SIN-CHN SCIENTIFIC PRESS PTE.LTD.

Molecular & Cellular Biomechanics 2024, 21(4), 832.
https://doi.org/10.62617/mcb832

Article

Unraveling molecular mechanisms in growth plate development advancing pediatric orthopedic interventions

Ningjing Zeng[1], Ningzhi Yu[1], Chuyu Huang[1], Peng Yang[2], Guangxi Chen[2], Yan Liu[2,*]

[1] The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou 501405, China
[2] Department of Sports Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510120, China
*** Corresponding author:** Yan Liu, liuyanguke008@126.com

CITATION

Zeng N, Yu N, Huang C, et al. Unraveling molecular mechanisms in growth plate development advancing pediatric orthopedic interventions. Molecular & Cellular Biomechanics. 2024; 21(4): 832. https://doi.org/10.62617/mcb832

ARTICLE INFO

Received: 19 November 2024
Accepted: 4 December 2024
Available online: 27 December 2024

Abstract: Dynamic Growth Plate based on Molecular Profiling (DGMP) represents a pioneering approach to understanding the intricate molecular processes governing growth plate development, essential for advancing pediatric orthopedic treatments. Growth plates, located at the ends of long bones, are pivotal for bone elongation during childhood and adolescence, but disruptions in their molecular and cellular regulation can result in developmental abnormalities and orthopedic deformities. DGMP integrates genomic, transcriptomic, proteomic, and epigenomic analyses to uncover cell-specific expression patterns and regulatory elements critical to growth plate formation. By leveraging high-throughput sequencing, single-cell RNA (Ribonucleic Acid) sequencing, and spatial transcriptomics, DGMP facilitates the identification of diagnostic biomarkers and enables the development of targeted pharmacological therapies tailored to children with defective growth plates. Furthermore, in silico models simulating cellular differentiation and pathway interactions provide predictive insights into the long-term effects of interventions on bone development. This innovative framework not only enhances early and accurate detection of growth-related disorders but also supports the design of personalized treatments, ultimately improving clinical outcomes for affected children. As a precision medicine tool, DGMP has the potential to transform pediatric orthopedics by resolving challenges related to molecular data integration, spatiotemporal dynamics, and therapeutic application, thereby advancing the understanding and treatment of growth plate disorders.

Keywords: unraveling; molecular mechanisms; growth plate; development; advancing; pediatric orthopedic interventions

1. Introduction

The molecular processes in growth plate formation have been investigated through histological observation, direct hybridization, and immunohistochemistry [1]. Through histology, the pictures of the growth plate structures, cellular arrangements, and tissue morphologies were reported, indicating the variations of chondrocyte distribution across growth plate zones [2]. Hybridization and immunohistochemistry in situ could be able to detect and locate the gene expression as well as protein localization through the detection of signalling molecules such as growth factors and transcription factors [3]. These technologies have the advantages but cannot solve complex molecular problems. They are not precise in the temporal and dynamics to write down the processes within cells or changes in molecular signalling due to mechanical pressure or hormone fluctuations [4]. These require considerable hands-on work, and a specialist's experience is required; hence these are not very scalable, and not of very high throughput for large analyses [5]. Knock-out models and other

traditional genetic methods have improved our knowledge they disrupt global gene expression rather than providing tissue-specific or conditional information [6], which can cause unclear developmental consequences. The lack of molecular resolution is a fundamental drawback, making it challenging to dissociate relationships in complex growth plate signaling networks [7]. Thus, these traditional explanations are unable to explain the pathophysiology of growth plate injuries and abnormalities in children or the complex molecular pathways that drive their development [8]. Solving these problems requires recent imaging and molecular biology advances. These advances may enable more precise and effective pediatric orthopedic therapies [9].

Growth plate biology is dynamic and complex, making it difficult to comprehend the molecular mechanics of growth plate development to develop orthopedic treatments for children [10]. Understanding chondrocyte proliferation and differentiation is complicated by complex cellular signaling networks that involve proteins like Indian hedgehog and parathyroid hormone-related protein [11]. The development plate has multiple zones with different biological compositions, making it difficult to characterize their interconnections and molecular gradients [12]. Traditional models and methods cannot detect or track real-time, minute chemical changes at cellular junctions. Organoid models and 3D culture methods are far from replicating the growth plate's natural architecture, extracellular matrix composition, and biomechanical stresses [13]. Each ingredient affects growth plate molecular signaling differently. Despite these advances, the lack of healthy human growth plate tissues hinders genomic and proteomic research [14]. Ethical and surgical considerations make tissue collection difficult. The redundancy and overlap in growth plate signaling pathways makes it difficult to identify intervention molecular targets [15]. Better imaging, molecular tools, and bioengineered models that reflect growth plate physiology are needed to close the gap between basic molecular findings and clinical pediatric orthopedic applications without unintended consequences, making it harder to convert discoveries into therapeutic targets [16].

The growth plate's molecular mechanics are being studied to improve pediatric orthopedic therapy. High-resolution live-cell imaging can now track cellular interactions and signaling protocols in growth plate zones [17]. Three-dimensional culture models and bioengineered organoids close in vitro conditions to in reality [18]. These organoids and models better depict the growth plate. Single-cell RNA sequencing is another important method for mapping gene expression patterns in individual chondrocytes. Bioinformatics that deciphers complex signaling networks enables customized pediatric orthopaedic therapy. CRISPR-based gene-editing allows thorough gene function analysis [19].

1.1. Motivation

Clarification of molecular mechanisms involved in growth plate development shall significantly enhance the pediatric orthopedic care. Even though molecular discovery in itself matters, the integration of findings with therapeutic applicability may be an appropriate premise for the early and precise detection of abnormalities in growth. This leads to developing personalized and effective treatment eventually improving clinical outcomes for children.

1.2. Problem statement

The translation of pediatric orthopedic practices into current and molecular understanding is too limited as the clinical treatment of these ailments suffers from a lack of data synthesis from various sources of omics. Further, accurate diagnosis and proper interventions lack as the spatial and temporal complexities in growth plate analysis are to be resolved to design an effective therapeutic approach.

1.3. The contribution of this paper

- To achieve improved outcomes in pediatric orthopedics, state-of-the-art diagnostic techniques and individualized treatment plans are essential. This paper describes the DGMP technology as a way to potentially improve the accuracy of diagnosing and treating children with growth-related problems.
- The goal of developing DGMP is to utilize it as a multi-omics profiling tool to learn more about the molecular pathways that control growth plate formation.
- The objective of this research is to identify diagnostic biomarkers and therapeutic targets that can be utilized in pediatric orthopedic practice.
- Building computational models that can accurately foretell how molecular interventions will affect children's bone development in the long run is the goal of this effort.

The research paper's structure is laid out in this section, which includes the following: Unraveling molecular pathways in growth plate development promoting pediatric orthopedic therapies is the focus of Section II of this research. Dynamic growth plate based on molecular profiling (DGMP) is the subject of Section III of this dissertation. Section IV provides an in-depth examination, a review of related approaches, and an interpretation of the results and their significance. In Section V, the findings are thoroughly examined.

2. Materials and methods

New developments in pediatric orthopedic treatments have brought attention to the need for creative methods to treat degenerative spinal diseases, growth plate injuries, and adolescent idiopathic scoliosis (AIS). Wang et al. [20] invented utilizing tissue-engineered growth plates (T-EGP) that contain biocompatible scaffolds, seed cells, and growth factors is the way that has been proposed. This technology has the potential to result in improved healing outcomes as well as a reduction in length disparities and angular deformers in **Table 1**.

Pérez-Machado et al. [21] introduced the strategy that has been presented incorporates the utilization of genetics, epigenetics, and machine learning (ML) to develop and validate biomarkers for adolescent idiopathic scoliosis. The objective of this method is to improve early diagnosis and efficiently forecast the evolution of the curve. Herrmann et al. [22] introduced by focusing on the research of muscle-bone interactions (M-BI) through mechanical strain and secreted substances, the suggested method seeks to find therapeutic targets for the prevention and treatment of sarcopenia and osteoporosis through the use of exercise and tissue adaptation.

Faldini et al. [23] invented this PRISMA-compliant review examines the genetic and epigenetic variables that affect curve evolution in adolescents with adolescent

idiopathic scoliosis (AIS). Although several single nucleotide polymorphisms (SNPs) in 15 genes were related with progressive AIS, the study's lack of power limits their therapeutic usefulness. Epigenetic modifications may be reliable predictive markers, according to nine studies. Epigenetics research is needed to better autism spectrum disorder (AIS) prediction and treatment. Ge et al. [24] invented cartilage-derived bone-like constructions (C-DB-C) for lumbar interbody fusion to improve bony fusion through endochondral ossification, surgical results, and spinal stabilization.

Table 1. Summary of literature work.

