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Economic Analysis of Population-Based Next Generation Sequencing for Breast Cancer

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by

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Abstract

Breast cancer develops due to accumulated DNA replication insults which causes cancer to uncontrollably proliferate. An individual's predisposition to developing cancer, as well as the composition of a tumor, can be sequenced using genetic tests. Myriad's BRACAnalysis CDx® seems to be the most utilized genetic test. However, Next Generation Sequencing (NGS) seems to be a better genetic test for breast cancer when compared to Myriad's BRACAnalysisCDx® in terms of return-time, accuracy, and healthcare cost. By using Next Generation Sequencing tests, stakeholders can save money on genetic testing which can be invested in more genetic tests. Payers can also save money by establishing a population-based testing strategy for breast cancer as compared to the family-history/clinical history-based distribution currently in place in America to reduce preventable deaths. There was found to be a large disparity between breast cancer emergence and survival rates between Black individuals and White individuals. To potentially address this disparity in the interest of equity, programs could use a population-based method of dispersal of NGS tests for breast cancer.

Keywords: BRCA, Population-Based Testing, Next Generation Sequencing (NGS), Myriad, Healthcare Disparity

What is Genetic Testing for Breast Cancer?

Breast cancer is characterized by an uninhibited proliferation of cells leading to a tumor in the breast or surrounding tissues.[9] All cancers are developed due to an accumulation of insults that occur which cause cells in the body to abnormally mutate and uncontrollably proliferate.[22] Cancer can be somatic, of hereditary origin, or develop due to errors in DNA replication that cannot be inherited, also known as germline cancer.[9] According to the CDC, 5-10% of breast cancers are somatic, meaning that 90-95% of breast cancers are germline and thus spontaneously occur.[9, 10]

Immunohistochemical staining has found that breast cancers can be organized into three molecular subtypes: Hormone Receptor-positive (HR+), Human Epidermal Growth Factor Receptor 2-positive (HER2+), and Triple Negative Breast Cancer (TNBC).[3, 39] At least about 70% of breast cancers are HR+, characterized by the presence or excess of estrogen and progesterone hormone receptors which stimulate DNA replication and tumor growth (Fig. 1).[3, 6] HER2+ positive breast cancers are characterized by their overexpression of HER2, stimulating the cancerous proliferation of cells, causing breast cancer (Fig. 2).[3] HER2+ mutations are responsible for about 20% of breast cancers.[3, 5] TNBC, otherwise known as Hormone receptor-negative (HR-)/Human epidermal growth factor negative (HER2-) breast cancer, is

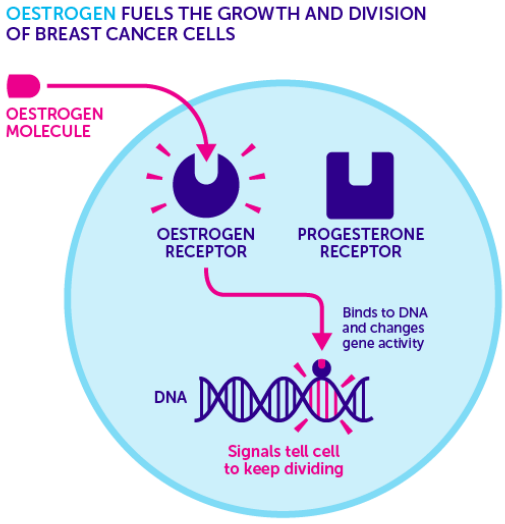

Figure 1. A figure from Emma Smith's "Solving a Breast Cancer Mystery – Why Do 'double-Positive' Women Do Better?" depicting a cell showing the activity of estrogen on an estrogen receptor on a normal cell. Estrogen binds to the receptor on the cell, stimulating cell production. If a cell has excessive estrogen receptors and is HR+, this can lead to cancer.[48]

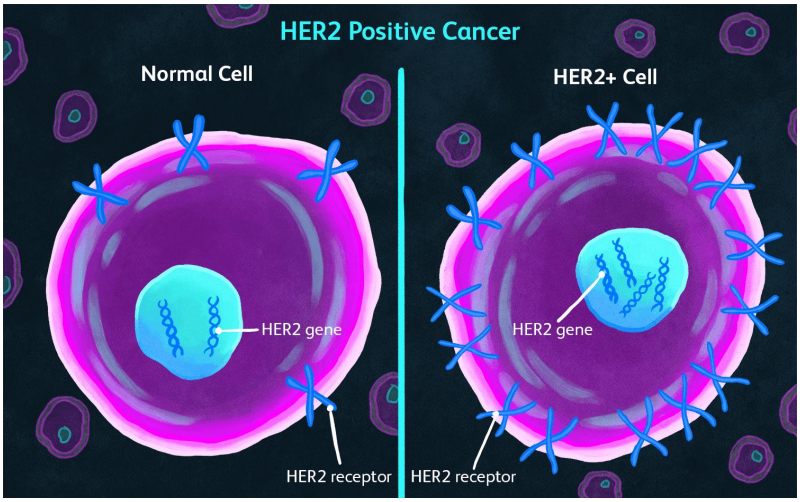

Figure 2. A normal cell with typical HER2 receptor replication (left) next to a HER2+ cancerous tumor cell (right) with atypical, excessive HER2 production, stimulating the proliferation of more cells, as depicted by Brianna Gilmartin at Verywell Health.[57]

characterized by the lack of progesterone and estrogen hormone receptors and normal or under expression of HER2.[7] About 15% of all breast cancers are TN.[3, 7]

The tumor suppressor BRCA1 (BReast CAncer gene 1) and BRCA2 are the most correlated genes to breast cancer, as they function to regulate DNA repair in breast tissues.[13] Having a mutation in one or both genes can increase an individual's risk of cancer by up to 80%, signifying the important role that these genes can have.[10]

Genetic tests for breast cancer identify mutations in BRCA1 and 2 which can predispose individuals to developing breast cancers of different subtypes. It was found that 77% of tumors in individuals with a BRCA2 mutation were HR+.[36] HER2+ breast tumors comprised 5.4% and 9.5% of cancers in BRCA1 and BRCA2 carriers, respectively.[53] BRCA1 mutations are notably correlated to a higher chance of TNBC development, constituting 70% of breast cancers with a BRCA1 mutation.[3, 42] Despite breast cancer potentially presenting with varying combinations of these subtypes and BRCA statuses, there is a relationship between both BRCA genes and the development of specific breast cancer subtypes that should be explored.

