The changing landscape of cancer medicine

Cancer has affected humans for thousands of years. It is responsible for around 10 million deaths annually and it is estimated over 600 million people globally will be diagnosed with cancer in their lifetime. Incidence of cancer has increased by 28% from 14.1 million cases in 2012 to 18.1 million cases in 2020.[1]

Meanwhile, advancements in detection and treatment have improved rates of survival. The mortality rate from cancer in the US has reduced by 33% since 1991, preventing an estimated 3.8 million cancer deaths.[2]

Cancer is not just one disease – there are over 200 types of cancer, each with a variety of individual factors contributing to every tumour. Treatments that work for one person's illness frequently do not work for another, and the cancer itself can change over time to become resistant to a treatment that is working and necessitate an entirely new strategy.

Cancers arise from oncogenic mutations that drive cellular proliferation, and the loss of tumour suppressor functions. The hallmarks of cancer offer a framework to understand its complexity.[3] There are ten core and four emerging hallmark capabilities (Figure 1) provide insight into cancer mechanisms and inform therapeutic strategies. Tumours develop unique mutations and adaptations to overcome barriers during tumorigenesis. The means of acquiring these functional capabilities are embedded in the enabling characteristics.

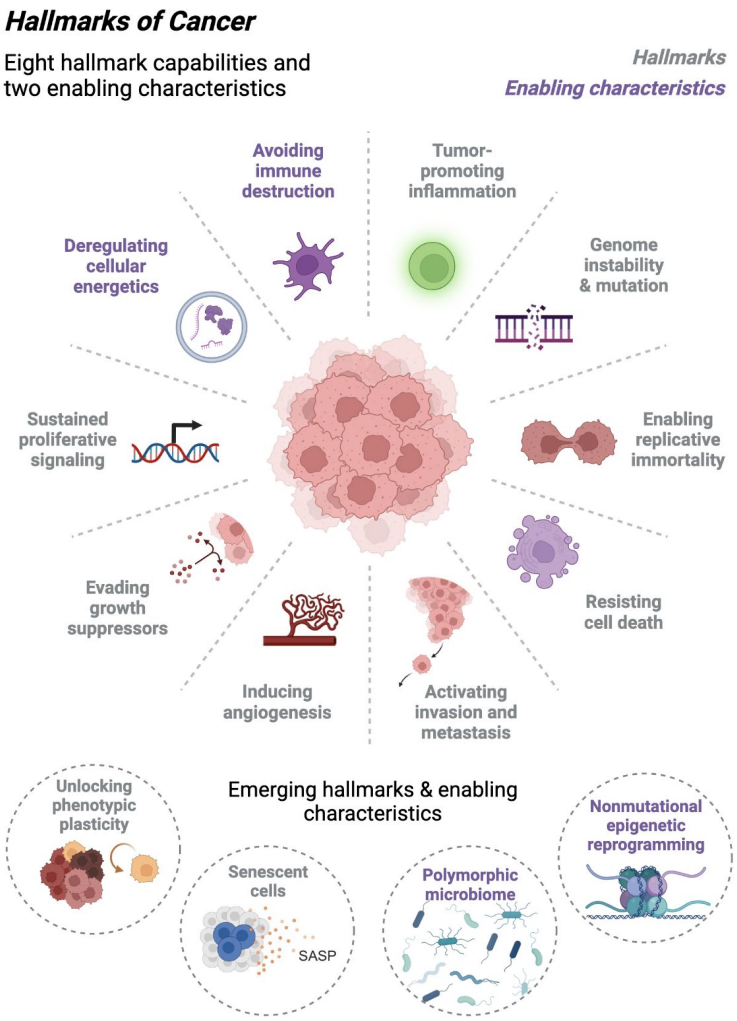

Figure 1
The Hallmarks of Cancer (adapted from Hanahan 2023)
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Precision medicine (PM) aims to maximise treatment response by tailoring treatment to the individual, and minimise toxicity to normal tissue. It involves investigation and classification of tumours, with improved understanding of cancer formation, intratumoral heterogeneity, and clonal evolution. This aids in diagnosis and development of new therapeutic targets. Oncology has largely shifted from conventional to stratified medicine, however there are some roadblocks to the adoption of total PM.

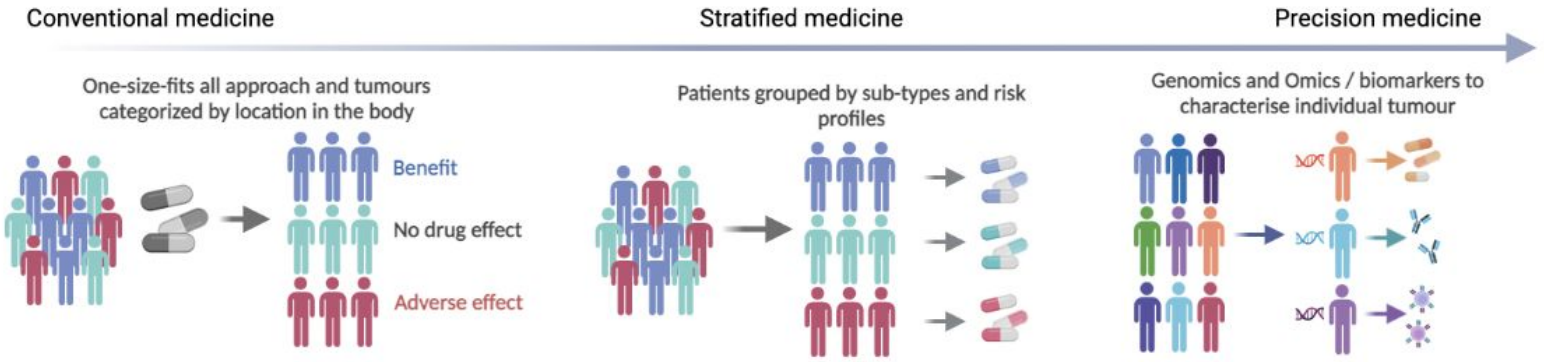

Figure 2 *The transition to precision medicine.* *Figure generated in Bio Render*