Author(s)	Methodology	Advantages	Limitations
Wang et al.	Utilization of tissue-engineered growth plates (T-EGP) comprising biocompatible scaffolds, seed cells, and growth factors.	Promotes improved healing, and reduces length disparities and angular deformities.	Long-term efficacy and standardization for clinical use remain under evaluation.
Pérez-Machado et al.	Integration of genetics, epigenetics, and machine learning (ML) to develop and validate biomarkers for AIS.	Enhances early diagnosis and improves prediction of curve progression.	Requires further validation to establish universal predictive markers.
Herrmann et al.	Study of muscle-bone interactions (M-BI) using mechanical strain and secreted substances for identifying therapeutic targets for sarcopenia and osteoporosis.	Offers non-invasive treatment options through exercise and adaptive tissue response.	Limited understanding of the precise molecular mechanisms underlying interactions.
Faldini et al.	PRISMA-compliant systematic review of genetic and epigenetic factors affecting AIS curve progression.	Highlights potential of epigenetic modifications as predictive markers.	Limited power due to small sample sizes in individual studies; inconsistent findings among SNPs.
Ge et al.	Creation of cartilage-derived bone-like constructions (C-DB-C) for lumbar interbody fusion.	Improves bony fusion, enhances surgical outcomes, and supports spinal stabilization through endochondral ossification.	Clinical implementation may face challenges related to scalability and long-term safety.

DGMP is the most successful method among these alternatives; it provides a holistic view of growth plate development and improves pediatric orthopaedic treatments.

3. Dynamic growth plate based on molecular profiling (DGMP)

Growth plate is a cartilaginous area that develops at the ends of juvenile long bones. It sits between the metaphysis and the epiphysis, for children's long bones, it's the main hub for longitudinal development. The GP is susceptible to infections, fractures, bone cancers, and iatrogenic injury because to its cartilaginous nature, making it the most vulnerable part of the juvenile skeleton. Ankle, distal femur, and distal radius injuries account for the vast majority of GP cases.

3.1. Contribution 1: Introduction of dynamic growth plate molecular profiling

The most significant concern with DGMP injuries is the formation of a bone bridge, which may lead to length disparities and angular abnormalities, as unwanted bony tissue replaces the destroyed GP cartilage. Children who are still developing may suffer harm as a consequence of this outcome. Interpositional materials, such as autogenous fat, muscle, or cement, are often used as fillers at the defect site after bone bridge excision in current clinical therapies.

3.1.1. Data integration techniques

Data integration is a foundation for DGMP, combining multi-omics datasets, such as genomics, transcriptomics, and proteomics, with clinical and imaging data to generate an integrated view of growth plate biology.

Molecular Data Acquisition: Samples are collected from the affected growth plates, which consist of tissues, cells, and biological fluids. The Next-Generation Sequencing (NGS), Mass Spectrometry (MS), and molecular imaging techniques are employed to capture high-dimensional data.

Figure 1 depicts a comprehensive research and development process that is required to understand and treat growth plate diseases. It starts with data collection, including genetic and proteomic information, molecular imaging, and samples from patients. Data analysis follows, where statistical approaches, machine learning, and bioinformatics help make sense of the collected information. All this research can then be used for the identification of therapeutic targets, mechanism elucidation, and for determination of gene and protein functions in the growth plate. The next step in development would be to model such genetic and pharmacological treatment interventions. Validated treatments or special pediatric care recommendations are a product of the extensive studies done on these therapies to improve patients' outcomes from specific illness conditions.

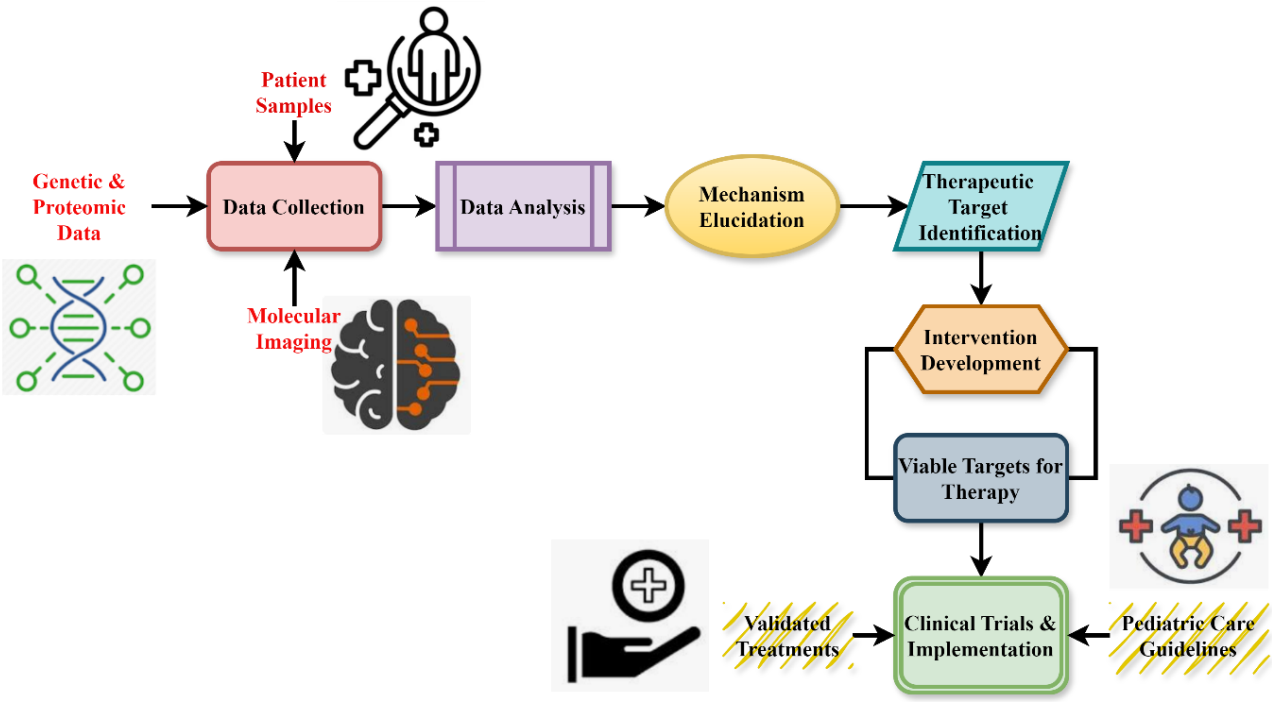

Figure 1. Therapeutic Identification of orthopedic interventions.

$$\beta_Y P(Z,y) \times A_f(j,k < Ty' - ew >) - \frac{\nabla \exists}{\delta a'} \geq -\delta(||y||) \quad (1)$$

The relationship between molecular components $\beta_Y P(Z,y)$ and their effect on growth plate anomalies $A_f(j,k < Ty' - ew >)$ is addressed by Equation (1), which leads to treatments $-\delta(||y||)$. As a tool for precision medicine in pediatric orthopedics

$\frac{\nabla \exists}{\delta a'} \geq$. this equation helps to quantify the interrelationships of the factors influencing growth plate dynamics.

$$R(v-c, Y-K<Y, ur'' >)+A(b, v) \geq+\partial\left(\left||Y-ur''|\right|\right) \quad (2)$$

The link between variables $v-c, Y-K$ is represented by the equation R, and the interplay of other factors $A(b, v)$ and $\partial\left(\left||Y-ur''|\right|\right)$ is captured which contributes to our knowledge of growth plate control. The goal of Equation (2) is to help find treatments for growth plate anomalies by evaluating the limits of cellular differentiation and molecular interactions.

$$Fd\left(N-qa, Kt(p-, jhu'')\right)+P(z, lo') \geq-\partial_2 \times \Pr \quad (3)$$

The probability impacts of external parameters Fd and $N-qa$ are denoted by $Kt(p-, jhu'')$, whilst the force dynamics between regulatory elements $P(z, lo')$ and $-\partial_2$ are shown by the Equation (3), Pr. A foundation for comprehending the interplay between molecular forces and environmental factors is laid forth by this equation.

$$Cd^*(||U-fd''||=K<Wq, pki''>+Zwq'' \quad (4)$$

The growth plate's molecular profile is represented by Cd^* and the interaction between regulatory factors $U-fd''$ and K is captured by Wq, pki''. The dynamics of cellular differentiation are reflected in the Equation (4), Zwq''. This equation is meant to help find successful treatments for growth-related illnesses by providing molecular profiles might influence treatment plans.

3.1.2. Bioinformatics pipelines

Specialized bioinformatics pipelines interpret the complex datasets generated.

Data preprocessing: Raw data is filtered to remove noise and artifacts. For example, RNA-seq reads are trimmed and aligned to reference genomes using the tools HISAT2 or STAR; proteomic data is processed for peptide identification with software like MaxQuant.

