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# A Review of How Bioinformatics and Genome Sequencing are Affecting Precision Medicine

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# “A Review of How Bioinformatics and Genome Sequencing are Affecting Precision Medicine”

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**Abstract**

Advancement in genomic sequencing and bioinformatics methods have been affecting biomedical research through precision medicine, especially in the area of cancer. Vaccine therapies can be developed using neoantigens that target specific mutations in tumors. The goals of this research are to identify mutations that lead to cancer and then define subpopulations in which patients can easily be identified. The future goal is to have targeted vaccines that are specific to each subpopulation ready to be used in treatment of their cancer. Limitations to reaching these goals have been due to tumor heterogeneity, cancer location, and difficulty in creating neoantigens for vaccines successfully. A literature review was conducted to better understand the current research being done to address the cancer epidemic through bioinformatics analysis and precision medicine. It was found that TP53, CLDN6, and IDH1 were crucial mutations leading to the development of multiple types of cancer, and more sophisticated, streamlined technology is needed to rapidly develop targeted vaccines to attack ever evolving cancers.

**Key Words**

Bioinformatics, Genome Sequencing, Precision Medicine, Cancer, Biological Sciences

## Introduction

Bioinformatics is a field of science where genomic information is analyzed to determine deeper information about the connections between genes and their biomedical phenotypes, including diseases using computer science and informational technology. Analysis results can be applied to biomedical research to, for example, develop treatment of different diseases. Human DNA has the power to unlock the mystery of destiny, as it can reveal what complications we may face in the future. Hidden within the human genome lie mutations in genes that lead to diseases, such as cancer or cystic fibrosis. As affected genes are expressed, the person takes on the phenotype of the disease. Genome sequencing is a process that is conducted in order to reconstruct the genomic information and reveal secrets that are hidden within. Next-generation sequencing technologies have made whole genome sequencing possible very quickly and economically (see Table 1 for the list of technologies described in this review). It can be done not only on one individual, but on multiple people at a population level.. This process is important because it has allowed scientists to be able to identify different disease markers coded in the genome. Tumors have their own set of mutations that can be revealed by sequencing the genome. Precision medicine, sometimes confused with personalized medicine, is a quickly evolving branch of medicine that seeks to develop treatments for different diseases based on their categorization. The scientists identify different subgroups, develop treatments for each subgroup, and then match patients to their subgroup. Personalized medicine would be when each patient is matched to their subgroup.

The medical field has begun to apply this goldmine of information to personalized plans of disease treatments. New, innovative ways to combat some of the deadly diseases that plague our populations have been developed constantly. Cystic fibrosis (CF) is caused by the cystic

fibrosis transmembrane conductance regulator (CFTR) gene (Chalmers, 2021). Gene therapy, using the CRISPR-cas9 gene-editing technology, for example, is being studied to treat CF by splicing the CFTR gene from a healthy person into the stem cells of a patient. The hope is that the new, healthy CFTR gene will be replicated in the patient's cells, causing a lessening of the disease symptoms.

One of the biomedical areas where bioinformatics research currently has the most influence is in cancer therapy. By analyzing the types of cancers as well as using the specific genetic data of their patients, oncologists and the research community are able to devise more creative and interactive approaches to fighting this versatile disease. For example, by analyzing genomic data, specific genes that are commonly mutated to cause breast and other cancers can be highlighted. By identifying biomarkers specific to each cancer, medical doctors are able to predict how the cancer will progress as well as if the cancer will relapse. The biomarkers also inform them which cancer drugs will be the most effective against specific cancers. Another innovation is that of nanoinformatics, which uses bioinformatics and nanotechnology to administer drugs to target cell receptors utilizing nanoparticles. Bioinformatics and genome sequencing are improving treatment outcomes for patients with many varieties of cancer through precision medicine.

This literature review will attempt to summarize the broad inventions and research that is being conducted to cure cancer in the modern world through personalized medicine techniques. First, we will explore how nanoinformatics are being implemented. Secondly, we will analyze the treatment of leukemia. Next, we will investigate the treatment of pancreatic, prostate, and colorectal cancers. Penultimately, we will inspect the current approaches to curing breast cancer.

Finally, we will examine the creative innovations being used to attack the difficult cancers of the brain.

## 1. Nanoinformatics and Neoantigens

Xie *et al*. (2023) explains that neoantigens are a newly discovered tumor marker. These antigens are tumor-specific and can be targeted with immunizations and treatments. The best part about neoantigens is that they are not found in healthy cells. Therefore, they are easily targeted and distinguishable. This treatment against neoantigens decreases autoimmunity. It has been a significant development for cancer research, as many traditional treatments eliminate healthy cells along with the diseased ones. Another perk of utilizing neoantigens, according to Khan *et al.* (2022), is that neoantigen treatments are noninvasive, and the drugs can be modified from patient to patient. Non-invasive treatments are very important, as common treatments, such as surgery, chemotherapy, and radiation, come with many, significant side effects and impact the compromised immune system. Tumors can be very difficult to treat, as they create an immunosuppressed environment. This can be overcome by using neoantigens in vaccinations. The only downside is that each tumor has unique neoantigens that must be sequenced and analyzed. Bioinformatics methods make these efforts much easier to accomplish. We will first look at how neoantigens are identified and then address how vaccines are developed for treatment.

