# The Effectiveness of Various Surgical Techniques in the Treatment of Local Knee Cartilage Lesions (Review)

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#### Abstract

**Background.** A large number of surgical methods are used in clinical practice to treat the limited lesion of the knee cartilage: isolated affected area debridement, stimulation of chondrogenesis, mosaic osteochondral repair, cell technologies, collagen membranes (matrices), and the combination of the above techniques. *The purpose of this review* – to compare the effectiveness of various surgical treatments for the limited lesion of the knee cartilage based on the content analysis of publications. *Materials and Methods.* The review includes 85 papers for the period from 2005 to 2020. The search was carried out in electronic scientific databases PubMed and eLIBRARY. *Results.* In the medium and long term, debridement and/or various options of chondrogenesis stimulation are clinically, radiologically and histologically inferior to all other surgical techniques, despite their wide popularity. Mosaic osteochondral auto- and allograft transfer, as well as transplantation of autologous chondrocytes culture with a collagen membrane, are characterized by the best 15 to 20-year outcomes, allowing most patients to maintain the same level of activity as it was before the trauma. The combination of matrices with other cellular products or microfracturing shows the similar mid-term results, but their long-term efficacy remains unknown. *Conclusion.* The use of debridement and/or chondrogenesis stimulation should be limited to the defects with the minimal area. Mosaic osteochondral graft transplantation is the optimal treatment method for cartilage lesion of up to 4 to 6 cm2 both from a clinical and economic point of view. The combination of membranes with various cellular products or microfracturing is indicated in case of extensive lesions or when the mosaic osteochondral graft transplantation is impossible

Keywords: knee, limited cartilage lesion, microfracturing, collagen membranes.

Local cartilage lesion (LCL) of the knee, or chondromalacia, is the disruption of the joint cartilaginous cover integrity resulting from injuries or diseases. Such a lesion is limited mainly to one area of the joint, extending to the depth of the articular cartilage or reaching the subchondral bone. There is no generalized degenerative-dystrophic joint disease. Chondromalacia was first described by K. Budinger in 1906. The term itself was used by O. Aleman in 1928 [1].

According to foreign authors, LCL is diagnosed both in isolation and in combination with other pathology in 30 to 60% of the patients during knee arthroscopy. Moreover, in 65% of cases, it is combined with meniscus pathology [2, 3, 4, 5].

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A. Aroen et al., analyzing the results of 1000 knee arthroscopies, found that in 11% of the patients there were full-thickness cartilage lesions required the surgical treatment. In 55% of the observations, the lesion area exceeded 2 cm<sup>2</sup> [6].

Approximately 200,000 surgeries for cartilage lesion are performed in the United States annualy. That means that the requirement ratio is 614 per 1 million people. The number of such surgeries is increasing by about 5% every year [7]. If the specified coefficient of demand is applied to the number of residents of the Russian Federation, the need for such surgeries can be up to 90,000 per year. It should be emphasized that taking into account social conditions, sports priorities and other features, this figure should be regarded as very approximate.

The low regenerative potential of hyaline cartilage is due to the peculiarities of its histological structure. This, in turn, leads to the early progressive development of total degenerative-dystrophic joint lesion, even when the affected area is limited [8, 9]. The degree of the degenerative process progression of the morphologically comparable osteochondral knee lesions in the long term (over 6 years) in the patients received the conservative treatment was significantly more pronounced compared to the patients undergone the surgery [10].

Scientific and clinical interest in the problem of choosing the optimal method of LCL surgical treatment is confirmed by an increase in the number of publications devoted to the issue in the special literature, but a consensus has not been reached to date [11, 12]. The high incidence of LCL, especially of the femoral condyles, the absence of a standardized algorithm for surgical treatment choosing, and suboptimal long-term results of a number of currently using methods served as the reason for writing this review.

*The purpose of this review* – to compare the effectiveness of various surgical techniques for the treatment of limited lesion of the

knee cartilage based on the content analysis of publications.

#### **Materials and Methods**

We searched for scientific publications on surgical methods for the treatment of the femoral condyles LCL in the electronic databases PubMed and eLIBRARY for the period from 2005 to 2020. Also, the review included a number of earlier fundamental scientific studies of the late XX-early XXI centuries on the topic and were fundamental in the development of a particular method of LCL treatment. The search was carried out using the following keywords: cartilage damage, chondral defect, osteochondral lesion, osteochondritis dissecans, Koenig disease, knee joint. As a result of the search, 85 (6 domestic and 79 foreign) relevant to the topic of the review publications were selected.