Lower cost and higher throughput of DNA sequencing is a driver of the evolution to PM. Next-Generation-sequencing (NGS) techniques investigate genomes, proteomes, epigenomes, and transcriptomes. Strategies include capturing protein-coding regions of genes, sequencing the whole genome (WGS), and sequencing exon regions (WES):

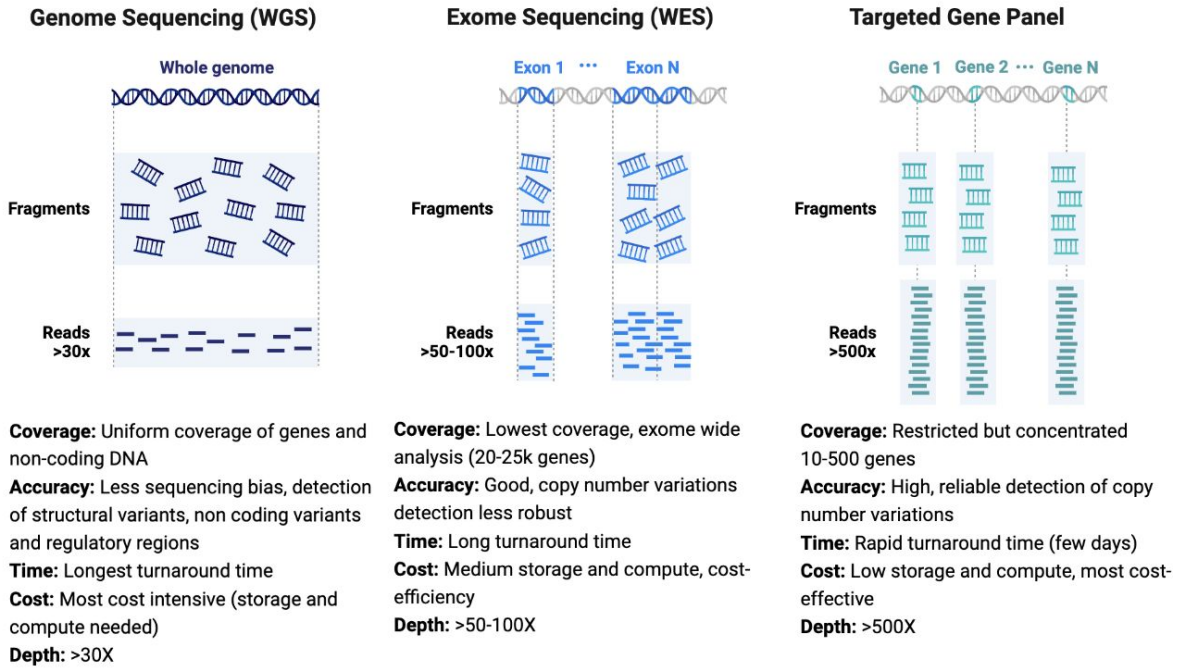

Figure 3 *Next-generation sequencing (NGS) (adapted from Gorcenco S et al)* *Figure generated in Bio Render*

The genetic complexity of individual tumours has been revealed by the discovery of hundreds of coding genes that can be altered in each subtype of cancer. WGS of cancers has shown that a single tumour can have up to 50,000 non-synonymous mutations impacting hundreds of genes, with a mutation rate of 0.5-20 per megabase.[5] Targeting driver mutations therapeutically may lead to adaptations to alternative mutation pathways, contributing to relapse and therapy resistance. WGS of multiple areas of a tumour can identify latent mutations [6] that may predict adaptive resistance, guiding subsequent treatment methods. These techniques identify signatures that serve as biomarkers, providing information from prognosis to intrinsic resistance mechanisms. Together, these approaches form a new molecular classification of cancer, enabling screening and detection of disease at its earliest molecular manifestations, and selection of specific drugs based on a patient's genetic makeup.

