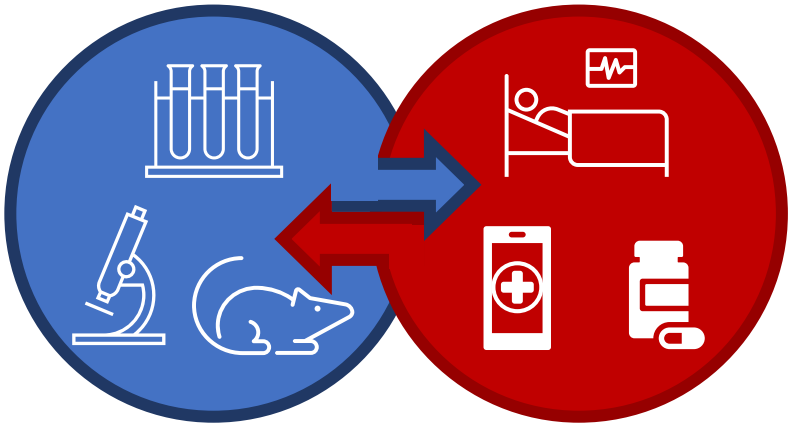
MEDICAL RESEARCH AGENCY

Translational Medicine Development Plan for the Years 2024–2036



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Radosław Sierpiński

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Acronyms

Acronym	English name
AD	Alzheimer Disease
ADME	Absorption, Distribution, Metabolism, and Excretion
AI	Artificial Intelligence
AMRI	European Alliance of Biomedical Research Infrastructures
ATMP	Academy of Translational Medicine Professionals
ATMP	Advanced Therapy Medicinal Products
B2B	Bench-To-Bedside
BEST	Biomarkers, EndpointS, and other Tools
CADD	Computer-Aided Drug Design
CAGR	Compound Annual Growth Rate
CDC	Centers for Disease Control
CDER	Center for Drug Evaluation and Research
CeZ	e-Health Centre (Pol. *Centrum e-Zdrowia*)
CML	Chronic Myeloid Leukemia
CNV	Copy Number Variation
CoU	Context of Use
CSF	Cerebrospinal Fluid
CTCG-HMA	Clinical Trials Coordination Group
DARPA	Defense Advanced Research Projects Agency
DL	Deep Learning
EATRIS	European Infrastructure for Translational Medicine
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ER	Estrogen Receptor
ESFRI	European Strategy Forum on Research Infrastructures
EUnetHTA	European Network for Health Technology Assessment
EUSTM	European Society for the Translational Medicine
FDA	Food and Drug Administration
G2MC	Global Genomic Medicine Collaborative
GA4GH	Global Alliance for Genomics and Health
gDNA	genomic DNA
GeT-RM	Genetic Testing Reference Material Coordination Program
HIS	Hospital Information System
HNSCC	Head and Neck Squamous Cell Carcinoma
IHI	Innovative Health Initiative
IL-6	Interleukin 6
IMI	Innovative Medicines Initiative
KIS	National Intelligent Specialisations (Pol. Krajowe Inteligentne Specjalizacje)
mCIA	Multiple Co-Inertia Analysis
miRNA	micro RNA
ML	Machine Learning
MPS	Microphysiological Systems
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry

NCATS	National Center for Advancing Translational Sciences
NCI EDRN	National Cancer Institute's Early Detection Research Network
NGS	Next-Generation Sequencing
NIH	National Institutes of Health
OTS	Office of Translational Sciences
PCa	Prostate Carcinoma
PD	Pharmacodynamics
PEA	Proximity Extension Assay
PET	Positron Emission Tomography
Pharmaco-EEG	Pharmaco-electroencephalography
phMRI	Pharmacological Magnetic Resonance Imaging
PK	Pharmacokinetics
PR	Progesterone Receptor
PSA	Prostate-Specific Antigen
RWD	Real-World Data
QSP	Quantitative Systems Pharmacology
TM	Translational Medicine
WES	Whole-Exome Sequencing
WGS	Whole-Genome Sequencing

1. Introduction

Translational medicine is a field of biomedical research aimed at translating scientific discoveries made in the laboratory into practical applications that will benefit human health. It is understood as a two-way concept, involving the flow of information from laboratories to clinical practice and inversely — from clinical practice to laboratories. The bench-to-bedside approach is expected to enhance the effectiveness of testing new therapeutic strategies developed via basic science, while bedside-to-bench feedback is intended to provide information on the application of new therapies and inform strategies for improving them.

