Artificial Intelligence Identifies Cancer and Viral Infections with Nanoscale

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ABSTRACT

Artificial intelligence (AI) is revolutionizing modern medicine, providing novel diagnostic capabilities that improve accuracy and efficiency in disease detection. Current applications include enhancing imaging techniques and identifying minor cellular changes associated with cancer and viral infections. However, the detection of such conditions, especially at early stages, remains challenging. This research introduces AI of the NUcleus (AINU), a groundbreaking AI tool that utilizes super-resolution microscopy and deep learning to detect cellular heterogeneity with nanoscale accuracy. AINU combines convolutional neural networks with single-molecule localization microscopy data, analyzing nuclear features such as RNA polymerase II (Pol II) localization, histone modifications, and DNA density to distinguish between cell types. The tool demonstrated almost 100% accuracy in identifying different human cell states, including somatic cells, human-induced pluripotent stem cells, and herpes simplex virus type 1-infected cells, even at extremely early infection stages. By focusing on chromatin structure changes, such as Pol II organization in nucleoli and nuclear-edge DNA density, the AINU provides insights into cellular phenotypic heterogeneity that are beyond the capabilities of conventional imaging.

The review highlights AINU's potential as a powerful diagnostic tool, enabling the identification of high-pluripotency stem cell clones and early detection of viral infections and cancer cells. This novel approach offers a significant advancement in the application of AI for conservative diagnostic methods, with broad implications for improving precision medicine in oncology, virology, and regenerative medicine.

Keywords: AINU, Cancer detection, Cellular heterogeneity, Chromatin structure, Convolutional neural networks, Super-resolution microscopy, Viral infection

Introduction

Artificial intelligence (AI) is a rapidly advancing field within computer science, aimed at creating systems capable of performing tasks that typically require human intelligence. AI encompasses various techniques, such as machine learning (ML), deep learning (DL), and natural language processing (NLP). Among these, large language models leverage DL methods and vast datasets to understand, summarize, generate, and predict text-based contents.[1–3] NLP, as a subfield of AI, focuses on the interaction between computers and humans through natural language, including understanding, interpreting, and generating human speech and text. Over the years, AI has evolved significantly, from early rule-based systems to advanced ML and DL algorithms that are now transforming multiple industries.[1–3]

In health care, AI's impact is particularly profound, with applications ranging from diagnostic tools to personalized treatment plans. It offers the potential to revolutionize clinical practice by analyzing large datasets, identifying patterns, and providing insights that would be difficult for humans to detect. This approach has already led to breakthroughs in areas such as genomics and drug discovery, as well as real-time disease prediction during global health emergencies.

The use of AI in medicine can be broadly divided into virtual and physical applications.[4] Virtual applications include software-based tools like electronic health records and neural network-guided treatment decisions, while physical applications involve robotics in surgeries, intelligent prostheses, and automated care for the elderly. Traditional evidence-based medicine has relied on statistical methods to establish clinical correlations, but AI's use of DL allows for a more dynamic approach, utilizing large datasets to detect patterns and associations that improve diagnosis and treatment accuracy.

AI's ability to assist in diagnosing complex conditions, such as cancer and viral infections, highlights its potential in clinical settings. For example, during the COVID-19 pandemic, AI was employed to predict outbreak hotspots using data from contact tracing and global travel.[5] Companies like BlueDot applied AI techniques to analyze vast amounts of information, accurately forecasting the virus's spread.[6]

Additionally, tech giants like Google and Apple collaborated on contact-tracing platforms, showcasing AI's role in responding to public health challenges.

David Baker, Demis Hassabis, and John Jumper have been awarded the 2024 Nobel Prize in Chemistry for their groundbreaking work in computational protein design and protein structure prediction. Hassabis and Jumper of DeepMind received half of the prize for AlphaFold (Figure 1), an AI system that predicts protein structures with extraordinary accuracy.[7] Knowing the structure of a protein is critical since it impacts its function and interactions with live organisms.

As AI continues to evolve, it presents an opportunity to enhance health-care services, making diagnosis and treatment more precise and accessible. The integration of AI into clinical practice holds great promise for the future, particularly in the accurate identification of cancer and viral infections, driving a new era of medical innovation.

