Considerations in Testing for Inherited Breast Cancer Predisposition in the Era of Personalized Medicine

Benjamin Powers, MD[a], Tuya Pal, MD[b], Christine Laronga, MD[a,*]

KEYWORDS

- Inherited breast cancer syndromes • Surgical considerations
- Personalized medicine • Germline mutation

KEY POINTS

- Multigene panel testing has led to an increase in the number of individuals (both affected and unaffected by cancer) being identified with a germline mutation (ie, pathogenic variant).
- Surgeons are often at the forefront of point of service for individuals at risk for inherited cancer syndromes and must stay current with identifying these at-risk individuals.
- Provision of care through a multidisciplinary team, inclusive of genetic counseling before and after testing, is imperative to appropriately counsel and manage individuals with inherited cancer syndromes.
- Surveillance and management of individuals is personalized based on the gene in which the pathogenic variant is identified, often in conjunction with the personal and family cancer history.

INTRODUCTION

Breast cancer remains the most common cancer and the second leading cause of death affecting women in 2017.[1] Women in the United States have a 12% lifetime risk of developing breast cancer,[2] with an increase in breast cancer incidence from 2004 to 2013, exclusively caused by increasing rates among nonwhite women.[3]

Studies of families have shown that the risk of breast cancer increases with the number of affected relatives.[4] Although most breast cancers are sporadic, 5% to

Disclosures: Dr C. Laronga is on the Speaker's Bureau at Genomic Health and receives royalties from Up-To-Date. Drs B. Powers and T. Pal have nothing to disclose.
[a] Department of Breast Oncology, H. Lee Moffitt Cancer Center, 10920 N. Mckinley Drive, Tampa, FL 33612, USA; [b] Department of Medicine, Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA
* Corresponding author.
E-mail address: christine.laronga@moffitt.org

Surg Oncol Clin N Am 27 (2018) 1–22
http://dx.doi.org/10.1016/j.soc.2017.08.003
surgonc.theclinics.com

10% of cases are caused by a germline mutation (which may also be referred to as a pathogenic variant) in an inherited cancer gene leading to hereditary cancer predisposition.[5] Mutations in these genes lead to a significantly higher risk of developing breast and other cancers compared with cancer risks among women with sporadic breast cancer.[6]

Over the last few years, important technological advances realized through next-generation sequencing (NGS) technologies coupled with the loss of the ability to patent genes have led to greatly decreased costs for genetic testing. NGS-based tests have led to paradigm shifts in genetic testing, enabling clinicians to test for multiple conditions simultaneously (called multigene panel testing) compared with the prior phenotype-directed approaches with sequential testing of 1 condition at a time through the use of Sanger sequencing. With the increasing use of multigene panel tests, the genetic counseling and testing landscape has continued to rapidly evolve. Furthermore, with the identification of more high-risk individuals, the hope is that this information may be leveraged to improve cancer outcomes and influence evidence-based screening, diagnosis, and treatment of patients with breast cancer. Despite the considerable technological advances in genetic testing, the surgical clinic remains the primary locus for identification and management of many of these high-risk patients.[7] However, lack of identification coupled with barriers in access and use of genetic services remain significant challenges to achieving equity through risk reduction strategies.[8,9] Furthermore, many busy surgeons lack the time needed to appropriately counsel patients regarding risk assessment, testing, and results interpretation, and some also have limited proficiency and lack formal training in genetics. These factors may lead them to recommend prophylactic surgery regardless of the gene in which the pathogenic variant (or even a variant of uncertain significance [VUS]) is encountered.

This article focuses on identification of individuals at high risk for inherited breast cancer and referral to (and/or conduct of) genetic counseling and testing for hereditary cancer syndromes, if appropriate. Referral in the context of a newly diagnosed patient with breast cancer or a suspected unaffected high-risk patient for further genetic evaluation is outlined. In addition, approaches for management of specific moderate-penetrance to high-penetrance hereditary breast cancer syndromes are reviewed.

IDENTIFICATION OF HIGH-RISK INDIVIDUALS

Identification of high-risk individuals is predicated on knowledge of the extent and magnitude of breast cancer risk factors and is a multistep process involving a multidisciplinary team of health care professionals. Multiple associations and societies have produced recommendations for screening for genetic predisposition to cancer. Based on recommendations from the National Comprehensive Cancer Network (NCCN), US Preventive Services Task Force, and the National Accreditation Program for Breast Centers (NAPBC), individuals at high risk for hereditary cancer should be offered genetic counseling.[10–12] Although the definition of high risk carries a subjective component, because patients may interpret personal risk differently, there remains an onus on clinicians to provide patients with an accurate assessment of risk to best equip the patients in the informed decision-making process.

The starting point in surgical practice for identification of high-risk (genetic and nongenetic) individuals is the clinical history and physical examination (**Table 1**). Clinical history should include a 3-generation family pedigree of any cancer occurrence and age at diagnosis, inclusive of both the maternal and paternal lineage, as well as all relatives given that family structure is also an important consideration when