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ASO PERSPECTIVES

Cancer Genetics Moves out of Its Winter of Discontent

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Francis Bacon helped to bring the human race into the Age of Enlightenment by organizing existing knowledge and framing the basic approach used in the scientific method. Humans have since made progress in innumerable areas, slowly losing our fear of the darkness of ignorance.

We are finally entering the Age of Enlightenment in terms of genetic testing. The 2013 Supreme Court decision that struck down the patent on the *BRCA* gene,[1] the astronomical decrease in the cost of genetic testing (due to the conversion from Sanger sequencing to next-generation sequencing),[2] the explosion of new knowledge regarding cancer genetics, and the codification of guidelines for most cancer genes (thanks to the National Comprehensive Cancer Network [NCCN] and others) has brought us out of the Dark Ages and into the light. We are no longer warily groping around in a dark cave, seeing danger behind every shadow. We are finally turning the corner from the maternalistic concern that patients need to be protected from the dangers of genetic testing to the realization that genetic testing will decrease the morbidity and mortality of cancer. It is becoming increasingly obvious that identifying a person as having a pathogenic variant and managing them by the established guidelines can be lifesaving. While it is regrettable that it has taken us this long to move forward, it is heartening to see more and more patients being tested by more and more providers and thus more and more carriers having their cancers prevented, found at an earlier and more treatable stage, or treated with more effective drugs or procedures. The barriers to genetic testing are finally falling, and almost everyone now understands that limiting the right to genetic testing to a small number of genetic counselors while enormous numbers of patients remain unaware of their pathogenic variant status is not good medical care.

The future requires some level of education for providers in order to maximize the benefit to patients and minimize the risk. Providers do need to understand how to provide informed consent to patients for testing, specialists must know how to manage screening, prevention, and treatment of cancers in their organ of interest, and anyone doing testing needs to know their limitations and what specialists should be consulted as pathogenic variants are found. And providers must understand that a variant of uncertain significance (VUS) is just that and should not be used to direct care. But it is irrational to pronounce that no one should do genetic testing unless they know everything about the genes they are testing. This is akin to suggesting that a breast surgeon cannot order a computed tomography of the abdomen because he or she does not know how to manage an adrenal mass that might be found.

In the age of increasing specialization, all of us must know our limitations and make referrals early and often. This is true for all of us and true for genetic testing results. In addition, we need to develop tools that make caring for patients easier. Clinical decision support tools need to be an integral part of our electronic medical records. Until they are, standalone apps and internet resources will need to fill the gap.[3,4]

To facilitate providers' integration of genetics, it seems worthwhile to consider a framework for understanding the numerous cancer susceptibility genes that are now being tested. One such framework would consider (a) the spectrum, (b) the penetrance, (c) the age of onset, and (d) the specific subtype of disease relative to each gene.

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The spectrum of diseases helps to clarify what family history might trigger testing, which organs might need added attention, and which specialists might be involved in management. As an example, *BRCA2* increases the risk of female and male breast cancer, ovarian cancer, melanoma, and prostate cancer, while *CDH1* increases the risk of gastric cancer and female breast cancer.[5–7] This dictates where to target our screening, prevention, or consultations for each gene.

The penetrance for each disease is critical to determine how aggressive we need to be with our management. As an example, both *ATM* and *BRCA2* increase the risk of ovarian cancer. The penetrance for *BRCA2* is 13–29%[8], and oophorectomy is recommended by NCCN.[9] But as the penetrance for *ATM* is $< 3\%$, the NCCN states there is insufficient evidence to recommend oophorectomy.[9]

The age of onset determines when to begin an intervention. For example, the risk of ovarian cancer begins to increase at around age 35 years in *BRCA1* but not until 45 years in *RAD51C*. For this reason, the NCCN suggests considering oophorectomy (if childbearing is complete) around age 35 years in *BRCA1* and around age 45 years in *RAD51C*.[9] This means a woman with *RAD51C* can benefit from 10 more years of natural hormones.

