

# **Effects of Molecular Genetics on Cancer Management**

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**Abstract:**

With the development of next generation sequencing, the availability and effectiveness of genetic cancer panels is at an all-time high. In the past, largely only single gene tests were available to test for the presence of some high penetrance genes, such as BRCA1 and 2. Single gene tests are less likely to give conclusive and clinically useful results due to the limited amount of data collected and heterogeneity of cancers. The benefits of full cancer panels from popular companies such as Myriad, GeneDx, and Ambry Genetics include greater sensitivity results and therefore a more conclusive estimate of potential risk. The major clinical implications of cancer panels can help influence the course of medical decisions by the practitioner. Interpreting results showing variants of unknown significance, effectively communicating and establishing patient understanding, and the psychological effects on the patient from increased knowledge are challenges that underline the implication of cancer panel use.

In the case of cancer development, molecular management strategies including tumor markers and other tumor expression profiling methods can be used to significantly improve patient therapy by creating a personalized treatment based on the clinical genomics of a patient's cancer.

## **Introduction:**

The scope of this paper aims to provide insight and an overview into the realm of cancer genetics. With the invention and development of next generation sequencing (NGS), scientist's fundamental understanding of cancers has grown markedly. On top of this, the clinical implications of cancer genetics have been able to open many doors for patient therapy. With cancer heterogeneity causing major road-blocks to improving patient outcomes to standard treatments, personalized medicine using cancer panel data, tumor genomics, and pharmacotherapy targeted therapies are the future of cancer treatments. Hopefully, as technology and our understanding of cancer biology continues to grow, medical researchers and professionals will be able provide patients with therapeutic methods specific to the patient's personal genome and their cancer's genome, with an overall much improved fight back against the cancer.

The first section of this paper describes different motivating factors for people to seek molecular data collection, ranging from personal curiosity to cultural susceptibility to tumor genomic information collection. Section II provides examples of specific genes correlating with cancer development such as BRCA 1 and 2, P53, and APC. The third section incorporates information from the previous two sections to establish the usefulness and challenges of cancer panels. Section IV overall illustrates how clinical genomic data can be used to improve patient treatment. This section will cover traditional tumor markers and their relevance to cancer therapy, expression profiling of tumors, and then transition into the development of targeted treatments based off molecular data.

## **Section I. Motivation for Molecular Data Collection**

As modern technology continues to advance and become more accessible to the public, the era of genetic testing has expanded its reach and effectiveness, changing the future of cancer treatment. Genetic testing can also be used for a variety of inherited diseases including Cystic Fibrosis, Huntington's, Phenylketonuria, and many more diseases commonly seen. While genetic testing is often used in reference to inherited disorders, other reasons people seek genetic testing include cancer gene panels, genetic screening for particular ethnic groups (example, African Americans with high chances of sickle cell disease), trouble getting pregnant after several miscarriages, testing for birth defects or disabilities, determining paternity or maternity, and forensics. Additionally, the more open access to genetic testing has satisfied many curious information-seeking people, even without familial-motivated reasons. Due to increased technology and availability of certain genetic tests, many people seek genetic tests to satisfy general curiosity or family history ("*Genetic Testing*," n.d.; "Genetic Counseling," n.d.). Companies like ancestry.com can fulfill these curiosities by other DNA tests that give information on ethnic make-up and ancestry for low costs fewer than one hundred dollars ("Ancestry", n.d.)

In 2005, next-generation sequencing (NGS) made its debut into the science world and the impact of this technological advancement will have major clinical implications for genetic testing. Next-generation sequencing's most useful impact has been its ability to sequence full genomes at a much faster rate and lower cost than the previously used Sanger method, which uses chain-termination sequencing technology. For example, testing for the breast cancer related genes BRCA 1 and BRCA 2 using the Sanger method

cost nearly \$4,000 and many weeks for data interpretation, however, NGS allows BRCA 1 and BRCA 2 to be tested with a nearly 60% reduction in cost and a much faster interpretation time (Chan, W-H Lee, & Wu, 2013). In sum, the evolution of NGS has changed the face of genetic testing by making more time and financially efficient sequencing technologies available.

In the field of oncology, genetic testing is hugely impacting the way cancer is assessed, understood, and targeted; however, these advancements create both challenges and benefits to modern medicine. Molecular diagnostics aim at sequencing specific genetic biomarkers for certain cancers; for example, specific mutations or levels of gene expression. With increased technology, researchers have found that many cancers have molecular subtypes, which is one major area of challenge for researchers and medical providers. Cancer can get more complicated if a molecular sub-type of cancer is heterogenic in nature and evolves, differing its course of progression from other molecular subtypes. Finding cancers that present with the same molecular subtype, obtaining accurate samples, analyzing the huge amount of data from genomic testing, and creating a universally accepted map of all the types of diverse cancer mutations are some of these challenges (“Cancer Genomics,” 2013). On the other hand, benefits from NGS include increased knowledge of the molecular genetics of individualized cancers; researchers can use this genomic information to help create more accurate therapeutic strategies that more specifically target the cancer. For cancer patients, genetic testing can be used to create personalized, targeted therapies based off a patient’s tumor and personalized genetics.

With increased technology also comes an increase in population size recommended for genetic screening for cancer. Until recently, the American Society of Clinical Oncology (ASCO) suggested those with a personal or family history of cancer should seek genetic counseling. In conjunction with the ASCO, The National Cancer Institute website states that individuals with a high amount of cancer risk factors, including personal history of cancer, first degree relatives with cancer history, known gene mutations linked to cancer, may need to seek appropriate genetic tests, be screened at a younger age, and may need to be screened more frequently (“Cancer Screening Overview, n.d.”). While historically only those with a family history of cancer were recommended to seek genetic testing, in 2015 the ASCO updated their website and recommendations about who should seek genetic testing due to recent technological advances. This was a monumental step in the realm of clinical oncology because these new recommendations state individuals without knowledge of familial cancer may now be considered candidates for genetic testing for cancer syndromes, if clinically relevant, interpretable, and analytic results are possible (Hiraki et al., 2014). Thus, recommendations for those who should seek cancer screenings are ever evolving and are not limited to a familial history of cancer.

While familial cancer or other inheritable disorders in someone’s history is not required for an individual to seek genetic testing, it is often one of the largest motivators. The American Cancer Society claims that often times in cases of cancers repeatedly seen across families or a common risk factor such as cigarette smoke, may be the source of cancers. Factors someone should take into consideration if contemplating seeking genetic screening for familial motivated reasons include if there have been multiple cases of a

more rare type of cancer, the onset of cancer occurs at an earlier age, multiple types of cancer present in one person, cancer occurs in organ pairs (ex: both eyes), or if the cancer affects two first degree relative (ex: brother and sister). It is also important to consider other factors such as the individual's relationship to the affected family member, age of the affected family member, lifestyle of the affected family member, and their smoking/smoke exposure history.