After immunohistochemistry (IHC) is used to determine the breast cancer subtype, Next Generation Sequencing (NGS), also Massively Parallel Sequencing, can be used to determine molecular mutations in BRCA genes, allowing for a more complex understanding of breast

cancer and therefore better intervention plans for those affected.[39] For instance, NGS has been used to genetically pofile breast cancers to address treatment resistance of HR+ tumors, having allowed more targeted therapies.[39]All breast cancer tumors have a dominant cell clone type which comprises 50-95% of a tumor, allowing for genetic profiling to reveal the most advantageous treatment plans.[18, 39] Comprehensive genetic tests are therefore important to determine an individual's risk of developing breast cancer, as well as testing tumor heterogeneity, both of which allow for the development of appropriate interventions.

Why Should There be Interest in this Proposal?

The CDC states cancer as the second leading cause of death in the United States, breast cancer specifically being the second leading cause of cancer mortality among women.[10] According to the National Cancer Institute, it is estimated that 3,886,830 women lived with breast cancer in 2020, with the number predicted to increase by 297,790 with a predicted 43,170 breast cancer related deaths in 2023 at a 5-year relative survival rate of 90.8% (Fig 3).[44] In 2022, there were about 4.1 million women with a history of breast cancer living in the US, including both women that have been treated and are currently being treated, with an overall lifetime 13% incidence rate of breast cancer and a deathrate of about 3%.[21]

Breast cancer not only affects the lives of diagnosed individuals, but the lives of their family, friends, and those around them. Themes of distress are common among women with breast cancer, especially related to uncertainty surrounding potential mortality, negative reactions of family and society, and potential hereditary effects on children that can significantly impact quality of life for a diagnosed.[1]

Figure 3. SEER depiction of the 5-year survival rate of individuals diagnosed with breast cancer between 2013 and 2019, based on SEER 22 data where green figures represent those that have survived at least 5 years.[44]

Due to the significant impact of breast cancer, treatment and coverage must be addressed by policies in public healthcare programs such as Medicare and Medicaid, as well as those in the private sector, such as United Healthcare. According to the World Health Organization, screening and early diagnosis are important factors that can significantly increase an individual's chance of recovery from breast cancer.[23] This means that detecting breast cancer early increases the likelihood of an ideal prognosis and saves unnecessary costs for more extensive cancer therapy.[23] Because breast cancer can be characterized by the accumulation of cellular mutations causing uncontrolled proliferation of cells, genetic testing should be used to identify an individual's predisposition to breast cancer, allowing for timely preventative treatment.[22]

What Genetic Tests Exist for Breast Cancer?

The genetic tests that are used for breast cancer today are largely impacted by the political history of genetic testing. From 1997 until 2013, Myriad Biotechnology had officially patented the BRCA gene, holding a monopoly on genetic testing for these genes which has persisted to the present.[33] For that time, "Myriad held a patent for isolated BRCA 1/2 genes and utilized genomic data exclusively for their own profit."[27] In 2013, the US Supreme Court ruled

that genes cannot be patented due to their being products of nature, and the removal of the patent increased the availability to and decreased the cost of genetic testing.[59] Single gene tests used mainly to identify BRCA1 and BRCA2 mutations were replaced throughout the past decade by multiple gene tests which "substantially increased rate of detection of any pathogenic variant."[30]

Next Generation Sequencing (NGS) is a form of Massively Parallel Sequencing test which seems to be a more cost-effective multiple-gene test which presents to be more accurate compared to BRACAnalysisCDx®, administered by Myriad, to sequence BRCA1 and BRCA2.[59] I will be comparing NGS to Myriad's BRACAnalysisCDx® in terms of the duration it takes for the results of the genetic test to return, accuracy, and healthcare costs.

Time for Tests to Return

NGS and BRACAnalysisCDx® test results return in a virtually tantamount time.

NGS results seemingly take longer to return than that of BRACAnalysis CDx® by an average of about 20 days, depending on which laboratory performs the test.[27] One study defined "delay" to the initiation of breast cancer intervention post-diagnosis as "more than 60 days."[12] Using this metric, the difference can be considered negligible.

In one study comparing result return times between BRACAnalysisCDx® test to BRCA genetic tests for breast cancer conducted by local laboratories in South Korea where the study was conducted, BRACAnalysisCDx® results returned in 10.5 days on average, much less than that of the local laboratory, which took 42 days on average.[27] This is surprising given that Myriad's tests must be performed and analyzed in Myriad's laboratory in Utah, but could be because Myriad has more resources at their disposal due to their monopoly for BRCA testing.[27]

NGS can now be accomplished within several days' time as compared to Sanger sequencing projects (like Myriad's BRACAnalysisCDx®) which previously took decades.[18] The time from tissue biopsy to acquiring NGS results for individuals with breast cancer took about 102 days in 2017 and decreased significantly to 28 days by 2019.[49]

Accuracy

NGS can be considered superior to BRACAnalysisCDx® in terms of accuracy.

Myriad uses their patented BRACAnalysisCDx® Sanger Sequencing test and supplementary BRACAnalysisCDx® Large Rearrangement Test (BART® CDx) to identify genetic variants and large deletions and duplications in the BRCA1 and 2 genes, respectively.[37] Myriad's tests detect approximately 98% of all genetic variants in both BRCA genes, where the other 2% must be detected with supplementary Alternate Primer Sequencing and Confirmatory PCR Analysis.[37] However, it must be noted that BRACAnalysis CDx® is a two-gene panel.[37]

NGS is a multi-panel assay which can "detect all mutations in 21 genes [tested], including BRCA1 and BRCA2, with inherited mutations that predispose to breast or ovarian cancer."[59] It was also found that NGS "identified a wide range of mutations in a variety of genes in 100% of … test cases with zero spurious mutations" and detected six important mutations "all of which would have been missed by standard sequencing."[59] Interpretation of genetic test results is becoming increasingly important because of conflicting interpretations and unknown significance of genetic variants, especially in minorities.[17, 27, 30, 63]

It was found that the concordant rate between the results of the BRACAnalysisCDx® and NGS was 100%.[26, 27] Given this information, both tests can be regarded as reliable. However, BRACAnalysisCDx® "cannot differentiate between duplications and triplications of genes,"

where NGS can detect these insertion errors and the "full spectrum of DNA mutations."[18, 26, 35] BRACAnalysisCDx® tests also draw notable false-positive and false-negatives under certain circumstances.[26] Thus, NGS could be considered more accurate than BRACAnalysisCDx®.

