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**DEVELOPMENT OF THE FIELD OF HUMAN TISSUE
AND CELL TRANSPLANTATION IN
THE REPUBLIC OF MOLDOVA**

321.24 - transplantology

Summary of Ph.D. Thesis in Medical Sciences

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THE INTRODUCTION

Actuality and importance of the problem tackled. Transplantology as a medical science and transplantation have recorded a significant progress over the past decades. Transplantation of human tissues and cells has registered an ascending increase in the success rate, not only in terms of the number of grafts transplanted but also in terms of the number of therapeutic indications. Every year, thousands of patients benefit from tissue and cell transplantation [1]. As to organs, the demand for certain types of tissues and cells to be transplanted goes beyond the available supply. Several studies show that the challenges of tomorrow in the field of transplantology will be to identify solutions to adapt supply to the needs of transplantation [2-4].

Deficiency of donated tissues and cells is the main factor limiting the development of transplantation and, therefore, this problem requires thorough examination [5]. Obtaining donated tissues and cells is a complex activity in medical practice and depends on the effort, motivation and professional training of doctors of various specialties [6, 7].

Human tissue transplantation is one of the priority fields for the Republic of Moldova, some directions such as corneal transplant or bone transplant are already well known and successfully implemented. The need to develop the tissue transplantation, especially the corneal transplant, emerges from the analysis of further increase in the corneal transplant waiting list, which reached in 2018 the number of 191 registered patients.

During the period 2010 - 2019 the activity in the field of human tissue transplantation at country level registered a number of 163 effective tissue donors with their increase from 1.4 per one million of population in 2011 to 10.8 in 2019, the European standard being ≈ 40 deceased donors per one million of population. The number of potential donors lost due to family refusals reached 31.2% in 2019, the European standard being $< 10\%$ [8]. Insufficiency of tissue donors requires the identification of optimal solutions to increase the number of donors and maintain adequate tissue stocks to cover the needs of practical medicine. The current provisions are insufficient to support an adequate and sustainable supply of tissues and cells in the context of a significant increase in demand.

Considering the above, it is obvious the need for consolidation and continuous development of the field of human tissue and/or cell transplantation in the Republic of Moldova, which defines the research problem, aimed at the argument of development directions of human tissue and/or cell transplantation within the national transplant system.

Research goal consists in the complex evaluation of the field of human tissue and/or cell transplantation and public attitude towards donation and transplantation, to ensure the functioning of the transplantation system and the efficiency of services provided, as well as arguing their development directions in the Republic of Moldova.

Research objectives:

1. Analysis of the evolution of the field of human tissue and/or cell transplantation;
2. Estimating the public knowledge and attitude towards human tissue and/or cell donation and transplantation at national and international level;
3. Studying the doctors' opinion regarding the provision of the health system with human tissue and/or cell grafts;
4. Evaluation of the key elements of human tissue and/or cell transplant service;
5. Elaboration of scientific support for the development of the field of human tissue and/or cell transplantation.

General research methodology. This study has been based on the information about transplant services rendered by the medical-sanitary institutions, as correlated with the national and international data and sources [1, 9-11]. The research had as theoretical and scientific support the knowledge and experience of scientists from the Republic of Moldova and abroad on development of human tissue and/or cell transplantation, regulatory documents, development policies and strategies of international organizations such as CoE, EU, WHO, SEEHN etc.

Research novelty and originality of the results obtained. In this study, for the first time, a complex assessment of the key elements of human tissue and/or cell transplant service at national level is realised. The scientific argumentation of the necessity and importance of providing the health system with human tissue grafts (cornea, bones, tendons, ligaments, skin, amniotic membrane) and cell (stem cells) grafts is made. At the same time, organizational, financial and educational problems have been identified that have a direct impact on the efficiency of the transplant system. During the study, the criteria for evaluating the effectiveness of the activity of donation and transplant institutions have been determined by establishing performance indicators for conducting an audit of donation and transplantation processes. The main factors that prevent effective donation and determine the potential of donation in the institution have been identified. Scientific support has been elaborated for the development of the field of human tissue and/or cell transplantation. The study evaluated the doctors' opinions about providing the health system with human tissue and/or cell grafts, the public knowledge and attitude towards human tissue and/or cell donation and transplantation.

Approval of the research results. The results of the research were discussed at international and national scientific forums, including: the 4th International Conference on Nanotechnologies and Biomedical Engineering, ICNBME 2019 (Chisinau, 2019); „Currents in ophthalmology”: Scientific-Practical Conference of Ophthalmologists with international participation (Chisinau, 2019); the 26th EATB Congress of the European Association of Tissue Banks (Treviso, Italia, 2017); International Paediatric Surgery Conference (Chisinau, 2017); „Current concepts of traumatology and osteosynthesis”: Scientific-Practical Conference of with international participation (Chernivtsi, Ukraine, 2017); the 4th ELPAT Congress on Ethical, Legal and Psychosocial Aspects of Organ Transplantation (Rome, Italy, 2016); the 25th Congress of the European Association of Tissue Banks (Hanover, Germany, 2016); „Strengthening the Transplant Agency of the Republic of Moldova and support in legal approximation in the area of quality and safety of substances of human origin”: Closing Conference of the Twinning Project (Chisinau, 2016); the 24th Congress of the European Association of Tissue Banks (Split, Croatia, 2015).

Keywords: donation, tissue donor, cell donor, tissue transplantation, cell transplantation, tissue and cell bank, biobank, biodepozit.

The study protocol was approved by the Ethic Committee of the Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau (No. 2, 27.10.2016).

The thesis was discussed and approved at the meeting of the Laboratory of Tissue Engineering and Cell Cultures, Nicolae Testemitanu State University of Medicine and Pharmacy (Protocol no. 85 of 18.01.2021) and at the meeting of the Profile Scientific Seminar „General medicine. Transplantology” at Nicolae Testemitanu State University of Medicine and Pharmacy (Protocol no. 02 of 25.02.2021).

The framework of the research. The thesis is written on 200 pages, contains the introduction, 5 chapters, general conclusions and practical recommendations. Bibliography

includes 221 references. The thesis includes 67 figures, 4 tables and a number of annexes. The results of the thesis were published in 29 scientific papers, together with 2 included in international databases, 2 without co-authors and 6 in reviewed editions.

SYNTHESIS OF CHAPTERS

1. EVOLUTION OF HUMAN TISSUE AND CELL TRANSPLANTATION FIELD

1.1. Historical aspects in the development of human tissue and/or cell transplantation field

The first documented bone transplant was carried out in 1668 by a Dutch surgeon, Job van Meekeren, when using a dog's skull (xenograft) to treat the defect of the skull to a soldier [12]. In 1869, the first fully documented transplantation of human tissue to human tissue transplantation - *skin transplant* was performed by Swiss surgeon Jacques-Louis Reverdin [13]. The first successes in tissue transplantation date back to the early twentieth century.

In the Republic of Moldova tissue transplantation has been practiced since the 1960s, mainly tubular and spongy bone segments [14, 15]. In 1962, according to the recommendations of University Professor Leonid Gladârevschi and University Professor Nicolae Testemitanu, was established „*The Laboratory of Tissue Procurement and Preservation within the Republican Blood Transfusion Station*” [15]. From November 1st, 2011, based on the Laboratory of Tissue Procurement and Preservation, the Human Tissue Bank was created within the Public Medical-Sanitary Institution Clinical Hospital of Traumatology and Orthopaedics, under the leadership of Professor Viorel Nacu [15, 16].

