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Mutations in Germline Cancer Susceptibility Genes - Understanding Tumor Initiation, Progression, Treatment and Prognosis through Genomic Profiling

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ABSTRACT

Cancer is primarily a genetic disease resulting from accumulated mutations that result in excessive proliferation, decline in replication regulation, evading growth suppressors, resist apoptosis, immortality of cells, and activation of tissue invasion and metastasis. The advent of next-generation sequencing (NGS) in the last decade has changed our knowledge of genetics, especially in diagnosing inherited cancer-susceptible genes. The cost-effectiveness and efficiency of sequencing multiple genes at once have led to its extensive use in research and clinical applications. This review aims to examine the genetic basis of germline susceptible genes, highlighting the significance of the key genetic mutations, the impact of NGS technologies, and the incorporation of artificial intelligence technology in cancer diagnosis, treatment, and prognosis. Genomic profiling and functional studies through NGS and AI-assistant technologies provide detailed insights into the heterogeneity of tumors, identifying key mutations and potential therapeutic targets. This technology enables personalized cancer treatment approaches, enhancing the efficacy of interventions and improving patient outcomes.

KEYWORDS: *Germline mutation, Next generation sequencing, AI in healthcare, Cancer biology, precision in medicine*

INTRODUCTION

Cancer is a significant global health concern, with an annual record of new cases of approximately 18.1 million people. In the United States, it is ranked as the second-leading cause of death with over 1.7 million cases diagnosed annually [Clancy, 2023]. The hallmark of cancer cells is mainly recognized for their uncontrolled growth which can develop by multifaceted modification and interaction between environment and genetic factors. There are over a hundred different cancer types, which vary significantly in their behavior, aggressiveness, and prognosis. Approximately 10% of cancer cases are heredity, caused by inheriting faulty genes. At the same time, some of the mutations could be a result of environmental exposure throughout life [Parsa, 2012., Brown et al., 2023].

Cancer cells begin to form when normal cells acquire the ability to proliferate without regulatory controls, lose their physiological functions, and invade resident localized normal tissues. The process of cancer development occurs in multiple stages, from benign changes to malignant tumors which can develop at different rates. These growths demonstrate the potential to metastasize, propagating from their primary site to distant tissues via either the blood vessels or the lymphatic system [Martin et al. 2013]. Weinberg and Hanahan (2000) identified key characteristics of cancerous cells, including genome instability and mutation. At its root, cancer is widely regarded as a genetic disease caused by the buildup of mutations impacting various cellular mechanisms such as cell signaling, growth suppressors evasion, resisting apoptosis, replicative immortality, angiogenesis induction, and invasion/metastasis activation [Weinberg & Hanahan, 2000].

Genetic mutations can occur during DNA replication or due to environmental interactions. Healthy cells make copies of their genetic material in the DNA, as the cells replicate there are occasional mistakes made in the new daughter cells or by interacting with additional causative molecules in the environment obtained naturally from food, polluted air, and surrounding ray exposures may result in alteration of the DNA structure [Watford & Warrington, 2023]. The accumulation of these genetic changes may lead to dysregulation of cellular differentiation, proliferation, and survival.

Tumor suppressors and oncogenes are central to cancer growth and progression [Morris & Chan, 2015]. Most cancer-risk-prone genes encode tumor suppressor proteins, which are responsible for restraining cell growth, triggering senescence, inducing cell death, and promoting cell differentiation by inhibiting cell cycle progression [Pierotti, 2017]. Tumor suppressors act as important regulatory checks that help detect DNA damage during cell division and stimulate repair mechanisms in identifying damage to the genome [Alhmoud et al, 2020]. On the other hand, oncogenes are mutated genes that often arise from normal cellular control genes called proto-oncogenes which can contribute to cancer development with only one mutated copy. This is because oncogenes typically encode proteins involved in cell growth signaling pathways, and a single mutation can lead to a gain-of-function effect, causing the protein to promote cell growth excessively [Tchounwou & Toscano, 2011]. Mutations in growth-promoting oncogenes, like *Abl, ErbB* family members (*ErbB1* and *ErbB2*), *kit, met, ret,* and others, can disrupt normal cell growth regulation. This dysregulation, often involves impaired signaling through receptor kinases, increasing cancer susceptibility [Saletta et al., 2015].