AI in Diagnostic Medicine: Recent Use Cases

Despite significant advancements in medical science, effective disease diagnosis remains a global challenge. The development of early diagnostic tools is hindered
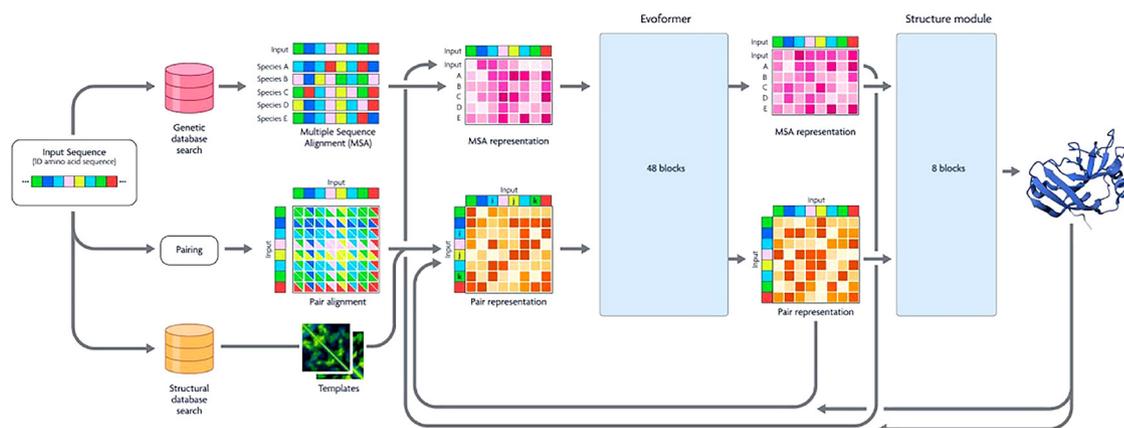
What Is AlphaFold?

Fig 1 | AlphaFold – Nobel Prize winner, an AI system that predicts protein structures

by the complexity of disease mechanisms and the diversity of symptoms. AI, particularly ML and DL, has the potential to revolutionize health care by enhancing the accuracy, efficiency, and speed of diagnostic processes. ML utilizes data as an input, with its performance highly influenced by the quality and quantity of data, allowing it to address some of the difficulties inherent in traditional diagnostic methods. With tools like convolutional neural networks (CNNs) and data mining, ML identifies key patterns across large datasets, making it highly effective for disease diagnosis, prediction, and classification.[8]

AI's capabilities extend to diagnosing conditions like diabetic retinopathy and cardiovascular diseases. For example, DL algorithms have been employed to detect diabetic retinopathy from retinal images, providing a fast and accurate alternative to manual screening.[9] In cardiology, AI has been used to analyze electrocardiogram data to predict risk factors for cardiovascular events. These algorithms can identify patterns in the data that may not be apparent to human clinicians, allowing for earlier intervention and better management of cardiovascular risks.[10,11]

AI's role in diagnostic imaging is further exemplified by its use in detecting pneumonia from chest X-rays. In a comparative study, an AI system demonstrated a sensitivity of 96% and a specificity of 64%, outperforming radiologists who achieved 50% sensitivity and 73% specificity.[12] Similarly, AI has been applied to predict acute appendicitis, with the random forest algorithm achieving an accuracy of 83.75% in a dataset of 625 cases.[13] The precision, sensitivity, and specificity metrics of this AI-based approach surpassed those of traditional diagnostic methods, providing a more reliable tool for early diagnosis.

Clinical laboratories are increasingly adopting AI to enhance the accuracy and speed of diagnostic tests. AI models are being developed to identify and quantify microorganisms, classify diseases, and predict clinical outcomes based on data, such as genomic information, gene sequencing, and microscopic imaging. For instance, ML techniques have been used to detect malaria-infected red blood cells using digital in-line holographic microscopy, offering a rapid and cost-effective diagnostic solution.[14] Automated AI-based systems are now common in blood cultures and susceptibility testing, leading to faster diagnostic results and better antibiotic selection.

In emergency medicine, AI helps address challenges such as overcrowding, resource allocation, and diagnostic errors. AI algorithms can triage patients based on the severity of their conditions, helping prioritize high-risk cases and optimize patient flow.[15,16] Additionally, AI-powered decision support systems can provide real-time diagnostic and treatment recommendations, reducing the risk of misdiagnosis. By predicting patient demand and suggesting optimal therapy options, AI can improve the efficiency of emergency departments, leading to shorter waiting times and better patient outcomes.