### *1.1 Neoantigens and the Major Histocompatibility Complex*

Neoantigens are displayed to T-cells utilizing the major histocompatibility complex (MHC). The MHC is present on antigen presenting cells (APCs), such as dendritic cells,

macrophages, and B-cells. This complex presents a degraded bacterium, virus, or other pathogen to a naïve T-cell that then initiates the adaptive immune response to target the disease.

When working with neoantigens and the identified mutations, researchers must identify the human leukocyte antigen (HLA) type (MHC in humans is called HLA) and the binding affinity in order to produce the most effective vaccination. Currently, the most widely used method for identifying the HLA involves a polymerase chain reaction (PCR) technology to amplify them (see Table 1). The exciting thing about neoantigen vaccinations is that, according to Miller *et al.* (2019), they have begun to show promise in the treatment of glioblastoma, an extremely deadly brain cancer.

In the article regarding the role of neoantigens, Shang *et al.* (2022) found that new algorithms are now 99% accurate for identifying Class I HLA. Class II HLA still needs more attention. It is important to identify the correct HLA in order to predict which neoantigens are going to bind most effectively to the cells in the patient's body. Without this information, the vaccinations and treatments will not yield results because the tumor antigens will not get presented on the cell.  It is fascinating to note that cancers with a larger number of mutations respond better to this treatment as there are more neoantigens that can be used.

### *1.2 Nucleotide Changes Causing Neoantigens*

There are many things to consider with neoantigens, as there are many different forms. There are single-nucleotide variations (SNVs) that are highly prevalent, as well as insertions/deletions (indels) in exons that cause a shift in the reading frame. According to Shang *et al*. (2022), SNV-based neoantigens have shown to be effective when used with immune checkpoint inhibitors, while the analysis across many cancers found that indel-based neoantigens

produce more immunogenicity and improve outcomes in patients with melanoma. This means that SNVs can spark an increased response from the immune system that allows it to overcome the cancer. In engineering neoantigens, Liu *et al.* (2022) also found that you can stimulate a great immune response utilizing a mutation in the arginine-132 residue of the IDH1 gene, which causes class II helper T-cells, IgG1 antibodies, and class II cytotoxic T-cells to kill tumor cells with powerful T-cell receptors (TCRs) (see Table 2 for the list of genes whose mutations are associated with cancers). This means that scientists can identify a mutation and develop neoantigens that target it to cause the immune system to attack a tumor. This all depends on the patient and the cancer type, but is needed to be successful in destroying the cancer. A neoantigen can also be the result of the fusion, inversion, mutation, duplication, or translocation of genes, as well as selective splicing, or RNA edits. Liu *et al.* (2022) also found that the neoantigens from indels introduced in a gene are most effective in stimulating T-cells, as they seem to have better binding capabilities.

Liu *et al.* (2022) found that when compared to non-synonymous, single nucleotide variant (nsSNV) indels created mutant neoantigens that yielded an immune response that was nine times stronger. They produce three times more neoantigens overall, and they yield longer survival rates by producing interferon gamma (INF-γ) and tumor necrosis factor alpha (TNF-α). INF-γ is a cytokine that initiates NK cells, neutrophils, and macrophages. TNF-α is another cytokine that leads to inflammation while also controlling cell signaling to induce apoptosis or necrosis. This study shows that when you are able to activate a more intense immune response the patient will have a better chance of overcoming the disease.

### *1.3 The Approaches Utilizing Tumor Mutational Burden vs. Tumor Neoantigen Burden*

Researchers have been using tumor mutational burden (TMB) to recognize which tumors are the best candidates for precision medicine therapeutics. However, now it may actually be that tumor neoantigen burden (TNB) is the biomarker that they should be paying attention to. TMB is a biomarker that is determined by the number of non-inherited mutations per million base pairs, whereas TNB is the amount of neoantigens per megabase. The TNB would be more effective, as it would describe the actual tumor rather than an assortment of mutations.

Shen *et al.* (2022) determined a positive relationship between TMB and TNB. However, TNB was connected with macrophage genes that produce cytokines and granzymes, as well as other genes that have resulted in better response to immunotherapy. Macrophages are a cell in the immune response, and the granzymes that it releases are used for targeted cell death, thus the tumor cells are eliminated.

### *1.4 Tumor-Specific Antigens in Vaccinations*

There have been several methods over the years that have allowed for the tumor-specific antigens (TSAs) to be identified for use in vaccines. Han, (2020) explained that the first improvement came with whole-exome and whole-genome sequencing technologies. This allowed for neoantigens with higher affinities to be identified and used to make predictions on which antigens will best match the tumor. The new and improved model uses next-generation sequencing methods to create a map of the mutations and then compare it against a normal genome. Liu *et al*. (2022) described the process further. Genes associated with the disease are identified, cataloged, and neoantigens are generated for future use in the treatment of that specific tumor. The selected mutations are then finalized after they are put through a pipeline of computational programs with a mutation catalog. This pipeline analyzes the genetic data and

false positives and false negatives are identified. A false positive means that a mutation was selected for that was not connected to the disease, while a false negative means that a mutation was not selected for that was connected to the disease. Finally, personalized vaccines can be developed for the person who the initial sample came from.