With the establishment of the Transplant Agency, the activities in the field of transplantation were relaunched, such as organ transplantation from a living donor, tissue transplantation from a deceased donor. The Transplant Agency in collaboration with the transplant coordinators from the authorized medical-sanitary institutions, the procurement and transplantation teams, the Human Tissue Bank during the years 2010 - 2019 organized and monitored the procurement and transplantation activities, as follows: monitoring of 603 cases of potential deceased donors, of which 65 became actual organ donors and 163 - actual tissue donors; 148 organ transplantations, of which 92 - kidney and 56 - liver; tissue transplantation: 195 - cornea, 1109 - bone, 326 - amniotic membrane, 116 - skin and 50 - tendon.

1.2. Medical, organizational and logistical particularities in human tissue and/or cell transplantation

We are entering a new era of medical and biotechnological progress [17]. An aspect of recent and rapid advances in biological and medical research is that human tissues and cells are used in a wide range of pathologies [18]. More than 4.000 tissue establishments collect and supply approximately one million donated tissues and cells each year, including cornea, heart valves, and bone marrow [19]. Transplantation as a treatment option has undeniable advantages. However, the use of human tissues and cells poses safety issues, quality and effectiveness, and presents new ethical dilemmas [20].

World Health Organization (WHO) presented two reports - First and Second Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation (2004 and 2006, respectively) providing an overview regarding the relevance and development of this field in different countries. The First WHO Report defines the tissue and cell grafts as a specific class of medical products with an important therapeutic value where almost no substitutes for restoring vital functions exist [21]. The other Report highlights the importance of

systems safe for traceability and biovigilance, underlining the fact that, for instance, annually, in Spain almost 10.000 patients get bone, tendon or corneal grafts [22].

The whole process of organizing of tissue and cell transplantation field is complex. The history in different types of tissue and cell banks underscore the complicated and interconnected ways the tissues and cells donated by one person may be used to help others or themselves [3]. Centralized management of tissue and cell donation could be an ideal mechanism [20]. Safe and sustainable supply of tissues and cells is an essential pillar in modern medical assistance and a priority for the health authorities at national level. The main aim to preserve human material for transplantation in a bank is to satisfy the clinical demand of tissues and cells. Discussions on how best to increase tissue and cell stocks often focus on the issue of donor motivation: in particular, how people can best be encouraged to donate different types of human material.

1.3. Legislative perspectives in the field of human tissue and/or cell transplantation

The European Commission carried out the first formal evaluation of EU legislation on human tissues and cells, starting with the basic acts adopted in 2004, and published the results on 10.10.2019 [19]. The evaluation of the legislation has shown that many of the current safety and quality standards are outdated and difficult to keep pace with rapid changes in the field, due to scientific and technological developments, diversification of digital tools, intensification of epidemiological outbreaks associated with increased global mobility.

While the legal framework encourages unpaid voluntary donation, the current provisions are insufficient to support an adequate and sustainable supply for tissues and cells. This evaluation also identified a lack of provisions and actions to ensure continuity of supply, both with substances of human origin and with devices needed to prepare these substances for use in emergencies. The results of the evaluation also suggest that the rules for national surveillance are not specific or appropriate, leading to divergent approaches in surveillance, reduced mutual trust and barriers to exchange and access to such therapies.

2. MATERIAL AND RESEARCH METHODS

2.1. The general characteristics of research methodology

Hypotheses defined in the research:

- The human tissue and/or cell transplant service is incorporated in and is a component part of the national transplant system;
- Systematic analysis of transplant activities is useful for identifying solutions to improve donation and transplantation processes;
- The separation of tissue donors and organ donors is largely artificial;
- Public attitudes towards donating tissues and/or cells are similar to attitudes towards receiving tissues and/or cells.

The research was conducted based on the information about the transplantation field of the health system, with reference to national and international data and sources. Underlying the research is analysis of key elements in the activity of donation and transplantation of human tissues and/or cells during the years 2011 - 2017.

2.2. The general characteristics of the surveyed lots

For the evaluation of the doctors' opinion, the general totality of all medical staff with higher education, involved in the provision of human tissues and/or cells donation and transplant services as well as of all medical staff from the medical-sanitary institutions, that is going to be

involved in the provision of these services was used. Through the questionnaire, the opinion of 161 doctors from 24 medical-sanitary institutions was evaluated.

The selective study was performed to determine the public attitude and knowledge towards tissue and cell donation and transplantation. The volume of the representative sample of respondents from the adult population was calculated based on the classic formula, proposed for the random survey without repetition, and constituted 427 respondents.

2.3. Research methods

The opinion poll was used as a research method with the elaboration of 2 questionnaires, addressed to doctors and respondents from the adult population.

2.4. Methods for statistical evaluation of the results

Statistical processing of the material was based on the special files elaborated where the primary data were coded - the results of the questionnaires. The analysis of the data was computerized using the software „Statistical Package for the Social Science” version 20.0 for Windows (SPSS, Inc., Chicago, IL, 2011). The results are based on descriptive and inferential statistics.

3. EVALUATION OF PUBLIC KNOWLEDGE AND ATTITUDE TOWARDS HUMAN TISSUE AND/OR CELL DONATION AND TRANSPLANTATION

3.1. The characteristics of respondents from the adult population

The self-administered questionnaire was voluntarily completed by 246 (57.6%) women and 181 (42.4%) men. Depending on age, the respondents were distributed as follows: 156 (36.5%) persons were aged within 18 - 34 years, 145 (34.0%) persons - within 35 - 54 years, 126 (29.5%) persons - within 55 - 82 years (figure 1).

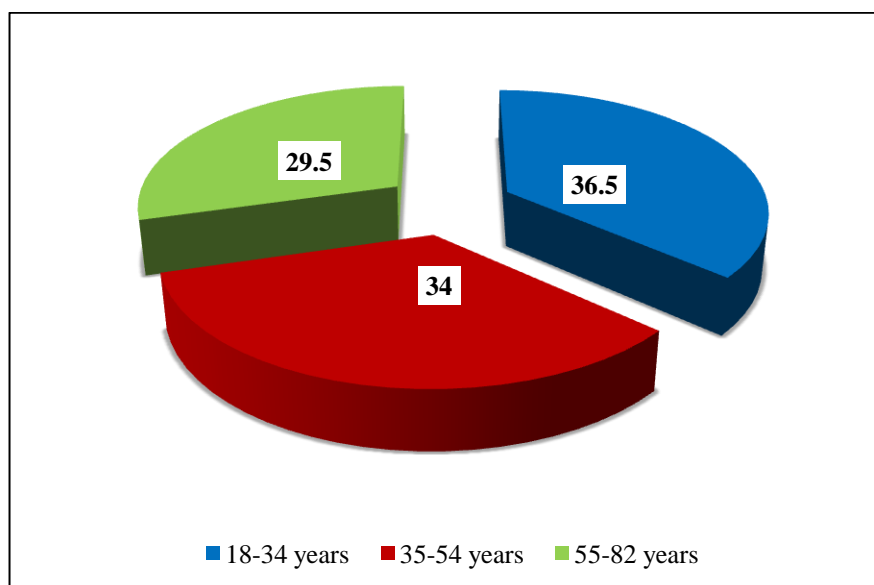


Figure 1. Distribution of the respondents depending on age (%)

The analysis of the distribution of respondents depending on age found, that the share of women under the age of 35 ($p < 0.05$) and men aged within 35 - 54 years ($p < 0.05$) significantly prevails among respondents. The survey showed that the respondent from the adult population was presented by an urban woman aged 18 - 34, with university education and was registered as an employee.

3.2. Consent to human tissue and/or cell donation

The respondents' attitude towards tissue and cell donation and transplantation has been analysed. We found that the vast majority of our respondents 346 (81.0%) agreed with tissue and cell donation and only 40 (9.4%) respondents did not accept this (figure 2). Statistically significant differences in those opinions depending on gender were not found ($p>0.05$).

