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AI-Driven Spatial Biomarker Discovery in the Tumor Microenvironment

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ABSTRACT

How a cancer develops and how well it responds to treatment isn't just about the cancer cells themselves anymore; the area around the tumour (the tumour microenvironment) is now understood to be hugely important, and this includes how the cells are organised within the tissue. As we've learned more about the location of cells in a tissue from recent developments in spatial biology, we've seen that where immune cells and cancer cells are in relation to each other, and how they interact, greatly affects how the disease will go (Erasha et al., 2025; Williams et al., 2024). Spatial biomarkers - which are defined by where cells are, how many of each type are in an area, and how they're positioned next to each other - give a much more detailed and accurate prediction of what will happen compared to the usual 'bulk' biomarkers (Faktor et al., 2024).

Using artificial intelligence (AI) with this spatial analysis has really sped up the finding of biomarkers, because it's able to pick out complicated patterns from a lot of information from images and what genes are being used. Machine learning and deep learning methods help us to find spatial patterns linked to immune cell movement into the tumour, how different the tumour cells are from each other, and resistance to treatments (Nguyen et al., 2021; Xu et al., 2024). Spatial transcriptomics and looking at digital pathology images are the foundations for this, providing the data for AI to work out what cells are near which others and what those relationships mean for biology (Du et al., 2023; Jin et al., 2024).

What's particularly exciting is that using AI to find these spatial biomarkers is showing great promise for predicting whether a treatment will work, especially with immunotherapies. We can now categorize tumours as either "hot" or "cold" for immune activity, and we can find patterns of keeping immune cells out of the tumour. These both improve how we decide which patients to treat in which ways (Melssen et al., tually, and therapeutic decisions (Melssen et al., 2023; Zuo et al., 2020). Moreover, newer computer programs that use graph-based methods and combine multiple kinds of data are making the predictions even more accurate and useful in the clinic (Kong et al., 2021; Mallya et al., 2025).

Even with all this progress, difficulties still exist: the data can be quite variable, it can be tricky to understand how the AI models are working, and we definitely need solid tests in the clinic to confirm the findings. However, the coming together of AI and spatial biology is completely changing cancer research, providing a level of understanding of how the tumour and the immune system interact that we haven't had before, and opening the door for treatment plans designed for each individual's specific tumour's spatial characteristics.

Keywords: Tumor Microenvironment, Deep Learning, Explainable AI, Immunotherapy Response Prediction, Digital Pathology

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1. INTRODUCTION: FROM MOLECULAR TO SPATIAL UNDERSTANDING OF CANCER

1.1 Background on Cancer Biomarkers

For a long time, cancer biomarkers have been vitally important in cancer treatment. They give us things we can measure to find out about a cancer, how it's likely to progress, and which treatments might work best. Traditionally, these biomarkers have come from looking at the genes, RNA, or proteins within cancer cells, and focusing on changes at the molecular level - things like cancer-causing mutations, which genes are being used, and how much protein is present. Although these approaches have been a huge step forward for precision medicine, they have a basic flaw. Because they look at a whole piece of tissue, they average out the signals from all the different cells in it (Yang and others, 2023).

This averaging hides the fact that a single tumour is actually made up of many different types of cells - something called intra-tumour heterogeneity - and this is a key part of what makes cancer respond to treatment (or not) in different ways, and also how it gets worse. To illustrate, different groups of cells within the same tumour can behave in very different ways, responding to treatment differently or being recognised differently by the immune system. As a result, these 'normal' biomarkers often don't capture how complicated a tumour really is, and their ability to accurately predict how a patient will do in the clinic isn't as good as we'd like (Williams and others, 2024).

Also, the way traditional biomarker research is done, by breaking things down into smaller and smaller parts, misses how cells act depending on where they are and how their surroundings affect them. Increasingly, evidence shows that cancer's progress and its ability to become resistant to treatment aren't just down to changes in the cancer cell's own genes. They are also affected by how it interacts with nearby cells and the material around them. This has led to a move away from only looking at the molecules within the cancer cell to a more complete approach that includes the location and environment.

1.2 What is the Tumor Microenvironment (TME)?

The tumour microenvironment (TME) is the complex and constantly changing area where cancer cells live alongside lots of other cells that aren't cancerous. These include cells of the immune system, fibroblasts, endothelial cells, and the structural support of the extracellular matrix. And it's much more than just something holding the cancer cells in place; the TME actually controls the cancer's behaviour via chemical signals, physical forces, and the exchange of materials (Erasha and others, 2025).

A really important part of the TME is what's happening with the immune system. Immune cells - cytotoxic T lymphocytes, regulatory T cells, macrophages, and dendritic cells - can either fight the cancer or help it grow, depending on how activated they are and how they interact with other cells. Tumour-associated macrophages (TAMs), for example, can change into different forms. Some are pro-inflammatory and fight the cancer, while others suppress the immune system and help the cancer, and the NF-κB signalling pathway is very important in controlling this (Cornice and others, 2024). Monocytes are also important in the TME, and they influence the cancer's progress by turning into macrophages and dendritic cells (Amer et al., 2022).

Beyond the immune system, the TME is influenced by the body as a whole and the environment, including the microbiome, which has been shown to affect how T cells work and how well treatments succeed (DiPalma and Blattman, 2023). What's more, things like how much oxygen is available (hypoxia) and how many nutrients are present create different areas within the tumour, increasing the variety of conditions within it.

All of these interactions make the TME a regulatory system that works on many levels. How cells behave is directed not just by their own genetic 'instructions', but also by the location and environment around them. Therefore, to really understand cancer, we must consider how this ecosystem is organised both structurally and in terms of what it does.

1.3 Why Spatial Organization Matters

Early studies of the TME were mostly about identifying which cell types were in it. But more recent research has shown how vital the arrangement of these cells is to what happens in the end. Where cells are in relation to each other within the tumour tissue determines how likely and what kind of interactions between them will happen, and this affects how the immune system spots the cancer, how the cancer grows, and how it responds to treatment.

One of the most important spatial patterns we see clinically is the difference between "immune hot" and "immune cold" tumours. Tumours that are 'immune hot' have lots of immune cells, especially cytotoxic T lymphocytes, right inside them and generally respond well to immunotherapy. 'Immune cold' tumours, in other words, either have very few immune cells or keep them at the edges of the tumour, and because of this, they usually don't respond to treatment (Melssen et al., 2023).

Lots of different factors explain why immune cells are arranged in these patterns. Immune cells can be blocked from getting into the tumour by physical obstructions, like a dense extracellular matrix and networks of other cells in the tumour. At the same time, signals from the tumour itself can create an environment that suppresses the immune system, stopping it from becoming active. These things create particular areas within the tumour, which are immune deserts, areas where the immune system is shut out, and regions where the immune system is working.

