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GENETIC RISK FACTORS FOR OSTEOPOROSIS AND THEIR SIGNIFICANCE IN MODERN TRAUMATOLOGY AND ORTHOPEDICS

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ABSTRACT
Osteoporosis is characterized by reduced bone strength and fractures resulting from minimal trauma; however, identified genetic associations have not provided a sufficiently precise basis for individual prognosis. In the fields of traumatology and orthopedics, the application of such data is complicated by the need to distinguish between identifying the hereditary cause of bone fragility, assessing fracture risk, and selecting an appropriate treatment strategy. This study aimed to critically evaluate genetic risk factors for osteoporosis and determine their potential utility in diagnosing bone fragility, predicting fractures, and managing patients. The analysis drew upon 43 sources, including original research, reviews, clinical guidelines, and professional organization statements published between 2022 and 2026. Literature searches were conducted via PubMed, as well as through the websites of scientific journals and relevant professional institutions. The study employed comparative analysis, systematization, and critical qualitative assessment of the data, accounting for sample composition, the specific genetic markers investigated, clinical outcomes, and the independent replication of findings. The diagnostic efficacy of identifying pathogenic variants was evaluated separately from the accuracy of polygenic risk prediction and the evidence supporting genotype-guided treatment. The review examined rare pathogenic variants, polygenic predisposition, epigenetic modifications, and genetic factors influencing bone recovery. This comparison helped differentiate between approaches that clarify the underlying cause of the disease and those whose clinical utility remains insufficiently substantiated. Key challenges identified include sample heterogeneity and the limited incremental accuracy provided by genetic data: causative variants were detected in 20.8% of 394 selected patients, while in another study, the inclusion of polygenic scores increased the area under the diagnostic curve from 0.72 to 0.74. To justify the use of genetic data, it has been proposed to evaluate diagnostic and prognostic approaches separately by comparing them against standard clinical assessment in independent patient cohorts, while also assessing changes in treatment strategy, the incidence of fractures, and surgical outcomes.

KEYWORDS: *osteoporosis; genetic predisposition; genetic polymorphism; polygenic risk; hereditary bone fragility; osteoporotic fractures; traumatology and orthopedics*

INTRODUCTION. Genetic risk factors for osteoporosis are studied to clarify the causes of bone fragility and predict fractures, but their influence on treatment decisions remains insufficiently substantiated. Regional data illustrate the scale of trauma care: in the Republic of Dagestan in 2024, 682 patients with proximal femoral fractures were registered, of whom 551 (80.8%) underwent surgery [41]. These figures reflect the burden on trauma services, not the prevalence of osteoporosis. The relevance of this review lies in determining when genetic data supplement standard assessment and support fracture prevention.
Russian studies address several aspects of this question. B. I. Yalaev, A. V. Tyurin, and R. I. Khusainova consider integrating genomic, epigenomic, and other molecular characteristics in osteoporosis research [5]. A. V. Tyurin and colleagues discuss molecular predictors for early diagnosis [6], while D. I. Valeeva and colleagues address the differentiation of inherited skeletal disorders [7]. These studies encompass two distinct clinical tasks: establishing a rare hereditary cause of bone fragility and assessing polygenic susceptibility to common osteoporosis. Their findings require separate interpretation: a pathogenic variant may explain disease etiology, whereas an aggregate genetic score must be evaluated for fracture-prediction accuracy and incremental value beyond standard assessment. The aim of this review is to synthesize and critically assess evidence on genetic risk factors for osteoporosis and their role in diagnosing hereditary bone fragility, predicting fractures, and managing patients in traumatology and orthopedics.

MATERIALS AND METHODS.
This analytical review included Russian and international publications from 2022–2026 and official documents of professional organizations. Literature was searched in PubMed and on the websites of scientific journals and relevant organizations. Search terms included osteoporosis, genetic predisposition, polygenic risk, hereditary bone fragility, low-energy fractures, osteoporosis genetics, polygenic risk score, monogenic osteoporosis, fracture risk

prediction, and fracture healing. Studies of genetic associations, sequencing and prediction models, systematic reviews, and clinical documents linking molecular findings to diagnostic and therapeutic decisions were selected. Three outcomes were evaluated separately: reduced bone mineral density, diagnosed osteoporosis, and fracture. Study design, sample size and ancestry, phenotype definitions, reproducibility of associations, and independent model validation were assessed. Laboratory and computational findings were distinguished from evidence of clinical effectiveness. Because populations, genetic measures, and outcomes differed, quantitative synthesis was not performed; studies were compared qualitatively.

