

Non-BRCA1/2 Breast Cancer Susceptibility Genes: A New Frontier with Clinical Consequences for Plastic Surgeons

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Summary: Twenty percent of breast cancer cases may be related to a genetic mutation conferring an increased risk of malignancy. The most common and prominent breast cancer susceptibility genes are BRCA1 and BRCA2, found in nearly 40% of such cases. However, continued interest and investigation of cancer genetics has led to the identification of a myriad of different breast cancer susceptibility genes. Additional genes, each with unique significance and associated characteristics, continue to be recognized. Concurrently, advanced genetic testing, while still controversial, has become more accessible and cost-effective. As oncologic and reconstructive advances continue to be made in prophylactic breast reconstructive surgery, patients may present to plastic surgeons with an increasingly more diverse array of genetic diagnoses to discuss breast reconstruction. It is therefore imperative that plastic surgeons be familiar with these breast cancer susceptibility genes and their clinical implications. We, therefore, aim to review the most common non-BRCA1/2 breast cancer susceptibility genetic mutations in an effort to assist plastic surgeons in counseling and managing this unique patient population. Included in this review are syndromic breast cancer susceptibility genes such as TP53, PTEN, CDH1, and STK11, among others. Nonsyndromic breast cancer susceptibility genes herein reviewed include PALB2, CHEK2, and ataxia telangiectasia mutated gene. With this knowledge, plastic surgeons can play a central role in the diagnosis and comprehensive treatment, including successful breast reconstruction, of all patients carrying genetic mutations conferring increased risk for breast malignancies. (*Plast Reconstr Surg Glob Open* 2017;5:e1564; doi: 10.1097/GOX.0000000000001564; Published online 21 November 2017.)

INTRODUCTION

Up to 20% of patients with breast cancer may possess a breast cancer susceptibility gene predisposing to an increased risk of malignancy.¹ Thirty to forty percentage of these hereditary breast and ovarian cancers are related to germline mutations in the autosomal dominant inherited breast cancer (BRCA) 1 or BRCA2 genes.²⁻⁴ Rates of breast cancer by 70 years of age range from 65% for BRCA1 to 45% for BRCA2 and can reach 85% in those with a positive family history.^{2,3} However, in all cases suggestive of he-

reditary breast and ovarian cancer, a predisposing gene is recognized at a rate less than 30%.⁴⁻⁶

Increasing interest in hereditary breast cancer has led to the identification of a myriad of additional genes acknowledged for their potential to increase risk of breast cancer development.¹ Concurrently, advanced genetic testing for these breast cancer susceptibility genes has been refined and is now widely available and cost-effective.^{1,4,7-9} Despite remaining controversial, the growth in genetic testing can be expected to increase the proportion of patients diagnosed with a breast cancer susceptibility gene.^{4,5,8,10-15}

Oncologic and reconstructive advances in surgical breast cancer prophylaxis, specifically with nipple-sparing mastectomy, have enabled surgeons to achieve safe, reproducible, and aesthetic results while minimizing reconstructive complications.¹⁶⁻²³ Meanwhile, patients with increased genetic breast cancer risk may present initially or early after their diagnosis to the plastic surgeon to discuss these surgical options. Furthermore, patients with breast cancer

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may present without a formal genetic diagnosis and possess a constellation of symptoms suggestive of an associated syndromic breast cancer susceptibility gene. This may impact patients' overall management as the risk of developing breast cancer will guide decisions to pursue either bilateral or contralateral prophylactic mastectomies that subsequently will influence a patient's optimal reconstructive options.²⁴ It is therefore imperative for plastic surgeons to be knowledgeable of these diverse, non-BRCA1/2 breast cancer genes and their clinical implications. Plastic surgeons must take a central role in advocating and assuring that these patients, as well as their families, receive appropriate, multidisciplinary care. This includes a complete discussion of surgical options and risks as well as oncologic and reconstructive implications related to prophylactic mastectomy and subsequent breast reconstruction. If not enacted before consultation with the plastic surgeon, consultations with genetic specialists, medical oncologists, and surgical oncologists, among others, should be arranged to ensure appropriate testing is ordered and risk interpretation is reviewed by these specialists.

We, therefore, aim to review the most common non-BRCA1/2 breast cancer susceptibility genetic mutations in an effort to assist plastic surgeons in counseling and managing this unique patient population presenting for breast reconstruction.