#### Results

The goal of LCL treatment is to replace the defect with the tissue with its mechanical properties closer to hyaline cartilage. In clinical practice, various methods of treatment are used, which can be divided into the following groups [13, 14]:

 debridement of the lesion area (removal of unstable cartilage and bone fragments, smoothing irregularities on the cartilage and bone surface);

- stimulation of chondrogenesis, that is, assistance in the restoration of a lesion by the formation of a blood clot with multipotent mesenchymal stem cells (MMSC) from the bone marrow migration into it. These cells are capable to differentiate into chondroblasts (tunneling, the technique of microfractures creation, spongialization or abrasive chondroplasty which is the resection of subchondral bone plate);

– implantation of tissues containing chondrocytes or cells capable of chondrogenesis – transplantation of bone-cartilage allo- and autografts: (mosaic bone-cartilage auto-/alloplasty (OATS), osteochondral autograft transfer system (OATS, mosaic plasty), cultures of autochondrocytes implantation (ACI, MACI), MMSC;

 a combined technique (membrane + microfractures): autologous chondrogenesis induced by collagen membrane that is autologous matrix-induced chondrogenesis (AMIC).

### Debridement

Debridement of a cartilage lesion is a simple resection of affected and unstable parts within the cartilage itself or up to the subchondral bone. It is the simplest and still the most frequently used technique. K.J. Hancock et al. presented the data that out of 25,938 surgeries due to cartilage lesion 80.23% debridement was performed in 80.23% of cases, the technique of microfractures creation - in 21.37%, and OATS – only in 2.1%, although in a number of cases, various techniques were combined [5]. S.R. Montgomery et al. analyzed the data of one of the largest databases of orthopedic surgery in the USA (Pearl Diver Patient Record Database) for a 6-year period (2004 to 2009). They found that various types of surgery were used in 163,448 of the patients with knee LCL, although about 98% of them were debridement and microfractures creation [4]. The positive clinical results of debridement deteriorated over time. Destructive changes rapidly progressed in the cartilage tissue leading to degenerative-dystrophic process in the joint in the mid- and long-term follow-up [9, 10]. Thus, S. Abram et al. found, based on the analysis of the statistics of all hospitalization in England from 2007 to 2017, that 8 years after knee debridement, 17.6% of the patients underwent subsequent arthroplasty [15].

### Stimulation of chondrogenesis

The methods of chondrogenesis stimulation by manipulation on the cartilage lesion and subchondral bone widely spread due to the satisfactory short-term results, the relative simplicity and low cost of the surgery [14, 16]. The accumulated experience of their clinical application revealed a number of significant disadvantages: the resulting fibrous cartilage had worse mechanical properties in comparison with hyaline. It is not stable to tangential forces and, under physiological stress, degenerates over time [17], it is problematic to achieve congruence of the articular surfaces. In about 50% of the cases, the hypertrophied growth of newly formed tissue occurred resulting in reoperations [18]. According to a number of authors, unsatisfactory mid-term functional results, observed in 5 years after microfracturing, were an indication for reoperation in 26 to 40% of the patients, in which total knee arthroplasty was performed in 56% of cases [19, 20, 21, 22].

Comparison of the clinical efficacy of chondrogenesis stimulation methods demonstrated the advantage of the results of the microfracture technique (a total of 90.0% of excellent and good results in 3 years and 69.3% in 7 years after the surgery) compared to tunnelization (82.4% in 3 years and 65,0% in 7 years) and abrasive chondroplasty (72.4% in 3 years and 55.6% in 7 years) [23]. The regeneration slowdown and rapid destruction of the newly formed tissue were observed in the patients over 35 years old, with a high level of physical activity, overweight, lesions to the intra-articular structures, axial deformities of the limb [14, 24].

The further striving of surgeons to improve the LCL treatment long-term results led to the development and clinical application of tissues implants contained chondrocytes or cells capable of chondrogenesis [12, 25, 26, 27, 28, 29].

