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Review Article

The 3D genome in medicine: Technological advances, disease mechanisms, and translational challenges

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ABSTRACT

Three-dimensional (3D) genome organization has reshaped our understanding of human disease by revealing regulatory mechanisms that cannot be explained by the linear genome alone. Rapid advances in chromosome-conformation technologies, single-cell genomics, spatial multi-omics and artificial intelligence have enabled increasingly precise characterization of genome architecture and uncovered common principles of chromatin dysregulation across diverse diseases. However, translating these discoveries into clinical practice remains challenging because of limited causal evidence, functional validation and standardized analytical frameworks. This review discusses recent technological advances in medical 3D genomics, summarizes the shared mechanisms of chromatin dysregulation in human diseases, and highlights emerging opportunities for molecular diagnosis, variant interpretation and therapeutic target discovery. It further examines the major challenges that must be overcome before genome architecture can be routinely integrated into precision medicine.

1. Introduction

Over the past two decades, three-dimensional (3D) genome research has evolved from the descriptive mapping of chromatin architecture to the mechanistic investigation of human disease. The 3D genome is organized across multiple spatial scales, including chromatin compartments,[1] topologically associating domains (TADs),[2] and chromatin loops,[3] which together shape long-range gene regulation. Increasing evidence indicates that disruption of genome architecture is not merely a consequence of altered transcription but can directly contribute to disease pathogenesis.[4] Structural variants that perturb chromatin topology and aberrant enhancer–promoter interactions have been implicated in developmental disorders, cancer, and other complex diseases.[5,6] More recently, advances in single-cell genomics, spatial multi-omics, and artificial intelligence (AI) have enabled cell-type-specific characterization of genome architecture.[7–9] These advances have expanded the capacity to interpret disease-associated non-coding variants, providing a stronger conceptual foundation for precision medicine.

Although genome-wide association study have identified numerous disease-associated loci, most variants lie in non-coding regions, making it difficult to identify their target genes and establish their functional consequences.[10] Traditional annotation commonly assigns non-coding variants to the nearest gene. However, the nearest gene does not necessarily correspond to the functional target, as distal enhancer–promoter communication is mediated by chromatin looping and constrained by TAD boundaries. By integrating chromatin interaction maps with epigenomic and transcriptomic information, 3D genomics links non-coding and structural variants to their target genes through spatial regulatory interactions. This framework provides mechanistic explanations for disease-associated variants that cannot be resolved by conventional linear genome analyses.

Despite these advances, no approved therapy currently enables locus-specific correction of disease-associated alterations in chromatin architecture. Although existing epigenetic therapies can modulate chromatin states and regulatory programs more broadly,[11,12] precise correction of pathogenic genome architecture remains largely experimental. At present, the principal clinical value of 3D genomics lies in improving the interpretation of non-coding and structural variants, uncovering disease mechanisms, and identifying candidate therapeutic targets. Nevertheless, ongoing advances in genome engineering, epigenome editing, and chromatin manipulation are progressively transforming genome architecture from a descriptive framework into a potential therapeutic dimension,[13] opening new opportunities for mechanism-guided intervention.

In this narrative review, we first summarize recent technological advances in medical 3D genomics, then discuss the common mechanisms of genome architecture dysregulation across human diseases, and finally highlight current opportunities and challenges for translating 3D genome knowledge into precision medicine.

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2. Technological advances in medical 3D genomics

2.1. From population-averaged maps to single-cell resolution

Bulk chromosome-conformation-capture approaches established the structural framework of the human genome. Hi-C enabled genome-wide identification of compartments, TADs, and chromatin loops,[1,3,14] while subsequent approaches such as Micro-C[15] and BL-Hi-C[16] improved the resolution and sensitivity of contact mapping through distinct experimental strategies. Targeted and protein-centric approaches, including Capture Hi-C,[17] ChIA-PET,[18] HiChIP,[19] and PLAC-seq,[20] further enriched interactions involving predefined genomic regions or specific regulatory factors, making them particularly useful for linking disease-associated regulatory elements to candidate target genes.[21] For example, promoter Capture Hi-C in human iPSC-derived cardiomyocytes linked 1999 cardiovascular disease-associated single nucleotide polymorphisms (SNPs) to 347 candidate target genes, with >90% of SNP–target interactions bypassing the nearest gene, illustrating the added value of cell-type-specific 3D contacts for interpreting non-coding disease loci.[22] However, such maps nominate regulatory targets rather than establish variant pathogenicity, and their interpretation remains dependent on the disease-relevant cell type and functional validation. At the population level, aggregation of signals across large numbers of cells provides relatively robust and reproducible maps, making bulk approaches well suited for identifying recurrent structural alterations across patient groups. Yet this population averaging obscures whether an interaction is ubiquitous, restricted to a particular cell type or confined to a rare pathological subpopulation, potentially diluting disease-relevant regulatory configurations associated with tumour subclones, transitional cell states or treatment-resistant populations and limiting the detection of clinically relevant cellular heterogeneity.

Single-cell methods have progressively addressed this limitation. The original single-cell Hi-C demonstrated extensive cell-to-cell variation in chromosome conformation, while combinatorial-indexing methods such as sci-Hi-C increased throughput sufficiently to classify cells according to their chromatin architecture. Dip-C combined high-coverage contact detection with haplotype imputation to reconstruct the maternal and paternal 3D genomes of individual diploid cells, thereby enabling analysis of allele-specific folding and nuclear organization. Other technologies extended single-cell measurements beyond pairwise contacts. sc-SPRITE captures multiway DNA interactions and long-range contacts organized around nuclear bodies,[23] whereas scNanoHi-C approaches use nanopore sequencing to recover long concatemers representing higher-order enhancer–promoter assemblies within individual cells.[24,25] Complementary to these sequencing-based approaches, spatial imaging directly measures the positions and physical distances of genomic loci within individual cells while preserving their nuclear context. Multiplexed DNA FISH and Oligopaint-based chromatin-tracing methods, including ORCA,[26] DNA-MERFISH,[27] and DNA seqFISH+,[28] have substantially expanded the number of loci that can be interrogated, enabling direct visualization of chromatin folding and cell-to-cell structural heterogeneity across genomic scales. Such approaches can additionally resolve spatial relationships with nuclear landmarks, including the nuclear lamina and nucleoli, which are not directly captured by proximity-ligation assays. Nevertheless, both sequencing- and imaging-based single-cell approaches face important trade-offs: sequencing-based methods are often limited by sparse per-cell contact coverage, whereas imaging approaches must balance genomic resolution, genomic coverage, imaging throughput, and experimental complexity. These constraints remain important barriers to their application in large patient cohorts.

