

Appendix 4. Understanding Genetic Counseling and Testing

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INTRODUCTION

This review focuses on educational tools that are available for providers (principally primary care and obstetrics and gynecology providers) to enhance understanding of basic genetics, genetic testing, and interpretations of results. More specifically, it sought to determine whether there are validated or other widely accepted tools that can be incorporated into practice to improve the identification of women at increased risk of early onset breast cancer (EOBC). To address this, the following questions were used to direct a literature search.

- 1. What resources are available for learning about basic genetics, genetic testing, and results?**
- 2. What validated tools or best practices are available for communicating to patients about referral for genetic counseling for EOBC or for understanding genetic tests and results relevant to EOBC?**
- 3. Are there validated tools or best practices from other areas that may be relevant?**
- 4. What are current major society or health services guidelines for communicating to patients about genetic counseling referral or testing for EOBC, including guidelines from other areas?**

P – Patient, Problem or Population. I – Intervention. C – Comparison, control, or comparator. O – Outcome(s) (PICO)

P: Primary care providers (principally obstetrics and gynecology providers) who care for women aged 18–45 who appear to have a high genetic risk for breast cancer

I: Carriers of pathogenic genetic variants that increase the risk of EOBC (eg, BRCA, PALB2, CHEK2, ATM, p53, PTEN); validated screening tools and appropriateness for use in obstetrics and gynecology practices

C: Educational tools aimed at providers who care for women at risk for EOBC regarding basic cancer genetic understanding that is relevant in the clinical arena; introduction to and use of risk assessment tools that are validated for identifying women at high genetic risk; and appropriate ordering/testing/interpretation of genetic testing, specifically:

- Who should be screened?
- Who should be tested?
- Who should be sent for genetic counseling and testing?
- Appropriate interpretation of the test

O: Identification of genetic carriers that increase the risk of EOBC; cost-effectiveness of various strategies of screening (eg, selected screening based on selection criteria, such as National Comprehensive Cancer Network [NCCN] vs population-based screening)

METHODS

Using the PICO criteria, the American College of Obstetricians and Gynecologists (ACOG) clinical reference staff searched the Cochrane, MEDLINE, and PubMed databases for all relevant references. Additional review was carried out for relevant guidelines published by ACOG, American Cancer Society, NCCN, American Society of Breast Surgeons, Society of Surgical Oncology, the American College of Radiology, the U.S. Preventive Services Task Force (USPSTF), and the American Society of Breast Disease. References within the included papers were reviewed for additional publications related to the topic and questions.

Literature Review

The review included titles and abstracts, as well as the full text if needed, to determine whether the articles were relevant to the questions posed. Studies were included if they addressed provider understanding of the need for referral to genetic counseling and interpretation of genetic testing related to EOBC and particularly if they included resources available for an understanding of basic cancer genetics or genetic testing, including interpretation of results. References with either validated tools or best practices that addressed these areas were also included. The review focused on screening for, and identification of, gene mutations that substantially increase the risk of EOBC (eg, autosomal dominant single gene mutations). The review of major society and health services guidelines sought to identify current recommendations for communicating to patients about genetic counseling referral or testing for EOBC.

Specific inclusion criteria were as follows:

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- U.S. and Canadian guidelines that address EOBC or enhanced screening in high-risk groups (including ACOG guidelines)
- Women aged 18–45
- U.S. and Canadian studies or United Nations Human Development Index
- Major society or health service guidelines, systematic review, meta-analysis, cohort study, case–control study, or randomized controlled trial
- Studies that compare different populations of interest
- English-language

Specific exclusion criteria were as follows:

- Average-risk women
- Pregnancy
- Pregnancy-associated breast cancer
- Male breast cancer
- Unavailable in English
- Case series and reports
- Studies done exclusively outside the United States

In addition, studies were excluded if they were not related to risk assessment, identification, counseling, or interpretation of cancer genetic testing results or involved techniques deemed nontransferable for the purpose of this review. Population-based studies or hypothesis-generating studies that did not address provider genetic education or counseling for risk assessment, identification, or interpretation of

testing results were excluded. Articles were not reviewed if they were related to breast cancer treatment decisions based on genetic status. The review excluded genetic interventions aimed at cancer specialists after diagnosis or aimed specifically at genetic counselors, not providers. Articles about genetic counseling that were not specific to cancer genetics (eg, prenatal counseling for noncancer genetic diseases) or related to cancer genetic counseling for non-breast-related syndromes (eg, Lynch) were excluded. Tools developed for research settings only or to help patients in understanding breast cancer and breast cancer management, not genetics, were not reviewed.

