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EXAMPLES OF ANOMALIES TO THE EBM MODEL AND THEIR METHODOLOGICAL ROLE AND EPISTEMIC STATUS

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Abstract. One of the well-established methodological approaches in contemporary medicine is the Evidence Based Medicine (EBM) model. There are two methodological ideas that support this model: hierarchy of evidence and Randomised Controlled Trials (RCT's). In this work, I will present the examples that are standing out of the EBM model explanatory power. I will also show the methodological power of the EBM model into the process of diagnosis and treatment in contemporary medicine. One of the important problems in the field of philosophy of science will be used to present the anomalies problem in medical theories. The anomalies problem presented as a methodological problem of the EBM model is an open discussion concerning paradigm change in medicine. At the end of the paper some other ideas about progress in medicine will be put in for consideration.

Keywords: philosophy of medicine; anomalies; EBM; diseases; theories; medicine; progress in medicine

Introduction

This text is centered on classical problems from the field of philosophy of science with respect to problems from contemporary philosophy of medicine. A central theme in terms of which the text has been developed presents the problem of anomalies in medical theory and practice. Philosophical investigations in previous 60 years in the philosophy of science have been given as a methodological guideline to two very influential models in contemporary medical science. The introduction and establishment of the Evidence Based Medicine model at the beginning of 90's in the twentieth century served as a main medical paradigm subsided today, while the new model in medical science emerges – the so called Personalised Medicine.

Anomalies

The problem of anomalies is discussed both in philosophy and in medicine. In this way the anomaly is defined as something that do not confirm or is not accepted to be in the same way as already established knowledge. It is important to keep in

mind that there are different contexts when we try to analyse the anomalies problem in philosophy and in medicine. In the field of medicine, the concept anomaly is defined by the terms as *malformations*, *disruptions* and *deformations* (Stevenson & Judith 2005, pp. 4 – 6). According to medical literature anomalies are one of these three types of alterations and one forth category – *dysplasia* (Spranger, Benirschke et al. 1982). According to Stevenson and Hall (Stevenson & Hall 2005) *malformations* are caused by genetic sense, *disruptions* are caused by destructive force acting upon an otherwise normal developing structure, *deformations* are caused by extrinsic force on a normally developing or developed structure and *dysplasias* are cellular or tissue disorganization (Stevenson & Hall 2005, p.7). Most of the causes of anomalies and malformations are unknown in medicine. There is no unified definition of anomalies in medicine and the reason for this, according to Stevenson and Hall (Stevenson & Hall 2005, p. 4), is the different priorities for different group researchers of anomalies in medicine. There is no unified language describing anomalies and existing terms are formed in Greek, Latin and English languages. Examples of some anomalies in medicine are *spina bifida*, *anencephaly*, *heart defects* and *orofacial clefts*. In medical literature, the anomalies are classified as *major anomalies* and *minor anomalies*. According to this classification the difference between them is that the major structural anomalies have medical and social consequences while the minor anomalies have no significant health or social burdens. One of the important roles for the research of anomalies in medicine plays molecular embryology. For contemporary medicine the anomalies problem is of big importance not only in medical aspect, but also in social and ethical ones.

Anomalies in philosophy of science

The problem of anomalies in philosophy of science plays very important role and has a specific status connected to the central problems in this field like the problem of theoretical change, the demarcation problem and discussions about progress in science. The anomalies problem into the field of philosophy of science has to be placed on methodological and epistemological grounds. In this way, the philosophical understanding of anomalies has some common and some different features with the problem of anomalies in medicine. Here I will present some of the main ideas concerning the place and status of anomalies according to the philosophical conceptions of Tomas Kuhn, Karl Popper and Imre Lakatos.