More recently, single-cell 3D genomics has shifted from measuring chromatin contacts alone toward directly linking genome architecture with cellular function. HiRES[29] and GAGE-seq[30] simultaneously profile chromatin conformation and gene expression within the same cells, enabling changes in genome architecture and transcription to be jointly examined along developmental or differentiation trajectories and revealing that their reorganization can occur with distinct temporal dynamics. MUSIC simultaneously measures multiplex chromatin interactions, RNA expression, and RNA-chromatin associations, resolving cell-type-specific chromatin architectural states and alterations associated with ageing and Alzheimer's disease pathology in the human cortex.[31] Droplet Hi-C further improves scalability and has demonstrated more direct potential in tumour profiling.[32] In an IDH-wildtype glioblastoma sample, chromatin-architecture information separated malignant from non-malignant cells and identified tumour-associated copy number variations (CNVs), structural variations (SVs), and *EGFR*-containing extrachromosomal DNA (ecDNA). In bone-marrow cells from a patient with secondary acute myeloid leukaemia, *MYC*-containing ecDNA and associated long-range enhancer contacts detected before azacitidine-venetoclax treatment were no longer detectable after treatment, coinciding with clinical remission.[32] These examples illustrate the potential of single-cell 3D genomics to complement molecular classification and longitudinal treatment monitoring by resolving structural alterations within specific tumour subpopulations. However, current evidence is based largely on exploratory studies and small numbers of patient samples, and sparse contact coverage, cost, and the absence of standardized clinical pipelines currently limit diagnostic or treatment-guiding use (Fig. 1).

2.2. Computational and AI-assisted interpretation of 3D genomes

Conventional computational approaches have been essential for extracting, quantifying, and annotating structural features from experimentally measured chromatin-contact data, including compartments, domains, and chromatin interactions. AI-based approaches extend this framework toward predictive and inferential tasks, including learning sequence-regulatory relationships, predicting variant-induced changes in genome architecture, and inferring cell-specific chromatin organization from sparse or multimodal data. A major challenge is the interpretation of non-coding variation: although chromatin-interaction maps can connect distal regulatory elements with their target genes, distinguishing functional variants from millions of non-coding polymorphisms remains difficult. Early convolutional neural network models, including DeepSEA[33] and Basenji,[34] demonstrated that DNA sequence is predictive of chromatin accessibility, transcription factor binding, and epigenomic landscapes. More recently, transformer-based architectures such as Enformer[35] have extended predictive windows from kilobases to hundreds of kilobases, improving the modelling of distal regulatory effects and long-range sequence dependencies. The emergence of genomic foundation models, including AlphaGenome,[36] Evo,[37] and Evo2,[38] has further extended sequence modelling to megabase-scale genomic contexts, creating opportunities to investigate regulatory effects involving multiple sequence variants within a unified sequence framework. Integrative approaches have also begun to combine sequence-based deep learning with chromatin interaction data for variant interpretation. One integrative deep-learning framework combined DNA sequence with Hi-C data to predict the effects of single-nucleotide alterations on chromatin-interaction probabilities, with putatively functional variants showing enrichment in genome-wide association studies (GWASs) and expression quantitative trait locus (eQTL) datasets.[39]

AI has further extended variant interpretation from local regulatory activity to higher-order chromatin architecture, which is particularly important for SVs whose pathogenic effects arise from altered genome topology rather than direct disruption of coding sequences. Sequence-based models such as Akita[40] and DeepC[41] predict how deletions, inversions and boundary-associated sequence alterations reshape chromatin contact maps, enabling *in silico* assessment of TAD disruption and regulatory rewiring. Importantly, such models can generate experimentally testable predictions at disease-relevant loci. At the *LMO2* locus, DeepC recapitulated domain fusion caused by a ~30-kb deletion encompassing multiple CTCF sites and predicted that deletion of individual sites was insufficient to reproduce the

