

IN FOCUS

Cancer Research in the Age of Spatial Omics: Lessons from IMAXT



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Summary: The Imaging and Molecular Annotation of Xenografts and Tumors Cancer Grand Challenges team was set up with the objective of developing the “next generation” of pathology and cancer research by using a combination of single-cell and spatial omics tools to produce 3D molecularly annotated maps of tumors. Its activities overlapped, and in some cases catalyzed, a spatial revolution in biology that saw new technologies being deployed to investigate the roles of tumor heterogeneity and of the tumor micro-environment.

See related article by Stratton et al., p. 22

See related article by Bhattacharjee et al., p. 28

See related article by Goodwin et al., p. 34

When the Cancer Grand Challenges initiative presented its first set of challenges in 2015—a time that now seems positively remote—one entire challenge was dedicated to 3D tumor mapping (<https://www.cancergrandchallenges.org/challenges/concluded-challenges/3d-tumour-mapping>). Although all the proposed themes were aspirational, the idea of identifying each and every cell of a tumor, defining their genetic and molecular make-up, and mapping them in space, seemed to be truly a “Grand” challenge.

Looking back from today’s vantage point, it seems clear that the Cancer Grand Challenges committee displayed a remarkable amount of foresight in identifying the intersection of two mounting waves in biological research. On one hand, it had become clear that the organization of the tumor micro-environment (TME) and the coexistence of multiple clones of tumor cells characterized by different mutation and copy number profiles had a huge importance in the disease progression, the evolution of therapy resistance, and its dissemination to form metastases (1). On the other, new technologies were starting to emerge, which made it possible to perform highly multiplexed measurements of gene and protein expression on single cells or spatially on tissue sections. Together, these things made the challenge worth pursuing and—if barely—addressable.

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Cancer Discov 2025;15:16–21

doi: 10.1158/2159-8290.CD-24-1686

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In 2017, the imaging and molecular annotation of xenografts and tumors (IMAXT) team was one of the two selected teams tackling this, together with the Rosetta (<https://www.cancergrandchallenges.org/rosetta>) team headed by Prof. Josephine Bunch. Almost 10 years later, spatial omics has burgeoned into a massive field of its own (2) with a commercial potential running into the billions of pounds, and, although the relevance of spatial biology for cancer research cannot be negated, we are still learning how to best leverage these new tools at scale to improve our understanding of basic tumor biology and improve patient health with better diagnoses and treatments. What follows is an account of the lessons learned while running IMAXT in such a time of change.

WHERE IMAXT STARTED

At the time of the IMAXT proposal, single-cell technologies had just started to scale up, and spatial omics was still in its infancy. Spatial transcriptomics technologies had been recently developed but were largely limited to the proof-of-concept stage. Imaging mass cytometry had been applied to tumor tissues but was still not broadly accessible, and other multiplexed immunohistochemistry technologies were similarly limited. All of the aforementioned methods were slow and limited to a limited number of samples. Whole-organ imaging had been enabled by advances in tissue clearing combined with light-sheet microscopy, but these largely prevented the collection of sections to use for downstream molecular annotation, and in any event largely destroyed molecular information. Serial two-photon tomography (STPT), our technique of choice for imaging, had not been yet demonstrated on tumors.

There was a growing appreciation in the field for the role of tumor heterogeneity, and of the TME, in many aspects of cancer such as progression, metastasis, and therapy resistance. Inter-tumor heterogeneity had been extensively documented in several tissue types, including breast cancer (3), showing the

presence of multiple sub-variants of the disease with specific genomic structure and gene expression. Several laboratories had shown an important role for intra-tumor clonal heterogeneity in driving processes such as metastasis, but the field was significantly hindered by the absence of high-throughput and hi-plex single-cell and spatial technologies. It was evident that almost every component of the local tumor niche could contribute to progression and drug resistance; hence, the TME had to be studied cell by cell rather than as a single entity. It was also relatively clear that heterogeneity manifested at multiple levels—genome structure, gene expression, and protein expression—highlighting a need for multi-omic methods. It is also worthy to note that, although there was a consensus on the importance of acquiring single-cell and spatial data, there was no proof that this would actually lead to better prognosis/diagnosis or provide actionable clinical data.

In this landscape, it was decided that the mission of IMAXT would be to assemble experts in a chosen list of novel imaging, spatial, and single-cell technologies (see the consortium member list); adapt their methods to work reliably on tumors and metastases; and combine them together to provide spatial, molecularly annotated datasets enriched with multiple layers of information. These technologies would be pushed to the point of being used to answer important questions in cancer (in particular breast cancer) and would be made available to the community. Finally, the deluge of data generated by these methods would need to be handled in such a way to make it readily interpretable and easy to visualize and analyze.

