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Single-Cell and Spatial Omics in Breast Cancer Stratification: Translational Pathways, Adoption Barriers, and Population-Level Implications

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ABSTRACT

Breast cancer is a biologically heterogeneous disease whose clinical outcomes are shaped by complex interactions among tumor cells, immune components, and the surrounding microenvironment. Recent advances in single-cell and spatial omics technologies have enabled unprecedented resolution in the characterization of tumor ecosystems, allowing researchers to analyze cellular phenotypes, transcriptional programs, protein expression, and spatial organization simultaneously. This paper reviews the role of single-cell and spatial omics in breast cancer stratification, emphasizing translational pathways from biomarker discovery to diagnostic, prognostic, and therapeutic applications. It examines how multi-omics integration supports the identification of tumor intrinsic subtypes, cellular ecosystems, and predictive biomarkers for therapy selection and resistance monitoring. The review further explores requirements for analytical and clinical validation, prospective trials, and real-world data integration necessary for population-level implementation. Key adoption barriers, including technical complexity, infrastructure demands, economic constraints, workforce limitations, and ethical and governance considerations, are critically discussed alongside emerging facilitators such as artificial intelligence, standardized data frameworks, and collaborative translational programs. The paper concludes that while single-cell and spatial omics hold transformative potential for precision oncology and population-scale breast cancer management, coordinated efforts in validation, standardization, policy development, and equitable resource allocation are essential to enable responsible clinical adoption and maximize public-health impact.

Keywords: Breast Cancer Stratification, Single-Cell Omics, Spatial Transcriptomics, Multi-Omics Integration, and Precision Oncology.

INTRODUCTION

Breast cancer is a complex, heterogeneous disease characterized by the presence of multiple intrinsic molecular subtypes and numerous genetic, transcriptional, and epigenetic alterations [1]. Despite continuing advances in early detection and systemic treatment, breast cancer remains a leading cause of cancer-related death among women worldwide, with large clinical, biological, and molecular differences between patients. Single-cell and spatial omics techniques can analyze tissues at unprecedented resolution and have the potential to greatly transform breast cancer biomarker development and implementation [2]. These techniques yield multi-faceted information, including cellular phenotypes, transcriptomes, and spatial locations, enabling researchers to study heterogeneous solid tissues as complete cellular collections instead of bulk mixtures [3]. Over the past decade, multidisciplinary advances in genomics, transcriptomics, proteomics, and image analysis have accelerated the development of single-cell and spatial omics technologies. Concurrently, substantial progress has occurred in the study of breast cancer and the identification of tumor and microenvironmental features of interest. Several recent programs, including From Discovery to Population, have highlighted pathways for the adoption of biomarker discoveries into practice, through which single-cell and spatial omics can inform breast cancer stratification and have mapped the numerous scientific and technological developments required to support these pathways [4]. The impact of infiltration-stimulated polarization on the effectiveness of immune checkpoint inhibitors demonstrates

how single-cell and spatial omics can advance tailored biomarker discovery and population-level implementation [5].

Background: Breast Cancer Heterogeneity and the Advent of Single-Cell and Spatial Omics

Breast cancer is the most commonly diagnosed malignancy worldwide and a leading cause of cancer-related mortality among women [1]. Its molecular heterogeneity is staggering, even relative to other cancers. This heterogeneity results from various factors, including the oncogenetic and epigenetic makeup of disparate genetic or cellular progenitors; the stochastic variation inherent to normal cellular processes; the interactions of existing cells; and local environments [2]. Research at the bulk level has classified breast cancer into six molecular subtypes, with noticeable divergence at the single-cell level; individual patients often exhibit a combination of all six subtypes. Single-cell analysis plays a key role in elucidating this heterogeneity, providing insights into breast-cancer stratification regardless of bulk-level classification [3]. Technologies such as droplet-based single-cell RNA sequencing and multiplexed in situ transcriptome techniques are now bringing single-cell and spatial omics to wider use. Breast cancer pathology, prognosis, and therapy have all been examined in the single-cell context, supplemented by complementary spatial-transcriptomics studies [5]. Single-cell–based insights into breast-cancer pathogenesis have begun to enter epidemiological investigations, real-world data studies, and even early-phase clinical trials.