Because so many medical disorders have genetic roots, seeking genetic testing is often helpful in family planning, prophylactic treatments, and making lifestyle choices. For example, if a couple decides to test for a heritable condition like Cystic Fibrosis, the information the couple may gain from the test may influence their decision to start a family. Furthermore, familial history as a motivation for genetic testing could help determine some prophylactic treatments, like prophylactic bilateral mastectomy (PBM), if breast cancer genes run in a family. If a patient sought out genetic testing and discovered he/she had an increased likelihood of cancer, that person may be more motivated from then on to adhere to a healthier lifestyle to reduce their risk factor potential. While a genetic screening may yield worrisome results to a patient, it can be beneficial by being an indicator of health changes for the patient; including increased blood tests, earlier mammograms or other screenings, etc. These examples underline the group of persons who may be motivated by past family histories to seek out genetic testing.

Another potentially motivating factor for seeking genetic testing is belonging to certain ethnic groups. For various reasons, some cancers/disorders more frequently present in some ethnic groups than others, and this could be reason enough for an

individual to seek genetic screening. However, while there may be higher rates of certain cancers and disorders in some ethnic groups, it is important to note that it is not always clear if this is a genetic commonality or an example of common exposure to certain risk factors. These risk factors may stem from multiple areas such as geography, diet, lifestyle, stress, etc. Examples of higher rates of a certain cancer in one ethnic group than in another is in African American women, who have a higher incidence of the most aggressive type of breast cancer compared with most other ethnic groups. Similarly, African American men have higher rates of prostate cancer compared with men from other ethnicities. For Native Americans, higher rates of kidney cancers have been observed (“Cancer Health Disparities,” 2016). There are multiple examples of cancers/inherited disorders that have higher rates in some ethnic groups compared to others, and while the cause of these disparities may be unknown, it still may be reason enough to serve as a motivating factor for someone to seek genetic screening.

Another reason someone may decide to seek out genetic screenings is simply due to personal curiosity. With the development of NGS and increased availability of genetic tests, genetic tests may appeal to people for reasons other than inheritable disorders/cancers. The company 23andMe receives salivary DNA samples that people send in and can send reports back that include information such as carrier status, ancestry reports, wellness reports, and traits reports. Hence, if a person was interested in filling in his/her family tree he/she may order an ancestry report or, if a person wanted to learn more about their “alcohol flush reaction” he/she may order the wellness report (23andMe, n.d.). Notice that neither of these motivating reasons were initiated by an inheritable disease, but stem from personal curiosity about other genetic determinants. It is plausible

that a person may also have desire to know simply know their mutation/ cancer risk for various personal reasons.

In addition to familial-motivated reasons, another group of individuals who may seek out genetic testing includes those with a current tumor. A new era of cancer treatments known as personalized medicine uses pharmacogenomics to look at a person's tumor cell genetic make-up and using the data to better understand how the cancer proliferates, interacts with its microenvironment, metastasizes, and responds to certain treatments. This area of oncology is a popular area of research with positive hopes for the futures, for example the MD Anderson Cancer Center Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy was formed "to support preclinical research and clinical trials in which a patient's tumor biopsy is assayed for abnormal genes and gene products to select therapy with agents targeting the product of those particular abnormal genes" ("Sheikh-Khalifa," n.d.). The personalized uniqueness of cancers, known as cancer heterogeneity, is one aspect that makes cancer therapy so difficult. Because no one person or the cancer may react to the same drug treatment or because different cancers may not have the machinery to utilize certain treatments, cancer therapy can be very tricky. Thus, someone currently living with a malignant tumor may seek genetic testing of the tumor to help determine the therapeutic path to take.

## **Section II – Examples of Specific Genes Correlating With Cancer Development**

While there are numerous reasons to seek genetic testing, historically only single gene panels have been available for patients for high-risk genes, such as the BRCA 1 and 2, using the old exon-by-exon Sanger method. This method, while revolutionary for its time, proved inefficient because it was more expensive, labor intensive, and problematic because you had to choose the specific genes to sequence; thus, when performing genetic testing for cancer, medical providers had to *know* what gene to search for. Researchers now know one type of cancer may result from mutations in multiple genes. With the invention of high throughput NGS, multiple genes can be tested at the same time, for less cost and more efficiently. With NGS, hundreds of thousands of small DNA segments are sequenced and consequently, research labs can now commercially offer gene panels. Gene panels exist now from anything between two genes and fifty genes sequenced. To highlight the immense benefits of gene panels, consider ovarian cancer as an example, for 15% of ovarian cancers stem from BRCA 1 or BRCA 2 mutations, yet another 5%-6% of ovarian cancers also result from a handful of other mutations, commonly seen in the same genes as Lynch syndrome (“Next Generation,” 2014).

One of the most commonly tested genes is the Breast Cancer related gene, BRCA 1 and BRCA 2. These genes code for tumor suppressor proteins, which are proteins that are “part of the system that regulates cell division. The tumor suppressor protein plays a role in keeping cell division in check” (“Tumor Suppressor,” n.d.). The BRCA genes are inheritable from both the father and mother; however, if the child is only a carrier of the BRCA gene (one allele affected) it takes a second mutation to induce the full mutation. In other words, BRCA genes are recessive and it takes two copies of a mutated BRCA gene

to see altered expression. If a child is born with one allele for the BRCA gene mutated, it causes cancer pre-disposition syndrome because only one more mutation is needed to render the protein product insufficient. When a tumor suppressor gene is mutated for the second time, it causes loss of function for the protein, and therefore regulation of cell growth is lost, leading to tumor development. BRCA 1 and 2 also help in repairing damaged or broken DNA. Hence, the DNA repairing function of BRCA 1 and BRCA 2 underline how when mutated, the fidelity of DNA replication is lost and unregulated cell growth may occur.

The next logical question when considering mutated BRCA genes is how much these mutations impact one's risk for cancer. For the general population, there is about a 12% risk for breast cancer; however, only about 5%-10% of breast cancers are familial inherited related. According to the National Cancer Institute (NCI), if someone has a BRCA1 mutation, the chances for breast cancer increase to nearly a 55%-65% risk over their lifespan. Similarly, if someone has a BRCA2 mutation, the chance of breast cancer development increases to about 45% by age seventy. In addition to breast cancer, BRCA mutations are also linked to ovarian cancers. Again according to the NCI, ovarian cancer risk from a BRCA 1 mutation is about a 39% likelihood of developing ovarian cancer and a BRCA 2 mutation is about an 11-17% risk. BRCA mutations have also been shown to increase risk for cancer of the fallopian tubes and peritoneal area in women, increased risk for prostate cancer in men, and increased risk for pancreatic cancer in both men and women (BRCA1 and BRCA2, 2015).