Mutations in germline genes are changes in reproductive cells that can be inherited from progenitors. They contribute to cancers in a dosage-dependent manner, suggesting that the risk of cancer increases with the number of mutated gene copies inherited[Birchler & Auger, 2013]. Individuals who inherit a single mutant copy of a tumor suppressor gene, such as BRCA1 or BRAC2, from one parent are considerably more likely to acquire certain malignancies than those who have two functional copies. However, inheriting two mutant copies of the TP53 gene another tumor suppressor gene is associated with earlier cancer onset and more aggressive disease progression [Gasco et al., 2002].

Both whole genome sequencing (WGS) and whole exome sequencing (WES) data are indispensable for genetic association studies in the detection of inherited gene predispositions to cancer and understanding the architecture of the cancer cells [Urbach et al, 2012]. The genetic heterogeneity of cancer even within the same tumor type, is due to the complex interaction between genetic, epigenetic, and environmental factors. Using DNA-based genetic testing, there is an increased chance of early cancer detection identifying individuals with a higher lifetime risk and genetic heterogeneity, allowing for genetic counseling, and personalized approaches to cancer therapy and management, that can significantly boost the chances of preventing cancer and improving prognostic outcomes.

GENOMIC PROFILING

Genomic profiling, also referred to as genetic testing or DNA profiling, is a process of analyzing the DNA of an individual to identify genetic variations and mutations that may be associated with certain traits, diseases, or predispositions [Franceschini et al., 2018]. Genetic profiling is a powerful tool with a wide range of applications in medicine such as disease screening tests, diagnosis, pharmacogenetics and pharmacogenomics, and personalized medicine [Singh, 2020]. Genetic profiling has revolutionized cancer diagnosis and treatment as it has proven useful in our comprehension of tumor microenvironments and the genetic aberrations during tumorigenesis and provides a guide in the treatment approach.Tumors are complex conglomerates of cells that can have different genetic landscapes due to the continuous mutational events that occur within the cell [Ramón et al., 2020]

The advent of genomic profiling techniques has revolutionized our comprehension of tumor microenvironments and the genetic aberrations during tumorigenesis. The use of next-generation sequencing (NGS) in the early 21st century has allowed the seamless sequencing of the entire genome of hundreds of people within a few days and has been evaluated for cost-effectiveness when compared with single-gene testing and low-throughput Sanger sequencing techniques. NGS has offered a more feasible and rapid detection of numerous mutations in the whole genomic DNA and RNA using small quantities of tumor tissue collected by needle biopsy or cell-free DNA (cfDNA) in plasma [Fernandes et al., 2017]. In contrast to conventional testing methods, which are often limited by a restricted set of analyzable genes or regions, NGS offers a more comprehensive approach. This technology not only empowers clinicians with a broader spectrum of information for therapy selection but also facilitates a more precise diagnosis of cancer subtypes and the evaluation of heritable cancer risk [Reitsma et al., 2019].

NGS technologies depend on acquiring normal, germline DNA, which contains single nucleotide variations also known as single nucleotide polymorphisms (SNPs). These SNPs are benign and must be distinguished from disease-causing mutations present in the tumor DNA of the same patient. The complete genome can be sequenced and scrutinized to identify mutations, including somatic copy number variants (CNVs) and various chromosomal structural alterations like translocations, transversions, and inversions. This analysis extends beyond coding regions to encompass non-coding portions of the genome as well. The accumulation of non-coding driver mutations during disease progression contributes to genomic instability, catalyzing neoplastic development and malignant evolution [Fernández-Marmiesse et al., 2017]. For instance, in colorectal cancer, CNVs have been linked to loss of heterozygosity in TP53 and APC or amplification in KRAS and FGFR1. These alterations are associated with a poorer prognosis due to drug therapy resistance [Debattista et al., 2022].

