Precision Medicine in Breast Cancer

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Breast cancer care has improved markedly in recent decades, but new advancements in diagnosis and treatment depend on translating genomics and precision medicine into clinical care. This article discusses the basics of genomics, breast cancer biomarkers and subtypes, and the effects of genomic advancements on future breast cancer diagnosis, treatment, and survival. The article also presents challenges related to introducing precision medicine into cancer care and the role of imaging in breast cancer diagnosis and treatment in precision medicine.

In 1928, Hermann Joseph Muller discovered the link between radiation and mutations. He and Thomas Hunt Morgan also noted a link between radiation and cancer. These men were on the brink of discovering the genetic workings of cancer cells, but soon became rivals and both failed to accept the contribution genetics could make to medicine. Even though microscopic study of cancer cells in the 1940s showed mitosis in samples of cancer tissue, researchers could not determine why the normal division of cells became chaotic in malignant tissue.1

Early study of breast cancer and the human genome found 127 genes with mutations in 1 sample tissue from a 43-year-old woman.1 This early example showed the heterogeneity in breast cancer.1,4 For all living beings, genetic variation is the rule, not the exception.3 Although breast cancer detection and treatment have advanced in the past few decades and significantly improved survival, a cure for this increasingly prevalent cancer in women remains elusive.2,3 The heterogeneous nature of breast cancer leads to wide variation in presentation, behavior, and therapeutic response, which in turn affects each individual’s prognosis (see Figure 1).4,5 Heterogeneity can relate to differences among tumors from 1 population to another, variations within a tumor, or temporal variability in tumor growth or treatment response.4

At the molecular level, multiple cells and interactions make up the complex and diverse nature of breast cancer, and cancer clearly is a genetic disease, whether the altered genes are inherited or acquired during a person’s lifetime.9,10 Studies have identified variations in how breast cancers express clinical biomarkers such as estrogen, and new sequencing methods also have shown that in some breast tumors, no 2 cells have identical genomic profiles.4 Research now focuses on identifying heretofore unknown molecular causes of breast cancer,7 which can lead to the

After completing this article, the reader should be able to:

- Describe genomic terms and concepts.
- Understand the role of genetics in the continuum of breast cancer care.
- List the genetic subtypes of breast cancer.
- Explain precision medicine and targeted treatment of breast cancer.
- List the challenges associated with incorporating genetics and precision medicine into breast cancer care.
kind of personalized care that optimizes the benefits of breast cancer diagnosis and treatment while minimizing any associated harms.\textsuperscript{11}

A major step toward a cure—or at least improved survival for some women with the disease—rests with new approaches at the molecular level.\textsuperscript{9} Successful cloning of the human genome is opening the door to new opportunities in the diagnosis and treatment of disease. By identifying the genes involved in breast cancer development and recurrence, physicians can begin to treat patients using personalized approaches.\textsuperscript{11}

As of the end of 2016, breast cancer was considered a set of at least 5 discrete subgroups based on molecular features.\textsuperscript{7} Identification of estrogen receptor and human epidermal growth factor receptor 2 (ERBB2, formerly HER2 or HER2/neu) markers and development of treatment targeted specifically for these breast cancer types has been an initial step in applying genomic knowledge to breast cancer care.\textsuperscript{13} For the most part, however, translation of genomic medicine to traditional clinical care has been sporadic and lacks structured coordination.\textsuperscript{14} Research continues to further identify genetic changes and features related to breast cancer, along with the complex interaction between genetics and lifestyle or environmental factors.\textsuperscript{15}

**Genetics and Genomics**

Genomics is a relatively new term related to mapping of the human genome. The Human Genome Project began in 1990 and was completed in 2003. Collaborative efforts led to sequencing all 3 billion base pairs in the human genome. The term genome refers to a complete set of DNA instructions.\textsuperscript{16} Genetics, which is the study of how individual genes are composed and function to affect inherited traits or disorders, can be traced back to Gregor Mendel’s tracking of traits in pea plants in the 1800s.\textsuperscript{17,18} The World Health Organization defines genetics as “the study of heredity.”\textsuperscript{18} Genomics expands on genetics by including all genes and how they interact with one another and their environment. For example, genomics addresses the effect of lifestyle on gene interactions.\textsuperscript{17,18} In the context of breast cancer, genetic testing and counseling might assist with the diagnosis and care of women at risk for the breast and ovarian cancer susceptibility gene (BRCA1) mutation, but genomics includes the study of how genetic variants contribute to cancer development in women who have BRCA1 mutations.\textsuperscript{14,19} The term epigenetics refers to the study of lifestyle factors’ effects on gene expression.\textsuperscript{20}

With 100 trillion cells containing DNA in each individual, mapping the genome or identifying the cause of cancerous cell growth can be an enormous task.\textsuperscript{15} Further, 99% of human genomes and DNA base pairs are the same for all people.\textsuperscript{15,21} Variations that cause diseases such as breast cancer make up only 1% of the genome.\textsuperscript{16} Each individual can inherit risk for disease from either biological parent’s chromosomes, which means there are 2 chances for variations.\textsuperscript{19} Analyzing
and computing genetic alterations that contribute to cancer is a complex effort.22

**Genetic Materials and Terms**

Although a gene carries information and genetic materials, the mechanics of a gene’s function and even how genetic information reaches or activates within a cell is key to understanding cancer and other diseases.3

**DNA**

DNA, which is located primarily in a cell’s nucleus, contains molecular codes that control growth, aging, and other processes or traits. DNA can replicate, or copy, itself to produce identical DNA in new and old cells that have divided.20,21 Cell-free DNA (cfDNA) contains nucleic acid fragments released during apoptosis, or programmed cell death. Cell-free DNA is found at higher levels in people with cancer than in healthy individuals.8 Circulating tumor DNA (ctDNA) is a portion of cfDNA that is present in greater amounts in the bloodstream than actual circulating tumor cells. The ctDNA remains in the bloodstream only for a matter of hours.8 A gene is 1 section of DNA that contains complete instructions to make a specific protein. Genes are DNA sections with complete instructions for specific proteins.20,21

**RNA**

Ribonucleic acid (RNA) provides the blueprint for genes and is involved in gene activation. Transcription refers to the process of copying the RNA from a gene sequence, and translation involves the communication between messenger RNA sequences and amino acids during protein synthesis.1,23 Messenger RNA (mRNA) molecules hold the genetic information that makes proteins.24 Hormones such as estrogen promote transcription by binding to estrogen receptors of some genes. Estrogen also can cause genomic instability, and elevated estrogen levels are associated with increased breast cancer risk.24

RNA provides the genetic messages that translate into proteins, which then carry out the encoded function of a gene.1 MicroRNA (miRNA) is a short RNA molecule that might not code messages, but nonetheless is critical in gene expression (see Figure 2).26 Epigenetically regulated miRNA molecules reside frequently within sites and genomic regions associated with cancer. When certain miRNAs normally associated with tumor suppression are downregulated because of epigenetic modifications, cancer cells can be more highly malignant or likely to metastasize.26 Research has identified several miRNAs that affect breast cancer. For example, miR-21 is known to target and regulate tumor suppressors.27