### *1.5 Dendritic Cell-Targeted Vaccines*

Currently the vaccine classes are peptides, DNA, RNA, and dendritic cell (DC) based, and each has their own perks and drawbacks (see Table 1). Liu *et al*. (2022) found that DC vaccines greatly expanded the diversity of TCRs, generated an increased effectiveness rate, control rate, and survival rate of the disease, no toxicity problems, and kept drug reactions low, making it the prime candidate for future vaccines. Another study by Ebrahimi *et al*. (2021) showed that DC vaccines also trigger strong immune responses and can activate natural killer (NK) and other immune cells. There has also been a push for necroptotic cells that induce cell death. Ebrahimi *et al.* (2021) explained that when cancer treatments can generate immunogenic cancer cell death (ICD) the treatment is more successful. This is a compounding effect, so as the cells die they induce an immune response and activate more dendritic and T-cells to continue to fight the cancer.

### *1.6 Neoantigen Selection*

Scientists have been developing programs to increase the accuracy of matching their neoantigens to tumors.. According to Roy (2020), it is crucial that laboratories are deliberate in analyzing the success of their computational programs and identify mistakes so that the correct mutations are identified in analysis and may be used for future genetic testing. Liu *et al.* (2022) explained how this works. Once the scientists have their predicted neoantigens, computational

methods also help them analyze cellular mutations, HLA genotypes, and other cellular information to generate a model that reveals which neoantigens will have the greatest binding affinities. The neoantigens with the highest scores are the ones that eventually make their way into the treatment plan. A combination of proteomics, genomics, and immuno-peptide-omics software has produced the best selection of neoantigens. The scientists here are studying proteins, genes, and immuno-peptides to scour the patient for neoantigens. Scientists want to cover all their bases, because missing the correct neoantigen for a tumor could be the difference between life and death in a patient.

In the role of neoantigens in tumor immunotherapy, Shang *et al*. (2022) stated that CLDN6, a neoantigen from fetal mice, could prove to be beneficial against solid tumors in uterine, testicular, ovarian, and lung cancers (see Table 2). This is important because one vaccination with this small protein could be used across several cancers! Based on the survival rates, patients that had the most responsive cytotoxic T-cells and the most neoantigens produced tended to fare better. Even if vaccines can be produced, the process currently can take months, which can impact survival outcomes due to disease progression. More research still needs to be done to improve screening methods to identify the correct neoantigens.

### *1.7 Chimeric Antigen Receptor T-cell Therapy*

Chimeric antigen receptor T-cell (CAR-T) therapy looks promising for the treatment of solid tumors. CAR-T therapy uses T-cells from the identified patient and then genetically manipulates them by adding the chimeric antigen receptor (CAR) as a gene (see Table 1). These cells are then given back to the patient. Research conducted by Wang and Cao (2020) used

neoantigen identification in tandem with CAR-T to produce T-cells with a high response to the cancer or tumor that the person has.

### *1.8 Limitations of Neoantigens and Treatment Development*

One downside of neoantigen vaccinations is that the cancer cells may develop mechanisms to mutate around the immune system by deleting certain genes that aid in initiating the attack. This is why neoantigens are most effective in combination with other treatments.

Shang *et al.* (2022) provides a good summary of the steps of developing a treatment for specific patients. First, samples of healthy and cancerous tissue are taken and sequenced to identify mutations. Then, HLA binding is matched and the highest responding neoantigens are selected based on expression and how well they match the tumor. Finally, vaccines are created and administered to patients using the best neoantigens. Bioinformatic is being applied to the study of different types of cancers to develop new treatments that target specific disease phenotypes.

## 2. Leukemia

Leukemia is cancer of the blood and blood-forming tissues, such as the bone marrow. A problem with this type of cancer is that the bone marrow is a major developmental organ for the immune system. Treating leukemia is a challenge, as the disease can develop drug resistance. Furthermore, the cells that are not killed by early treatments can replicate. Precision medicine could help this by targeting the tumor specific antigens and eradicating problematic cell types. It may be important to bring clarity to why so much testing is necessary to determine gene loci and individual mutation events and biomarkers. One of the significant properties of cancer is the

heterogeneity, in which tumor genotypes vary from person to person, or even from cell to cell. This is why one treatment approach will not always fully clear the disease. There may even be two different tumors that appear to be one. Heterogeneity may also be the reason why cancers are able to relapse or metastasize, as certain drugs that kill one cell type may actually invigorate other cell types, or some cells may remain after treatment and come back more entitled the second time around. Because of this, the improvements that have been made towards curing a type of cancer may come to a halt. At this point, computational genomic analysis may still provide some viable strategies for improving patient outcomes by using neoantigens to produce a stronger immune response against the cancerous cells.