The problem of the dynamics of theoretical change is central to the field of philosophy of science. According to Kuhn (Kuhn 1962) one of the important role in this process of change is played by the scientific community. The most prominent Kuhn's idea is the so called "paradigm shift". According to him, scientists work in two different circumstances. The first phase of scientists' researches is spread in the so called "normal science" where scientists from different communities work according to standards stated by the scientific paradigm. This phase is followed by

the process named the “scientific revolution” where the old paradigm is abandoned/rejected and the new paradigm is established. The key role into the process of rejection of a paradigm in Kuhn’s philosophy play the anomalies. Here, some of his central ideas about the role of anomalies into the process of theories change or replacement of old theory by the new one, will be presented. The definition of “normal science” as a cumulative process discloses the importance of accepted beliefs by the scientific community. In this period scientists develop their researches according to those established by the paradigm criteria. In this way science and especially scientific theories are objective, extended and interconnected, or as Kuhn writes *“It is what scientists are trained to do, ...”* (Kuhn 1970, p. 250). The normal science period is build on the settled achievements in science that necessitate the rules and methods of scientific investigation models. This is the process that establishes the paradigm in science and in this way the trends of the scientific researches are paradigm-based. Hence, it can be pointed that the idea of paradigm has been defended by the process of normal science and vice versa. The paradigmatic period of science is characterized as cumulative process according to Kuhn. Here, is important to extract the main features of this normal sciences phase. One of the salient characteristics in this period does not allow contradictions to accepted paradigm model in science. He describes the period of normal science as “puzzle-solving” (Kuhn 1962, pp. 35 – 42), or the process where scientific researches are focused on solving puzzles and adding new facts to support the accepted paradigm. It is important to bear in mind that in this period (“puzzle-solving”) anomaly does not play an important role. As a result the methodological role of anomaly is only to pay attention to the puzzles and to provoke the beginning of their solving by scientists. An important element of Kuhn’s philosophical model is the process of accumulation of unsolved anomalies. When this process comes to light the period of the “crisis” in science begins. Thence the methodological role and epistemic status of the anomalies are definitely different from those that are only prerequisite to puzzle-solving.

“When, for these reasons or others like them, an anomaly comes to seem more than just another puzzle of normal science, the transition to crisis and to extraordinary science has begun. The anomaly itself now comes to be more generally recognized as such by the profession. More and more attention is devoted to it by more and more of the field’s most eminent men. ... Through this proliferation of divergent articulations (more and more frequently they will come to be described as ad hoc adjustments), the rules of normal science become increasingly blurred.” (Kuhn 1965, p. 85)

The examples that Kuhn (Kuhn 1962) gives to promote the power of the anomalies to the period of crisis in science and consequently for the establishment of the new paradigm, are the emergence of *Lavoisier’s oxygen theory* (1777 - give the name oxygen and the name hydrogen (1783) as chemical elements) of

combustion, the Leyden jar as early experiments in electricity (1745 – 1746) – principles of electrostatics and the discovery of X-rays by Röntgen (8.11.1895)). In this way the epistemic status of anomalies is presented by their importance to the process of successful explanation through the principles of established paradigm or so called puzzle-solving actions. Here it is important to focus our attention to the methodological role of anomalies. Thus, the process of accumulation of unsolved anomalies in science is a strong argument to talk about crisis according to Kuhn and to introduce the idea of the “scientific revolution”. Accordingly, the important methodological role of the anomalies accumulation is given in relation to this view.

One of the prominent critiques to Kuhn’s idea of normal science in philosophy of science has been given by Karl Popper. According to Popper, scientific theories cannot be described as keepers of the dogmatic frames. He presents the idea of critical view to the problem of theoretical change in science. As it has been shown by him (Popper 1963) we can learn from our mistakes. One of the central Popper’s ideas is that only scientific theories can be described at the same time as falsifiable (theory is in conflict with basic statements) and falsified (theory is empirically refuted) or this is the so-called “criterion for falsifiability” that gives the solution to the problem of demarcation.

“One can sum up all this by saying that the criterion of the scientific status of a theory is its falsifiability, or refutability, or testability” (Popper 1963, p. 35)

Standing on these positions Popper cannot accept the Kuhnian idea of normal science because from the position of critical realism it is not allowed to keep theories from refutations. He argues that the idea of normal science is “dogmatic” and “not-too-critical” (Popper 1970, p. 52). In this direction he does not accept as relevant the idea of protection and defending of theories, but insists on a process of refutation of scientific theories. The Popper’s criterion for falsifiability presents a critique to attempts for protection from refutations of scientific theories. One of the important steps in his methodology, which has a negative evaluation, is the introduction of ad-hoc hypotheses in scientific theories. The negative connotation of ad-hocness in Popper’s philosophy comes from his idea about the possibility of theory refutation. Introduction of ad-hoc explanations of the anomalies to the theory, is criticised by him.