Genomic heterogeneity contributes to the onset of treatment resistance by enabling the emergence of various subpopulations of cancer cells that respond differently to therapy. These resistant cell populations result from levels of

proteins expressed which can promote disease progression and hinder the effectiveness of standard treatments. NGS allows for the detailed analysis of genetic diversity within tumors and aids in specifying key mutations driving the cancer as well as potential treatment targets [Fernández-Marmiesse et al., 2017]. The presence of heterogeneity supports tumor adaptation and evolution, ultimately resulting in the emergence of aggressive cancer phenotypes, enhanced invasiveness, and metastatic capabilities [Lüönd et al., 2021].

The use of NGS has provided the platform for a thorough evaluation of genotype-phenotype relationships which has helped in the identification of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) which are essential non-coding RNAs that can contribute to various cellular regulatory processes. These miRNAs bind to messenger RNA (mRNA) molecules of genes that promote cell growth and division. By binding, they prevent the mRNA from being translated into proteins, effectively slowing down cell proliferation [Nair et al., 2021].

DNA PROFILING, GERMLINE CANCER SUSCEPTIBILITY GENE, CANCER DEVELOPMENT, PROGRESSION AND PROGNOSIS

With the increasing adoption of genomic methodologies such as whole genome sequencing (WGS), there is a growing increase in the understanding of hereditary mutations in genes that predispose individuals to cancer [Kamps et al., 2017]. New DNA sequencing tools reveal that 5% - 12% of cancer patients have inherited one or more germline mutations that increase their risk of developing cancer [McGee & Nichols, 2016]. Even in seemingly healthy individuals, approximately 1% carry germline mutations that can predispose them to cancer. These mutations are inherited from the parents and passed within the germline and silently increase an individual's susceptibility to developing cancer at some point in their life. Clinical studies of individuals and families with a history of cancer allow for the identification and investigation of germline mutations. Offering genomic and cascading tests, along with pretest counseling, has the potential to improve patient outcomes and the overall quality of life with or without developing cancer. These approaches facilitate identifying other at-risk family members for further evaluation [Gong et al., 2021]. Some of the major germline mutations that have been implicated in cancer development, progression, and prognosis are discussed below.

Germline TP53 gene mutation

Li-Fraumeni syndrome (LFS)is a condition characterized by mutations in the TP53 gene. LFS significantly increases the risk of various cancers at a young age. Most individuals diagnosed with LFS have inherited a pathogenic TP53 variant from at least one parent, as the condition is inherited in an autosomal dominant manner. Mutation in tumor suppressor gene TP53 significantly increases susceptibility to a wide range of cancers. This includes breast cancer, leukemias, adrenocortical bone, brain cancer, bone carcinoma, and soft-tissue sarcomas. Accounting for about 80% of cancer cases, females with a germline pathogenic TP53 variant face a significantly increased risk of breast cancer [Elremeli et al., 2023]. The pathogenic variants have also shown an aggressive expression with resistance to treatment and the potential of developing radiation-induced secondary tumors.

Germline *TP53* pathogenic variants result in a constitutive defect of p53 binding to the DNA and modulation of transcription in response to DNA damage. The p53 protein levels are maintained at low levels by a negative regulatory feedback mechanism mediated by the MDM2 protein thus upon MDM2 binding to p53, marking the cell for degradation [Schneider et al., 1999]. Exposure to genotoxic stressors (e.g. UV radiation, radiation therapy, and other chemical carcinogens), weakens the MDM2-p53 binding resulting from induced phosphorylation of p53 and MDM2 thus reducing the ability to target p53 for degradation.The accumulation of loss-of-function p53 impacts the activities of many downstream genes that control essential cellular functions such as cell cycle regulation, programmed cell death, and the aging process [Pflaum et al., 2014].