Another tumor suppressor gene as infamous as the BRCA genes is a gene known as p53, this is short for 'tumor protein 53' ("TP53," 2015). This gene requires both

chromosomal copies to be mutated, so if a child only has one parent donate the p53 mutation, the child is merely a carrier. While initially thought to be an oncogene, this gene was the first tumor suppressor gene to be discovered almost three decades ago. P53 works similarly to BRCA, where its function is regulating cell growth and inhibiting proliferation of abnormal cells; in other words, p53 works to prevent tumor growth from occurring. More specifically, the p53 protein resides in the nucleus of a cell and when the DNA of the cell undergoes stress (ex: UV radiation, chemical exposure, etc.), p53 directs the cell to either undergo apoptosis (cell death) or serves as an activator for stimulating the expression of other genes encoding proteins involved in initiating DNA repair to other genes to initiate DNA repair processes. This essential gene requires both chromosomal copies to be mutated, and if p53 is rendered inactive, uncontrolled cell growth and proliferation will ensue. P53 has often been termed the “guardian of the genome” and it is easy to see what an essential role p53 plays in cell growth regulation (“TP53,” 2015).

How common is a p53 mutation in cancers? Some research indicates that a p53 mutation may be in as many as 50% of all cancers, both inherited mutations or somatic (non-inherited) (Gasco, Shami, & Crook, 2002). Cancers commonly seen with p53 mutations include breast, bladder, head and neck squamous cell carcinomas (HNSCC), ovarian cancer, and Li-Fraumeni syndrome. In breast cancer, the majority of the p53 mutations is non-inherited and occurs spontaneously. As mutations accumulate throughout many years, the p53 protein is less able to help promote apoptosis and DNA repair. As DNA damage occurs, this may lead to tumor development in the body. Breast cancers with p53 mutations are likely to be more aggressive, resistant to treatment, and

have a poorer prognosis. With bladder cancer, non-inheritable mutations in p53 alter the protein so that it cannot bind to DNA and help activate DNA repair genes. Similar to breast cancer, abnormal DNA is likely to cause tumor growth without regulatory process inhibiting this process. Furthermore, the presence of a p53 mutation helps determine whether the bladder cancer will spread and if the will cancer relapse. Lastly, in HNSCC, somatic p53 mutations occur in nearly half of the cancer cases, with tumors presenting in the head, mouth, and nose, and throat areas.

A rare cancer syndrome that also embodies a p53 mutation is known as Li-Fraumeni Syndrome (LFS). This cancer syndrome is notable because of the hereditary component. In 1969, Dr. Fredrick Li and Dr. Joseph Fraumeni noticed how some families had a wide range of cancers within them and all were categorized by early onset. The connecting point in these cases was an inheritable mutation, the p53 gene mutation, present in nearly 70% of families. (Another common genetic mutation in Li-Fraumeni Syndrome is the Check2 mutation). The most common cancers associated with Li-Fraumeni Syndrome include cancers of the bone, soft-tissue, breast, brain, as well as acute leukemia and adrenal cortical tumors (“Li-Fraumeni,” 2012).

There are two ways to diagnose Li-Fraumeni Syndrome, through the classical method and Chompret Criteria. For the classical method, a person with LFS has a sarcoma, a first-degree relative, and another first-degree relative or second-degree relative, all before the age of 45. The Chompret Criteria was established more recently to increase the sensitivity of diagnosing LFS, and incorporates three different criterion categories differing in types of cancer, relatives affected with cancer, and age of onset.

Li-Fraumeni Syndrome occurs in about one of every 5,000 to 20,000 people and the chances of an LFS patient developing cancer is about 90%. Nearly half of these cancers will have an onset before the patient turns 30 (“Li-Fraumeni,” 2012). Altogether, LFS is a cancer pre-disposition syndrome that more often than not results from a heritable p53 mutation and has been a popular target for single-gene testing for many years due to the commonality of the mutation in many cancers and LFS.

A third example of a common gene tested for by historically-used single gene tests is for the APC gene, which can result in the hereditary disorder: familial adenomatous polyposis (FAP). An APC gene mutation has been shown to cause most commonly colorectal cancers, but also cancers of the stomach, lung, pancreas, esophagus, and breast cancer (Furuuchi et. al, 2000). The APC gene stands for “adenomatous polyposis coli”, as dictated in the name of the disorder FAP. The APC gene codes for a tumor suppressor protein, which plays a role in many cellular processes. This tumor suppressor protein plays a crucial role in cell signaling by preventing unregulated cell growth, determining how a cell will attach to other cells, and whether or not a specific cell will move to other locations in the body (“APC,” 2013). Other pathways the APC protein cooperates with are pathways that function in signal transduction, stabilizing effects of the cytoskeleton, apoptosis, and cell cycle regulation (Fearnhead, Britton, & Bodmer, 2001). Overall, the APC gene is another historically infamous gene that has been the target of single gene tests because of its widespread role in cell growth, longevity, and regulation.

Narrowing in on FAP, the most common tumors in this hereditary disorder are in the large intestine (colon) as well as the rectum; classical FAP occurs when a patient has

over 100 polyps (benign growths) in the colon (“Familial Adenomatous Polyposis,” 2015). If the polyps are left untreated, it is nearly guaranteed that the patient will progress to having cancerous growths. Typically the polyps will develop at a younger age, around the teenage years, so it is very important to remove the polyps to prevent cancer development at such a young age. Another characteristic of this disease is the development of what is known as desmoid tumors, which are fibrous, noncancerous growths in the colorectal area that will not metastasize. A subset type of FAP is known as attenuated FAP, which is delayed growth of the polyp and the general age of onset is 55, compared to age 39 for classical (non-attenuated) FAP. It is not uncommon in both types of FAP to see hundreds of thousands of polyps (unless autosomal recessive FAP is indicated in the patient, then fewer polyps will be observed). It is important to note that while FAP is characterized by cancerous growths, there are other symptoms associated such as abnormal tooth developments, hypertrophy of retinal cells, adrenal masses, and noncancerous skin growths. Typically about 1 in 7,000 to 22,000 people will suffer from FAP (“Familial Adenomatous Polyposis,” 2015).

In conclusion, even though DNA sequencing technology has come a long way in recent years, the older Sanger exon-by-exon method was still useful because professionals were still able to test for specific, high-risk genes causing a high likelihood of developing cancer and other disorders. Three genes that are common targets for genetic testing include BRCA 1 and 2, p53, and APC. These genes are tumor suppressor genes, meaning they have a significant role in regulating processes such as DNA repair, cell growth regulation, and other cell-signaling cascades. The advantages of screening for BRCA, p53, and APC are many; namely, knowing genetic status, family planning, cancer

prevention, and lifestyle influences. Table 1 (below) includes major genes and their associated cancers/disorders, including BRCA, p53, and APC.