We are now adding increasing knowledge about the fourth element in our framework, the specific subtype of cancer that the gene predisposes a patient to. The recent work by the Breast Cancer Association Consortium helps to clarify that not all breast cancer genes cause garden-variety breast cancer.[10] This multicenter, international case–control study involved 42,680 breast cancer patients and 46,387 control participants, all of whom were sampled independently of family history, from 38 participating studies (22 countries worldwide). The enrolled patients and controls were sequenced for the protein-truncating variants and rare (population frequency $< 0.1\%$) germline missense variants of nine breast cancer susceptibility genes, including *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53*. The authors categorized breast cancer into five intrinsic subtypes based on immunohistochemistry and grade: HR^+ERBB2^- low (intermediate) grade, HR^+ERBB2^+, HR^+ERBB2^- high grade, HR^-ERBB2^+, and triple negative (TN).

Substantial heterogeneity was identified among the associations between breast cancer susceptibility genes and intrinsic subtypes. The strongest disease subtype association for each gene was TN disease for *BRCA1* (odds ratio [OR], 55.32; 95% CI, 40.51–75.55), *RAD51C* (OR, 6.19; 95% CI, 3.17–12.12), *RAD51D* (OR, 6.19; 95% CI, 2.99–12.79), and *BARD1* (OR, 10.05; 95% CI, 5.27–19.19); HR^+ERBB2^- high-grade disease for *ATM* (OR, 4.99; 95% CI, 3.68–6.76), *BRCA2* (OR, 11.53; 95% CI, 8.92–14.90), and *PALB2* (OR, 9.43; 95% CI, 6.24–14.25); and HR^+ERBB2^+ disease for *CHEK2* (OR, 3.17; 95% CI, 2.36–4.26) and *TP53* (OR, 7.14; 95% CI, 3.34–15.28).

It was noted that *BRCA1* was associated with increased risk of all subtypes, but the ORs varied widely from 2.27 (HR^+ERBB2^+) to 55.32 (TN). In contrast, the associations between *BRCA2* and disease subtypes were more homogeneous (OR range 3.38–11.53). Increased risk of TN disease was associated with all genes except for *ATM*, *CHEK2*, and *TP53*.

Age is an important factor associated with the prevalence of pathogenic variants and the risk of different disease subtypes. These nine genes were associated with 14.4% of all breast cancer in women aged ≤ 40 years but less than 4% in women aged ≥ 60 years. Among the former group, the highest prevalence of combined variants was observed in those with TN disease (27.3%). For most genes and disease subtypes, increasing age was associated with decreasing risk. The highest cumulative risks were estimated for *BRCA1*–TN disease (40% by age 80 years) and *BRCA2*– HR^+ERBB2^- low-grade disease (22% by age 80 years). While the association between age and risk was formerly seen to indicate low utility for testing older patients, we now understand that the implications of a rare pathogenic variant in an older patient extend far beyond the individual patient to her family.

This study highlights the short-sightedness of testing only the most common genes. While *BRCA1* is likely to cause mostly TN disease, this does not mean that all hereditary TN disease is caused by *BRCA1*. The paper clearly shows that TN disease can also be caused by pathogenic variants in at least five other genes, including *BARD1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*. This speaks to the need for large genetic panels and supports the American Society of Breast Surgeons' guideline that all breast cancer patients should be offered genetic testing.[11]

We need to increase our knowledge even further about all genes, not just the genes we think might be the reason for our patients' cancer. We need to come to grips with the realization that the cost of whole-exome sequencing is rapidly approaching the current cost of a cancer panel. It will not be long before whole-exome sequencing or whole-genome sequencing is available to all of our patients, and we will need tools to manage this deluge of information.

We have gained tremendous understanding about what cancers are increased by what genes, when that risk begins to accrue, and how penetrant that risk is. We are now gaining insight into the specific subtypes of cancer by gene.[10] Adding this new knowledge gives us a greater ability to determine not just a general screening and prevention strategy for each gene but one targeted at the most common subtype.

The rate of genetic testing has been restrained for decades for fear of the unknown. As the unknown world becomes the known world, those restraints must be lifted. Genetic testing has joined the mainstream for many cancer doctors. It's time to get on board.

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