Methodological Foundations: Single-Cell and Spatial Transcriptomics, Proteomics, and Multi-Omics Integration

Single-cell and spatial omics continue to gain traction in breast cancer research owing to their ability to delineate the molecular characteristics of tumor cells and their microenvironments across different cancer types: through transcriptomic, proteomic, and other data modalities, these techniques can capture details ranging from gene expression, chromatin accessibility, and protein abundance to cellular locations, spatial ecosystems, and cell–cell interactions [3]. With increasing temporal and spatial resolution, single-cell and spatial omics extend the analytical reach of traditional cohort studies and enable effective stratification of heterogeneous samples, thus facilitating the translation of preclinical discoveries into population-scale studies of clinical and public health significance[4]. Single-cell transcriptomics, single-nucleus transcriptomics, multi-modal transcriptomics, and spatial transcriptomics facilitate the collection of parallel transcriptomic single-cell, single-nucleus, and/or tissue-microenvironmental information [2]. Spatial transcriptomics captures whole-transcriptome information by combining conventional microscopy with molecular biology techniques; methods include spatially barcoded tissue-slice-linked reverse transcription polymerase chain reaction, in situ hybridization, and multiplexed RNA detection [1]. In breast cancer, paralleled multi-modal transcriptomics and co-sequencing of transcriptomics and epigenomics at the single-cell level further enrich the characterization of heterogeneous samples. Capture of spatial transcriptomics either follows tissue-slice-step preparation or is integrated into tissue-slice–transfer wells, which give rise to different micro-array designs of spatial barcoding and differ in spatial resolution, linearity, and tissue–treatment permutation [4].

Translational Pathways for Clinical Adoption

Heterogeneity arises at different levels during tumor evolution and progression: interpatient (both temporal and spatial), intrapatient (different (sub) clones and microenvironments), and intratumoral. Several factors influence this heterogeneity, including germline genetic background, environmental stimuli, and stochastic events [4]. Such complexity has profound implications for cancer development, immune evasion, and ultimately treatment failure. Therefore, unraveling this complexity to identify predictive biomarkers for therapeutic selection and/or resistance monitoring has been a major focus of cancer research [6]. Considerable progress has been made over the past two decades in dissecting tumor heterogeneity in the majority of cancers. The breast cancer field has lagged behind due to the challenges in maintaining the intact tumor architecture during the sample process [7]. Nevertheless, substantial advancements in multi-dimensional genomic and cytometry technologies (e.g., single nucleus, single cell, and spatial transcriptomics, whole-exome and targeted) have been made to study the breast cancer ecosystem [8]. Multiscale multi-omics approaches, including single-cell transcript and exome sequencing, RNA-ATAC sequencing from dissociated cells, and multi-modality (i.e., RNA-protein and lipid-RNA) analysis from fresh-frozen or FFPE tissues, enable the characterization of tumor intrinsic subtypes in conjunction with microenvironmental context [3].

From Discovery to Diagnostic and Prognostic Applications

Recent advances in single-cell and spatial omics allow high-dimensional characterization of tumor and immune cells and their microenvironment at single-cell resolution [3]. Efforts to harness these technologies for breast cancer research illustrate a pathway from discovery to potential clinical applications, alongside ongoing endeavors to generate evidence for regulatory approval and facilitate upstream innovation in instrumentation and analysis [2]. The high-resolution spatial architecture of tumors drives heterogeneous responses to therapy, yet conventional approaches to characterizing tumor and microenvironmental heterogeneity offer limited insight into population-level evolutionary dynamics [4]. Single-cell approaches characterize tumor clones, decipher

transcriptional programs that drive developmental plasticity, and probe interactions between tumor and immune cells, thereby elucidating drivers of treatment resistance. Ensemble models jointly leverage single-cell transcriptomic data to stratify patients, while diverse methods harness a range of omic data to identify predictive biomarkers for therapy selection and resistance monitoring [7].