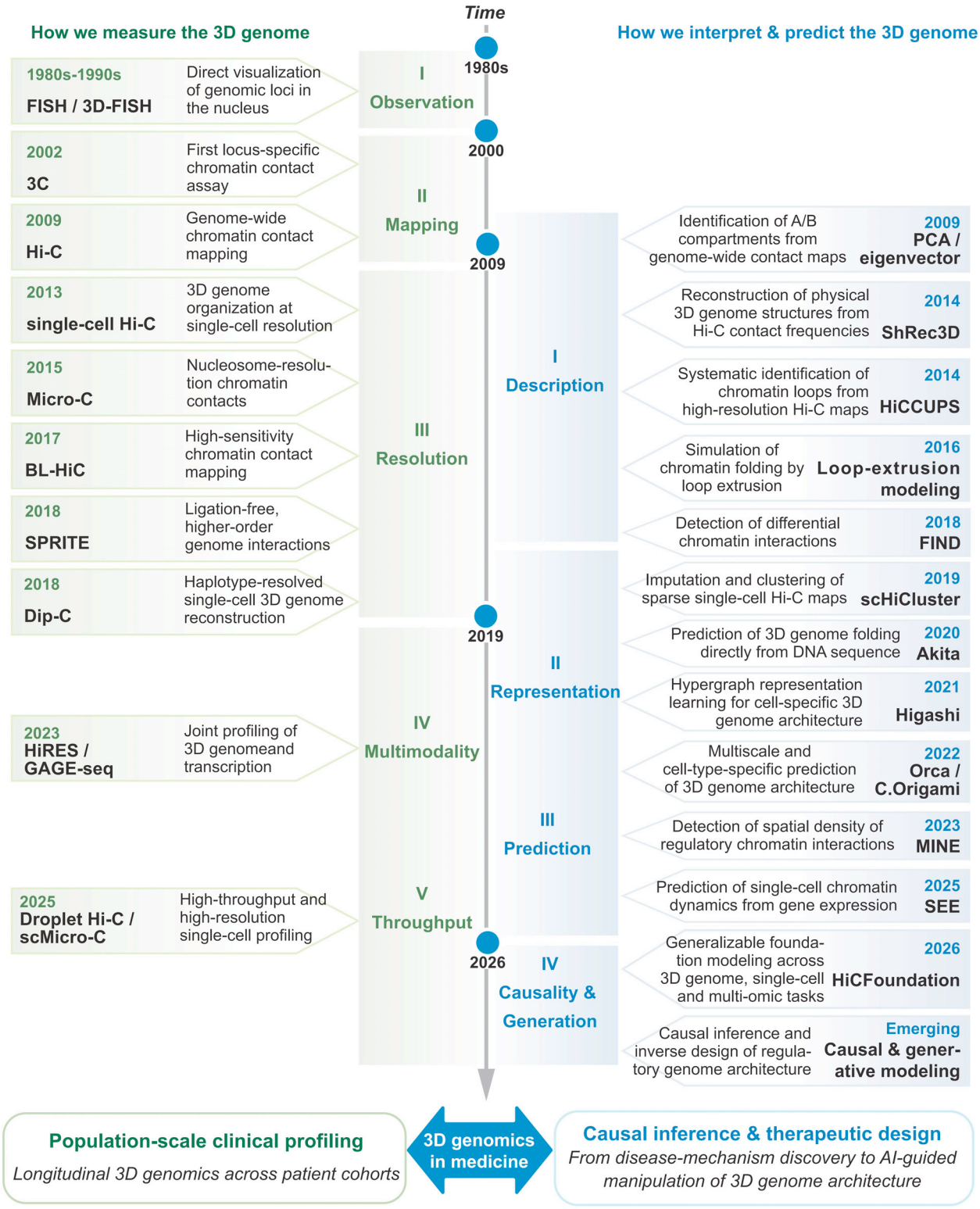


Fig. 1. Technological evolution of medical 3D genomics. The timeline summarizes representative advances in experimental measurement (left, green) and computational interpretation and prediction (right, blue) of 3D genome organization. Experimental technologies are grouped into five stages: (I) Observation, direct visualization of genomic loci; (II) Mapping, locus-specific and genome-wide chromatin-contact mapping; (III) Resolution, single-cell, high-resolution, ligation-free and haplotype-resolved measurements; (IV) Multimodality, joint profiling of genome architecture with transcriptional or other molecular features; and (V) Throughput, high-throughput single-cell profiling. Computational advances are grouped into four stages: (I) Description, identification and reconstruction of architectural features; (II) Representation, computational reconstruction and representation learning from sparse or cell-specific data; (III) Prediction, sequence- and machine-learning-based prediction of genome folding and regulatory interactions; and (IV) Causality and generation, emerging causal, generative and inverse modelling of genome architecture. Methods associated with specific years represent published advances, whereas "Emerging" and the bottom outlook boxes indicate prospective directions, including population-scale longitudinal profiling and mechanism-informed therapeutic design. FISH: fluorescence in situ hybridization; 3C: chromosome conformation capture; BL-Hi-C: bridge-linker Hi-C; SPRITE: split-pool recognition of interactions by tag extension; PCA: principal component analysis.

architectural defect, suggesting redundancy in boundary insulation.[41] The same framework linked the asthma-associated variant rs12936231 at the 17q21 *ORMDL3* locus to cell-type-specific loss of insulation and altered chromatin contacts, illustrating how a single non-coding variant can perturb 3D regulation.[41] These examples illustrate the potential added value of sequence-to-structure models for prioritizing non-coding or structural variants whose functional consequences may be missed by coding-focused annotation. However, predicted changes in chromatin architecture do not establish pathogenicity and require validation in the relevant cell type and, ideally, by genetic perturbation.

A further challenge is that disease-associated architectural alterations are often restricted to specific cell populations and can therefore be obscured in bulk contact maps. AI-based approaches are increasingly addressing this problem by learning cell-type-specific genome organization from sparse single-cell data. Methods such as SEE[42] and Higashi[43] further leverage representation learning and multimodal information to recover cell-specific regulatory or chromatin features from sparse single-cell data. Higashi uses hypergraph representation learning to reconstruct scHi-C maps and identified inhibitory-neuron-specific architecture around *GAD1* and an oligodendrocyte-specific boundary near *THBS2* in the human prefrontal cortex.[43] More recently, scGrapHiC integrated scRNA-seq with bulk Hi-C and architectural features to reconstruct cell-type-specific contact maps across developmental stages and tissues.[44] Collectively, whereas conventional computational methods primarily extract and quantify features from experimentally measured contact maps, AI-based approaches extend 3D-genome analysis toward variant-effect prediction, sequence-to-structure modelling, and cell-type-specific inference from sparse or multimodal data. These model-based predictions can reveal regulatory alterations obscured by bulk analyses but require experimental validation before mechanistic or clinical interpretation.

Taken together, current 3D-genome technologies provide complementary levels of medically relevant information: targeted interaction maps can improve variant-to-gene assignment, single-cell and multimodal approaches can resolve disease-associated cellular heterogeneity and treatment-related clonal dynamics, and AI models can prioritize variants and architectural alterations for functional testing. However, these applications remain predominantly investigational. Most studies involve limited patient cohorts, disease-relevant tissues are not always accessible, and neither experimentally observed nor computationally predicted chromatin contacts alone establish pathogenicity or clinical actionability (Fig. 1).