**Somatic vs Germline Variants**

Germline variants, also called mutations, are hereditary changes in DNA sequence, passed through biological germ, or reproductive, cells (sperm and egg). Somatic alterations can occur in any of the body’s cells other than germ cells, including tumor cells; somatic

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Figure 2. MicroRNAs (miRNAs) are small molecules critical to gene expression. Researchers are creating artificial miRNAs capable of binding to and silencing genes associated with cancer. Delivering such miRNAs to their target is another challenge. This image shows self-assembled nanoparticles (in red) carrying miRNAs to an aggressive breast tumor in a mouse model and sticking to the tumor target with the help of an adhesive glue. Image courtesy of Joao Conde, Nuria Oliva, and Natalie Artzi, and the National Cancer Institute/Koch Institute for Integrative Cancer Research at MIT.
variants also can cause cancer. Germline variants are passed on to offspring, but somatic variants are not transferred. Somatic variations also are called acquired variations or mutations.3,24 Mutation of the BRCA gene is an example of a germline variant in breast cancer (see Figure 3). An example of a somatic variant is tumor protein p 53 (TP53).29

Proteins

Proteins are made up of amino acids and regulate most cellular functions.1,6 They also are receptors for other proteins. Proteins affect cellular pathways (combinations of genes working together) and the networks formed in cells, tissues, and organisms.1,6,21 For example, a number of specific proteins support DNA repair.20 By manufacturing enzymes, proteins can initiate biochemical reactions in cells. Although proteins control chemical processes in cells, environmental and lifestyle factors also affect chemical processes.1,6,21 Increased cellular proliferation in cancer cells requires metabolic resources (eg, nutrients) and genetic materials (eg, protein) to create supportive cellular pathways.31

Microbiome

A microbiome is the sum of genetic material in a cell or other microbe. The term also applies to groups of genetic material that share an environment. Trillions of microbes live inside each human body and can change depending on lifestyle, illness, and the physical environment. Recent study of the microbiome has found that some microbes live inside the body and cannot survive outside of its confines.32

Epigenome

The epigenome includes chemical compounds on genes that modify the genome to affect genomic behaviors. Epigenetic markers are not part of DNA, but can pass among cells as cells divide or regenerate. Genes are permanent, but epigenetic expression can change depending on the influence of lifestyle and environment.20,33 Epigenetic modifications have been found to affect many diseases, explaining differences in complex diseases such as breast cancer. Epigenetic changes could explain late onset of disease in some individuals or the variation in symptoms among people who have the same disease.36

Biomarker

A biomarker is a characteristic that can be measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacologic responses.3 Typically, biomarkers are found in blood or urine testing or through biopsy of tumor cells.34 Also called tumor markers, biomarkers provide specific information about tumor cell make-up or behavior and likeliness to recur or respond to treatment.34 They are determined by biomarker assays.35

Human Genome Project

An international consortium was formed in the 1980s with a goal of producing a reference sequence for the human genome. The U.S. Congress supplied funding for the project through the National Institutes of Health and the Department of Energy to encourage coordination of genome mapping.36 Known as the Human Genome Project, the first draft of genomic sequencing was released in 2001, and the project was completed in 2003. By the final publication, the
their genetic risk for breast cancer and then are faced with making decisions about risk and preventive care before even developing cancer.\(^{13}\)

Still, fewer than 10% of breast cancers are associated with hereditary breast and ovarian cancer syndromes. In-depth genetic testing of \(\text{BRCA}\) genes further targets the genomics behind the mutations' effects on cancer cells by identifying germline mutations.\(^{44}\) Genomic information can enhance the use of traditional risk factors in treatment and prognostic decisions.\(^{7,43}\)

For example, being overweight or obese in the years following menopause is considered a risk factor. The reason most likely is that adipose tissue is the primary source of estrogen in women following menopause. Yet not every woman who is overweight develops cancer, nor do all women with breast cancer have high body mass indices (BMIs).\(^{43,46}\) Guo et al studied previously identified genetic sequences related to high BMI in European populations.\(^{46}\) According to the authors, these genetic changes are present from birth and not related to lifestyle or other outside factors. The authors noted they were surprised to find that women with a predicted high BMI based on genetics were less likely to have breast cancer than were controls, which suggests further study of this lifestyle risk factor is warranted.\(^{46}\)

Other traditional risk factors for breast cancer include early menstruation, late or no pregnancy, inactivity, history of radiation treatment, dense breast tissue, and use of combination hormonal therapy. In addition, known genetic mutations responsible for breast cancer or family history play roles in genetic risk.\(^{43}\) Age also is a factor. Being older than 50 years increases risk of developing breast cancer, but developing the disease at a younger age (typically \(\leq 45\) years old) increases risk of poor prognosis.\(^{53,47}\)

Azim et al showed that tumors differ biologically depending on whether they occur in younger or older (\(\geq 70\) years) women. The breast cancers also differed in RNA and DNA make-up. Older patients’ tumors had more genetic mutations and more copy number variations than younger ones. The variations are important in breast cancer biology.\(^{7}\) Although current methods help stratify individual risk factors for breast cancer, researchers are working on models that can identify multiple risk factors.\(^{42,48}\)

**Role of Genes in Breast Cancer**

Although researchers do not entirely understand how breast tissue changes from normal to malignant, they know enough to begin incorporating new therapies to target molecular changes in therapy development.\(^{41}\) Often, new efforts to understand the genomics behind breast cancer are combined with known risk or prognostic factors. For example, Evans et al reported that using information on a woman’s breast density and DNA in risk models on large populations of women resulted in more precise risk estimates than did traditional screening methods.\(^{42}\)

**Risk**

Cancer risk factors warn individuals about the chance that they will develop cancer or have a poorer prognosis if cancer is diagnosed. Traditional clinical and pathologic risk factors guide screening and management decisions but do not address specific individual risk.\(^{7,43}\) These factors traditionally have been based on age, tumor type and size, histologic grade, and presence or absence of hormone receptors.\(^{7}\) Study of \(\text{BRCA1}\) and \(\text{BRCA2}\) mutations since their discovery late in the 20th century has advanced the risk stratification and role of genetic testing and counseling for women with breast and ovarian cancers.\(^{44,45}\) Carriers of variations learn of...
Recurrence and Metastasis

As many as one-third of patients who have breast cancer experience a recurrence of the malignancy, and the recurrence often results in death. Those who have a local-regional recurrence average an 80% 5-year survival rate vs a 25% 5-year rate for women with metastases. Genomics is improving the understanding of recurrence risk and could one day contribute to the assessment of a tumor’s history and prognosis, along with its potential to metastasize. Under current methods, morphology and physical properties of a tumor often guide treatment and recurrence prediction. Disease staging information and changes in tumor size help physicians determine treatment effectiveness. More recent studies have identified biomarkers, or biological indicators (such as metabolites) that help predict recurrence and other prognostic factors. Chen et al recently identified cellular pathways associated with risk. A cellular pathway involves molecular mechanisms made up of or regulated by genes. All 8 pathways the researchers found relate to drug response and immune regulation.