Finally, a separate search sought to identify any additional relevant guidelines, resources, or tools from other professional societies and health service organizations in the United States. The search was conducted using Google and Google Scholar and included terms to capture titles that might not have been identified in the systematic search by ACOG staff. Documents from this process were included if they were relevant to the study questions; met the inclusion and exclusion criteria; and were endorsed by major U.S. medical societies or health service organizations that might be generally recognized as authoritative by U.S. primary care providers or obstetric and gynecologic providers.

RESULTS

The search returned 116 results. After review, 30 studies were included based on the listed criteria. The secondary online review for resources identified an additional six documents.

What resources are available for learning about basic genetics, genetic testing, and results?

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A number of online and published resources are available for providers to learn about basic cancer genetics, genetic testing, and genetic test interpretations. The National Institutes of Health maintains a periodically updated list of approximately three dozen online resources specifically designed to educate and assist health care providers on various topics ranging from basic genetics, understanding risk assessment, criteria for referral to genetic counseling, and interpretation of genetic test results.¹ Other collaborations of national societies have provided genetics “toolkits” or published guidance to educate providers on basic cancer genetics, risk assessment, and referral recommendations.^{2,3} In addition, each of the following groups has educational material with goals to improve understanding of genetics, risk assessment, and referral recommendations by providers, consumers, or both:

- American Society of Human Genetics
- Association of Professors of Human or Medical Genetics
- National Society of Genetic Counselors
- American College of Medical Genetics
- American Board of Genetic Counseling
- American Board of Medical Genetics
- National Coalition for Health Professional Education in Genetics
- International Society of Nurses in Genetics
- Council of Regional Networks (discontinued)
- Association of Genetic Technologists (formerly the Association of Cytogenetic Technologists)
- Genetic Society of America
- Council of Medical Genetics Organizations

Providers can also learn about these topics through other mechanisms, such as continuing medical education courses sponsored by universities, academic medical centers, and the National Institutes of Health, as well as resources from national laboratories that provide services related to genetic testing. Funding for these education courses varies and includes monies derived from federal grants, industry-supported grants, and not-for-profit foundation grants, among other sources. Many are self-funded and offer their services at no charge or are supported by website advertisements. Some offer continuing medical education credit and have specific learning objectives; for others it is not clear whether materials have been subject to peer or other expert review. The depth and detail of the material covered range from superficial (eg, short videos) to online courses that take place over several months. Almost none of the online courses provide a validated assessment of competency or certification to determine their level of expertise in providing counseling to patients. Nonetheless, some practitioners rely on such tools to learn how to better counsel patients about genetic risk. A partial list of online educational sites is included as additional material (Table 1).

What validated tools or best practices are available for communicating to patients about referral for genetic counseling for EOBC or for understanding genetic tests and results relevant to EOBC?

In a 2014 review, USPSTF determined that there is sufficient evidence to recommend that primary care providers should perform risk assessment based on family history for women at risk for EOBC and refer women who screen positive to cancer genetic counselors (Category B recommendation).⁴ This recommendation remains essentially unchanged in the 2019 draft guideline recommendations.⁵ All of

the available validated tools are specific for evaluating who should be referred for BRCA testing, not just for identifying women at risk for EOBC. However, given that women with BRCA genes constitute the greatest proportion of those at genetic risk for EOBC, these tools are reasonable proxies for genetic screening for EOBC. There are several familial risk stratification tools that can identify the need for referral for genetic counseling, including the Ontario Family History Assessment Tool,⁶ Manchester Scoring System,⁷ Referral Screening Tool (B-RST),⁸ Pedigree Assessment Tool,⁹ and FHS-7.¹⁰ The [Breast Cancer Genetics Referral Screening Tool \(B-RST\)](#) is a relatively simple and quick screening tool to guide providers on who may benefit from further risk assessment by a genetic counselor and, possibly, genetic testing. To clarify ease of use of one of these tools, the B-RST has six questions (see the [B-RST](#)).