3. 3D genome dysregulation in human diseases

3.1. Common principles of 3D genome dysregulation across human diseases

Although the genetic and cellular origins of human diseases are remarkably diverse, accumulating evidence suggests that disease-associated perturbations of genome architecture converge on a limited set of recurrent architectural consequences. These include altered domain insulation, rewiring of enhancer–promoter communication and broader reorganization of higher-order chromatin environments. Such alterations can modify regulatory relationships between genes and distal cis-regulatory elements without necessarily disrupting protein-coding sequences.[5,45,46] Importantly, however, similar architectural abnormalities can arise through distinct upstream mechanisms and differ substantially in their causal contribution to disease. Thus, 3D-genome dysregulation is best viewed not as a single pathogenic mechanism, but as a set of shared regulatory consequences arising in the context of diverse genetic, epigenetic, and cell-state perturbations (Fig. 2).

At the local regulatory level, altered domain insulation and enhancer–promoter rewiring represent recurrent consequences of disease-associated genomic perturbations.[5,46] However, their origins and biological consequences are strongly context dependent. In developmental disorders, constitutive structural variants or boundary perturbations can misdirect enhancer activity during restricted developmental windows, whereas in cancer, somatically acquired rearrangements can create or reinforce oncogenic regulatory interactions that may subsequently be subject to clonal selection.[45,46] Regulatory rewiring can also extend beyond individual enhancer–promoter pairs to higher-order enhancer hubs and transcriptional condensates.[48] Conversely, redundancy among CTCF sites and cis-regulatory elements can buffer some architectural perturbations,[4,49] helping to explain why apparently similar structural alterations can produce different transcriptional and phenotypic consequences across cell types and developmental contexts.

At broader scales, architectural dysregulation can involve perturbation of genome-folding machinery as well as changes in compartment organization and chromatin positioning relative to nuclear landmarks.[50–53] Germline defects affecting CTCF, cohesin or its regulatory machinery provide genetic examples in developmental syndromes,[51,52] whereas broader compartment and nuclear reorganization can accompany changes in cell identity and cellular state.[50,53] These distinctions are important when interpreting disease-associated 3D-genome alterations. Developmental disorders often involve constitutive genetic lesions acting within specific developmental windows,[5,54,55] whereas cancers frequently acquire somatic architectural rewiring that can be further shaped during tumour evolution and therapeutic adaptation.[46,56–58] By contrast, immune, neurological, and metabolic diseases more often exhibit state- or environment-associated architectural remodelling,[59–61] for which causal contributions to disease progression remain less consistently established. Thus, similar changes in insulation, regulatory connectivity or higher-order organization across diseases do not necessarily imply equivalent pathogenic mechanisms or levels of causal evidence (Fig. 2).

3.2. Developmental abnormalities and congenital disorders

Embryonic development is sensitive to perturbations of 3D genome architecture because precise spatiotemporal gene expression relies on accurately coordinated enhancer–promoter communication.[5,49] During organogenesis, developmental genes are often regulated by multiple distal enhancers that are insulated within TADs, restricting inappropriate enhancer access to non-cognate promoters.[62] Disruption of this spatial organization frequently results in developmental disorders despite intact protein-coding sequences.[52,63] Consequently, congenital disorders provide some of the clearest examples in which pathogenicity arises from altered genome topology rather than direct disruption of protein-coding sequence.[64] This concept, commonly referred to as a position effect,[65] has fundamentally reshaped the interpretation of structural variants in clinical genetics by showing that genomic rearrangements may alter regulatory architecture without directly disrupting genes.

Among the best-characterized mechanisms is disruption of TAD boundaries, which permits enhancers to ectopically activate neighboring developmental genes that are normally insulated from their regulatory influence.[66] The *Wnt6/Ihh/Epha4/Pax3* locus represents a paradigm for this mechanism: deletions, inversions, and duplications that alter TAD boundaries generate ectopic enhancer–promoter interactions and cause distinct limb malformation syndromes, including brachydactyly, F-syndrome, and polydactyly, without directly disrupting the relevant developmental genes.[5] Similar regulatory mechanisms have been identified at other disease-associated loci, including *SOX9*,[67,68] *TWIST1*,[69] and *MEF2C*,[70,71] where structural variants can reposition or disconnect distal regulatory elements and alter local chromatin architecture, leading to skeletal, craniofacial and neurodevelopmental disorders. Related 3D regulatory mechanisms have also been described at the *LMNB1* locus in adult-onset leukodystrophy.[72,73] Beyond isolated developmental loci, high-resolution mapping of *Hox* clusters has shown that their spatiotemporal activation is accompanied by dynamic chromatin reorganization and sequential CTCF–cohesin-mediated insulation;[74] perturbation of these boundaries can derepress inappropriate *Hox* genes and produce homeotic transformations.[75] Furthermore,