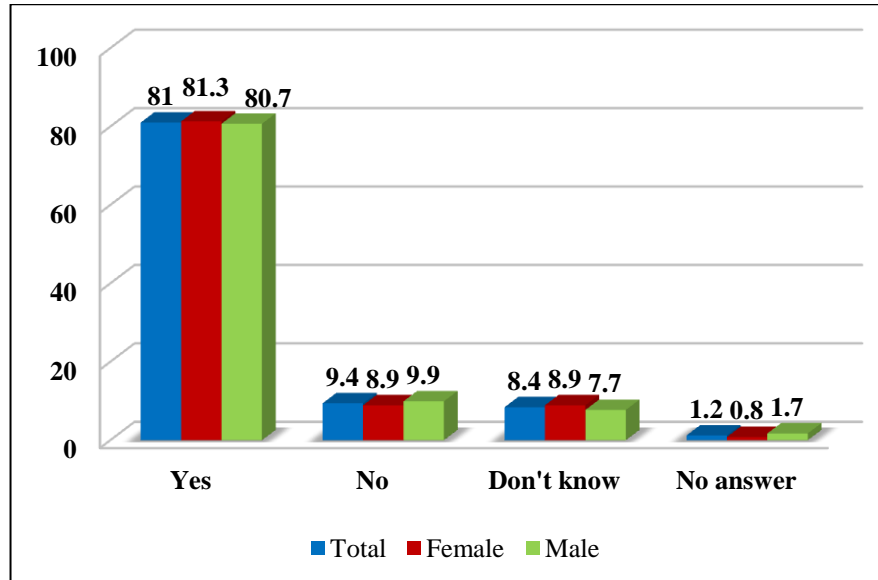


Figure 2. Willingness to donate tissue and/or cell (%)

The estimation of frequency of this opinion depending on educational level found statistically significant differences. The respondents with university education agreed with tissue and cell donation, statistically more frequently compared to the respondents with incomplete secondary education (87.0% and 67.1%, respectively; $p<0.001$), and the respondents with high school or college education agreed with donation, statistically more frequently compared to the respondents with incomplete secondary education (85.1% and 67.1%, respectively; $p<0.01$) (figure 3).

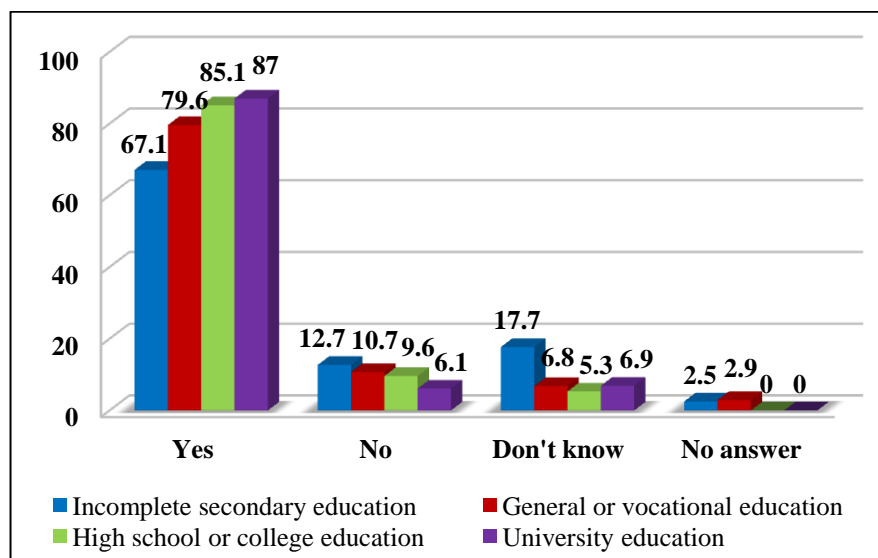


Figure 3. Willingness to donate tissue and/or cell by educational level (%)

3.3. Consent to human tissue and/or cell transplantation

The study showed that if necessary, the significant majority of the respondents 291 (68.1%) would agree to receive tissues and cells from other people, 61 (14.3%) respondents would not accept this, 69 (16.2%) respondents did not know and 6 (1.4%) respondents did not answer (figure 4).

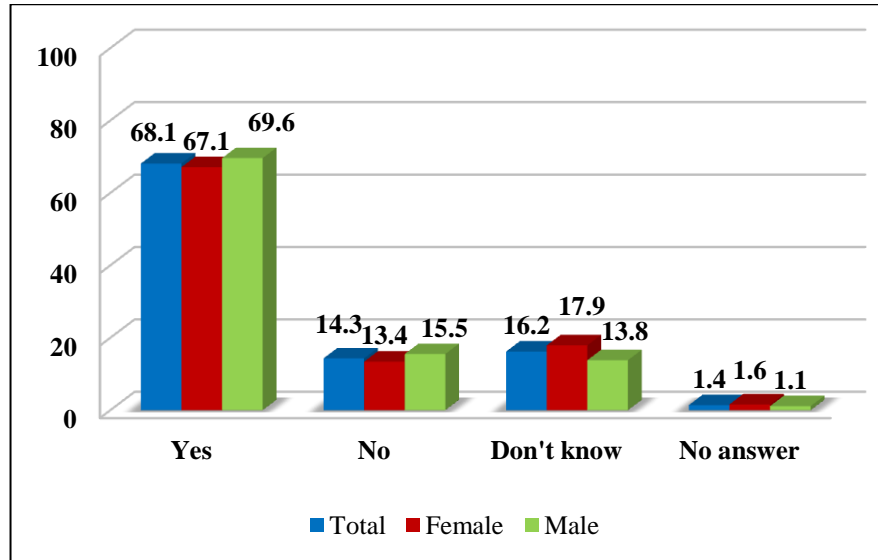


Figure 4. Willingness to receive tissue and/or cell from other people (%)

3.4. Public knowledge in the field of tissue and/or cell donation and transplantation

The evaluation of the quality and quantity of information on tissue and/or cell donation and transplantation found that 183 (42.9%) respondents considered they had insufficient information, 157 (36.8%) respondents considered this information sufficient, 71 (16.6%) respondents did not know, 16 (3.7%) respondents did not answer (figure 5).

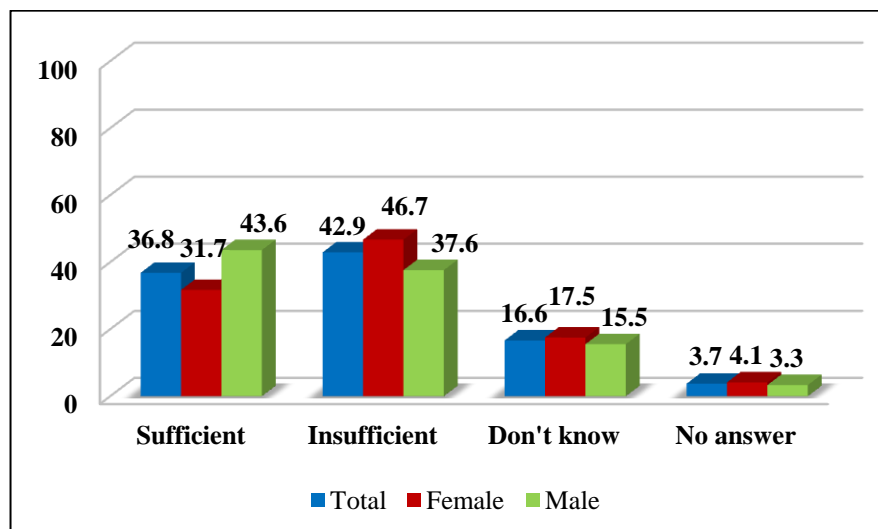


Figure 5. Volume of information on tissue and/or cell donation and transplantation (%)

4. PERCEPTION OF DOCTORS FROM THE FIELD OF HUMAN TISSUE AND CELL TRANSPLANTATION ON THE SERVICES PROVIDED

4.1. The characteristics of the respondents (doctors) involved in the transplantation field at national level

Depending on the specialty, the respondents in the study group were distributed as follows: 75 (46.6%) of orthopaedic traumatologists and combustologists, 36 (22.3%) of doctors with another surgical profile (oncologists, neurosurgeons, gynecologists, urologists), 28 (17.4%) of general surgeons and 22 (13.7%) of ophthalmologists (figure 6).

