

# Evidence-Based Surgical Hypothesis

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## The case against BRCA 1 and 2 testing

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### **HYPOTHESIS**

*The DNA base pair sequence in all humans is 99.6% identical*

*and*

*Epigenetic factors influence substantively the RNA processing and translational requisition of the initial DNA message*

*and*

*There are thousands of sequence variants of the BRCA1 and BRCA 2 genes<sup>1</sup>*

*and*

*Family history always trumps BRCA 1 and 2 status so*

*For screening and therapeutic purposes, BRCA 1 and BRCA 2 genetic testing is an expensive way of determining what can be accomplished more expeditiously by speaking with your patient.*

WE are all comfortable with the fundamental concepts of molecular biology—that a sequence of nucleotide pairs in DNA encodes complementary RNA, which directs the synthesis of proteins in our ribosomes. Then the trouble starts. Without appearing arrogant, humans like to think of ourselves as special. So, how can most of our distinguishing genes encoding human proteins also be so expressed egalitarianly in cows, sloths, and rats? And, how is it that a perfect human being can be constructed from a DNA recipe that contains only 20,000 genetic instructions when both roses and cows<sup>2</sup> sport more. Or, perhaps even less conceptually acceptable, how can it be that the admirably erudite coeditors of this journal enjoy a DNA code that is at least 99.6% identical to that of the Marx Brothers?

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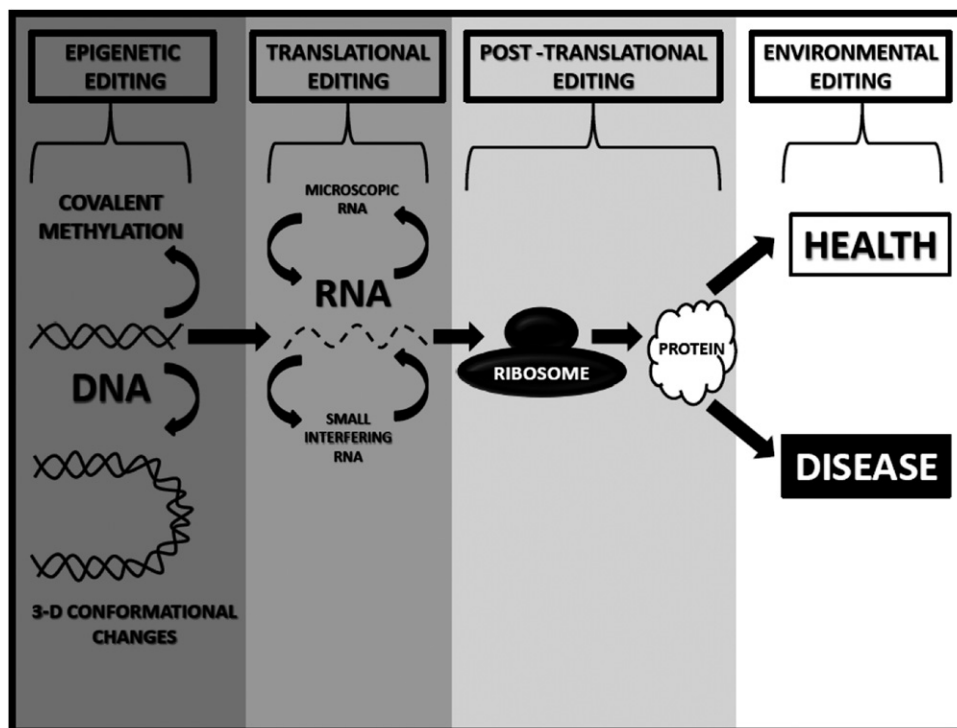
It turns out that, like a book, a gene can be “read” both backward and forward. Small sections (or chapters) within a big gene can be “read” alone. The three-dimensional structure of DNA controlled by site-to-site methylation prevents many chapters from being “read” at all. In addition, short segments of RNA (22 base pair micro-RNA) can cycle back to control DNA transcription. So, DNA is just the starting point, and like flour, you do not know whether the chef is going to cook a croissant or a tortilla with it. Or, Interstate 80 connects San Francisco straight through to New York City; but, relatively few cars leaving San Francisco on I-80 end up in New York. Are BRCA 1 and BRCA 2 unique? Or just like other genes, is their expression controlled by the inner cellular attitudes (both epigenetic and environmental) of the individual patient (Fig 1)?

### **WHAT IS BRCA (BREAST CANCER SUSCEPTIBILITY GENES)?**

BRCA 1 and 2 code nuclear proteins, also known as tumor suppressor genes, capable of repairing damaged DNA. BRCA 1 is located on chromosome 17 and BRCA 2 on chromosome 13. Both mutations increase the lifetime risk of breast cancer in a woman. Less than 5% of women diagnosed with either ductal carcinoma in situ or invasive ductal cancer are a result of inherited BRCA genes. Of genetic carriers of mutated BRCA1 and/or 2 diagnosed with unilateral breast cancer, up to half will be diagnosed with contralateral cancer within 5 years compared with non-BRCA carriers.