IMAXT PHILOSOPHY AND LESSONS LEARNED

A few central tenets were kept front and center while designing the structure of the IMAXT project. Some of these proved very important as IMAXT evolved over the years, whereas others provided unexpected lessons.

Technologies Can Be Combined to Pair Their Strengths

The methods chosen for our project all had important limitations in speed, throughput, or number of parameters measured. Often there was an inverse relationship between methods that were high-plex, but low throughput, and vice versa. At the same time, we knew that the heterogeneous and non-stereotypical nature of tumors meant that multiple technologies would need to be applied on the same sample to produce coherent information and done at scale to generate statistically sound data. The solution was to combine multiple technologies to leverage the advantages of each. This often meant a focused technology development effort directed to making methods compatible with each other. The result was the “IMAXT pipeline” (see Fig. 1), a combination of technologies enabling an initial large-scale 3D imaging of whole organs, followed by the selection of individual sections of interest to be profiled using high-plex methods (4).

Although combining spatial proteomic, transcriptomic, and genomics methods on the same exact tissue section is starting to become possible, this is still coming at the expense

of depth of profiling or data quality. Instead, we took advantage of our data registration pipeline to run different methods on consecutive serial sections, obtaining deeper data at the resolution of cell neighborhoods.

Spatial Methods Can Be Supercharged by Single-Cell Methods

Although the final mission of IMAXT was to produce a map, spatial methods were still limited in terms of depth of molecular profiling. Disaggregated “survey sequencing” of samples was therefore paired with spatial profiling in order to identify fine-grained cell types to map in space using more limited marker sets. This proved important, especially given the incredible development of single-cell DNA sequencing methods such as Direct Library Preparation (DLP+) (5) over the course of the project and the corresponding lack of reliable spatial genomics methods for profiling copy number profiles or mutations. The single-cell disaggregated method also proved invaluable as a tool to identify the best genes and proteins to profile in panel-based methods.

Big Data Requires Big Resources and Dedicated Analysis

The data output of IMAXT was expected to be in the order of hundreds of terabytes. This was out of reach of our computing capabilities at the time. Not only would substantial hardware resources be needed but also the ability to retrieve data quickly and make it available to collaborators worldwide with little delay. Most spatial data would come in the form of images, which would have to be co-registered and segmented to produce cellular and molecular data for analysis and integration. Analysis algorithms for spatial data were also largely unexplored and would need development. Our strategy was to exploit the expertise within our collaboration, in particular within Cambridge’s Institute of Astronomy, with their prior experience working with extreme data throughputs from work on, for instance, galaxy mapping with the Global Astrometric Interferometer for Astrophysics (GAIA) mission. That team had already successfully translated some of their algorithms to biological images.

Data Visualization Required Some New Methods

Humans are highly visual animals, but our strengths in pattern recognition serve us poorly when facing complex, multidimensional molecular data, especially at the scale IMAXT would collect. If ways to convert this complexity to visual cues could be developed and fast, interactive, and user-friendly data exploration tools built, the potential of the data would be unlocked in a way previously impossible. Virtual reality (VR), with its potential for immersive data exploration, seemed an ideal format for this. IMAXT collaborated with a small number of programmers and VR developers to create an interactive, multiuser data visualization tool to explore these opportunities. In addition, this VR tool proved hugely successful for engagement and education, being featured among other things in a rock music festival, an international book fair, and a year-long museum exposition. Today, thanks to a new breed of user-friendly, cable- and setup-free headset