How close cells are to each other allows them to communicate directly through matching molecules on their surfaces, and this is vital for activating and suppressing the immune system. For example, for the immune system to effectively fight the tumour, T cells and cancer cells need to be very near one another so the T cells can recognise the cancer and kill it. If they are further apart or separated, the immune system is much less effective.

And importantly, the way things are arranged spatially also shows the levels of different molecules, like cytokines spreading out and differences in how the tumour cells use energy, all of which then affect what the cells do. Because of this, the spatial layout of a tumour gives us an idea of both how it's built and how it's functioning. Finding these patterns has led to 'spatial biomarkers', which are a more complete and accurate way to understand a tumour and predict what it will do than older methods (Faktor et al., 2024).

1.4 How Artificial Intelligence is Being Used in Cancer Treatment

The rapid progress of technologies that look at where things are within a tissue (like multiplex imaging, looking at digital pathology images, and spatial transcriptomics) has created enormous, complicated sets of data that are too much for usual analytical techniques to handle. So Artificial Intelligence (AI) – including machine learning and deep learning – has become essential for finding useful information in these very complex, high-dimensional datasets. and is now essential.

AI algorithms are especially good at spotting non-linear patterns and relationships in large datasets, allowing them to find subtle arrangements within the tissue that people might miss. In cancer, these methods have been used successfully for categorising the disease, identifying subtypes, and predicting how well a treatment will work, using many different kinds of data (Nguyen et al., 2021; Han and Wu, 2024).

When it comes to spatial analysis, AI helps with many important tasks, including automatically identifying individual cells, sorting cells into types based on their characteristics,

and measuring spatial relationships such as how far apart cells are, how they clump together, and what other cells are in their immediate vicinity. More sophisticated models, including graph-based neural networks, allow tissue structure to be represented as a network of connected cells, and so capture both the details of the immediate area and the bigger picture of the tumour (Kong et al., t 2021).

What's more, AI can combine multiple types of data, bringing together information from spatial transcriptomics, proteomics, and imaging to make a complete picture of the tumour's biology. This ability to integrate is vital for finding strong spatial biomarkers that show both the molecular and structural features of the tumour microenvironment (TME) (Du et al., 2023; Jin et al., 2024).

However, even though AI has huge potential for transforming cancer treatment, it’s not without its difficulties. Problems with the data being different from one place to another, understanding how the AI is making its decisions, and needing large amounts of carefully labelled data are all significant obstacles to getting AI used in the clinic. But improvements to computing methods and the standardisation of data are gradually reducing these issues.

In short, the combination of AI and spatial biology is completely changing cancer research. By allowing us to systematically analyse how things are arranged in the TME, AI is redefining how we discover biomarkers and is leading to more accurate predictions of how treatments will work and more personalised treatments.

2. SPATIAL BIOMARKERS: CONCEPTS AND BIOLOGICAL SIGNIFICANCE

2.1 Definition of Spatial Biomarkers

Spatial biomarkers are a more sophisticated kind of biological sign, because they combine what cells or molecules are present with where they are within the tissue itself. Unlike standard biomarkers, which come from mixed-up samples, these biomarkers keep track of how cells relate to each other, letting us measure biologically important interactions.

More specifically, spatial biomarkers are features with many dimensions, built from the location, relationships, and surrounding environment of biological parts in a certain area. They include things like how far apart cells are from each other, how similar locations are (spatial autocorrelation), how grouped cells are (clustering coefficients), and what types of cells are nearby. These descriptions show properties of the area around the tumour (the TME) that we can't understand just from knowing how much of a molecule is there (Faktor et al., 2024).

The real importance of spatial biomarkers is that they connect how something is built with what it does. Processes in the TME—immune system activation, the way the tumour spreads, and why treatment might not work—are fundamentally about location, happening because of how close things are and the specific conditions in the local environment. So spatial biomarkers give us a more accurate picture of how a tumour works by placing molecular information in its natural tissue context.

The development of spatial biomarkers has been possible because of improvements in technology that can measure things in a spatially specific way. Spatial transcriptomics maps gene activity across the entire genome, but importantly, remembers where each piece of information comes from. Multiplex imaging lets us simultaneously see multiple proteins at the level of individual cells (Du et al., 2023; Jin et al., 2024). These advances have changed the way we look at tissues from simply describing them in two dimensions to a quantitative spatial science, and have provided the basis for discovery using artificial intelligence.

2.2 Key Spatial Features in the Tumor Microenvironment

The TME has many spatial features that together define how it's functioning, and these aren't separate from each other; they all work together to create complicated spatial patterns that affect how the disease gets worse and how well treatment works.

Immune cell infiltration is one of the best-known of these features in the TME. But it's not just about how many immune cells are present. Where immune cells are in relation to the tumour is what determines how well they can do their job. For example, cytotoxic T lymphocytes (cells that kill tumours) deep within the tumour itself mean the immune system is actively fighting it, whereas if they're only around the edges, it suggests something is stopping them from getting in, or they've been disabled (Melssen et al., 2023).

And the way these cells get in is influenced by both the physical structure and the chemical signals of the area. A dense area of connective tissue and oddly formed blood vessels can restrict immune cell movement, and the tumour itself releases chemicals and signals that can change where immune cells end up. This leads to differing infiltration patterns, and these are important spatial biomarkers for how well treatment will work (Zuo et al., 2020).

The point where the tumour and immune system meet is a critical area for direct contact between cancer cells and immune cells. Spatial biomarkers from this area – how often they touch, for how long, and what cells are present – give us clues about how well the immune system is watching for and attacking the tumour.

A lot of interaction, with effector T cells and tumour cells making frequent, lasting contact, is linked to the immune system correctly identifying the tumour and killing it. A weak or sparse connection at this point might mean the tumour is avoiding the immune system, perhaps by displaying signals that stop the immune response or by having immunosuppressive cells present (Williams et al., 2024). So measuring the structure of this interface is now a key aim in spatial biomarker research.

Within the TME, cells arrange themselves into distinct areas or neighbourhoods, which reflect the biological processes happening and the function of those cells. We can define these neighbourhoods by the types of cells in them, how they interact, and the local conditions.

For example, areas with lots of tumour-associated macrophages and regulatory T cells often create areas that suppress the immune system and stop it from attacking the tumour. Areas with many activated T cells and antigen-presenting cells are where the immune system is actively engaging with the tumour. Finding these neighbourhoods gives us insight into how immune activity is controlled in specific places and suggests where we could intervene with treatment.

Recent research has even shown that these neighbourhoods have a hierarchy, with smaller areas within larger structures. This complicated organisation across many scales shows how complex the spatial arrangement within the TME is, and we need analytical tools that can understand interactions at all these different levels. The tumour microenvironment (TME) isn't just made of distinct clumps of cells; it also has steadily changing levels of things like oxygen, nutrients, pH, and signalling molecules throughout it. Because of these changes, different areas of the tumour do different things biologically.