METHODS

A literature search of the online MEDLINE database was performed to find relevant articles discussing the risks of breast cancer for the most common non-BRCA1/2 breast cancer susceptibility genetic mutations. Specific keywords including "breast cancer," "susceptibility genes" "non-BRCA," "tumor suppressor gene," "DNA repair," "checkpoint kinase," "germline mutations," "genetic counselor," and "prophylactic mastectomy" were utilized in various combinations in the search protocol. Titles and subsequently abstract were screened to identify the appropriate articles to be analyzed. Non-English articles, published abstracts, and articles solely discussing BRCA mutations were excluded. Data were organized by specific mutation type in syndromic and nonsyndromic cases and was compiled for each gene from multiple sources.

SYNDROMIC BREAST CANCER SUSCEPTIBILITY GENES

TP53

TP53 is a highly penetrant tumor suppressor gene involved in regulation of apoptosis (Table 1).^{4,8} Germline mutations in TP53 lead to Li-Fraumeni Syndrome and subsequently an increased susceptibility in developing breast cancer, sarcomas, brain cancer, lung cancer, and leukemia, among other malignancies.^{1,5,8,25} These cancers tend to develop in childhood or early adulthood.¹ Responsible for nearly 1% of all cases of hereditary breast cancer, women with TP53 mutations have a risk of developing breast cancer up to 50% by age 60 and 56–90% overall, with a notably increased risk if patients are exposed to ionizing radia-

tion.^{1,8,12,14} Breast cancer in these patients present early, with a median age at diagnosis of less than 35 and tends to be human epidermal growth factor receptor 2 positive.¹

Establishing absolute screening criteria and treatment algorithms is difficult, given the rarity of the mutation.^{1,8} Magnetic resonance imaging (MRI) screening and prophylactic mastectomy, along with appropriate counseling and complete cancer screening, is recommended for most patients carrying a TP53 mutation based upon National Comprehensive Cancer Network guidelines.^{1,8,14} However, given the paucity of women with TP53 mutations who develop breast cancer after 50 years, recommendations for patients diagnosed after age 50 are less clear.¹¹

PTEN

PTEN, another highly penetrant gene, is a tumor suppressor gene regulating cell proliferation.^{4,8} Mutations in PTEN results in PTEN hamartoma tumor suppressor syndrome, the incidence of which is approximately 1/200,000.^{1,8} Women with PTEN mutations have a 25–85% lifetime risk of developing breast cancer, which is often premenopausal.^{1,14,26} PTEN mutations also increase risk for endometrial, thyroid, renal, and colon cancer in men and women.^{1,8,25,27} Additional symptoms include benign breast disease, hamartoma formation, macrocephaly, high-flow vascular malformations, and plantar keratosis, among others.^{1,8} Annual breast screening with MRI is recommended after a PTEN mutation is diagnosed. Surgical prophylaxis should also be offered based upon National Comprehensive Cancer Network guidelines.^{8,11,14} Similar to TP53 mutations, complete cancer screening for associated malignancies should begin at a young age.⁸

E-Cadherin 1 (CDH1)

The highly penetrant CDH1 gene acts as a tumor suppressor and inhibits cellular invasion.⁸ Mutations in CDH1 result in hereditary diffuse gastric cancer syndrome.^{1,4,25,28} Women with CDH1 mutations also possess a greater risk of developing breast cancer, specifically invasive lobular carcinoma.^{1,12} Identified in less than 1% of pathogenic mutations, breast cancer risk in CDH1 carriers ranges from nearly 40–60% over a woman's lifetime.^{1,14} Notably, a personal or family history of gastric cancer, in the case of de novo mutations, are not required for development of breast cancer within this syndrome.¹ These patients are also at increased risk for colorectal malignancies.⁴

Annual radiographic breast surveillance, utilizing MRI as an adjunct, is recommended despite a lack of evidence demonstrating a reduction in mortality with this practice.^{8,11} Meanwhile, surgical prophylaxis, despite conflicting recommendations, may be offered according to National Comprehensive Cancer Network guidelines and can be based on family history.^{1,8,11,14} Prophylactic gastrectomy should be strongly considered in patients with CDH1 mutations.⁸