Results and Discussion. Genetic risk comprises common variants with small effects and rare pathogenic changes that may cause marked bone fragility. The latter help explain disease mechanisms, but findings cannot be generalized to common primary osteoporosis without validation [8, 9]. A. Costantini, R. E. Mäkitie, and colleagues describe early-onset forms associated with LRP5, WNT1, PLS3, and SGMS2 [8]. In a clinical cohort studied by R. Oheim, E. Tsourdi, and colleagues, causative variants were identified in 20.8% of 394 adults with low bone mass at a young age and/or pathological fractures [9]. C. Rouleau and colleagues detected heterozygous pathogenic variants in 27% of children and young adults referred for idiopathic primary osteoporosis using panel sequencing [10]. Differences in recruitment and assessment limit comparisons between these proportions and their application to age-related osteoporosis.

A larger cohort likewise did not yield a genetic explanation for most patients. M. Mancini, R. Chapurlat, and colleagues investigated 577 individuals with primary osteoporosis using a 21-gene panel and obtained a genetic explanation in approximately 18% [12]. E. Busse, B. Lee, and S. C. S. Nagamani emphasize testing when monogenic bone fragility is suspected [11]. Family studies complement sequencing: M. Schembri and M. M. Formosa discuss cosegregation of variants with clinical features as evidence for their significance [14]. A negative panel result should therefore be interpreted in light of the genes included, phenotype, and family history.

Different molecular defects may produce similar bone fragility. COL1A1 and COL1A2 encode type I collagen chains; pathogenic variants alter protein quantity or structure and the properties of the organic matrix [8, 9]. LRP5 and WNT1 have a different role in the WNT signaling pathway regulating bone formation [8]. Regulatory variants are also under investigation. B. I. Yalaev, R. V. Deev, A. V. Tyurin, and colleagues reported associations of microRNA-binding-site variants with fractures and reduced bone density, including variants in COL1A1, FGF2, VDR, and SPARC [17].

Epigenetic findings require separate interpretation. B. I. Yalaev, A. V. Tyurin, K. E. Akhiiarova, and R. I. Khusainova studied differences in RUNX2 methylation in primary osteoporosis [18]. This does not establish inherited transmission of risk; age, disease status, and other factors may influence the result. Table 1 compares genetic and epigenetic alterations, their investigated significance, and interpretive limitations.

Table 1 – Genetic and Epigenetic Mechanisms of Bone Fragility and Their Interpretation

Category	Genes or alterations	Investigated relevance	Interpretive limitation
Matrix formation	COL1A1, COL1A2	Hereditary bone fragility	Effect depends on the specific variant
Bone formation regulation	LRP5, WNT1, SOST	Bone mass and strength	Monogenic and common variants have different effects
Cellular bone turnover	PLS3, SGMS2	Early-onset bone fragility	Rare conditions limit sample sizes
Post-transcriptional regulation	MicroRNA-binding-site variants	Bone density and fractures	Independent replication required
Epigenetic regulation	RUNX2 methylation	Potential biomarkers	Whether changes precede disease is unknown
Structural genomic changes	Deletions, duplications, and other variants	Additional genetic variability	Association does not establish pathogenicity

The collagen genes COL1A1 and COL1A2, cellular regulatory components, and structural genomic changes represent different mechanisms of bone fragility. A pathogenic variant, a statistically associated locus, and an epigenetic marker should therefore not be treated as equivalent diagnostic findings.

Sequencing broadens the characterization of genetic risk. J. Greenbaum and colleagues examined associations between genomic variants and femoral-neck and spinal bone density in a multiethnic cohort of 4,981 participants [27]. K.-J. Su and colleagues identified structural variants associated with bone density at different skeletal sites in 4,982 individuals [28]. C. Yuan and colleagues used multimodal data to define molecular osteoporosis subtypes [29], while X.-F. Chen and colleagues investigated regulatory-element function [30]. N. Lovšin reviewed copy-number variation [31]. These approaches clarify potential variant effects, but their diagnostic and prognostic performance requires testing in clinical cohorts.