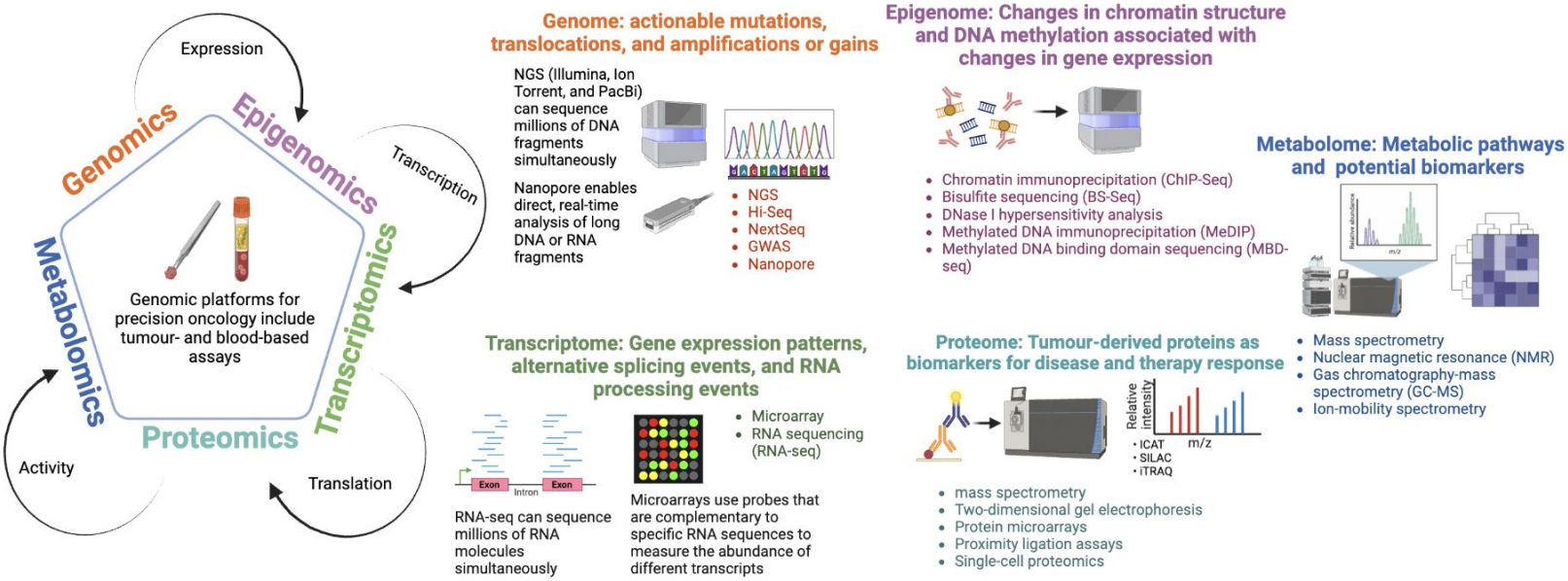

Figure 4 *Multi omics approach to investigate cancer.* *Figure generated in Bio Render*

Epigenetics

Epigenetics is a critical aspect of PM. A complex regulatory network controls gene expression. Epigenetic changes or mutations in genes that organise, control, and maintain chromatin architecture, are increasingly discovered and functionally related with cancer hallmarks. It involves modifications to the structure of DNA that allow for inheritance of information based on gene expression. This can influence DNA transcription through DNA methylation and histone modification.

Chromosomes are made of tightly packed DNA around histones called chromatin. Gene expression depends on chromatin structure, packaging density of DNA, and accessibility of gene regulatory regions. Loosely packed DNA is more accessible to regulatory proteins and actively transcribed, while tightly bound DNA is inaccessible to transcription factors and silenced. Histone tails can be modified in various ways including methylation, acetylation, phosphorylation, and ubiquitination which alter the function of the nucleosome and ultimately impact gene expression. Abnormal modifications, such as hypermethylation of histone H3 at lysine 27 (H3K27me3), have been linked to the repression of tumour suppressor genes. On the other hand, the acetylation of histone H3 at lysine 9 (H3K9ac) can activate oncogenes.[7]

DNA hypermethylation silences tumour suppressor genes such as p16, and hypomethylation can activate proto-oncogenes and promote cell proliferation, while abnormal methylation patterns can disrupt gene activity and increase the likelihood of mutations. Research has uncovered regulatory proteins and enzymes involved in methylation mechanisms and control.[8] Certain DNA hypermethylation patterns have been identified as potential biomarkers for assessing cancer risk, detecting cancer early, and predicting response to therapy.[9-10]

In addition to genes and regulatory sequences, the human genome contains noncoding RNA regions that play a crucial role in regulating gene expression. MiRNAs regulate gene expression post-transcriptionally by binding to complementary mRNA targets. Histone variants are non-canonical histones that have unique amino acid sequences and functions in various cellular processes. Dysregulation of histone variants, such as H2A.Z, has been associated with cancer development and progression.[11]

Epigenetic changes are believed to occur earlier in tumorigenesis than other genetic changes, making them an interesting area of research within circulating tumour DNA (ctDNA). Epigenetic changes can potentially be reversed, unlike genetic mutations which are generally fixed and stable. This encourages the use of epigenetic targeting drugs, such as DNMT inhibitors (DNMTi) and HDAC inhibitors (HDACi), which are being tested for various cancers.[12] Future treatments may involve combining epigenetic and non-epigenetic drugs.

Multi-omics

Integrating clinical information with data generated by high-throughput technologies can help untangle the complex interplay of epigenetic mechanisms and gene regulatory networks, enabling identification of therapeutic targets. To develop precision medicine, it is important to understand the molecular, biological, and physiological connections between genetics and epigenetics. Currently, genomics, epigenomics, and other -omics studies are usually conducted separately. The integrated understanding of genetic variation and epigenetic deregulation and the manifestations of that through the translation to proteins and activity (figure 5). This requires an integrated approach across a number of technologies shown in Figure 4.