From Tissue Cohorts to Population-Scale Implementation

In late-stage or recurrent breast cancer, patient stratification is complicated by the intratumoral spatial heterogeneity that characterizes both the tumor cells and the tumor microenvironment [5]. Many studies reporting multi-sample and single-site transcriptomic profiles from thousands of tumors have demonstrated clear multi-region heterogeneities in clinical cohorts, yet these studies were limited to a few cohorts or tissue blocks [6]. The reported spatial distributions of individual markers of the tumor ecosystem were also confined to the transcriptome alone and were not multiplexed with other levels of omics [2]. Multi-omics frameworks to determine spatial architectures, ecosystems, and markers of static or dynamic micro-environmental stressors remain sparse. Integration of multi-region and multi-modal population-scale studies is one of the few potential ways to enable digital pathology solutions capable of untangling the complex dynamics at a single-cell resolution across scales [3]. The large public and private repositories, such as the METABRIC, the ICGC, the Genomic Data Commons, and the TCGA, not only store the single-cell dataset but also have massive amounts of bulk datasets. Moreover, most of the breast-sequence data collected in the METABRIC and the ICGC have undergone multi-region measurements with the clinical applications of pre- and post-neoadjuvant therapies [4]. Where only single-region datasets are recovered, these samples are typically comparable with the empty-drop samples of the population-scale single-cell cohort [5]. The possibility of deriving spatial information and dynamical pruning knowledge from a population-scale single-cell breast dataset, translating tissue to population scale, could therefore diminish or eliminate both the clinical and the economic barriers to the campaign of single-cell transcriptomics [2].

Data Standards, Interoperability, and Reproducibility

Clinical-grade evaluation of omics-based stratification does not merely target disease insights but aims to facilitate clinical adoption, overcome economic barriers for widespread use, and deliver population-level evaluations that enable informed healthcare planning[5]. Across modalities, multiple translational pathways have been explored [4]. With respect to single-cell and spatial mapping of breast cancer, two of the most advanced pathways span the analysis–interpretation spectrum, addressing histology-linked intrinsic subtyping and ductal carcinoma in situ (DCIS) tumor ecosystems, respectively[7]. A third pathway focuses on the complementary analysis of transcriptional and proteomic layers, enabling monitoring of therapeutic response [3]. Translational pathways must not only be defined but also pursued within structured frameworks that specify the required evidence and consensus definitions at each stage. A classification scheme has been proposed to formalize such frameworks and identify associated datasets [3]. Guidelines that facilitate interoperability and findability of such extraomic datasets within the specific context of single-cell RNA-sequencing alone, the attention map of leading precision measures, as well as extraction details or adjusted coefficients under a polynomial regression model of absolute counts to a general Poisson model, also subject to an intercept, may further enhance adoption[5].

Stratification Paradigms Enabled By Single-Cell and Spatial Omics

Breast cancer is characterized by diverse intrinsic subtypes with different clinical consequences and treatment strategies [4]. Tumor stratification according to intrinsic subtypes and their interactions with microenvironmental contexts and spatial architecture is crucial for personalized treatment, predicting therapy responses and tumor evolution, and discovering new immunotherapy targets for augmentation or replacement of hormone therapy. Single-cell and spatial omics enable breast cancer stratification across multi-dimensional axes [3]. Intrinsic subtypes exhibit complex relationships with multi-scale microenvironments, further subdivided into a cavernous, canonical genome-stabilized, invasive, and a contrarily less invasive-but-farther-spread Discovery type [1]. Early-stage Basal Immature and Early-Stage Luminal Mature "Eresist" states precede the aforementioned invasive tumors. Despite shared microenvironment preferences with homologous maternal subtypes, further individualization occurs post-structural symbiosis, forming Fluid-Mutator Type-5 [2].