Healthcare Cost

In general, NGS is less expensive than BRACAnalysisCDx®.

According to Walsh et al., BRACAnalysisCDx® for both BRCA 1 and 2 costs $3,340, with additional BART® CDx supplementary testing at an extra $650, and additional sequencing for other non-BRCA "genes can add thousands more dollars."[59] However, using NGS to identify breast cancer would lower the cost to $1,500 per sample, and with an efficient data organization method, is predicted to cost approximately $500 a sample or less.[59] While also costing less per test, NGS can sequence the 25 genes that have been found to be associated with breast cancer where BRACAnalysisCDx® only sequences BRCA1 and BRCA2, making it more efficient.[37,54,59]

NGS also appears more inexpensive in terms of testing costs than BRACAnalysisCDx® when analyzing Incremental Cost Effectiveness Ratio (ICER) and Quality Adjusted Life Year (QALY) metrics, but this data is nuanced. ICER is a cost-effectiveness analysis score calculated by multiplying the survival in life years by the utility score, a measure of health states where 1 is representative of perfect health and 0 signifies death.[34] In an economic review, NGS was found to be cost-effective in the US in 63% of studies funded by public entities, and at least 93% of studies funded by private payers evaluated deemed NGS cost-effective.[61] NGS used to identify the recurrence of breast cancer was found to have an ICER which was cost effective.[61] It was also found using probabilistic analysis that although ICER results were varied among many studies, NGS remained a cost-effective genetic analysis tool.[61]

Data economically evaluating BRACAnalysisCDx® was difficult to find under any given testing criteria.

Policy Suggestions

Racial/Ethnic Disparities Among Breast Cancer Patients

There is a significant racial and ethnic disparity in breast cancer statistics, especially between White and Black breast cancer patients.[4, 11, 12, 17, 21] Disparate breast cancer rates between Black women and White women are due to systematic racism and have persisted throughout health economics.[8, 21] It was found throughout history that "White [breast cancer] rates improved substantially over the 20-year study period, while Black rates did not." (Fig. 4) [17]

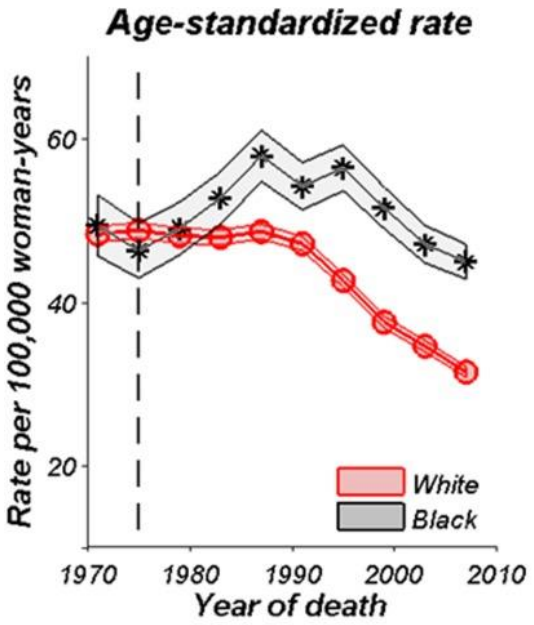

Figure 4. Comparing breast cancer mortality rates for the Black vs White populations using SEER9 data by Daley et al.[17]

Black women have a 4% lower breast cancer emergence rate than White women, but have a 40% higher breast cancer mortality rate, data which has peaked and remained consistent over the past decade due to systematic racism (Fig 5). [4, 21, 46]

According to SEER data, relative 5-year breast cancer survival rates are lower by approximately 8% for Black women when compared to both survival rates among White women and the average survival rates for all races and ethnicities.[44] Of those with covered by government insurance, White individuals had significantly shorter diagnostic times than Black individuals, with the averages being 12 and 39 days, respectively.[17] The National Health Institute also disclaimed errors in reporting deaths of races who are not White and found that they contributed to an undercalculated mortality rate of other races.[30, 44] Black survival rates lowest for every breast cancer subtype and stage, besides stage I.[21]

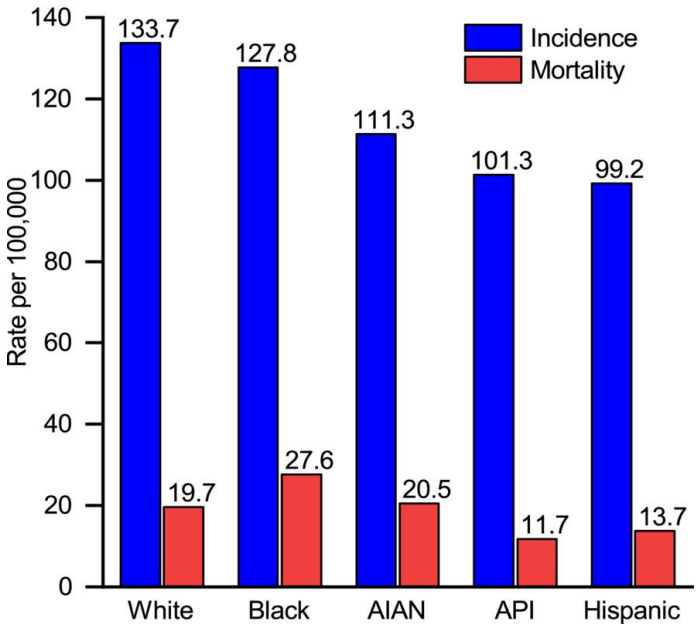

Figure 5. Breast cancer incidence (2015-2019) and mortality rates (2016-2020) from Giaquinto et al's Breast Cancer Statistics. *Race does not consider Hispanic origin.*[21]

