without being cumbersome and simple to use without sacrificing discriminatory capacity.

Although it has become acceptable to use a $\geq$10% threshold with BRCAPro, or to follow any of the relevant guidelines, these are not widely known among primary care providers, and the time involved to access them is not

insignificant. Furthermore, most are updated frequently when new information about the syndrome becomes available. Clinicians could carry a pocket card outlining the guidelines for each syndrome, but this is not feasible for identifying 188 hereditary syndromes.

Therefore, we believe there is a need for the development of electronic tools that can manage patient family history data and provide meaningful CDS.

To understand the need for a new approach, it is important to understand the magnitude of the gap between the current status quo and where we would like to be in the identification and management of *BRCA1/2* mutation carriers. In this article we have attempted to quantify the level of success that has been made in the identification of HBOC, and estimate the size of the task that remains. We focus on the identification of mutation carriers by genetic testing as a primary measure. We have used a variety of data sources, estimations, and assumptions that can be applied to estimate the scope of the problem. Our attempt is to provide a first order approximation that will facilitate a rational argument for the dissemination of the tools we feel will help save lives.

CURRENT STATUS

The result of our analysis is an estimate that there are 941,155 *BRCA1* or *BRCA2* mutation carriers in the United States, of whom 348,274 are women age 20 or older. We further estimate that only 48,754 have been identified by genetic testing to date. Table 1 provides the parameters and their estimates that we have used to arrive at these figures. This poor success rate comes despite the 14 years of educational efforts that have been made to disseminate genetic testing technology.

TABLE 1 Parameters and estimates used to assess *BRCA1/2* mutation prevalence

Parameter	Estimate
Incidence of *BRCA1/2* mutations	
Ashkenazi	1:40
Non-Ashkenazi	1:350
US population (2000)	281 million
Ashkenazi	2.20%
Non-Ashkenazi	97.80%
No. of women aged >20 years	104,140,289
Breast cancers due to *BRCA1/2*	5%
Breast cancer survivors in the United States	2.5 million
Breast cancer survivors, women aged >20 years	100%
No. of women tested who had cancer	75%
Test positive rates	
Full gene sequencing	10%
Allele-specific oligonucleotide	33%
Ashkenazi panel	10%

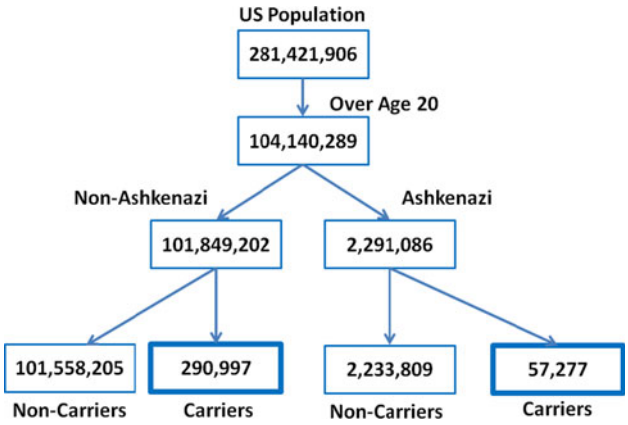

FIG. 1 Estimated *BRCA1/2* mutation prevalence in the US population by Ashkenazi heritage [9,11,13–14]

The first parameter we consider is the incidence of *BRCA1* and *BRCA2* mutations in the U.S. population (Fig. 1). The Ashkenazi Jewish population has a carrier incidence of approximately 1 in 40 for *BRCA1/2* mutations. Although the exact value is uncertain, we use an estimated carrier incidence of 1 in 350 for the remaining population.[13] Next, the U.S. population in 2000 was 281,421,906, with 2.2% of the population being Jewish, mostly Ashkenazi.[14] It would then follow that the number of mutation carriers in the United States was 941,155, with 154,782 coming from the Ashkenazi population. We then limit this calculation to the population most at risk of cancer, women age 20 and over, and estimate that there are 348,274 mutation carriers in that crucial group alone (Fig. 2).

The benefit of identifying individuals at high risk for heritable disease is in the prevention or reduction in the morbidity of the disease. In the case of breast cancer, enhanced screening for carriers can lead to earlier cancer

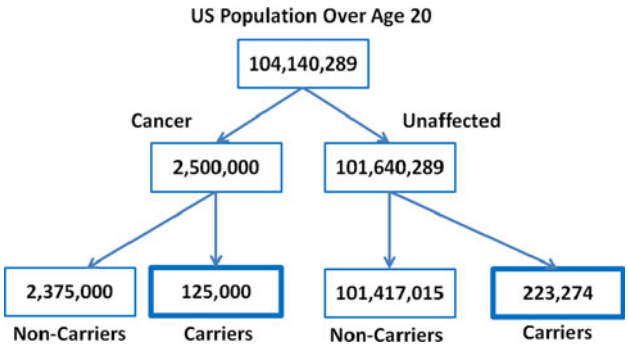

FIG. 2 Estimated *BRCA1/2* mutation prevalence in the US population over 20 years of age by cancer status [9,14,16]

detection, and surgical intervention can prevent disease, especially in younger women.[15] These strategies cannot be implemented for carriers unless these individuals are identified before they develop cancer. We thus ask this question: how many unaffected carriers are there, and how many of those have been identified?