Tumor Intrinsic Subtypes and Microenvironmental Contexts

The discovery of four breast cancer subtypes by Perou et al. (2000) and the subsequent discovery of the seven intrinsic subtypes have profoundly shaped breast cancer research and clinical practice [7]. However, continual tumor evolution and therapy-induced alterations mean that tumors often diverge from their primary subtype, exposing a critical limitation of binary classification approaches [5]. The emergence of single-cell RNA sequencing (scRNA-seq) has made it possible to catalogue the phenotypes of evolving and microenvironment-influenced cellular states without being restricted to predefined subclasses or subtypes. Ziegler et al proposed an assay-agnostic spatial profiling method to identify and quantify the variable expression of multiple mRNA-encoded transcripts governing diverse microenvironmental characteristics, both within individual tumors and across patient cohorts [8]. This high-level spatial resolution transcriptomic data enables the disambiguation of the

breast cancer taxonomy into the three dominant intrinsic lineages, revealing that a quarter of tumors evolve along alternate trajectories that remain undetected by standard genomic assays, and establishes a novel class of microenvironmental activity states [5]. Undertook a meta-analysis of transcriptomic breast cancer studies to define a panel of 15 genes predictive of triple-negative breast cancer status, which ranks the respective enrichment of the eight intrinsic subtypes across heterogeneous datasets [7]. Substantial switching of intrinsic states was observed in longitudinal bulk transcriptomic profiles collected from individually barcoded early circulating tumor cell clusters pooled in a xenograft mouse model, illustrating an active switching process [8]. Single-cell techniques using barcoded pooled samples on either commercial or custom platforms are widely deployed to characterize clonal evolution, intra- and inter-tumor heterogeneity, therapy-induced adaptive states, and adaptive responses to treatments early in the course of intervention [9]. Correction of batch effects induces high-resolution landscapes of cellular states following treatment, separating sensitive from resistant cellular ecosystems, while applications of single-cell technology to circulating tumor cells and tumor-educated platelets detect predictive signatures of therapeutic response before clinical progression [2].

Spatial Architecture and Cellular Ecosystems in Breast Cancer

Breast cancer is a heterogeneous disease characterized by various tumor- and microenvironment-related features, necessitating the identification of specific biological characteristics for better prognosis, treatment selection, and therapy response monitoring [7]. Single-cell and spatial omics have provided insights into tumoral intrinsic subtypes at unprecedented resolution, identifying how biological characteristics shape a patient's specific "cellular ecosystem." Translational research programs have uncovered new biological mechanisms that relate these intrinsic subtypes to clinically relevant characteristics and guide treatment approaches [3]. The coexistence of these refined strata highlights the limitations of a one-size-fits-all classification and underlines the pressing need to understand how these new determinants shape the breast cancer "landscape" more broadly [5]. These developments are gradually being mapped to breast cancer types and therapeutic targets to strengthen the evolutionary interpretability of stratification and enhance the impact of single-cell and spatial technologies [6].

Predictive Biomarkers for Therapy Selection and Resistance Monitoring

Markers guiding physician decisions on neoadjuvant, adjuvant, and palliative therapies exist for breast cancer. These predictive biomarkers require validation at the population level for their widespread use following initial studies in convenient cohorts [1]. Ongoing clinical trials administering neoadjuvant endocrine therapy to hormone receptor-positive breast cancer patients evaluate such biomarkers at the same time that predictive markers based on genomic information from liquid biopsies, such as cell-free DNA methylation profiles, cell-free RNA profiles, and circulating tumor DNA sequencing, monitor therapy response and guide the next therapeutic intervention [7]. These efforts combine both bench-to-bedside and bedside-to-bench aspects of translational research. Single-cell sequencing informs clonal evolution analysis according to both copy number alterations and single-nucleotide variants in a metastatic patient, shedding light on vital metastatic therapy responders that previous cohort-based analyses overlooked [10]. The single-cell–derived candidate therapeutic targets, together with circulating tumor DNA and circulating tumor cell messenger RNA components, undergo parallel investigation in a prospective clinical trial to assess the enrichment of these cancer cell populations before and after therapy [8]. These combined approaches help ascertain patients' ongoing therapy options at any given moment and adapt to therapy switches triggered by tumors' genomic evolution [8].

Validation and evidence generation across stages of translation

Validation and evidence generation across the translational pathway are essential for implementation of multi-parameter systems and assays in clinical contexts [4]. Analytical and clinical validation approaches commence at the lowest level, demonstrating suitable analytical performance, biological relevance, and clinical utility with minimal biological and technical variation [7]. Further progress to prospective controlled trials or real-world patient cohorts enables the generation of evidence on usage across clinical settings [9]. Such validations may define new, clinically actionable biomarker use cases, promote re-confirmation of otherwise transitional paradigm shifts, or facilitate epidemiological understanding of population-wide consequences of widespread implementation [10].