The need to develop translational medicine is dictated by the universally acknowledged necessity of reducing to practice the scientific discoveries and the enormous technological progress made in science in the 21st century. Due to the wide range of research techniques used within many subspecialties and specialties, the multiplicity of models, field-specific nomenclature and clinical approaches, there is often no consistency between the results obtained, which makes it difficult to draw conclusions. It is therefore the responsibility of the Translational Medicine Strategy to align the discoveries achieved at the level of fundamental “bench” research with “bedside” interventions and therapies. Translational research aims to direct the transfer of discoveries into clinical applications and clinical findings into an understanding of the fundamental mechanism of action of a therapy. **Translational Medicine Development Plan for the Years 2024–2036** (abbreviated in the document as “The Plan”) focuses primarily on directing research efforts towards personalised healthcare based on individualised models of patient treatment and **intends to eliminate the main organisational, financial, and regulatory barriers.** These include the unavailability of grants for translational research, difficulties in cooperation between basic science and clinical research, the lack of consensus in evaluating research results, and the absence of regulations allowing the actual authors to own some of the intellectual property rights.

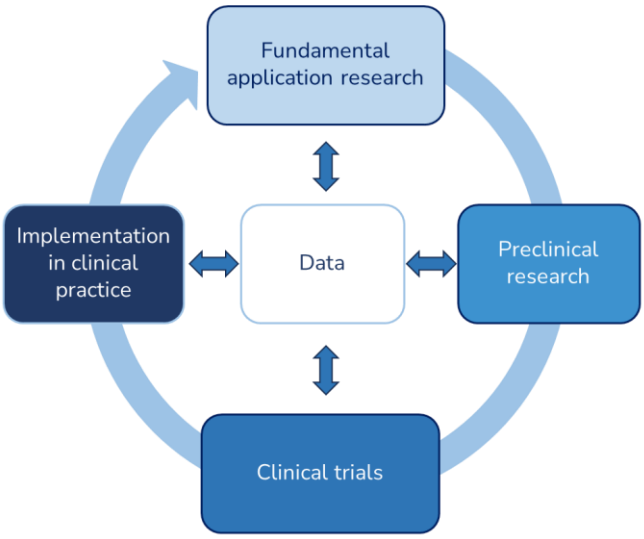
2. Translational Medicine

A technology development within translational medicine is often falsely understood as a linear pipeline, while translation from scientific discoveries to the clinical practice is in fact

a multi-stage, multi-domain, multidisciplinary network with a recurrent flow of technologies and data obtained during research, development, and implementation activities.

Multidisciplinary collaboration between healthcare professionals and scientists who carry out fundamental or clinical research is the starting point of any activities within the field of translational medicine. These activities can be divided into four stages:

- **Fundamental application research:** this stage consists of laboratory research aimed at identifying the basic mechanisms underlying a disease or medical condition.
- **Preclinical research:** this stage involves testing new therapies or diagnostic tools *in vitro* in cell models or on animals to assess safety and efficacy.
- **Clinical trials:** this stage consists in testing new therapies or diagnostic tools in humans in order to evaluate their safety and efficacy.



- **Implementation:** at this stage, new therapies, diagnostic tools or preventive measures are incorporated into clinical practice.

The ultimate goal of translational medicine is to improve patient outcomes by accelerating the development and implementation of effective new diagnostic and treatment methods, as well as providing more personalised and accurate healthcare.

Translational medicine is meant to combine disciplines, resources, know-hows and techniques to promote advancements in prevention, diagnostics, and therapies. For example, using new IT tools for network analysis e.g. of metabolomic profiles, and thereclassification of genetic variants as pathogenic or potentially pathogenic, combined with clinical information, provides for a more effective risk stratification and explains why mutations in the same gene do not reflect similar phenotypes. This is how integrated clinical

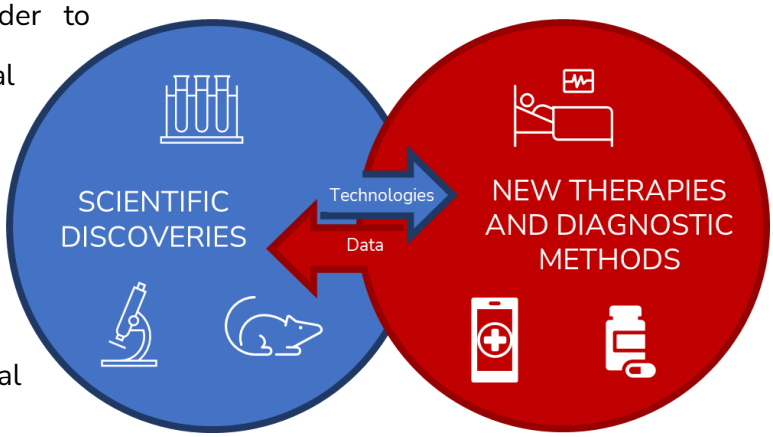
data can be reduced to practice to provide patients with personalised medical care depending on the established risk profile.