AI's application in cancer diagnosis has shown promising results, particularly in detecting breast cancer. A study in the UK used an AI system to analyze a large dataset of mammograms, leading to an absolute reduction in false positives and false negatives by 5.7% and 9.4%, respectively.[17] In South Korea, a comparison between AI-assisted breast cancer diagnosis and radiologists' assessments revealed that AI had a higher sensitivity (90%) for detecting cancerous masses compared to radiologists (78%). Moreover, AI demonstrated superior performance in detecting early-stage breast cancer, achieving 91% accuracy versus 74% for radiologists.[18] These findings indicate that AI can enhance the accuracy of breast cancer screening, potentially leading to earlier detection and better patient outcomes.

AI has also been utilized in dermatology to improve the detection of skin cancer. A DL model using CNNs was able to diagnose melanoma cases with a high degree of accuracy, outperforming dermatologists in

some instances.[19,20] The AI system could not only identify cancerous lesions but also suggest appropriate treatment options. These capabilities make AI a valuable tool in dermatological practice, where early and accurate diagnosis is critical for patient survival.

Conservative Diagnostic Methods for Cancer and Viral Infections

The clinical management of cancer diagnosis typically begins with a physical examination to detect abnormalities across various anatomical locations. This preliminary step is followed by a series of laboratory tests involving blood and urine analysis, complemented by non-invasive imaging techniques from radiology and nuclear medicine (Figure 2). Common imaging modalities include computerized X-ray scans (CT scans), ultrasonography, magnetic resonance imaging (MRI), bone scans, and positron emission tomography (PET) using tracers like fluorodeoxyglucose or prostate-specific membrane antigen. These imaging methods are often accompanied by minimally invasive needle biopsies or surgical biopsies, followed by a histopathological examination to confirm the cancer type and stage.

For hematological malignancies, such as leukemias, immunological probes and flow cytometric analysis play a critical role in diagnosis and prognosis. While these approaches have traditionally been the foundation of cancer detection and management, they are generally more effective in detecting cancers at moderate or advanced stages. Their limited specificity at early stages underscores the need for more refined diagnostic tools. Early detection of cancer significantly improves prognosis because treatments are generally more effective in the early stages, and targeted therapies can reduce off-target effects.

Cancer diagnostics are evolving rapidly, driven by continuous advancements in our understanding of the disease and technological innovations.[21] Modern diagnostic approaches include sophisticated two-dimensional and three-dimensional imaging modalities, such as PET, MRI, single-photon emission computed tomography, CT, and X-ray imaging. These techniques allow for the visualization of tumors and assessment of their characteristics, aiding in cancer management. Additionally, molecular analysis methods—such as metabolic, proteomic, genomic, and transcriptomic profiling—provide deeper insights into the unique signatures of cancer cells.[22]

Despite the wide range of diagnostic options, challenges remain regarding clinical and cost-effectiveness, as well as strategies for evaluating risks and monitoring therapeutic responses. Imaging remains the most accessible and widely used diagnostic tool due to its non-invasiveness, making it suitable for cancer screening and staging and monitoring progression based on tumor-related phenotypic characteristics.

Conventional diagnostic methods are often complex, requiring lengthy multi-step laboratory procedures that may not be accessible to all communities. This limitation has sparked interest in developing point-of-care (PoC) tests that can detect clinically significant cancer biomarkers.[23] For instance, PoC diagnostic tools have been developed for cancers like prostate and breast, enabling the detection of disease-specific biomarkers with high specificity, low cost, ease of use, and accuracy.[24] These tests are particularly valuable for detecting low-concentration biomarkers in biological fluids, requiring highly sensitive diagnostic methods to distinguish between normal and cancer-related levels.

The use of whole-genome technologies in cancer diagnostics represents a major leap forward. Comparing the genetic sequence of a tumor DNA with that of a normal tissue can reveal specific mutations that drive cancer progression. Genome expression profiling further identifies differences in gene activity between the tumor and its tissue of origin.[25] However, data from such screenings are often complex, as multiple genetic mutations are usually present in any given tumor by the time it is detected. These mutations extend beyond the original genetic changes that initiated the cancer, as continuous mutation occurs as cancer cells divide.