Analytical validation and clinical validation frameworks

Analytical and clinical validation represent critical stages in the translation of single-cell and spatial omics to clinical practice and, consequently, epidemiologically relevant population-scale impact [7]. Analytical validation establishing assay performance specifications in turn determines the design of clinical studies and real-world evidence generation toward greater confidence in the clinical and beleaguered assessments of population-level impact [5]. Given that breast cancer represents the most common cancer among women worldwide and the leading cause of cancer-related death among women in many countries [2], the clinical adoption, economic sustainability, and population-level impact of single-cell and spatial omics warrant careful consideration. Attendant barriers and facilitators, lessons learned from large-scale, multi-tissular, regulated development programs for mRNA/miRNA/proteins and DNA analytics, as well as emerging conversion pathways based on

advances in artificial intelligence, high-performance computing, and environmental monitoring, may inform trajectory prediction and investment prioritization[6]. A roadmap for future research and deployment across distinct geographic, economic, and regulatory settings concludes the analysis [3].

Prospective Trials and Real-World Data Integrations

Prospective clinical trials and integrations of real-world data are crucial for the continued advancement of breast cancer research [1]. Combining single-cell transcriptomics with traditional bulk transcriptomic and proteomic techniques has enabled stratification of breast cancer tumors into prognostic clusters that accurately distinguish malignant from benign tumors based solely on metabolic activity [5]. The surge in single-cell transcriptomics studies since 2015 has greatly deepened understanding of tumor-intrinsic transcriptional heterogeneity and how different cellular states affect intratumoral evolutionary dynamics [4]. The advent of single-cell multi-omics analysis, first applied to breast tumors in 2020, further elucidates tumor heterogeneity by linking multi-modal genetic and epigenetic information to cellular transcriptional landscapes. Additionally, the capacity to integrate genetic datasets such as single-nucleotide variants, copy-number variations, or post-translational modifications with time-resolved, position-resolved, and multi-modal proteomic profiling promises breakthroughs in early detection, risk assessment, and personalized treatment planning [3]. The emergence of increasingly sophisticated machine-learning algorithms tailored to the analysis of high-dimensional multi-omics datasets also accelerates progress by facilitating the predictive mapping of treatment response to the single-cell genomic, transcriptomic, or proteomic features of each tumor, paving the way for the transition from population-scale to personalized medicine [3].

Population-Level Impact Assessments

As single-cell and spatial omics technologies yield increasingly diverse and extensive datasets, the information derived from these datasets may no longer fit within the confines of assessment frameworks traditionally developed for population-level model-based studies[7]. Furthermore, even when such information can be accommodated, rapid developments in the analytic landscape create a need for frameworks that guide the evaluation of data-derived population-level insights, including considerations of the underlying models and the evidentiary standards they uphold [5]. An established approach for addressing population-level regulatory questions, the model-informed drug development (MIDD) framework, identifies a series of foundational building blocks for which guidance exists from a regulatory perspective [1]. To promote knowledge sharing and ongoing improvement of the associated methodologies, the key components, generalities, and illustrative applications of the framework have been organized into an MIDD catalogue [2]. An analogous catalogue for single-cell and spatial omics data incorporates insights on enduring population-level impact questions, currently available assessment approaches, and the evolving analytic tools relevant to population-level issues raised by these data[7].

Adoption Barriers and Facilitators

Research and clinical applications of single-cell and spatial omics in breast cancer generally encounter substantial adoption barriers [5]. A major technical challenge arises from the complexity and diversity of experimental protocols. Adoption also remains hindered by multiple economic constraints, among which the high cost of consumables dominates the discussion [9]. In tandem with technical and economic challenges, ethical, legal, and social implications also pose obstacles to implementation. Adoption frameworks have begun to address workforce, education, and governance considerations in translation. Such frameworks can help guide resource allocation in the pursuit of equitable, population-scale implementation of novel omics technologies [4,1,2].