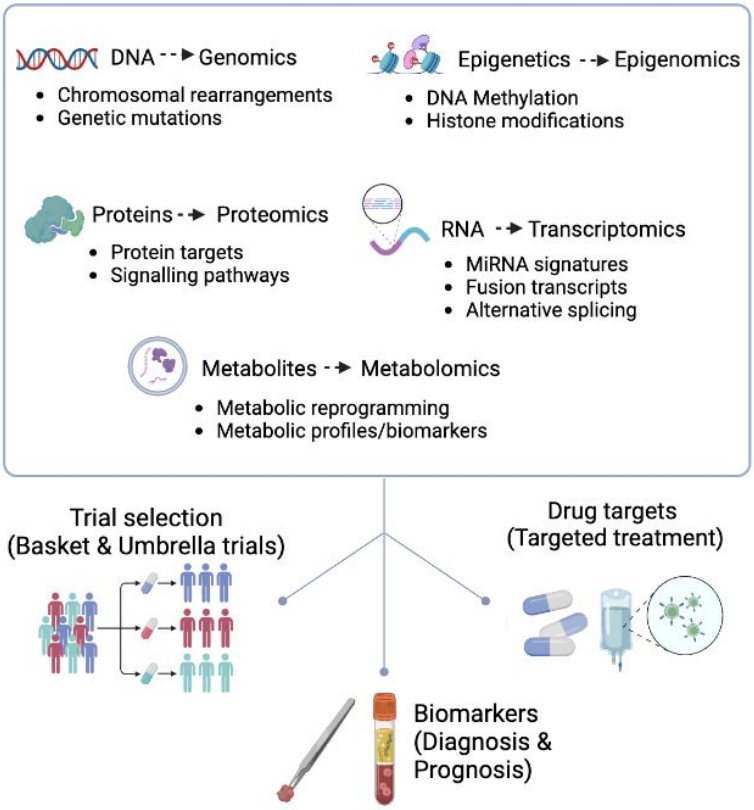

Figure 5 *Multi omics approach to investigate cancer*
Figure generated in Bio Render

Diagnosis

Cancer diagnosis historically relied on physical exams and imaging like X-rays and CT scans. Imaging provides information as to where the cancer is located, but typically a tissue biopsy is used to investigate the genetic and molecular makeup. Traditional biopsy is invasive and not always possible, but newer diagnostic tools like liquid biomarkers and molecular imaging can provide more information to monitor progress and treatment efficacy. These tools can detect risk-factors, establish diagnosis as well as predict and monitor treatment response, survival, and recurrence. Both imaging and genomic biomarkers are critical, since imaging can inform location of cancer and detect changes at the cellular level that may not be apparent in the genome, while genomics can detect genetic abnormalities. Bayesian-based imaging involves the use of mathematical models to analyse medical images and interpret the results. This approach allows for the identification of even the smallest tumours.[14] Genomic biomarker-driven stratification involves the identification of specific genetic biomarkers that are associated with recurrence (fig. 6). Integrating imaging in the mm to micron scale with genomics can offer a comprehensive understanding of clonal evolution and treatment response in cancer.

Figure 6
Map displaying the role of imaging in combination with molecular analysis with tissue and liquid biopsy.
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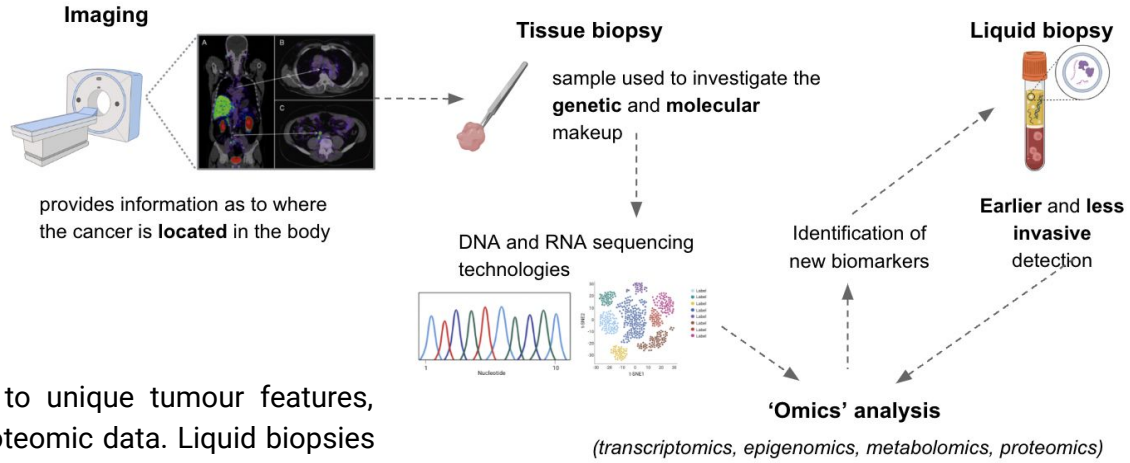

Liquid Biopsy

PM aims to tailor therapy to unique tumour features, including DNA, RNA, and proteomic data. Liquid biopsies (LBs) assess both genomic and proteomic tumour components, to be used in combination with sensitive imaging methods to identify specific cancer subtypes, provide treatment options, and detect resistance. LBs provide information about DNA mutations, gene copy-number alterations, transcriptome/proteome profiling, epigenetic changes, and metabolite profiling. This information is found in different biomarkers, such as circulating tumour DNA, proteins, microRNAs, autoantigens, autoantibodies, and metabolites (Figure 7). While LBs have limitations in recognising diverse tumour forms, they can provide detailed tumour-molecular characterization and real-time information on therapeutic cancer targets. Establishing standardised procedures can help to overcome the barriers to LB application in translational and clinical practice.