For example, areas with low oxygen (hypoxic regions) are frequently linked to a more aggressive tumour, a failure of treatment to work, and an increase in cells that suppress the immune system. Also, how much cytokine is in a place can affect how immune cells become active and move around, and therefore changes where the immune response happens (Jin et al., 2024). Spatial biomarkers - things we can measure that show these gradients - give us valuable information about how dynamic and adaptable a tumour’s ecosystem is.

2.3 Biological Mechanisms Underpinning Spatial Patterns

The way the TME is arranged in space comes about from many complicated biological processes, happening at different scales.

A key thing that creates this arrangement is how the tumour avoids the immune system. Tumour cells actively change their surroundings to stay hidden from immune cells. They do this by releasing immunosuppressive cytokines, attracting regulatory immune cells (that turn down the immune response), and building physical barriers to stop immune cells from getting in. All these things lead to 'exclusion zones' where immune cells that would normally attack the tumour are either not present or aren't working properly (Melssen et al., 2023).

Communication between cells is also central to how the TME is organised. Many signalling pathways within the TME only work when cells are very close together, needing either direct contact or signalling molecules to travel a short distance. Interactions between proteins on tumour cells and immune cells, for instance, are vital for both activating and suppressing the immune system. So where these cells are in relation to each other directly affects how well and how these interactions work.

Tumour heterogeneity – the fact that not all tumour cells are the same – is important, and this isn't just at a molecular level, but in terms of where the different cells are. Different groups of tumour cells (subclones) may live in different parts of the tumour because of pressures from low oxygen, competition for food, and the immune system looking for them. These separate groups of cells can have different characteristics, like how quickly they grow, how likely they are to spread, and how resistant they are to treatment (Yang et al., 2023).

Furthermore, things from outside the body, like the microbiome, have been shown to change how immune cells act within the TME, and therefore contribute to the variety in immune activity across the tumour (DiPalma and Blattman, 2023). All these different mechanisms working together create a constantly changing landscape where how things are structured and what they do are closely linked.

2.4 Clinical Relevance of Spatial Biomarkers

Using spatial information when looking for biomarkers has a big effect on clinical oncology, and especially on making treatment more precise and reliable.

Spatial biomarkers have already proven very useful for predicting how well a therapy will work, particularly immunotherapy. How immune cells are arranged around the tumour cells can show how likely it is that the immune system will successfully destroy the tumour. For example, tumours with a lot of immune cells inside them, and in a good arrangement, are more likely to respond to immune checkpoint inhibitors, while those with no immune cells inside them or with areas that suppress the immune system are often resistant (Williams et al., t 2024).

But they don't just predict; spatial biomarkers also tell us about how the disease will progress and how long a patient will live. Certain spatial patterns - like clumps of immunosuppressive cells, or a complete lack of immune cells in the tumour - have been linked to worse outcomes for patients (Li et al., 2025). This shows how important the location of things is to how the disease develops.

Spatial biomarkers allow for treatment plans designed for each person. By mapping out the unique arrangement of cells within a person's specific tumour, doctors can find particular features of the microenvironment to target, to improve how well treatment works. For instance, treatments that change the TME - like getting more immune cells into the tumour or breaking down immunosuppressive areas - can be chosen based on the patient's spatial biomarker results.

Despite being promising, using spatial biomarkers in the clinic isn't easy. We need standard ways to collect and analyse the data, and we need large studies to prove they are dependable and apply to many people (Krull et al., 2025). Also, the data is complicated and

requires a lot of computer power to deal with, so that needs to be addressed for them to be used routinely.

However, the increasing evidence that spatial biomarkers are clinically useful shows how much potential they have to improve cancer treatment. By giving us a fuller, more contextual understanding of how tumours work, spatial biomarkers are likely to become a central part of improving precision medicine.

Table 1: Comparison of Traditional vs Spatial Biomarkers

Feature	Traditional Biomarkers	Spatial Biomarkers
Analytical Basis	Molecular abundance	Spatial relationships + molecular data
Data Structure	Bulk, averaged signals	High-dimensional, spatially resolved
Biological Insight	Limited to intrinsic properties	Captures interaction-driven behaviour
Sensitivity to Heterogeneity	Low	High
Clinical Application	Established diagnostics	Emerging predictive and stratification tools
Example	Oncogenic mutation	Immune–tumour proximity patterns

3. AI TECHNOLOGIES ENABLING SPATIAL ANALYSIS

3.1 Data Acquisition Technologies

How AI technologies allow us to examine location within biology is the subject of this section. And the success of finding biomarkers in a place-specific way using AI absolutely depends on how good the data is, what level of detail it has, and how many different things are measured. In the last ten years, huge improvements in technologies that look at where things are in a tissue have changed tissue analysis into something that generates lots of detailed data, and lets us get both molecular information and how the tissue is built, all within the original biological sample.

One of the easiest and most commonly used of these is digital pathology, specifically looking at whole slides of stained tissue sections. Scanning these haematoxylin and eosin (H&E) stained slides at high resolution keeps the visual characteristics of the cells, how the tissue is arranged, and what the supporting tissue (stroma) is like. These pictures are the basic data for AI models; they can pick out simple characteristics (like texture or colour strength) as well as more complex patterns (such as the edges of a tumour, or how things are positioned). Importantly, digital pathology connects normal hospital practice with advanced computer work and makes it easier to apply research to patient care (Krull et al., 2025).

Going further than just the look of things, multiplex imaging technologies can detect many different protein markers in one slice of tissue at the same time. Methods like multiplex immunofluorescence and imaging mass cytometry let us identify different kinds of cells and what they are doing at a single-cell level. Because the location of each cell is maintained, we can reconstruct the groups of cells around each one and how they interact, and this is vital for finding place-based biomarkers.

Spatial transcriptomics is a particularly important new development. It measures gene activity across the entire genome while keeping track of where everything is. Unlike standard RNA sequencing, spatial transcriptomics knows where each gene activity reading comes from, and can map patterns of gene activity across areas of the tissue. This has shown us that there's more variety in tumours than we thought, including different areas of activity linked to specific jobs (Du et al., 2023; Jin et al., 2024). New computer methods have also improved how well

we can use and understand spatial transcriptomics data, giving a more accurate picture of how cells interact (Xu et al., 2024).

Also appearing are multi-omics spatial platforms that combine transcriptomics (gene activity), proteomics (protein levels), and epigenomics (how genes are switched on or off) all within a single location-based system. These platforms make very complicated data sets that show many levels of biological information, and give a full picture of how a tumour is organised and functions. However, the sheer size and complexity of this data mean that we need sophisticated AI to put it together and analyse it.

3.2 Machine Learning and Deep Learning Approaches

Artificial intelligence is the computing power behind analysing these huge, complex spatial data sets, allowing us to find useful patterns and make predictions. Both traditional machine learning and newer deep learning methods are useful here, and work well together.