Subasri et al., (2023) investigated the potential contribution of epigenetic factors in refining cancer risk assessment for LFS patients. Their study explored the role of inherited non-coding epimutations such as *ASXL1*, *ETV6*, and *LEF1* in increased cancer predisposition. Although these histone modifications do not alter the DNA sequence, they have been implicated in modulating gene expression patterns associated with cancer development in LFS patients. Interestingly, they also identified modifier variants within the WNT signaling pathway which appears to be linked to resilience mechanisms potentially explaining why some TP53 variant carriers have a lower cancer incidence or better survival outcomes during cancer management.

A study by Reed et al., [2021] employed a comparative transcriptomics approach to identify gene overexpression in LFS. Their findings revealed high expression of STAT1 and STAT2 genes in LFS patients with gliomas of high tumor grade. The use of adhesive and organoid cultures derived from LFS patient cells shows that the LPS patient cells exhibited the highest sensitivity to ruxolitinib, a JAK1/2 inhibitor, compared to cells that showed a diminished expression of STAT1 and STAT2. These results suggest that ruxolitinib, which has the potential to block the JNK/STAT pathway, could be a promising therapeutic candidate for LFS patients [Rocca et al.,2022].

Germline BRCA1/2 gene mutation

BRCA1 or BRCA2 (*BRCA1/2*) are germ-line genetic signature tumor suppressor genes whose genetic mutation has been associated with contributing to different cancer types including the hereditary breast and ovarian cancer (HBOC)

susceptibility. Most mutations in *BRCA1/2* may cause either gene silencing or over-activation which impacts the structure and function of the gene products. Some mutations are missense types, altering amino acids without truncating the protein [Shah et al., 2018]. During the assessment of the *BRCA1/2* alterations, sequencing the entire coding region as well as exon and intron junctions has helped in the understanding of its aggressive variants and penetrance.

The most prevalent types of mutations include insertions, deletion, premature transcription termination, and splicing errors. Small insertions and deletions cause frameshift mutation which results in major alterations to the protein. Mutations in splicing areas can produce a protein that lacks normal functioning [Mehrgou & Akouchekian., 2016]. According to the Breast Information Core (BIC), a significant proportion of mutations associated with breast cancer in the BRCA1/2 genes result in the synthesis of shortened proteins due to nonsense mutations and frame shift mutations [Pohlreich et al.,2005].Some SNPs found in the BRCA1/2 genes have been associated withpathogenic classification in different cancer types. For example, the missense exonic SNP designated as rs1799966 has been associated with poor cancer prognosis in colorectal cancer, pancreatic cancer, and brain tumor glioblastoma multiform [Zhu., 2017, Nageeb et al., 2022].

Although, it has been said that mutations in BRCA1/2 genes resulted in unfavorable survival, the introduction of NGS technologies enables women to know their BRCA mutation carrier status before or around the time of breast cancer diagnosis, helping them make decisions about surgical treatment. This information also aids clinicians in deciding on risk-reduction strategies, especially with the use of polymerase inhibitor agents such as poly(ADP-ribose) polymerase1 (PRAP1) targeting mutations which have provided more improved outcomes and increased life expectancy of the carriers and the family [Nageeb et al., 2022].

Women who test positive for inherited BRCA1/2 mutation can be advised on varieties of treatment or options to lower the risk of developing breast cancer. This includes early breast cancer screening at a young age, having more frequent screenings, or using magnetic resonance imaging (MRI) alongside mammography. Women may choose to have prophylactic surgery by removing some “at-risk” tissue that has not shown any sign of cancer. Surgeries to remove the two breasts also known as bilateral risk-reducing mastectomy may be done in an attempt to prevent the risk of developing breast cancer. A 2019 research of 6223 female BRCA1/2 mutation carriers from 10 countries found a substantial rise in the adoption of bilateral preventive mastectomy in women after genetic testing, this has reduced the risk of breast cancer by at least 90% in BRCA1/2 mutation carriers [Metcalfe et al., 2019 , Record at al., 2024].