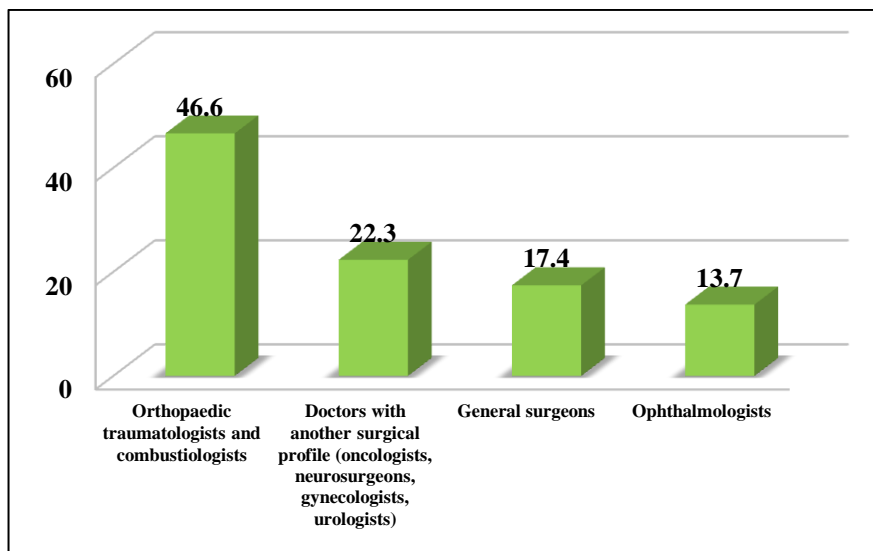


Figure 6. Distribution of doctors depending on the speciality in 2018 (%)

4.2. Opinion of the doctors surveyed on the availability of tissue and/or cell grafts

The estimation of doctors' opinion regarding the availability of the grafts showed the following: 63 (59.4%) respondents consider that their institutions have enough grafts, 23 (21.7%) respondents consider that their institutions deal with exceptional cases of lack of grafts, 14 (13.2%) respondents consider that there are sufficient grafts for urgent patients and, sometimes, for non-urgent patients, where 6 (5.7%) respondents consider that grafts are enough only for patients in emergency need (figure 7).

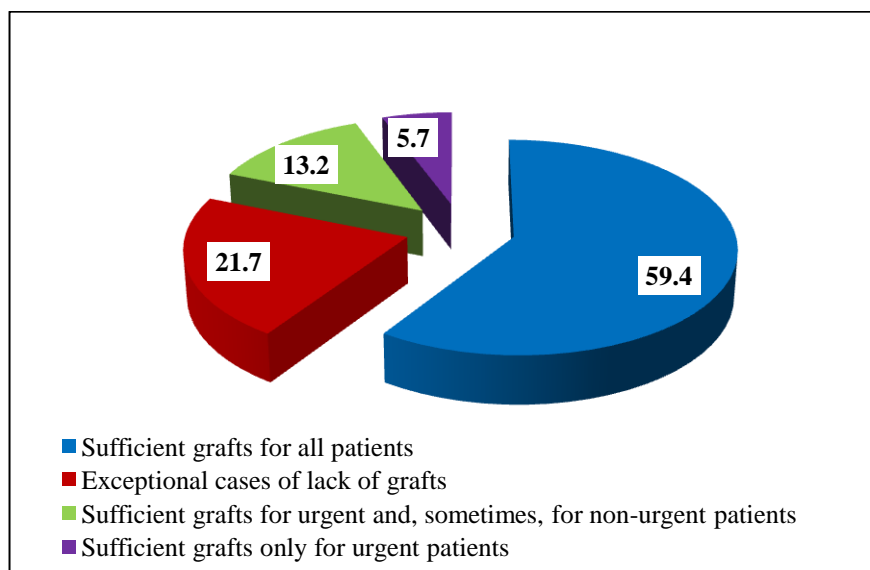


Figure 7. Doctors' opinion regarding the availability of tissue and/or cell grafts (%)

4.3. General perspectives of human tissues and/or cells transplantation

The results of the survey showed that 100 (94.3%) doctors from the medical-sanitary institutions with activities in the field of tissues and cells donation and transplantation consider that the increasing in number of tissue grafting surgeries performed in their institutions would contribute to improve the patient's life quality, about 64 (94.1%) doctors declared that enlarging the types of tissue transplanted is a very necessary measure (figure 8). Over 2/3 (117 - 72.7%) of doctors from all medical-sanitary institutions participating in the survey consider that increasing the number of transplanted patients in the next 5 years is a priority for the institution management.

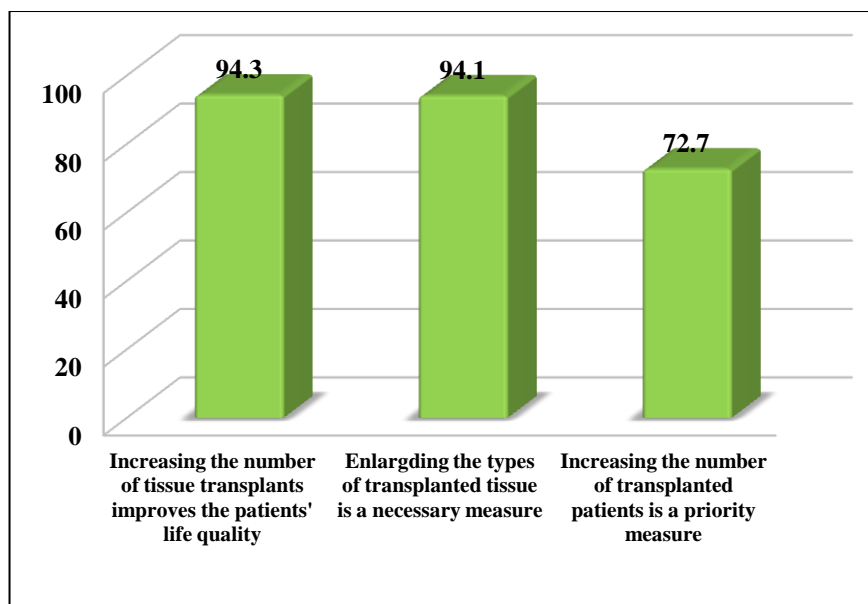


Figure 8. Opinion of doctors from the institutions with transplant activities regarding the perspective of human tissues and/or cells transplantation (%)

5. THE FIELD OF HUMAN TISSUE AND/OR CELL TRANSPLANTATION IN PUBLIC HEALTH INSURANCE

5.1. Activities in the field of human tissue and/or cell transplantation in the Republic of Moldova

As a result of the research, it was established that the human tissue and/or cell transplant service is a component part of the national transplant system of the Republic of Moldova and includes the following components:

1) the Transplant Agency, as a public institution, is responsible for organizing and supervising all transplant activities at the national level;

2) 16 public and private medical-sanitary institutions authorized from 2011 to 2017 to carry on tissue procurement and transplantation, including 2 laboratories to carry out mandatory biologic tests for donors;

3) 8 transplant coordinators for identifying, evaluating the potential donors and organizing procurement activities, 16 doctors and 5 medical assistants responsible for transplantation activities;

4) the national waiting list for corneal transplantation, developed in accordance with the legislative provisions in the field of transplantation to ensure the distribution of corneal grafts

according to common rules, approved in the Standard on the organization and conduct of procurement and transplantation of human organs, tissues and cells;

5) the Human Tissue Bank is the specialized unit that carries out activities of processing, conservation, storage and distribution of human tissues and cells for transplantation;

6) electronic databases: „TRANSPLANT” Automated Information System, additional automated information systems „Potential of Donation” and „Waiting list for corneal transplantation” ensures the record and management of activities in the field of human tissue and/or cell donation and transplantation.