Tumors that are estrogen receptor (ER)-positive and ERBB2-positive represent some of the most common types of breast cancer. Although endocrine therapy has been used to treat many patients with these types of tumors successfully, risk of recurrence has remained significantly high. This percentage includes women who have had extensive surveillance and monitoring. Knudsen et al added cyclin dependent kinase (CDK) 4 and 6 inhibitors to treatment and found that the combination therapy suppressed genes associated with recurrence and induced a class of genes found to improve survival.

Up to 30% of breast cancer recurrences present as metastases. Traditional theories describe the complex interaction of malignant cell soiling and seeding. Metastatic tumors are made up of cells from the primary cancer, but research now shows that the genomic profiles of cells from primary tumors and metastatic ones can be markedly different. Researchers theorize that as the disease progresses, the genomics of cancer cells evolve, leading to these differences.

Prognosis and Survival

Mounting evidence shows that underlying tumor biology affects risk of breast cancer recurrence or death. Worldwide, people with breast cancer typically want to know the cause. Much of the information they receive on risk factors for the disease, and especially on remaining free of cancer following initial treatment, comes from media, social media, and similar sources. When women are looking to modify lifestyle to remain healthy and prevent recurrence or adverse treatment effects, they look for factors they can control.

Many studies have reported on the value of hormone receptor expression in prognosis. Studies also have consistently shown that a patient’s baseline ctDNA status affects prognosis for breast cancer. As research continues, genetic expression profiling of breast tumors could identify subgroups of patients and more individualized management of their disease and prognosis. Research involving large-scale genomics already has revealed that breast cancer is a group of molecular subtypes that are associated with different responses to treatment and prognoses.

Physicians caring for breast cancer patients also should be able to provide evidence-based information to support women’s desire to control their disease. For example, dietary intake of certain minerals affects genomic stability. Availability of key micronutrients can affect stability pathways, including how an individual’s body and cells react to exposure to carcinogens or the ability of DNA to repair itself. Al-saran et al reported that most adults do not receive the recommended levels of zinc from their diets, including an average of less than half the recommended amount for U.S. adults. The trace element is critical in the formation or function of proteins and transcription factors associated with DNA damage response and repair, along with tumor suppressor gene regulation.

Evidence already exists regarding the psychosocial benefits of predictive testing for women who have a family history of genetic breast cancer and for high levels of long-term distress in patients and survivors with positive BRCA breast cancer results; genetic information and counseling can support decision-making for women and how they can reduce their risk.

Germline Mutations

Cancer from germline mutations, or inherited cancer, makes up only 5% to 10% of all cancers. A
germline mutation in the BRCA1 or BRCA2 gene increases lifetime risk of breast, ovarian, and other cancers.\textsuperscript{47} When normal, both genes produce proteins that suppress cell growth of tumors by helping repair DNA and keeping the genetic material in cells stable. When the genes are mutated, tumor suppressor protein production is halted or the resulting protein does not function as it should in DNA repair. Fewer than 10% of all breast cancers occur because of hereditary genetic mutations; BRCA-related breast cancers make up nearly 20% of those hereditary cancers. In addition, ovarian cancer, fallopian tube cancer, male breast cancer, and others are associated with BRCA mutations.\textsuperscript{48}

As many as 45% of families who have multiple breast cancer diagnoses are linked to BRCA1.\textsuperscript{42} Recommendations for genetic testing for BRCA vary, but typically, genetic testing for this mutation is based on family history of breast cancer before age 50 years, both breast and ovarian cancers occurring in the same family, and other signs.\textsuperscript{37,48}

The high penetrance gene TP53 has been associated with more human cancer than any other somatic genetic alteration.\textsuperscript{39} The TP53 mutation can cause a condition called Li-Fraumeni syndrome. The syndrome is associated with increased risk for breast cancer, along with brain tumors, soft tissue sarcoma, and osteosarcoma. The breast cancer risk from TP53 variations is particularly high in carriers younger than 30 years.

Less is known about the degree of breast cancer risk from other genes known to increase risk. Notably, the phosphatase and tensin homolog (PTEN) gene, which leads to Cowden disease, also is linked to breast cancer. Serine/threonine kinase 11 (LKB1/STK11) mutations can lead to breast cancer and Peutz-Jeghers syndrome. A mutation that is known to cause gastric cancer also can increase familial breast cancer; the gene is cadherin, type 1 (CDH1).\textsuperscript{46} Among other possible breast cancer susceptibility genes are:\textsuperscript{47}

- Checkpoint kinase 2 (CHEK2) is a rare mutation that affects a protein involved in DNA repair. Studies have shown that a specific variation in CHEK2 causes truncated protein; although the mutation is present in about 1.1% of healthy people, about 5.5% of people with familial breast cancer have the mutation. Carriers of the CHEK2 allele mutation have more than a 2-fold relative risk of breast cancer.
- ATM serine/threonine kinase (ATM) gene mutations are associated with a condition called ataxia-telangiectasia, which makes children who have the mutation more susceptible to cancer. The protein kinase on ATM is involved in complex functions of DNA repair. The gene's contribution to elevated breast cancer risk varies, depending on the type of mutation carried.
- BRCA-interacting protein C-terminal helicase 1 (BRIP1) is a rare mutation associated with breast cancer risk. The gene affects DNA repair and BRCA1 gene activities.
- Neurofibromatosis type 1 increases the risk of tumors in carriers and can cause a moderate increase in breast cancer risk.
- Partner and localizer of BRCA2 (PALB2) can increase risk in some carriers of this mutation that affects how a protein on the gene interacts with BRCA2.

Some genes, such as fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor (VEGF), are known to promote growth of endothelial cells and angiogenesis. This means variation in the genes can be associated with multiple cancers.\textsuperscript{47} Even with current research, at least three-fourths of cases of familial breast cancer have no known associated gene.

Breast Cancer Molecular Subtypes

Traditionally, genetic testing in breast cancer focused on identified gene mutations that increased risk of inherited breast cancer, primarily BRCA1 and BRCA2.\textsuperscript{48} In 2000 and 2001, researchers used gene expression analyses and other methods to attempt to explain the variation among breast cancer types. The analyses were based on 496 genes that helped separate naturally occurring molecular subtypes.\textsuperscript{6,7} These subtypes, organized by cell line, help predict a patient's prognosis and response to therapy and form the basis for integrating genomics into traditional breast cancer research and care.