All of these tools appear to have utility in predicting which women should be referred for genetic counseling because of increased risk for EOBC from potentially harmful BRCA mutations. While the tools have been validated in some populations (mostly non-Hispanic whites) and are currently available, it is unclear how frequently they are used in practice by primary care or obstetric and gynecologic providers. Specialty societies (eg, ACOG, NCCN, American Society of Clinical Oncology, and National Society of Genetic Counselors) have developed similar tools that list indications for further genetic counseling or appropriateness for genetic testing or both.¹¹⁻¹³ These documents are produced by experts, and while their assessment questions generally overlap with the validated tools, they have not necessarily been validated. Because new research results in changes in indications for referral or testing, and these expert documents are updated at different time intervals, the indications for referral or genetic testing can vary from document to document depending on when providers consult them.

Once testing has been performed, the interpretation of results and posttest counseling is very important to guide patients in appropriate decision making about subsequent management.^{4,14} Interpretation of results is complex; test results for genetic mutations are reported as positive (ie, potentially harmful mutation detected), variants of uncertain significance, uninformative-negative, or true negative. Genetic counselors are specifically trained to inform patients about the meaning of their test results and can assist providers in this interpretation to guide clinical decision making. Typically, such assistance is provided in person but, increasingly, counseling services (pretest and posttest) are being provided by telephone or through secure communication channels to identify genetic susceptibility to EOBC. (The list of online education resources in Table 1 under additional materials includes some online communication mechanisms.)

Are there validated tools or best practices from other areas that may be relevant?

There are sufficient validated tools to guide providers in assessing women who might be at increased risk for EOBC, but most of these tools assess for gene mutation carriage rather than assess all women at risk for EOBC. A number of additional tools are available to estimate invasive breast cancer risk, and while each calculates a lifetime risk, the predicted age of onset is not included. See Table 2 under additional materials for a comparison of four commonly used risk assessment models, including the different items assessed and some of the limitations in using each model for EOBC assessment.

A relatively recent systematic analysis and meta-analysis evaluated 17 published breast cancer predictive models.¹⁵ After conducting this thorough evaluation, the authors had substantial concerns. First, there were no accepted standards or templates in the field of predictive model methodology, akin to the successful Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach for systematic reviews or the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized controlled trials. Second, meta-analysis was difficult because of variations in reporting and the fact that there were few validation studies. The authors recommended that primary studies be conducted to compare all of the models using the same dataset(s), a methodology that has proved successful in other fields.¹⁶ It remains uncertain how frequently these tools are used within primary care practices. If they are used, it is not clear how well they function in generating appropriate referrals to genetic counselors or, for patients who are not referred, whether appropriate genetic counseling is performed within primary care practices.

Newer approaches using genome-wide association studies have identified multiple single nucleotide polymorphism (SNPs) that occur more frequently in women with breast cancer. Unlike autosomal dominant genes, such as BRCA, multiples of these SNPs are being combined into a polygenic risk scoring approach that may perform better than current breast cancer risk assessment models.^{17,18} Such studies are being performed in cancer genetics as well as other fields (eg, cardiovascular disease risk). At present, while some commercial laboratories state they have validated studies and are prepared to provide clinical testing for patients,¹⁹ none of these risk scores have been subjected to peer review; as such, the testing is not yet ready for use in clinical practice. Moreover, polygenic risk scoring will likely

need to be combined with other risk factors (eg, family history, reproductive risk factors, and environmental exposures) to create a more accurate score.

What are current major society or health services guidelines for communicating to patients about genetic counseling referral or testing for EOBC, including guidelines from other areas?