One possible way to address the healthcare disparity between races caused by perpetuated systemic discrimination – housing inequality, food insecurity, social ostracization, etc. – within the context of breast cancer could be expanding breast cancer genetic testing policies.[46]

Increasing access to care for more people would allow for a timelier diagnosis and the development of better treatment options for breast cancer patients, thereby also accelerating advancement against cancer and minimizing breast cancer inequalities.[46] The relationship between Medicaid expansion and timely treatment among individuals with metastatic breast cancer "reported a statistically significant decrease" in inequalities, represented by a greater benefit for Black patients versus White patients.[12] This means that not only could there be policy

expansion, but a regular screening strategy in place to identify breast cancer as early as possible in the interest of equity. It should be noted that when Medicaid expansion was implemented under the Affordable Care Act in 2014, the disparity between Black and White populations for timely first-line treatment of cancer significantly statistically diminished post-expansion.[65] The 2-year survival rate of newly diagnosed patients with breast cancer increased after the ACA, and the Black population and those residing in rural areas were most positively benefited by these changes.[67]

Systems of Distribution

Strategic distribution of those limited medical resources to the most vulnerable populations allows for maximized benefit while saving payers money. Population-Based testing has been shown to be more cost-effective and increase detection of variants more often that Family History (FH)-based testing, as is the criteria in America.[34]

Despite approximately 90% of breast cancers being somatic, most programs have reserved genetic testing for breast cancer to individuals with severe FH of breast cancer, and testing is usually limited to only the BRCA genes when performed.[10, 59, 63] Testing is also usually only offered for individuals which are believed to exceed a 10% chance threshold for a positive BRCA variant result.[50, 63] Unfortunately, this means that "FH-based BRCA testing misses a large proportion of BRCA carriers who can benefit from screening/prevention," failing at identifying approximately 50% of pathogenic breast cancer variant carriers.[34, 50] Due to restrictions in place which have limited access genetic testing for breast cancer, "Only 20% to 30% of eligible patients are referred and access testing, and 97% of estimated carriers in the population remain unidentified," blocking individuals from receiving preventative care or allowing for breast cancer to develop only to be identified much later.[50] Aside from BRCA mutations, "age at breast cancer

diagnosis nor family history of ovarian or young breast cancer predicted for other mutations," signifying the importance of comprehensive testing and further research.[54] If FH is unknown under FH-based criteria, an individual with a genetic predisposition to breast cancer could then not be eligible for testing and can then fail to take actions that lead to the development or worsening of breast cancer, potentially preventing them from accessing potentially lifesaving interventions, especially if they are uninsured.

Table 1. Analysis of cost-effectiveness of BRCA testing considering respective economic guidelines for each country compiled by Manchanda et al.[34]

Country-Specific Analysis Based on Local Health Economic Guidelines Where they Exist														
	Population-Based Testing				# FH-Based Testing				ICER				WTP Threshold ($/QALY)	
	Health effects		Costs		Health effects		Costs		Cost/LY		Cost/QALY (95% Credible Intervals)			
	LY	QALY	Payer	Societal	LY	QALY	Payer	Societal	Payer	Societal	Payer	Societal		
UK Π	23.55	23.51	2263	16,570	23.55	23.50	2053	16,601	29,273	−4309	24,066 (16,407, 33,590)	−3543 (−10452, 4901)	28,471	42,857
USA	25.23	25.18	7250	21,951	25.22	25.17	7122	21,982	20,997	−5097	16,552 (4435, 30,280)	−4018 (−15947, 8764)	50,000	100,000
Netherlands ∫	34.58	34.51	1968	19,109	34.57	34.49	1725	19,153	20,796	−3752	17,655 (12,948, 23,766)	−3185 (−7568, 2319)	24,390	60,976

Population-Based criteria could therefore not only be used to best direct treatments for vulnerable communities in the interest of equity, but to also save stakeholders money. BRCA testing would be more cost-effective under a population-based strategy as compared to FH-based testing.[34] According to an analysis performed by Manchanda et al. evaluating the cost-effectiveness of BRCA1 and BRCA2 testing between FH and Population-Based testing, population-based testing is more cost-effective for all parties involved BRCA carriers receive reasonable interventions.[34] Population-based BRCA testing in the United States from a societal

perspective has an ICER of $−4018 per QALY, making it cost-effective in the USA (Table 1).[34] From a payer's perspective, BRCA testing is also highly cost effective with a USA-ICER of $16,552 per QALY (Table 1).[34] Preventing an estimated additional 2,319 to 2,666 breast cancer cases as compared to our current FH-based system (Table 1), and "can prevent tens of thousands more BC [(breast cancer)] cases."[34] Population-based testing was also shown to prevent 2,386 breast cancer cases per million people in the United States per year by Yip et al.[63]

Thus, unselected, high-risk, population-based multigene testing for breast cancer patients was found to be "extremely cost effective" as compared to testing based on FH, also strongly suggesting that current policies should be expanded to increase access to genetic testing.[50] The finances saved by using NGS compared to BRACAnalysis CDx® could allow for more genetic testing resources to be applied to a wider range of the population than the current norm.[59]

Future Direction

Gaps in Literature

Because there is no universally accepted standard of genetic testing for BRCA1 and BRCA2 testing, "including methods, types of software and analytical tools, criteria for interpreting test results, databases utilized, categories, types of clinical information referenced, or types of references used for considering population frequency," economic analyses are difficult to perform.[27] A strong lack of heterogeneity among studies and approaches make it incredibly difficult to quantify data, perform cost and other analyses, and therefore meaningfully modify policies.[13, 27, 45, 51] An exhaustive documenting system could become implemented to allow for more accurate economic systematic reviews to be performed, necessarily, on the impact of different genetic testing methods on breast cancer as to better inform policies.