5.2. Organization of the Human Tissue Bank

The Human Tissue Bank is a component part of the national transplant system. From the moment of procurement until the graft is transplanted, a series of stages are followed, systematized according to a certain protocol, structured depending on the source used for its preparation.

The general and ethical principles underlying the financing process are: the marketing of tissues and cells is not permitted; the fee must include direct and indirect costs, which are reimbursable costs and may include a part for research and development; tissue and cell transplantation is an activity of general interest, as well as organ transplantation; each stage is subject to an authorization process; transparency is the key to reliability; data on human tissue and cell transplantation activities are controlled and monitored by the Transplant Agency. Assessment of tissue and cell transplant needs at the national level is the key to the procurement adaptation process. Structural financing of this field includes the following basic aspects: financing for the identification of deceased donors, for the actual activity of the Human Tissue Bank and for tissue transplantation, being independent of each other.

We propose there to be the Human Tissue Bank financing as follows: only one funder should be involved in creating a general budget, which should be called a structural budget for any type of expenditure (both general and resources), in order to control the management and sustainability of the Human Tissue Bank. It should also be possible to readjust this structural budget, considering the future activity and the number of professionals involved in the work of the Human Tissue Bank.

In order to record and manage all the activities of the Human Tissue Bank, the Automated Information System has been developed, which ensures the confidentiality, integrity, protection and audit of the data stored in the system and is based on a number of international standards. The implementation of this system will allow the creation of a secure system for collecting, processing, storing, distribution of tissue and cell grafts at the level of contemporary requirements.

5.3. Traceability and biovigilance in human tissue and/or cell transplantation

In order to ensure the traceability of all tissues and/or cells, „a set of information and measures, documented and recorded, has been established, which allow: the establishment of links between the donor and the bank supplying processed tissues and/or cells, on the one hand, and recipient and the authorized the medical-sanitary institution that uses the tissues and/or cells, on the other hand; tracking and identification of tissues and/or cells during each stage”.

To ensure the implementation of quality and protection standards for tissues and/or cells used for transplantation, a biovigilance system has also been developed to identify, report and investigate serious adverse events and reactions related to transplant activity. Biovigilance is a fundamental non-punitive tool for improving the safety of tissues and/or cells in transplantation,

which includes: a list of possible *events* that could occur at each stage of the process; a list of possible *adverse reactions* by tissue type; minimum information for reporting; the *actions* required in case of notification of serious adverse reactions or events; recommended *tests* for accumulating information and investigating a serious adverse event.

5.4. The needs for human tissue and/or cell grafts

An organ donor after brain death became also a tissue donor for the first time in the Republic of Moldova in 2014. From year to year this figure increases and in 2016, already 8 organ donors out of 31 deceased donors became multiple tissue donors (25.8% of the total number of actual tissue donors). Then in 2017, 11 organ donors out of 23 deceased donors also became multiple tissue donors (47.8% of the total number of actual tissue donors) (figure 9), an increase of 140%.

The research confirms that in the Republic of Moldova, as in other countries of the world, the separation of tissue donors and organ donors is largely artificial. During the research period, the population of the Republic of Moldova gave consent for tissue donation 2.4 times more frequently than for organ donation, a situation similar to that of many countries in the world.

Therefore, during the research, an average of 6.8 actual deceased tissue donors and 6.4 actual living tissue donors per million of population were registered annually (figure 50, 51).

During the study, a comparative analysis of data on the number of actual donors in EU countries for 2018 was performed with data from the Republic of Moldova.

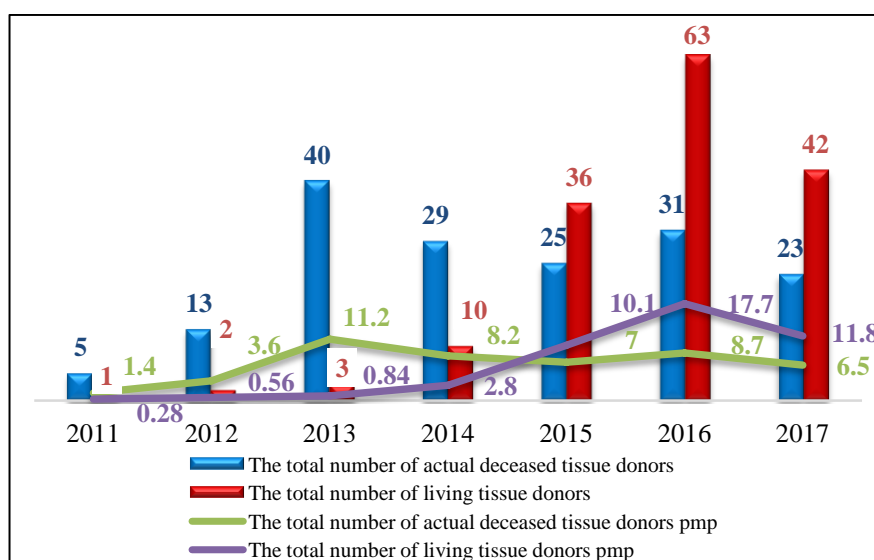


Figure 9. Number of actual tissue donors, deceased and living, in the period 2011 – 2017

At the level of EU countries in 2018, the number of actual deceased tissue donors was 275.8 per million of population (data presented by 20 countries with 414.8 million of population) (figure 10).

In the Republic of Moldova, the estimated annual needs are at least 31.5 tissue and/or cell donors per million of population (11.4 deceased donors and 20.1 living donors), but actually donate 2.4 times less (figure 10).

Availability of corneal grafts. The small number of donors and the insufficiency of tissues and/or cells for the treatment of many serious pathologies represent a major problem faced by the Republic of Moldova. The need for transplants exceeds the rate of tissue donation.