Gene (synonym(s)) <sup>a</sup>	Syndrome	Hereditary pattern	Second hit	Pathway <sup>b</sup>	Major heredity tumor types <sup>c</sup>
<b>Tumor-suppressor genes</b>					
<i>APC</i>	FAP	Dominant	Inactivation of WT allele	APC	Colon, thyroid, stomach, intestine
<i>AXIN2</i>	Attenuated polyposis	Dominant	Inactivation of WT allele	APC	Colon
<i>CDH1</i> (E-cadherin)	Familial gastric carcinoma	Dominant	Inactivation of WT allele	APC	Stomach
<i>GPC3</i>	Simpson-Golabi-Behmel syndrome	X-linked	?	APC	Embryonal
<i>CYLD</i>	Familial cylindromatosis	Dominant	Inactivation of WT allele	APOP	Pilo-trichomas
<i>EXT1,2</i>	Hereditary multiple exostoses	Dominant	Inactivation of WT allele	GLI	Bone
<i>PTCH</i>	Gorlin syndrome	Dominant	Inactivation of WT allele	GLI	Skin, medulloblastoma
<i>SUFU</i>	Medulloblastoma predisposition	Dominant	Inactivation of WT allele	GLI	Skin, medulloblastoma
<i>FH</i>	Hereditary leiomyomatosis	Dominant	Inactivation of WT allele	HIF1	Leiomyomas
<i>SDHB, C, D</i>	Familial paraganglioma	Dominant	Inactivation of WT allele	HIF1	Paragangliomas, pheochromocytomas
<i>VHL</i>	Von Hippel–Lindau syndrome	Dominant	Inactivation of WT allele	HIF1	Kidney
<i>TP53</i> (p53)	Li-Fraumeni syndrome	Dominant	Inactivation of WT allele	p53	Breast, sarcoma, adrenal, brain...
<i>WT1</i>	Familial Wilms tumor	Dominant	Inactivation of WT allele	p53	Wilms'
<i>STK11</i> ( <i>LKB1</i> )	Peutz-Jeghers syndrome	Dominant	Inactivation of WT allele	PI3K	Intestinal, ovarian, pancreatic
<i>PTEN</i>	Cowden syndrome	Dominant	Inactivation of WT allele	PI3K	Hamartoma, glioma, uterus
<i>TSC1, TSC2</i>	Tuberous sclerosis	Dominant	Inactivation of WT allele	PI3K	Hamartoma, kidney
<i>CDKN2A</i> (p16 <sup>INK4A</sup> , p14 <sup>ARF</sup> )	Familial malignant melanoma	Dominant	Inactivation of WT allele	RB	Melanoma, pancreas
<i>CDK4</i>	Familial malignant melanoma	Dominant	?	RB	Melanoma
<i>RB1</i>	Hereditary retinoblastoma	Dominant	Inactivation of WT allele	RB	Eye
<i>NF1</i>	Neurofibromatosis type 1	Dominant	Inactivation of WT allele	RTK	Neurofibroma
<i>BMPR1A</i>	Juvenile polyposis	Dominant	Inactivation of WT allele	SMAD	Gastrointestinal
<i>MEN1</i>	Multiple endocrine neoplasia type I	Dominant	Inactivation of WT allele	SMAD	Parathyroid, pituitary, islet cell, carcinoid
<i>SMAD4</i> ( <i>DPC4</i> )	Juvenile polyposis	Dominant	Inactivation of WT allele	SMAD	Gastrointestinal
<i>BHD</i>	Birt-Hogg-Dube syndrome	Dominant	Inactivation of WT allele	?	Renal, hair follicle
<i>HRPT2</i>	Hyperparathyroidism. Jaw-tumor syndrome.	Dominant	Inactivation of WT allele	?	Parathyroid, jaw fibroma
<i>NF2</i>	Neurofibromatosis type 2	Dominant	Inactivation of WT allele	?	Meningioma, acoustic neuroma
<b>Stability genes</b>					
<i>MUTYH</i>	Attenuated polyposis	Recessive	?	BER	Colon
<i>ATM</i>	Ataxia telangiectasia	Recessive	?	CIN	Leukemias, lymphomas, brain
<i>BLM</i>	Bloom syndrome	Recessive	?	CIN	Leukemias, lymphomas, skin
<i>BRCA1, BRCA2</i>	Hereditary breast cancer	Dominant	Inactivation of WT allele	CIN	Breast, ovary
<i>FANCA, C, D2, E, F, G</i>	Fanconi anemia	Recessive	?	CIN	Leukemias

**Table 1:** Major genes and correlating cancer risk (Vogelstein,& Kinzler, 2004).

### **SECTION III: Usefulness of Cancer Panels**

While testing for single, high risk genes was helpful for diagnosing cancers and disorders, NGS has not only changed the way the genetic code is sequenced, the number of genes tested, but also the availability of multiple gene testing. At first these multiple gene panels may seem like screening-overkill, however, in cancer specifically, the complexity of a genetic disorder is often beyond single gene mutations. There is a huge benefit of using multiple gene tests, for they increase testing sensitivity levels. In addition, NGS and multi-gene testing benefits patients with lower costs and faster processing times. One of the largest benefits of multiple-gene tests is the clinical impact. The scope of this impact is changing, and will continue to change as technology grows, the use of genetic testing in clinical use. Multi-gene panels are helpful with diagnosing, determining treatments, predicting outcomes, and monitoring cancer progression.

The first positive outcome of to cancer panel use results from the greater sensitivity of cancer panels, which ultimately leads to better risk assessment for patients. Greater sensitivity, or an increased amount of indicated positive results, in essence casts a wider net of catching a mutation in a patient; thus, someone who may have had a less likely detectable mutation, will have better chances of catching the mutation. Similarly, multi-gene panels will sort out patients who have high-risk gene mutations versus other low to moderate penetrant genes versus normal population risk (Hiraki et al., 2014). Penetrance is based on how often the specific mutated gene is associated with a certain cancer/disorder; some gene mutations are high penetrance, intermediate penetrance, and low penetrance. Thus, if a cancer gene panel shows a mutation in the BRCA 1 or 2 genes, there is much higher risk associated than a panel that shows a variant of unknown

significance (VUS) or a lower penetrating gene. A VUS is a polymorphism in the genetic code that is not significant enough to cause a known change in phenotype, but still is a change in the DNA. Together, increased sensitivity and improved risk assessment are major benefits of cancer gene panels compared to a single gene test.