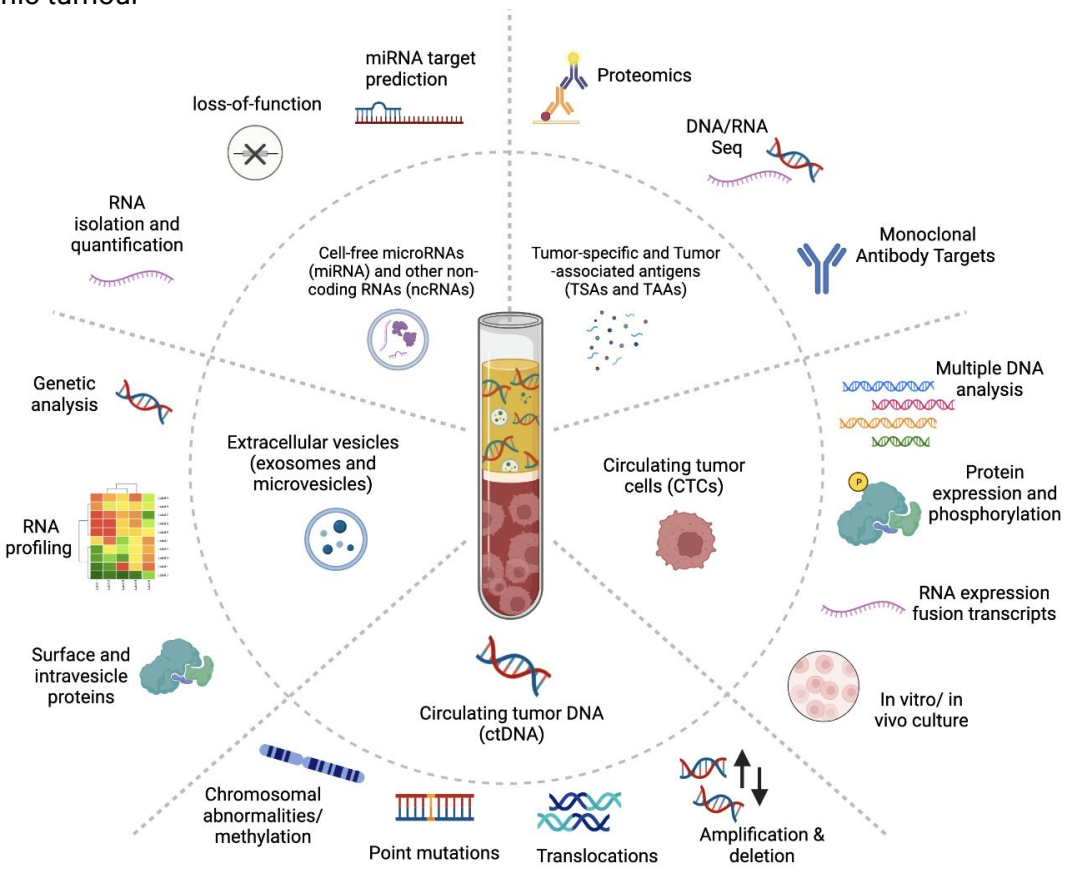

Figure 7: *Liquid Biopsy: a map of biomarkers and some of the information they provide (adapted from Lone et al)* [13] *Figure generated in Bio Render*

Treatment

Clinicians tailoring treatments to unique characteristics of a patient's cancer is adapting the traditional pillars of cancer care, as well as introducing two new pillars (molecular targeted therapies and immunotherapies) that are increasingly incorporated into the treatment paradigm:

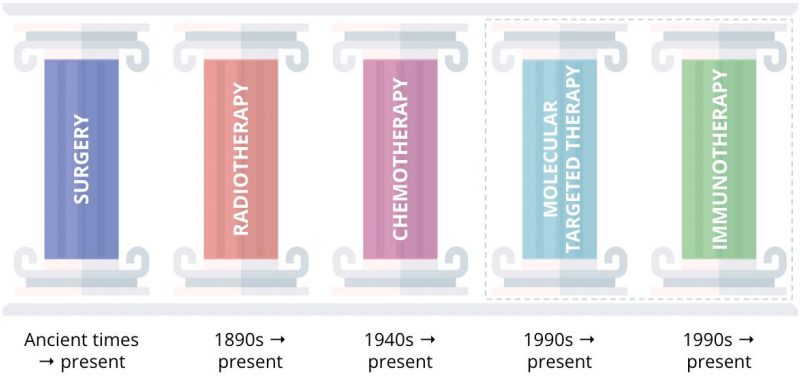

Figure 7: Pillars of cancer care
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Molecular profiling can personalise the degree of surgery required, needs for adjuvant chemotherapy or radiation therapy. While it is clear that improved selection methods are urgently needed to identify patients at high-risk of metastases. For example expression of S100A2 and S100A4 calcium-binding proteins in pancreatic ductal adenocarcinoma (PDAC) is associated with poor survival and was used to develop a biomarker-based preoperative nomogram to stratify patients with resectable pancreatic cancer into three prognostic groups and identify those at high risk of early recurrence.[15]

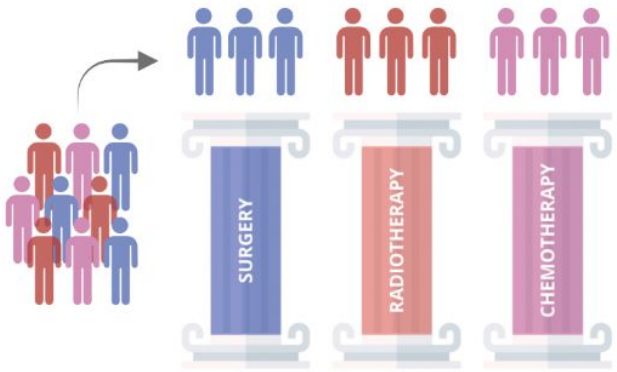
The serendipitous discovery of nitrogen mustard's cytotoxic effects led to the development of chemotherapy drugs that kill rapidly dividing cancer cells. This marked the beginning of modern chemotherapy and the study of how interacting with DNA can treat cancer. Nitrogen mustards are alkylating agents that bind to DNA and produce cross links that inhibit the DNA double helix from unwinding and separating, causing cell death in rapidly proliferating cells.