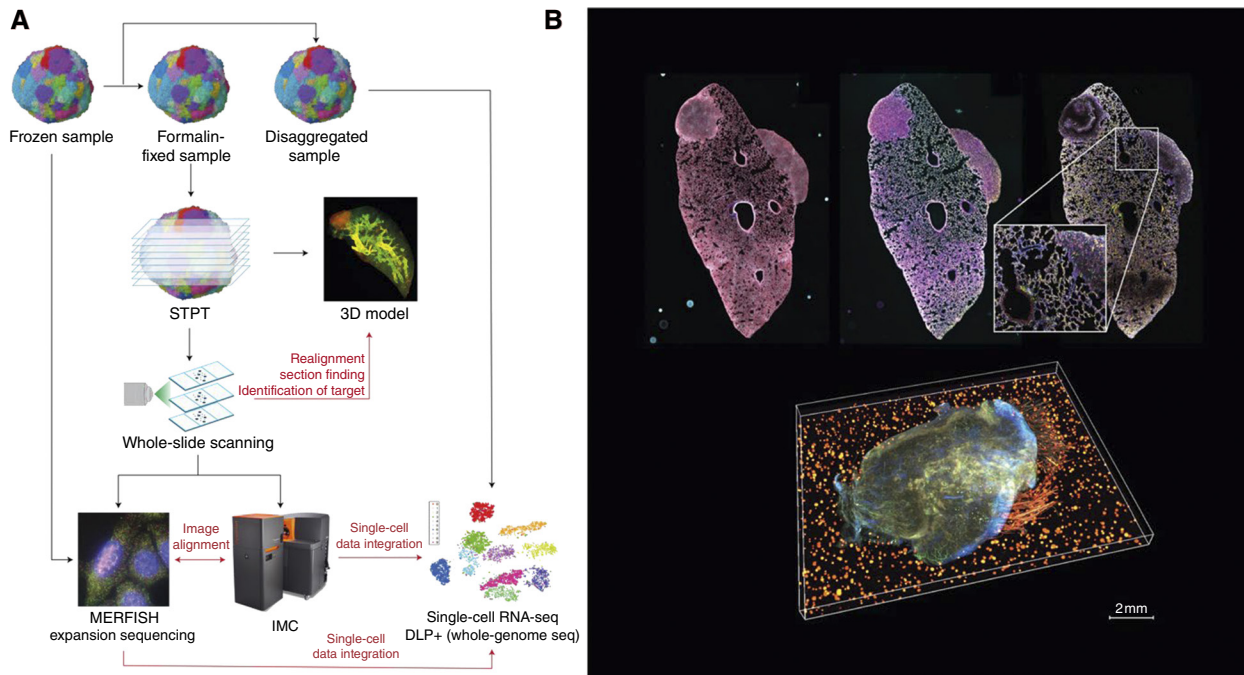


Figure 1. **A**, IMAXT pipeline. **(B)** Multimodal analysis in 3D of a 4T1-derived tumor. Top, Lung with two metastatic lesions derived from a mouse primary triple-negative breast tumor. The figure shows how the registration of the different imaging modalities to a cellular level allows one to segment individual cells and identify tumor cell populations, differentiate hypoxic areas, and identify increased fibrosis and infiltration of immune cells and blood and lymphatic vessels by staining with a panel of 35 cell markers at the same time. Bottom, Sample in 3D depicts a murine primary tumor grown in the mammary gland of a mouse, showing the power of the Spatial Profiling and Annotation Centre of Excellence pipeline to produce and visualize large volumes (typically ~100,000 individual images registered and stitched and up to 500 TB of data). The orange fluorescent beads are clearly visible in the medium outside the biological tissue. These alignment landmarks proved to be crucial for all stages of multimodal registration.

becoming available, VR is finally ready to become a commonplace tool in laboratories, and our work in this area continues thanks to a recently funded spin-off company.

Flexible and Hub-and-Spoke Design

The Cancer Grand Challenges initiative offered the possibility to deploy a very large amount of funds. Although the simplest way would have been to allocate these evenly to the different research groups, this choice could lead to fragmentation and difficulty in adapting to a shifting scientific landscape. Instead, a new sub-team in Cambridge was created—the IMAXT laboratory—which would act as a central aggregator of resources and sample processing. The hub interacted with each of the partner laboratories largely focusing on individual projects and technologies. Approximately half of our budget was kept in reserve ready to be deployed for investment in particularly promising technologies. “IMAXT associate members” were also introduced: group leaders receiving support under the sponsorship of an existing consortium member to address specific challenges in a focused way.

Put Junior Investigators in Charge

We were fortunate enough to have many world-class group leaders as co-investigators on IMAXT, including the inventors of most of the technologies that we employed. A flip side of having such a senior team, distributed over a 12-hour time difference gap, was the difficulty in getting everybody to meet

regularly and push our agenda. Although each of the principal investigators committed a huge amount of their time, an early decision was to put junior researchers in charge whenever possible. Senior postdoctoral scientists were given agency and responsibilities, and as a result, the team was able to proceed in a much nimbler and more effective way. An example of this was the establishment of “tiger teams” and cross-laboratory groups working on specific issues led by junior investigators with their own agenda and resources.