To date, ACOG, NCCN, the American Society of Clinical Oncology, the Society of Gynecologic Oncology, American Society of Genetic Counselors, and USPSTF have all developed or reported guidelines to assist providers in communicating with patients about referral to genetic counseling or testing or both for EOBC.¹¹⁻¹³ Communication of results is included in some of the guidelines, but other specialty societies have produced separate guidance specifically addressing the interpretation of genetic test results and how to communicate these results to patients.¹⁴ Depending on the source, updates to the guidelines can be regular (eg, annual)¹¹ or periodic (every few years),^{4,12,13} and the rationale or determination for how frequently these guidelines are updated is neither stated nor implied. All of the guidelines recommend that all women be screened for personal and family history of breast, ovarian, and other genetic-related cancers to determine whether they meet criteria for referral for genetic counseling or testing or both. In addition, all of the guidelines recommend that determination for testing, including pretest and posttest counseling, should be performed by individuals with appropriate training (eg, certified genetic counselors). The background, training, and ongoing competence evaluation of individuals with this expertise is not specified.

ASSESSMENT OF THE LITERATURE

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Strengths

There are at least moderate-quality data indicating that risk assessment, referral for genetic counseling, and genetic testing provide net benefit to those with a family history of cancers associated with EOBC.⁴ Several guidelines are available to assist providers in determining whether there is sufficient risk for referral to a genetic counselor. Correct identification of women who carry pathogenic variants in EOBC genes (ie, BRCA1, BRCA2, PALB2, TP53, CDH1, NF1, PTEN, STK11) that have an autosomal dominant pattern of inheritance allows the employment of intensive surveillance for early detection or risk reduction methods.

Weaknesses and Gaps in Information Pertinent to Making Recommendations

There are numerous weaknesses or gaps in the information on genetic testing:

- The bulk of the data available on risk assessment and testing are for BRCA mutations only, and studies were performed in academic research centers.
- The outcomes data tend to focus on short-term outcomes (eg, early breast cancer detection, node-positive vs node-negative disease).
- There is a paucity of data comparing the different tools (or various approaches using these tools) as to how effective they are for screening and counseling high-risk women and which are most effective in improving access to genetic counseling.

- While tools are available, the specific training needed for persons other than trained genetic counselors to provide effective genetic counseling has not been determined.
- Despite some use of genetic counseling by telephone or online, in-person counseling remains the primary method by which women are counseled. Notably, the shortage of genetic counselors in the United States has been identified as a barrier to effective counseling.^{20,21} Further study is necessary to determine which methods of delivery of genetic counseling represent best practice, and particularly which methods can increase access to genetic counseling in low-resource, low-health-literacy, or rural settings. Moreover, there is limited access to certified genetic counselors in the United States, which creates another potential barrier to timely and effective counseling.
- In a recent consensus statement based on a literature review, the American Society of Breast Surgeons recommended that all women with a history of breast cancer (regardless of age of onset or cancer biology) be offered testing for BRCA 1 or BRCA 2.²² Panel testing in all breast cancer patients has been espoused in another recent publication.²⁰ While it is likely that many pathogenic variants are missed by following current guidelines, there are insufficient studies to determine whether this expanded approach would improve outcomes and what the unintended consequences of more widespread screening might be. Moreover, it is unclear whether limiting testing to just BRCA 1 or BRCA 2 genes, as opposed to more inclusive testing (panel testing) with other known genes associated with EOBC, would provide more benefit. Given the paucity of data, adoption of these recommendations should await more validation to determine both harms and benefits to effectively counsel women presumed to be at high risk.

- There are differences in the various validated tools and national guidelines for risk assessment, recommendations for referral for counseling, and recommendations for referral for testing. Given that no one tool has been tested in the various settings and populations in which health care is delivered in the United States, confusion remains as to which guideline should be used. Under these circumstances, the resource updated annually is likely the most useful guide—that is, NCCN’s guidelines.
- Resource barriers, including lack of insurance coverage and the unavailability of appropriate professionals to perform risk assessment and counsel patients about genetic risk, remain poorly understood. It is necessary to determine what unmet need exists in the United States to reduce the morbidity and mortality related to EOBC.