Another benefit of cancer gene panels is an increased target audience. Historically, someone may have only sought out genetic testing for a specific gene linked to known familial risk, such as BRCA 1 and 2 with hereditary cases of breast cancer. With the availability and ease of access to gene panels, more members of the general population who may not typically meet “high risk” criteria may be screened. As noted in the 2014 review “Cancer Risk Assessment Using Genetic Panel Testing: Considerations for Clinical Application,” this could be due to a multitude of reasons such as “incomplete penetrance of the syndrome, sex-limited expression, or lack or limited personal and/or family history” (Hiraki et al., 2014). Reflecting on these reasons, the American Society of Clinical Oncology (ASCO) recently changed their recommendations on who should seek genetic testing, including a larger population than just those with familial risk. These recommendations suggest that people without familial history may be indicated for genetic testing if “analytical and clinical utility has been established” (Hiraki et al., 2014).

Increased sensitivity, more gene targets, better risk assessment, and increased target populations are all benefits of increased technology and multi-gene cancer panels that ultimately lead to improved clinical decisions. On the medical provider side of things, these benefits can be greatly significant in medical decision-making process by helping weigh out benefits and risks of medical intervening strategies. The more

information gathered from a genetic screening, the more informed of a decision the provider can advise. Likewise, on the patient side of things, the benefits of cancer gene panels can help guide his/her understanding of risk, preventive or therapeutic strategies he/she may want (or not want) to partake in, and general knowledge that may be significant for family planning. Overall, increased sensitivity, risk assessment, and target populations from cancer panels also benefit the medical decision making process on both the provider side and patient side.

While there are many benefits to the availability and development of gene panels, it opens the question how certain genes are selected for to be available on a variety of gene panels. The majority of this discussion delves into extensive research based on genes most likely to succumb to a mutation and most commonly involved in different biochemical pathways in the human body. For example, an increased understanding of the Fanconi Anemia-BRCA Pathway, CHECK 2 Pathway, and Mismatch Repair (MMR) Pathway have helped narrow down at-risk cancer genes to test for on a panel (Hiraki et al., 2014). In breast cancer 14 genes in the Fanconi Anemia Pathway (FA)-BRCA Pathway have been identified which work along with BRCA genes in DNA-repair pathways. Additionally, in the CHEK2 Pathway, CHEK2 protein is phosphorylated when DNA gets mutated, and then CHEK2 works with BRCA1, p53, and ATM in a responsive manner. In the MMR Pathway, genes for the proteins MSH1-6, MLH1, MLH2, MLH3, PMS1, and PMS2 all play critical roles in base-repair mechanisms. However, research is still being done to understand the relationship between MMR Pathway proteins and breast cancer onset. Thus, these genes in these pathways are also common genes to include on a panel because of integral role they play in DNA repair. To summarize, with

increased depth of understanding of the biochemical pathways and interactions as such in the (FA)-BRCA, CHEK2, and MMR Pathways multiple genes have been able to be identified and incorporated into gene panels.

The example of the relationship between the (FA)-BRCA, CHEK2, and MMR Pathways and breast cancer demonstrates how multi-gene panels help with identification of mutations associated with one type of cancer, yet it's necessary to consider how many of these genes are commonly found in other cancers/disorders. As a result, a patient who might get a genetic panel screening for breast cancer may potentially find increased risk for something else entirely. This may serve beneficial to help take clinical precautionary steps towards more than one disorder, thus increasing clinical sensitivity. The mutation in the gene p53 exemplifies this concept because a mutated p53 is linked to breast cancer via the CHEK2 Pathway, but it is also known to cause Li-Fraumeni syndrome, as previously discussed in Section II. A second example is the gene ATM, also part of the CHEK2 Pathway, that when mutated can cause ataxia-telangiectasia (rare neurological disorder) as well as increase risk for breast cancer (Hiraki et al., 2014). These two examples show how one gene mutation doesn't cause one correlating condition, thus underlining the complex nature of gene mutations and cancer heterogeneity.

In the United States there are a variety of companies that offer gene panel testing; moreover, there are often multiple types of panels available, initiating a consumerism-like approach to gene panels. Major companies on the market include GeneDx, Ambry Genetics, and Myriad Genetics. Ambry Genetics offers hundreds of different panels that test genes associated with disorders/cancers by bodily system (ex: cardiology), certain disorder or cancer, or simply by specific gene ("Ancestry," n.d.). For instance, the

OvaNext panel sequences 24 genes associated with breast/ovarian/uterine cancer risk while PancNext tests only 13 genes associated with hereditary pancreatic cancer (“Tests,” n.d.). GeneDx has very similar panels available that cover a wide range of specific genes incorporated into different tests. Myriad Genetics is another company that offers a long list of genetic panels, and this Utah company used to own a patent over the BRCA 1 and 2 genes; however, in June of 2013, the Supreme Court of the United States ruled in the case *Association for Molecular Pathology v. Myriad Genetics, No. 12-398*, that human DNA was no longer able to be patented. Due to the high court’s decision, BRCA 1 and 2 are now included in many other companies’ gene panels, and also reduced in price (Liptak, 2013). Multi-gene testing panels are not original to the United States either. Sistemas Genomicos in Spain and CeGaT in Germany are examples of international companies that offer genetic panels.

While the invention of multi-gene cancer panels has been largely beneficial, there are also a handful of challenges these panels present. First and foremost, the implication of cancer panels is accompanied with increased complexity and sheer volume of test results, hence complicating test result interpretation. Because of the multiple degrees of variance possible for each gene, and multiple genes being screened, this opens the doors to numerous different results for each patient. In particular, the VUS’s greatly increase complexity of test results and interpretation because there is little scientific data to support a fundamental understanding of risks associated with each VUS. This is due to the unknown effects of some rare variants on the gene-products’ functioning. Furthermore, while gene panels increase clinical oncology sensitivity, there is always the risk of increased false positive test results as well.

In addition to the increase in complexity of results, another challenge with the use of gene panels is the stress on health care providers to provide accurate risk estimates; with complex results detailing the sequencing of multiple genes, approximating risk estimate is a perplexing task. This challenge is again due to the lack of evidence of VUSs and variants on low to moderate penetrance genes. If a patient has one gene with multiple mutations, this will also affect risk calculation; however, this is dependent on the gene penetrance. Another possibility to complicate risk assessment is if a patient has mutations in multiple genes. It is hard to assign a cumulative cancer risk in these scenarios because multiple genes are associated with multiple different cancers, but with different penetrating frequencies. To add yet another layer to the complicated equation, other factors need to be taken into consideration to assess potential risks on top of gene mutations such as familial history, lifestyle, and other risk factors.

Alongside complex test results and interpretation, it is also a challenge to communicate test results to patients. A totally negative test result with no gene variants detected could possibly instill a false sense of confidence in the patient that he/she is “free from cancer” because his/her genetic test didn’t have mutations. It is important to communicate that a negative cancer panel screening does not make the patient exempt from the other causes of cancer such as environmental carcinogens or random mutation. On the other hand, communicating the intricate and complex nature of a cancer panel that has results indicative of mutation is also challenging because of the often time unknown risk assessment. For each gene variant and associated cancer syndrome, there are different availabilities of prevention, lifestyle changes (risk reduction), and treatment methods. Overall, the elaborate and complicated multi-gene cancer panel results are

challenging for the provider to interpret and to effectively communicate the results of these tests with the patient.