Supervised learning is often used for things like identifying cells, dividing up tissue, and predicting how a patient will do. These models learn to connect inputs (features of the data) to known outputs, and need labelled data to do this. For instance, a supervised system can tell the difference between tumour cells, immune cells, and stroma based on how they look or their molecular makeup. And if it's been trained on data about patient outcomes, it can predict how well a treatment will work or how long a patient will live.

Unsupervised learning, on the other hand, is especially good for exploring data to find new patterns or structures. Clustering can reveal previously unknown groups of cells or location-based arrangements, and methods to reduce the number of dimensions in the data make it easier to visualise complex spatial relationships. These are important for forming ideas and discovering new biomarkers based on location.

Deep learning has moved the field forward by allowing complete analysis of the raw data, without the need to manually select features. Convolutional neural networks (CNNs) are particularly good at image-based tasks, including finding and categorising tumours, and extracting spatial features. CNNs learn a hierarchy of how the data is represented, and can capture both small and large patterns of location, making them very good at analysing the mixed populations of cells within a tumour (Nguyen et al., scale 2021).

Most recently, graph-based learning is becoming a strong way to model the spatial relationships within the tumour microenvironment. In these, cells are 'nodes', and how they relate to each other in space or function are 'edges'. Graph neural networks (GNNs) can be used to study these networks, and they're good at finding complicated ways things relate to each other, going beyond just looking at pairs of things. In fact, they're particularly suited to how the tumour microenvironment (TME) works as a changing, connected system, and have been promising in predicting how well a treatment will work by looking at how things are arranged in space (Kong et al., 2021).

Also, models that mix deep learning with probability or standard statistical methods are being created more and more to make them easier to understand and more reliable. These attempt to get a good balance between how accurately they predict things and whether they make sense from a biological point of view, which is essential if they are going to be used in the clinic.

3.3 Image and Spatial Data Processing

Turning raw spatial data into useful information needs several steps in a computer process, each of which helps get and refine details about location.

First, in looking at space, is precisely identifying each cell in the images. This means marking the edges of each cell, often in areas where cells are packed closely together and are very varied. Deep learning improvements, specifically fully convolutional networks and

transformer-based designs, have really improved how accurately cells are segmented, allowing analysis of very large amounts of data with very little need for someone to do it by hand.

After the cells are outlined, they are labelled with details about what kind of cell they are or what they are doing. This could mean saying if a cell is a T cell, a macrophage, or a cancer cell, or whether it is 'activated' or 'exhausted'. Accurate labelling is vital because it's the foundation for all the spatial analysis that follows.

Then, lots of spatial features can be calculated once cells are identified and categorised. These include pairwise distance distributions (how close different cell types are to each other), spatial density and intensity measures (how many cells are in a particular area), clustering and dispersion metrics (how much cells gather together or spread out), spatial autocorrelation statistics (how similar nearby areas are) and neighbourhood composition profiles (what cells make up a small area of the microenvironment).

These features change descriptions of how things look in space into numbers, which allows for statistical analysis and creating models.

Integrating many kinds of data is a key problem in spatial biology, with the different data being images, transcriptomics, and proteomics. AI models are now being designed to deal with these multiple data types, combining information about structure and molecules into a single way of representing things.

For instance, spatial transcriptomic data (gene activity in location) can be matched to pictures from histology to find links between how genes are expressed and how things look. Proteomic data (protein levels) from multiple image types can be combined with transcriptomic profiles to give extra insight into what cells are doing. These combined approaches strengthen spatial biomarkers and make them better at predicting outcomes (Du et al., 2023).

3.4 Challenges in AI Implementation

Despite the quick progress in AI for spatial analysis, quite a few problems with methods and in practice still need to be solved.

One main worry is the variability of the data, which happens because of differences in how samples are prepared, how they are stained, what imaging equipment is used, and how sequencing is done. These differences can create systematic errors and mean the model doesn't work as well on different sets of data or in different hospitals.

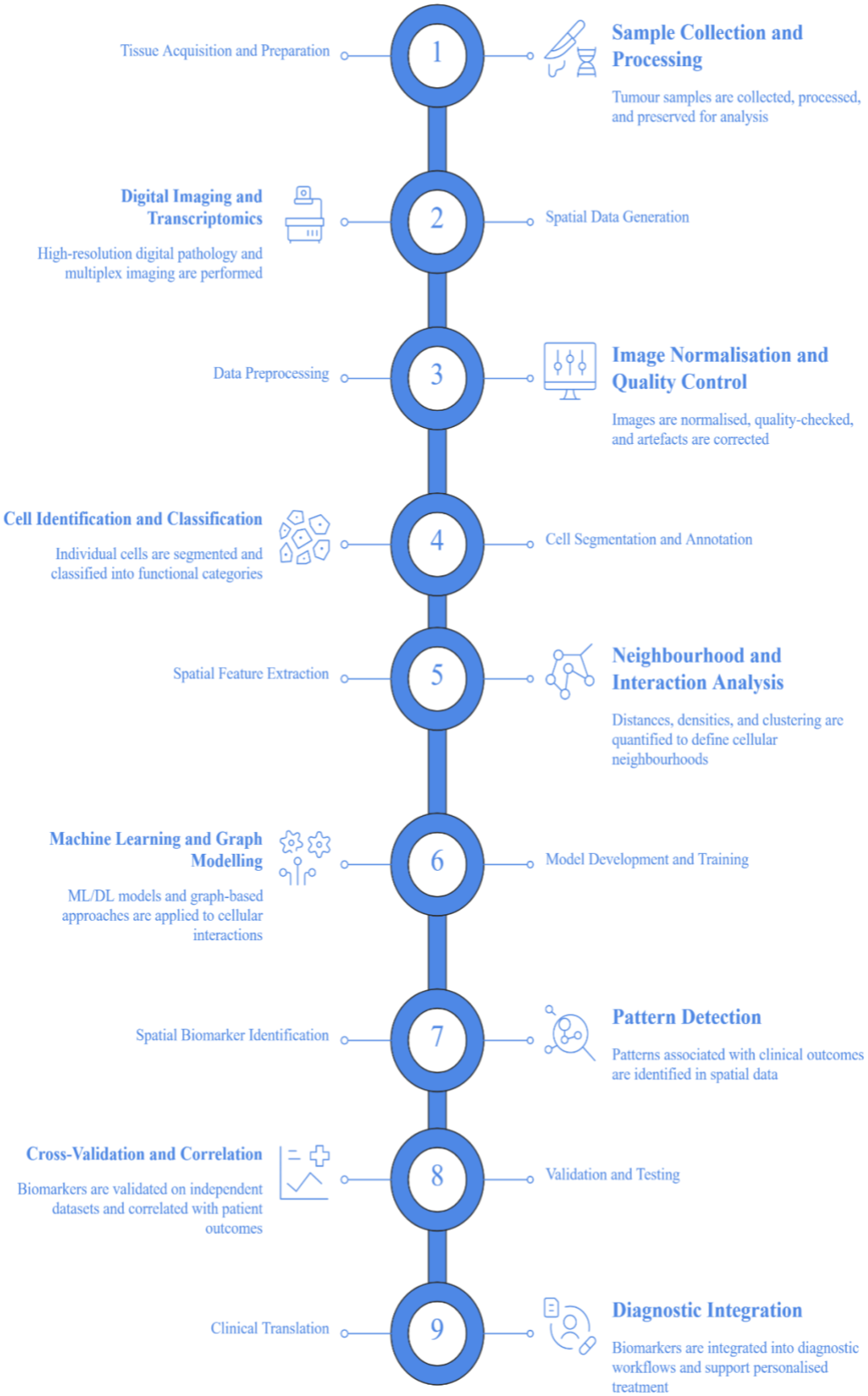
Another big issue is how understandable the models are. Deep learning is good at predicting things, but it's often not clear why it's made a certain decision. This 'black box' effect stops them from being used in the clinic, where you need to be able to see how a decision was reached and explain it. People are trying to solve this by developing explainable AI, which aims to show which features and patterns are causing the model to make its predictions.