### *2.1 Chronic Lymphocytic Leukemia*

Chronic lymphocytic leukemia (CLL) is a form that affects B-cells in the bone marrow. Lin (2022) found 109 novel genetic drivers of leukemia and constructed a genetic map that allows doctors to track the disease progression. These genes that have developed new functions provide landscapes that researchers can use as a guide in developing personalized medicine plans. The author was able to develop new drugs that target the identified genes. Lin (2022) also developed a program called TuFEst (Tumor Fraction Estimator). This computational program analyzes TMB levels and cell-free DNA (cfDNA) (see Table 1). cfDNA, flows freely through the bloodstream and is not contained inside of a cell. cfDNA can be scanned for ctDNA, or circulating tumor DNA, that has been released by a tumor into the bloodstream. This allows scientists to see what mutations the tumor has, as the ctDNA will have the same mutations. A perk of using cfDNA is that it can be screened without performing a tumor biopsy, which decreases the chances of disrupting a tumor or the patient developing an infection.

### *2.2 Acute Lymphocytic Leukemia*

Acute Lymphocytic Leukemia (ALL) is leukemia of the lymphoid blood cells. A study done by Ramesh *et al.* (2021) confirmed that the genes mutated in ALL are PTEN, FLT3, NOTCH1, JAK1/2, KRAS, PAX5, U2AF1, NF1, and TP53 (see Table 2). Next-generation sequencing and RNA-seq were utilized to identify these genes (see Table 1). These results are extremely important for validating the reproducibility and accuracy of previous studies. These genes can be classified as biomarkers of ALL and pharmaceuticals can be developed that are specific for these gene locations.

### *2.3 RNA Analysis for ALL Mutation Identification*

A study conducted by Severgnini *et al.* (2022) used conjoined genes in childhood leukemia and cataloged the transcriptional activities that occur in patients with ALL to analyze common genetic mutations and identify their patterns. Conjoined genes occur when two or more genes on the same chromosome exchange genetic information to produce a new gene. The goal of this research was to identify novel genes in the patients, or genetic mutational events that have not been seen before. Severgnini *et al.* (2022) found that in BCR-ALL patients (B-cell precursor), there were almost ten thousand mutational events, but found few led to actual meaningful mutations, or those that lead to disease development. Further, they found that conjoined genes, or gene mutations from contiguous genes, made up a high percentage of the mutations that were consistent with developing leukemia. This is exciting because this points to a relationship between leukemia and these conjoined genes, and the researchers were able to specify fourteen new genetic events that had not been indexed yet. Whenever cancerous mutations are recognized, they are added to a database that contains all the known genes

associated with each specific cancer type, such as the Precision Medicine Analytics Platform (PMAP). As the database grows, the treatment options increase while the turnover time for patient care decreases.

**3. Pancreatic Cancer**

Pancreatic cancer is the cancer of the pancreas. The only chance at survival with pancreatic cancer is with early detection. In most cases, pancreatic cancer is fatal.

No diagnosis is music to the ears, but a pancreatic cancer diagnosis is extremely disheartening. In a study done by Hu *et al.* (2018) on mismatch repair, the researchers looked at seven patients with MMR-D (mismatch repair deficiency). With MMR-D, the DNA cannot be repaired as in normal cells and these mutations are often the cause of cancer. They found that the associated mutations were MLH1, MSH2, MSH6, and PMS2 (see Table 2). This study is important because there is limited research that has been done on MMR-D and these mutations can be added to the growing database. Small studies like this are important for the patients involved also, as they need treatments specific to their cancer, not someone else's from a database.

Pancreatic cancer has high heterogeneity, which means that tumors are unique across patients. This makes it necessary that multiple treatments or individualized treatments be used to attain the desired outcomes. In a study done by Sorber *et al*. (2016), the researchers analyzed three different cell lines through whole-genome sequencing to identify what may cause or speed up the progression of pancreatic cancer. They found that a mutation in the Plexin A1 receptor (PLXNA1) led to increased proliferation of a pancreatic adenocarcinoma, SB.06, which then infiltrates T-cells, resulting in a cascade of effects and increased disease progression (see Table

2). The PLXNA1 mutation is a gain-of-function mutation that causes either a new pattern of expression or a new molecular function to occur in the gene product. The researchers also followed the growth patterns of these cell lines to examine how the disease progresses and spreads. An interesting point to note was that Sorber *et al*. (2016) found that a different cell line (SB.07) grew cell-to-cell sheets, while cell line SB.06 did not touch and had atypical growths, like spindles, that stretched off of the main areas.

This finding shows the heterogeneity of pancreatic cancer. There is an overall lower mutation rate in pancreatic cancer compared with other cancers, which shows that quantity does not matter as much as the quality of mutations for cancer disease lethality. There was another study done that showed that there is promise for extending life through precision medicine for pancreatic patients. Unfortunately, most of the patients in the study were unable to complete the study because the disease progressed much faster than they were expecting, and a few patients dropped out due to lack of adequate data. In a trial done by Hidalgo *et al.* (2022), the researchers found that the median survival rate improved by almost a year for patients who were treated through personalized medicine, or precision medicine tailored to them, compared to those who did not complete the study. Although they were unable to cure these patients, the extra year of life was surely a gift, and the study supports the efficacy of precision medicine.