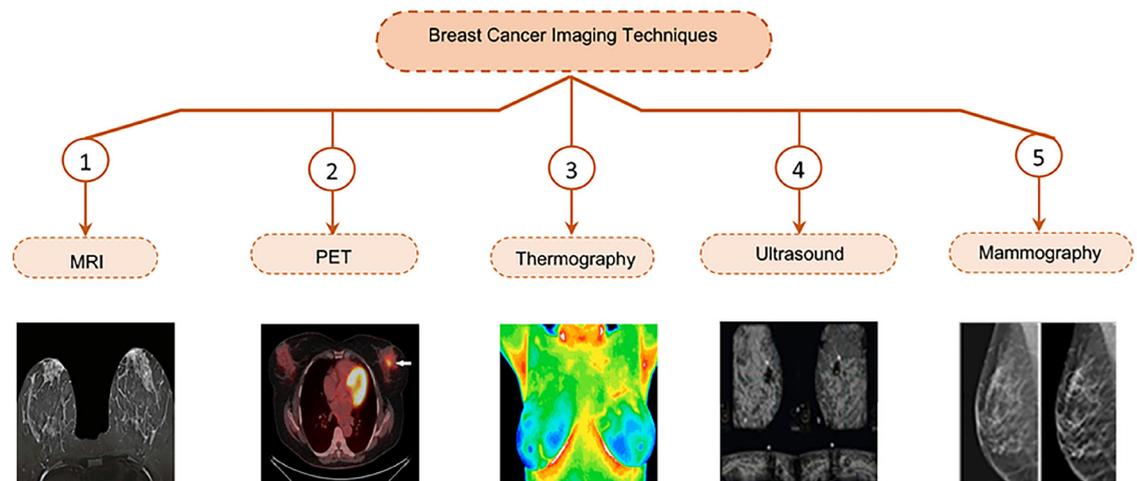In a typical tumor, numerous gene mutations and changes in gene expression are expected, which can

Fig 2 | Breast cancer imaging techniques

complicate diagnosis and therapeutic decision-making. Nevertheless, understanding these genetic alterations can help identify new therapeutic targets and improve our knowledge of cancer biology.

AINU: AI of the NUcleus

Researchers at the Centre for Genomic Regulation, the University of the Basque Country, the Donostia International Physics Center, and the Fundación Biofisika Bizkaia (based at the Biofisika Institute) have created an AI: the AI of the NUcleus (AINU), a revolutionary diagnostic tool to detect cancer cells and viral infections with nanoscale precision.[26] Developed to explore cellular phenotypic heterogeneity, the AINU provides insights into the structure of chromatin and its role in biological processes, such as cancer progression and viral infections. By combining advanced imaging techniques and DL, the AINU offers a novel approach to identifying subtle differences in cellular states, even at extremely early stages. The findings, published in the journal *Nature Machine Intelligence*, open the path for enhanced diagnostic techniques and disease monitoring systems.

Cellular phenotypic heterogeneity—variability in cell characteristics within the same tissue—plays a crucial role in many biological functions. It may arise from external factors, such as viral infections that significantly alter chromatin structure,[27,28] or from internal chromatin modifications themselves, which are often associated with cancer. For instance, most of the global adult population is seropositive for herpes simplex virus type 1 (HSV-1), indicating the widespread viral

influence on cell variability.[29,30] Understanding the chromatin arrangement in individual cells can reveal important details about cellular heterogeneity and potentially guide diagnostic efforts.

To investigate chromatin structure at the nanoscale, the researchers previously used single-molecule localization microscopy (SMLM) (Figure 3), specifically stochastic optical reconstruction microscopy (STORM). This approach enabled them to map out the nanoscale organization of chromatin fibers, discovering that nucleosomes tend to group together in clusters called clutches.[31] The density and number of nucleosomes per clutch serve as key indicators of a cell's state—whether it is a somatic cell or a stem cell.[31,32] Furthermore, active transcription sites were found to be enriched with RNA polymerase II (Pol II), which is essential for gene expression.[33] STORM also helped visualize variations in clutch-associated DNA compaction linked to different epigenetic states.[34]