However two individuals with identical cancers may respond differently to the same chemotherapy regimen, due to genetic differences. By analysing genetic mutations in the cancer cells themselves or in the patient's germline DNA, doctors can tailor chemotherapy regimens to the individual patient and avoid potential harm.

Radiotherapy is administered to reduce or remove tumours or to prevent local recurrence. It accounts for around 40% of curative cancer treatments and can be given alone or in combination with chemotherapy. Radiotherapy can be given in a variety of ways, including as neoadjuvant therapy for esophageal cancer, adjuvant therapy for breast cancer, and definitive therapy for prostate cancer. Tissues can tolerate different doses, which is why the tolerance dose concept is important. Modern conformal radiotherapy is delivered using volumetric arc therapy (administering radiation in fractions), which helps to minimise the dose to critical organs at risk and can be delivered using different types of radiation, such as photon and electron therapy.[16]

Proton therapy uses positively charged particles to deliver radiation. It requires more infrastructure investment than photon radiotherapy, but its physical properties mean that there is reduced radiation damage to adjacent tissues. Brachytherapy involves inserting radioactive sources directly into the tumour, concentrating the dose in the target area. Personalised radiation dose prescriptions using the GARD model have been proposed based on individual tumour genomics. This has the potential to further personalise radiotherapy and select patients.

Reforming the traditional pillars of cancer care (surgery, radiotherapy and chemotherapy) to have greater precision and be used in patients predicted to have favourable response



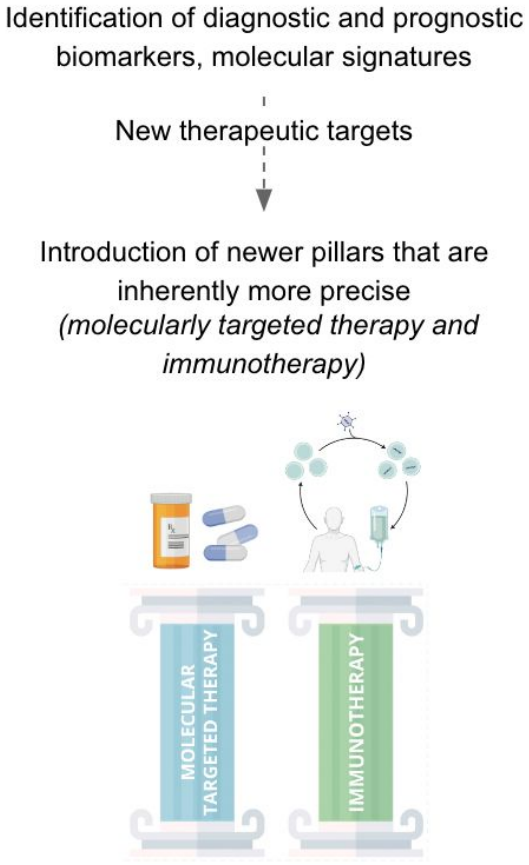
Targeted Therapies

A major aim of PM is targeting specific mutations present in the tumour, rather than treating cancer based on its location in the body. The success of Imatinib in treating chronic myeloid leukaemia (CML) raised expectations for targeted drugs. However, in many cases, targeted therapies only provide temporary results, and relapse or progression is common, even within the same subtype.This highlights the importance of considering a patient's tumour biology and genetics.

Monoclonal antibodies (mAbs) can cause tumour cell death by blocking growth factor receptor signalling. They recruit the host immune system and use complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cell-mediated cytotoxicity. They are highly specific to their target where they bind antigens via the Fab portion, linking effector cells via their Fc portions. Effector cells induce target cell death via cytotoxic granule release, Fas signalling, and initiation of reactive oxygen species.

Trastuzumab used for HER2-positive breast cancer only saw a 30% response, indicating that they do not rely on HER2 signalling for growth. Non-responsive tumours have mutations that activate other growth pathways, such as IGF1, EGF, or PI3K. The activation of PI3K serves as a biomarker to predict trastuzumab resistance.[17] Cetuximab targets epidermal growth factor receptor (EGFR) and causes apoptosis by preventing ligand binding and receptor dimerization. EGFR is present in most cases of positive metastatic colorectal cancer (mCRC), however only 10% of mCRC patients respond to cetuximab.[18] The drug is not effective in people with certain mutations, such as KRAS, NRAS, BRAF, PIK3CA, and HER2, even if they have high levels of EGFR. KRAS and PI3K are downstream in the HER2 and EGFR signalling pathways, which may explain why cetuximab and trastuzumab don't work when RAS and PI3K are not activated. Next generation mABs are developed to overcome resistance mechanisms, combination therapy, aim to direct drugs with different mechanisms of action together and biomarkers are used to monitor resistance.