IMAXT ACHIEVEMENTS

In the last 7 years, IMAXT expanded to become a multinational consortium with almost 100 people involved from more than 10 different laboratories. This enabled a very diverse body of work, with projects and technology development efforts of different sizes and scope and with a varying degree of success. Some of the achievements that we are most proud of are described below.

Spatial Data Has Prognostic Potential

One of the most critical questions conditioning the success of this Cancer Grand Challenge was whether tumor mapping would indeed produce useful information to improve patient prognosis and diagnosis. The Bodenmiller Lab, in collaboration with other groups in our team, led a project using imaging mass cytometry (IMC) to profile breast tumors from

hundreds of patients (6). This showed that neighborhood structure and other spatial measurements correlate strongly with the outcome. This seminal work was extended to lymphatic metastases (7), identifying specific TME motifs with prognostic potential. More recently, the infrastructure put together for IMAXT was leveraged to launch an effort, funded by the Wellcome Leap program, to study therapy resistance in triple-negative breast cancer and build a computational model capable of predicting relapse.

Tools for 3D Whole-Tumor Imaging Were Improved, Enabling Their Combination with Spatial Omics Methods

IMAXT collaborated with TissueVision, the company developing STPT, to evolve this technology into a tool enabling high-throughput whole-organ fluorescence imaging of almost every tissue at subcellular resolution, while producing single-cell thickness histological sections amenable for downstream molecular profiling. We developed improved embedding chemistries allowing sectioning of challenging tissues, identified optimal fluorophore combinations as well as label-free nonlinear imaging modes, and devised ways to incorporate reference landmarks for highly efficient registration of images taken on individual sections after slicing (4). This allowed the use of histologic dyes, such as hematoxylin and eosin, and antibody staining, which would not permeate whole-mount tissues, to produce whole-organ 3D models. We showed that STPT is compatible with both IMC and (although with some limitations) spatial transcriptomics, which makes it an extremely powerful tool to screen large volumes of tissue and identify smaller or rare areas of interest to prioritize for analysis.

New Tools for Spatial Transcriptomics and Multi-omics Were Developed

The initial technology IMAXT picked for spatial transcriptomics, MERFISH, has been complemented by new methods developed within our team. The Boyden Laboratory developed expansion sequencing (8), a new method that substantially improves profiling resolution and depth and produces more accurate single-cell data, operating in both an untargeted mode, potentially producing whole-transcriptome data, and on panels of ~300 genes. Over the past few years, IMAXT also developed barcoding by activated linkage of indices (BALI), a conceptually new spatial profiling method capable of making simultaneous multi-omic measurements of transcriptomes, proteins, and genomes/epigenomes by a combination of light activation and spatial barcoding (bioRxiv 2024.05.20.595040).

3D Profiling Was Demonstrated to Be Superior to 2D Profiling, and 3D Tumor Models Were Produced

One of the aims of IMAXT was to perform molecular profiling on tumors in three dimensions, re-creating virtual models of the disease. This was achieved using different strategies. The Bodenmiller Lab produced several 3D models of human tumors by processing serial ultra-thin formalin-fixed, paraffin-embedded sections via IMC and

realigning the resulting data (9). We showed that collecting 3D spatial information is superior to traditional 2D profiling as it allows the detection of more complex cell-cell interactions and increases the chance of detecting rare features such as micro-invasions from in situ tumors or coarse structural heterogeneity in the tumor landscape. In parallel, we also developed a protocol for serial ablation, which can be used to obtain “confocal” IMC data on a single thicker section.

Tools for Scaled-up Single-Cell DNA Sequencing and Multimodal Data Integration Were Developed and Used to Study the Clonal Evolution of Tumors

The Aparicio and Shah groups developed an optimized strategy (DLP+) for single-cell DNA sequencing (5), which enabled the profiling of more than a million cells over the course of the project. Among other things, these were used to profile a wide range of primary human samples including breast and ovarian cancers as well as pre-cancerous lesions, describing “foreground” mutation patterns that likely contribute to the genomic variation and evolution of cancer clones in these heterogeneous diseases (10). IMAXT was also among the first to develop methods to realign single-cell RNA sequencing and whole-genome copy number (DLP+) data, using gene dosage effects, to obtain lineage-specific transcriptomics (11). Finally, IMAXT created methods to integrate spatial and disaggregated data (12, 13). In both cases, we were able to reproject the much deeper molecular annotation obtained in the methods acting on disaggregated cells to space by integrating it with less information-dense spatial data.