Genome-wide association studies (GWAS) identify trait-associated variants without a predefined candidate-gene list. Studies of fractures themselves are particularly relevant to traumatology. M. Nethander, S. Movérare-Skrtic, and colleagues combined 100,026 forearm-fracture cases across discovery and replication stages and initially

identified 59 independent genome-wide significant signals [19]. The strongest signal near WNT16 showed anatomical specificity without a comparable association with hip fracture [19]. Models therefore require validation across fracture sites. T. Lu, V. Forgetta, and colleagues incorporated rare as well as common variants when evaluating bone density and fracture risk [20]. Their aggregate effects must then be quantified.

Polygenic risk scores (PRS) provide such an aggregate measure. Q. Wu and J. Jung developed a model incorporating 103,155 variants and evaluated it in independent data from 15,776 individuals; the highest score decile was associated with more major osteoporotic fractures [21]. However, X. Xiao and Q. Wu found limited incremental prognostic information in external model validation involving 455,663 participants of European ancestry [22]. In a subsequent study, the authors combined 11 components selected from scores for 16 fracture-related traits. The concordance index increased from 0.638 to 0.644, but the difference was not statistically significant [24]. Separation of extreme risk groups does not necessarily imply meaningful improvement in prediction across the entire population.

In clinical practice, genetic testing serves different purposes. In early-onset, recurrent, or familial bone fragility, it can distinguish similar conditions, clarify the cause of fractures and deformities, and indicate the need for multidisciplinary follow-up [7, 11].

Investigating hereditary causes must be combined with excluding secondary disturbances of bone metabolism, as recommended in Russian osteoporosis guidelines [42]. A. Cohen, J. Hostyk, and colleagues performed exome sequencing in 75 women aged 20–49 years with idiopathic osteoporosis. Potentially relevant variants explained some cases, but group analysis did not identify novel genes with genome-wide significant associations [39]. Interpretation depends on phenotype, family history, and cohort composition. The UK National Osteoporosis Guideline Group (NOGG) guidance places evaluation of suspected osteogenesis imperfecta primarily within specialist care [2].

Russian clinical-genetic models illustrate a different task: identifying prevalent osteoporosis and related phenotypes. B. I. Yalaev, A. V. Tyurin, I. Prokopenko, and colleagues developed models for women in the Volga–Ural region. The area under the receiver operating characteristic curve (AUC) was 0.740 for classification by low-energy fracture history and 0.790 for reduced bone density [15]. B. I. Yalaev, A. V. Novikov, I. R. Minniakhmetov, and R. I. Khusainova analyzed 152 loci in 701 women and 501 men; AUC for low bone density reached 0.82 and 0.81, respectively [16]. The cross-sectional design of the latter study addresses recognition of an existing condition; these values do not measure prediction of future fractures.

Incremental prognostic value is evaluated by adding genetic scores to the Fracture Risk Assessment Tool (FRAX), which estimates ten-year fracture probability. In 2026, A. Liu, J. Liu, and Q. Wu increased time-dependent AUC from 0.72 to 0.74 by adding Bayesian polygenic scores [25]. In another study of 10,135 postmenopausal women, the same authors reported that scores based on forearm-fracture genetics increased AUC from 0.683 to 0.690–0.693 [26]. Y. Qian and colleagues also reported modest improvement from combining multiple genetic scores with clinical factors [40]. Such gains must be assessed in terms of whether they alter testing or treatment decisions, particularly near intervention thresholds.

After fracture, bone repair becomes the principal clinical concern. Genetic determinants of impaired union and of fracture occurrence concern different outcomes. M. Sadat-Ali, H. K. Al-Omar, and colleagues summarized associations between nonunion and variants in BMP2, FGFR1, NOG, NOS2, CYR61, and other genes [33]. These findings suggest a hereditary contribution to impaired repair but do not justify a universal preoperative test. Interpretation must also account for fixation stability, injury characteristics, vascular and infectious complications, and comorbidities.

M. Chandran, K. E. Åkesson, M. K. Javaid, and colleagues showed how difficult it is to separate the effects of osteoporosis on healing from age and comorbid changes [34]. Health-service utilization is likewise not equivalent to surgical outcome. The greater use of orthopedic care among carriers of LRP5, PLS3, and WNT1 variants reported by S. J. E. Verdonk and colleagues reflects disease burden [13], not evidence for selecting an implant according to genotype. That decision would require comparative treatment studies with directly measured surgical outcomes.