Tyrosine Kinase Inhibitors (TKIs) are used to slow or stop the growth of cancer by blocking the overactivation of tyrosine kinase signalling pathways that cause uncontrolled cell growth and resistance to cell death signals. Chronic myeloid leukaemia (CML) is characterised by the Philadelphia chromosome, which



forms a fusion gene encoding the BCR-ABL1 oncogenic protein, causing persistently enhanced TK signalling.
Imatinib, a TKI that binds to the active site of the ABL portion and prevents ATP binding, is commonly used to treat CML. Resistance to imatinib can occur due to point mutations or alternate signalling pathways, resulting in relapses that are common within the first 6 months. Ph1-negative patients, which account for 5%-10% of CML cases, often have a worse response and shorter survival time than Ph1-positive cases.[19] Second-generation TKIs aim to overcome resistance with less susceptibility to mutations.

There is significant variety within a single tumour due to factors like regional clonal evolution, self-seeding of cancer cells, and the heterogeneity of potential cancer stem cells. Cells that make up the tumour-supportive stroma can also affect tumour response to therapy. This intra-tumoral diversity, which frequently reflects the presence of numerous subclonal tumour populations, may contribute to the development of secondary treatment resistance. Tracking tumour heterogeneity during treatment is crucial since cancer cells that acquire evasion mechanisms (such as mutations and loss of heterozygosity at HLA loci, disrupted antigen presentation, negative selection of neoantigens) are more likely to survive. TRACERx found that tumours with a

higher clonal neoantigen burden had better survival rates and responded better to pembrolizumab. Patients who did not respond more commonly had chemotherapy-induced subclonal neoantigens.[20] Different immune escape mechanisms indicate the strength of selection pressures from the immune system, which is important in designing immunotherapies. Targeting multiple trunk/clonal events in every cell and neoantigens that stimulate the immune system might improve outcomes.

Tumours develop mechanisms to evade immune surveillance. Those with DNA repair defects can accumulate mutations that create neoantigens. Tumour mutational burden correlates with the presence of neoantigens and can predict response to immunotherapy. T-cell activation requires the TCR to bind with antigen-presenting cells, initiating T-cell activation. Immune checkpoints regulate the signals that limit the duration of T-cell activation. CTLA4 and Programmed cell death protein 1 (PD-1) are immune checkpoints involved in maintaining self-tolerance and modulating the immune response to prevent autoimmune reactions.[21] However, cancers often hijack these checkpoints to evade immune destruction. The clinical effectiveness of **immune checkpoint inhibitors** suggests this is a common mechanism of evasion. CTLA-4 blockade enhances antitumor immunity by regulating T-cell proliferation in lymph nodes. This led to the development of anti-CTLA-4 mABs. PD-1 has two ligands, PD-L1 and PD-L2, which can be expressed in tumour cells and other cells in the tumour microenvironment, making it more difficult for T cells to eliminate the cancer, and is also blocked via certain drugs, allowing immune cells to identify and attack cancer cells. Immune checkpoint inhibitors have achieved remarkable clinical responses, but resistance and autoimmune adverse events are common and again requires identifying patients most likely to respond to these agents.

Advanced therapy medicinal products

Advanced therapy medicinal products (ATMPs) are tissue-engineered medicines for human use that are based on genes, tissues or cells. Cells are genetically manipulated to harness the power of the immune system by recruiting immune cells into the tumour microenvironment and enhancing anti-tumour immunity.

CAR-T: Cancer cells are derived from the host, and evade the immune response, expressing proteins that resemble normal host proteins, or by avoiding detection altogether. Adoptive cellular immunotherapies modify the host's immune cells to be able to recognize and attack cancer.

Four major trials paved the way for widespread commercial development of CAR-T (Figure 9). For example, the first FDA-approved CAR-T therapy, Kymriah, for relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL), achieved durable response rates of 50%, compared to past survival rates between 15% and 27% for recurrent cases.[22] However, several issues associated with CAR-T therapy still exist, such as the management of severe toxicities and the frequent occurrence of both antigen-positive and antigen-negative relapse. Severe side effects include cytokine release syndrome (CRS) and neurotoxicity which are systemic inflammatory responses caused by the release of cytokines from activated immune cells. CAR-T treatments target only antigen-positive cancer cells, which can lead to antigen-negative relapses and T-cell exhaustion can reduce their effectiveness.

TCR

CAR-T therapies have revolutionised the treatment of haematological malignancies, but their impact on solid tumours has been limited. In contrast to haematological malignancies, demand for new interventions for solid tumours is increasing. CAR-T cells have receptors that target naturally occurring antigens. However, the immune system is not recruited to aid in the response, besides loaning out T-lymphocytes. On the other hand, TCR therapy targets intracellular tumour neoantigens in solid tumours that lack specific surface tumour markers. TCR therapy relies on the major histocompatibility complex (MHC) to mark cancer cells with antigens and recruit host-immune cells. TCR therapies have the advantage of being able to target a wider range of antigens and are less susceptible to antigen-negative relapse than CAR-T therapies.