If we assume there are 2,500,000 breast cancer survivors in the United States, that most are women age 20 and over, and that 5% are *BRCA* mutation carriers, then there are 125,000 carriers who have had breast cancer and 223,274 carriers who have not had breast cancer.[16]

To estimate the number of carriers that have been identified to date, we look to data from Myriad Genetics, where almost all of the *BRCA1/2* testing in the United States has been performed. Our approach was to build a cost model for genetic testing and then apply Myriad's reported income for testing to determine the number of tests conducted, and from that subsequently calculate the number of carriers identified.

Myriad Genetics intermittently publishes the detection rates from testing in both the Ashkenazi and the general population, along with the number of observations made in both groups (26,015 and 162,914, respectively).[9] From these data, we reason that 13% of the tests performed for *BRCA1* and *BRCA2* are for the Ashkenazi mutations. Furthermore, from personal communication from Myriad Genetics, we assume that 1 positive finding is the result of every 10 full gene sequencing tests performed, and that 1.1 single-site mutation tests are performed for each positive finding on a full gene sequencing test.

We then figure an average price of $3000 for full gene sequencing, $400 for single-site, allele-specific oligonucleotide and $400 for the Ashkenazi panel. From the annual reports filed for the years between 1997 and 2009, we know that Myriad collected $1,005,255,788 for diagnostic molecular testing.[17] Assuming that almost all revenue of this type was from *BRCA* testing, we estimate that Myriad has done 405,986 genetic tests in this time period, with 322,358 full gene sequences, 35,459 single-site mutation tests, and 48,169 Ashkenazi panels.

If we then assume a 10% positive rate for full gene sequencing and for the Ashkenazi panel, and if we assume a 33% positive rate for single-site mutation testing, this would lead us to believe that Myriad has identified 48,754 carriers. If we assume that few mutation carriers in the United States have been identified by a laboratory other than Myriad, and if we assume that the vast majority of the mutations found by Myriad were in the U.S. population, we could then assume that this is a fair estimation of all the mutation carriers currently known in the United States.

We further assume that 75% of those who tested positive already had cancer (personal estimation; no data exist), and that most patients tested were women age 20 and above. We thus conclude that in the 14 years since the introduction of *BRCA* testing, only 36,566 of the 125,000 carriers with cancer (29.3%) and 12,189 of the 223,274 carriers without cancer (5.5%) have been identified.

A TECHNOLOGICAL SOLUTION

These back-of-the-napkin calculations seem relatively consistent with the work of Levy et al., who studied 35,116 unaffected women from the 2000 and 2005 National Health Interview surveys and found that 0.96% were at high risk for hereditary breast/ovarian cancer.[18] Of those only 54% were aware of genetic testing, only 10.4% had discussed genetic testing with a clinician, and only 1.4% had undergone genetic testing.

It becomes clear that the availability of testing and education alone has been insufficient in the quest to identify every *BRCA1* and *BRCA2* mutation carrier before he or she develops cancer. As hereditary breast ovarian cancer caused by *BRCA1/2* mutations is perhaps the syndrome most recognized and tested for, it is likely that there is even less success at identifying individuals with the other 187 major adult hereditary syndromes.

The only logical solution is to use information technology, and specifically CDS, to assist the clinician in identifying patients who might be candidates for genetic testing and changes in clinical management. In this context, we consider CDS to represent the use of computer software to apply knowledge bases, guidelines, and algorithms to patient data to identify the best course of action, and then present that result to the clinician in a way that helps the clinician understand why that is the best course of action.

As discussed, numerous guidelines and algorithms exist that suggest who might be best served by genetic testing for HBOC, but none of those guidelines can be easily applied to a patient without the aid of a computer. Computers can do the work if sufficient data are entered, but the amount of data needed typically precludes real-time data entry and analysis in the midst of a busy clinic session.