STK11

Mutations in the high penetrance tumor suppressor gene STK11, inherited in an autosomal dominant fashion, result in Peutz-Jeghers syndrome.^{1,4,8,25} Peutz-Jeghers syndrome is characterized by mucocutaneous pigmentation and small

Table 1. Features of Common Syndromic Non-BRCA1/2 Breast Cancer Susceptibility Genes

Breast Cancer Susceptibility Gene(s)	Syndrome	Breast Cancer Risk	Select Breast Cancer Characteristics	Select Associated Features	Recommendations for Breast Cancer Prevention
TP53	Li-Fraumeni syndrome	Up to 60% by age of 50 years, 56–90% overall	Risk with ionizing radiation, age at diagnosis less than 35, often HER2 positive	Sarcoma, lung cancer, brain cancer, leukemia	Annual breast MRI screening, prophylactic mastectomy, less clear guidelines for patients diagnosed at age greater than 50 years
PTEN	Cowden syndrome	25–85% lifetime risk	Often premenopausal	Endometrial, thyroid, renal, and colon cancers, benign breast disease, hamartoma formation, macrocephaly	Annual breast MRI screening, prophylactic mastectomy
CDH1	Hereditary diffuse gastric cancer syndrome	40–60% lifetime risk	Often invasive lobular carcinoma	Gastric cancer, colorectal cancer	Annual breast MRI screening, prophylactic mastectomy
STK11	Peutz-Jeghers syndrome	30–55% lifetime risk	Median age at diagnosis of 30–40 years	Ovarian, pancreatic, gastrointestinal, and lung cancers, mucocutaneous pigmentation, small bowel hamartomas	Annual breast MRI screening, prophylactic mastectomy controversial
Mismatch repair genes (MSH2, MLH1, MSH6, PMS2, EPCAM)	Lynch syndrome	Inconclusive, 18% lifetime risk reported with MLH1 mutations	—	Colon, endometrial, ovarian, and stomach cancer	Annual breast mammography and/or MRI screening suggested, prophylactic mastectomy not recommended without additional personal or family risk factors
NF1	Neurofibromatosis type 1	2- to 6.5-fold increased risk by age 30–39 years, lifetime risk approaching 60%	May be associated with worse prognostic features and increased mortality	Neurofibromas, café au lait spots, Lisch nodules ovarian cancer, pheochromocytoma, gastrointestinal tumors, sarcoma	Annual breast mammography and/or MRI screening from young age suggested, prophylactic mastectomy not recommended without additional personal or family risk factors

HER2, human epidermal growth factor receptor 2.

bowel hamartomas.¹ Found in less than 1% of pathogenic mutations, women with STK11 mutations have a lifetime risk of 30–55% for development of breast cancer.^{1,8,11,14} This risk increases over patients' lives with a median age at diagnosis of 30–40 years.^{1,8} Patients also have an increased risk of ovarian, pancreatic, gastrointestinal, and lung malignancies.^{1,8} Current guidelines recommend yearly breast screening with MRI while surgical prophylaxis, despite incomplete evidence, may also be reasonably offered.^{1,8,14}

Mismatch Repair Genes (MSH2, MLH1, MSH6, PMS2, EPCAM)

Mutations in a variety of mismatch DNA repair genes, including MSH2, MLH1, MSH6, PMS2, and EPCAM, result in Lynch syndrome.¹ These patients are at increased risk for colon, endometrial, ovarian, and stomach malignancies.¹ With reports of breast cancer risk near 18% by age 70 in MLH1 mutation carriers, breast cancer susceptibility has been suspected but not definitively established with these mismatch repair genes as population-based studies remain inconclusive.^{1,26,29,30} Genetic instability has also been identified in breast cancer samples from patients with Lynch syndrome.⁸ Annual screening surveillance with mammography and MRI has been suggested in this population.²⁹ No recommendations exist, however, for surgical prophylaxis at this time and treatment should be individualized based on personal and family risk factors.²⁹

Neurofibromin (NF1)