The two different positions of Popper and Kuhn reflect on two opposed philosophical approaches to the problem of anomalies in scientific knowledge. Regardless of the differences between them the problem of methodological role of anomalies to scientific theories is presented in their philosophical endeavors. According to this, the problem of anomalies is presented through the idea of “paradigms” in science, the idea of “falsificationsm” of scientific theories and connected to them by the idea of “research programmes”. Here I will present the philosophical project of Imre Lakatos (Lakatos 1970, pp. 91 – 195) in connection to the problem of progress in science. The problems that have been discussed

around the so called “context of discovery” and “context of justification” debate in philosophy of science, are still actual and even more, the debates are culminating around discussions of AI to the different contexts of contemporary science and society. The methodology of research programmes according to Lakatos presents the idea of scientific growth as “*progressive and degenerating problem-shifts*” (Lakatos 1970, p. 191). The main characteristic of scientific societies is “*continuity*” between members of scientific communities. The methodological rules of the programme define two type of *heuristic*: *negative and positive* ones. The role of the *negative heuristic* is to protect the so called “*hard core*” of the programme. To accomplish this, scientists can introduce auxiliary hypotheses and the goal here is to protect the hard core. The reason to build this hard core shield is to establish conditions that will make possible to produce only progressive problem-shift. So, the scientific growth is implemented and then the research programme is defined as successful (Lakatos 1970, p. 191). But if the research programme produces only “*degenerating problem-shift*”, then it is unsuccessful one. The example of the successful research programme, according to Lakatos, is Newton’s gravitational theory.

“When it was first produced, it was submerged in an ocean of “anomalies” (or if you wish, “counterexamples”), and opposed by the observational theories supporting these anomalies.” (Lakatos 1970, pp. 192)

Therefore, the most important for Lakatos is the ability to protect Newtonian laws (three laws of dynamics and law of gravitation) from refutations. And to achieve this, we must explain the existing anomalies by auxiliary hypotheses so as to protect the hard core. The *positive heuristic* tries to build its own models ignoring existing anomalies (counterexamples). The important idea here presents the theory building process as abduction from anomalies. Heuristics here is created on methodological ground and does not depend on observations or data, but are implemented instead of them (anomalies).

EBM model

As it has been presented here there are different contexts - in medicine and in philosophy – where the problem of the anomalies is analyzed. Kuhn’s idea of paradigm is well accepted into the discussions about the most influential methodology in contemporary medicine. There are big amount of papers where the so called Evidence Based Medicine (EBM) is defined as contemporary paradigm in medicine. Here, it will be presented the main important elements of EBM methodology. Gordon Guyatt introduced the term “Evidence-Based Medicine” in 1990 to mark the new method in medical practice. In the 1991 the Journal of American Medical Association (JAMA – Evidence Based Medicine Working Group. 1992, 268:2420 – 5) started new series that have to promote a new approach to the process of medical treatment of patients by clinicians. Into the heart of this new intention

is the idea to encourage clinicians to reflect on results of recent medical research when they practice medicine. The philosophers of medicine (Howick 2011) notice that some main ideas behind the so called new methods or the EBM have been evolving through the long historical tradition of medicine. The main resources for development of the EBM movement are methods from statistics and epidemiology. The Working Group at McMaster University (in Hamilton, Ontario, Canada) included Dave Sackett, Gordon Guyatt, Brian Haynes, and Peter Tugwell who introduced the new method into the process of clinical practice and respectively into the process of studying medicine. According to the EBM methodology, the importance of the mechanistic reasoning (pathophysiologic rational) is substituted by the so called clinical research into the process of medical practice. Thus, the most important for the new method in medical reasoning is focused on observation of the hypothesised outcome in control treatment. Here I present the two main methodological requirements of the EBM. The first of them is given by the idea of *evidence hierarchy*. The main thought here is how to range the different methods according to which the evidences in medicine are received. There are more than 80 different ranking classifications and one of this is presented in 1995 by Guyatt and Sackett (Guyatt, Sackett et al. 1995). The ranking list considers different type of evidences in medicine according to their reliability into the process of medical practice. In this way the most reliable method is the so called *systematic reviews* and meta-analyses standing on randomised control trials (RCTs) and placed on the top of the hierarchy pyramid. After that, and below them are placed *RCT*. And on the latest position in the base of the pyramid are the different *observational studies* as: *case studies*, *case series*, *case control studies*, *cohort studies* and *historically controlled studies*. At the beginning of the 2000 the Grading of Recommendations of Assessment, Development and Evaluation (GRADE) was presented (Guyatt, Oxman et al. 2011). The GRADE categorizes evidence in medicine from high to low (very low) levels and develop specialised software to make the assessment of different diagnosis, prognosis, meta-analysis and public health. This evaluation method presents the RCT's as more reliable method for medical practice and evaluates as low one all observational studies. The methodological model of EBM presented by hierarchy of evidence has been one of the most criticised element by philosopher of medicine (Bluhm 2005, Howick 2011, Stegenga 2011).