The early subtypes identified included basal-like, luminal A, luminal B, normal-like, and ERBB2-positive (HER2-enriched). Later, the normal-like (also called
tumor suppressor, malignant cells can grow unchecked by senescence or apoptosis. Research continues to identify and add molecular characterization to common and rare morphological subtypes of cancer. For example, the osteoclastic giant cells of infiltrating ductal carcinoma are positive for the cluster of differentiation 68 (CD68) molecule, and the tumor cells usually are positive for hormone receptors but negative for ERBB2. Further, efforts to discover and record all cancer-causing genomic alterations in the Cancer Genome Atlas continue, but no research has outlined the correlation between cell lines and tumor tissues and all known genomic factors, namely copy number variations, mutations, and gene and protein expression. Still, steps are being made to compare all available genomic characteristics of these molecular subtypes.

Luminal A

Luminal A breast cancers are called ER-positive cancers because most of the subtype’s tumors have positive estrogen status. The tumors tend to be progesterone receptor (PR)-positive and negative for ERBB2. Overall, luminal A breast cancer tends to be low grade when diagnosed and associated with a favorable prognosis.

### Table

**Breast Cancer Molecular Subtypes**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Typical Immunochemistry Profile</th>
<th>Characteristics</th>
<th>Approximate Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER+/PR+/ERBB2−/Ki-67−</td>
<td>Low-grade tumor. Associated with low recurrence and good prognosis.</td>
<td>24</td>
</tr>
<tr>
<td>Luminal B (HER2−)</td>
<td>ER+/PR+/ERBB−/Ki-67+</td>
<td>Progesterone can be negative in some luminal cancers. Higher grade than luminal A. Can have high recurrence risk. Prognosis worse than luminal A but better than luminal B (ERBB2+).</td>
<td>39</td>
</tr>
<tr>
<td>Luminal B (HER2+)</td>
<td>ER+/PR+/ERBB2+/Ki-67+</td>
<td>Poor prognosis.</td>
<td>14</td>
</tr>
<tr>
<td>ERBB2+ (HER2+)</td>
<td>ER−/PR−/HER2+</td>
<td>Often seen in ductal carcinoma in situ. Associated with poor outcomes.</td>
<td>11</td>
</tr>
<tr>
<td>Basal-like/triple negative</td>
<td>ER−/PR−/ERBB2−/basal marker+</td>
<td>Overlap between intrinsic basal-like tumors and triple-negative breast cancer. Triple-negative cancers can include special, typically rare, histologic subtypes. BRCA− and associated with poor prognosis.</td>
<td>12</td>
</tr>
</tbody>
</table>

*Prevalence of subtype as percentage of all breast tumors and based on multiple data sources.

ERBB2 is synonymous with HER2/neu. The literature often uses HER2.

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; Ki-67 is a protein on the marker of proliferation gene MK167.
Research has identified GATA-binding protein 3 (GATA3) mutations as influencers of ER-regulated transcription and binding of ER to DNA. The GATA3 gene upregulates ER-α and other protooncogenes that promote tumorigenesis in luminal cancer. Using multigene signatures can help clinicians differentiate among luminal A breast cancers and improve prognosis for patients.41

Luminal B
Luminal B breast cancer also is ER-positive but PR-negative or low in progesterone receptors. Luminal B cancers are further divided into ERBB2-negative or ERBB2-positive types. Although luminal A and B breast cancers share common characteristics, subtle differences can affect prognosis and effectiveness of existing or developing therapies. Genomic characteristics of luminal A cancers are absent in luminal B tumor cells. Multigene expression can determine recurrence risk, which can be high in luminal B breast cancer.41 Luminal B cancer cells tend to proliferate faster than luminal A cells and are associated with greater risk of recurrence and worse prognosis.5,55

ERBB2-positive
The ERBB2 receptor is expressed in up to 25% of breast cancers. This receptor affects cell proliferation and epithelial cell survival.62 Breast cancers that overexpress ERBB2 (HER2) also are called nonluminal cancers.61 They are distinct in that they are positive for ERBB2, but can be ER positive or negative. Ductal carcinoma in situ tumors are often of this molecular subtype and associated with a poor prognosis.7

Basal-like/Triple Negative
Basal-like breast cancer usually is triple negative, which means it lacks gene expression for ER, PR, and ERBB2.61 The cells in basal-like carcinomas have high mitosis and proliferation rates, and the tumors often are large and medullary.7 Rarely, a tumor in this group shows the signs of basal-like cancer such as high molecular weight cytokeratins, but not all triple-negative breast tumors have the basal-like phenotype, and not all basal-like cancers are triple negative.7

A large proportion of patients with triple-negative breast cancer also have BRCA mutations. The percentage is highest in women who are younger (17%-49%) and those considered high risk (12%-62%).67 Overall, triple-negative breast cancer makes up 12% to 15% of all invasive breast cancers and is more common among young women and African Americans.67 The prognosis for patients with triple-negative cancer is worse than for other subtypes because the cancer acts more aggressively and presents a greater likelihood of relapse, even when found in early stages.62 As of February 2016, there were no targeted therapies available to improve outcome among these patients.63

Biomarkers
The molecular subtype grouping is a step toward improved treatment and prognostication,64 and cell lines that better describe genetics of breast cancer are an important step. However, genomics can provide more information. With biomarkers, researchers begin to link genetic materials to the mechanisms that drive or suppress specific subtypes of cancer.65 In addition to heterogeneity among cancer types, it is evident from cytogenic studies that various biomarkers are expressed within a specific breast tumor.4

To be effective, prognostic biomarkers should be highly specific and appropriately sensitive for the type of tumor being evaluated.6 In 2015, the American Society of Clinical Oncology (ASCO) updated guidelines regarding use of biomarkers in breast cancer care. Specifically, the guidelines emphasize that biomarker tests should have clinical utility and guide the choice of specific treatment. This means that benefits from conducting the tests outweigh potential harms. For example, identifying a biomarker leads to a targeted treatment that either improves patient survival or a patient’s quality of life. In addition, the evidence supporting use of a specific biomarker should be reliable and from studies that are well designed and implemented.35

As of February 2016, the most common biomarkers for breast cancer were ER, PR, and ERBB2.34 The 3 biomarkers are assessed as part of standard practice.9 Many biomarkers of genetic mutations and drug response are under study as genomic knowledge expands.9,66 Examples of these include:

- A protein called Ki-67, which is on the marker of proliferation gene MK167, is gaining acceptance as...
a breast cancer biomarker and has been identified as an indicator of cell proliferation. Large studies have shown that cancers positive for Ki-67 were associated with greater likelihood of relapse and poorer prognosis than those negative for the protein.29

- The study of transcription in tumor specimens before immunotherapy is initiated and following treatment has helped define molecular pathways that lead to immune-mediated rejection of tumors. The biomarkers related to immune responses could help improve prognosis in patients with ERBB2-positive tumors.64

- Huang et al used a blood-based metabolomics method to identify metabolites associated with breast cancer pathways. Taurine is a metabolite associated with insulin and glucose-binding in cells and an indicator of alanine and glutamate metabolism. Hypotaurine is associated with oxidative stress and membrane damage, known processes in malignancy.28

- Marcotte et al found that phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations are markers for bromodomain and extraterminal domain protein inhibitor (BETi) resistance. BETi domain proteins regulate transcription of certain genes involved in breast cancer growth.60,65 The PIK3CA mutations occur most often in luminal tumors.52