NF1 encodes a protein involved in the RAS signal transduction pathway.^{5,31} Mutations in NF1 result in neurofibromatosis type 1, a syndrome characterized by multiple neurofibromas, café au lait spots, and Lisch nodules, among other characteristic symptoms.^{5,32} Women with NF1 mutations carry a 2- to 6.5-fold increased risk of developing breast cancer by age 30–39 with a lifetime risk approaching 60%.^{5,33,34} Moreover, breast cancers with NF1 mutation may be associated with worse prognostic features as well as decreased survival.³⁵ Patients with NF1 also have increased risk of ovarian cancer, pheochromocytoma, gastrointestinal tumors, and sarcomas.^{5,35} Given a lack of universal screening recommendations with NF1 mutations, breast cancer screening from a young age is advised while surgical prophylaxis appears to be reserved for cases with additional personal or family risk factors.³⁵

NONSYNDROMIC BREAST CANCER SUSCEPTIBILITY GENES

Partner and Localizer of BRCA2 (PALB2)

PALB2 is a tumor suppressor gene with an important role in DNA repair that appears to interact with both BRCA1 and BRCA2 (Table 2).^{1,4,6,8,36,37} Monoallelic mutations in PALB2 predispose to breast cancer while biallelic

Table 2. Features of Common Nonsyndromic Non-BRCA1/2 Breast Cancer Susceptibility Genes

Breast Cancer Susceptibility Gene(s)	Breast Cancer Risk	Select Breast Cancer Characteristics	Select Associated Features	Recommendations for Breast Cancer Prevention
PALB2	23–91% lifetime risk, dependent on age and specific mutation type	Diagnosis at a young age, high grade and triple negative cancers, increased mortality, improved survival with chemotherapy regimens	Male breast, ovarian, prostate, and pancreatic cancers	Annual breast MRI screening, prophylactic mastectomy
CHEK2	20–37% lifetime risk	More likely to be diagnosed at younger age, have positive family history, develop a second primary cancer, have estrogen receptor-positive breast cancer, increased mortality	Male breast, thyroid, colon, and ovarian cancers, more prevalent in northern and eastern European Caucasian populations	Annual breast MRI screening, prophylactic mastectomy not recommended without additional personal or family risk factors, hormonal chemoprevention may be beneficial
ATM	Two-fold increased risk overall, 5-fold increased risk in patients younger than 50 years, 20–70% risk by 80 years dependent on type of mutation	—	Pancreatic cancer, biallelic carriers develop ataxia-telangiectasia disorder	Annual breast MRI screening, prophylactic mastectomy not recommended without additional personal or family risk factors
MRN complex (RAD50, MRE11, NBN/NBS1)	Relative risk of 2.5 in some studies	—	Involved in ATM-mediated DNA repair pathway	No current recommendations or suggestions for screening imaging or surgical prophylaxis until further supporting data established
RAD51C/D, BRIP1, BARD1, MUTYH, XRCC, additional FANC variants, RECQL, FAM175A, BLM	Unclear risk with RAD51C/D, BARD1, and MUTYH, 2-fold risk reported with BRIP1 although contradictory data in population-based studies	Increased triple-negative cancers reported with RAD51C/D, earlier onset reported with BRIP1	Increased risk of gynecologic cancer and prophylactic BSO recommended with RAD51C/D, ovarian cancer risk with BRIP1, colorectal cancer risk with MUTYH	No current recommendations or suggestions for breast cancer screening imaging or surgical prophylaxis until further supporting data established

BLM, Bloom syndrome protein; BSO, bilateral salpingo-oophorectomy.

mutations result in Fanconi’s anemia, a disease characterized by bone marrow failure, developmental anomalies, and cancer development.^{1,5,8,12,25,26,36,38} PALB2 appears to be a moderate-to-high penetrance gene and, while mutations have been identified in approximately 2–5% of familial breast cancer cases, it may be population specific (van Marcke, Cobain, Kraus). Patients with germline mutations of PALB2 possess a 23–91% risk of developing breast cancer by 70–75 years of age, dependent on age, family history, and specific mutation type.^{1,8,36,39,40} Male breast, ovarian, prostate, and pancreatic cancer have also been associated with germline PALB2 mutations.⁴⁰