I found less cost-analysis information reviewing NGS, and even less for BRACAnalysisCDx®. I theorize that this is due to the monopoly that Myriad holds on genetic testing for breast cancer. Future studies could focus on economically comparing NGS and Myriad's BRACAnalysisCDx® in the United States for different BRCA variations. Research regarding the implementation and methods of implementation of population-based testing could also be done within the context of American healthcare.[34] More research regarding different genetic tests for breast cancer are needed to better inform policies geared toward equity and cost-efficiency.[34] Despite many areas of inequality within genetic breast cancer testing that have existed for decades, there is also a lack of research surrounding "health-related social needs risk" in breast cancer screenings that could be explored.[8] Research to understand unknown genetic variants is increasingly important considering racial disparities, especially for minorities.[17, 30] This signifies the importance of using multi-gene testing methods to better understand cancer and treatment, although variants of unknown significance can result in less obvious healthcare strategies.[30, 54] Future research could be performed to identify the clinical implications of cancer susceptibility genes to provide an evidence-based framework for established policies, as multi-panel genetic tests are becoming increasingly utilized.[54]

The Ethical Dilemma

In any given healthcare system, resources are limited and services cost money. However, the source of that money depends on the economic system which governs monetary flow in any respective country. Considering that both the money to pay for breast cancer genetic tests and the testing resources are limited, the distribution of genetic breast cancer tests becomes an ethical

dilemma of how to most successfully distribute these tests to have the most benefit while maximizing stakeholder profits.

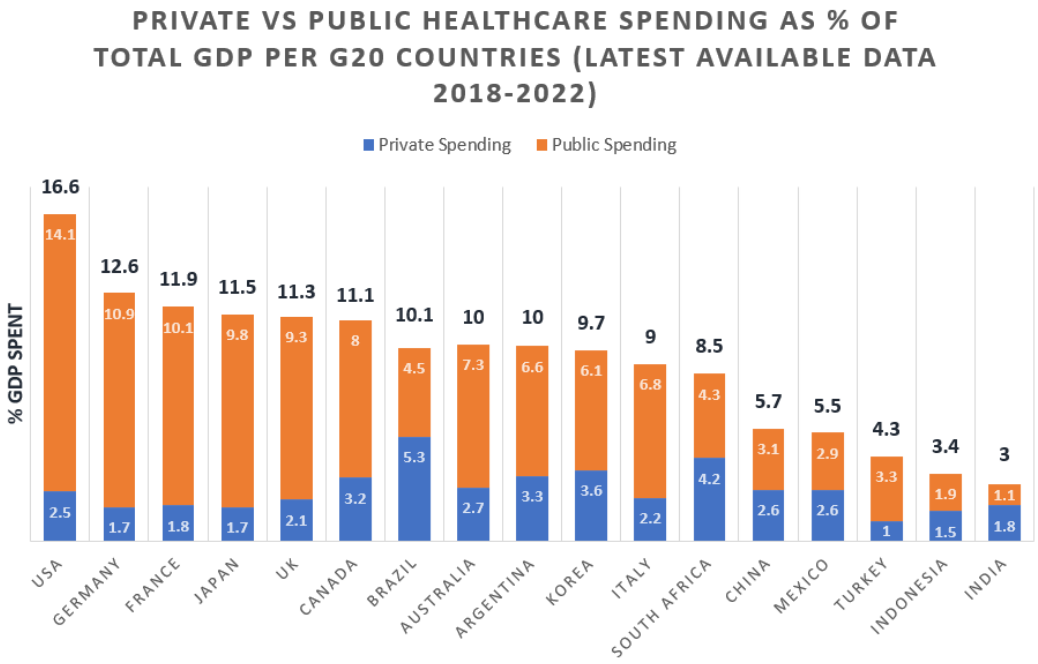

Figure 6. Private vs. Public spending as a share of % GDP per country based on OECD data for the world's top 20 most influential economies, created using data from the OECD.[40]

Per OECD data, America spends the most on healthcare as a share of our Gross Domestic Product (GDP) out of any other country in the world at exactly 16.6%, 4% more than Germany, in second place (Fig. 6).[40]

Americans also spend the largest portion of our GDP compared to any other country in the public sector (on programs such as Medicare and Medicaid) at 14.1%, yet the money spent in the private sector of healthcare (such as private insurance companies and employee-provided insurance) was comparable to that of any other country at only 2.5%.[40] The concern is why American healthcare is so expensive compared to other countries, especially considering that

Americans do not consume more healthcare than any other country, and our health outcomes are worse than other countries which spend much less on healthcare.[16]

In America, our healthcare system is set in a business model where the interests of stakeholders are at direct odds with the healthcare states of patients.[43] Payers, publicly traded insurance companies, are reluctant to pay off benefits.[43] Insurance companies lose money when this occurs because they are aligned with making their shareholders a profit, not with the best wishes of the patient.[43] Because insurance companies, as payers, are for-profit, they make money by charging a premium out of many healthcare consumers and risk-sharing while relying on paying out claims for only a small number of individuals while collecting premiums to make a profit.[43] Payer shareholders therefore have a lot of power in their financial resources whereas patients have minimal power, leaving the patient at the mercy of their insurance company, effectively making this a social justice issue.

The conflict of interest between payers and patients pertains to genetic testing in that it costs payers money when genetic tests for breast cancer are performed. Within a neoliberal lens which stands for-profit exists the argument that ordering genetic testing could be detrimental to individuals because excessive genetic testing could lead individuals to wrongfully be concerned for their health, therefore raising the need for secondary, confirmatory tests. I would argue that although testing can be inconclusive, it is more beneficial for patient stakeholders to be aware of their health risks to be able to make educated decisions about their health.