**4. Prostate Cancer**

Prostate cancer is a cancer that develops in the prostate gland. As we are looking at these cancers, it is interesting to note that gene patterns can lead to different disease development in men and women, adding another layer of difficulty to research. One such example is that of the breast cancer gene (BRCA) that we will look at later. Although it generates breast cancer in

women, it also leads to the development of prostate cancer in men (see Table 2). Even though important biomarkers like BRCA have been identified, often these markers are only applicable to a certain subset of patients. In a study conducted by Alarcón-Zendejas *et al.* (2022), the researchers looked at a compilation of the current research in prostate cancer. They found that biomarkers related to mortality included JMJD3, MGMT, and DNMT1 (see Table 2). All three of these genes are correlated with DNA methylation, a process that alters how genes are expressed in a cell, and these alterations can be passed down. This makes sense, as we often see patterns of prostate and breast cancers being hereditary diseases.

Alarcón-Zendejas *et al.* (2022) also highlighted the increasing importance of artificial intelligence (AI) in implementing and identifying these new treatments in record times (see Table 1). The article discussed that the cancer research community is developing ways to transfer the vast data that is being collected to generate machine learning models. This is a technology that teaches computers how to construct models from the data it is given and learn from it. The AI then detects patterns, and this helps doctors determine patient diagnoses or effective treatment strategies. Decisions like this used to rely on hours of human intellect scouring the information to find a key to the puzzle, but now algorithms are able to produce outcomes rapidly. It would be difficult to see important breakthroughs develop, but not have the capacity or the technology to develop these new therapies ahead of disease progression. AI may be the solution.

**5. Colorectal Cancer**

Colorectal cancer is cancer that occurs either in the colon, the rectum, or both. Early detection of non-metastatic colorectal cancer has a high survival rate. However, once it spreads,

survival drops dramatically. However, if the research proves promising, they can use what they find and apply it to a wider range of patients.

In a paper published on colorectal cancer by Dashti *et al*. (2022), the researchers ran a giant cluster of the somatic point mutations from a selection of over 500 patients contained in the International Cancer Database. This was to determine different subtypes of colorectal cancers to be able to more easily identify the subtypes into which patients would fall, by analyzing their disease phenotype. Dashti *et al*. (2022), compiled gene mutations and patient survival rates and classified seven different subtypes. These subtypes were described by gene sets that were non-overlapping. This data set has vital information, because this tells medical doctors which genes to target with immunotherapy. In addition, in case they had missed a crucial mutation that had arisen in those proteins, doctors could target the other genes in the subtype as a precaution. This study seems to be a blueprint to the future for how researchers can begin to translate their data into treatment plans. They can begin to develop neoantigen therapies that are readily on hand depending on which subtype is identified. It can be disheartening for researchers when their datasets diminish due to the loss of life. Studies like this could dramatically decrease the current turnover time between diagnostics and precision therapies.

**6. Breast Cancer**

In this section, we will inspect the current approaches to curing breast cancer. When breast cancer is non-metastatic, the survival rates are very high. One of the most difficult decisions for women facing breast cancer is whether to have a lumpectomy or a mastectomy. It can be very difficult because the wrong choice can lead to death, but the other may leave these women feeling stripped of their womanhood and femininity. The research being done in

bioinformatics is laying the groundwork to predict cancer relapse to aid in making this crucial decision.

### *6.1 Utilizing cfDNA in Breast Cancer Treatment*

As previously discussed, Lin (2022) developed a program called TuFEst that estimates TMB and cfDNA. This program has been used to detect breast cancer relapse 262 days earlier than other identification methods. Through development of highly sensitive technology like this, doctors can predict disease recurrence based on the levels of tumor DNA found in the cfDNA that has been released by tumors into the bloodstream. The safest option is always to do a mastectomy, but it would be beneficial to know the likelihood of a relapse.

### *6.2 Utilizing ctDNA in Minimal Residue Disease Treatment*

Janni *et al*. (2022) aimed to utilize ctDNA in patients with minimal residue disease to gain insight into mutations in women where tissue samples are extremely limited. Minimal residue disease occurs when a mastectomy, lumpectomy, or other treatment is conducted, and cancer cells are leftover in the body. These cells can proliferate and cause the cancer to come back. This is not something that can usually be sampled. Janni *et al*. (2022), looked at collected samples of plasma during early-stage breast cancer, either during first occurrence or recurrence. They successfully spotted ctDNA during or before recurrence, and in a few patients, they were able to get a lead time of between 3-18 months before disease development. This extra time is vital to cancer survival. Some patients did not suffer recurrence, so no circulating tumor DNA was found. This is also important because there are cases where individuals are not able to have their tumors sampled, but everyone can spare some of their plasma for analysis.

This study proves that ctDNA technology is worth exploring more in the future, and other studies are already being conducted to improve upon and confirm what was shown here. Researchers have also begun to work with liquid biopsies. The hope is that with this technology they will be able to monitor disease progression and mutation by watching how the DNA levels in the blood change.