The second methodological layout defended by EBM is focused on the importance of RCT for contemporary medical researches. The big differences between observational studies and randomised control trials lay on the evidence criterion in methodology of EBM. According to this the role of RCT is important to get over some bias in observational studies as: *self-selection bias*, *allocation bias* and *performance bias*. In this way randomisation is presented as *randomly allocated* to different groups: an experimental or a control one. The methodological role of randomisation is to warrant the process of evidence from biases. In this way

it is important to organise a trial following condition according to which neither the group of participants in the trial nor the group of professional attendants knows the distribution by groups. In the end it is important to mention the role of *control* through the trial. Here, the two different groups are presented – the group that take the treatment and the control group.

Methodological Anomalies

In the current work the examples of anomalies to EBM methodology is in the focus of the research. Here, three different examples for the methodological anomalies to EBM model, will be presented. The first example is the group of the so called *rare diseases* or *orphan diseases*. Naming the diseases as “*rare*” is based on statistical evaluation of the diseases that affect population. The definition of this group of diseases known as “orphan” is connected to low interest in researches which focus on treatments and in this way they are defined as neglected diseases in some way. At the beginning of the 1980, the interest to those diseases started to increase. Some of the reasons for this are connected to scientific investigations of human genome, developments in the sphere of genomic technologies, government policies (budgets for researches of orphan drugs) and others. The Examples with this not well defined group of diseases can help to emphasise on the role of anomalies for testing the EBM model in specific or rare medical condition. Previously described methodological requirements in this model cannot be successfully applied to medical researches on the rare diseases. This is the main reason why here rare diseases are valued as a methodological anomaly of the EBM model. According to this, the central methodological role and epistemic status of the RCT’s change. The growth in number of the rare diseases these years (in the previous 30 years) is a marker for the increase of anomalies importance and reevaluation of EBM model applicability and reliability in the contemporary medicine. In this way trustees in “golden standard” method in medicine is trembled.

The other example for methodological anomaly to EBM model is the so defined *undiagnosed diseases*. There is a statistics from the Undiagnosed Diseases Network (UDN) that

“... 85% of the over 7,000 identified rare diseases affect less than one in a million people, most doctors will never see two patients with the same ultra-rare disease” (source: <https://udnf.org/what-is-an-undiagnosed-disease/>).

The UDN presents specific approach into contemporary medical science and practice that investigates into the specific diseases or diseases condition. The focus here is on the absence of concrete diagnosis that is supported by evidence or medical facts. Here the UDN is presented as an example that indicates the methodological boundaries of EBM model. In this way the role of statistical data into the process of diagnosis in medicine is not enough for medical research concerning rare diseases or different canid of syndromes (without medical diagnosis). According to UDN

there are big variety of medical conditions that are not classified or syndromes and symptoms without clear diagnosis that have to be managed by physicians. The Undiagnosed Diseases Network International (UDNI), that focuses on providing diagnoses and encouraging research on novel diseases (mechanisms, pathways), had been established at 2014. This medical network focused on medical units that are beyond the boundaries of methods established by EBM model in medicine. According to analysis in philosophy of science (Popper, Lakatos) one of the criterion for progress of knowledge, in this example in medicine, is connected with a possibility for a new explanation of examples accepted previously as anomalies. The UDNI establishment shows that possibility to enlarge medical science, or to introduce new knowledge to medicine, passes through new research of anomalies in medical science and practice.