Relying on large amounts of labelled data is also a problem. Getting good quality labels needs experts, and it takes a lot of time and money. Semi-supervised and unsupervised learning might help, but they aren't quite good enough yet to completely replace the methods that need someone to label everything.

Also, the computer and infrastructure needs can stop AI technologies from being used, especially where there isn't much money. Analysing high-resolution spatial data needs a lot of computer processing power, specific software, and skilled staff.

Finally, proving things work in a clinical setting and agreeing on standards are still very important. Spatial biomarkers need to perform consistently on different groups of patients and have been properly tested in clinical trials (Krull et al., 2025) before they can be used in the clinic.

Workflow: AI-Driven Spatial Biomarker Discovery Pipeline



1. Tissue Acquisition and Preparation
- Collection of tumour samples (biopsy or resection)
- Standardised processing and preservation

2. Spatial Data Generation
- Digital pathology imaging
- Multiplex imaging and spatial transcriptomics

3. Data Preprocessing
- Image normalisation and quality control
- Noise reduction and artefact correction

4. Cell Segmentation and Annotation
- Identification of individual cells
- Classification into functional and phenotypic categories

5. Spatial Feature Extraction
- Quantification of distances, densities, and clustering
- Construction of cellular neighbourhoods

6. Model Development and Training
- Application of ML/DL models
- Graph-based modelling of cellular interactions

7. Spatial Biomarker Identification
- Detection of patterns associated with clinical outcomes

8. Validation and Testing
- Cross-validation on independent datasets
- Correlation with patient response and survival

9. Clinical Translation
- Integration into diagnostic workflows
- Support for personalised treatment decision-making

4. PREDICTING TREATMENT RESPONSE USING SPATIAL AI MODELS

4.1 Linking Spatial Patterns to Therapy Outcome

How spatial AI models can predict how well a treatment will work is the focus here, and specifically, how the arrangement of things within a tumour relates to how effective the treatment will be. Spatial biomarkers are useful because they show the tumour and its surroundings as a functioning whole, not just separate bits and pieces. More and more evidence shows that how immune cells and cancer cells are positioned in relation to each other - and this dictates how well the immune system can find and destroy the tumour - hugely impacts how successful treatment is, especially immunotherapy.

The common way to categorize tumours as "hot," "cold," or "excluded" in terms of the immune system shows how important the location of things is for treatment. "Hot" tumours have lots of immune cells (specifically cytotoxic T lymphocytes) inside the tumour itself and respond well to immune checkpoint inhibitors because the immune system is actively attacking. "Cold" tumours, on the other hand, don't have many immune cells infiltrating them; either the immune system isn't recognizing the tumour or the body is broadly suppressing the immune system, and as a result, treatment doesn't work well (Melssen et al., 2023; Williams et al., 2024).

The "excluded" tumour type is a little more complex and emphasizes placement. Immune cells gather at the edge of these tumours but can't get into the core. This separation is often because of physical obstacles like dense material around the cells, or because signals are stopping the immune cells from moving. Even though immune cells are present, they aren't where they need to be to be effective.

Crucially, how things are arranged spatially also represents biological processes that are changing: immune activation, suppression, and adaptation. For example, areas where the immune system is shut down - containing regulatory T cells, tumour-associated macrophages, and cytokines that block the immune system - can stop immune activity even in tumours that would usually attract an immune response. These small, localized areas within the tumour are very important for the tumour becoming resistant to treatment and the disease getting worse.

Therefore, spatial biomarkers create a direct connection between the structure of the tissue and how the patient will respond to treatment, giving a more precise explanation of why some patients benefit from treatment, and others don't.

4.2 AI Models for Response Prediction

Artificial intelligence transforms complicated spatial data into quantifiable models that can predict outcomes and help doctors make decisions. AI models, by bringing together different spatial characteristics, can see patterns within the tumour microenvironment both locally and as a whole, and offer a complete way to predict how treatment will go.

AI is used to categorize patients' risk and predict how their disease will progress. These risk stratification models use the profile of the spatial biomarkers and include things like how many immune cells there are, how they are clustered, and how close they are to the tumour cells, to estimate the chances of the disease getting worse. Because they take into account the variations within the tumour, they are better at predicting outcomes than traditional methods that look only at the size of the tumour or its molecular makeup.

For instance, spatial patterns showing immune exclusion or areas of immune suppression are linked to a higher chance of the cancer coming back or spreading. A good distribution of immune cells and active interaction between the tumour and the immune system, conversely, are linked to positive outcomes (Li et al., t 2025).

Machine learning models, after being trained on spatial data, can forecast clinical results like how long someone will live overall and how long they will live without the disease getting worse. These models use a large number of characteristics to find complex, non-linear links between how the tumour is organised and how the patient does.

Deep learning, specifically when used with images of the tumour under a microscope, can pull out characteristics that predict outcome directly from the image. These models look at spatial patterns at many different scales - from the appearance of the cells to the structure of the tissue - providing a full view of the tumour microenvironment (Nguyen et al., 2021).

A major use for spatial AI is to develop models that predict how someone will respond to a specific treatment. In immunotherapy, these models look at:

- where the T cells are in relation to the cancer cells,
- How many immune cells are at the border between the tumour and normal tissue, and what types they are?
- whether there are areas where the immune system is blocked or where it's suppressed.

These characteristics are used to estimate the likelihood of responding to immune checkpoint inhibitors or other targeted treatments (Williams et al., 2024).

Recently, deep learning models used on entire images of a tissue sample have been shown to predict treatment response without needing someone to specifically define which characteristics to look for. These models can identify subtle arrangements within the tumour that relate to how well the treatment works, and offer a way to do this on a large scale in the clinic (Mallya et al., 2025).

At the same time, using graphs to model the tumor microenvironment (TME) as a network of cells talking to each other is a really powerful method. Cells are shown as points in the network, and how they interact is the lines connecting them. This shows how things are arranged in space, which is very important to understanding how well a treatment will work.