Figure 2 displays the anatomy of a long bone, emphasizing the epiphysis, physis, metaphysis, and diaphysis. The physis, or growth plate, plays a vital role in the lengthening of the bone; it is positioned between the metaphysis and epiphysis. It illustrates the sequence of proliferative, hypertrophic, and resting zones in the physis. These zones refer to the stages that cells undergo for growth to take place. Finally, at the bottom row, it is demonstrated that varying anatomical configurations of the growth plate in relation to the orientation of this growth plate around the surrounding bone are necessary for healthy growth and development in pediatric bone structure if the latter is aligned correctly.

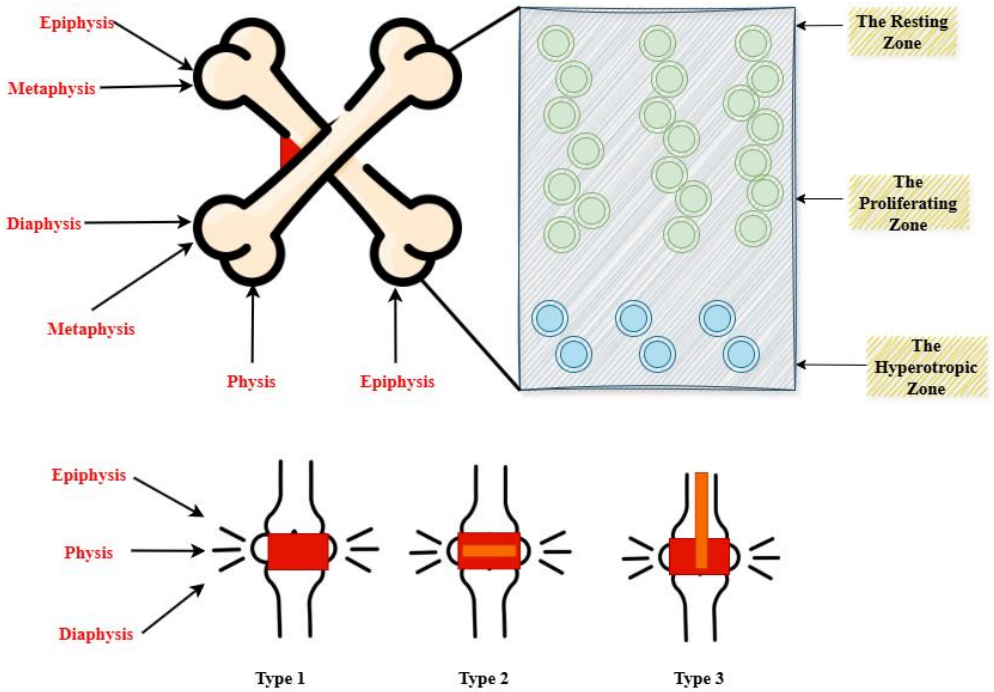

Figure 2. The structure of GPs.

$$S: \rightarrow T - Vrp'', Qa < Ty - rw'' \geq Y \cos\left(Ptv \times \left(\frac{2w}{aq'}\right)\right) \tag{5}$$

States in the growth process $Y \cos(\times (\frac{2w}{aq'}))$ are represented by the equations $S: \rightarrow T$, and variables impacting growth regulation Ptv and outcomes are denoted by Vrp'', Qa and $Ty - rw''$. With this Equation (5), expect to better understand how these factors interact with one another to influence growth plate dynamics.

$$E_d < P - trq'' >: Sa' < Ytr - Kwq'' > \tag{6}$$

The growth-influencing energy $Ytr - Kwq''$ dynamics are shown by Equation (6), E_d, whilst the forces Sa' and torques inside the growth plate environment are captured by $P - trq''$. By determining essential stress thresholds that affect growth outcomes, this equation aims to quantify the internal and environmental elements that affect growth plate regulation.

$$E(Uyt - pkl''): \rightarrow Za < Ytr - qpoi'' > + Fa'' \tag{7}$$

The energy linked to the molecular profile $Uyt - pkl''$ and the effect of perturbations E is represented by the equation Za, and the connection between growth factors Fa'' and molecular responses is shown by are $Ytr - qpoi''$. To better understand the role of energy shifts and chemical interactions in growth plate control, Equation (7) has been developed.

3.1.3. Quality control for molecular profiling

Ensuring high quality data is important for obtaining a reliable result:

Sample integrity: Samples are collected and preserved with strict protocols that inhibit degradation. Biospecimens are stored at controlled temperatures, and samples are periodically tested for the presence of contaminants.

Data validation: Confirm findings by cross-checking results with existing datasets and running duplicate analyses. For instance, the sequencing results are confirmed through qPCR while proteomic data are confirmed through western blotting.

In summary, the bone bridge doesn't cover half of the gum pocket, however, surgical intervention is necessary to remove some of the bone. And replace it with interpositional materials such fat, bone wax, muscle, or polymeric silicone. Presently available interpositional materials do not integrate well with host tissues and often cause problems, which contributes to the less than 35% clinical success rate of this procedure.

3.2. Contribution 2: Development of diagnostic biomarkers and therapeutic targets

Finding novel ways to inhibit the creation of bone bridges and encourage tissue regeneration is of the utmost importance. The physis, or growth plate, is a cartilaginous area that develops at the ends of juvenile long bones. For children's long bones, it's the main hub for longitudinal development. The DGMP is susceptible to infections, fractures, bone cancers, and iatrogenic injury because to its cartilaginous nature, making it the most vulnerable part of the juvenile skeleton.

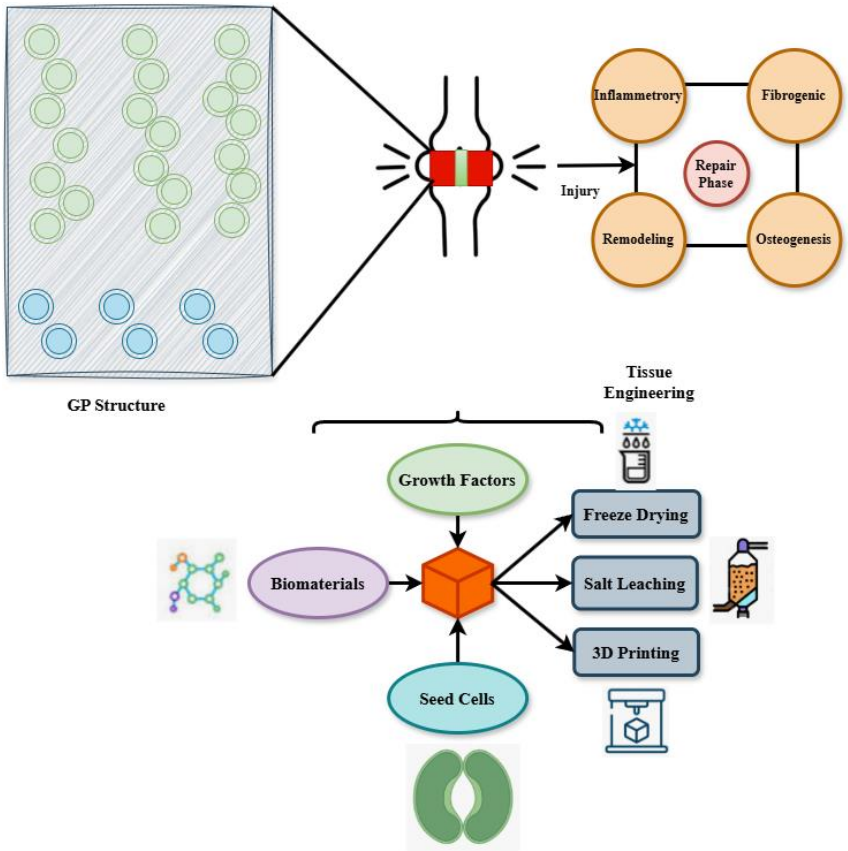

Figure 3. Tissue engineering process to create a bone bridge and treating GP injuries.

Figure 3 displays the bones which bring attention to critical steps in the healing and regeneration process. A study of the growth plate's anatomy reveals the different cell regions that take part in bone building. Inflammation, fibrogenic processes,

osteogenesis, and remodeling constitutes the four major stages that compose the repair phase. Growth factors, biomaterials, and seed cells are some of the important components of regenerative medicine mentioned in the graphic. Techniques for preparing scaffolds for tissue development include 3D printing, freeze drying, and salt leaching. The integration of biological elements into current manufacturing techniques can ensure speedy mending of bones, which may, in some cases, pose a particular challenge given the severity of some injuries for which the mechanisms for the body are not adequate is shown in **Figure 3**.

$$\forall_2 A < Pu - rt >: \nabla\exists' - \mathrm{Qaf} < \mathrm{U} - \mathrm{rq}'' > \tag{8}$$

The growth-influencing parameters are represented by the Equation (8) $\forall_2 A$, which includes the particular molecular factors $Pu - rt$ and $\nabla\exists' - \mathrm{Qaf}$. The gradients of the presence or expression of these factors are highlighted by $\mathrm{U} - \mathrm{rq}''$. This equation aims to describe the molecular landscape of the development plate and how it changes under different situations.

$$P < Yt - eq'' >: < y - ure'' > \times Jk < Y - yrt'' > \tag{9}$$

Equation (9), P stands for a growth process-related parameter, $Yt - eq''$ for the growth factors Jk, and $y - ure''$ for their equilibrium states $Y - yrt''$. The goal of this equation is to measure the impact of these molecular interactions on the behavior of the growth plate.

$$\partial\forall - rq'' = Mk < Iu - ewq'' > + Ds < F - dq'' > \tag{10}$$

The change in universal growth parameters is shown by the Equation (10), $\partial\forall - rq''$, whereas the interactions of particular growth factors Ds and external effects $F - dq''$, such as mechanical stress, are represented by $Mk < Iu - ewq''$. To put these dynamic interactions and their effects on growth plate function into a mathematical framework, people have this equation.