Connected with the previous example (UDNI), the third example of methodological anomaly to EBM model is the so-called *Medically Unexplained Symptoms* (MUS). According to Henningsen, Zipfel and Herzog, the Functional somatic syndromes (FSS) are described as:

“FSS are characterised by patterns of persistent bodily complaints for which adequate examination does not reveal sufficiently explanatory structural or other specified pathology.” (Henningsen, Zipfel & Herzog 2007, p. 946)

Physicians Arthur J. Barsky (MD) and Jonathan F. Borus (MD) describe FSS as:

“The term *functional somatic syndrome* has been applied to several related syndromes characterized more by symptoms, suffering, and disability than by consistently demonstrable tissue abnormality.” (Barsky & Borus 1999, p. 910)

In this way the MUS definition connects to the symptoms that have not been medically explained or which have no medical evidence for disease diagnose. If it is not possible to support explanation with data or present evidence for nosological unit, then this presupposes the treatment problem in medical practice. In this regard, FSS is a case where the EBM model cannot provide a reliable or secure method to justify the processes of diagnosis and treatment in medicine. On the basis of this the MUS is an example of anomaly to EBM model.

Here we have to notice that there is a close relation between UDN and MUS, but there are differences. The network UDN is directed to physicians, which have to find scientifically grounded methods to research into medical cases that have not been diagnosed, but needs medical treatment. The central problem in MUS is connected with epistemological problem of explanation in medical science and practice. Here epistemological emptiness has to be studied and eliminated by a new way of treatment and new nosological unit. One of the appropriate examples that can demonstrate this MUS situation in medicine comes from analyses in the field of narrative medicine. One of the rare diseases is Tarlov cysts (meningeal cysts or perineural cysts) and as most of the rare diseases this one has no reliable medical explanation concerning exact causes of appearing, but there are really

painful syndromes. Bozhidar Ivkov (Ivkov 2022a, Ivkov 2022b), presented and analyzed the problem of rare diseases (Tarlov cysts) from the patient position. He applies the so-called “biography micronarrative method” to focus on patient pain and the hard and long way to come to correct diagnose – Tarlov cyst. As most of the rare diseases, the way to diagnose is difficult but it is more difficult to find correct medical treatment. There is a big amount of rare diseases that can be given as examples. Here I will give one more example for a rare disease – ashy dermatosis (macular pigmentation of uncertain aetiology). As an asymptomatic disease ashy dermatosis compromises the quality of life of patients. There is no established treatment but the appearance of skin (especially face) causes lots of social problems, and suffering as a result.

Personalised Medicine

All examples here – RD, UDN and MUS – are presented as methodological anomalies to the EBM model. In conclusion, it is important to stress on the fact that medical methodology presents a new approach to all those examples that are exceptions from the method presented in EBM. The Development of Personalised Medicine (PM) model or Precise Medicine model promotes new dimensions for medical knowledge (Georgieva & Georgiev 2022). Here it is important to stress that there are no contradicting elements between EBM and PM models, but only collaboration. In this way, we can describe those models as commensurable elements into the contemporary medical science. The introduction of the PM emerges as a model that can study and explain the examples that are anomalous to the EBM model. In 2004 an organisation of 20 institutions was established that represents different sectors of the health system. The PM model focusses on individual medical history to realise medical prevention and treatment of patients:

“Personalised medicine is an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms that impact health. By combining data from diagnostic tests with an individual’s medical history, circumstances, and values, health care providers can develop targeted prevention and treatment plans with their patients.” (<https://www.personalizedmedicinecoalition.org/personalized-medicine-101/>;10.06.2024)

Focused on individual patient condition the PM model presents a new approach to diagnosis, nosological units and their treatment. An important role here has been given to AI technologies implemented to different elements of medical practice (diagnosis, treatment and care).

Conclusion: The role of anomalies to the development of new approach in contemporary medicine – Personalised medicine – presented here, defend the idea of methodological anomalies as markers for progress in science. The examples with RD (rare diseases), UDN (Undiagnosed Diseases Network) and MUS

(Medically Unexplained Symptoms) focus attention to anomalies as falsificators of EBM model and to the introduction of the new model in the research programme of contemporary medicine. Personalised medicine through development of AI technologies introduce innovative method to RD, UDN and MUS. Respectively, this new field presents more reliable approaches to these diseases.