However, risk-reducing surgery has not been the complete guarantee that cancer will not develop because not all at-risk tissue can be removed by these procedures. Studies have shown that BRCA1/2 mutation carriers who got mastectomy surgeries may develop locoregional recurrence after some years. 2.6% of BRCA1/2 patients developed cancer reoccurrence in the original site in the chest wall or nearby lymph nodes after a median follow-up of 5.8 years [Webster et al., 2023]. In recurring breast tumors in BRCA1/2 mutation carriers, tumor cells produce a shorter isoform of BRCA2 mRNA, resulting in a more stable BRCA2 protein with improved DNA repair capabilities. Tumors that survive DNA-damaging drugs and radiation therapies may return due to enhanced DNA repair capabilities. A study by Shah et al. (2022), discovered that primary and recurrent tumors show variabilities in the loss of heterozygosity which impacts the therapeutic resistance mechanism. Further research is necessary to analyze the expression of checkpoint proteins, such as PARP1 and RAD51, in primary and recurrent tumors associated with BRCA1/2 mutations, as these proteins may be potential targets for immunomodulatory therapies [Shah et al., 2018,Lines et al., 2020].

Germline MEN1 gene mutation

Wermer syndrome, also called Multiple Endocrine Neoplasia Type 1 (MEN1), is a rare high penetrance endocrine tumor syndrome that follows an autosomal dominant inheritance pattern. Inactivation mutations in the germline of the MEN1 tumor suppressor gene or menin gene located on chromosome 11q13 locus lead to the manifestation of MEN1 Syndrome [Kamilaris & Stratakis, 2019]. MEN1 mainly leads to neoplasia in the parathyroid glands, neuroendocrine tissue of gastro-entero-pancreatic organ systems, and the anterior pituitary gland. The majority of cases, around 90%, involve the inheritance of the mutations, with the remaining 10% resulting from de novo mutations causing the syndrome [Pieterman et al., 2021].

Tumor growth in MEN1 patients has been linked to men in loss, however, tumor development may also be influenced by other genes in related pathways. This may aid in the diagnosis of tumors and the creation of novel therapies. The Menin protein is known to interact with these pathways, which are involved in critical biological processes like cell development and death. Through the use of WGS analysis, Lines et al. [Lines et al., 2020]discovered more than 54,000 variations in 300 genes between C57BL/6 Men1+/- and 129S6/SvEv Men1+/-mice, which may have the ability to find MEN1 genetic modifiers. Frameshift mutations, including I85fs and R521fs, were recurrently identified within MEN1, potentially leading to early termination of protein production [Nelakurti et al., 2020]. Gene variations associated with tumorigenic pathways were found in functional analysis studies. These genes include Kras, Wnt2b, Il3ra, and Tnfrsf10a, which are engaged in signaling pathways that include Wnt, apoptosis, interleukin, and Kras, respectively.

An association between a Cdkn1b variant (c.326T>G) and tumor multiplicity in MEN1 patients has been reported. While no variants in Cdkn1b (encoding p27kip1) were identified from WGS data, variants in Ccne2, regulated by p27kip1, were also observed. Ccne2 encodes cyclin E2, which, in complex with Cdk2, is inhibited by p27kip1. Cyclin E-Cdk2 substrates vary in different cell types. Conversely, MEN1 tumorigenesis in the pituitary and pancreatic islet requires Cdk4 but not Cdk2 [Lines et al., 2020, Gillam et al., 2015]. These studies identifying the genomic profile of Wermer syndrome show how the loss of Men1 protein alters the phenotypic expression of pancreatic neuroendocrine tumors. This, in turn, will provide a model to better understand and develop therapeutic targets of the MEN1 mutations in different patients.