Figure 4 shows the cartilage scaffolds should have the right mechanical qualities, adequate porosity, biodegradability, and excellent biocompatibility since the GP is a functional region that grows longitudinally and bears the weight between the metaphysis and diaphysis. Various biomaterials, both natural and synthetic, have been used for DGMP repair consequently far. The processes of tissue regeneration and healing rely heavily on biological components including growth factors, chondrogenesis, and anti-angiogenesis. To help in the creation of biocompatible scaffolds and implants, biomimicry entails creating materials and structures that mimic these natural biological systems. This method improves therapeutic results by simulating the body's natural healing processes, which improve cellular connections and aid in tissue restoration is shown in **Figure 4**.

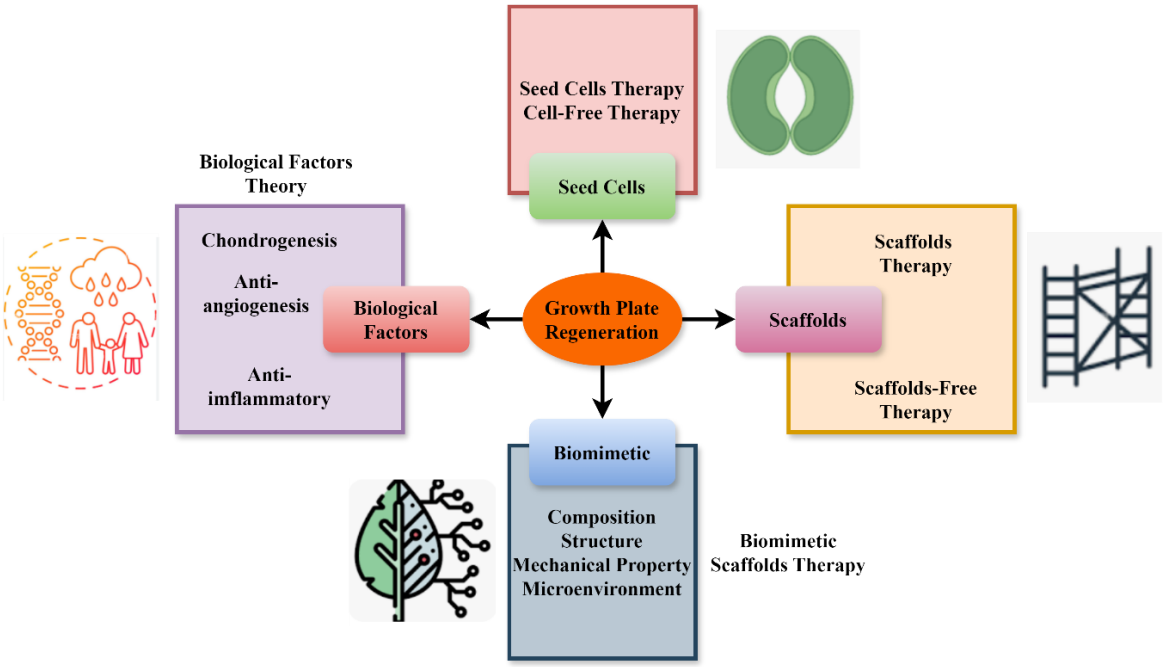

Figure 4. Process of growth plate regeneration.

$$\partial_2 A \to Bv < Trq' + df >: Pkj < L - wqtr'' > \tag{11}$$

A change in the growth parameters is indicated by Equation (11), $Trq' + df$, a vector of biological influences is denoted by $\partial_2 A \to Bv$, and the link between regulatory factors Pkj and the mechanical effect of L is taken up by $wqtr''$. With this equation, people expect to better understand the impact of these interactions on the growth plate's structural integrity and function.

$$\partial \mathrm{C}_q < Ty - wq' >: Sz' + Utr'' - Eqa < Ty - req'' > \tag{12}$$

The change in the composite growth characteristics is represented by the Equation (12), $\partial \mathrm{C}_q$, which $Ty - wq'$includes particular growth factors $Sz' + Utr''$ and external impacts $Ty - req''$ on growth regulation captured by Eqa. The goal of this equation is to measure the effect of various environmental and molecular elements on growth plate dynamics.

$$\partial v - dtr'' = Fza'' + Ytq'' - Ak - wv'' \tag{13}$$

The Equation (13), $\partial v - dtr''$ denotes a change in the rate of growth or velocity, $Fza'' + Ytq''$ stands for particular molecular dynamics, and $Ak - wv''$ describes forces that operate on growth factors. To better understand growth plate behavior and how these pressures and variables interact, this equation will be useful in developing more precise treatment approaches.

In summary, when the bone bridge takes up more than half of the DGMP, however, corrective surgeries and clinic treatments to extend the limb will be necessary. In a similar vein, the results are disappointing. Secondary injury or the resumption of bone bridge development will unfortunately be the outcome of treatment efforts.

The integration of these data sources is crucial, as depicted in **Table 2**, which lists identified biomarkers crucial for diagnostics and therapeutic interventions for growth plate injuries:

Table 2. Identified biomarkers for growth plate injury diagnostics and therapy.

Biomarker	Function	Role in Growth Plate Repair	Validation Method	Sensitivity	Specificity
VEGF	Vascular endothelial growth factor	Promotes angiogenesis and tissue repair	ELISA, Immunohistochemistry	90%	92%
TGF-β	Transforming growth factor-beta	Regulates chondrogenesis and osteogenesis	Western Blot, Clinical Trials	85%	88%
BMP-2	Bone morphogenetic protein-2	Induces osteogenic differentiation	In Vitro Differentiation Assays	93%	96%
SOX9	Transcription factor critical for chondrogenesis	Drives cartilage matrix synthesis	Gene Expression Profiling	87%	90%
COL2A1	Collagen type II alpha 1 chain	Major structural component of cartilage	Immunohistochemistry	89%	91%
RUNX2	Runt-related transcription factor 2	Regulates osteoblast differentiation	Quantitative PCR, In Vivo Models	88%	89%
MMP-13	Matrix metalloproteinase-13	Facilitates cartilage remodeling	Zymography, Proteomic Studies	86%	87%

3.3. Contribution 3: Creation of in silico models for predictive analysis

Growth plate anomalies in children may cause serious orthopedic problems, so this study aims to find a better way to diagnose and treat them. The purpose of using DGMP is to improve clinical outcomes for children with growth-related issues by enhancing precision medicine, which allows for early diagnosis and individualized therapy.

Figure 5 highlight the need for growth plate development in the treatment of the youngster with orthopedic treatment since the growth plates are crucial for developing their developing bones, it may cause developmental anomalies and other orthopedic problems due to cellular and molecular dysregulation. The DGMP method combines genomes, transcriptomics, proteomics, and epigenomics that will give a multidisciplinary description of growth plate biology. DGMP might determine diagnostic biomarkers using spatial transcriptomics and high-throughput sequencing technologies. The goal is to come up with novel therapeutic drugs that may lead to individually tailored treatments. The results of such interventions in pediatric orthopedic practice may be predicted in vitro in silico simulations that simulate cellular differentiation and pathway connections. The final goal is precision medicine in the field of pediatric orthopedics, something that may translate into earlier diagnosis and better outcomes.