AINU was developed as a CNN-based AI tool to analyze nuclear features at the nanoscale using minimal training data. CNNs have become the de facto standard for medical and health-care imaging applications, as well as computer vision.[35-39] By integrating SMLM with DL, AINU effectively identifies cellular heterogeneity and distinguishes between various cell states.[26] They utilized STORM imaging to capture the nanoscale distribution of Ser 5-phosphorylated RNA Pol II, histone H3, and DNA across different cell types, including human somatic cells, human-induced pluripotent stem cells (hiPSCs), HSV-1-infected cells, and cancer cells. AINU combines
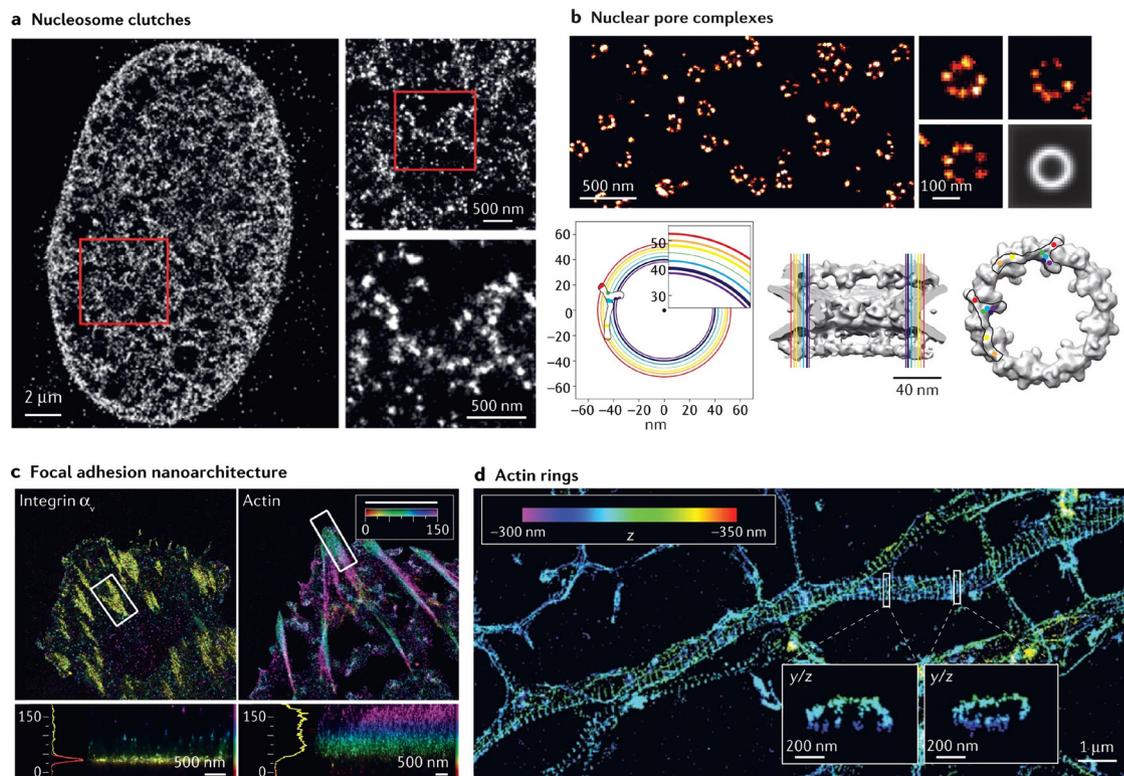
Fig 3 | High-resolution microscopy images demonstrate precise cellular structures, including chromatin, nuclear pore complexes, and cytoskeletal components, from SMLM

CNN algorithms with SMLM data, allowing it to detect small nuclear differences that traditional diffraction-limited imaging methods would miss.

AINU demonstrated an exceptional ability to accurately distinguish between different cell types within a heterogeneous sample. Using SMLM data collected from samples marked for Pol II, histone H3, or DNA, AINU achieved near-perfect accuracy in identifying somatic cells, hiPSCs, and HSV-1-infected cells at very early stages of infection, including just one hour post-infection (Figure 4). The tool's interpretable AI algorithms revealed that one key feature for identifying hiPSCs was the distinct spatial organization of Pol II within the nucleoli, a characteristic not observed in somatic cells.[26]

While most DL models require extensive training datasets based on whole-cell fluorescence intensity images, AINU benefits from super-resolution imaging data that captures the spatial distribution of nuclear structures with nanoscale precision.[40] By focusing on nuclear features such as the arrangement of core histones, Pol II, and DNA, AINU provides an innovative approach for training DL models. Future research may involve incorporating additional epigenetic markers, such as transcriptionally active or repressive histone modifications (e.g., H3Ac, H3K9me3, and H3K27me3), to enhance AINU's ability to classify precise cell-state heterogeneity more effectively.