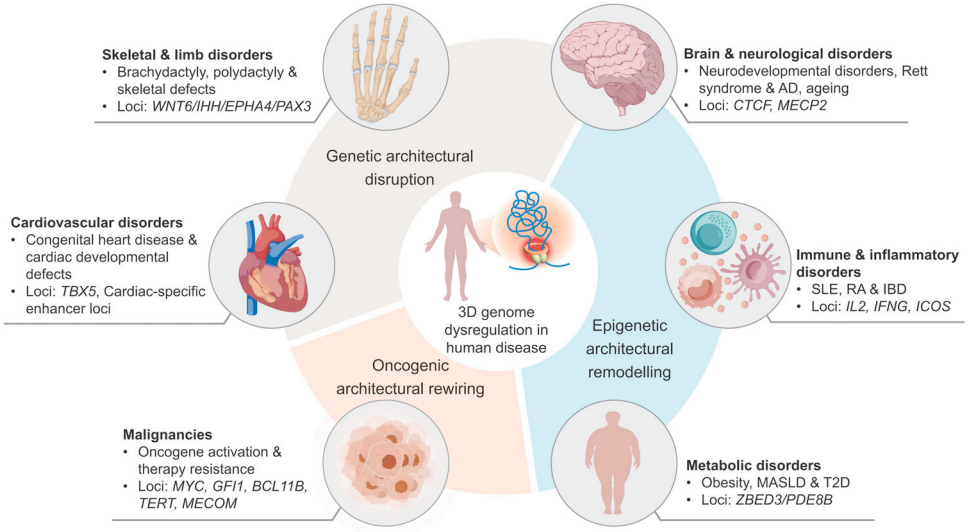


Fig. 2. Major patterns of 3D genome dysregulation in human disease. Disease-associated alterations in 3D genome organization are summarized into three broad, overlapping mechanistic patterns. Genetic architectural disruption primarily involves germline or constitutive alterations that perturb regulatory elements, chromatin contacts or domain insulation, as illustrated by developmental disorders. Oncogenic architectural rewiring encompasses somatically acquired alterations in cancer, including enhancer hijacking and aberrant regulatory interactions associated with tumour progression and therapeutic resistance. Epigenetic architectural remodelling refers to changes in genome organization associated with altered epigenetic or cellular states in neurological, immune/inflammatory and metabolic diseases. These categories are not mutually exclusive, and individual diseases may involve overlapping genetic, somatic, epigenetic, and state-dependent mechanisms. Representative loci illustrate examples discussed in the text and do not imply one-to-one causal relationships with the corresponding disease categories. AD: Alzheimer's disease; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; IBD: inflammatory bowel disease; MASLD: metabolic dysfunction-associated steatotic liver disease; T2D: type 2 diabetes. Some graphical elements were obtained from GDP.[47]

recent rare-disease whole-genome sequencing and functional genomic studies indicate that pathogenic regulatory disruption is not restricted to large structural variants.[76] Small-scale non-coding variants can also disrupt developmental regulation through distinct mechanisms. Functional screening of de novo non-coding variants in congenital heart disease identified variants that altered cardiac enhancer activity, with selected variants further affecting nearby gene expression in iPSC-derived cardiomyocytes.[77] Similarly, cell-type-aware functional annotation can facilitate the nomination of non-coding variants affecting developmental regulatory elements in Mendelian disorders.[78] At the architectural level, in vivo perturbation of individual or clustered CTCF-binding sites at the *Epha4–Pax3* boundary demonstrated cooperative insulation, with progressive boundary disruption altering chromatin interactions, gene expression and developmental phenotypes.[55] Together, these studies show that non-coding alterations can disrupt developmental gene regulation through both enhancer activity and chromatin insulation, with their consequences shaped by cell type, genomic context, and developmental context.

Recent studies further indicate that developmental phenotypes cannot be understood solely from static snapshots of chromatin architecture.[79] The pathogenic consequences of variants affecting genome architecture are highly dependent on developmental timing, tissue context and cell identity.[80] Congenital heart disease provides a recent example, with reduced *TBX5* dosage disrupting 3D genome organization during cardiomyocyte differentiation.[54] Single-cell 3D genome and spatial multi-omic studies increasingly reveal that regulatory architecture is highly dependent on cell identity and developmental stage, suggesting that the consequences of disease-associated variants may emerge only in specific progenitor populations or developmental windows.[79,80] To functionally validate these highly context-dependent regulatory mechanisms, human pluripotent stem cell-derived organoids and embryonic developmental models are increasingly being combined with CRISPR genome engineering and single-cell multi-omics to reconstruct disease-associated chromatin rewiring *in vitro*.[74,81,82] These findings have shifted the field from viewing congenital disorders as simple consequences of boundary disruption toward a dynamic model in which genome topology, developmental trajectories and cell-state-specific regulatory programs jointly shape disease phenotypes and susceptibility. Such a framework is also reshaping clinical diagnostics by improving the interpretation of non-coding variants and structural rearrangements that are frequently overlooked by conventional sequence-based analyses.[83]

3.3. *Tumour initiation, progression, and therapeutic resistance*

During cancer development, chromatin architecture can undergo dynamic, stage-specific remodelling that accompanies the acquisition of malignant transcriptional programs.[84] One of the best-established mechanisms is enhancer hijacking, in which structural variants reposition active elements to ectopically activate oncogenes such as *MYC*,[85] *GFI1*,[86] *BCL11B*,[87] *TERT*[88] and *MECOM*.[89] In parallel, focal amplifications, inversions and translocations generate new chromatin domains (neo-TADs) or remodel pre-existing chromatin loops.[57] Rather than acting through isolated pairwise contacts, oncogenic transcription can also be organized through higher-order enhancer–promoter hubs[58] and transcriptional condensates,[90,91] which concentrate regulatory factors at super-enhancer-associated loci and support robust transcriptional programs. Large-scale profiling of primary human cancers has identified three archetypes of enhancer usage, namely static, selective gain and dynamic rewiring, while longitudinal and stage-resolved studies further show that 3D genome organization changes during tumour progression.[84,92] Beyond sustaining cell-autonomous oncogene expression, regulatory rewiring can also facilitate therapeutic adaptation through progressive chromatin reprogramming and reinforcement of stress-response programs.[92] Together, these findings link 3D-genome reorganization to tumour evolution, with perturbation studies at selected loci providing evidence that specific architectural alterations can contribute causally to malignant phenotypes.

3D genome reorganization may represent one mechanism through which cancer cells remodel transcriptional programs during the acquisition of therapeutic resistance,[58] consistent with broader evidence that non-genetic epigenetic plasticity supports adaptive cell-state

transitions during cancer therapy.[56] Single-cell studies further suggest that resistance involves both selection of pre-existing cell states and treatment-associated remodelling of chromatin and transcriptional programs. Recent single-cell 3D-genome analyses have identified treatment-associated architectural changes, including remodelling of ecDNA organization in glioblastoma.[32] Acquired resistance can also involve reorganization of enhancer–promoter networks[58] or alternative regulatory strategies that preserve transcription despite disruption of distal regulatory contacts.[93] An emerging paradigm is provided by ecDNA, whose circular and non-chromosomal organization facilitates extensive enhancer rewiring and the formation of transcriptionally active ecDNA hubs.[94] Because ecDNA is not constrained by conventional chromosomal domain organization, regulatory elements on distinct circular amplicons can engage in unusually permissive intermolecular interactions, promoting high oncogene expression, intratumoral heterogeneity and rapid adaptation under therapeutic pressure.[95,96] In parallel, recurrent alterations in chromatin-remodelling complexes, particularly the SWI/SNF (BAF) family,[97] reshape enhancer accessibility and regulatory organization and create context-specific dependencies that can be therapeutically exploited through synthetic-lethal strategies.[98,99] Collectively, these findings suggest that therapeutic resistance may involve remodelling of the cancer regulatory architecture alongside genetic selection and epigenetic adaptation. Integrating single-cell 3D genomics with spatial and functional multi-omics may therefore provide a powerful framework for identifying predictive biomarkers and context-specific therapeutic vulnerabilities.