# Transplantation of bone-cartilage allo- and autografts

The first technology that made it possible to replace articular surface lesions with hyaline cartilage, was mosaic plasty (OATS). Transplantation of allogeneic bone-cartilage grafts popularized by A.P. Newman and R.F. Convery et al. allowed achieving positive outcomes in 72.0 to 77.5% of the patients with follow-up periods from 2 to 7 years after the surgery. The best results were achieved after transplantation of freshly frozen tissues [26, 27]. In a systematic review of 19 studies, including 1036 patients, F. Familiari et al. demonstrated that the effectiveness of this technique in the longer term remained very high: 86.7% in 5 years; 78.7% in 10 years; 72.8% in 15 years and 67.5% in 20 years. The number of unsatisfactory outcomes over such a long follow-up was 18.2%, and reoperations were required in 30.2% of the patients [30]. The undoubted advantage of this approach is the ability to restore defects of any extent because the donor material is unlimited.

Mosaic autograft transplantation (OATS) developed and introduced into clinical practice by L. Hangody, V. Bobic, and Y. Matsusue et al., presents an opportunity to use cylindrical grafts of various diameters and fill 80 to 100% of femoral condyles deep lesions up to 4 to 6 cm<sup>2</sup> with a material contained 80–90% of hyaline cartilage and 10–20% of fibrous tissue [28, 29, 31, 32, 33]. The typical zones of autografts collection are the peripheral low-load sections of the patellar groove and intercondylar fossa of the femur. If the lesion area is more than 6 cm<sup>2</sup>, then additional autografts can be taken from the contralateral knee.

Positive results of OATS in 80-90% of the patients persist for 5 to 10 years after the surgery [31, 34]. The long-term results of OATS have been studied in 3 randomized clinical trials. R. Gudas et al. showed that, on average, in 10.4 years (9 to 11 years), this technique both clinically and radiologically was superior to microfracturing. 75% of professional athletes were able to maintain the same level of activity as it was before injury in contrast to 37% after microfracturing. The OATS failure rate was 2.7 times lower: 14% compared to 38% [20]. On the contrary, S. Ulstein et al. found no differences in the scoring of the knee function, muscle strength, and X-ray picture in 9.8 years after applying the both techniques. However, revisions after microfracturing were performed more often (54%) than after OATS (36%) [35]. In a comparative assessment of the outcomes of OATS and microfracturing in at least 15 years (15 to 17 years), E. Solheim et al. revealed that the first method was characterized by significantly better clinical results with a greater proportion of good and excellent outcomes, the score for knee function was significantly higher, the need for arthroplasty occurs less frequently: 5 vs 15% [36].

Thus, the long-term results of the high level of evidence studies indicated that OATS was a reliable and clinically more effective method of repairing knee cartilaginous and osteochondral lesions compared with subchondral bone microfracturing.

#### Autochondrocyte culture transplantation

In the first decade of the XXI century, the considerable interest of researchers was attracted by the possibility of using autologous cell cultures (chondrocytes, MMSC) for the LCL treatment [28, 29]. The first attempts to use the intra-articular injection of chondrocytes, isolated by proteolytic enzymes from the cartilage of low weight-bearing parts of the joint and cultured in vitro for the purpose of their expansion and adhesion into the lesion area, demonstrated promising short-term clinical, X-ray, MRI and histological results. The problem was to maintain the phenotype of chondrocytes in monolayer culture. There also was a risk of inhomogeneous distribution of cell suspension in the lesion zone [28, 37]. To increase the autochondrocytes concentration and to keep them in the cartilage lesion area, a ACI technique was developed for implanting cells under the periosteal flap. The analysis of long-term surgical results was controversial: with an average follow-up period (5.0 to 7.5 years), reoperations were observed in 8.0 to 8.18% of the patients [38, 39]. An increase in the follow-up to 10 years revealed the need for revision in 25% of the cases. Knee arthroplasty was performed in 36% of the patients [39]. The opposite results were presented by J. Carey et al. 13% of the patients received ACI for knee osteochondritis dissecans needed additional surgery in the first 10 years after the primary surgery, 15% – within 15 years and 18% – up to 20 years. Knee arthroplasty was performed only in two cases out of 55 (3.7%) [40]. E. Kon et al. emphasized the following limitations of the technique: it was technically difficult to harvest the periosteum and create an airtight cavity in the area of cartilage lesion; there were frequent cases of hypertrophic proliferation of the new tissue, as well as arthrofibrosis required mobilization interventions [41].