Although further research is necessary to draw definitive conclusions, greater incidences of high grade and triple negative cancers at a young age as well as increased mortality have been found in patients with PALB2-associated breast cancer.^{6,11,39–42} With this in mind, current guidelines for women with a PALB2 mutation recommend screening using breast MRI as an adjunct.⁴² Surgical prophylaxis in women with PALB2 mutations remains somewhat controversial.¹¹ However, given an increased risk of death from breast cancer, which places unaffected women with PALB2 mutations at a similar risk of death compared with unaffected patients with BRCA1, prophylactic mastectomies may be appropriately offered based upon Na-

tional Comprehensive Cancer Network guidelines.^{11,14,25,43} Consideration of patients’ family histories in this decision making process is imperative.⁴⁰ Lastly, reduced mortality with chemotherapy has been suggested in PALB2-positive tumors.⁴²

Checkpoint Kinase 2 (CHEK2)

The CHEK2 gene, which is moderately penetrant, encodes for a checkpoint kinase that responds to breaks in DNA, regulating DNA repair and cellular proliferation.^{4,8,37} Although multiple mutations in CHEK2 have been identified, a 1100delC polymorphism in the CHEK2 gene has been linked most decisively with breast cancer susceptibility.^{1,12,25,38} CHEK2 gene mutations have also been associated with thyroid, colon, and ovarian cancer.¹ More prevalent in Northern and Eastern European Caucasian women, CHEK2 mutations have been identified in approximately 5% of BRCA-negative breast cancer cases.^{7,37}

Lifetime breast cancer risk with CHEK2 mutations depends on family history and ranges from 20% to 37%.^{1,8} Notably, patients with a CHEK2-associated breast cancer are more likely to be diagnosed at a younger age, have a family history of breast cancer, develop a second primary cancer, have estrogen receptor-positive breast cancer, and have higher rates of cancer-related mortality compared

with non-CHEK2 carriers.¹ Male patients with CHEK2 mutations also have an up to 10-fold higher risk of breast cancer.^{1,4} MRI screening is recommended for patients with CHEK2 mutations; however, it has been proposed that surgical risk reduction be considered based on family history and other patient-specific risk factors.^{8,14,25,27} These patients may be candidates for hormonal chemoprevention, given suggested higher rates of estrogen receptor-positive malignancies.^{1,11}

Ataxia Telangiectasia Mutated

Monoallelic mutations in the moderately penetrant ataxia telangiectasia mutated (ATM) gene, which helps initiate and suspend cell division during DNA repair, have been associated with various types of cancer including breast and pancreatic cancer.^{1,4,8,12,25,38,44} Roughly 2% of the Caucasian population in the United States carries a germline mutation in ATM.¹ Biallelic carriers develop the ataxia-telangiectasia disorder, which is inherited in an autosomal recessive pattern.¹ Heterozygous female carriers of ATM mutations have approximately twice the risk of developing breast cancer compared with the general population.^{1,7} Importantly, carriers younger than 50 years of age at the time of diagnosis have a 5-fold risk increase for developing breast cancer.⁸ Furthermore, breast cancer risk with ATM is dependent on the type of mutation.⁴ Truncating mutations carry a 20% risk by age 80, whereas missense mutations yield a risk of nearly 70%.⁴ Although screening MRI is generally recommended for all patients with ATM mutations, surgical prophylaxis should be planned individually based upon personal and family risk factors as well as consideration of mutation type.^{4,8,14,25}

MRN Complex (RAD50, MRE11, NBN/NBS1)

The MRN complex responds to double strand breaks in DNA and recruits DNA repair mechanisms, specifically the ATM-mediated pathway.^{1,5,8,37} Mutations in the genes involved in the MRN complex, including RAD50, MRE11, and NBN/NBS1, appear to yield an intermediate risk for the development of breast cancer based on pooled data for all of these genes.^{1,8,9,13} Their prevalence in pathogenic mutations is less than 1% while relative risk for breast cancer with MRN complex mutations has been suggested to be approximately 2.5 in some studies.^{4,11,37} It is notable that only specific mutations of these genes appear to increase breast cancer risk and that these mutations appear population-specific through a potential founder effect.^{4,8}

RAD51C/D

The impact of germline mutations in the RAD51C/D genes, which encode BRCA-interactive proteins involved in DNA recombination repair, on breast cancer risk is unclear despite its association in case reports.^{1,4-6,8,11,14,41,45} These reports have also suggested an increased risk of triple negative breast cancers with these mutations.^{6,41} The incidence of RAD51C in subjects undergoing genetic testing was found to be less than 1%.¹¹ Both genes have been associated with gynecologic cancers and prophylactic bilateral salpingo-oophorectomy is recommended in many cases, especially with RAD51C mutations.^{1,8,11}