3.4. Immune, neurological, and metabolic diseases

Immune, neurological, and metabolic diseases often involve cell-state- and environment-responsive remodelling of genome architecture, in addition to constitutive genetic or structural lesions. In immune cells, lineage differentiation and activation are accompanied by extensive reorganization of enhancer–promoter contacts and regulatory hubs that coordinate cytokine production and inflammatory responses.[60,100] Non-coding risk variants for systemic lupus erythematosus,[101] rheumatoid arthritis,[102] and inflammatory bowel disease[103] are frequently enriched in cell-type-specific regulatory elements, with some exhibiting stimulus-dependent activity such that their functional effects and target genes become apparent only in the relevant immune cell type or activation state. In innate immunity, transient stimulation can also produce long-lasting epigenetic and metabolic reprogramming.[104] Persistent enhancer–promoter contacts at selected inflammatory loci may provide a structural substrate for transcriptional memory,[105] although the persistence and generality of such 3D “topological memory” remain to be established across immune cell types and disease contexts.

The nervous system depends on dynamic genome organization to support neuronal maturation and activity-dependent gene regulation.[106,107] Congenital disruption of CTCF,[52] cohesin,[108] or MeCP2[109,110] can impair neural development, whereas post-mitotic neurons require cohesin-dependent long-range chromatin contacts to maintain neuronal maturation and cell-type-specific transcriptional programs.[108] During ageing and neurodegeneration, 3D genome organization shows widespread and cell-type-specific dysregulation.[31] Single-cell multiplex profiling of the ageing human cortex showed that reduced short-range chromatin interactions correlated with older transcriptional states and Alzheimer’s disease pathology, while cell-type-specific chromatin contacts between cis-eQTLs and promoters helped link regulatory variants to their target genes.[31,61] These observations indicate age- and disease-associated remodelling of neuronal and glial genome organization, although whether such changes contribute causally to neurodegeneration or arise secondarily from disease progression remains unresolved.

Metabolic tissues also exhibit dynamic 3D-genome remodelling in association with nutritional, hormonal, and circadian states.[59,111,112] In hepatocytes,[59] adipocytes,[111] and pancreatic β cells,[113,114] changes in enhancer–promoter connectivity are associated with metabolic gene programs involved in lipid handling, thermogenesis, and insulin secretion. At the locus level, thermogenic stimulation is accompanied by altered enhancer–promoter looping at *Ppargc1a* and *Ucp1*,[111] whereas human pancreatic-islet 3D maps connect T2D-associated regulatory elements with candidate target genes, including *PDE8B* at the *ZBED3* locus.[113] However, these architectural changes have largely been observed alongside altered metabolic states, and whether they act as causal drivers or consequences of metabolic dysfunction remains unclear.

Collectively, these findings identify context-dependent genome reorganization as a shared feature of chronic immune, neurological, and metabolic diseases, while emphasizing the need for longitudinal single-cell 3D genomics to distinguish transient adaptation, persistent regulatory memory, and irreversible architectural deterioration.

4. From mechanistic insights to clinical translation

4.1. 3D genome-guided precision diagnosis and therapy

One of the most immediate clinical applications of 3D genomics is the interpretation of non-coding and structural variants that remain unresolved after conventional genetic testing.[4,115] Rather than assigning a variant to the nearest gene, chromatin-contact maps identify the promoters, enhancers, and insulated domains that may be affected in the disease-relevant cell type.[22,116,117] This approach is particularly valuable for balanced translocations, inversions, and copy-number variants whose pathogenic effects arise through boundary disruption, enhancer adoption, or neo-TAD formation rather than direct gene interruption.[4,64,118] Long-read sequencing has substantially improved the detection, breakpoint resolution, and phasing of complex structural variants,[119,120] whereas Hi-C, promoter-capture Hi-C, and targeted conformation assays can provide complementary spatial information for prioritizing affected regulatory elements and target genes.[17,121] In previously unsolved rare-disease cases, long-read and structural-variant analyses can uncover cryptic genomic rearrangements that become mechanistically interpretable when combined with patient-specific 3D genome mapping and functional assays. For example, a balanced t(6;18) translocation underlying central iris hypoplasia was shown by patient-derived Hi-C to create ectopic interactions between chromosome 6 enhancers and *APCDD1* on chromosome 18,[118] whereas a 149-kb interchromosomal insertion causing hereditary spastic paraplegia was demonstrated through patient-derived iPSCs, neural differentiation, Hi-C, and CRISPR perturbation to rewire the *SOX3* regulatory domain.[65]

Beyond variant interpretation, 3D genome profiles may support molecular classification, prognosis, and treatment selection. Tumours with similar histopathological features can exhibit distinct enhancer–promoter networks, compartment states, and structural-variant-driven regulatory dependencies.[92,122] Integrated conformation, accessibility, and transcriptomic analyses have identified subtype-specific architecture in acute myeloid leukaemia,[122] bladder cancer,[123] metastatic prostate cancer,[124] and colorectal cancer (CRC),[84] revealing regulatory features that are not captured by coding-mutation profiles alone. Targeted chromosome-conformation assays, including EpiSwitch-based signatures, offer a potentially more scalable biomarker strategy than genome-wide conformation profiling. In prostate cancer, a blood-based Prostate Screening EpiSwitch (PSE) test integrating chromosome-conformation markers with continuous prostate-specific antigen (PSA) was developed and tested using samples from 109 men in the PROSTAGRAM screening pilot and 38 additional samples from an Imperial College NHS cohort, achieving 86% sensitivity and 97% specificity in the 101-sample test cohort.[125] A subsequent single-centre real-world study of 187 men undergoing prostate-cancer evaluation further examined its clinical utility, although biopsy confirmation was available for only 53 patients and outcomes in the remaining 134 were assessed by predictive modelling.[126] In CRC, EpiSwitch NST was evaluated in 325 individu-