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ADDITIONAL MATERIALS

Table 1. Websites Designed to Provide Education on Genetics, Genomics, and Genetic Counseling and Testing*

Website	Address	Brief Description	Intended Audience[†]
Access Excellence	http://www.accessexcellence.org/	A series of learning modules on multiple science and health topics, including biotech and genetics; sponsored by the National Health Museum, a non-profit organization	G
About Genetic Counseling (National Society of Genetic Counselors)	http://aboutgeneticcounselors.com/	Website to introduce the concept of genetic counseling to patients, discussing the process and value of genetic counseling, genetic testing, and some genetic conditions	G
American Medical Association: Family History Tools	https://www.ama-assn.org/delivering-care/precision-medicine/collecting-family-history	Tools for gathering family history	P

Diving into the Gene Pool	www.exploratorium.edu/genepool/genepool_home.html	An online exhibition exploring genetics and the Human Genome Project from a variety of perspectives, produced by the Exploratorium of San Francisco, CA	G
The DNA Files	http://www.dnfiles.org/	A series of 14 one-hour public radio documentaries and related information	G
DNA From the Beginning	http://www.dnaftb.org/dnaftb	An animated primer on the basics of DNA, genes, and heredity	G + P
DNA Interactive	https://dnalc.cshl.edu/	DNA and genome-related teaching guides and lesson builders, personalized web pages, <i>My DNA</i> , student activities, and more	G
DNA Learning Center	http://www.dnalc.org/	“DNA Learning Center's mission is to prepare students and families to thrive in the gene age, envisioning a day when all elementary students are exposed to principles of genetics and disease risk; when all high school students have the opportunity to do hands-on experiments with DNA; and when all families have access to	G

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		genetic information they need to make informed health care choices.” Includes an interactive DNA timeline	
Genetic Alliance Publications	http://geneticalliance.org/resources/publications	Website aimed at patients to provide both information and toolkits to self-assess risk and education about specific cancer genetic disease states	
Genetic Testing Registry	https://www.ncbi.nlm.nih.gov/gtr/	Information for health professionals about hundreds of genetic tests	P
Genetic Testing: What It Means for Your Health and Your Family's Health	https://www.genome.gov/Pages/Health/PatientsPublicInfo/GeneticTestingWhatItMeansForYourHealth.pdf	From the Trans-NIH Genetics Working Group for the Public	G
Genetics and Disease Prevention Information	https://www.cdc.gov/genomics/default.htm	Centers for Disease Control and Prevention website with resources on genetics, including journals, reports, and fact sheets; also includes online multimedia presentations ranging from basic genetics to latest research	G,P

Genetics Education Center	http://www.kumc.edu/gec/	A comprehensive listing of genetics education resources, including networking sites, documentary films, lectures, booklets, activities, and programs, compiled by the Genetics Education Center, University of Kansas Medical Center	G, P
Genetics Home Reference	http://ghr.nlm.nih.gov/	National Library of Medicine's website for consumer information about genetic conditions and the genes or chromosomes related to those conditions	G, P
Genetics in Primary Care	https://genes-r-us.uthscsa.edu/resources/genetics/primary_care.htm	Training program curriculum materials	P
Human Genome Resources	http://www.yourgenome.org/	Comprehensive one-stop genomic information center, hosted by the National Center for Biotechnology Information of the National Library of Medicine	G

Human Genome Epidemiology Network	http://www.cdc.gov/genomics/hugenet/default.htm	International collaboration for sharing population-based human genome epidemiologic information	
Human Genome Project Education Resources	https://web.ornl.gov/sci/techresources/Human_Genome/index.shtml	An extensive collection of publications, teaching aids, and additional internet resources, hosted by the Human Genome Program of the U.S. Department of Energy	
Information for Genetics Professionals	www.kumc.edu/genetics/geninfo.html	Educational, clinical, and research resources	
Michigan Department of Health and Human Services	https://www.michigan.gov/mdhhs/0,5885,7-339-73971_4911_4916_47257_68337-356210--,00.html	General Information about hereditary cancer and public health in Michigan, including hereditary breast and ovarian cancer and early genetic mutations that may cause early onset breast cancer	
National Coalition for Health Professional Education in Genetics: Principles of Genetics for Health Professionals	https://www.ncbi.nlm.nih.gov/books/NBK115543/	Provides basic guidance to a broad range of individuals and groups as they plan educational initiatives in genetics and genetically based health care	