Graph neural networks have been very successful at predicting how patients will do, because they use both the immediate relationships between cells and the overall structure of the tissue (Kong et al., 2021).

4.3 Spatially Informed Therapeutic Decision-Making: Conceptual Case Scenarios

The best way to understand how useful spatial biomarkers are is to look at how they could be used in real medical situations:

- Good Immune Cell Positioning
  If a tumor has a lot of immune cells that kill cancer cells right in the middle of the tumor, and those immune cells are really interacting with the tumor, the tumor is likely to respond well to immunotherapy. Artificial Intelligence (AI) can spot these patterns and suggest using immune checkpoint inhibitors as the first treatment.
- Immune Cells Kept Out, and Barriers Caused Problems
  If the immune cells are only around the edges of the tumor, a spatial analysis might show physical or biochemical barriers stopping them from getting in. In this case, a combination of treatments - things like drugs to reduce scar tissue or treatments that alter the levels of signalling molecules - might be needed to help the treatment work.
- Small Areas Where the Immune System is Suppressed
  If there are small, concentrated groups of cells that suppress the immune system, the tumor is likely to be resistant to standard immunotherapy. AI can find these areas and help doctors choose treatments that affect the way the immune system controls itself, or change the behaviour of macrophages.
- Different Areas of the Tumor Respond Differently
  Tumors that are arranged in a very varied way spatially might have parts that respond to treatment, and other parts that don't. Spatial AI can find these different parts of the tumor, which means treatments can be aimed at specific areas, or treatment can be adjusted as you go along.

These examples show how spatial biomarkers can do more than just predict what will happen; they can actually help with planning and improving treatments.

4.4 Advantages Over Traditional Predictive Methods

AI-based spatial models are considerably better than the ways we usually predict things, and for several important reasons.

First, they give you information in many ways, combining details about the structure, the molecules present, and how the cells interact, all in one system. Traditional biomarkers typically look at just one thing and don't manage the complexity of the TME.

Second, spatial AI models are more accurate at predicting because they consider both what the cells are made of and how they’re organized. Adding in the spatial information allows these models to tell the difference between tumors that seem biologically the same, but are actually behaving differently.

Third, these methods allow for precision oncology for each individual patient. Treatment plans can be made to fit the specific spatial arrangement of each person's tumor. This is a big step forward from treating everyone the same way.

Fourth, AI models can combine different kinds of data - images, information about gene activity (transcriptomics), and information about proteins (proteomics) - to create predictions that are stronger and more thorough. Being able to put all this information together is essential to understanding the full complexity of cancer (Du et al., 2023).

Finally, spatial AI models can be used to monitor changes in the spatial arrangement over time and adjust treatments as the tumor evolves, offering ongoing and evolving analysis.

4.5 Limitations and Considerations in Clinical Application

Even though they have the potential to be revolutionary, there are several obstacles that need to be overcome before spatial AI models can be used in clinics as a matter of course.

A main issue is that they need a lot of thorough testing in clinical trials. The prediction models need to work consistently with lots of different patients, cancer types, and in different clinical environments. If they don't have this testing, there is a risk of the model being too specific to the data it was trained on and not working well with new data.

How understandable the model is is another important concern. Because AI models, especially deep learning ones, are complicated, it can be hard to understand why* they have come to a particular decision. Therefore, it's important to develop AI that is easier to explain so doctors can understand and have confidence in the predictions the model makes.

Problems with the data itself, including how consistent and high-quality it is, can also affect how well the model works. Standard ways of taking images, looking at genes, and processing data are needed to ensure studies can be repeated and compared.

Also, using AI in clinical practice raises ethical and legal questions, including keeping data private, avoiding bias in the algorithms, and being accountable for the decisions made. It’s particularly important to make sure everyone has equal access to these technologies, so they don't make existing inequalities in healthcare even worse.

Finally, the amount of computing power needed for spatial AI analysis could limit where it can be used, particularly in places with fewer resources. Solving these challenges will require improvements in how efficiently these calculations are done.

5. FUTURE DIRECTIONS AND CLINICAL TRANSLATION

5.1 Integration into Precision Medicine

The future of precision oncology will probably be much improved by bringing together spatial biology and artificial intelligence (AI), moving us away from treating everyone with a cancer type in the same way and toward treatments specifically tailored to each person. Because they detail the particular structure and function of each patient’s tumour environment (TME), spatial biomarkers give us a basis for grouping patients for treatment.

In clinics, AI-powered spatial analysis can make diagnoses more accurate and help decide what treatment to use. For instance, looking at where immune cells are and how they interact with the tumour can help doctors choose immunotherapy, find those who would benefit from a combination of therapies, and work out how resistance to treatment might develop. This fits with the increasing use of companion diagnostics - using what biomarkers tell us to give patients the therapies that will work best for them (Williams et al., 2024).

Spatial AI can also be used to monitor patients over time, allowing doctors to see how a tumour’s structure changes. This kind of ‘dynamic’ analysis can detect treatment resistance developing early on and allow treatment plans to be altered, and so improve how well people do. As spatial profiling becomes more readily available and more standardized, it's expected to be used in regular clinic work.

5.2 Emerging Innovations in Spatial AI and Oncology

The discovery of spatial biomarkers is progressing quickly, with continuous advances in both how experiments are done and how we compute the results. Several new developments will likely define the future of spatial oncology.

A major area of improvement is quicker and higher-volume spatial analysis. Better imaging and sequencing technologies are enabling us to get data faster and with more detail, allowing us to assess a tumour’s structure almost immediately. Combined with AI, this could mean decisions being made during surgery or at the point of care.

Another important trend is to integrate data from many 'omics' sources – spatial transcriptomics, proteomics, epigenomics, and metabolomics – all within a single way of analyzing things. This complete view provides a fuller understanding of how the tumour works, showing how things interact at many different levels of control (Du et al., 2023; Jin et al., 2024). AI models that can combine these different types of data are expected to create more solid and biologically relevant spatial biomarkers.

The creation of explainable AI (XAI) is a vital step to getting it used in clinics. By giving understandable explanations of a model's predictions, XAI can increase doctors' confidence in it and make it easier to get approval from regulators. This is particularly important in cancer treatment, where decisions have a large effect on a patient's outcome.

Furthermore, developments in foundation models and transfer learning mean that AI systems that have been pre-trained can be used on different types of cancer and different sets of data. These methods reduce the amount of large, labelled data needed and improve how well the model works in general, dealing with one of the biggest problems with spatial AI (Mallya et al., 2025).

5.3 Ethical, Regulatory, and Practical Considerations

However, translating AI-driven spatial biomarker discovery into clinical use comes with a lot of ethical, regulatory, and practical issues that need careful consideration.

Keeping patient data private and secure is extremely important, especially as the data used in spatial analysis is very sensitive. Strict rules for how data is managed are needed to meet ethical standards and legal requirements.