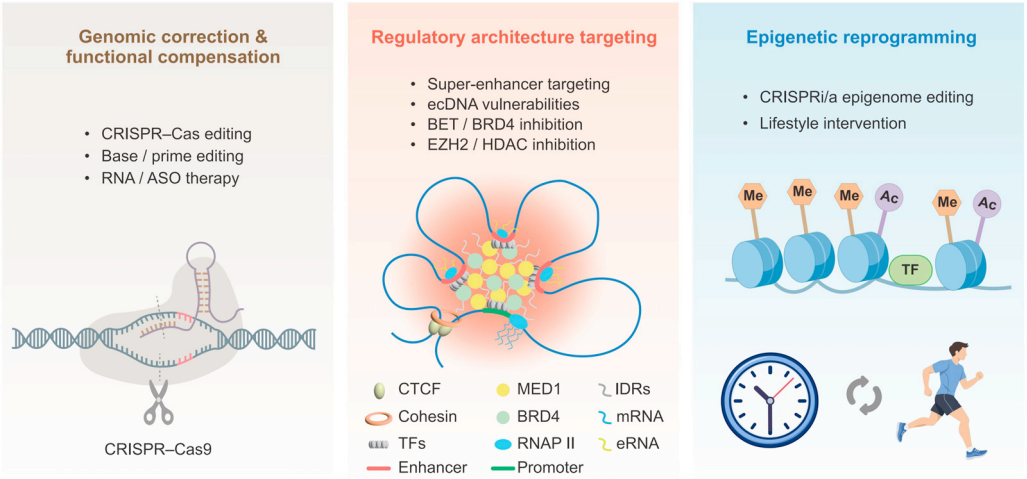


Fig. 3. Therapeutic strategies for 3D-genome-associated disease mechanisms. Therapeutic approaches informed by disease-associated 3D-genome alterations are grouped into three broad categories. Genomic correction and functional compensation includes genome editing to correct causal genetic lesions and RNA- or ASO-based strategies to mitigate downstream consequences. Regulatory architecture targeting exploits regulatory dependencies associated with aberrant genome organization, including super-enhancer- and extrachromosomal DNA (ecDNA)-associated vulnerabilities. Epigenetic reprogramming encompasses programmable modulation of regulatory or epigenetic states, including CRISPR interference/activation (CRISPRi/a) and epigenome editing. Lifestyle intervention is included as a prospective direction; whether it can reproducibly remodel disease-associated 3D-genome architecture for therapeutic benefit remains unclear. These categories represent broad therapeutic modalities and do not necessarily imply direct effects on chromatin topology; direct approaches such as synthetic chromatin looping and engineered insulation represent largely preclinical proof-of-concept strategies. CRISPR: clustered regularly interspaced short palindromic repeats; ASO: antisense oligonucleotide; ecDNA: extrachromosomal DNA; BET: bromodomain and extraterminal domain; BRD4: bromodomain-containing protein 4; EZH2: enhancer of zeste homolog 2; HDAC: histone deacetylase; CTCF: CCCTC-binding factor; MED1: mediator complex subunit 1; TF: transcription factor; RNAP II: RNA polymerase II; IDR: intrinsically disordered region; mRNA: messenger RNA; eRNA: enhancer RNA.

als comprising 171 patients with CRC, 44 with colorectal polyps, and 110 colonoscopy-negative controls; a blinded validation of 251 samples achieved 90% sensitivity and 79% specificity for CRC, with 84% sensitivity for stage I–II disease.[127] Beyond diagnosis, EpiSwitch-derived chromosome-conformation signatures have also been investigated as predictive biomarkers for immune-checkpoint inhibitor response across multiple tumour types,[128] with subsequent interim evaluation of the CiRT assay in an ongoing prospective real-world study of 205 patients with advanced solid tumours.[129] Collectively, these studies illustrate the potential of targeted 3D-genome signatures for blood-based diagnosis, patient stratification, and treatment selection. However, differences in study design, selected or enriched patient populations, and limited prospective validation constrain the generalizability of the reported findings. Larger independent prospective studies in intended-use populations, together with direct comparisons against established biomarkers where appropriate, are therefore required to establish clinical utility.

3D-genomics-guided precision therapy represents a more experimental extension of this framework. Disease-associated alterations in genome organization may inform therapeutic strategies at several levels (Fig. 3). Genetic lesions that drive pathogenic regulatory rewiring could, in principle, be corrected using CRISPR–Cas, base or prime editing, whereas RNA- or ASO-based approaches may mitigate downstream molecular consequences without necessarily restoring the underlying chromatin architecture. In cancer, 3D-genome maps can reveal regulatory dependencies with potential therapeutic relevance, including SV-driven enhancer hijacking in CRC,[130] hyperconnected oncogenic hubs in glioblastoma,[131] and *KLF5*-dependent 3D transcriptional programs with BRD4 vulnerability in epithelial cancers.[132] These dependencies may be perturbed genetically through CRISPR interference[133] or dCas9-based epigenome editing,[134] or pharmacologically through inhibitors of BET proteins, transcriptional CDKs or chromatin-remodelling machinery.[135,136] Such approaches primarily target regulatory machinery or transcriptional consequences associated with aberrant genome organization and should therefore be distinguished from direct manipulation of chromatin topology. Synthetic chromatin looping[137,138] and CTCF-based engineering of chromatin insulation[66,139] provide more direct proof-of-concept strategies for modifying regulatory contacts or domain insulation, although their therapeutic application remains at an early stage. Lifestyle interventions may also influence epigenetic and chromatin states, but whether they can reproducibly modify disease-associated 3D-genome architecture for therapeutic benefit remains unclear. Thus, the near-term translational value of 3D genomics lies primarily in identifying disease-associated regulatory dependencies and candidate therapeutic targets, whereas direct and controllable correction of pathogenic genome architecture remains largely preclinical.