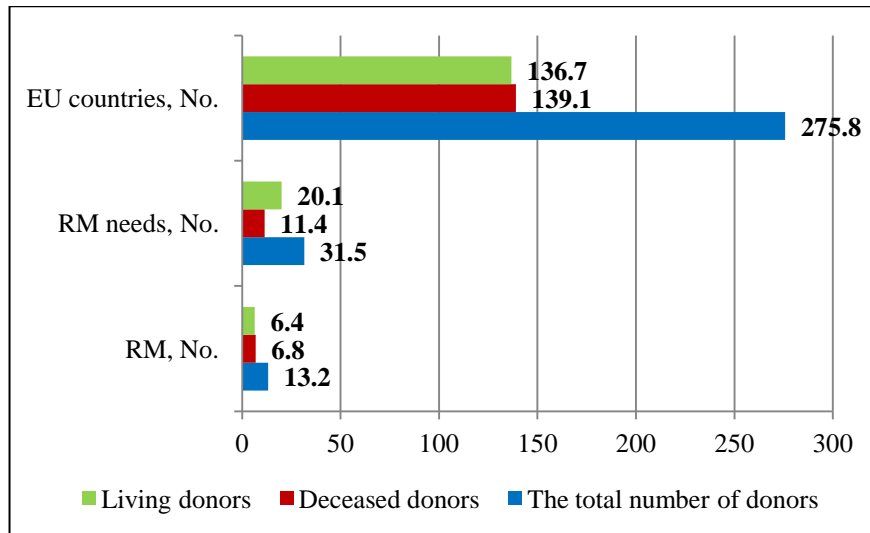


Figure 10. **Number of actual donors, per million of population in 2018**

The waiting list for corneal transplants is growing steadily, the average of 27.25 ± 9.9 patients per year, or 7.8 patients per million of population. The rate of patients who received corneal transplants compared to patients enrolled in the waiting list varied depending on the actual number of donors, and was the highest in 2013 and accounted for 77%, then decreased to 11.8% in 2015, and subsequently increased to 21.1% in 2017 (figure 11).

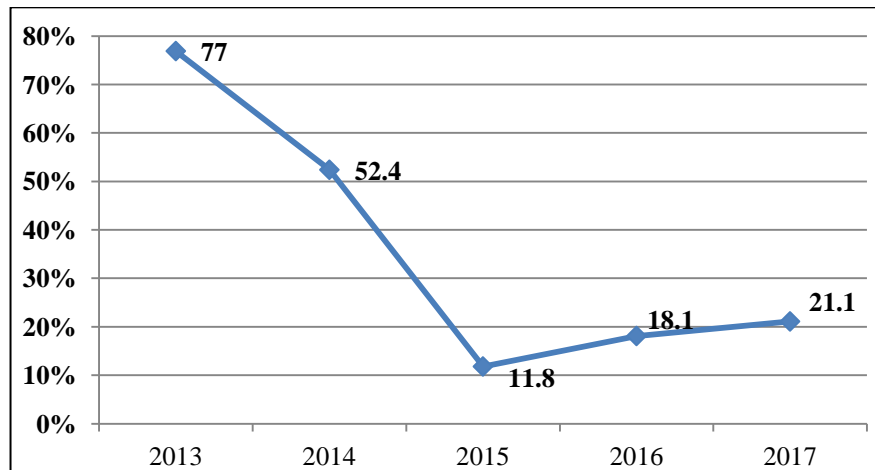


Figure 11. **Rate of patients who received corneal transplants in the report with patients enrolled in the waiting list in the period 2013 – 2017 (%)**

During the research period, the total annual number of corneal transplants in average was of 9.5 with 9.5 grafts per million of population (figure 12). The rate of transplanted patients compared to patients on the waiting list averaged $36.1 \pm 11.7\%$ (10.3 patients per million of population), that is, only 1 cornea available for almost 3 patients in need of a transplant. Thus, in order to achieve 100% coverage of corneal transplant services in relation to needs, it would be necessary to perform ≈ 26.3 corneal grafting surgeries per million of population annually (figure 12).

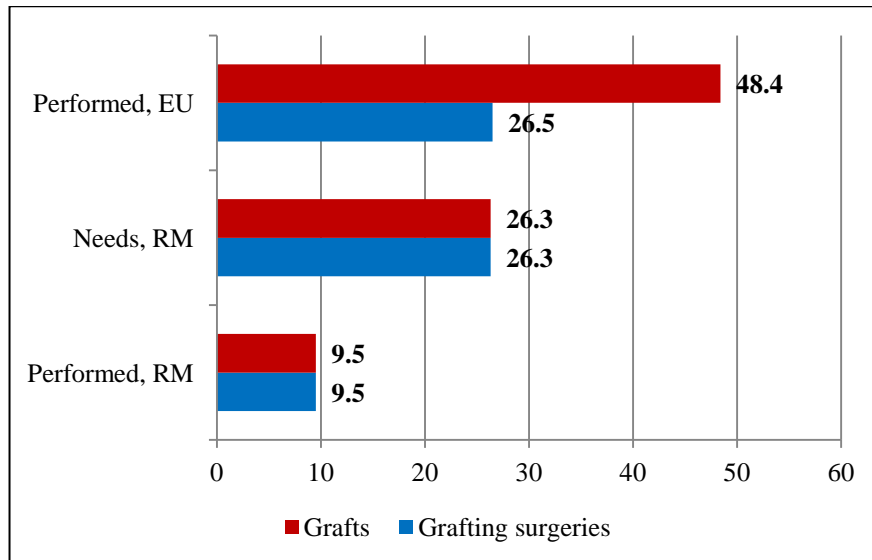


Figure 12. **The number of corneal transplants per million of population in 2018**

The study carried out a comparative analysis of average data on tissue transplants in EU countries for 2018, with data from the Republic of Moldova. At the level of EU countries, in 2018, 26.5 ophthalmic tissue transplants were performed with 48.4 grafts per million of population (data provided by 21 countries with 416.0 million of population) (figure 12). Therefore, the estimated annual needs for the Republic of Moldova correspond to the number of corneal grafting surgeries performed in EU countries.

Availability of bone and ligaments/tendons grafts. During the study, the total annual number of musculoskeletal tissue transplants in average was of 39.2 with 76.5 grafts per million of population (figure 13). The estimated annual needs are at least 55.7 musculoskeletal tissue grafting surgeries with 108.2 grafts per million of population, so it requires 1.4 times more grafts than are transplanted (figure 13). At the same time doctors need bone grafts provided in other forms than the frozen one.

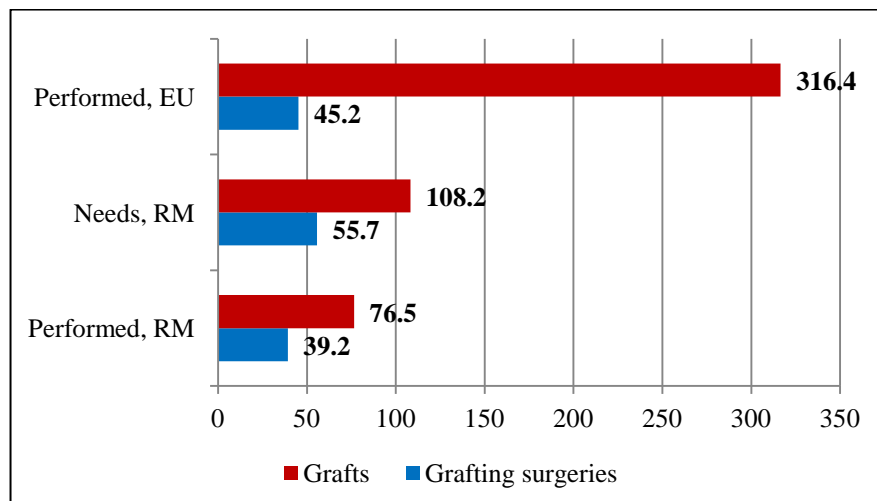


Figure 13. **The number of musculoskeletal tissue transplants per million of population in 2018**

At the level of EU countries, in 2018, 45.2 musculoskeletal tissue transplants were carried with 316.4 grafts per million of population (figure 13). So, the number of musculoskeletal tissue

transplants performed in the Republic of Moldova is approaching the number of those carried in EU countries.

Availability of skin grafts. During the research period, the total annual number of skin transplants in average was of 4.8, with 26.0 grafts on a surface of 3178.8,8 cm² per million of population.