A State-of-the-Art Cloud-Based Computational Ecosystem Was Developed for Data Visualization and Analysis

Spatial profiling and 3D imaging techniques routinely produce terabytes of data and require processing power beyond what is commonly available to most laboratories. Computing cluster architectures commonly used for genomic data are not suited for this type of data as they are largely focused on textual input. Data visualization and exploration in particular are very challenging as merely rendering a typical sample on regular hardware/software can be so slow as to effectively block the ability of researchers to extract insight. The IMAXT science platform, a state-of-the-art computing architecture hosting all of the data produced by the project in a central repository, was developed to allow users to perform interactive analysis “in the cloud” using their preferred pipelines and scripts without downloading data locally. IMAXT also developed software packages to accelerate visualization of terabyte-sized 3D data, as well as optimized pipelines for the efficient registration and integration of spatial data and for cell segmentation from IMC and other modalities.

A Link between the Genetic Structure of a Tumor, Its Mutational Background, and Its Microenvironment Was Demonstrated

A long-standing question in cancer biology is whether the structure and composition of the TME are consistently driven by the genetic features of the tumor itself. We investigated this

using three different technologies: We performed an extensive profiling of serially passaged Patient Derived Xenografts (PDX) models using STPT, observing that individual tumors repeatedly elicited characteristic TME structures both at the macroscopic and microscopic levels. These structures were maintained across passages and showed consistent marker signatures detectable both by single-cell RNA sequencing and IMC. Similar results were obtained by the Aparicio Lab, which observed consistent and repeatable dissemination to specific distal organs from specific PDXs. A novel single-cell expressible clonal barcoding method, WILD-Seq, was used to observe clonal dynamics in the 4T1 and D2A1 tumor models during chemotherapy while measuring single-cell transcriptomic information, identifying clones responsible for therapy resistance and its potential mechanism (14). Finally, multiple TME contexts associated with primary ovarian tumors and their secondary metastases were identified, showing that different immune contexts correlated with tumors of specific mutational origin, yielding evidence of different strategies of immune-evasion linked to the tumor genomic structure (15).

REFLECTIONS ON THE FUTURE

Most of the spatial measurement technologies piloted by IMAXT have now become much more robust and compatible with a wider range of tissue types, and throughput is improving. Most of them are also becoming commercially available, and the spatial proteomics and transcriptomics fields now provide many different options, each with pros and cons. However, the barrier of adoption for these methods remains high because of their high cost and the substantial know-how required to use them effectively and to analyze the resulting data. For this reason, we envision that spatial omics technologies will be deployed, in the short-term future, in the context of larger research institutions or in collaboration with experienced laboratories or centers capable of providing support on experimental design, access to equipment and probe panels, protocols, and data processing. With this in mind, the “Spatial Profiling and Annotation Centre of Excellence” (SPACE) was just launched in Cambridge, which is leveraging funding from the Wellcome Leap program and Cancer Grand Challenges to establish what aspires to be the one of the largest spatial molecular profiling hubs in the UK and beyond and to catalyze the widespread adoption of spatial and single-cell measurements in as many aspects of cancer research as possible, while at the same time providing opportunities for early translation to the clinic.

More generally, we expect to see two main trends in the field in the upcoming years: First, we expect that the technologies that IMAXT and others pioneered will be ported to other tumor types. We expect this process to be largely a matter of time rather than requiring substantial new advancements, as many of the key innovations required to adapt technologies to different tissue types have been tackled. Second, we expect spatial methods to be increasingly applied at scale on large cohorts of human samples coming from tissue repositories and clinical trials. This will be enabled by substantial improvements in both robustness and sample throughput. As an example, IMC has become $\sim 5\times$ faster since the inception of IMAXT,

whereas some spatial transcriptomics options can cope with centimeter-scale sections in just a few days of processing time. This throughput will be absolutely essential to produce robust and actionable discoveries from future projects as it will allow the acquisition of patient cohorts large enough to provide a representative sampling of the differences between individual tumors, with each sample being large enough to capture intra-tumor heterogeneity over multiple scales. Importantly, the concepts of sample size calculation and power analysis for spatial omics datasets are starting to be explored, and some guidelines are emerging on replication and statistical analysis. This was a much overdue advancement, which will undoubtedly contribute significantly to the growth of the field in the next few years.