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NOTES

1. For more see: Expert Consult by Kenneth Lyons Jones, Miguel Del Campo, Marilyn C. Jones, 2013. Smith's Recognizable Patterns of Human Malformation. Saunders. Jones, Kenneth Lyons, Marilyn C Jones, and Miguel del Campo. Smith's Recognizable Patterns of Human Malformation / Kenneth Lyons Jones, Marilyn C. Jones, Miguel Del Campo. Seventh edition. Philadelphia, PA: Elsevier Saunders, 2013. Print.
2. There are different statistical parameters connected to rare diseases in different countries. In USA according to "Rare Disease Act of 2002" (United States Congress) "any disease or condition that affects fewer than 200,000 people in the United States" or this is about 1 in 1,500 people; In EU the definition about rare disease is connected to low prevalence as 1 on 2000 people.
3. "biography micronarrative method" in Bulgarian see: „метод на биографичния микронаратив“ Ivkov, B. (2022) Траектории на страданията и болката. Helikon Kazanlak ISBN: 978-619-91958-0-2; pp. 8.

REFERENCES

- BLUHM, R., 2005. From hierarchy to network: a richer view of evidence for evidence-based medicine. *Perspect Biol Med.* 2005 Autumn, vol. 48, no. 4, pp. 535 – 547. ISSN:1529-8795. Link:10.1353/pbm.2005.0082.
- BRANCACCIO, G., BALATO, A., MALVEHY, J., PUIG, S., ARGENZIANO, G., & KITTLER, H., 2024. Artificial Intelligence in Skin Cancer Diagnosis: A Reality Check. *Journal of Investigative Dermatology*, vol. 144, pp. 492 – 499. ISSN:0022-202X.
- EVIDENCE BASED MEDICINE WORKING GROUP. 1992. Evidence-based medicine. A new approach to teaching the practice of medicine. *Journal of the American Medical Association*, vol. 268, pp. 2420 – 2425. ISSN:0098-7484 (print);1538-3598 (web).
- FRUEH, F., 2009. Back to the Future: Why Randomized Controlled Trials Cannot Be the Answer to Pharmacogenomics and Personalized Medicine. *Pharmacogenomics*, vol. 10, no. 7, pp. 1077 – 1081. ISSN: 1462-2416 Print; ISSN: 1744-8042 Online.

- HOWICK, J., 2011. *The Philosophy of Evidence-based Medicine*. John Wiley & Son. ISBN:9781405196673. Online ISBN:9781444342673. DOI:10.1002/9781444342673. [In Bulgarian]
- IVKOV, B., 2022a. *Traektorii na stradaniето i bolkata*. Helikon Kazanlak ISBN: 978-619-91958-0-2.
- IVKOV, B., 2022b. *Konflikt na interpretatsiite v meditsinata i zdraveopazvaneto*. Balgarska asotsiatsia po filosofia na meditsinata i Sdruzhenie na taplovite patsienti v Bulgaria-lechenie bez granitsi. ISBN: 978-619-91958-3-3.
- JONES, K., JONES, M., & CAMPO, M., 2013. *Smith's Recognizable Patterns of Human Malformation*. Kenneth Lyons Jones, Marilyn C. Jones, Miguel Del Campo. Seventh edition. Philadelphia, PA: Elsevier Saunders, Print. ISBN-13:978-1455738113.
- BRANCACCIO, G., BALATO, A., MALVEHY, J., PUIG, S., ARGENZIANO, G., & KITTLER H., 2024. Artificial Intelligence in Skin Cancer Diagnosis: A Reality Check. *Journal of Investigative Dermatology*, vol. 144, pp. 492 – 499; doi:10.1016/j.jid.2023.10.004. ISSN:0022-202X. Link: [https://www.jidonline.org/article/S0022-202X\(23\)02964-0/pdf](https://www.jidonline.org/article/S0022-202X(23)02964-0/pdf).
- GEORGIEVA I. & GEORGIEV G., 2022. Narrative self-recreation in virtual reality. *Frontiers in Virtual Reality*, vol. 3 , p. 854333. <https://www.frontiersin.org/articles/10.3389/frvir.2022.854333/full>
- GAUYATT, G., SACKETT, D., SINCLAIR, J., HAYWARD, R., COOK, D., & COOK, R., 1995. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. *JAMA*, vol. 274, no. 22, pp. 1800 – 1804. ISSN: 0098-7484 (print);1538-3598 (web).
- GAUYATT, G., OXMAN, A., SCHUNEMANN, H., TUGWELL, P., & KNOTTERUS, A., 2011. GRADE guidelines: A new series of articles in the *Journal of Clinical Epidemiology*. *Journal of Clinical Epidemiology*, vol. 64, no. 4, pp. 380 – 382. ISSN: 0895-4356.
- KUHN T., 1962. *The Structure of Scientific Revolutions* (1st ed.); (1970) Enlarged (2nd ed.). University of Chicago Press. ISBN: 0-226-45803-2 (clothbound); 0-226-45804-0 (paperbound).
- KUHN, T., 1965. Paradigm and some misinterpretations of science. In: D. Shapere (Ed.) *Philosophy of science in the twentieth century*, pp. 83 – 90. New York: The Macmillan company. ISBN: 978-0-631-18358-7.
- KUHN, T., 1970. Reflections on my critics. In: LAKATOSI. & MUSGRAVEA. (Eds.) *Criticism and the Growth of Knowledge: Proceedings of the International Colloquium in the Philosophy of Science*, pp. 231 – 278. London. Cambridge University Press. ISBN: 9781139171434 (online); DOI: <https://doi.org/10.1017/CBO9781139171434>.