BRCA1 Interacting Protein C-Terminal Helicase 1 (BRIP1)

BRIP1 is a moderate penetrance gene that affects DNA repair through interactions with BRCA1.^{1,4,5} BRIP1 represents a set of uncommon protein truncating mutations associated with less than 1% of breast cancer cases.^{4,11} Although a 2-fold increase in breast cancer risk with earlier onset of disease has been attributed heterozygous female carriers with a positive family history, confirmatory data are limited and contradictory population-based data questions this relationship.^{1,4,5,8,11} BRIP1 mutations, however, do appear to increase risk for ovarian cancer.^{1,5,8}

BRCA1-Associated RING Domain Protein (BARD1)

BARD1 encodes a protein involved in the DNA repair mechanism and possesses a similar structure to BRCA1.¹ Observed in 0.2–0.3% of patients with genetic testing, BARD1 has not been definitively linked to an increased risk for breast cancer despite its observation in familial BRCA1/2-negative breast cancer cases.^{5,11}

MUTYH

The MUTYH gene is involved in DNA repair and has been found to increase individual's risk of colorectal cancer, especially in biallelic carriers.¹ Found in nearly 1% of the overall population, increased risk for breast cancer has been implicated in both mono- and biallelic carriers of MUTYH mutations.¹ However, this has not been confirmed in case-control studies.^{1,4,46,47}

Until higher quality evidence establishes the definitive risk for breast cancer with germline mutations in BRIP1, RAD51C/D, BARD1, MRN complex, and MUTYH genes, patient counseling and surgical planning should remain largely based on personal and family risk factors using traditional risk calculation models as no recommendations or suggestions currently exist.⁴³

Additional Genes of Uncertain Clinical Significance

Notably, x-ray repair cross-complementing (XRCC2), various Fanconi anemia factor variants, ATP-dependent DNA helicase Q1 (RECQL), FAM175A, and Bloom syndrome protein are all genes involved in DNA repair and have been observed in breast cancer cohorts.^{5,10,48,49} However, their significance in elevating risk for developing breast cancer remains unestablished, and no recommendations exist or have been suggested for breast cancer screening and/or prevention with these genes.^{5,50-52}

CLINICAL CONSIDERATIONS FOR PLASTIC SURGEONS

The non-BRCA1/2 breast cancer susceptibility genes presented in this review are rare, whereas associated risk estimates vary and remain to be fully defined. However, they carry clinical significance for patients who will present to plastic surgeons' office. Unfortunately, current guidelines for management of these patients from the National Comprehensive Cancer Network are indistinct, frequently evolving, and only include the most prominent of these breast cancer susceptibility genes.^{8,11,14} In many cases, patients' family history will reflect a par-

ticular gene's penetrance and expression, impacting an individual patient's risk and potential benefit (or lack thereof) from prophylactic mastectomy. Plastic surgeons should be aware of up-to-date data and guidelines for these genetic mutations, not only to improve the patient-surgeon relationship, but to be able to properly discuss the implications of reconstructive surgery in the context of long-term risks and planning based on individual patient's genetic predisposition. Most importantly, plastic surgeons must work in close concert with oncologic specialists and genetic counselors, who are the authorities on these topics and are responsible for appropriately counseling patients, to provide fluid and comprehensive oncologic and reconstructive care for these patients as part of a multidisciplinary care team.

CONCLUSIONS

The most prominently recognized breast cancer susceptibility genes remain BRCA1 and BRCA2. However, a myriad of additional genes portending risk of breast cancer continue to be identified and investigated, each with unique qualities. Meanwhile, advanced genetic testing is becoming more common and cost-effective. Hence, an increasing number of patients can be expected to present to the plastic surgeon, with or without a prior diagnosis, carrying increased risk for breast cancer to discuss breast reconstruction. It is therefore vital for plastic surgeons to be intimately aware of these breast cancer susceptibility genes and their clinical implications to, as appropriate, assist in diagnosis, ensure comprehensive multidisciplinary care for the patient and their family, and plan a safe and successful breast reconstruction, from both oncologic and reconstructive perspectives.

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