### **BUT BRCA 1 AND 2 MAY SPEAK WITH MANY VOICES**

Polymorphisms are naturally occurring single nucleotide variations of a gene present in more than 1% of the population. Polymorphisms and other single-nucleotide variants have been identified within the BRCA 1 and BRCA 2 genes. Indeed, more than 500 mutations in BRCA 1 alone have been documented and most render their proteins



**Fig 1.** Words, like genes (frequently even the same words), can be used to sing a song or scourge a society. The sequencing and editing of the words distinguishes beauty from bombast. Similarly, the initial genetic nucleotide sequence is just a starting point. A single “protein-encoding gene” can yield multiple genetic progeny. Epigenetic “editing” is accomplished by 3-dimensional conformational changes through covalent methylation. Tiny RNA fragments (microscopic RNA or small interfering RNA) can feed back to “edit” RNA translation. Posttranslational “editing” via chemical cleavage and folding of the target protein further modifies the message. Finally, a myriad of nutritional and lifestyle factors promote both health and disease.

inactive—so, some BRCA genes seem to be shooting blanks. And a single nucleotide polymorphism, albeit only a single nucleotide change, can have a formidable influence on protein expression. Sequence variant S1613G, for instance, results in increased mutational risk of BRCA 1 neoplastic expression, whereas a variation in K1183R is related *inversely* to cancer risk. It seems that some polymorphisms may actually have a *protective* effect.<sup>3</sup>

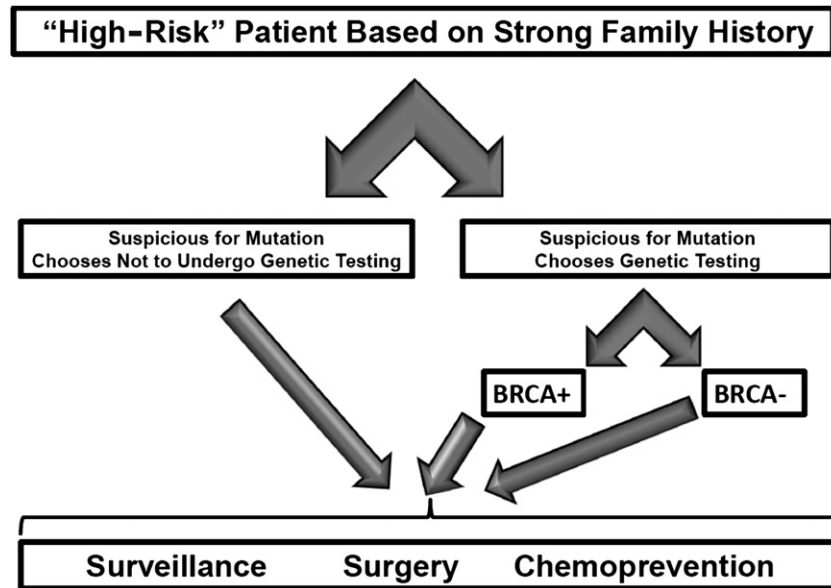
#### WHY WE TEST FOR BRCA 1 AND 2

The primary argument in favor of genetic testing is that the results will change the patient’s choice of screening or preventive strategy. In 2007, the American Cancer Society released guidelines advocating the use of magnetic resonance imaging (MRI) as an adjunct to mammographic screening in “high-risk” women, who are defined as (1) carriers of a BRCA mutation, (2) first-degree relatives of BRCA carriers, and (3) women with a >20% lifetime risk of breast cancer, as determined by family history. In 2002, Grann et al<sup>4</sup> used

a computerized model of family history to assess the benefits on survival and quality-adjusted benefits of preventive strategies compared with surveillance alone. They found that among women with a strong family history who also tested positive for BRCA mutations, those who elected prophylactic surgery or chemoprevention were calculated to survive longer (by 3.7 years) than those who do not. This survival benefit seemed to be most pronounced within the first 20 to 30 years of the intervention, after which the benefits disappeared. These added years of survival accrued not in old age but during a woman’s most active and productive years.<sup>4</sup> So, chemoprevention and surgical prevention programs seem to work.

#### HOW IS “HIGH RISK” APPRECIATED?

Not all women with a family history of breast cancer are tested for BRCA 1 and 2 mutations. A variety of criteria has been proposed by authoritative institutions to define those patients who are at “high risk” of hereditary breast cancer and define the likelihood of a patient carrying a germline



**Fig 2.** The 3 accepted prevention strategies include surveillance (routine or enhanced), prophylactic or preemptive mastectomy, and/or chemoprevention. The combined anxiety of the patient and physician, based on the patient's personal experience/witnessing of a family member with breast cancer, dictates overwhelmingly the choices of surveillance and prevention.<sup>5</sup>

mutation, which is based on ethnicity and the age when a relative developed breast cancer.