- Gouri et al emphasized the ability of 2 compounds in the plasminogen-activator system (urokinase-type plasminogen activator [hPA] and plasminogen activator inhibitor-1 [PAI-1]) to predict metastasis and improve the precision of breast cancer care. Plasminogen is an inactive substance that converts into active plasmin. Plasmin affects several physiological processes, including degradation of the proteins on cell surfaces that help protect cells or promote cellular activities. As a result, plasmin has multiple effects during cancer invasion and metastasis.4

Molecular Diagnostics

Screening for breast cancer is common in the United States and around the world; in the United States alone, nearly 37 million breast cancer screening examinations take place each year. To date, screening programs have followed primarily evidence-based clinical guidelines. In breast cancer, mammography is the foundation of screening; other imaging methods such as magnetic resonance (MR) imaging are recommended for women at high risk of breast cancer. An increasing demand for personalized screening from patients and harm/benefit ratios is introducing new frameworks for screening that incorporate molecular diagnostics.11

Genetic testing and counseling already is available for patients at risk for or known to have hereditary cancer risk (germline variations). Physicians typically offer genetic counseling and, if appropriate, testing for women with a strong family history of breast cancer who might carry the BRCA gene mutations.10,45,54 Genetic testing has not been used for widespread screening, and the cost is high, even for patients at risk for BRCA mutations.57

The differences are particularly clear among countries, with varied implementation of genomic medicine. In many high-income countries, women might have genetic testing for breast cancer risk when they have no sign or diagnosis of breast cancer. In South Africa, however, genetic testing has been available for more than a decade, but to conserve resources only women already known to have breast cancer undergo the testing.35

Still, more efficient and less expensive technology can sequence an entire genome and reveal the DNA in a breast cancer biomarker and has been identified as an indicator of cell proliferation. Large studies have shown that cancers positive for Ki-67 were associated with greater likelihood of relapse and poorer prognosis than those negative for the protein.29

Genetic Counseling

Those individuals with a strong family history of breast or ovarian cancer can be referred for genetic counseling to help them make informed decisions about their health and cancer risk in a confidential and neutral environment. A genetic counselor and a team of physician and genetic specialists are involved in gathering information and counseling an individual.24 The process facilitates decision-making for patients and their physicians, and provides some psychosocial
support as patients face potentially troublesome findings and difficult decisions. Typically, the counseling involves assessing one or several family members’ risk of genetic diseases such as breast cancer because of the BRCA mutation. After assessing family and medical history, the counselor recommends appropriate tests to learn more about an individual’s genetic risk for cancer and provides education on how to reduce risk or prevent cancer.

**Clinical**

Use of genomic tests for clinical prognosis has increased. According to Goldhirsch et al, the tests have changed treatment decisions in up to 30% of cases. Often, the findings of biomarker assays or gene profiling tests are combined with clinical information and cancer registry or atlas data for improved prediction. Clinical trials continue to evaluate the usefulness of the score results for making informed therapeutic decisions. Somatic variants that lead to cancer typically can be found and measured from blood, cancer tissue, and secreted fluid samples.

Immunohistochemistry tests measure a tumor sample’s protein expression levels, including ER, PR, ERBB2, and Ki-67 proteins. Germline testing attempts to identify suspected genetic variants associated with hereditary cancer risk. The tests can include generally suspected genes or target a specific disease such as breast cancer. For germline mutations, linkage analyses help to localize genes that increase the risk of cancer. The analysis compares the genotypes of affected and unaffected individuals to find evidence of inherited genetic markers. Linkage analysis is designed to uncover rare genetic variants, but some individuals with familial cancer risk develop a cancer that is not part of the germline mutations but occurs sporadically because of other risk factors or somatic mutations.

Gene expression profiles identify all genes in a cell or tissue (such as a tumor biopsy sample) that make mRNA. The profiles are used to help diagnose cancer and other diseases and evaluate treatment response. MammaPrint and Oncotype are examples of gene expression profile tests. Prediction Analysis for Microarrays (PAM50) is a common gene expression profile for breast cancer. A breast cancer patient might have gene expression profiling and immunohistochemistry tests as appropriate to provide information on the molecular subtype of cancer and risk of recurrence. Tests to determine recurrence risk usually are conducted after surgery and incorporated into histological findings and grade.

Multigene panel tests, whole-exome sequencing, and whole-genome sequencing tests are appearing rapidly on the market and being included in breast cancer management. Several multigene tests are used clinically. Tumor sequencing can include germline DNA sequences to help distinguish among somatic and inherited DNA alterations; many tumor-based panels also help evaluate familial cancer risk. Targeted multigene testing can include several known genes. Physicians use the 21-gene Recurrent Score (Oncotype DX, Genomic Health) to help guide decisions about adjuvant chemotherapy or endocrine therapy. The tests provide prognostic and predictive information. Sequencing tests for tumors can help identify germline pathogenic variants.

Biomarker tests, or assays, test for a number of characteristics of biomarkers, such as amplification or mutations in the gene that activate processes like overexpression. Panel tests, which are similar to standard laboratory tests such as complete blood count, test for biomarkers that could indicate several types of breast cancer. Biomarker assays also can compare results for a patient with an algorithm, or signature, that helps to categorize prognosis.

Next-generation sequencing is a method to process multiple DNA sequences at one time in an individual and identify several types of genomic alterations, such as deletions. The technology, which promises more rapid turnaround than alternative tests, is becoming available in an increasing number of diagnostic laboratories. At least 10 genes associated with breast cancer risk can be identified through next-generation
Research with whole-genome sequencing has shown that primary breast cancer can be explained by genetic differences in disseminated tumor cells. Physicians hope that next-generation sequencing can find additional biomarkers in somatic and germline mutations. One day, these findings could guide treatment decisions. Germline mutations can be identified from blood samples, but tumor cells typically are evaluated using formalin-fixed, paraffin-embedded clinical specimens. The amount of DNA isolated from these samples can be limited and affect results. The National Cancer Institute has funded several clinical trials designed to apply new genomic technologies to samples from biopsies of metastatic tumors, which could help target therapy.

**Guidelines on Testing**

Debate is ongoing regarding the clinical use of genetic testing. Molecular diagnostics are not necessary for most patients with low-risk (ER-positive, ERBB2-negative) breast cancer. Likewise, patients known to be at high risk for recurrence, metastasis, or mortality (eg, inflammatory breast cancer or tumors > 5 cm) might not need molecular diagnostics because they should receive chemotherapy regardless, at least until such time that more precisely targeted therapy for multiple gene signatures becomes available.

Germline genetic testing already has proven useful to identify inherited forms of cancer, but the usefulness of somatic testing for indicators such as drug sensitivity remains controversial. There is little to no regulatory oversight for genetic testing of cancer, and bad biomarker tests are unhelpful and even harmful. The tests should have analytical validity based on well-defined and accurate information. Clinical validity also is important; this involves how well the test results can help divide a population based on outcome differences. Clinical utility means reliable evidence shows that the assay’s results can affect treatment decisions or patient outcome.