## **Section IV: Clinical Genomics to Improve Treatment**

### **Part A: Traditional Tumor Markers**

Section IV, Clinical Genomics to Improve Treatment, will transition from the discussions on who should seek cancer screenings, types of cancer screenings, and benefits and challenges of cancer panels, to a more focused approach on manifestations of cancer, and then later how medical providers can use NGS and our understanding of human and cancer genomes to personalize treatment for cancer patients. Part A will narrow in on the traditional methods of characterizing tumors while Part B will explain how, with modern technology and increased understanding of cancer biology, researchers have been able to expression profile certain genes for patients based on their personal cancer characteristics. Part C will conclude by summarizing the idea of personalized medicine, and how medical professionals can implement targeted treatments based on genomic data.

To begin, the National Cancer Institute defines a tumor marker is a substance that is made “by cancer or by other cells of the body in response to cancer or certain benign (noncancerous) conditions (“Tumor Markers,” 2015).” While a cell may under normal conditions produce a certain protein, it is under cancerous conditions that the cell will produce that product in excess. Proteins are common tumor markers, however, they are not the only ones. Other tumor markers include antigens, hormones, glycoproteins, immunoglobulins, and also changes in gene expression. Depending on the specific tumor markers, they are measured by sending patient serum, urine, stool, or excised tumor tissue to a laboratory and testing the relative level of the tumor marker (“Tumor Markers,” 2015). The tumor marker most likely is

measured for a certain extended duration of time in order for medical professionals to monitor tumor marker changes, for these sequential tests are often more informative than a single test.

Hundreds of tumor markers have been identified and offer valuable clinically relevant information, however the unfortunate side of these markers is that no one tumor marker can be used to diagnose or detect a specific cancer. Some challenges with tumor markers include that some are associated with multiple cancers, sometimes “tumor markers” are not tumor-derived at all, and other times a cancer patient will have no tumor makers produced from cancer. These challenges to tumor markers do not stem from lack of research. For many years scientists have been trying to understand and use tumor markers as a way to screen for cancers. For example, in a randomized controlled study sponsored by the National Cancer Institute known as PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial, prostate-specific antigen (PSA) screening exams were evaluated for how beneficial they were for reducing prostate cancer risk. PSA is a tumor marker that can be elevated with prostate cancer. Nevertheless, it is not diagnostic for prostate cancer because increased PSA levels are also found with other cancers or in non-cancerous patients. The PLCO Trials overall saw that screening for PSA only resulted in a small number of avoided prostate cancer deaths (“Tumor Markers,” 2015). In sum, tumor markers are not specific enough to be used diagnostically or to act as a pre-symptom cancer screen.

While tumor markers are not able to solely diagnose a cancer condition, they can still be of clinical relevance and use in a patient’s treatment plan. Three areas of clinical relevance are diagnostic support, therapeutic utilization, and recurrence. First, when

combined with other diagnostic tests such as biopsies, X-rays, MRIs, etc., tumor markers can provide a supportive role to a diagnosis. Another way tumor markers can be of use clinically is helping the medical provider implement appropriate therapeutic methods. It is also important that tumor markers be measured in a serial fashion in order to monitor the success of the treatment. For instance, if a tumor marker returns to normal levels post cancer therapy, this could be a positive, indicative sign the therapy has worked. After cancer treatments have ended, tumor markers may be used to monitor for relapse. In conclusion, tumor markers are an interesting component to cancer because they cannot be used as screening methods or a sole diagnosing test, however, they can be used as supportive information for therapy choice, amount, duration, and cancer relapse.

## **Part B: Expression Profiling**

Traditional tumor markers only offer some clinical uses and cannot be diagnostically relevant on their own, but another type of tumor characterization is gene expression profiling. Gene expression profiling is the use of newer technologies to examine the gene expression, and consequently, the activity of the cancer cell specifically. The information derived from expression profiling has led to increasing scientists' understanding of cancer biology, major advances for guiding treatments, and even helpful information for cancer diagnosis (Marchionni et al., 2008). Moreover, gene expression profiling has helped researchers characterize tumors by identifying gene changes as the tumor matures and to help find tumor markers. Gene expression profiling works by examining “the composition of cellular messenger ribonucleic acid (RNA) populations. The identity of the RNA transcripts that make up these populations and the number of these transcripts in the cell provide information about the global activity of the genes that give rise to them. The number of mRNA transcripts from a given gene is a measure of the ‘expression’ of that gene (Marchionni et al., 2008).” As a result, the cellular functioning of the cell is largely determined by the cell's protein makeup, which mRNA codes for. Cancer DNA can be tested for by four different tests, using quantitative Real Time (qRT) - Polymerase Chain Reaction (PCR) or microarray technology, including immunohistochemistry (IHC), fluorescent in situ hybridization (FISH) (Marchionni et al., 2008).

While the evolution of gene expression profiling is exciting and promising, there are multiple challenges to the validity of gene expression testing. Gene expression profiling technologies need to be reliable because of the clinical usage of the tests with

cancer patients. One of the largest areas of concern in testing is sources of variability. Because tissue samples are taken in vivo, it is possible to obtain cells from both the normal tissue and the cancerous tissue; if a mixed sample of tissue occurs, it is possible to profile the normal tissue and not the cancerous tissue. Thus, it is of critical importance to perform an accurate tissue excision on the patient for gene expression profiling purposes. Another reason variability may occur during testing is because of instability of RNA, and depending on the different protocols used on the tissue sample, the RNA may be compromised in some tests. For example, when isolating RNA different laboratories may use different approaches such as formalin-fixed, paraffin-embedded (FPET), laser-captured, and micro-dissected, the use of frozen samples or fresh samples all affect the RNA quality (Marchionni et al., 2008). Overall, while gene expression profiling has promising features and is useful, there are some drawbacks with the level of variability that need ironed out before total reliability is accomplished.

Gene expression profiling of tumors can have a lot of clinical relevance in oncology, and one area where gene expression profiling has taken off in is with breast cancer. Certain types of breast cancer have been shown to have different gene expressions, translating into large differing biological functioning via differing gene activity, and these differences can have major clinical implications for prognoses and selected therapies. For example, one of the most common tests is Oncotype Dx (Breast), which provides both prognostic and therapeutic information because the genes help demonstrate the chances of recurrence (via an algorithmically determined Recurrence Score) and if post-surgical chemotherapy use would be useful. There are multiple expression tests that the patient can have done (Table 1) (Oncotype Dx Test, 2016).