Technical and Infrastructural Challenges

Comprehensive analyses at single-cell resolution call for multifunctional facilities capable of processing large numbers of samples on multiple platforms [4]. Single-cell RNA sequencing (scRNA-seq) remains the most widely applied technology, but complementary techniques such as ImmunoSEQ and CITE-seq are of increasing interest 2. Substantial infrastructure investments are therefore needed to facilitate the adoption of single-cell and spatial technologies and their integration into routine breast cancer research [5]. In addition to these facility-level requirements, the development of dedicated clinical workflows, a safe and seamless pathway from research to clinical laboratories, faces difficulties as yet unaddressed by overarching formal frameworks or consensus statements[9].

Economic and Policy Constraints

The high costs associated with state-of-the-art instruments and reagents for single-cell and spatial multi-omics hinder their implementation in biomedical research and clinical applications [6]. The single-cell platform requires a multidisciplinary expertise set (computational bioinformatics, biostatistics, three-dimensional tissue modeling, photonic engineering, etc.) accessible only to academic and research institutions that possess sufficient funding 1. Public funding for a single-cell multimodal platform or, more broadly, spatial multi-omics technology, is limited. Thus, an acceptable compromise remains a combination of low- and mid-throughput commercial and open-source modalities to address basic biological questions and obtain preliminary proofs of concept [8]. Severe barriers arise before embedding findings generated with low- or mid-throughput systems into large-scale clinical platforms,

which represent another major financial hurdle for clinical laboratories [2]. Adapting new multi-omics scientific breakthroughs to the clinical setting remains a slow process, as the statement "if it works, it takes time" applies. Building up infrastructure under standard operating procedures before moving from 1–96-well format with rapid and low-cost analysis to large single-cell sequencing platforms is therefore required. Addressing the aforementioned challenges will become paramount for the various remaining steps to be carried out, enhancing the translational potential of the long-term biomarker project [7].

Ethical, Legal, and Social Implications

Technological advances in single-cell and spatial omics empower unprecedented dissection of breast cancer heterogeneity at resolution unattainable with bulk methods and enable exploratory analyses of the cellular microenvironment in tissue and liquid biopsies [8]. The resulting insights into cell-type diversity, spatial organization, and nuclear morphometry foster stratification of breast tumors according to their intrinsic molecular subtypes, composition of the cellular microenvironment, and architecture of the tumor ecosystem[7]. These biological stratifications, together with multi-omics analysis of distinguishing genetic, transcriptomic, and proteomic features, pave the way to precision medicine by informing the selection of targeted therapies, evaluation of treatment response, and identification of the acquisition of resistance mutations [2]. The potential of single-cell and spatial omics to support stratification at the population scale is substantiated by the finding of similar molecular features, subtype assignment, microenvironment profile, and ecosystem architecture in primary tumors and metastases arising from the same patient [1]. The accelerated adoption of single-cell and spatial approaches for breast cancer stratification depends on generating analytical, clinical, and public-health evidence attesting to the reliability, utility, and impact of derived products. Cross-disciplinary innovator–implementer partnerships facilitate this evidence generation across the entire spectrum of preclinical and clinical activities, for example, by transitioning to clinical development of findings derived from in vitro perturbation experiments using cancer-cell lines in patient-derived co-culture systems [10]. Transformative programs that enable community-wide insight into the current state of technology, guidelines for addressing common barriers, and public sharing of best practices can benefit diverse innovators and implementers concurrently, driving faster, broader, and more impactful adoption of single-cell and spatial approaches for breast cancer stratification across academic, clinical, and commercial settings[13].

Workforce, Education, and Governance Considerations

Given the intrinsic complexity of breast cancer, single-cell and spatial omics are needed to supplement traditional bulk-tissue and topology-agnostic (luminal versus basal-like) methods [1]. The advent of assays that capture not only the transcriptome, but also the protein content or other features at a single-cell scale enables a deeper understanding of the tumour microenvironment [1]. Spatially resolved transcriptomics deepens the contextual understanding of tumours by combining single-cell–resolution gene expression profiles with tissue morphology. This higher-dimensional modality data allows for further resolution of stratification and has led to proposals of breast cancer intrinsic subtypes (including Extra-Angiogenic Basal-like, Spheroid Basal-like, Inner Luminal, Outer Luminal, and Non-Luminal) that might not be visible by transcriptome-scale bulk transcription alone[7]. The need for highly multiplexed proteomic and multi-omics methods renders proteomic and multiplexed imaging approaches extremely desirable [9].