AINU's training with SMLM data revealed its capacity to detect early signs of viral infections. For instance, HSV-1-infected cells showed differences in DNA density at the nuclear edge, consistent with compacted heterochromatin observed in somatic cells. These subtle changes allowed AINU to identify infected cells as early as one hour post-infection, even before the formation of viral replication compartments, which typically occur three hours post-infection.[26] This early detection capability suggests that AINU can recognize minute changes in chromatin structure associated with the virus's influence on the host cell's nuclear organization.

The interpretable AI analysis also showed that AINU distinguishes hiPSCs by recognizing Pol II's presence in the nucleoli, which is linked to increased transcription of certain non-coding RNAs. These RNAs, transcribed from intergenic regions near ribosomal RNA genes, may play a role in maintaining the nucleolar structure and cell integrity. This finding indicates that AINU can identify unique molecular signatures in specific cell types, which could aid in diagnostics.

Conclusion

The integration of AI into traditional diagnostic methods is transforming cancer and viral infection detection. New tools like AINU, which uses advanced imaging techniques and DL, are opening the way for more precise and non-invasive diagnoses. Traditional approaches such as imaging and histopathological evaluation remain crucial, but AI-powered techniques now provide nanoscale accuracy in recognizing the smallest cellular variations that are key for early diagnosis.

AINU is a significant breakthrough in the field of AI. It uses super-resolution microscopy and CNNs to detect cellular heterogeneity at the chromatin level, which is key for distinguishing between somatic cells, cancer cells, and virus-infected cells. The AI system's ability to recognize unique nuclear characteristics, such as the arrangement of Pol II within nucleoli, enables the reliable detection of hiPSCs and early-stage viral infections before significant morphological alterations occur. This specificity demonstrates AINU's ability to identify high-grade pluripotent stem cell clones and detect viral infections shortly after exposure.

These advancements in AI-powered imaging have significant implications for clinical practice. They pave the way for in-depth investigations into early-stage disease biomarkers and could reshape diagnostic protocols. By enabling earlier detection of diseases such as cancer and viral infections with nanoscale precision, tools like AINU may enhance personalized treatment plans and improve overall patient outcomes, marking
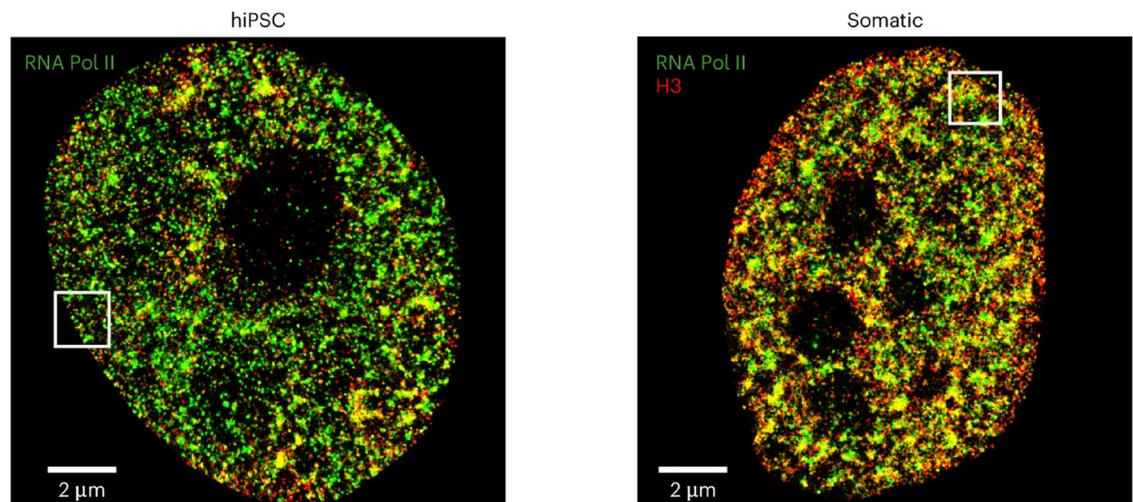
Fig 4 | AINU with high accuracy identifying somatic cells and hiPSCs

Image from: A deep learning method that identifies cellular heterogeneity using nanoscale nuclear features

a shift toward more proactive and targeted medical interventions.

Despite the remarkable accuracy, questions remain about how these technologies can be further optimized to differentiate more delicate or rare cellular states. Future research could explore integrating additional nuclear features or multimodal data sources to enhance diagnostic precision.

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