The elimination of these disadvantages was facilitated by the method of implantation of autochondrocytes under collagen membranes/ matrices (MACI), demonstrated the potential of chondroinduction and chondroconduction in vivo, the possibility of complete purification from non-collagen proteins, a low immunogenic effect and high biological compatibility [12]. Several types of membranes are currently available: Chondro-Gide (Geistlich Biomaterials), ChondroCelect (TiGenix), Carticel (Genzyme Biosurgery), Novocart Basic (Aesculap). Collagen membranes have a positive effect on the differentiation of MMSC culture toward the chondrogenic direction. As a result, the extracellular matrix characteristic of hyaline cartilage is formed and the synthesis of key proteins, such as type II collagen, aggrecan, local release of the bioactive factor TGF-β1 increases. These favor the cartilage tissue regeneration [42, 43, 44]. The disadvantages of the MACI technique are considered to be the technical complexity and the high cost of the surgery, a long rehabilitation period, problems of cultivation and maintenance of the phenotype, uniform distribution and retention of implanted cells in the lesion area [45, 46].

A number of systematic reviews concluded that the use of a collagen matrix made it possible to significantly reduce the level of revisions compared with a periosteal flap: according to A. Pareek et al. – from 52.6 to 15.1%, and J.D. Harris et al. 5.3 times – from 8 to 1.5% [47, 48]. However, there are no randomized clinical trials comparing 10-year or longer-term results for the both methods.

The accumulated experience of the clinical application of MACI was reflected in a large number of works published in the last 5 years [46, 49, 50, 51, 52]. The results, according to multicenter studies, were good and excellent in 84% in 4 years follow-up after the surgery [38], with an extension of follow-up to 10 years, the results remained the same in 80 to 90% of the patients [46, 47]. P. Kreuz et al. in a prospective study of 21 patients with full-thickness cartilage lesions assessed the long-term results of the MACI technique. The patients had significantly higher indicators than before surgery in 12 years after the surgery according to the subjective scales of IKDC, KOOS, Lysholm, Noyes. The complete or almost complete replacement of a cartilage lesion was achieved in 10 cases out of 14 according to MRI data [52]. Nevertheless, the failure rate in MACI could reach 14.9 to 19.0%. Most of them developed within the first 5 years, requiring total or unicompartmental knee arthroplasty [50, 51].

## *Multipotent mesenchymal stem cell transplantation*

The wish to overcome the problems and reduce the material costs associated with the cultivation of autochondrocvtes, to avoid additional trauma to the cartilage during the cells collection, the experimentally and clinically proven ability of MMSC to differentiate into chondrocytes, stimulated by collagen membranes, promoted the use of stem cells for LCL treatment by their intraarticular injection [53, 54] or implantation under the collagen membrane [14, 55]. Immediate and mid-term outcomes of such operations demonstrated encouraging clinical, X-ray, MRI and histological results [55, 56]. A. Teo et al., based on a comparative analysis of 62 patients treatment results after MMSC transplantation and the ACI technique with a minimum follow-up of 10 years, concluded that there were no significant subjective clinical differences between the groups. These both techniques were equally effective in the long term, with reoperations after ACI required in 6 cases, while using MMSC – in 5, including one arthroplasty [57].

# *Combination of the techniques: microfractures and collagen membrane*

Similar arguments served as a theoretical justification and wide clinical application of the combined technique (membrane+microfractures/AMIC), which provides the formation of a "super clot" from the blood, entering the area of cartilage lesion after subchondral bone microfractures, stable fixation by the collagen membrane and MMSC differentiation into chondrocytes, stimulated by the membrane [58, 59, 60].

A significant number of researches and publications are devoted to the study of the AMIC effectiveness [58, 59, 60, 61, 63, 64, 65, 66, 67]. The clinical results assessed by functional scales were found to be comparable to the clinical outcomes of ACI in 1 and 2 years after the surgery [58, 60, 62, 63, 66]. The high functional scales indicators, the degree of patient satisfaction (subjective assessment), and restoration of the homogeneous morphology of the cartilaginous lesion from moderate to complete according to MRI data remained in 5 years [61, 67].