Germline Lynch Syndrome

Lynch syndrome is an inherited disorder associated with an increased risk of colorectal cancer. It is also known as hereditary non-polyposis colorectal cancer (HNPCC). Individuals with Lynch syndrome is also predisposed to developing cancers of the endometrium (uterine lining), stomach, and pancreas [Steinke et al., 2013].Lynch syndrome arises from mutations in cell mismatch repair (MMR) genes resulting in the inactivation of MLH1, MSH2, MSH6, and PMS2 genes. Mutations in these genes impair their capacity to repair mistakes in DNA replication, raising the risk of developing cancer. Lynch syndrome could also result from non-MMR gene mutations such as epimutations in MLH1 gene deletions in EPCAM which induce epigenetic silencing of *MSH2* [Yurgelun & Hampel., 2018]. It has been suggested that the MSH6 mutation might result in functional redundancy of the MSH6 protein characterized by milder and more variable clinical presentations in Lynch syndrome compared to mutations in MLH1 and MSH2 [Kašubová et al., 2018].

In a 2022 study in the Asian population, Li et al., found a striking difference in the frequency of mutations within SALL4, WAS, ARID2, INPP4B, TLL1, and FZD2, genes between individuals with germline Lynch syndrome and those with sporadic somatic colorectal cancer. This finding suggested that the underlying etiology can influence the pathological characteristics of colorectal cancer. Studies have implicated the SALL4 gene which is crucial for embryonic development, efficient cell proliferation, and cell fate determination in the progression and metastasis of colorectal cancer [Moein et al., 2022,Forghanifard et al., 2013].

Incorporating AI in NGS Derived Results

The integration of AI with NGS data is revolutionizing genomics and the translation of its characteristic enormous and complex data into clinical applications, especially in precision medicine [Xu et al., 2019]. Researchers need to work on thoroughly analyzing the large data volume obtained from NGS but because of its large size, they tend to be error-prone and may not provide the complete oversights that are required. In oncology research, AI acts as a bridge, connecting the genomics, transcriptomic, and proteomic data to practical applications in the clinic [Liao et al., 2022, He et al., 2017].

The advanced neural networks and machine learning tools in AI technology can emulate human brain functions, allowing them to recognize, interpret, and classify input data, such as images, with minimal error. These applications are improving cancer diagnostics, prognostic predictions, and making decisions about treatment options. Moreover, deep-learning AI technology ensures the accuracy of gene alignment during comparative analysis, biomarker prediction, variant annotation, and their role in disease progression. When combined with medical imaging, AI delivers high-resolution images, enhancing diagnostic accuracy and patient outcomes [He et al., 2017, Malone et al., 2020]. Despite these advances in AI technology human input with sufficient clinical and analytical expertise remains indispensable [Dlamini et al., 2020].

It has been suggested that gene-specific and disease-specific approaches yield more effective results compared to genome-wide methods [Kang et al., 2023]. AI technologies can facilitate these targeted approaches, significantly advancing cancer gene susceptibility studies, diagnostics, and treatment of several germline gene mutations such as *BRCA1/2* in breast cancer, p53 and PTEN in prostate cancer, KRAS in pancreatic cancer, BRAF in colorectal cancer, and ERBB2 in lung cancer. A novel study by Khandakji et al., (2023) developed a BRCA1-specific machine learning model to predict the pathogenicity of all BRCA1 variant types and apply this model to assess variants of uncertain significance (VUS) among breast cancer patients [Khandakji et., 2023]. This was similar to another research by Kang et al. (2023) who identified 1068 rare missense variants of 28 genes associated with *BRCA1/2* hereditary cancers. These variants had a gnom AD minor allele frequency (MAF) of less than 0.005, indicating their rarity in the population. These rare missense variants develop a gene-specific machine-learning model for predicting the pathogenicity of *BRCA1/2* [Kang et al., 2023].