Oncotype DX (Breast) works by excising tumor tissue and preserving the tissue via FPET, and then examining 21 genes. The expressions of the genes tested in the Oncotype DX (Breast) test are essential genes in breast cancer gene expression pathways (see Table 2) (“Development” n.d.). A patient who plans to carry out an Oncotype DX Breast test must be estrogen receptor positive, HER2 receptor negative, lymph node negative, and estrogen receptor positive. While the Oncotype DX test originated with breast cancer, recently more tests have been developed for colon cancer (Stage II patients) and prostate cancer, and these tests also offer clinical utility.

Another very common, FDA approved, breast cancer genome profiling test available to patients is MammaPrint. MammaPrint differs from Oncotype DX (Breast) because instead of using qRT-PCR, it uses RASTER technology. RASTER stands for Microarray Prognostics in Breast Cancer and utilizes microarray methods, which makes DNA for single genes “arrayed on a solid surface by covalent attachment to chemically suitable matrices, or directly synthesized them” to examine the genes of a tumor sample (Marchionni et al., 2008). Additionally, MammaPrint tests 70 genes, opposed to the 21 from Oncotype DX (Breast), that are associated with seven pathways of cancer pathogenesis (growth and proliferation, angiogenesis, local invasion, intravasation, survival in circulation, extravasation, and adaptation to the micro-environment step) (“MammaPrint,” n.d.). Moreover, a patient can receive a MammaPrint test regardless of the estrogen receptor status. Similar to Oncotype DX (Breast), the ultimate purpose of the MammaPrint test is to predict the risk of recurrence and determine if chemotherapy would be beneficial to the patient. Agendia, the company that offers the MammaPrint test, also offers BluePrint and TargetPrint assays that aim to comb

through the heterogeneity of breast cancer sub-types. The Blueprint assay is an 80-gene assay that seeks to differentiate between Basal-type, Luminal-type, and HER2-type sub-types and the TargetPrint is an unbiased gene expression test for receptor status of the breast tumors (“Mammaprint,” n.d.).

<b>Cancer Pathway Category:</b>	<b>Proliferation</b>	<b>Invasion</b>	<b>HER2</b>	<b>Estrogen</b>	<b>Other</b>	<b>Reference Genes (Normalize Gene Expression)</b>
<b>Genes:</b>	Ki-67 STK15 SURVIVIN CYCLIN B1 MYBL2	STROMELYSIN 3 CATHEPSIN L2	GRB7 HER2	ER2 PR BCL-2 SCUBE2	GSTM1 CD68 BAG1	BETA-ACTIN GADPH RPLPO GUS TFRC

Table 2: The 21 genes examined in Oncotype DX (Breast) test.

<b>Test:</b>	<b>Company</b>	<b>Who is eligible?</b>	<b>Number of genes tested:</b>	<b>Goal of Test:</b>	<b>FDA Approved:</b>
OncoType DX - Breast	Oncotype DX	-Stage I or II breast cancer -Invasive -Estrogen-receptor positive -Node-negative -Diagnosed with DCIS (ductal carcinoma in situ)	21	-Recurrence risk  -Benefit from chemotherapy  -Benefit from radiation therapy if treated for DCIS	Approved
Mammaprint	Agendia	-Stage I or II breast cancer -Invasive -<5cm tumor -Estrogen receptor positive or negative	70	-Recurrence after 10 years	Approved
Mammostrat	Clariant Diagnostic Services	-Stage I or II breast cancer -Hormone-receptor positive	5	-Recurrent risk	Not Approved
Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50)	NanoString	-Stage I or II breast cancer with node-negative -Stage II with 1-3 nodes-positive -Hormone-receptor positive -Invasive -Post-surgery and hormone therapy patient	58	-Recurrence after 5-10 years  -Benefits of hormone therapy after 5 additional years in postmenopausal women	Approved
EndoPredict	Sividon Diagnostics (distributed by Myriad)	-Stage I or II breast cancer -Hormone-receptor positive -HER-2 negative -Node-negative -3 or more nodes-positive	12	-Chance of metastasis after 10 years of diagnosis	Not approved

Breast Cancer Index	bioTheranostics	-Early-stage breast cancer (stage I-III) -Node-Negative -Hormone-receptor positive -HER2-2 negative -Taken hormone therapy for 4-5 years	7	-Recurrence after 5-10 years  -Benefits of hormone therapy after 5 additional years	Not approved
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Table 1: Genomic tests available for breast cancer patients.

## **Part C: Targeted Breast Cancer Treatments Motivated Based on Molecular Genetic Information**

The use of expression profiling has huge clinical applications for cancer patients, and this area of oncology is likely to continue to expand as technology grows; in fact, some long-term studies are in place or have concluded to analyze the overall benefits of tumor gene expression profiling. One such example is the TAILORx Breast Cancer Trial published some preliminary results on September 28, 2015 that women with a Recurrence Score of less than 10 had less than a 1% chance of cancer recurrence in five years when treated with Tamoxifen therapy alone (“Clinical Trials,” n.d.). TAILORx stands for Trial Assigning Individualized Options for Treatment (Rx) and the estimated completion date is December 2017 (“Hormone Therapy,” 2006). These long-term test results will solidify the validity of tests with gene expression profiling that also provide clinical utility, such as Oncotype Dx, and continue to allow medical providers to individualize cancer therapies based on tumor gene expression.

Another trial that took place to examine the effectiveness of gene expression profiling in tumor cells is the MINDACT trials, sponsored by European Organization for Research and Treatment of Cancer (EORTC). MINDACT stands for Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy and this trial began in December of 2006 and finished in October of 2015. The primary goal of the MINDACT trials was to “compare a molecular profiling approach (70-gene signature) vs. usual clinical assessment only in assigning adequate risk categories [and the need to receive adjuvant chemotherapy or not] to breast cancer patients with 0-3 positive lymph nodes”. These results of this trial demonstrate the “distant-metastasis-free survival at five

years” after 70-gene expression tests (“Hormone Therapy,” 2006). The results of the study showed an absolute 14% reduction in chemotherapy use after surgery in early stage breast cancer patients using genomic expression profiling (“MINDACT: Mammaprint,” 2016). Overall, clinical trials like TAILORx and MINDACT demonstrate how gene expression profiling in breast cancer cells, and hopefully other cancers of other cells someday in the future, has enormous clinical implications because it can dictate whether a not a patient has to undergo adjuvant chemotherapy and the often unpleasant side-affects that accompany it.

One the biggest accomplishments of the TAILORx trial and the MINDACT trials is the positive influence they have had over the development of personalized medicine. Personalized medicine is the practice of doctors using a person’s genetic makeup and studying how the patient’s tumor grows to create a therapy plan and predict risk of recurrence. Expression profiling epitomizes the major areas of personalized medicine, and perhaps in the future personalized medicine will also help medical providers create better screening and prevention methods. Personalized medicine differs from standard clinical treatments because in standard patients today, it is common for the different people with the same cancer to receive the same treatment. However, as the gene panels from Onocotype DX, Mammaprint, etc. illustrate, every cancer can be expressed differently in each individual person, and thus, often required personalized treatments to best suit the patients’ cancer molecular sub-type. The two main areas of personalized medicine are targeted treatments and pharmacogenomics. Targeting specific genes and proteins that allow the tumor to survive with certain drugs underlines the mechanism in

targeted treatments and in pharmacogenomics, genetic testing lends information on how the patient's body responds to certain drugs ("What is," 2015).