ASCO has stated that tests for risk of breast cancer or recurrence should be clinically useful, particularly beyond standard indicators already in place, and that the benefits of the tests outweigh potential harms. As of February 2016, the society’s recommendations included testing for ER, PR, and ERBB2 biomarkers as appropriate. For example, molecular diagnostics are unlikely to change treatment plans or prognosis in patients with ER-positive, ERBB2-negative disease, no lymph node involvement, and a small tumor (< 1 cm). It is unlikely that physicians would order chemotherapy to treat these patients. Conversely, patients at high risk because of a tumor larger than 5 cm, inflammatory breast cancer, extensive lymph node involvement, or low ER positivity would most likely be given chemotherapy regardless of additional molecular findings.

A priority of the guidelines is to determine the most appropriate use of testing to guide systemic therapy decisions. On its patient information website, the society recommended 5 tests to determine recurrence risk for early-stage breast cancer positive for ER or PR, but negative for ERBB2. These include Oncotype DX and PAM50 testing. The recommendations also suggested that several tests not be used because research on their effectiveness for predicting recurrence was lacking. These include MammaPrint, Mammastrat, and Ki-67 testing.

Even with guidelines, however, new tests are being developed at a rapid pace, including panels for germline and somatic mutations. The rapid introduction of new technology can be confusing to physicians and patients. In addition, some guidelines recommend a particular test or assay for certain biomarkers, and another test or assay for additional biomarkers. Collaboration between health care organizations, government agencies, researchers, and pharmaceutical companies is improving the database of genetic information available, which can improve testing utility.

Research continues on the clinical utility of several genetic tests. Cardoso et al reported that use of the 70-gene signature MammaPrint test for women with early-stage breast cancer who are at high clinical risk but low genomic risk for recurrence can avoid unnecessary chemotherapy. The authors found that women in this group could forgo chemotherapy, and the 5-year survival rate was only 1.5% lower than for women who received chemotherapy. The authors suggested that the 70-gene signature is most effective for patients who would like to forgo chemotherapy if their genetic risk is low. The authors will follow up on the study’s patient
population to determine whether the minor difference in survival rates continues as more time passes.69

Efforts are underway to implement a more structured approach to biomarker testing. The potential of incorporating molecular and genetic information into targeted treatment is essential to precision medicine, but only if the tests are accurate, necessary, and effective.3

Precision Medicine
In 2014, President Barack Obama announced in his State of the Union address that we were entering an era of precision medicine. Also called personalized medicine, precision medicine has many complex nuances, but boils down to moving from standard to customized treatment,7 or providing “the right therapy to the right patient at the right time, schedule, and dose.”71 President Obama announced the Precision Medicine Initiative early in 2015; the goal of the initiative is to “account for individual variability in genetics and environment.”74,75 The Precision Medicine Initiative aims to recruit 1 million volunteers to contribute longitudinal genetic information.68

In June 2016, Vice President Joe Biden announced the launch of an open-access database of genomic and clinical data from cancer patients. The new database, called the Genomic Data Commons, is managed by the National Cancer Institute. It began with detailed clinical data on 12,000 patients and is likely to grow as researchers add information on the molecular nature of cancers. The initial data comes from existing sources such as the Cancer Genome Atlas, but the goal is to add to the database and make it easily available to scientists.71

Precision medicine can address the variation in patient response to therapy and tailor cancer screening strategies.72,73 The approach should prove particularly useful for addressing the heterogeneity of breast cancer.57 Breast cancer care has led the way in personalized medicine with development of molecular subtypes that are beginning to replace the traditional morphology-based TNM (tumor, node, metastasis) staging system.4 As understanding of cancer biology and how genetic and molecular factors affect cancer risk, tumor growth, and metastasis improves, precision medicine should become more effective and lead to a better understanding of where and how to treat—or not treat—each individual patient’s disease.72

Targeted Breast Cancer Treatment
Genetic tests such as tumor sequencing detect the somatic variants in DNA that form the basis for precision medicine. By identifying driver mutations, the tests allow physicians to treat cancers with more specific, targeted therapy.29 Researchers are beginning to understand the variation in primary tumor genetic features and those of metastatic tumors in women with late-stage breast cancer.8 Circulating tumor DNA levels in a patient’s plasma can demonstrate changes in tumor burden and therefore assist physicians with real-time evaluation of treatment response in women who have metastatic breast cancer.4

Evolving Treatment Approach
Use of current treatments such as adjuvant chemotherapy, and even the application of clinical guidelines are somewhat objective and can vary widely.99 Typically, treatment decisions for women with breast cancer are based on morphological characteristics of a tumor and hormone receptor or ERBB2 status.99 Endocrine therapy works partly by suppressing cell cycle progression. The addition of CDK4 and CDK6 inhibitors, which halt or slow cell proliferation in many types of cancer, could help block cell cycle progression, especially in cancer that is ER-positive and ERBB2-negative.56 There are fewer systemic treatment choices for breast cancer patients with tumors that do not express these hormone and oncogene targets.7

A precision medicine model can identify markers that indicate how aggressively a recently diagnosed breast cancer will behave and how well it will respond to available therapies.7 This ability can improve treatment of aggressive or late-stage breast cancer and help address overtreatment. Many patients receive chemotherapy and other treatments that have toxic adverse effects and little to no benefit. Using molecular signatures, clinicians can spare specific patients unnecessary adjuvant therapy.69 In addition, researchers have found a potential genetic predisposition to development of late tissue complications in the breast following radiation therapy. The genetic link appears to be in DNA methyltransferase enzymes. These enzymes possibly play a role in fibrogenesis and radiation response and could more accurately predict long-term effects in
breast cancer survivors who have undergone radiation therapy.

Current genomic research is focused on treatment for late-stage tumors and supporting less aggressive treatment when possible to improve quality of life for patients and survivors. Use of genomic tests for prognosis has helped physicians alter treatment in up to 30% of cases worldwide. As a result, there has been a decrease in use of adjuvant chemotherapy in breast cancer patients. Likewise, genomic studies are showing that residual disease following chemotherapy is less of a concern in patients with luminal A or hormone-receptor-positive, ERBB2-positive disease than for those with nonluminal ERBB2-positive and triple-negative subtypes of breast cancer (see Figure 4).

The use of trastuzumab for ERBB2-amplified breast cancer has greatly improved breast cancer care. The monoclonal antibody targets the ERBB2 extracellular domain and has led to significant improvements in the prognosis for patients with ERBB2-positive breast cancer. Clinical trials have shown the effectiveness of neratinib, a tyrosine kinase inhibitor, as a single agent to support trastuzumab therapy, and more trials on the therapy are underway. Researchers also are studying how ESR1 and PIK3CA variations affect patient response to endocrine therapy and patient survival.