Sant *et al*. (2022) explained that another reason to study ctDNA is that there are often tumors in metastasis that cannot be reached with biopsies, so ctDNA can be used to evaluate clonal evolution, progression and heterogeneity of tumors, and gives a broader picture of the genomic make-up of tumor cells. This prevents mistyping of the tumor and allows doctors to monitor the progression and evolution of the tumor to evolve treatment targets in real time.

### *6.3 Obstacles to Breast Cancer Treatment*

Sant *et al*. (2022) further addressed some current obstacles to implementing bioinformatics, genome sequencing, and the computational analysis of mutations. Many of these mutations are not breast-cancer specific, but are applicable to any cancer informatics research. Sant *et al.* (2022) explained that there is not currently a low-cost, repeatable model that is available for treating patients. In addition, adequate cloud space must be encrypted to house all the generated data that is coming out of current studies, and technicians must be trained to analyze and synthesize this data. There also seems to be a call to action across many of the papers for researchers to share their results in a public, collective forum so that all new data can be utilized by the research community to improve upon their own results. This is being addressed by collective database programs, like PMAP, that were discussed earlier. Some studies may need

support or confirmation from other researchers to synthesize the massive amount of information that becomes available every day.

### *6.4 Identifying Mutations in Breast Cancer*

Kumar *et al*. (2022) followed a group of breast cancer patients in India and found that in all individuals, mutations occurred in Notch, WNT, Hippo, RTK-RAS, p53 (TP53), NRF2, PI3K, Myc, TGF-B, and cell cycle pathways (see Table 2). They also identified hotspot mutations, driver genes, and tumor suppressor gene alterations. This study provides a panel of genes to monitor that seem to occur in the majority of breast cancer patients and can be used, once again, to develop targeted therapies.

### *6.5 Triple-Negative Metastatic Breast Cancer*

Hammash *et al*. (2022), looked at triple-negative, metastatic breast cancer cells. Triple-negative cells do not have any of the biomarkers that are usually used to identify breast cancer. These markers are estrogen, HER2 protein production, and progesterone. Once breast cancer, or any cancer for that matter, becomes metastatic, it becomes extremely deadly. There is an occurrence of breast cancer in which metastasis pushes into the brain. Hammash *et al*. (2022), discovered that when miR-623, a microRNA gene, is downregulated, the matrix metalloproteinase-1 (MMP1) is turned on. As further explained, MMP1 allows for the brain metastasis of TNBC (triple negative breast cancer cells) by encouraging their transfer across the blood brain barrier
(see Table 2). The research conducted in Hammash *et al*. (2022) explains how the TNBCs are able to migrate and helps scientists know how to prevent this fatal form of metastasis. This is a

small peek into the research being conducted on breast cancer, but it showcases several studies that have many possibilities for future and more in-depth studies to branch off from.

## 7. Brain Cancer

Finally, we will examine the creative innovations being used to attack the difficult cancers of the brain. There can be both malignant (cancerous) and benign tumors found in the brain. The struggle with brain cancer is that doctors cannot use normal drugs to treat it because of the blood-brain barrier. This barrier is used to keep toxins from depositing in the brain while also delivering needed nutrients and oxygen to the brain, but this is troublesome when it comes to treating diseases.

Pharmaceuticals must be designed to mimic the shapes of other compounds that are allowed to cross. Another reason that brain cancer is especially difficult to treat is because surgical removal of tumors can be extremely dangerous and lead to brain damage or death. The margin of error can sometimes be as thin as the scalpel that they are cutting with. In response to this, researchers have begun to develop targeted chemotherapeutics, and the future looks promising. This topic cannot be adequately addressed here, but this is another current area of personalized medicine that may prove extremely effective for treating brain cancer.

### *7.1 Medulloblastoma Research*

Cancer tumors usually take several years, as many as 10-30 years, to develop as the body continues to accumulate cells in which the tumor suppressor genes have been inactivated and an unregulated cell cycle is produced. However, scientists are beginning to see a rare condition occur called chromothripsis. Chromothripsis occurs when there is a cataclysmic event in the

genome that induces a major disruption and rearrangement of chromosomes causing severe mutations to occur. This event has been found in a patient with a medulloblastoma. Rausch *et al*. (2012), followed a female patient with a Sonic-Hedgehog medulloblastoma, a malignant tumor in the sonic-hedgehog pathway of the brain. They conducted whole-genome sequencing of the patient and found that a mutation in TP53 was the cause (see Table 2). The researchers went on to compare more results with three other medulloblastomas, and none of them were found to have a chromothripsis character to them. This study further goes to show the difficulty of precision medicine in that, truly, research often only can be applied on a case-by-case basis.