<p>Online Mendelian Inheritance in Man</p>	<p>www.ncbi.nlm.nih.gov/omim</p>	<p>Information about human genes and disease.</p>	
<p>Cancer Genetics Overview (PDQ)— Health Professional Version</p>	<p>https://www.cancer.gov/about-cancer/causes-prevention/genetics/overview-pdq</p>	<p>A website designed for professionals to assist in understanding genetic counseling, familial cancer susceptibility syndromes, methods of genetic analysis, and gene discovery</p>	
<p>The Virtual Genetics Education Centre</p>	<p>https://www2.le.ac.uk/projects/vgec/healthprof</p>	<p>Website contains evaluated genetics teaching resources for educators and teachers in schools and higher education, health professionals, and the general public; resources include simple experiments suitable for all ages, tutorial material videos on useful techniques, current and relevant links to other evaluated resources, created by the Department of Genetics at the University of Leicester (UK)</p>	

*Adapted from National Human Genome Research Institute. Genomic education websites. Available at:
<https://www.genome.gov/about-genomics/teaching-tools/Genomics-Education-Websites>. Retrieved
October 22, 2019.

†G, general; P, providers.

Table 2. Comparison of Four Validated Models That Estimate Individual Risk of Breast Cancer

Model	Product (s)	Inclusive Items	Limitations for Early Onset Breast Cancer
Breast Cancer Risk Assessment Tool (modified Gail model, National Institutes of Health website)*	<ul style="list-style-type: none"> • 5-year breast cancer risk • Lifetime breast cancer risk (to age 90) 	<ul style="list-style-type: none"> • Age • First-degree female relatives with breast cancer • Ethnicity/race • Age at menarche • Age at first birth • Prior breast biopsies (and if atypia present) 	<ul style="list-style-type: none"> • Not validated prior to age 35 • Ignores all breast cancer except female first-degree relatives • Does not include any potential related cancers (eg, ovarian) • Cannot be used in women with prior ductal carcinoma in situ, lobular carcinoma in situ, or thoracic radiation
Tyrer-Cuzick [†]	<ul style="list-style-type: none"> • Calculates lifetime risk of breast cancer 	<ul style="list-style-type: none"> • Family history (breast and ovarian, includes both maternal/paternal and three generations) 	<ul style="list-style-type: none"> • Does not include breast density, though subsequent studies have added breast

	<ul style="list-style-type: none"> Generates graph that estimates cumulative breast cancer risk by age 	<ul style="list-style-type: none"> Age Age at menarche Parity Age at first birth Age at menopause Prior breast biopsies with atypia or lobular carcinoma in situ Use of hormone replacement therapy Ashkenazi Jewish heritage Height/body mass index 	<p>density to the Tyrer-Cuzick model[‡]</p>
Claus model [§]	<ul style="list-style-type: none"> Risk of invasive breast cancer predicted by age of onset of disease (10-year increments starting at age 20–29) 	<ul style="list-style-type: none"> First- and second-degree relatives with breast cancer and age of onset 	<ul style="list-style-type: none"> Largely a model to predict the likelihood of an autosomal dominant allele Only Caucasian patients Factors beyond family history not included

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BOADICEA ¹¹	<ul style="list-style-type: none"> • Risk of carrying BRCA 1 or BRCA 2 pathogenic variant • Risk of proband developing invasive breast cancer, calculated in 5-year increments (starting at age 25) 	<ul style="list-style-type: none"> • Family history of breast and ovarian cancer and age of onset 	<ul style="list-style-type: none"> • Complex modeling using segregation analysis of breast and ovarian cancer occurrence • Uses family history only
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* Data from National Cancer Institute. The Breast Cancer Risk Assessment Tool. Available at: <https://bcrisktool.cancer.gov/>. Retrieved October 22, 2019.

† Data from Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med.* 2004;23(7):1111–30.

‡ Data from Brentnall AR, Harkness EF, Astley SM, Donnelly LS, Stavrinou P, Sampson S, et al. Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. *Breast Cancer Res.* 2015;17(1):147; and Warwick J, Birke H, Stone J, Warren RM, Pinney E, Brentnall AR, et al. Mammographic breast density refines Tyrer-Cuzick estimates of breast cancer risk in high-risk women: findings from the placebo arm of the International Breast Cancer Intervention Study I. *Breast Cancer Res.* 2014;16(5):451.

§ Data from Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early onset breast cancer. Implications for risk prediction. *Cancer.* 1994;73(3):643–51.

¹¹ Data from Antoniou AC, Pharoah PPD, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br J Cancer*. 2004;91(8):1580–90.