Current national guidelines recommend that carriers of PALB2 mutations discuss prophylactic mastectomy with their physicians and that those having the BRCA1, BRCA2, BRCA1 interacting protein C-terminal helicase 1 (BRIP1), RADSIC, and RADS1D variations, or are carriers of Lynch syndrome consider prophylactic salpingo-oopherectomy. By adding biopsy of metastatic cancer to identify multiple features present in metastatic cells, clinicians can target therapy based on the heterogeneity between primary cancer and metastatic cells. In addition, by identifying specific molecular drivers of cancer in patients, physicians can tailor treatment based less on anatomical site (ie, the breast) and more on specific molecular targets of individual tumors.

**Molecular Subtype Therapies**

Basing therapy decisions on molecular subtypes can make targeted treatment more precise. For example, patients with luminal A breast cancer typically receive endocrine therapy, but the usefulness of cytotoxic therapy varies widely among patients. Tests such as gene profiling that provide molecular subtype information typically are performed before surgery or neoadjuvant therapy to help with treatment decisions or following surgery on the primary tumor to guide decisions regarding chemotherapy.

Clinical trials have investigated mechanistic target of rapamycin (mTOR) inhibitors such as everolimus and a steroidal agent called exemestane as combination treatment for postmenopausal women who have metastatic luminal cancer. ERBB2-enriched tumors now can be treated with a combination of trastuzumab and pertuzumab to reduce levels of ERBB proteins and improve therapeutic response. Basal-like tumors with BRCA mutations could soon be treated with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors. In general, clinical decisions based on molecular subtype

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**Figure 4.** A triple-negative breast cancer cell undergoing retraction and apoptosis (cell death) after treatment with a combination of the chemotherapy drug cisplatin and a mitochondrial division inhibitor drug called mdivi-1. Actin in red; mitochondria in green; nuclei in blue. Understanding how drugs work at the molecular level contributes to better cancer treatments. Image courtesy of Wei Qian and the National Cancer Institute/University of Pittsburgh Cancer Center.
apply to men with breast cancer as well, but the bulk of research has been conducted on women.66

Although progress has been made, clinicians continue to research more precise approaches to treating breast cancer based on molecular subtype.67 As new discoveries about the genomic characteristics of breast cancer gain widespread acceptance, stratification and treatment by molecular subtype is likely to lead the way toward personalized treatment.7

The Future of Targeted Treatment

Profound changes to current breast cancer treatment are needed, and the framework is in place to conduct large clinical trials and develop consistent approaches to information gathered from genetic profiling.68 Targeted treatment for breast cancer already is available. The U.S. Food and Drug Administration approved trastuzumab as a targeted therapy in 1998 to treat patients with metastatic breast cancer and overexpression of the ERBB2 protein.69 In addition, PARP inhibitors are used to treat ovarian cancer associated with BRCA mutations. Still, although BRCA mutations increase risk, they do not guarantee that a woman will develop breast cancer. Further refining risk assessment can help prevent unnecessary preventive measures such as prophylactic mastectomy.13,45

Profiling of somatic mutations is essential to personalizing breast cancer treatment. New methods to evaluate advanced breast cancer include liquid biopsy when it is not possible to diagnose tumor tissue. The new method can examine circulating tumor DNA in a patient’s blood.40 In addition, numerous biomarkers related to growth factors or tumor suppression offer opportunity for new targeted modalities. The progress depends on efforts to standardize and improve reporting or information sharing about molecular features of breast cancer and on improved translation of research technology into standard clinical practice.7

Role of Imaging in Precision Medicine

Breast cancer screening is intended to detect cancer early and reduce mortality. Guidelines for screening are based largely on individuals at average risk for breast cancer. Decisions based on screening results are made according to scientific evidence of risk but also must consider individual, personal patient preferences. The availability of an increasing amount of genomic information is contributing to a move away from population-based breast cancer screening and toward personalized screening approaches. Personalized screening regimens should be built on validated risk factors such as age and family history; new risk models based on genetic research then are added as they become accepted. New risk models are likely to refine personalized decision-making for clinicians and their patients.11

Experience with women who test positive for BRCA variants provides some insight into the effects of genetic testing on breast imaging. Larouche et al found that women who had positive test results for BRCA1 and BRCA2 mutations and women who had inconclusive results on BRCA tests increased their use of mammography screening following testing.70 Those whose test results showed they were not carrying the mutation did not increase screening frequency.71 Still, some women continue to have mammograms or MR scans at the frequency associated with high risk for breast cancer even after a negative result for the BRCA mutation.75

Genome-wide association studies have identified genetic variants that can be added to abnormality prediction. Burnside et al estimated risk in women referred for breast biopsy by comparing the predictive nature of demographic risk factors, germline genetic variants, vs Breast Imaging Reporting and Data System (BI-RADS) density categories and features of mammography abnormalities.19 The investigators used 10 identified genetic variants that predict breast cancer and matched biopsy results from participants with a diagnostic mammogram acquired within 12 months before biopsy. The authors reported that mammography features such as spiculated margins better predicted malignancy than did genetic variants. However, demographic and genetic information, as well as breast density, were better for predicting the long-term risk of malignancy.19

Studies have shown that MR images have higher sensitivity for malignancy than mammograms or sonograms, particularly for younger women, and that MR is better than ultrasound imaging as an adjunct to mammography.66 Detecting recurrence in breast cancer survivors is critical to reducing mortality, and mammography can assist with surveillance. The addition
Analyzing metabolite, protein, and gene expression data can be combined with positron emission tomography (PET) to identify metabolic clusters of activity within some breast tumors. For example, glutamate is enriched in some breast cancer patients and a ratio of glutamate to glutamine is associated with ER status. Use of metabolomics in some imaging modalities such as nuclear medicine and MR scanning, can quantify the biological activities of specific lesions. PET-CT is particularly helpful to assess metastases. Increased tumor marker levels in survivors with no symptoms are correlated with higher sensitivity of PET and PET-CT compared with other imaging modalities. Drawbacks to its use include cost and the biological cost of radiation associated with PET-CT.

Structural and targeted functional data from medical imaging should continue to have a role in precision medicine that incorporates genomic information (see Figure 5). Biomarkers also could be used in imaging to evaluate treatment response for cancer patients. A study presented at the 2016 Radiological Society of North America meeting showed that MR biomarkers could predict breast cancer treatment response sooner than existing methods. Typically, physicians look at metrics such as volume or surface area that relate to tumor morphology. MR biomarkers that incorporated 57 metrics into computer-aided detection technology and radiologist interpretation detected changes in tumors following treatment sooner than standard diameter or volume measurements.