Algorithmic bias is another key problem, and can happen because of imbalances in the data used to train the AI. If this isn't dealt with, the bias could lead to the model performing differently in different groups of patients and could worsen existing inequalities in healthcare.

Standardization and getting consistent results are also important challenges. Differences in how data is collected - including the imaging and sequencing technology used - can affect how consistent spatial biomarker measurements are. Standard procedures and ways of confirming the results are vital to ensuring that AI analyses are reliable (Krull et al., 2025).

In practice, using spatial AI needs a lot of infrastructure and specialized staff, including powerful computers and experts. This may restrict access, particularly in low and middle-income countries. Dealing with these differences will be essential to make sure these technologies are adopted fairly.

Lastly, getting regulatory approval and clinical confirmation are still major hurdles to using these technologies widely. Before AI models become part of regular medical care, they need thorough testing to prove they are safe, work well, and are useful in a clinical setting.

5.4 Conclusion

As for the main point of this discussion, the rise of finding spatial biomarkers with the help of artificial intelligence is a really big change in how we think about and do things in modern cancer treatment. Instead of seeing cancer just as a problem with genes or molecules, this new idea is that tumours are complicated, changing communities within a location, and how cells interact with their surroundings is a major factor in how the disease gets worse and how well treatments work. By putting together spatially specific biological information with sophisticated computer models, researchers can now examine the structure of a tumour with an incredible amount of detail.

A key advantage of this method is that it gets around the natural limits of how we've usually looked for biomarkers. Traditional molecular biomarkers are helpful, but they're limited because they only give an average reading, hiding the differences within a tumour and ignoring where cells are and how they are behaving in relation to each other. Spatial

biomarkers, on the other hand, give information about the context, showing us not only what the tumour's environment (the TME) is made of, but also how those parts relate to each other. This move from a single snapshot to analysing interactions gives a more correct picture of how cancer works and opens up new possibilities for using this in clinical treatment.

Using AI makes the potential of discovering spatial biomarkers even more powerful because it allows for a systematic analysis of huge amounts of varied data. Machine learning and deep learning models help us identify complicated patterns in how things are arranged in space that wouldn't be easy to spot using normal analytical methods, and graph-based methods provide good ways to model how cells interact inside the TME. These improvements in computing have actually led to real benefits in the clinic, specifically in predicting how well treatment will work; spatial AI models have been more accurate at grouping patients and deciding on the best treatment (Nguyen et al., 2021; Mallya et al., 2025).

And the ways this new approach could be used in a clinical setting aren't just about predicting things; they also include creating and improving treatments. By working out the spatial processes behind how the immune system is activated, suppressed, or becomes resistant to treatment, spatial biomarkers can help create better treatment plans, including combinations of therapies that target both the cancer cells and their environment. For example, being able to accurately define 'hot,' 'cold,' and 'excluded' immune areas within a tumour gives a good reason for customizing immunotherapy and overcoming the ways cancer resists it (Williams et al., 2024).

However, to actually use AI-driven spatial biomarker discovery as a regular part of clinical care, we need to solve a number of important problems. Issues with data being different from place to place, standardising how things are done, and understanding why a model gives a particular answer are all major obstacles. We also need a lot of large, well-labelled sets of data, and careful checking with clinical trials, which highlights the need for scientists working together across computing, biology, and medicine (Krull et al., t 2025). Importantly, we must carefully manage ethical issues - including keeping data private, avoiding bias in the algorithms, and ensuring everyone has equal access.

In the future, as spatial technologies and AI methods continue to develop, we can expect even more progress in this area. Combining data from many 'omics' sources, creating AI systems that can explain their reasoning, and using real-time spatial analysis will likely improve both the precision and usefulness of spatial biomarkers. Applying these methods to many different types of cancer and clinical situations will also be important to prove they are applicable to many cases and will have a lasting effect.

So, AI-driven spatial biomarker discovery isn't just a new piece of technology; it's a complete change in how we study and treat cancer. By shifting our attention from single molecular events to how cells in an ecosystem are arranged in space, this approach offers a more complete and mechanistic understanding of cancer. It therefore has the potential to completely change precision oncology, allowing for more accurate forecasts, more effective treatments, and, eventually, better outcomes for patients.

In short, bringing together spatial biology and artificial intelligence is a vital new area in cancer research - it goes beyond breaking things down into parts and towards a more complex view that considers the context. Despite the challenges, current research strongly suggests that spatial AI will become essential to oncology in the future and will shape the next generation of ways to diagnose and treat cancer.

REFERENCES

Amer, H. T., Stein, U., & El Tayebi, H. M. (2022, November 1). The Monocyte, a Maestro in the Tumor Microenvironment (TME) of Breast Cancer. *Cancers*. MDPI. https://doi.org/10.3390/cancers14215460

Bracken, A., Reilly, C., Feeley, A., Sheehan, E., Merghani, K., & Feeley, I. (2025, December 1). Artificial Intelligence (AI) – Powered Documentation Systems in Healthcare: A Systematic Review. *Journal of Medical Systems*. Springer. https://doi.org/10.1007/s10916-025-02157-4

Chen, W. T., Lu, A., Craessaerts, K., Pavie, B., Sala Frigerio, C., Corthout, N., … De Strooper, B. (2020). Spatial Transcriptomics and In Situ Sequencing to Study Alzheimer's Disease. *Cell*, *182*(4), 976-991.e19. https://doi.org/10.1016/j.cell.2020.06.038

Cornice, J., Verzella, D., Arboretto, P., Vecchiotti, D., Capece, D., Zazzeroni, F., & Franzoso, G. (2024, February 1). NF-κB: Governing Macrophages in Cancer. *Genes*. Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/genes15020197

DiPalma, M. P., & Blattman, J. N. (2023). The impact of microbiome dysbiosis on T cell function within the tumor microenvironment (TME). *Frontiers in Cell and Developmental Biology*. Frontiers Media S.A. https://doi.org/10.3389/fcell.2023.1141215

Du, J., Yang, Y. C., An, Z. J., Zhang, M. H., Fu, X. H., Huang, Z. F., … Hou, J. (2023, December 1). Advances in spatial transcriptomics and related data analysis strategies. *Journal of Translational Medicine*. BioMed Central Ltd. https://doi.org/10.1186/s12967-023-04150-2

Erasha, A. M., El-Gendy, H., Aly, A. S., Fernández-Ortiz, M., & Sayed, R. K. A. (2025). The Role of the Tumor Microenvironment (TME) in Advancing Cancer Therapies: Immune System Interactions, Tumor-Infiltrating Lymphocytes (TILs), and the Role of Exosomes and Inflammasomes. *International Journal of Molecular Sciences*, *26*(6). https://doi.org/10.3390/IJMS26062716

Faktor, J., Kote, S., Bienkowski, M., Hupp, T. R., & Marek-Trzonkowska, N. (2024). Novel FFPE proteomics method suggests prolactin-induced protein as a hormone-induced cytoskeleton remodeling spatial biomarker. *Communications Biology*, *7*(1). https://doi.org/10.1038/s42003-024-06354-8