Biology is, at this point, inextricably married with data science, and cancer biology is no exception. We expect that biological laboratories will not only increasingly feature bioinformaticians in their ranks but will also expand to include experts in data visualization, computer learning, and data processing/management. Data visualization will become critically important in an age in which the typical dataset is so large and complex that it overwhelms the processing power of a typical personal computer and the visual discrimination capacity of a typical human. Artificial intelligence will also enter the field more and more (as it already has), offering tools to digest the ever-increasing complexity of data and extracting predictions on tissue functional states as well as on disease progression and evolution.

We certainly live in interesting, and exciting, times. Like all the best grand challenges, we believe that IMAXT has left the field with more open questions than it started with. At the same time, we hope that our effort, and the generous funding we received from Cancer Grand Challenges, provided a toolbox to tackle some of these and enable a new generation of research.

Authors' Disclosures

D. Bressan reports personal fees and other support from Suil Vision Ltd; other support from Elyx Ltd; and grants from Cancer Research UK, the US Department of Defence OCRP Program, NIH, and Wellcome Trust LEAP program during the conduct of the study, as well as personal fees from Eleven Therapeutics and Bit.Bio outside the submitted work and a patent for WO2021116715A1 Spatial Barcoding pending, a patent for WO2023242560A1 Methods for spatial genomic, epigenomic, and multi-omic profiling using transposases and light-activated spatial barcoding pending, and a patent for EP4065978B1 Novel linker compounds issued. N. Walton reports grants from Cancer Research UK during the conduct of the study. G.J. Hannon reports other support from Suil Interactive during the conduct of the study, as well as other support from Faeth Therapeutics and Eleven Tx outside the submitted work and a patent for barcoding by activated linkage of indices, which is a spatial profiling technology, pending. No disclosures were reported by the other authors.

Acknowledgments

This work was delivered as part of the IMAXT team supported by the Cancer Grand Challenges partnership funded by Cancer Research UK (reference C9545/A24042). IMAXT Cancer Grand Challenge Consortium (in alphabetical order): Mohammad Al Sa'd, Bruno Albuquerque, Hamid Raza Ali, Martina Alini, Samuel Aparicio, Heather

Ashmore, Thomas Ashmore, Vinci Au, Shankar Balasubramanian, Caroline Baril, Giorgia Battistoni, Sean Beatty, Robby Becker, Bernd Bodenmiller, Alina Bollhagen, Carla Boquetale, Edward S. Boyden, Dario Bressan, Alejandra Bruna, Marcel Burger, Carlos Caldas, Maurizio Callari, Ian Gordon Cannell, Hannah Casbolt, Nick Chornay, Nikki Coutts, Ali Dariush, Lauren Deighton, Khanh N. Dinh, Natalie Duncan, Yaniv Eyal-Lubling, Ilaria Falcatori, Jean Fan, Atefeh Fatemi, Debarati Ghosh, Carlos González-Fernández, Eduardo A. González-Solares, Wendy Greenwood, Flaminia Grimaldi, Gregory J. Hannon, Owen Harris, Suvi Harris, Nicole Hemmer, Kui Hua, Melis Irfan, Cristina Jauset, Johanna A. Joyce, Tatjana Kovačević, Laura Kuett, Russell Kunes, Aybuke Küpcü Yoldaş, Daniel Lai, Emma Laks, Max Lee, Hsuan Lee, Giulia Lerda, Yangguang Li, Jack Lovell, Yangning Lu, John Marioni, Andrew McPherson, Neil Millar, Alireza Molaeinezhad, Claire M. Mulvey, Natasha Narayanan, João C.F. Nogueira, Fiona Nugent, Ciara H. O'Flanagan, Marta Paez Ribes, Isabella Pearsall, Sarah Pearsall, Brett Pryor, Fatime Qosaj, Clare Rebbeck, Andrew Roth, Oscar M. Rueda, Teresa Ruiz, Kirsty Sawicka, Leonardo A. Sepúlveda, Sohrab P. Shah, Abigail Shea, Anubhav Sinha, Austin Smith, Leigh Smith, Simon Tavaré, Ignacio Vázquez-García, Sara Lisa Vogl, Nicholas A. Walton, Spencer S. Watson, Joanna Weselak, Tristan Whitmarsh, Sophia A. Wild, Elena Williams, Jonas Windhager, Chenglong Xia, Chee Ying Sia, Ruihan Zhang, Chi Zhang, Pu Zheng, Xiaowei Zhuang.

Note

Supplementary data for this article are available at Cancer Discovery Online (<http://cancerdiscovery.aacrjournals.org/>).

Published first January 13, 2025.

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