It seems essential to address the crucial work being done by St. Jude's hospital to make sure that pediatric survival rates continue to increase. Smith *et al*. (2020), cataloged patient-derived orthotopic xenograft (PDOX) models for children with medulloblastoma, atypical teratoid rhabdoid tumor, ependymoma, and embryonal tumor (see Table 1). The models are to create a streamlined system to evaluate novel therapies. PDOX models are constructed by extracting tumor cells from various patients with rare brain tumors. These cancerous samples are molecularly mapped and are then grafted into an animal model, usually mice. The models are then observed for cancer growth and development. This data can then be used and manipulated by researchers for their specific patients. If the tumors can be successfully transferred to the animal models, the scientists can then observe all the inner workings of the tumor's evolution and can develop treatments that evolve alongside the disease.

### *7.2 Glioblastoma and the EGFRvIII Gene*

Glioblastomas are the most aggressive brain tumors, but other gliomas can be deadly as well. The survival rate for this potent cancer is horribly low. In an effort to address this,

researchers set out to develop a pipeline that could be used in the treatment of certain glioblastomas. Before effective immunotherapy can be developed, doctors and researchers need a pipeline through which they can run each patient's genome so that genes can be sifted and the correct mutations to target can be identified. Miller *et al*. (2019) took special interest in a gene called EGFRvIII when developing a pipeline specific to glioblastoma treatments (see Table 2). Miller *et al.* (2022) stated that this gene is not usually found in tumors outside the brain or in low-grade gliomas but could be used to decrease the need for invasive procedures, as this gene is correlated with high rates of malignant transformation.

The researchers saw a need to develop this pipeline because there was not a current computational method that was able to readily identify EGFRvIII. The scientists utilized a wide range of tumors to generate a baseline data set. Miller *et al*. (2019) used next-generation sequencing and amplified EGFRvIII and ran a group of glioblastoma samples, as well as utilized AmpliSeq to develop a cost-effective pipeline (see Table 1). They used it to successfully identify a grade IV glioblastoma that did not present the typical signs. AmpliSeq is a form of PCR that is able to amplify, or copy, many targeted sequences with a small amount of sample DNA. It is hoped that this technique can be used for tumors that are not well sampled in the future. Biomarkers are extremely difficult to use overall because they can be difficult to identify, like EGFRvIII, but then they must also be analyzed for their prognostic value in addition to their ability to be targeted for immunotherapy. As one can see, it is an arduous process to validate even a single biomarker as a target.

**Conclusion**

Bioinformatics and genome sequencing are improving treatment outcomes for patients with many varieties of cancer through precision medicine. Bioinformatics is greatly impacting leukemia, pancreatic, colorectal, brain, and breast cancer, leading to better treatment outcomes for these patients. Genome sequencing and nanoinformatics are instilling hope and light into the dark, bleak words of a cancer diagnosis. There is the question of ethics to consider as well. In the future, precision medicine will have to address how to best handle the information that is being gathered on their patients.Precision medicine has a long journey to complete before it is attainable for all patients, but as new information is synthesized, the finish line gets a little bit closer. The timely development of target vaccinations and therapies could be the difference between life and death for many patients. If researchers can catalog all of the disease biomarkers, screening can be done earlier to identify cancer before it begins, but this type of technology is still years away.

From the neoantigen literature, the future lies with DC vaccinations as these pose the least risk to the patient while also maximizing effectiveness in treating and preventing cancer. Dendritic cells are responsible for some of the strongest responses of the immune system, so these vaccinations could prove vital to curing cancers that are still deadly.

It was found that mutations in TP53, a tumor protein, are major causes of cancer across many different categories. Mutations in IDH1 and CLDN6 also are responsible for several different cancers. It would prove beneficial to develop precision medicine therapies that successfully attack these mutant proteins because therapies that address them would serve the most patients. A therapy that increased dendritic cell response to these mutations and their antigens would also be ideal. The cancers and their mutations that were discussed in this review should also be analyzed and placed into subtypes, like the study that was done on colorectal

cancer by Dashti *et al*. (2022). If these groups and patterns could be established, this would both cut down time of identification and provide other genes to target. This could possibly be done using AI.

In addition to this, the PDOX models being used in medulloblastomas should be translated to other cancer types, especially pancreatic cancer. This would allow doctors to follow the progress of the tumor and observe which treatments work best for that specific tumor. This grafting would dramatically change how cancer is treated and may prove the key to beating pancreatic cancer. Furthermore, researchers should create several PDOX models of the same tumor and try different treatments simultaneously. This would not only help the patient but would create an opportunity to collect vast amounts of data on tumor evolution and subsequent treatment.

ctDNA from the blood should be used in the treatment of brain cancer as well. ctDNA may be able to help scientists reach genetic information that their scalpels are not able to get to in tissues, and will be vital to the treatment, successful remission, and early detection of cancer. ctDNA also could be implemented by medical doctors in normal blood testing as a method for early detection of cancer.

Cancer disease progression can be rapid, so time is of the essence and is crucial to patient survival. A computational method needs to be developed to analyze a patient tumor sample, identify its biomarkers, and translate it into what the neoantigen needs to look like. It seems that AI-based methods are close to recognizing the patterns, but there seems to be a large chasm between identification and development. Researchers could also develop AI programs that can categorize and predict which biomarkers will prove most effective for each patient based on their

genotype. Instead of wasting so much time with several different computational programs or AI, researchers should develop an integrated technology that includes a sequencer, a catalog of mutations, and a computational program to streamline the process.