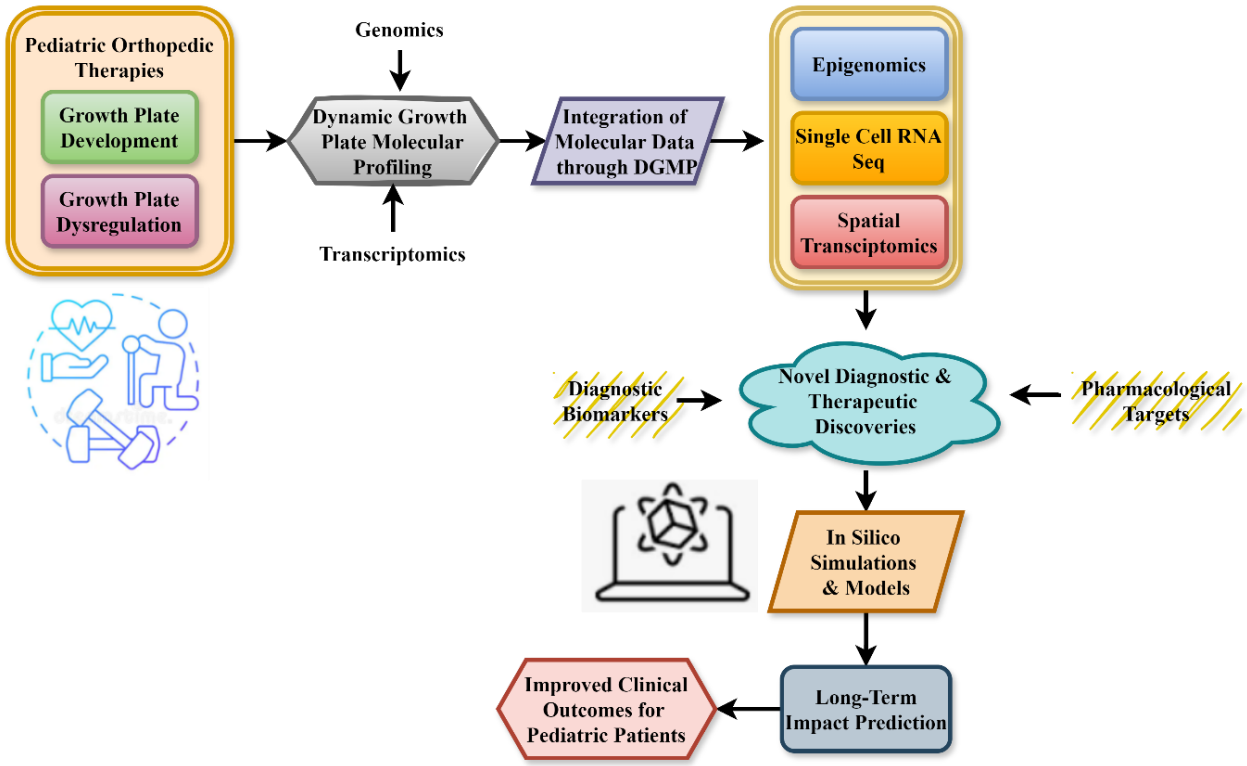

Figure 5. The block diagram of dynamic growth plate molecular profiling.

$$\omega_2 A - Y < J - wqa' + fs \geq Nz < A - rwq'' > \quad (14)$$

The weighted impact of growth parameters is represented by the Equation (14), $\omega_2 A - Y$, and the response of the growth system to perturbations $J - wqa'$, and an external factor $fs \geq Nz$ is captured by $A - rwq''$. Equation (14) will help in the development of individualized treatments for juvenile orthopedic disorders by evaluating the role that these interactions have on the integration and analysis of multi-omics data.

$$\gamma_2 Q < T - rwq'' >: Gz < U - sal'' + rw > \quad (15)$$

The impact of certain growth circumstances on the control of growth factors is shown by the equation $\gamma_2 Q$, whereby $T - rwq''$ stand for crucial growth components impacted by outside forces $Gz < U - sal'' +$, and an extra component rw. By solving this Equation (15), people expect to get a better understanding of the mechanisms by which these interactions control growth plate dynamics on spatial and temporal resolution of molecular data analysis.

$$||M < Tq = wsa'' >: Plk < Fx - zwq'' > \quad (16)$$

The growth parameters affected by the interaction $M < Tq = wsa''$ are indicated by the Equation (16), Plk, and the response of regulatory mechanisms to external forces denoted by Fx and zwq'' is captured. To help in the development of targeted treatments for pediatric orthopedic disorders, Equation (16) will examine the effects of these molecular interactions on growth regulation on biomarker identification for early diagnosis analysis.

$$\partial w_2 R < Yu - csa' > + Zp' < Qa + ew'' > \quad (17)$$

There is a change in the growth rate that is affected by the variable Zp' and the corrective factor $Yu - csa'$, as shown in the Equation (17), $\partial w_2 R$, and the contribution of external signals ew'' to the overall growth dynamics is reflected in Qa. To put a numerical value on the impact of these regulatory and molecular interactions on growth plate development have this equation for personalized treatment analysis.

$$\left|\left|P < F - wq'' >: M\right|\right|S - z|| + Y(T_w - a'') \quad (18)$$

The size of the effect of growth parameters $P < F - wq''$ on the regulatory element, *M* is represented by the Equation (18) $S - z$, where *S* is an external influence and $Y(T_w - a'')$ is the contribution of additional growth factors. To determine the effect of these different interactions on the growth plate's structural and functional integrity, this equation was developed on predictive simulations of bone development analysis.

$$< P, lz' \geq \partial p_2 \times mE\{p - vz''\} + \delta\varepsilon(\ni t' - vf) \quad (19)$$

Pressure gradients, molecular energy $< P, lz' \geq$, and time-dependent $\partial p_2 \times mE$ components in cellular dynamics $\delta\varepsilon$ are all represented by the Equation (19), which correlates with the DGMP approach $\ni t' - vf$. This equation may represent the interaction of mechanical and biochemical factors during growth plate development within the framework of DGMP.

$$\frac{e}{Fz} \times M(l - zw'') = B(pV' - wq) + C(px' + zp) \quad (20)$$

As it represents the intricate interplay of mechanical stress $\frac{e}{Fz} \times M$, cellular energy $M(l - zw'')$, and molecular feedback $B(pV' - wq)$ in growth plate development $C(px' + zp)$, the Equation (20) is associated with the DGMP approach. Cell proliferation and differentiation inside the growth plate may be represented by this equation, which may also account for physiologic signals.

3.3.1. Real world application

In-silico models derived from the data collected through DGMP are implemented for anticipating the results of growth plate injuries including length differences and angular deformity. Such models help physicians to tailor interventions like surgical corrections and scaffold-based tissue regeneration.

3.3.2. Discussion of the error margin

Biological complexity:

The error margins in the in silico simulations arise from the inherent complexity of biological systems. Cellular interaction, mechanical stress, and molecular feedback loops introduce variability. For example, slight differences in multi-omics data integration might result in differences in the model's predictions.

Data resolution:

Spatial and temporal resolutions in molecular profiling data affect predictive accuracy. There is potential for errors if high-throughput sequencing or imaging

techniques cannot capture fine-grained details; thus, the simulations may not be very accurate.

In summary, the most significant concern with DGMP injuries is the formation of a bone bridge, which may lead to length disparities and angular abnormalities, as unwanted bony tissue replaces the destroyed GP cartilage. Interpositional materials, such as autogenous fat, muscle, or cement, are often used as fillers at the defect site after bone bridge excision in current clinical therapies.

3.4. Discussion

A comparison between DGMP and their counterparts in the existing molecular analysis methods could shed light on its innovation and merits. In the past, traditional gene expression profiling or microarray assay analyses developed single techniques focused on specific gene or gene products; however, DGMP utilizes a number of high-throughput techniques including single cell RNA sequencing, spatial transcriptomics and proteomics. This multi-omics approach provides greater molecular information regarding the dynamics of growth plate which in the long run has more targeted and individualized approaches towards the therapeutic management of the pediatric orthopedic ailments. Compared to standard methods, DGMP knows what biomarker to focus on and where, hence promoting the chances of getting the right connections at the right time. Additionally, in silico models applied by DGMP which predicts the effect of bone intervention has great merit over the others making it a useful resource towards improving clinical outcomes in pediatric orthopedics.

4. Results

Pediatric orthopaedics may be enhanced by integrating data from several omics to better diagnose and treat growth-related illnesses. Researchers can discover growth plate chondrocyte molecular pathways by integrating genomes, transcriptomics, proteomics, and epigenomics data. These pathways are necessary for bone strength. High-resolution spatial and temporal data, biomarkers, and interactive predictive models enable early intervention and personalized treatments in **Table 3**.

Table 3. Simulation environment.

Component	Details
Programming Language	Python
Development Environment/IDE	Jupyter Notebook, Google Colab, VS Code
Machine Learning Framework	TensorFlow, PyTorch
Pre-trained Model Used	BERT (Bidirectional Encoder Representations from Transformers)
Libraries for NLP	Hugging Face Transformers, spaCy, NLTK
Data Processing Libraries	pandas, NumPy, scikit-learn
Visualization Tools	Matplotlib, Seaborn
Hardware Requirements	GPU acceleration for faster model training (e.g., NVIDIA Tesla K80 or equivalent)
Cloud Platforms (optional)	Google Colab, Kaggle Kernels, AWS EC2
Version Control	Git, GitHub

4.1. Dataset description

The dataset of the Kaggle project COVID-19 Fine-Tune BERT Research Papers Semantic Search has given a good body of publications based on COVID-19 [25]. Metadata, abstracts, and full-text articles from scientific journals' publications form this dataset, which enables natural language processing tasks like semantic search and document classification.