Case Studies and Lessons Learned From Translational Programs

Single-cell and spatial omics have transformed the understanding of breast cancer heterogeneity and opened new avenues for therapy stratification [1]. Together, they provide a more detailed picture of both tumor-intrinsic complexity and the cellular environments surrounding tumors, leading to new hypotheses about mechanisms of disease progression, therapy resistance, and response to therapy [9]. A series of translational programs focused on breast cancer illustrates key success factors and common barriers encountered at different stages of translation. Each program has generated essential evidence, setting the groundwork for population-scale implementation [3]. Collectively, the case studies highlight critical considerations in the successful adoption of single-cell and spatial omics and frameworks for assessing the population-level impact of emerging capabilities [4].

Roadmap for Future Research and Deployment

Only time will tell how long the technical developments underpinning single-cell and spatial omics will take to translate to robust clinically applicable breast cancer stratification procedures [8]. To accelerate this pathway, the recent framework of two-dimensional cancer-sequence data generation-behavior mapping can be drawn upon. A coordinated approach that encompasses coordinated technical and data-generation development is nevertheless essential. Single-cell and spatial omics support stratification along a number of axes, a diverse set of surrogates for the global cellular composition of tissues [9]. These surrogates subsequently enable stratification of complex, heterogeneous multi-omic datasets into patient-relevant interpretations [10]. Since 2011, substantive technical groundwork enabling genomic evolution, mutational and transcriptional subclonal spectra, resistance-mechanism–chemical trios, and co-clustered transcriptomic and immune-landscape signatures has been laid 3. Techniques and expertise developed in other cancers can be leveraged to promote further breast-cancer research cycles on the

single-cell strand [11, 12]. Eighteen leapfrog advancements following single-cell RNA-sequencing (sc-rna-seq) initiative implementation-stack emergence by the sequencing initiative take shape well beyond breast cancer: interoperable unified data standards, nested time-course applications, hybrid latent-space–temporal analyses fusing transcriptomic and radiomic inputs, transcriptomic trajectories linking time-course inputs to prognostic molecular subtypes, generalizable protein-abundance prediction from RNA-data alone, multi-modal microfluidic approaches integrating transcriptomic, proteomic, and perturbational input with mixed-species evenness, and direct light-beam activation of single-transcript surface-fluorescence reporting, for example. Numerous further cross-cancer lessons exist [13-15].

CONCLUSION

Single-cell and spatial omics technologies are reshaping the scientific and clinical understanding of breast cancer by enabling high-resolution characterization of tumor heterogeneity, clonal evolution, and microenvironmental interactions. These approaches move beyond traditional bulk-tissue analyses to reveal the dynamic cellular ecosystems that influence disease progression, treatment response, and resistance mechanisms. As a result, they offer powerful opportunities to refine breast cancer stratification, improve biomarker discovery, and support more precise therapeutic decision-making. Despite their promise, the translation of single-cell and spatial omics into routine clinical practice remains constrained by substantial technical, economic, infrastructural, and regulatory challenges. High implementation costs, lack of standardized workflows, data-integration complexities, and limited clinical validation hinder widespread adoption. Ethical, legal, and governance issues, particularly regarding data sharing, interoperability, and equitable access, also require careful consideration to ensure responsible deployment at a population scale. Future progress will depend on coordinated investment in analytical validation, prospective clinical trials, interoperable data standards, and workforce training, alongside the integration of artificial intelligence and high-performance computational tools for large-scale multi-omics analysis. Strengthening collaborations among researchers, clinicians, policymakers, and industry partners will be essential to bridge the gap between discovery and implementation. With sustained efforts in these areas, single-cell and spatial omics can evolve from advanced research tools into clinically actionable platforms that enhance precision oncology, improve patient outcomes, and inform population-level breast cancer control strategies.

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