S. Bark et al., analyzing 28 studies, including 3122 patients, devoted to comparing the outcomes of the microfracture and the AMIC technique, concluded that the clinical and MRI results of the AMIC are superior to those of microfracturing in the mid-term perspective [68]. M. Volz et al. compared the results of microfracturing and AMIC achieved in a randomized controlled trial. Improvement of clinical results by the knee function scales and MRI indicators was observed in both subgroups in 2 years after the surgery. However, 5 years later, a stable positive functional result was maintained and the filling of the lesion, according to MRI data, was more complete, while these parameters significantly worsened in the microfracturing subgroup [69]. Although a few randomized clinical trials indicated that the beneficial effect of AMIC could last up to 9 years [70]. Nevertheless, the authors of a recent systematic review of 28 studies of this technique, stated that there were only few well-conducted studies evaluated AMIC in comparison with more thoroughly studied techniques for creating microfractures, OATS and ACI. This made it difficult to determine clear clinical indications for using of the AMIC [71].

Currently, a promising alternative to the AMIC is the use of various types of special hydrogels, which are porous synthetic or biological polymers with a cross-structured composition that can be used as a matrix instead of a collagen membrane [72]. Evaluation of the nearest results showed that in terms of up to 2 years, the use of hydrogels led to filling of the cartilage lesion by more than 90%, which, in subjective assessment, exceeded the results of microfracturing [73, 74]. However, the longer-term results are needed to compare the clinical efficacy of hydrogels with other treatments of LCL.

### How often are various cartilage restoration techniques used in real clinical practice?

It is interesting to compare the popularity of so many techniques used to treat LCL in everyday clinical practice.

R.M. Frank et al., based on the analysis of the Large US Commercial Database, contained information on 47,207 LCL surgeries, published the following data on the frequentness of various methods: microfracturing were used in 43,576 patients, OATS – in 1383, bone-cartilage alloplasty - in 714, and ACI in 640 patients. In 65% of the cases, the simultaneous meniscectomy was performed. Two years later, 29.69% of the patients underwent reoperations after ACI, 14.65% - after microfracturing, 12.22% - after osteochondral alloplasty, and 8.82% - after OATS [75]. It remains unclear why OATS, which is the most effective, technically not complex and does not require large material expenditures, is used in clinical practice quite infrequently both in our country and abroad?

Also, the figures on the rate of revisions differ significantly. According to the German Cartilage Registry for 2013–2017, only 3.3% of the patients, out of 2659 cases of knee LCL surgery, required reoperation in 12 months. There were no statistically significant differences in the number of revisions depending both on the surgical technique used and on the location of the lesion [76].

The similar data were presented by C. Riboh et al. They compared the effectiveness of the microfracture technique, OATS, 1st generation ACI, and MACI in 855 operated patients. Within 2 years after the surgery, there was no significant difference among the above groups in the number of revisions and the achieved functional results according to the functional scales. However, 5 years later, the level of revisions became higher after microfracturing. 10 years later, the "rating of effectiveness" of the techniques was presented as follows: MACI - ACI - OATS - microfracturing [77]. B.M. Devitt et al. published their own "rating of effectiveness" based on the results of a 10 years follow-up: MACI - OATS - microfracturing [78]. In contrast, in a multicenter, randomized clinical trial, 15 years after the surgery, the authors were unable to identify any significant differences in the treatment outcomes between the groups of patients received microfracturing and ACI [79]. The latest systematic review, published in 2020 by R. Zamborsky et al., showed that in the long term (10 or more years) microfracturing was significantly inferior in the effectiveness and the number of complications to other methods of LCL treatment. In addition, the authors found only few qualitative enough studies compared the results of ACI, MACI and AMIC. They concluded that to assess the long-term effectiveness of these methods it was necessary to conduct the appropriate randomized clinical trials [80].

The size of the lesion is an important factor in comparative assessment of vari-

ous LCL treatment methods effectiveness. R. Ossendorf et al. conducted a comparative assessment of 10-year results of 44 LCL patients treatment using microfracturing and ACI. According to the subjective scales IKDC, KOOS, VAS, as well as the MRI indicators, no significant differences were found between the groups. The study indicated that the area of the lesion was significantly larger in the ACI group (4.34 cm2 vs 2.37 cm2), which had a significant impact on the final results [81].