Hopefully, advances in bioinformatics would come so far that the technology could also include something that would be similar to a 3D printer, but for neoantigens. Another option would be having AI programs select the best treatment option, and doctors would be able to go to a medical fridge and already have the corresponding vaccination on hand. Science often has to catch up with our dreams, as technology as sophisticated as this is still a long way down the road.

Imagine a future where, when diagnosed with cancer, medical doctors immediately sequence your genome using a micro-sequencing machine and develop a dendritic cell vaccination with neoantigens that solicit a vigorous response from your cytotoxic T-cells to attack and eliminate your tumor. This is the future of cancer treatment.

There is great hope that comes from between the lines of these studies. A cure is on the horizon. This is just a small glimpse into the vast research being done to finish the fight against cancer. With continued research, grit, dedication, and love, bioinformatics may prove to be the technology that finally yields a cure, and we can hold on to those we love a little longer.

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**Table 1. Treatments and Technologies used in Bioinformatics Research**

| **Treatments/ Technologies** | **Explanation/Types** |
|---|---|
| AmpliSeq | Ultra- high, multiplexed PCR that utilizes an extremely tiny DNA sample and makes thousands of copies, thus "amplifying" the specific sequences desired so that hundreds of genes can be analyzed at the same time. |
| Artificial Intelligence (AI) | Computational methods that recognize patterns in mutations and biological data can be used to predict cancer evolution or other mutations. |
| CAR-T Therapy | Placing chimeric antigen receptors (CAR) on T-cells to improve immune response. |
| Cell-free DNA (cfDNA) /circulating-tumor DNA (ctDNA) | DNA from the bloodstream/DNA released from tumors |
| Next-generation sequencing | Sequences DNA or RNA to study how genetic information is connected to disease |
| Patient-derived Orthotopic Xenograft (PDOX) Models | Grafting of tumors onto an animal model to observe evolution. |
| Polymerase chain reaction (PCR) | Used to amplify DNA and produce millions of copies of it to get to a level that is able to be studied. |
| RNA-seq | RNA sequencing using next-generation technology |
| Tumor Fraction Estimator (TuFEst) | Utilizes biomarkers to determine cancer severity. |
| Vaccinations | Peptides, DNA, RNA, Dendritic Cell targeted options |
| Whole-genome sequencing | Sequencing a person's complete genetic code. |

**Table 2. Genes Where Mutations Have Been Found to be Connected with Cancer Development**

| Gene | Cancer Types | Gene Description |
|---|---|---|
| IDH1 | All Types | Cytoplasmic enzyme used in the TCA cycle |
| CLDN6 | Uterine, testicular, ovarian, and lung cancers | A small protein from the claudin family used in treatment of solid tumors. |
| TP53 | Acute Lymphocytic Leukemia (ALL), colorectal, breast, and brain (medulloblastoma) cancers | Tumor suppressor gene |
| PTEN | ALL | A phosphatase tumor suppressor gene |
| FLT3 | ALL | A cytokine receptor gene |
| NOTCH1 | ALL, Breast Cancer | A transmembrane protein gene |
| JAK1/JAK2 | ALL | Protein coding genes used in the immune system |
| KRAS | ALL | A gene that relays signals to the nucleus. |
| PAX5 | ALL | Encodes the protein responsible for early B-cell differentiation |
| U2AF1 | ALL | Codes for a subunit protein on the spliceosome |
| NF1 | ALL | Gene that makes a protein that hydrolyzes GTP |
| MLH1 | Pancreatic Cancer | DNA mismatch repair protein |
| MSH2 | Pancreatic Cancer | DNA mismatch repair protein |
| MSH6 | Pancreatic Cancer | DNA mismatch repair protein |
| PMS2 | Pancreatic Cancer | Mismatch repair endonuclease |

| | | |
|---|---|---|
| PLXNA1 | Pancreatic Cancer | Transmembrane protein in the nervous system |
| BRCA | Breast and Prostate Cancer | Tumor suppressor gene |
| JMJD3 | Prostate Cancer | Protein coding gene that controls gene repression |
| MGMT | Prostate Cancer | Protein coding gene that maintains the genome by preventing errors in DNA replication. |
| DNMT1 | Prostate Cancer | Initiates the transfer of methyl groups |
| WNT | Breast Cancer | Signaling protein |
| Hippo | Breast Cancer | Signaling protein in cell proliferation/apoptosis |
| RTK-RAS | Breast Cancer | Plasma membrane binding protein |
| NRF2 | Breast Cancer | Protein transcription factor |
| PI3K | Breast Cancer | Protein coding gene involved in cellular functions such as differentiation and proliferation |
| Myc | Breast Cancer | Protein transcription factor gene |
| TGF-B | Breast Cancer | Growth factor cytokine |
| miR-623 | Triple Negative Breast Cancer | microRNA gene |
| EGFRvIII | Glioblastoma Brain Cancer | Epidermal growth factor |