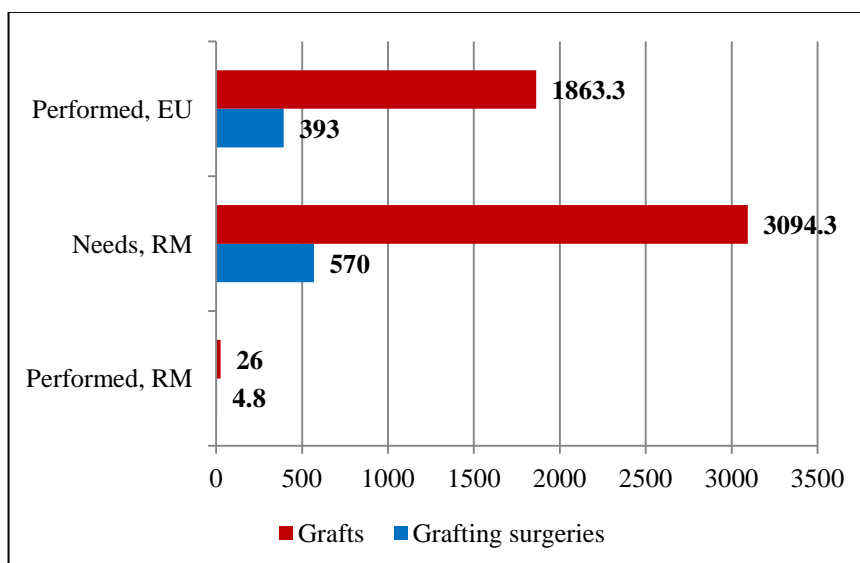


Figure 14. **The number of skin transplants per million of population in 2018**

The estimated annual needs are at least 570 skin grafting surgeries with 3094.3 grafts on a surface of 377285.7 cm² per million of population, so it requires 119 times more grafts than are transplanted (figure 14).

At the level of EU countries, in 2018, 393 skin transplants with 1863.3 grafts were carried per million of population (figure 14). Therefore, the estimated annual needs for the Republic of Moldova exceed the number of skin transplants performed in EU countries.

Availability of amniotic membrane grafts. During the study, the total annual number of amniotic membrane transplants in average was of 15.6, with 18.1 grafts per million of population in case of ocular pathologies, and of 4.4 transplants, with 11.5 grafts per million of population with burns.

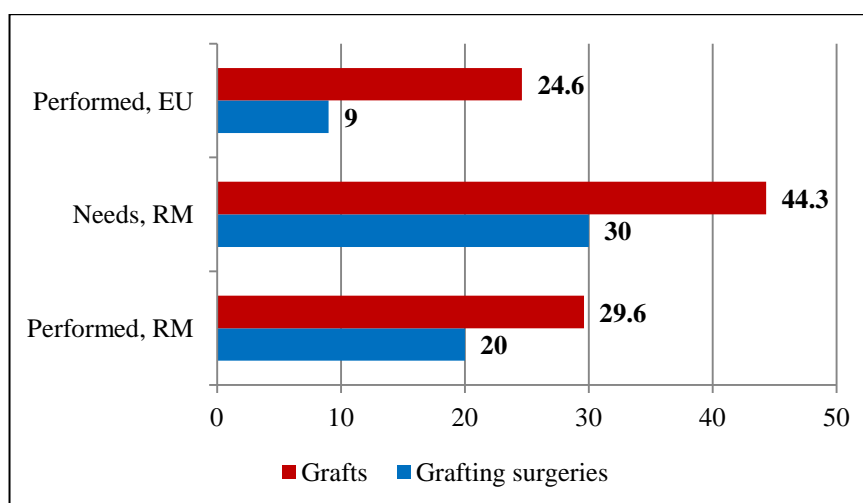


Figure 15. **The number of amniotic membrane transplants per million of population in 2018**

The estimated annual needs are at least 23.4 amniotic membrane grafting surgeries with 27.15 grafts per million of population in the case of ocular pathologies, 6.6 grafting surgeries with 17.2 grafts per million of population in the case of burns, so it requires 1.5 times more grafts than are transplanted (figure 15).

At the level of EU countries, in 2018, 9 amniotic membrane transplants with 24.6 grafts were performed per million of population (figure 15). So, the number of amniotic membrane transplants performed in the Republic of Moldova exceeds twice the number of those performed in EU countries.

Availability of stem cell grafts. Hemoblastosis are common in the Republic of Moldova. In 2018, there was an incidence of 22.9 per 100 thousand population, the morbidity through these tumours among the adult population, as well as among children is increasing. Among children, the number of new cases of malignancies was 12.1 per 100 thousand children in 2018. Therefore, in the Republic of Moldova 64.6 patients per million of population require annual stem cell transplants (figure 16).

At the level of EU countries, in 2018, 112.9 stem cell transplants were performed in 96.5 patients per million of population, of which 46.5 autologous transplants to 35.6 patients per million of population, that is, 36.9% of patients per million of population benefited from autologous transplantation (data presented by 20 countries with 426.8 million of population) (figure 16).

In the Republic of Moldova, the needs can be estimated based on data from EU countries, so 75.6 transplants to 64.6 patients per million of population per year would be required, of which 23.8 (36.9%) patients per million of population can benefit from 28.6 autologous grafts (figure 16).

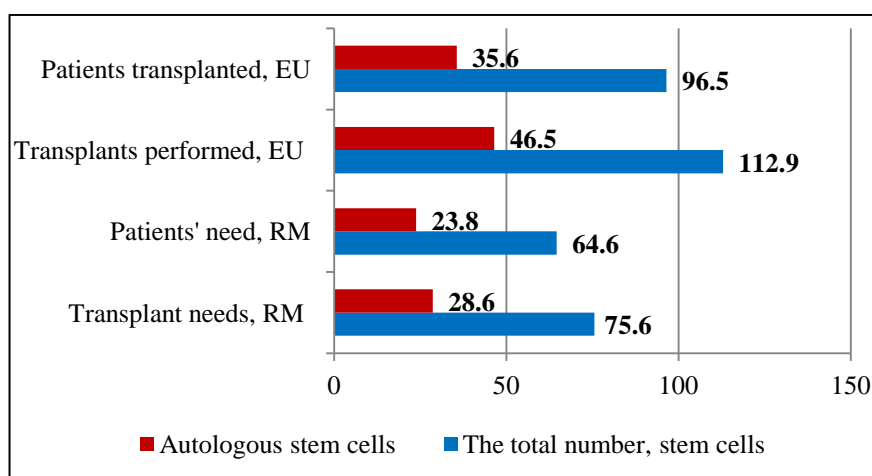


Figure 16. **The number of stem cell transplants per million of population in 2018**

GENERAL CONCLUSIONS AND PRACTICAL RECOMMENDATIONS

Conclusions

1. The national health authorities are responsible to ensure that the patients' needs are satisfied with a safe, qualitative and appropriate source of tissues and cells. The central role of the human tissue and cell bank is in providing tissues and cells for treatment, as well as for research. To perform complex tasks are required: proper assessment of the demand for human tissues and/or cells for transplantation and innovative treatments, storage services, purchase of

state-of-the-art materials for safe, high-quality procurement, processing and preparation of the allografts.

2. The evaluation of public attitude towards tissue and/or cell donation and transplantation showed that the majority of our respondents (81.0%) generally agreed with human tissues and/or cells donation, and 81, 7% would agree to donate their tissues and/or cells during their lifetime for a family member. More than two-thirds of respondents would agree to have the tissues and/or cells transplanted from other people and would accept post-mortem self-sampling of healthy tissue to be transplanted to others.