Haleem, A., Javaid, M., Asim Qadri, M., Pratap Singh, R., & Suman, R. (2022, January 1). Artificial intelligence (AI) applications for marketing: A literature-based study. *International Journal of Intelligent Networks*. KeAi Communications Co. https://doi.org/10.1016/j.ijin.2022.08.005

Han, S., & Wu, J. (2024). Artificial intelligence (AI) meets biomaterials and biomedicine. *Smart Materials in Medicine*, *5*(2), 251–255. https://doi.org/10.1016/j.smaim.2024.03.001

Hong, M., Clubb, J. D., & Chen, Y. Y. (2020, October 12). Engineering CAR-T Cells for Next-Generation Cancer Therapy. *Cancer Cell*. Cell Press. https://doi.org/10.1016/j.ccell.2020.07.005

Horodyski, P. (2023). Recruiter's perception of artificial intelligence (AI)-based tools in recruitment. *Computers in Human Behavior Reports*, *10*. https://doi.org/10.1016/j.chbr.2023.100298

Jin, Y., Zuo, Y., Li, G., Liu, W., Pan, Y., Fan, T., … Peng, Y. (2024, December 1). Advances in spatial transcriptomics and its applications in cancer research. *Molecular Cancer*. BioMed Central Ltd. https://doi.org/10.1186/s12943-024-02040-9

Kong, Y., Gao, S., Yue, Y., Hou, Z., Shu, H., Xie, C., … Yuan, Y. (2021). Spatio-temporal graph convolutional network for diagnosis and treatment response prediction of major

depressive disorder from functional connectivity. *Human Brain Mapping*, *42*(12), 3922–3933. https://doi.org/10.1002/hbm.25529

Krull, D., Haynes, P., Kesarwani, A., Tessier, J., Chen, B. J., Hunter, K., … Anguiano, E. (2025). A best practices framework for spatial biology studies in drug discovery and development: enabling successful cohort studies using digital spatial profiling. *Journal of Histotechnology*, *48*(1), 7–26. https://doi.org/10.1080/01478885.2024.2391683

Li, N., Zhang, N., & Wang, G. (2025). Overexpression of MMP14 is associated with poor prognosis and immune cell infiltration in colon cancer. *Frontiers in Oncology*, *15*. https://doi.org/10.3389/fonc.2025.1564375

Li, R., Li, N., Yang, Q., Tong, X., Wang, W., Li, C., … Feng, Y. (2024). Spatial transcriptome profiling identifies DTX3L and BST2 as key biomarkers in esophageal squamous cell carcinoma tumorigenesis. *Genome Medicine*, *16*(1). https://doi.org/10.1186/s13073-024-01422-4

Mallya, M., Mirabadi, A. K., Farnell, D., Farahani, H., & Bashashati, A. (2025). Benchmarking histopathology foundation models for ovarian cancer bevacizumab treatment response prediction from whole slide images. *Discover Oncology*, *16*(1). https://doi.org/10.1007/s12672-025-01973-x

Melssen, M. M., Sheybani, N. D., Leick, K. M., & Slingluff, C. L. (2023, April 18). Barriers to immune cell infiltration in tumors. *Journal for ImmunoTherapy of Cancer*. BMJ Publishing Group. https://doi.org/10.1136/jitc-2022-006401

Mohd Amin, M. R., Ismail, I., & Sivakumaran, V. M. (2025, January 1). Revolutionizing Education with Artificial Intelligence (AI)? Challenges and Implications for Open and Distance Learning (ODL). *Social Sciences and Humanities Open*. Elsevier Ltd. https://doi.org/10.1016/j.ssaho.2025.101308

Mu, Q., & Najafi, M. (2021, September 15). Modulation of the tumor microenvironment (TME) by melatonin. *European Journal of Pharmacology*. Elsevier B.V. https://doi.org/10.1016/j.ejphar.2021.174365

Nguyen, T. M., Kim, N., Kim, D. H., Le, H. L., Piran, M. J., Um, S. J., & Kim, J. H. (2021, November 1). Deep learning for human disease detection, subtype classification, and treatment response prediction using epigenomic data. *Biomedicines*. MDPI. https://doi.org/10.3390/biomedicines9111733

Su, J., & Zhong, Y. (2022). Artificial Intelligence (AI) in early childhood education: Curriculum design and future directions. *Computers and Education: Artificial Intelligence*, *3*. https://doi.org/10.1016/j.caeai.2022.100072

Vaishya, R., Javaid, M., Khan, I. H., & Haleem, A. (2020). Artificial Intelligence (AI) applications for the COVID-19 pandemic. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, *14*(4), 337–339. https://doi.org/10.1016/j.dsx.2020.04.012

Wang, C., Zhang, R., Zhang, J., Ren, Y., Pang, T., Chen, X., … Yu, Y. (2025). Multi-feature fusion RFE random forest for schizophrenia classification and treatment response prediction. *Scientific Reports*, *15*(1). https://doi.org/10.1038/s41598-025-89359-5

Wiese, J. J., Manna, S., Kühl, A. A., Fascì, A., Elezkurtaj, S., Sonnenberg, E., … Schumann, M. (2024). Myenteric Plexus Immune Cell Infiltrations and Neurotransmitter Expression in Crohn's Disease and Ulcerative Colitis. *Journal of Crohn's and Colitis*, *18*(1), 121–133. https://doi.org/10.1093/ecco-jcc/jjad122

Williams, H. L., Frei, A. L., Koessler, T., Berger, M. D., Dawson, H., Michielin, O., & Zlobec, I. (2024, December 1). The current landscape of spatial biomarkers for the prediction of response to immune checkpoint inhibition. *Npj Precision Oncology*. Nature Research. https://doi.org/10.1038/s41698-024-00671-1

Xu, H., Fu, H., Long, Y., Ang, K. S., Sethi, R., Chong, K., … Chen, J. (2024). Unsupervised spatially embedded deep representation of spatial transcriptomics. *Genome Medicine*, *16*(1). https://doi.org/10.1186/s13073-024-01283-x

Yang, P., Yang, W., Wei, Z., Li, Y., Yang, Y., & Wang, J. (2023, July 1). Novel targets for gastric cancer: The tumor microenvironment (TME), N6-methyladenosine (m6A), pyroptosis, autophagy, ferroptosis, and cuproptosis. *Biomedicine and Pharmacotherapy*. Elsevier Masson s.r.l. https://doi.org/10.1016/j.biopha.2023.114883

Zuo, S., Wei, M., Wang, S., Dong, J., & Wei, J. (2020). Pan-Cancer Analysis of Immune Cell Infiltration Identifies a Prognostic Immune-Cell Characteristic Score (ICCS) in Lung Adenocarcinoma. *Frontiers in Immunology*, *11*. https://doi.org/10.3389/fimmu.2020.01218