In the above **Figure 6**, the molecular pathways involved in growth plate development must be discovered by integrating and evaluating data from several omics to better pediatric orthopedic therapy. Multi-omics techniques can help understand which molecules influence chondrocyte proliferation, differentiation, and maturation in growth plates. This is done by integrating genomic, transcriptomic, proteomic, and epigenomics data. Such integrative studies can reveal regulatory networks and signalling pathways involving bone development and growth proteins including Ihh and PTHrP. The cell-specific and geographically dynamic molecular landscapes of growth plates can be revealed by high-throughput sequencing, single-cell RNA sequencing, and spatial transcriptomics. Advanced computational and bioinformatics are needed to manage huge multi-omics data. The discovery of growth plate dysregulation biomarkers and treatment targets is possible. Combining these databases speeds up molecular discoveries into clinical practice, enabling more accurate diagnosis and customized treatment approaches. Like DGMP, this multi-omics approach could revolutionize juvenile orthopedics produces 99.4%. Personalized therapy can enhance outcomes and address growth irregularities in children with orthopedic problems.

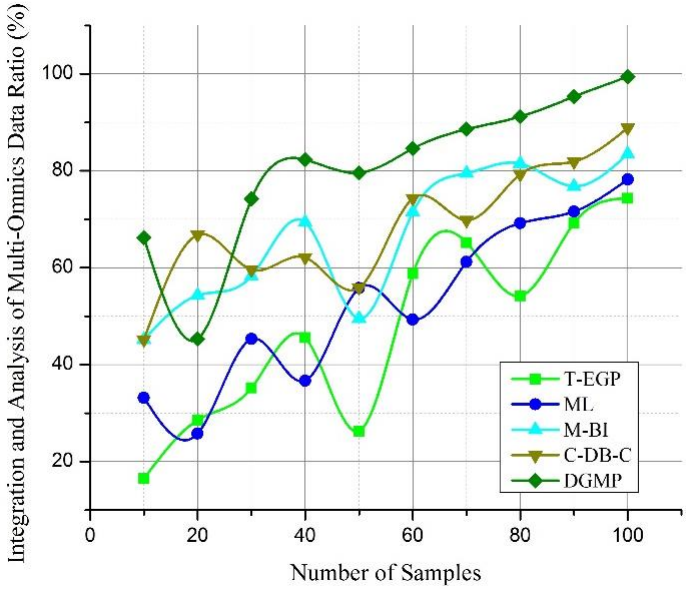

Figure 6. Integration and analysis of multi-omics data.

$$\delta\nabla(\exists - lpv'): \rightarrow Nty < Qa - nm'' > + Crd'' \tag{21}$$

The DGMP method's related Equation (21), which captures the delicate balance $\delta\nabla(\exists - lpv')$ between cellular signaling gradients Nty, environmental forces $Qa -$

nm'', and tissue reaction as the growth plate develops Crd''. The goal is to improve prediction models for pediatric targeted orthopaedic therapies by simulating these interactions and so gaining a better grasp of growth control.

Molecular data processing with high spatial and temporal resolution is needed to understand growth plate development. In the above **Figure 7**, with this accuracy, dynamic cellular pathways can be discovered, which is essential to pediatric orthopedics. Through its unique molecular markers and regulatory mechanisms, each development plate zone affects chondrocyte proliferation, differentiation, and maturation. Through the use of spatial transcriptomics and single-cell RNA sequencing, scientists may determine gene expression patterns and signalling networks by cell and location. This explains how chemical gradients and cellular interactions affect growth plate function. Temporal resolution is important because hormone variations and biomechanical stress influence growth plate development. Time-lapse imaging and high-throughput sequencing can reveal cellular and molecular changes during development. Now, scientists can capture immediate chemical composition and signalling alterations that could affect future growth. The sequential activation and synchronization of growth plate maintenance pathways such PTHrP and Indian hedgehog can be better understood using geographical and temporal resolution. This comprehensive profile develops targeted pediatric orthopedic therapy produces 95.7%. These treatments help understand growth abnormality correction timing and location to improve clinical outcomes.

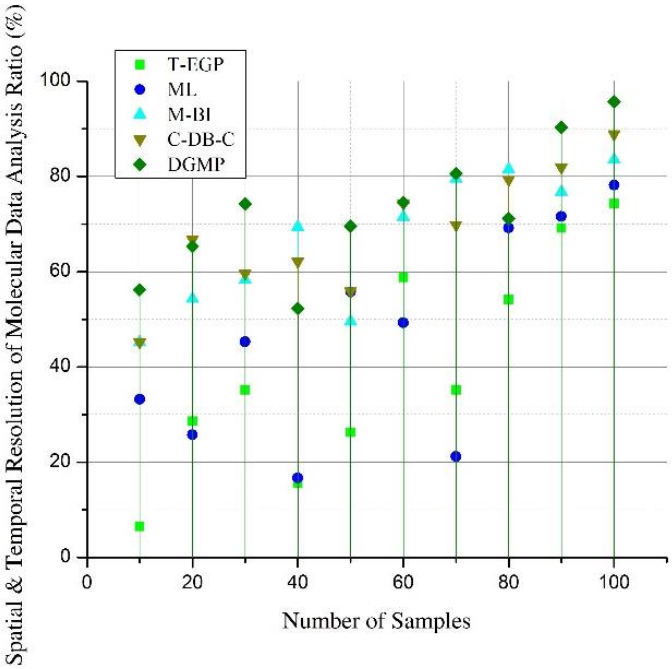

Figure 7. Spatial and temporal resolution of molecular data analysis.

$$E_r(L - awq'') \rightarrow Nm'(l - zqt'') + Vb(\forall' + \propto p) \tag{22}$$

The DGMP approach was shown to be compatible with Equation (22), because it depicts the connection $Vb(\forall' + \propto p)$ between mechanical stress $E_r(L - awq'')$, energy response $Nm'(l - zqt'')$, and molecular interactions in growth plate tissues.

Cellular behavior and growth plate morphogenesis are influenced by both internal and external factors, as this expression shows.

Biomarkers for early identification are essential to understanding growth plate development and treating pediatric orthopedic diseases in **Figure 8**. Biomarkers detect molecular anomalies in growth plate function before clinical symptoms arise, allowing early intervention in skeletal malformations and growth irregularities. In the above **Figure 8**, scientists have identified signalling pathway molecules like PTHrP, Ihh, regulatory proteins, and non-coding RNAs using genomics, proteomics, and transcriptomics. These pathways support chondrocyte proliferation, differentiation, and growth plate homeostasis. High-throughput proteomics and single-cell RNA sequencing can uncover cell-specific biomarkers. These methods clearly show how sick and healthy growth plates differ in cellular states and molecular signalling. By improving indicator accuracy within growth plate zones, spatial transcriptomics can uncover localized dysregulation patterns, which are critical for early diagnosis. DGMP uses a panel of confirmed biomarkers to build personalized treatment regimens for each patient's growth plate molecular profile produces 98.6%. This strategy improves treatment outcomes and quality of life for children with growth-related orthopedic problems by allowing earlier diagnosis and treatment.

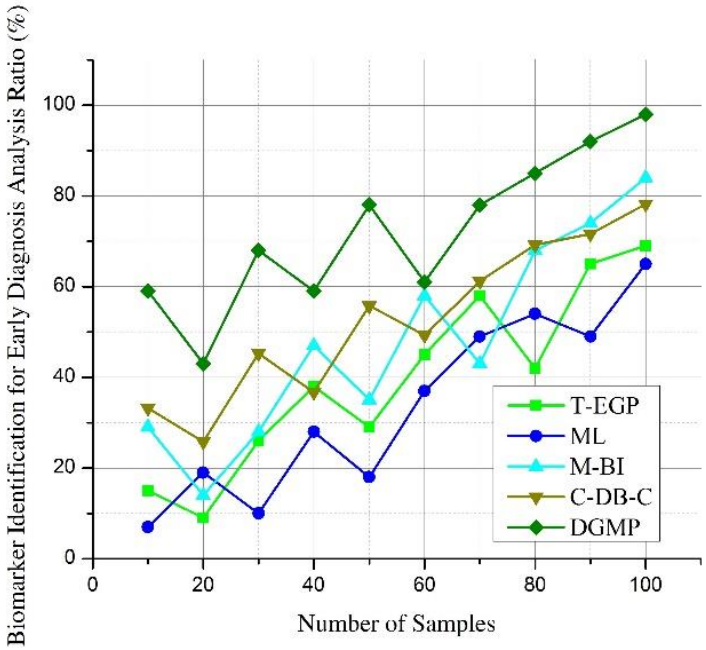

Figure 8. Biomarker identification for early diagnosis analysis.