Electronic health record (EHR) vendors have been unable to fill this need. Of the 150 or more EHR vendors, none have created a useful family history section that uses CDS to help in patient care. In 2008, the American health Information Community identified the core data set for family history that would be sufficient for CDS.[19] The Healthcare Information Technology Standards Panel identified the HL7 Pedigree Model as the standard for transmitting family history information between EHRs and CDS software.[20] However, no EHR vendor has adopted to date either standard. As a result, EHRs remain incapable of storing granular family history data, drawing pedigrees, or using robust CDS software. On the basis of discussions with vendors, we think that it will be some time before this deficiency is addressed. For this

reason, we developed freeware called HughesRiskApps[21] (HughesRiskApps.Com, freeware), which uses data entered by the patient or by staff (via a tablet PC or the Internet) to run the BRCAPro, Claus, Gail, and Myriad models.[22,23] Patients who are at a ≥10% risk of mutation are given an information sheet about hereditary risk or sent a letter suggesting that they make an appointment in the risk assessment clinic.

The system has been installed at over 131 sites to date. At our inaugural site, the Newton Wellesley Hospital, the application was installed in April 2007. Since then, we have collected 50,034 unique family histories and identified 2255 women with a ≥10% risk of mutation. The software displays the result as a table and a pedigree, and generates patient education materials, resulting in an easily comprehensible assessment of level of risk and appropriate management options.

Once a large number of women at high risk have been identified, these women require counseling and access to testing. The current model of counseling is time-consuming and unsustainable. The time involved in risk assessment and counseling is partly due to redundant data entry and excessive administrative work performed by high-level personnel. Family history collection is accomplished, on paper or by interview, and then the data are typically entered into CaGene (http://www4.utsouthwestern.edu/breasthealth/cagene/) to analyze risk and into a pedigree drawing software such as Progeny (Progeny Software, Wolfville, Nova Scotia, Canada) to produce visualization. The information from CaGene and the pedigree drawing are reviewed to assess risk level, face-to-face counseling takes place, and letters and notes are generated by dictation or templated paragraphs. For the risk counselor, this risk assessment totals an average of 4 hours per patient. If we assume, as stated above, that there are 296,577 female carriers age 20 and above who should be tested, and if we assume that 10 women need to be tested for each carrier identified, 2,965,770 women need to be counseled in order to find these carriers. At 4 hours each, and assuming a 48-week work year, this work totals 6179 full-time person-years.

HughesRiskApps includes a risk clinic module that aims to help the counselor be more efficient and provide higher quality care through CDS. Family history is entered by the patient via tablet PCs or Web sites, risk analyses are run on those data, and a pedigree is drawn. The pedigree and risk calculations are presented in an easily understood visualization that can be reviewed before the counselor sees the patient. Face-to-face counseling then can take place with all risk calculations available, and the family history can be edited in real-time as new information is drawn out through the interview. Finally, letters and notes are generated automatically, ready for editing by the counselor.

HughesRiskApps is available online for free. This clinical information system can be setup on a single workstation or on a corporate network as part of an enterprise solution. Because it is meant to be robust, its complete integration with existing systems and workflows can be complicated, and may require IT support. HughesRiskApps is a clinical tool, with a tablet PC survey piece as the primary patient interface. A prototype of the online patient interface, which is currently under development, can be accessed by contacting the authors.

Software of this type is meant to decrease the workload of entering data, running algorithms, and matching the data against standards of care. It can be applied to any hereditary condition at the identification level or at the risk clinic level. In lieu of each EHR vendor recreating similar systems from scratch, we strongly believe in the modular approach to the EHR implementation. Similar to other computer operating systems, it would make sense for the EHR to serve as a data repository, while other specialized programs, such as PenRad (Minnetonka, MN), serve to interact with those data. This distinction would allow experts in all areas (e.g., colon, breast, genetics, pediatric cardiology) to develop their own modules specific to their workflow and their needs. These modules could then be added to the EHR to provide a specialty specific view of the underlying data.

CONCLUSION

In summary, despite 14 years of *BRCA* testing availability, with extensive education of professionals and even marketing to the general public, only a small proportion of *BRCA1* and *BRCA2* carriers has been identified. It is time to rethink traditional models and move into the information age. EHR vendors must develop family history and CDS capabilities to help in the identification and management of high-risk individuals, for HBOC as well as all hereditary syndromes. This transition can be done independently by vendors within the confines of their own products or within a modular approach with the seamless incorporation of niche software into the EHR.

The modular approach is widely used in many everyday experiences: How many iPhone users have only a single application on their phone? Who would choose to use Excel to file taxes if TurboTax were available? Who would choose to keep appointments in a Microsoft Word document when a calendar program is available?

Correspondingly, most breast imaging departments do not use an EHR to manage day-to-day practice. By using specialized software like PenRad or MRS (Materials Research Society, Warrendale, PA), they send reports to the EHR. Pathology departments do not use the EHR for day-to-day work but a pathology management system

before sending reports to the EHR. Clinical specialists deserve the same level of specialty specific software. Computers have been running niche software for years. It is time for EHR vendors to catch up. It is critical not only for hereditary disease, but also for all of healthcare.

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