Convolutional neural networks (CNNs), a deep learning network architecture that learns directly from raw data have been utilized to significantly enhance the prediction of germline BRCA mutations in breast cancer using whole-slide histopathological images from patients. Wang et al. (2021) developed a deep learning model (ResNet) to predict the presence or absence of BRCA mutations using data from whole-slide images. The model successfully identified BRCA mutational status from high-magnification images, capturing cellular-level details and recognizing morphological features within tissue structures from whole-slide images. They suggested that this prediction model for germline BRCA gene mutations could significantly benefit patients likely to

respond to PARP inhibitor-targeted therapy and help identify healthy mutation carriers within their families [Wang et al., 2021].

Recurrent patients with gynecologic cancer face challenges in utilizing immune checkpoint inhibitors due to mismatch repair genes and microsatellite instability [Khushman et al., 2024]. A study by Kim et al. (2021) developed a random forest (RF) machine-learning model when combined with germline Lynch syndrome-related mutation markers (MLH1, MSH2, MSH6, and PMS2), they were able to predict and distinguish patients who may benefit from immune checkpoint inhibitors. This approach highlights the potential of AI technology to personalize treatment decisions based on individual genetic profiles, potentially leading to more effective and targeted interventions for recurrent gynecologic cancers [Kim et al., 2021].

The large size and complex structure of the TP53 gene present a significant challenge in accurately classifying variants identified through WGS [Soussi et al., 2024]. These mutations can occur at various locations within the gene, and their impact on protein function varies which may hinder the correct interpretation of TP53 variants for clinical stratification. In response, Ben-Cohen et al. (2022) developed the TP53_PROF model which leverages machine learning techniques to predict the functional consequences of TP53 missense mutations based on a comprehensive dataset. This computational prediction was able to accurately predict whether a germline TP53 mutation is likely to affect protein function thus predicting susceptibility to hereditary cancer [Ben-Cohen et al., 2022]. Identification of the functional TP53 variants informs clinical decisions, such as prognosis and treatment strategies for hereditary cancer patients such as colorectal, non-small lung cancer, and breast cancer [Cifci et al., 2022, Bilal et al., 2021].

CHALLENGES AND FUTURE DIRECTIONS

Genetic profiling and functional studies allow researchers to classify disease populations into simple subgroups based on their genetic makeup and how their genes function. This stratification helps develop more targeted treatments and improve patient outcomes. As polygenic risk analysis advances, more diseases will be treated based on individual or combined genetic markers. Personalized medicine, which uses genetic stratification, is already being applied in oncology and will continue to expand into other medical fields as more disease molecular signatures are identified [Ghoussaini et al., 2023].

One of the major challenges lies in the inherent complexity of cancer genomes. Tumors are not static; thus, they evolve through somatic mutation selection. NGS techniques have demonstrated that the tumor mutational burden in malignant cells is significantly higher than in normal cells. When analyzing genetic profiles of primary malignant neoplasms, particularly in predisposed genes linked to DNA associated with DNA repair mechanisms such as *BRCA1/2*, p53, MMR, and BAP1 genes, they quickly develop into poly-metastatic spread. This heterogeneity presents a significant obstacle that increases the rapid evolution of the tumor at the expense of the host and potentially leads to inaccurate treatment decisions [Doig et al., 2022,Ottaiano et al., 2023].

AI-assisted technology offers the potential to process vast amounts of information providing insights and options for understanding the underlying drivers of tumors, especially in making informed decisions in the treatment of genetic mutations in cancer and predicting optimal risk-reducing surgeries [Comes et al., 2023]. Further studies should focus on the use of AI in the identification of druggable genes, emphasizing the development of novel drugs to address unmet medical needs in treating advanced cancers and overcoming drug resistance.

CONCLUSION

The integration of NGS and AI holds immense promise for revolutionizing clinical diagnosis, pharmacological design, and genomic applications, especially in the early identification of germline mutations that confer susceptible tumor development. Advancements in bioinformatics, robotics, and automation techniques are expected to significantly improve NGS speed and accuracy. By leveraging AI for rapid and accurate biomarker analysis in germline mutations, this integrated approach will serve as a step forward in the direction of personalized medical interventions against treatment resistance and improved patient outcomes.

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