4.2. *Technical bottlenecks and future clinical challenges*

Despite remarkable technological advances, several fundamental challenges must be overcome before 3D genomics can become a routine component of precision medicine. The first major barrier is distinguishing causal architectural alterations from secondary changes associated with cell state or transcription.[4,140] Differences in compartments, TAD insulation, or chromatin loops between diseased and healthy tissues do not by themselves demonstrate that altered folding drives pathology. Robust causal inference is strengthened by allele-specific analyses, temporal profiling, and targeted perturbation, ideally followed by rescue of both gene expression and phenotype. This is particularly important for structural variants, because variants with similar breakpoint locations may produce distinct regulatory consequences depending on enhancer activity, developmental stage, and cellular context. Encouragingly, pooled CRISPR perturbation platforms coupled with single-cell transcriptomic and epigenomic readouts, including Perturb-seq and newer multi-omic extensions, now enable high-throughput functional interrogation of genes and regulatory elements, accelerating the transition from correlation to causality.[141,142] Nevertheless, functional validation in patient-derived cells, organoids, and appropriate animal models remains critical before topology-based evidence can be incorporated into clinical variant interpretation.

The second challenge lies in measurement and clinical applicability. Clinical biopsies are frequently small, heterogeneous, fixed or collected after treatment, whereas high-resolution chromosome-conformation

assays require substantial sequencing depth and carefully controlled sample preparation. Although low-input Hi-C, single-cell Hi-C, and Micro-C continue to improve resolution and sensitivity, single-cell contact maps remain highly sparse,[32] limiting robust identification of chromatin loops and TADs in individual cells. More importantly, much of our current understanding of human genome architecture still derives from immortalized cell lines or experimental model systems rather than primary patient tissues. Future studies should therefore increasingly prioritize primary cells, patient-derived organoids, and clinically annotated disease cohorts. Interpretation of disease-associated chromatin architecture should also be integrated with genotype, CNV, DNA methylation, chromatin accessibility, and transcriptomic and proteomic data, rather than relying on chromosome-conformation information alone. Computational imputation can partially compensate for sparse datasets, but predictions remain dependent on model assumptions. Standardized experimental protocols, quality-control metrics, reference datasets, and prospective multi-centre benchmarking will therefore be essential for translating 3D genome profiling into reproducible clinical practice.

Finally, successful clinical implementation requires not only technological improvements but also rigorous evidence that 3D genome information provides actionable value beyond conventional genomics. Reference maps must adequately capture genetic ancestry, developmental stage, tissue specificity, and treatment history, while AI models require extensive external validation to minimize batch effects and population bias. Large longitudinal patient cohorts will also be indispensable for identifying the determinants of genome architectural integrity and distinguishing pathogenic chromatin remodelling from normal inter-individual variation during disease initiation, progression, and therapeutic response. Therapeutic manipulation of genome topology presents additional challenges because a single chromatin boundary or architectural protein often regulates multiple genes, raising concerns regarding unintended regulatory rewiring, mosaic editing, and long-term safety. Consequently, the near-term priority is not routine patient-wide Hi-C profiling or direct correction of TAD architecture, but the standardized, targeted, and functionally validated integration of 3D genome information into selected clinical scenarios where conventional genomic analyses remain insufficient.

5. Conclusions

3D genomics has transformed our understanding of how genetic variation contributes to human disease. These advances have highlighted the role of 3D genome organization in gene regulation and cellular identity, with important implications for understanding disease susceptibility. By revealing physical interactions between distal regulatory elements and their target genes, 3D genomics has improved the interpretation of non-coding and structural variants that cannot be explained by the linear genome alone. Evidence from developmental disorders, cancers, and chronic diseases further demonstrates that the consequences of architectural perturbation are highly context dependent, with distinct spatial and temporal characteristics across development, tumor evolution, and disease progression. Together, these advances have moved the field beyond descriptive chromatin maps toward a mechanistic and increasingly predictive understanding of how genome architecture contributes to human disease.

Recent technological innovations are accelerating this transition. Single-cell and spatial 3D genomics, long-read sequencing, and AI are enabling increasingly comprehensive characterization of genome architecture across cell types, developmental stages, and disease states. Combined with pooled CRISPR perturbation and single-cell multi-omics, these approaches are beginning to bridge the gap between association and causation. Future efforts will increasingly move beyond static descriptions of chromatin folding toward quantitative models of 4D genome dynamics that predict how regulatory architecture evolves across development, ageing and disease progression. Integrating these models with longitudinal patient cohorts encompassing genetic variation, genome architecture, and clinical phenotypes will be critical for defining the principles governing architectural stability and its disruption across diverse human populations.

Although direct therapeutic manipulation of chromatin topology remains largely at the proof-of-concept stage, the translational potential of 3D genomics is becoming increasingly evident. In the foreseeable future, its greatest clinical impact is likely to arise from improving molecular diagnosis, refining patient stratification, identifying context-specific therapeutic targets, and guiding precision interventions through the integration of spatial genome information with genomic and epigenomic medicine. Ultimately, the next frontier of precision medicine may extend beyond reading genome sequence to understanding how its 3D regulatory architecture shapes disease and, eventually, learning how to manipulate that architecture with sufficient precision and safety. As experimental genomics converges with advances in AI and genome engineering, 3D genomics has the potential to provide an increasingly powerful framework for mechanistically informed diagnosis, patient stratification, and therapeutic target discovery.

Authors' contributions

Yong-Li Bao: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. Ming-Hong Li: Writing – review & editing. Xue-Yuan Li: Writing – review & editing. Yang Chen: Supervision, Funding acquisition, Conceptualization.

Declaration of generative AI and AI-assisted technologies use

During the preparation of this work, the authors used ChatGPT to assist with language editing and translation. After using this tool, the authors closely reviewed and edited the content as needed and take full responsibility for the final content of the publication.

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Conflict of interest disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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