A related concern arose in 2009 when the United States Preventive Services Task Force (USPSTF) changed mammogram guidelines to recommend yearly mammograms instead of biennial screening for women 50 to 74 of age.[15, 64] It was also recommended by the USPSTF that selective breast cancer screening for women start at 50 instead of 40 years old.[15, 64] The USPSTF

found that one death is prevented for every 1,339 women screened for 10 years between 50 and 59 years, but one death is prevented for every 1,904 women screened between 40 and 49 years.[55] The Task Force concluded that the harm of initiating breast cancer screening at 40 years old outweighs the benefits of early intervention, despite screening being shown to save lives.[15, 55] It is more likely that these changes could practically have taken place to save payers money on breast cancer screening, especially as of 2023, when the USPSTF changed guidelines back to starting screening at 40 years old based on evidence from the National Cancer Institute.[55] The NCI found that breast cancer incidence rates have increased approximately 2% per year from 2015 to 2019.[55] This was a "highly controversial change," creating confusion among many healthcare agencies.[29] This change most likely took place in the name of austerity and has cost lives only to save shareholders money.

Much is left to be discovered regarding breast cancer genetic variants, especially among minority groups.[17, 30] It is therefore important that genetic testing for breast cancer be performed not only for individuals to understand their risks and take appropriate measures, but also for the deeper understanding of genetic pathways and the accumulation of data as a basis for more effective and inexpensive treatment innovation. Thus, within America, distribution of genetic breast cancer testing could be population-based for those most vulnerable, eligibility could be expanded, and NGS could be used as a more cost-effective and comprehensive testing method than BRACAnalysisCDx®.

References

1. Al-Azri, Mohammed, et al. “Psychosocial impact of breast cancer diagnosis among Omani women.” *Oman Medical Journal*, vol. 29, no. 6, 22 Nov. 2014, pp. 437–444, https://doi.org/10.5001/omj.2014.115.

2. Baicker, Katherine, et al. “The Oregon Experiment — effects of medicaid on clinical outcomes.” *New England Journal of Medicine*, vol. 368, no. 18, 2 May 2013, pp. 1713–1722, https://doi.org/10.1056/nejmsa1212321.

3. “Types of Breast Cancer.” *Breast Cancer Network Australia*, www.bcna.org.au/resource-hub/articles/types-of-breast-cancer/.

4. “Breast Cancer Facts & Figures 2022-2024.” American Cancer Society, 2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf

5. “Breast Cancer HER2 Status.” *Cancer.org*, American Cancer Society, 25 Aug. 2022, https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer diagnosis/breast-cancer-her2-status.html

6. “Breast Cancer Hormone Receptor Status.” *Cancer.org*, American Cancer Society, 8 Nov. 2021, https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html

7. “Triple-negative Breast Cancer.” *Cancer.org*, American Cancer Society, 1 Mar. 2023, https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/triple-negative.html

8. Carlos, Ruth C., et al. “Linking structural racism and discrimination and breast cancer outcomes: A Social Genomics Approach.” *Journal of Clinical Oncology*, vol. 40, no. 13, 1 May 2022, pp. 1407–1413, https://doi.org/10.1200/jco.21.02004.

9. “Basic Information about Breast Cancer.” *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, www.cdc.gov/cancer/breast/basic_info/index.htm#:~:text=Except%20for%20skin%20cancer%2C%20breast.

10. “Hereditary Breast Cancer and BRCA Genes.” *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, www.cdc.gov/cancer/breast/young_women/bringyourbrave/hereditary_breast_cancer/index.htm#:~:text=About%205%25%20to%2010%25%20of,from%20your%20mother%20or%20father.

11. Chapman, Christina Hunter, et al. “Identifying equitable screening mammography strategies for black women in the United States using simulation modeling.” *Annals of Internal Medicine*, vol. 174, no. 12, 2 Oct. 2021, pp. 1637–1646, https://doi.org/10.7326/m20-6506.

12. Chavez-MacGregor, Mariana, et al. “Medicaid expansion, chemotherapy delays, and racial disparities among women with early-stage breast cancer.” *JNCI: Journal of the National Cancer Institute*, vol. 115, no. 6, June 2023, pp. 644–651, https://doi.org/10.1093/jnci/djad033.

13. Chen, Haixia, et al. “Association between BRCA status and triple-negative breast cancer: A meta-analysis.” *Frontiers in Pharmacology*, vol. 9, 21 Aug. 2018, https://doi.org/10.3389/fphar.2018.00909.

14. Chen, Sining, and Giovanni Parmigiani. “Meta-analysis of brca1 and brca2 penetrance.” *Journal of Clinical Oncology*, vol. 25, no. 11, 10 Apr. 2007, pp. 1329–1333, https://doi.org/10.1200/jco.2006.09.1066.

15. Collier, R. “New United States mammogram guidelines ignite debate.” *Canadian Medical Association Journal*, vol. 182, no. 2, 5 Dec. 2009, pp. E101-2, https://doi.org/10.1503/cmaj.109-3124.

16. Gunja, Munira Z, et al. “U.S. Health Care from a Global Perspective, 2022: Accelerating Spending, Worsening Outcomes.” *U.S. Health Care from a Global Perspective, 2022 | Commonwealth Fund*, The Commonwealth Fund, 31 Jan. 2023, www.commonwealthfund.org/publications/issue-briefs/2023/jan/us-health-care-global-perspective-2022.

17. Daly, Bobby, and Olufunmilayo I Olopade. “A perfect storm: How tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change.” *CA: A Cancer Journal for Clinicians*, vol. 65, no. 3, 9 Apr. 2015, pp. 221–238, https://doi.org/10.3322/caac.21271.

18. Desmedt, Christine, et al. “Next-generation sequencing in breast cancer.” *Current Opinion in Oncology*, vol. 24, no. 6, 17 June 2012, pp. 597–604, https://doi.org/10.1097/cco.0b013e328359554e.

19. Drummond, Michael. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press, 2015.

20. Foote, Jonathan R., et al. “Cost comparison of genetic testing strategies in women with epithelial ovarian cancer.” *Journal of Oncology Practice*, vol. 13, no. 2, 3 Jan. 2017, pp. E120–129, https://doi.org/10.1200/jop.2016.011866.

21. Giaquinto, Angela N., et al. “Breast cancer statistics, 2022.” *CA: A Cancer Journal for Clinicians*, vol. 72, no. 6, 3 Oct. 2022, pp. 524–541, https://doi.org/10.3322/caac.21754

22. Gibbs, W. Wayt. “Untangling the Roots of Cancer.” *Scientific American*, Springer Nature America, 1 July 2008, www.scientificamerican.com/article/untangling-the-roots-of-cancer-2008-07/.