- LAKATOS, I., 1965. Falsification and the Methodology of Scientific Research Programmes. In: LAKATOS, I., MUSGRAVE, A. (Eds.), 1970. Criticism and the Growth of Knowledge: Proceedings of the International Colloquium in the Philosophy of Science, pp. 91 – 196. London: Cambridge University Press: ISBN: 9781139171434 (online); DOI: <https://doi.org/10.1017/CBO9781139171434>.
- LI, C., SHEN, C., XUE, K., SHEN, X., JING, Y., WANG, Z., et al., 2019. Artificial intelligence in dermatology: Past, present, and future. Chinese Med J., vol. 132, pp. 2017 – 2020. ISSN: 0366-6999. Online ISSN: 2542-5641.
- SPRANGER, J., BENIRSCHKE, K., HALL, J., LENZ, W., LOWRY, R., OPITZ, J., PINSKY, L., SCHWARZACHER, H., & SMITH, D., 1982. Errors of morphogenesis: concepts and terms. Recommendations of an international working group. J Pediatr, vol. 100, no. 1, pp. 160 – 165. doi: 10.1016/s0022-3476(82)80261-8. PMID: 7057306.
- STEVENSON, R. & JUDUTH, G., HALL, 2005. Human malformations and related anomalies., second edition, Oxford University Press. doi: 10.1136/adc.2006.098269. PMCID: PMC2083405.
- STEGENGA, J., 2011. Is meta-analysis the platinum standart. *Stud Hist Philos Biol Biomed Sci.*, vol. 42, no. 4, pp. 497 – 507. ISSN 1369-8486. <https://doi.org/10.1016/j.shpsc.2011.07.003>. (<https://www.sciencedirect.com/science/article/pii/S1369848611000665>).
- POPPER, K., 1963. Conjectures and Refutations. The Growth of Scientific Knowledge. London, England: Routledge. ISBN 9780415285940.
- POPPER, K., 1970. Normal science and its dangers. In: LAKATOS I. and MUSGRAVE A. (Eds.) Criticism and the Growth of Knowledge: Proceedings of the International Colloquium in the Philosophy of Science. London: Cambridge University Press. ISBN: 9781139171434 (online); DOI: <https://doi.org/10.1017/CBO9781139171434>.
- SACKETT, D., HAYNES, B., & TUGWELL, P., (Eds) 1985. Clinical Epidemiology: A Basic Science for Clinical Medicine, 2nd edn. Boston: Little, Brown. ISBN-10: 0781745241. ISBN-13: 978-0781745246.
- VISIBELLI, A., RONCAGLIA, B., SPIGA, O., & SANTUCCI, A., 2023. The impact of artificial intelligence in the odyssey of rare diseases. *Biomedicine*, vol. 11, no. 3, p. 887. EISSN 2227-9059. [In Bulgarian]

Internet resources:

<https://udnf.org/what-is-an-undiagnosed-disease/>; 10.06.2024

<https://www.personalizedmedicinecoalition.org/personalized-medicine-101/>; 10.06.2024

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