Pharmacogenetics investigates associations between genotype and drug response. Á. del Real, C. Valero, J. M. Olmos, and colleagues studied 192 women receiving oral aminobisphosphonates and 51 receiving selective estrogen receptor modulators [32]. FDPS and FNTA variants were associated with changes in hip bone density during bisphosphonate treatment, while estrogen-pathway variants were associated with response to the other drug class. Bone density remained the endpoint. These associations require testing in studies comparing clinical outcomes under genotype-guided and conventional treatment strategies.

For now, treatment selection is primarily based on clinical risk, fracture history, and achieved bone density, consistent with recommendations discussed by F. Cosman, E. M. Lewiecki, R. Eastell, and colleagues [3, 35]. Fracture liaison services have been assessed using recurrent fractures as an endpoint. In a meta-analysis by M. S. Danazumi, N. Lightbody, and G. Dermody, the relative risk with at least two years of follow-up was 0.68 [36]. In the NoFRACT study, C. Andreasen and colleagues also reported fewer subsequent fractures following service implementation among 100,198 individuals [37]. Additional genetic technologies must therefore demonstrate benefit beyond established fracture-prevention services [4]. Table 2 summarizes the evidence for the clinical applications considered.

Table 2 – Clinical Significance of Genetic Data in Traumatology and Orthopedics

Clinical task	Potential genetic contribution	State of evidence
Identifying the cause of early-onset bone fragility	Detect pathogenic variants and hereditary disease	Diagnostic yield demonstrated in selected cohorts
Fracture prediction	Add aggregate genetic risk to clinical factors	Accuracy gains vary and are often modest
Predicting nonunion	Identify variants associated with bone repair	Predominantly exploratory evidence
Selecting surgical strategy	Account for a diagnosed hereditary disorder	Insufficient evidence to choose fixation or implants using genetic scores
Selecting medication	Consider differences in pharmacological response	Genotype-guided treatment strategy requires testing

Searching for pathogenic variants in early-onset bone fragility has a clearer diagnostic basis than selecting fixation methods or drugs from a genetic score. For the latter tasks, evidence that genetic information changes treatment decisions and outcomes is still needed.

The comparison in Table 2 demonstrates differing clinical value of genetic information. Causative variants were identified in 20.8% of 394 patients with early-onset bone fragility [9], whereas adding polygenic scores to a clinical model increased AUC from 0.72 to 0.74 [25]. These findings cannot be judged by a single criterion: the first identifies a hereditary disease cause, while the second refines estimated fracture probability. Diagnostic yield in a selected cohort does not justify population-wide testing, and a small gain in predictive accuracy requires assessment of whether treatment decisions change. Interpretation of polygenic scores must account for the source population: a high score denotes relative predisposition, not inevitable disease [43].

The central challenge is the gap between a statistical genetic association and evidence of patient benefit. X. Xiao and Q. Wu did not confirm the association of the investigated scores with fractures in the African-ancestry group, although associations were observed in European- and Asian-ancestry groups [23]. Endpoints also constrain interpretation: the pharmacogenetic study of 192 women on aminobisphosphonates and 51 on selective estrogen receptor modulators assessed changes in bone density [32]. It did not establish whether genotype-guided prescribing reduces fracture incidence. Transfer of models across populations and translation from laboratory markers to treatment decisions therefore require separate validation.

Given these limitations, three applications should be evaluated separately: diagnosis of hereditary bone fragility, fracture prediction, and genotype-guided treatment selection. For the first, age at onset, family history, and consistency between the variant and clinical phenotype must be considered. For the second, model accuracy should be tested in an independent cohort, including how many patients have a justified change in management. The third requires comparative studies recording recurrent fractures, nonunion, and fixation complications. Proposed molecular targets and targeted therapeutic approaches must be distinguished from prescribing based on an individual's genotype [38]. Clinical outcomes determine the value of additional tests. In a meta-analysis of fracture liaison services, the relative risk of subsequent fractures after at least two years was 0.68 [36]. Any additional benefit of genetic testing within existing care pathways remains to be demonstrated.

Conclusion. Genetic information has its strongest established application in clarifying the cause of early-onset or familial bone fragility. Polygenic prediction, assessment of nonunion risk, and genotype-guided treatment remain limited by heterogeneous cohorts and insufficient direct comparisons of clinical outcomes. Broader implementation in traumatology and orthopedics requires demonstrated improvements in diagnosis and treatment outcomes compared with standard assessment.

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