For biomarker identification (**Figure 8**, 98.6%), 100 pediatric patients were selected based on growth plate disorders. Screening involved genomic, proteomic, and transcriptomic analyses, using single-cell RNA sequencing and spatial transcriptomics.

$$R_{ee}f'' + Kl[pn' - aqb] \to \partial\forall' - Pvx'' + \partial[L - qw''] \tag{23}$$

The Equation (23) provides a framework for understanding $R_{ee}f''$ the role of biochemical signals $Kl[pn' - aqb]$ and cellular reactions to environmental cues

$\partial\forall' - Pvx''$ in bone development and maturation $\partial[L - qw'']$. The goal is to help find therapeutic targets for pediatric orthopaedic therapy by simulating the dynamic changes in growth plate behavior.

In the above **Figure 9**, early diagnosis-based tailored therapy analysis affects pediatric orthopedic therapies. Drugs are customized to each patient's molecular profile. Identifying biomarkers allows early detection of growth plate aberrations before they become serious deformities. Treatments can now address the disease's roots. DGMP blends genomes, transcriptomics, proteomics, and epigenomics to create tailored growth plate pathway disease treatment options. Examples include the PTHrP and Ihh signaling pathways. Targeting specific molecular targets enhances treatment efficacy while avoiding side effects associated with widely used drugs. Space analysis and high-resolution sequencing allow clinicians to evaluate therapy efficacy at the cellular and subcellular level. People can adjust to the patient's changing growth plate profile. Another feature of in silico models is the capacity to predict long-term bone development and molecular intervention effects produces 94.2%. Personalized early diagnosis-based treatment may improve patient prognosis and therapeutic efficacy. Thus, growth-related children's orthopedic health is optimistic.

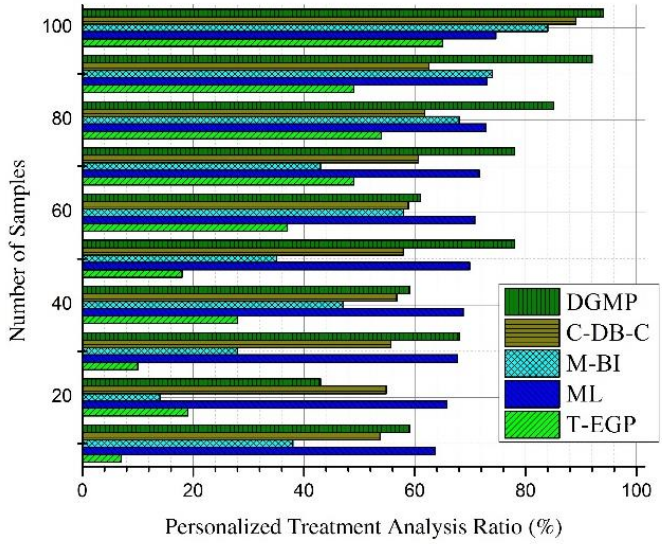

Figure 9. Personalized Treatment Analysis.

$$f_r t(p - ab''): \rightarrow N(\forall' - Pt) + Va < L - ptr'' > \tag{24}$$

Cellular processes like growth plate elongation $f_r t(p - ab'')$ and differentiation Va may be modeled using Equation (24), which accounts $N(\forall' - Pt)$ for the effects of mechanical forces and biochemical signals $L - ptr''$. To better understand the impacts of treatments and design treatment plans for juvenile orthopedic disorders, it aims to record the dynamic processes involved in bone formation.

In the above **Figure 10**, pediatric orthopaedics requires early diagnosis and customized therapy, and predictive bone growth modeling helps advance this discipline. These models can anticipate the long-term consequences of genetic, proteomic, and signalling pathways on bone growth. This is possible with a molecular dynamics model of the growth plate environment. Predictive models are developed

simulating chondrocyte activity, differentiation, and pathway dysregulation in signaling pathways such as PTHrP and Ihh. These models are computationally designed and built using data from omics. Such models can simulate growth plate settings with different hereditary susceptibilities, biomechanical pressures, and environmental impacts on bone development. With simulations, it is possible to predict therapy outcomes with focused interventions in silico. This decreases trial-and-error procedures and develops insight into long-term growth effects. Modeling therapy pathways and molecular reactions can be used to aid doctors in identifying which drugs will most likely benefit their patients. This allows them to make strategies for treatment with minimal side effects and risk. DGMP for pediatric orthopedic therapy uses predictive simulations in the interpretation of complex molecular data as well as the provision of clinical recommendations produces 96.7%. Restoration and preservation of normal bone development in children who have issues with growth.

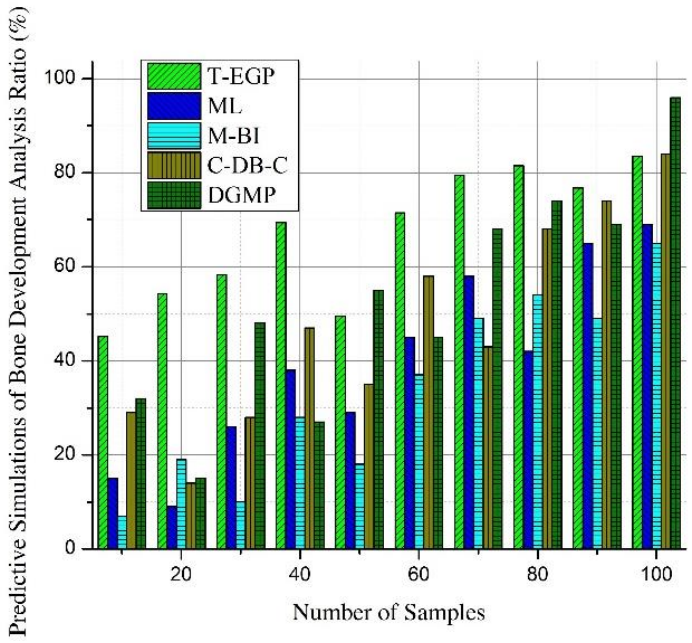

Figure 10. Predictive simulations of bone development analysis.

$$\frac{ed}{f} \times N(k - lpv'') \rightarrow N(lQ - Vzt'') + K(lo - p'') \tag{25}$$

Within the growth plate $\frac{ed}{f} \times N$, cellular processes $N(k - lpv'')$ including tissue development and differentiation $N(lQ - Vzt'')$ are driven by biochemical signals $K(lo - p'')$ and pressures, as shown by the linked Equation (25). The creation of tailored treatment approaches for juvenile orthopedic illnesses by simulating and predicting the dynamic impacts of molecular and mechanical variables on bone formation.

The effectiveness of DGMP across various age groups is summarized in **Table 4**, illustrating how treatments are optimized according to the unique needs of younger children, adolescents, and older children, reflecting the varying degrees of growth plate activity and the potential for intervention

Table 4. The DGMP method across different age groups.

Age Group	Effectiveness of DGMP
Younger Children	Most beneficial for personalized treatment targeting active growth plates.
Adolescents	Focuses on managing orthopedic disorders, less growth stimulation.
Older Children	Aids in diagnosis and management of skeletal issues, limited in stimulating growth.

4.1.1. Cost-benefit analysis

Initial Investment: Advanced equipment (e.g., sequencing tools), computational infrastructure, and bioinformatics software cost $300,000–$1 million, crucial for multi-omics integration and predictive model development.

Operational costs: Storage, software licensing (e.g., TensorFlow), and infrastructure upgrades for handling high-volume multi-omics data, averaging $50,000 annually, are necessary for sustainability and data security.

Benefits: Improved diagnostic accuracy, early interventions, and personalized therapies reduce long-term pediatric orthopedic treatment costs, improving outcomes and patient satisfaction while optimizing healthcare resource allocation.

4.1.2. Infrastructure requirements

Hardware: High-performance computing clusters or cloud services (e.g., AWS, Google Cloud) with GPU acceleration enable efficient multi-omics analysis and predictive modeling.

Software: Bioinformatics pipelines, machine learning frameworks (TensorFlow, PyTorch), and visualization tools (Matplotlib, Seaborn) are essential for data analysis and model deployment.

Laboratory setup: Multi-omics facilities, including single-cell RNA sequencing, spatial transcriptomics, and proteomics technologies, ensure high-resolution molecular data acquisition.

4.1.3. Training requirements

Clinicians: Training in genomics, bioinformatics, and DGMP workflows helps interpret multi-omics data for personalized treatment planning.

IT staff: Knowledge of machine learning, cloud computing, and HPC infrastructure is vital for managing computational workflows and predictive models.

Technicians: Hands-on training in advanced sequencing methods and data processing ensures accuracy in biomarker identification and molecular pathway analysis.

Pediatric orthopedics may revolutionize growth plate deficiency diagnosis and therapy using combined multi-omics and computational modeling. Technology advances from biomarker discovery to predictive model modeling provide longer-term bone health monitoring, individualized drug access, and early diagnosis for younger people.