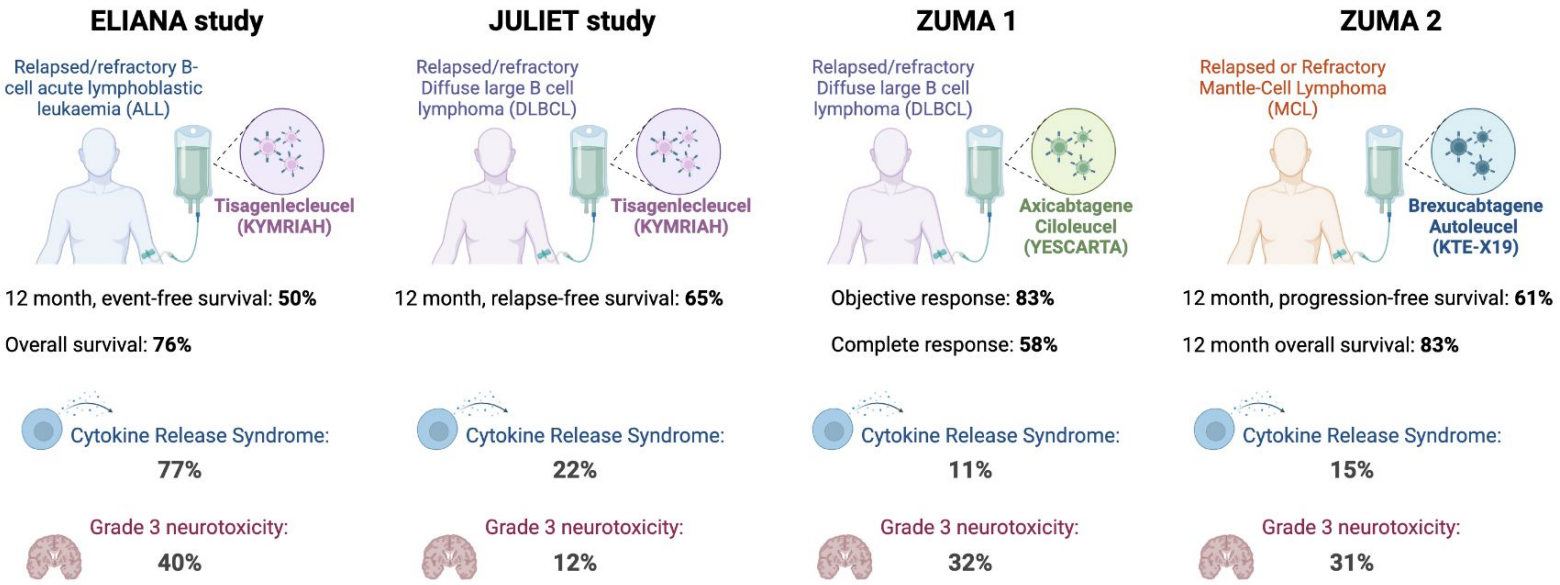


Figure 9: *CAR-T therapy trials, data sourced from clinical trials. Figure generated in Bio Render*

Bringing the Targeted Treatment Paradigm into Practice

The development of targeted therapies has led to the use of basket trials, which evaluate a single targeted therapy across multiple diseases with shared molecular alterations. For example, National Cancer Institute's Molecular Analysis for Therapy Choice (NCI MATCH). This eliminates the need for multiple separate trials, providing a more efficient and cost-effective way to bring targeted therapies through to clinical translation. FDA officials predict that they will approve 10 to 20 cell and gene therapies per year by 2025, however as ATMP manufacturers reach commercialisation, the manufacturing processes must be scalable. Many systems used to manufacture autologous therapies for research or clinical settings have not yet been proven on a large scale in commercial settings, and equipment used in clinical stages does not have to meet the regulations for commercial GMP manufacturing. This poses a unique challenge to get life-changing therapeutics to patients at scale.

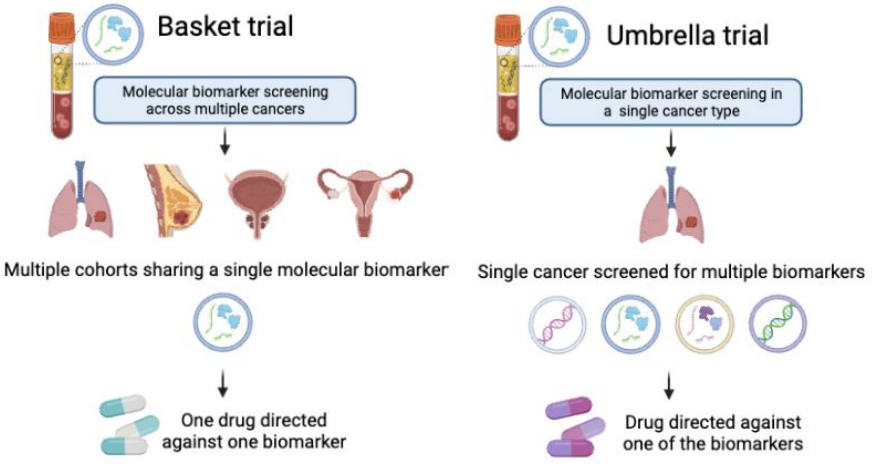


Figure 10: *Basket and umbrella clinical trial designs*

In conclusion, PM is rapidly advancing, with new technologies being developed. The integration of genomics, epigenomics, and other -omics studies is providing a more comprehensive picture of cancer biology, while LBs and molecular imaging offer new ways to diagnose and monitor the disease. Targeted therapies, such as mABs, TKIs, and checkpoint blockers enable inhibition of specific molecules related to cancer progression and enhance antitumor immunity. However the variability and durability of response highlights the need to classify and match patients to the appropriate therapy. ATMPs have revolutionised treatment for haematological malignancies, and show promise for solid tumours. However, challenges remain in bringing targeted treatments to clinical practice, including the need for larger and more efficient clinical trials and improved manufacturing processes for scalability. Future work in PM will continue to investigate the complexity of tumour formation and progression as seen in the ever-evolving cancer hallmarks framework. But aside from biology, a focus will be on shifting policy and regulations as well as requiring significant tech and manufacturing innovations. This calls for cross-industry collaboration and improved scientific communications across specialities in order to bring revolutionary treatment into practice faster.

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