Figure 5. Precision medicine is the future of cancer therapy. Structural and functional information from imaging is combined with immunohistochemical and genomic information to make personalized treatment decisions. A. Breast cancer (arrow) is largely obscured on mammogram. B. Variable uptake of gadolinium contrast agent on a breast magnetic resonance image (arrow) indicates heterogeneity of intratumoral blood flow. C. Variable uptake of fluorodeoxyglucose (FDG) radiotracer (blue arrow) shows the heterogeneity of glucose metabolism in primary breast cancer. Extra-axillary nodal disease also is demonstrated (black arrow). D. This information is combined with immunohistochemical assays and mRNA expression (E) to determine a full tumor profile for treatment planning. The image originally was published in JNM. McDonald ES, Clark AS, Tchou J, Zhang P, Freedman GM. Clinical diagnosis and management of breast cancer. J Nucl Med. 2016;57(suppl 1):14S; © by the Society of Nuclear Medicine and Molecular Imaging, Inc.
Challenges

The process of integrating genetic data with existing methods of cancer prevention, diagnosis, and treatment presents a major challenge. Issues related to use of genomics in practice include limited knowledge of genomics and precision medicine among clinicians and patients, inconsistency in test development and acceptance, privacy and data security, cost and reimbursement, and the need to change routine medical practices to incorporate genomic information.

Incorporating research findings into clinical practice takes an average of 17 years to include only 14% of original research. Genomic and DNA data require extensive review before the information can be used in breast cancer treatment. Clinical inertia is the relative stability and reluctance of clinicians to change standard practice. This inertia can be beneficial if clinicians adopt new practices only when evidence-based research proves effectiveness vs harm. However, once practice guidelines and other leading or authoritative statements support new technology, the technology typically becomes more standardized and broadly accepted. Many clinicians cite time constraints as a barrier to learning about and implementing new precision medicine technologies and processes. Sharing findings and engaging clinicians through short courses, fact sheets, or assistance from genetic counselors can help integrate genomics into precision medicine practice.

Cost effectiveness and the availability of molecular diagnostics such as multigene assays are ongoing challenges as technology and adoption of expanded reliance on genetic data increase. All tests are not available in all clinical settings, particularly outside the United States and similarly developed countries. With an inconsistent regulatory environment, few biomarker tests on the market have undergone the type of analytical and clinical validity studies needed to prove their effectiveness. Once a test gains clinical acceptance, insurance reimbursement supports its expanded use. However, payment for these tests also is inconsistent.

Sharing genetic profiling results and similar data presents logistical and ethical challenges. For example, women who receive a positive genetic test result can experience distress and other psychosocial effects related to breast cancer risk and decision-making. Still, the combination of honest results, information, and genetic counseling can help support difficult decisions about prevention and treatment. In 2016, cancer patients filed a complaint against Myriad Genetics for failing to give patients access to their own genomic data. The data are considered a portion of medical records, which means patients should have access to full reports and be able to make decisions about how to manage or store genetic information.

The company contended that benign data was not worth releasing, but the American Civil Liberties Union stated that this position violated patient rights under the Health Insurance Portability and Accountability Act (HIPAA). Cancer patients argued that they were entitled to the full test results and many expressed their desire to share their information to contribute to the growing body of genetic data on cancer.

Finally, the success of personalized, or precision, medicine lies in the ability of clinicians and their patients to understand and act upon genetic data. Gene panel results should offer information to support decision-making. Informed consent for genetic sequencing introduces challenges in both clinical and research settings. This includes how to communicate with patients about findings that have no clear pathogenicity, and uncertainty about whether or how the variants contribute to disease. The sequencing also introduces ethical considerations regarding notifying family members about germline mutations. The role of imaging modalities will depend largely on data showing improved accuracy and relative harms. In a precision medicine approach, potential risks can vary from 1 individual to another.

Initiatives such as Healthy People 2020, which promotes the use of genomic-based tools to improve health, can make genetic information a more natural tool in cancer care (see Box). Healthy People 2020 has a goal specifically devoted to increasing the number of women with a family history of breast or ovarian cancer who receive genetic testing.

Conclusion

As technology and the infrastructure for precision medicine continue to advance, the role of genomics in breast cancer care should expand and offer new opportunities for detecting, diagnosing, and treating the disease. Institutions already have started
molecular tumor boards to discuss results from next-genome sequencing and other genomic data. Imaging continues to play a critical role in screening, diagnosis, and management as breast cancer care transitions to a personalized approach. The use of advanced imaging in breast cancer care will depend largely on a modality’s effectiveness and economic value. Additional clinical trials are needed to advance the knowledge of genomics and translation of findings into precision medicine.

References


Precision Medicine in Breast Cancer


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Read the preceding Directed Reading and choose the answer that is most correct based on the article.

1. Heterogeneity of breast cancer can relate to differences:
   1. among tumors in populations.
   2. within a tumor.
   3. temporal variability of growth.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

2. Variations that cause diseases such as breast cancer make up _______ % of the genome.
   a. 99
   b. 50
   c. 10
   d. 1

3. A characteristic that can be measured and evaluated as an indicator of normal biological or pathogenic processes is a(n):
   a. allele.
   b. microRNA.
   c. biomarker.
   d. microbiome.

4. Azim et al showed that compared with younger patients, older women’s breast tumors had:
   1. more genetic mutations.
   2. more copy number variations.
   3. fewer variations of any kind.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3
5. Research has shown that genomic profiles of cells from a primary cancer and metastatic cancer cells of the primary cancer are markedly different.
   a. true
   b. false

6. The high penetrance gene _______ has been associated with more human cancer than any other somatic alteration.
   a. BRCA
   b. TP53
   c. PTEN
   d. ERBB2

7. A rare mutation on the CHEK2 gene causes:
   a. Cowden syndrome.
   b. truncated protein.
   c. DNA repair.
   d. gastric cancer.

8. Which of the following are molecular subtypes of breast cancer?
   1. luminal A
   2. basal-like
   3. triple-negative
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

9. Luminal A subtype tumors tend to be:
   a. high grade and associated with poor prognosis.
   b. estrogen receptor negative and difficult to treat.
   c. low grade and associated with favorable prognosis.
   d. prone to recurrence.

10. Ductal carcinoma in situ tumors often are of the _______ molecular type and associated with a poor prognosis.
    a. basal-like
    b. ERBB2-positive
    c. luminal A
    d. luminal B

11. The molecular subtype of breast cancer associated with the worst prognosis typically is _______ breast cancer.
    a. luminal A
    b. luminal B
    c. ERBB2-positive
    d. basal-like/triple negative

12. Which protein is gaining acceptance as a breast cancer biomarker for cell proliferation?
    a. Ki-67
    b. hypotaurine
    c. PIK3CA
    d. hPA

13. Which tests measure a tumor sample’s protein expression levels?
    a. biomarker
    b. genome-wide association
    c. germline
    d. immunohistochemistry

14. As of February 2016, the American Society of Clinical Oncology recommended testing for:
    1. estrogen receptors.
    2. progesterone receptors.
    3. ERBB2 biomarkers.
    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3
15. The potential genetic link to tissue complications following breast radiation therapy is most likely from:
   a. DNA methyltransferase enzymes.
   b. estrogen receptors.
   c. CDK4 inhibitors.
   d. endocrine therapy effectiveness.

16. Which of the following modalities is more sensitive than radiography for assessing metastasis in bone marrow?
   a. computed tomography
   b. ultrasonography
   c. magnetic resonance imaging
   d. positron emission tomography