Breast cancer has arguably seen the most clinical applications of personalized medicine because of the information provided about the molecular sub-type of cancer from gene expression profiling. One component of personalizing breast cancer therapy is by testing for the presence of the protein, human epidermal growth factor receptor-2 (HER2). This protein is a receptor on breast tissue that helps control normal, healthy breast cell development. It also plays a critical role in breast cancer cell repair, however, in 1/4 to 1/5 breast cancer patients, this protein malfunctions and causes breast cells to grow uncontrollably by the over-expression of the HER2 receptors. Breast cancer patients with HER2 positive status tend to have more aggressive cancers and higher chance of recurrence. While HER2 positive status is associated with higher risk, there are targeted therapies available, such as Herceptin (trastuzumab). This drug works by blocking the HER2 receptors and stopping the propagation of growth signals and signaling to the body's immune system to attack the cancer cells with Herceptin-bound HER2 receptors ("HER2 Status," 2016). The HER2 receptor/ Herceptin case exemplifies how by knowing the genetics of a tumor, and thus its molecular sub-type, can make a significant difference in choice of therapy.

Another example of personalizing medicine in breast cancer is analyzing the presence of the enzyme CYP2D6, which plays a major role in Tamoxifen metabolism. Tamoxifen is a commonly prescribed cancer drug to estrogen receptor positive patients. Tamoxifen is a SERM, selective estrogen receptor modulator, and its breakdown-metabolites compete with estrogen receptors by blocking the binding of co-activators.

The end result of Tamoxifen metabolites competing with the estrogen receptors is that it blocks gene expression, and therefore, slows the cancer growth. The status of a patient's CYP2D6 status is important because when this enzyme (and other contributing CYP enzymes) is present in sufficient levels will Tamoxifen be metabolized to endoxifen, and it is this metabolite that has the greater affinity for the estrogen receptor, resulting in a blocking of gene expression. There are twelve different alleles involved in CYP2D6 expression, so a patient's genes play a major role in determining how he/she will respond to Tamoxifen (Langer, 2016). Depending on the genetic makeup of the patient, he/she may be an ultra-metabolizer, extensive-metabolizer, intermediate-metabolizer, or a poor-metabolizer. Genotyping a patient for their CYP2D6 status can have major clinical implications: any class, but the poor-metabolizer and maybe the intermediate-metabolizer, have the option to receive Tamoxifen (assuming estrogen receptor positive). A poor-metabolizer is exempt because he/she may see little to no benefit from this drug. If the patient is not indicated for Tamoxifen use, another estrogen-lowering therapy approach must be implemented. The CYP2D6 status and Tamoxifen anti-cancer drug once again illustrate the use of personal genomics to personalize cancer treatments.

As discussed previously, OncotypeDx (Breast) can also influence a breast cancer patient's course of therapy. After taking a sample of breast cancer, the genes are profiled and a Recurrent Score is produced, ranging between 0-100. A lower score means that the patient's particular type of cancer will not benefit substantially from chemotherapy, the cancer is non-aggressive and hormone therapy alone will suffice. A lower score also means a lower risk of recurrence. On the other hand, a higher score means a more aggressive cancer, a therefore higher risk of recurrence, and the patient needs both

chemotherapy and hormone therapy use. In the end, the molecular genetics of the patient's breast cancer allows for individualized cancer treatments best suited to beat the cancer. Oncotype Dx (Breast) has proven to be very useful for medical providers and patients, for over 10,000 doctors across the world have ordered this test for nearly a quarter of a million patients ("Oncotype Dx Test," 2016).

Similar to the Oncotype Dx (Breast) test for invasive cancers is the Oncotype Dx (Breast) cancer test for breast cancer ductal carcinoma *in situ* (DCIS). A gene expression profiling test is performed on breast cancer tissue, this tissue is derived from a lumpectomy, opposed to a mastectomy which is the surgery performed when breast cancer is invasive. The results of the genomic profiling are provided in a DCIS Score (between 0-100) and mapped onto two separate graphs. The DCIS Scores is similar to the Recurrence Score because it influences the proceeding course of therapy for the patient. A low DCIS Score means a lower risk of reoccurrence and a higher score is a higher risk of reoccurrence (of either DCIS or invasive cancer). On the second graph, the chances of the tumor returning in the same breast as invasive are given. The results of the DCIS score also guide medical providers and patients in making treatment choices based on the chance of reoccurrence ("What is the Oncotype," n.d.). In sum, breast cancer gene profiling can be very helpful in dictating the course of treatment for the patient; whether testing HER2 status, Recurrence Score, or DCIS Score, these tests consider the uniqueness of every cancer and resultantly treat it as needed.

## **Section V: Conclusion**

In conclusion, this literature review considered the many faces of the development of cancer genomics, expression profiling, and the clinical implications. There are many motivating reasons for people to seek genetic testing, such as familial history, family planning, personal curiosity, cultural susceptibility, and many more. With the invention and utilization of next generation sequencing (NGS), the lower cost of gene panels and higher output has made genetic testing much more open and feasible for the public.

While in the past only single gene tests were available for high penetrance genes more frequently found in cancers such as BRCA 1 and 2, p53, and APC, the use of NGS has led to the invention cancer gene panels; which are genetic tests that sequence multiple genes commonly seen in cancers. Patients have the option to choose from a variety of different panels, each with their own genes of interest included. Cancer gene panels from companies such as Myriad and Ambry Genetics offer many benefits such as increased clinical sensitivity, better cancer monitoring, more personalized treatments, improved prognoses, and increased target audiences. On the other side however, are a handful of challenges such as increased complexity from test results, increased pressure on the medical provider to effectively and accurately communicate test results to the patient, and patient understandings and reactions. Despite some challenges, molecular data collection in cancer patients can be used to improve treatment. Whether traditional tumor markers, gene expression profiles from a cancer sample, personalizing the therapeutic approach based on the molecular subtype of the cancer can improve patient outcomes. Breast cancer is a main area of oncology where clinical genomics has proven to be beneficial. Considerations such as estrogen receptor status, HER2 receptor status, lymph node status,

CYP2D6 enzyme expression, and genomic test results from Oncotype Dx (Breast) or MammaPrint, guide the medical provider in specifying the most personalized therapy that will best help the patient fight their cancer. Hopefully, this can be the future for many cancers as the world of clinical genomics takes off with improved technological developments.

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