23. Ginsburg, Ophira, et al. “Breast cancer early detection: A phased approach to implementation.” *Cancer*, vol. 126, no. S10, 29 Apr. 2020, pp. 2379–2393, https://doi.org/10.1002/cncr.32887.

25. Gruber, Jonathan, director. *Lecture 25: Health Economics*. *Principles Of Microeconomics*, Massachusetts Institute of Technology , 16 July 2020, https://ocw.mit.edu/courses/14-01-principles-of-microeconomics-fall-2018/resources/lec-25-health-economics/.

26. Gunderson, Camille C, and Kathleen N Moore. “Bracanalysis Cdx as a companion diagnostic tool for Lynparza.” *Expert Review of Molecular Diagnostics*, vol. 15, no. 9, 13 Aug. 2015, pp. 1111–1116, https://doi.org/10.1586/14737159.2015.1078238.

27. Hong, Joohyun, et al. “Local laboratory testing of germline BRCA mutations vs. myriad: A single-institution experience in Korea.” *Diagnostics*, vol. 11, no. 2, 22 Feb. 2021, p. 370, https://doi.org/10.3390/diagnostics11020370.

28. Howlader, Nadia, et al. “Improved estimates of cancer-specific survival rates from population-based data.” *JNCI: Journal of the National Cancer Institute*, vol. 102, no. 20, 20 Oct. 2010, pp. 1584–1598, https://doi.org/10.1093/jnci/djq366.

29. Kiviniemi, Marc T, and Jennifer L Hay. “Awareness of the 2009 US Preventive Services Task Force recommended changes in mammography screening guidelines, accuracy of awareness, sources of knowledge about recommendations, and attitudes about updated screening guidelines in women ages 40–49 and 50+.” *BMC Public Health*, vol. 12, no. 1, 24 Oct. 2012, https://doi.org/10.1186/1471-2458-12-899.

30. Kurian, Allison W., et al. “Uptake, results, and outcomes of germline multiple-gene sequencing after diagnosis of breast cancer.” *JAMA Oncology*, vol. 4, no. 8, Aug. 2018, pp. 1066–1072, https://doi.org/10.1001/jamaoncol.2018.0644.

31. Le Blanc, Justin M., et al. “Association of medicaid expansion under the Affordable Care Act with breast cancer stage at diagnosis.” *JAMA Surgery*, vol. 155, no. 8, 1 July 2020, pp. 752–758, https://doi.org/10.1001/jamasurg.2020.1495.

32. Łukasiewicz, Sergiusz, et al. “Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review.” *Cancers*, vol. 13, no. 17, 25 Aug. 2021, p. 4287, https://doi.org/10.3390/cancers13174287.

33. Lynch, Julie A., et al. “Genetic tests to identify risk for breast cancer.” *Seminars in Oncology Nursing*, vol. 31, no. 2, May 2015, pp. 100–107, https://doi.org/10.1016/j.soncn.2015.02.007.

34. Manchanda, Ranjit, et al. “Economic evaluation of population-based BRCA1/BRCA2 mutation testing across multiple countries and Health Systems.” *Cancers*, vol. 12, no. 7, 17 July 2020, p. 1929, https://doi.org/10.3390/cancers12071929.

35. Mancini-DiNardo, Debora, et al. “Detection of large rearrangements in a hereditary pan-cancer panel using next-generation sequencing.” *BMC Medical Genomics*, vol. 12, no. 138, 17 Oct. 2019, https://doi.org/10.1186/s12920-019-0587-3.

36. Metcalfe, Kelly, et al. “Oestrogen receptor status and survival in women with BRCA2-Associated Breast Cancer.” *British Journal of Cancer*, vol. 120, no. 4, 6 Feb. 2019, pp. 398–403, https://doi.org/10.1038/s41416-019-0376-y.

37. “Bracanalysis CDX® Germline Companion Diagnostic.” *Myriad Genetics*, myriad.com/genetic-tests/bracanalysiscdx-germline-test/.

38. Nelson, Bryn. “How structural racism can kill cancer patients.” *Cancer Cytopathology*, vol. 128, no. 2, 4 Feb. 2020, pp. 83–84, https://doi.org/10.1002/cncy.22247.

39. Nourieh, Maya, et al. “Next-generation sequencing in Breast Pathology: Real Impact on routine practice over a decade since its introduction.” *Histopathology*, vol. 82, no. 1, 8 Dec. 2022, pp. 162–169, https://doi.org/10.1111/his.14794.

40. “Health Resources - Health Spending - OECD Data.” *OECD*, 2023, data.oecd.org/healthres/health-spending.htm.

41. Parthasarathy, Shobita. “Architectures of Genetic Medicine.” *Social Studies of Science*, vol. 35, no. 1, Feb. 2005, pp. 5–40, https://doi.org/10.1177/0306312705047172.

42. “Triple Negative Breast Cancer (TNBC).” *Pennmedicine.Org*, www.pennmedicine.org/cancer/types-of-cancer/breast-cancer/types-of-breast-cancer/triplenegative-breast-cancer#:~:text=These%20risks%20include%3A,a%20higher%20rate%20of%20TNBC.

43. Sawyer, Nick. “In the U.S. ‘healthcare’ is now strictly a business term.” *Western Journal of Emergency Medicine*, vol. 19, no. 3, 13 Mar. 2018, pp. 494–495, https://doi.org/10.5811/westjem.2018.1.37540.

44. SEER. Cancer Stat Facts: Female Breast Cancer. https://seer.cancer.gov/statfacts/html/breast.html.

45. Shields, Gemma E., and Jamie Elvidge. “Challenges in synthesising cost-effectiveness estimates.” *Systematic Reviews*, vol. 9, 9 Dec. 2020, p. 289, https://doi.org/10.1186/s13643-020-01536-x.

46. Siegel, Rebecca L., et al. “Cancer statistics, 2023.” *CA: A Cancer Journal for Clinicians*, vol. 73, no. 1, 12 Jan. 2023, pp. 17–48, https://doi.org/10.3322/caac.21763.