In 1996, the American Society of Clinical Oncology published guidelines recommending genetic testing for women with at least a 10% chance (based on family history) of finding a mutation in a breast cancer susceptibility gene. In 2003, these guidelines were updated, and no numeric "risk" cutoff was identified for genetic testing. Other guidelines are cited commonly, such as the U.S. Preventive Services Task Force, the National Comprehensive Cancer Network, and Kaiser Permanente. These algorithms incorporate family history, ethnicity, and a personal history of breast cancer. Additionally, the International Consensus Panel on Breast Cancer Risk suggests that genetic testing be offered to all individuals who present already with medullary type breast cancer or with a triple-negative (basal-like) phenotype, particularly if the patient is <50 years old. Although the mathematical modeling strategies of calculating "risk" vary, the dominant independent variables are consistently the age at which a patient or her relatives acquired breast cancer.

#### MANAGEMENT OPTIONS FOR HIGH-RISK WOMEN

Regardless of the guidelines used to determine "high risk," we can agree that each of the following 3 groups may be categorized as high risk: (1) a cancer-free woman with a strong family history of breast and/or ovarian cancer, but unknown

genetic mutation status; (2) a cancer-free woman who is a known carrier of a BRCA mutation; and (3) a breast cancer survivor with a family history of breast and/or ovarian cancer (Fig 2).<sup>5</sup>

Surveillance, chemoprevention, and prophylactic surgery are accepted options for managing known mutation carriers, although no randomized, prospective trials have tested these strategies.<sup>6-9</sup> The benefit of early intervention (surveillance and surgery) for these women is intuitively appealing; but as yet, it is presumptive. Fig 2 explores surveillance and treatment options for a woman with a BRCA mutation.

Intuitively, complete surgical mastectomy should eliminate, and tamoxifen should reduce, the risk of breast cancer. Unfortunately, the physical and psychosocial morbidity of both approaches are not trivial. No randomized prospective trials comparing these strategies to aggressive mammographic/MRI screening of "high risk" (based on family history ± BRCA testing) exist—and, for emotional reasons—almost certainly never will.

Interestingly, decisions made on cancer-prevention strategies among mutation carriers differ from country to country. Metcalfe et al<sup>5</sup> investigated these differences and remarkably found that a family history of breast cancer in a mother or sister predicted the decision of the mutation carrier on whether to undergo a prophylactic mastectomy. Madlensky et al<sup>10,11</sup> investigated the influence of a family history of breast cancer on both breast cancer

survivors and cancer-free women. In both groups, strong family histories of breast cancer translated into the patient's risk perception, resulting in an increased likelihood to undergo surgical preventive measures. These data support the conclusion that regardless of mutation carrier status, family history trumps all.

#### **WHAT IF THE BRCA GENOTYPE AND FAMILY HISTORY PHENOTYPE DO NOT MATCH?**

It is useful to think of the family of BRCA genes as a "plan." When a conscientious diplomat arrives in the Middle East with a "plan for peace," it may be a laudable plan—but we must recognize that the barriers of family history to successful rapprochement are formidable. When a cancerophobic patient presents with a clean family history, a gene study, if negative, is unlikely to assuage her anxiety, and a positive BRCA result is just a first-class way of pouring high-octane fuel on a spark. This patient deserves an increased frequency of surveillance and some compassionate counsel.

Conversely, it is presumptuous scientifically to permit the care of a patient with a strong family history to be influenced by an inscrutable microarray. The constellation of genes, proteins, cell signals, and socioeconomic factors in this patient's pedigree have already proven their capacity to negotiate the circuitous route to cancer. A negative BRCA is false assurance. A surgeon who dips his or her toe into cutting-edge molecular biology should not confuse this "cutting" with responsible surgical care.

#### **THE DISAPPOINTING DIALECTIC OF DNA**

A decade ago, President Clinton heralded effusively the completion of phase 1 in the Human Genome Project. The price tag was \$3 billion or approximately \$1 for each nucleotide pair. The Human Genome Project was touted as the solution to such diverse diseases as cancer, atherosclerosis, and senile dementia. This concept was, of course, fatally flawed. Darwin's version of natural selection ferrets out gene sequences that compromise procreation and, conversely, champions qualities that favor early survival, such as swiftness of foot and seductive eyes. Darwin's operative genes really do not care about wrinkles, cancer, and old age.

Genome scanning studies have "associated" multiple gene variants with heart disease. Indeed, Paynter and colleagues<sup>11</sup> recently reported tracking 101 of these "heart disease" genes in 19,000 women over 12 years and came up empty. What a

disappointment! A little bit like peace in the Middle East or the Cubs winning the pennant: A single, charismatic Israeli ambassador or a superstar shortstop alone does not do it—it takes a village.

BRCA 1 and 2 may wear black hats, but even a tough kid can come clean with caring parents, good teachers, and a nurturing environment. A couple of special genes require unique molecular and environmental conditions, plus a lot of luck, to achieve cancer. If mom and a couple of sisters have pulled this off previously, that is a whole lot more ominous than some inscrutable gene chip. A macro discussion with your patient always trumps a microarray.

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