3. The results of the estimation of doctors' opinion regarding the availability of human tissue and/or cell grafts showed that 40.6% of doctors consider that there are reserves in providing patients with tissues and/or cells. Depending on the type of grafts, from 44.7% to 57.5% of doctors from the medical-sanitary institutions with activities in the field of tissue and/or cell donation and/or transplantation would transplant more grafts, 64.2% of doctors plan to expand the types of transplanted tissues and/or cells over the next 5 years and 88.2% of doctors will need bone grafts offered in other forms than the frozen one.

4. The human tissue and/or cell transplant service is incorporated in and is a component part of the national transplant system of the Republic of Moldova. Although the national legislation in the field of human tissue and/or cell transplantation supports donation, and the regulatory system authorizes and inspects procurement and transplantation centres, the Human Tissue Bank still faces organizational, financial, educational problems that have a negative impact on transplant efficiency and requires solution by developing a clear strategy for continuous development.

5. Complex assessment of the structure and key elements of human tissue and/or cell transplant service at national level, as well as an estimate of the degree of insurance of the health system in the Republic of Moldova with tissue grafts (cornea, bones, ligaments/tendons, skin, amniotic membrane) and cell grafts (stem cells), with the scientific argumentation of further development directions determined that the provision of tissue and cell grafts is sufficient in the opinion of only 63 (59.4%) of doctors surveyed.

6. To meet the needs of practical medicine and to ensure minimum stocks in the Human Tissue Bank, as well as to ensure increasing requirements for other types of tissues and cells, at least 31.5 actual tissue and/or cell donors are needed, 26.3 corneal grafts, 108.2 musculoskeletal tissue grafts, 3094.3 skin units, 44.3 amniotic membrane units and 75.6 stem cell grafts per million of population.

7. During the research, the financing mechanism and the Regulation of the Human Tissue Bank activity were elaborated, with the stipulation of clear attributions and complex tasks, which would guarantee the supply and promotion of the proper use of human tissues and cells and support an adequate and sustainable supply of tissues and cells, in the context of the significant increase in demand, as well as to ensure strategic stocks of tissues, which will be very useful in case of exceptional situations in the country (e.g. skin grafts, amniotic membrane in case of large fires, explosions, etc.).

Practical recommendations

The Ministry of Health, Labour and Social Protection:

1. To identify a minimum number of human tissue and/or cell transplants that an institution must perform in order to be authorized or to maintain its authorization, as well as determine the number of institutions that must be authorized, depending on the number of population;
2. To introduce the performance indicators to assess the effectiveness of the activities of authorized medical-sanitary institutions dealing with donation and procurement from deceased donors and audit of donation and transplantation processes: the number of actual organ/tissue donors shall make at least 5% of the total number of deaths per ICU, the number of actual tissue donors shall make at least 2.5% of the total number of deaths per medical-sanitary institution;
3. To monitor the transplant activities based on the following indicators: „*incidence of diseases requiring tissue transplantation (cornea, musculoskeletal, skin, amniotic membrane) per 1 million of population; the incidence of diseases requiring stem cell transplantation per 1 million of population; tissue transplant rate (bone, skin, ligaments/tendons, cornea) per 1 million of population; the rate of corneal transplanted patients compared to patients on the waiting list; success rate of tissue transplant treatment (cornea, musculoskeletal, skin, amniotic membrane); coverage rate with tissue transplant services (cornea, musculoskeletal, skin, amniotic membrane) and stem cells*” [186];
4. To implement the donation program, based on public awareness strategies, which should promote not only organ donation, but also tissues and cells donation; on the effective systems to facilitate the recruitment of living donors in an ethical manner and to ensure their safety and well-being, as well as the identification and referral of all potential deceased tissue donors; on the appropriate training of professionals involved in the recruitment or identification of donors;
5. The national autonomy of the Human Tissue Bank with its relocation to a place that meets international standards and allows the development of specific activities of the Bank, ensuring the health system of the Republic of Moldova with safe, harmless and effective grafts in the treatment of various human diseases, strengthening the Bank's capacity and creating the possibility of human cells storing;
6. It is suggested to promote the training of specialists based on the best practices and advanced experiences; endowment the medical-sanitary institutions with the necessary medical equipment.

The Transplant Agency:

1. To adoption and implement the Barcelona Principles in order to ensure compliance with the rules and monitoring of all stages, from donation to human application of human tissues and/or cells, in the interests of patient safety and public transparency;
2. To implementation the biovigilance system, which would allow the identification, reporting and investigation of serious events and adverse reactions that occurred during transplantation, with the involvement of the Human Tissue Bank;
3. To implement a financing model for human tissue and/or cell transplant activities based on reliable methodologies for cost assessment (tissue processing is a standardized activity); separate funding at each stage (procurement, processing and storage) so that the Human Tissue Bank can cover losses resulting from tissue invalidation;
4. Annual assessment of the degree of assurance of the health system with different types of human tissues and cells and ensuring minimum stocks in the Human Tissue Bank to cover the needs of practical medicine, including new types of tissues and cells. This requires a complex analysis of the donation and transplantation process at the national level, the activity of the

Human Tissue Bank, the morbidity of the population through various diseases that require transplantation;

5. To implement the coding of grafts according to the unique European codes within the automated information system, which will facilitate the identification of grafts produced in the Human Tissue Bank;

6. To elaborate the authorization procedure for the procurement of human tissues and cells for the production of advanced therapy medical products in the Republic of Moldova;

7. To identify effective methods to promote the donation and transplantation activity, leading to an increase in the level of information and awareness of the population on the importance of donating human tissues and/or cells to save other lives.

The Human Tissue Bank:

1. To strengthen capacity of the Human Tissue Bank, create a complex system of the Human Tissue Bank activity, with a view to its subsequent authorization by the EU and inclusion in the EU Compendium of tissue establishments;

2. The financing of the Human Tissue Bank cannot be directly associated with the activity of human tissue and/or cell transplantation, because the Tissue Bank also has a national destination - to ensure strategic tissue stocks, which will be very useful in the case of exceptional situations in the country (for example skin grafts, amniotic membrane in case of big fires, explosions, etc.);

3. When calculating the operational costs of the unique public Human Tissue Bank in the Republic of Moldova and maintaining its long-term viability, it is important that the clinical need be analyzed annually for different types of human tissues and/or cells and costs related to procurement, processing, storage, distribution, personnel, transport, infrastructure and administration, as well as to the incorporation of state-of-the-art processes and equipment be managed efficiently;

4. To implement the automated information system for the registration of grafts within the Human Tissue Bank with subsequent interconnection with „TRANSPLANT” Automated Information System to ensure the traceability of tissues and cells procured and transplanted;

5. To implement the coding of grafts according to the unique European codes within the automated information system, which will facilitate the identification of grafts produced in the Human Tissue Bank and the tracking of their path and, at the same time, will allow the integration in the European network of tissue banks.

The authorized medical-sanitary institutions:

1. Procurement of medical equipment necessary for carrying out the activities of human tissue and/or cell transplantation;

2. Each authorized institution should continuously carry out internal audits of donation and transplantation processes, assess its donation potential and effectiveness on the basis of indicators developed in the current research. Depending on the results of the evaluation, the managers of the institutions should allocate appropriate budgets and implement the national transplant program.

The Ministry of Education, Culture and Research:

1. To create the working group, with the representatives of the Transplant Agency, the Human Tissue Bank, for the elaboration of teaching materials on the subject of donation and transplantation of human organs, tissues and cells, within the Curriculum of the optional subject „Health Education” for secondary education.

The scientific community:

1. To recognize that human tissue and cell transplantation plays a key role in modern medicine, medical research in this field is promising due to rapid scientific and technological

developments, providing effective solutions, including in the context of increasing epidemiological outbreaks associated with global mobility (COVID-19);

2. To develop clinical research projects with the use of advanced therapy medical products and their approval by the competent authority.

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