47. Smigal, C., et al. “Trends in breast cancer by Race and ethnicity: Update 2006.” *CA: A Cancer Journal for Clinicians*, vol. 56, no. 3, 2006, pp. 168–183, https://doi.org/10.3322/canjclin.56.3.168.

48. Smith, Emma. “Solving a Breast Cancer Mystery – Why Do ‘double-Positive’ Women Do Better?” *Cancer Research UK - Cancer News*, Cancer Research UK, 12 Apr. 2021, news.cancerresearchuk.org/2015/07/08/solving-a-breast-cancer-mystery-why-do-double-positive-women-do-better/.

49. Sturgill, Emma G., et al. “Next-generation sequencing of patients with breast cancer in Community Oncology Clinics.” *JCO Precision Oncology*, no. 5, 19 Aug. 2021, pp. 1297–1311, https://doi.org/10.1200/po.20.00469.

50. “Triple Negative Breast Cancer (TNBC).” *Pennmedicine.Org*, www.pennmedicine.org/cancer/types-of-cancer/breast-cancer/types-of-breast-cancer/triplenegative-breast-cancer#:~:text=These%20risks%20include%3A,a%20higher%20rate%20of%20TNBC.

51. Tan, Owen, et al. “Application of next-generation sequencing to Improve Cancer Management: A review of the clinical effectiveness and cost-effectiveness.” *Clinical Genetics*, vol. 93, no. 3, 19 Dec. 2017, pp. 533–544, https://doi.org/10.1111/cge.13199.

52. Tierno, Domenico, et al. “Next-generation sequencing and triple-negative breast cancer: Insights and applications.” *International Journal of Molecular Sciences*, vol. 24, no. 11, 2 June 2023, p. 9688, https://doi.org/10.3390/ijms24119688.

53. Tomasello, G., et al. “Characterization of the HER2 status in BRCA-mutated breast cancer: A single institutional series and systematic review with pooled analysis.” *ESMO Open*, vol. 7, no. 4, 7 July 2022, p. 100531, https://doi.org/10.1016/j.esmoop.2022.100531.

54. Tung, Tung, Nadine, et al. “Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer.” *Journal of Clinical Oncology*, vol. 34, no. 13, 1 May 2016, pp. 1460–1468, https://doi.org/10.1200/jco.2015.65.0747.

55. U.S. Preventive Services Task Force. “Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement.” *Annals of Internal Medicine*, vol. 151, no. 10, 17 Nov. 2009, pp. 716–726, https://doi.org/10.7326/0003-4819-151-10-200911170-00008.

56. Venkitaraman, Ashok R. “Cancer susceptibility and the functions of BRCA1 and BRCA2.” *Cell*, vol. 108, no. 2, 25 Jan. 2002, pp. 171–182, https://doi.org/10.1016/s0092-8674(02)00615-3.

57. Eldridge, Lynn. “HER2 Positive and Negative Breast Cancer: Differences.” Edited by Lindsay Cook, *Verywell Health*, Verywell Health, www.verywellhealth.com/her2-positive-vs-her2-negative-breast-cancer-4151792.

58. “The Real Reason American Health Care Is so Expensive.” *YouTube*, Vox, 30 Nov. 2017, https://www.youtube.com/watch?v=tNla9nyRMmQ.

59. Walsh, Tom, et al. “Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing.” *Proceedings of the National Academy of Sciences*, vol. 107, no. 28, 28 June 2010, pp. 12629–12633, https://doi.org/10.1073/pnas.1007983107.

60. Wang, Grace, et al. “Eligibility criteria in private and public coverage policies for BRCA genetic testing and genetic counseling.” *Genetics in Medicine*, vol. 13, no. 12, Dec. 2011, pp. 1045–1050, https://doi.org/10.1097/gim.0b013e31822a8113.

61. Weymann, Deirdre, et al. “Economic evaluations of next-generation precision oncology: A critical review.” *JCO Precision Oncology*, 23 Aug. 2018, pp. 1–23, https://doi.org/10.1200/po.17.00311.

62. Yadav, Siddhartha, and Fergus J. Couch. “Germline genetic testing for breast cancer risk: The past, present, and future.” *American Society of Clinical Oncology Educational Book*, no. 39, 17 May 2019, pp. 61–74, https://doi.org/10.1200/edbk_238987.

63. Yip, C. H., et al. “Global disparities in Breast Cancer Genetics Testing, counselling and management.” *World Journal of Surgery*, vol. 43, no. 5, 4 Jan. 2019, pp. 1264–1270, https://doi.org/10.1007/s00268-018-04897-6.

64 “Draft Recommendation: Breast Cancer: Screening | United States Preventive Services Taskforce.” *US Preventive Services Taskforce*, US Preventive Services Taskforce, 9 May 2023, www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/breast-cancer-screening-adults#fullrecommendationstart.

65 Adamson, Blythe JS, et al. “ACA Medicaid expansion association with racial disparity reductions in timely cancer treatment.” *The American Journal of Managed Care*, vol. 27, no. 7, 19 July 2021, pp. 274–281, https://doi.org/10.37765/ajmc.2021.88700.

66. Han, Xuesong, et al. “The impact of dependent coverage expansion under the Affordable Care Act on time to breast cancer treatment among young women.” *PLOS ONE*, vol. 13, no. 6, 13 June 2018, https://doi.org/10.1371/journal.pone.0198771.

67. Han, Xuesong, Jingxuan Zhao, K Robin Yabroff, et al. “Association between Medicaid expansion under the Affordable Care Act and survival among newly diagnosed cancer patients.” *JNCI: Journal of the National Cancer Institute*, vol. 114, no. 8, 18 May 2022, pp. 1176–1185, https://doi.org/10.1093/jnci/djac077.

68. United States, The White House. The Effects of Earlier Medicaid Expansions: A Literature Review. *Issue Briefs*, 22 June 2021, *The White House*, https://www.whitehouse.gov/cea/written-materials/2021/06/22/the-effects-of-earlier-medicaid-expansions-a-literature-review/