G. Bentley et al., comparing the results of OATS and MACI in 100 patients in 10 years after the surgery, came to the following conclusions: during the 1st two years, the results of OATS were more than satisfactory, but then there was a sharp deterioration of the functional scales scores, while the level of achieved results in the MACI group did not change during 10 year follow-up. Functional outcomes and survival rate were also significantly better in the MACI group. The mean period between primary surgery and revision was 5.1 years for the patients in the MACI group and 4.3 years for the patients in the OATS group. The 10-year surgery outcome after mosaic chondroplasty in 55% of the patients was assessed as unsuccessful, compared with 17% in the MACI group [82].

V. Fossum et al., conducting a prospective randomized clinical study of AMIC effectiveness in comparison with MACI, did not find any significant differences between the two groups of the patients in terms of pain syndrome severity and knee functional state in 2 years follow-up. Although after AMIC, two patients required total knee arthroplasty [83].

It is of interest to study the minimally significant differences in assessing the longterm results of using various methods of surgical repair of cartilage lesions, assessed by the patients themselves. According to the results of 89 studies, including 3894 cases, with various scoring systems of knee functional assessment, only OATS and ACI demonstrated high effectiveness over a period of more than 10 years [84]. The long-term results of randomized clinical trials of the effectiveness of various methods of knee LCL treatment are presented in the Table.

The economic effectiveness analysis of various LCL treatment methods is also important. Thus, J. Schrock et al. estimated the cost of microfracturing at \$3989, OATS – at

\$6110, and ACI – at \$10,195. The latter method was also characterized by the highest cost of revisions (on average \$730) due to regenerated tissue hypertrophy or contracture development. The cost of one point of functional improvement was \$200 for microfracturing, \$313 for OATS, and \$536 for ACI [85].

Table

The results of randomized clinical trials evaluated the long-term effectiveness
of various methods of LCL treatment

Author, (year)	The size of the lesion, cm <sup>2</sup>	Method	Number of patients	Follow-up, years	Relapse/ unsatisfactory outcome	р
Gudas R.G. (2012) [20]	2.8 (1-4)	Microfracturing OATS	29 28	10.4	38% (11 из 29) 14% (4 из 28)	<0.05
Gudas R.G. (2012) [20]	3.5 (2-5)	Microfracturing OATS	20 20	15	80% (16 из 20) 40% (8 из 20)	<0.05
Knutsen G. (2016) [79]	2-10	Microfracturing ACI	40 40	15	32.5% (13 из 40) 42.5% (17 из 40)	0.356
Bentley G. (2012) [76]	4.0 (1–20) 4.4 (1–10)	OATS ACI	42 58	10-12	55% (23 из 42) 17% (10 из 58)	<0.001
Volz M. (2017) [69]	3.6 (2-10)	Microfracturing AMIC	9 30	5	66% (6 из 9) 7% (2 из 30)	<0.01

Thus, despite the fact that during the past two decades, new methods of LCL surgical treatment using membranes and cell technologies (MMSC, ACI, MACI, AMIC) were introduced into clinical practice, they remain quite expensive, and their long-term benefits are insufficiently studied. Technically simple and cheap methods of stimulating chondrogenesis by forming a blood clot are inferior in their clinical effectiveness and reliability to all other methods and therefore should be used extremely limitedly, only in minimal defects. OATS is a simple, easily reproducible and time-tested option for the restoration of chondral and osteochondral lesions, therefore, in our opinion, it can be recommended as the method of choice. The combination of membranes with various cellular products or microfractures is indicated in case of extensive LCL or when OATS is impossible.

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#### Authors' contributions

*T.A. Kulyaba* – review idea and concept, analysis and interpretation of publications search results on the topic, final editing.

*S.A. Bantser* – publications search on the topic and their analysis, text preparation.

*P.A. Trachuk* – publications search on the topic, their analysis and description.

*N.N. Kornilov* – review idea and concept, analysis and interpretation of publications search results on the topic, final editing.

All authors made a significant contribution to the research and preparation of the article and read and approved the final version before its publication. They agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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TRAUMATOLOGY AND ORTHOPEDICS OF RUSSIA

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