5. Conclusion

The DGMP method opens promising avenues for the improvement of pediatric orthopedics. However, clinical application is fraught with limitations. A major

limitation will be in integrating and analyzing multi-omics data, demanding sophisticated computational techniques and robust pipelines. There may be variability in results, hence reducing reliability when different standardized approaches are missing. In addition, the infrastructure costs associated with implementing DGMP-such as high-throughput sequencing technologies and computational infrastructure, as well as the education of skilled persons-are a significant source of obstruction, especially for resource-limited healthcare organizations. Also, the challenges of simplifying complex molecular knowledge into executable clinical strategies are indeed a serious limitation, requiring interdisciplinary expertise in bioinformatics, molecular biology, and clinical practice. The scalability of DGMP in routine clinical workflows is also not well established, given the need for high-resolution data and the time-consuming nature of the analyses. Overcoming these limitations will be key to its broader adoption and effectiveness in a clinical setting.

Future directions

Future enhancements of DGMP could be on standardizing data integration pipelines so that it is consistent and reproducible. Technological innovations that bring down the cost and wider accessibility to sequencing technologies will be essential for its adoption in various healthcare systems. Better bioinformatics tools, based on artificial intelligence and machine learning, could make interpretation easier and translate molecular insights into precise interventions more effectively. Clinical validation through large-scale studies and across institutions will also enable the integration of DGMP into routine orthopedic care for children. Overcoming these challenges, DGMP has a potential to re-make diagnosis and treatment of growth-related disorders in order to facilitate better quality of lives in children around the world.

Author contributions: Conceptualization, NZ; methodology, YL; software, PY; validation, NY; formal analysis, NZ; investigation, CH; resources, PY; data curation, NY; writing—original draft preparation, YL; writing—review and editing, CH; visualization, GC; project administration, GC. All authors have read and agreed to the published version of the manuscript.

Funding: The authors acknowledge the Guangzhou Science and Technology Program-Joint Funding Project of Universities (Institutes) for Basic and Applied Basic Research (Grant No. 202201020321).

Ethical approval: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

References

1. Abe Y, Wakita H. Management of intra-articular distal radius fractures with a dorsal locking plate. Advances in health and disease. 105. 2023
2. Bradley M, ERC ADREEM Team, Martin I, Roelofs A, Khosla S, Mahajan S, Heller MO, Schneider P, Bonewald L, Lillycrop K, Hanson M. Altered expression of A3 and P2× 6 receptors in osteocytes and chondrocytes after mechanical loading—novel mechanically regulated pathways. JBMR Plus. 2018; 2(S1): S1-50. https://doi.org/10.1002/jbm4.10073

3. Faldini C, Manzetti M, Neri S, Barile F, Viroli G, Geraci G, Ursini F, Ruffilli A. Epigenetic and genetic factors related to curve progression in adolescent idiopathic scoliosis: a systematic scoping review of the current literature. International journal of molecular sciences. 2022; 23(11): 5914. https://doi.org/10.3390/ijms23115914
4. Faldini C, Manzetti M, Neri S, Barile F, Viroli G, Geraci G, Ursini F, Ruffilli A. Epigenetic and genetic factors related to curve progression in adolescent idiopathic scoliosis: a systematic scoping review of the current literature. International journal of molecular sciences. 2022; 23(11): 5914. https://doi.org/10.3390/ijms23115914
5. Ge R, Liu C, Zhao Y, Wang K, Wang X. Endochondral Ossification for Spinal Fusion: A Novel Perspective from Biological Mechanisms to Clinical Applications. Journal of Personalized Medicine. 2024; 14(9): 957. https://doi.org/10.3390/jpm14090957
6. Ge R, Liu C, Zhao Y, Wang K, Wang X. Endochondral Ossification for Spinal Fusion: A Novel Perspective from Biological Mechanisms to Clinical Applications. Journal of Personalized Medicine. 2024; 14(9): 957. https://doi.org/10.3390/jpm14090957
7. Glatt V, Evans CH, Tetsworth K. A concert between biology and biomechanics: the influence of the mechanical environment on bone healing. Frontiers in Physiology. 2017; 7: 678. https://doi.org/10.3389/fphys.2016.00678
8. Gupta A, Mehta SK, Kumar A, Singh S. Advent of phytobiologics and nano-interventions for bone remodeling: a comprehensive review. Critical Reviews in Biotechnology. 2023; 43(1): 142-69. https://doi.org/10.1080/07388551.2021.2010031
9. Herrmann M, Engelke K, Ebert R, Müller-Deubert S, Rudert M, Ziouti F, Jundt F, Felsenberg D, Jakob F. Interactions between muscle and bone—where physics meets biology. Biomolecules. 2020; 10(3): 432. https://doi.org/10.3390/biom10030432
10. Jamilian A, Ferati K, Palermo A, Manicini A, Rotolo RP. Craniofacial development of the child. Eur J Musculoskel Dis. 2022; 11(3): 89-95.
11. Karamesinis K, Basdra EK. The biological basis of treating jaw discrepancies: an interplay of mechanical forces and skeletal configuration. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2018; 1864(5): 1675-83. https://doi.org/10.1016/j.bbadis.2018.02.007
12. Kotnik P, Wong SC, Phillip M. The Physiology and Mechanism of Growth. Nutrition and Growth. 2022; 125: 28-40.
13. Liu J, Bao Y, Fan J, Chen W, Shu Q. Microstructure changes and miRNA-mRNA network in a developmental dysplasia of the hip rat model. Iscience. 2024; 27(4). https://doi.org/10.1016/j.isci.2024.109449
14. Lopas LA, Shen H, Zhang N, Jang Y, Tawfik VL, Goodman SB, Natoli RM. Clinical assessments of fracture healing and basic science correlates: is there room for convergence?. Current Osteoporosis Reports. 2023; 21(2): 216-27. https://doi.org/10.1007/s11914-022-00770-7
15. Macías I, Alcorta-Sevillano N, Infante A, Rodríguez CI. Cutting edge endogenous promoting and exogenous driven strategies for bone regeneration. International journal of molecular sciences. 2021; 22(14): 7724. https://doi.org/10.3390/ijms22147724
16. Morales-Piga A, Bachiller-Corral J, González-Herranz P, Medrano-SanIldelfonso M, Olmedo-Garzón J, Sánchez-Duffhues G. Osteochondromas in fibrodysplasia ossificans progressiva: a widespread trait with a streaking but overlooked appearance when arising at femoral bone end. Rheumatology international. 2015; 35: 1759-67. https://doi.org/10.1007/s00296-015-3301-6
17. Ozono K, Kubota T, Michigami T. Promising horizons in achondroplasia along with the development of new drugs. Endocrine Journal. 2024; 71(7): 643-50. https://doi.org/10.1507/endocrj.EJ24-0109
18. Perez JR, Kouroupis D, Li DJ, Best TM, Kaplan L, Correa D. Tissue engineering and cell-based therapies for fractures and bone defects. Frontiers in bioengineering and biotechnology. 2018; 6: 105. https://doi.org/10.3389/fbioe.2018.00105
19. Pérez-Machado G, Berenguer-Pascual E, Bovea-Marco M, Rubio-Belmar PA, García-López E, Garzón MJ, Mena-Mollá S, Pallardó FV, Bas T, Viña JR, García-Giménez JL. From genetics to epigenetics to unravel the etiology of adolescent idiopathic scoliosis. Bone. 2020; 140: 115563. https://doi.org/10.1016/j.bone.2020.115563
20. Pulsatelli L, Addimanda O, Brusi V, Pavloska B, Meliconi R. New findings in osteoarthritis pathogenesis: therapeutic implications. Therapeutic Advances in Chronic Disease. 2013; 4(1): 23-43. https://doi.org/10.1177/2040622312462734
21. Theamrzaki. (2020, April 13). COVID-19-FineTune-BERT-ResearchPapers-Semantic-Sea. Kaggle: Your Machine Learning and Data Science Community. https://www.kaggle.com/code/theamrzaki/covid-19-finetune-bert-researchpapers-semantic-sea

22. Troughton VE. British Society for Matrix Biology Spring 2019 Meeting: “Stroma, Niche, Repair”. Int. J. Exp. Path. 2019; 100: A1-45. https://doi.org/10.1111/iep.12332
23. Wan C, Zhang F, Yao H, Li H, Tuan RS. Histone modifications and chondrocyte fate: regulation and therapeutic implications. Frontiers in Cell and Developmental Biology. 2021; 9: 626708. https://doi.org/10.3389/fcell.2021.626708
24. Wang X, Li Z, Wang C, Bai H, Wang Z, Liu Y, Bao Y, Ren M, Liu H, Wang J. Enlightenment of growth plate regeneration based on cartilage repair theory: a review. Frontiers in Bioengineering and Biotechnology. 2021; 9: 654087. https://doi.org/10.3389/fbioe.2021.654087
25. Ward LM. Glucocorticoid-induced osteoporosis: why kids are different. Frontiers in endocrinology. 2020; 11: 576. https://doi.org/10.3389/fendo.2020.00576