Translational medicine is a highly interdisciplinary field and involves the academia, clinical sites, industry, and regulatory institutions. Translation is primarily based on major aspects of clinical pharmacology, biomarker research, omic research, and research aimed at understanding the underlying mechanisms of disease and treatment response, which are key elements of this highly heterogeneous branch of science.

2.1 Definition of Translational Medicine

As part of this Translational Medicine Development Plan for the Years 2024–2036, the MRA has adopted the definition of translational medicine (translational science, translational biomedicine, translational research) proposed by the European Society for Translational Medicine (EUSTM). According to the EUSTM, translational medicine (TM) is an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, i.e. basic research; bedside, i.e. individual patient level; and community — healthy individuals, patients, and physicians. The pathway is often referred to as bench-to-bedside (B2B) translation. The goal of TM is to combine disciplines, resources, expertise and techniques to promote enhancements in therapy, diagnosis, and prevention. Accordingly, translational medicine is a highly interdisciplinary field whose primary objective is to coalesce assets of various natures in order to significantly improve the global healthcare system. A consequence of this approach is planning research projects that comprise fundamental research and selecting projects for further clinical and implementation studies.

The objective of this Translational Medicine Development Plan is agile adaptation of scientific discoveries to clinical practice.



2.2 Biomarkers as Tools of Translational Medicine

According to the initial definition given by the NIH-FDA Biomarker Definition Working Group, a biomarker is "*a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*.[1]" This definition has since been modified, and the preferred version (last update 29/11/2021) according to the NIH/FDA defines a biomarker as a "*defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers."* A biomarker is not an assessment of how an individual feels, functions, or survives.[2] This definition is similar to the one developed by EMA, which reads: "*An objective and quantifiable measure of a physiological process, pathological process or response to a treatment (excluding measurements of how an individual feels or functions).*" According to the BEST (Biomarkers, EndpointS, and other Tools) Resource developed by FDA and NIH, there are seven types of biomarkers, categorised by use: susceptibility/risk biomarkers, diagnostic biomarkers, monitoring biomarkers, prognostic biomarkers, predictive biomarkers, pharmacodynamic/response biomarkers, and safety biomarkers[3]. Historically, the classification of biomarkers and their assignment to individual groups was attempted in 2003 by Rolan and team, who divided biomarkers according to their mechanistic nature, such as genotype, phenotype, or target function.[4] For a time, the prevailing definition was the one formulated by the National Institutes of Health, which divided the existing spectrum of biomarkers into three categories: direct biomarkers, surrogates or surrogate endpoints (closely related to endpoints), and clinically relevant endpoints.[5] Assessing the changes in biomarker levels has been identified by the NIH as an important part of the translational process which can effectively "translate" the processes taking place in the body into the

[1] BEST (Biomarkers, EndpointS, and other Tools) Resource. https://www. ncbi.nlm.nih.gov/books/NBK326791/
[2] Ibidem
[3] Ibidem
[4] Rolan P, Atkinson AJ Jr, Lesko LJ; Scientific Organizing Committee; Conference Report Committee. Use of biomarkers from drug discovery through clinical practice: report of the Ninth European Federation of Pharmaceutical Sciences Conference on Optimizing Drug Development. Clin Pharmacol Ther. 2003 Apr;73(4):284-91. doi: 10.1016/s0009-9236(02)17625-9
[5] Califf RM. Biomarkers, putative surrogates, surrogates, and decision making. Circ Cardiovasc Imaging. 2013 Jan 1;6(1):6-7. doi: 10.1161/CIRCIMAGING.112.982538

symptoms of disease. Therefore, already at the level of definition, the wide range of possibilities for the use of biomarkers, also in bridging the translational gap, are clearly to be seen.[6] It has been shown that including biomarkers at the early stages of drug development is associated with a greater probability of success compared to projects without biomarker use.[7] Currently, biomarkers can also be classified as molecular, cellular, physiological, imaging and digital.[8] Whenever biomarkers are used, also in clinical trials, it is crucial to define the context of use (CoU).[9] The CoU may include diagnosis, safety monitoring, response to PD, as well as predictive and prognostic biomarker applications.[10] Prognostic biomarkers are used to identify the relationship between the biomarker level and the response in the control or standard of care group. Prognostic biomarkers are also used to predict aggressive disease course, regardless of the experimental treatment implemented. Predictive biomarkers, on the other hand, help to assess response to therapy in patients who have a specific biomarker versus patients found not to demonstrate it.[11] Thus, both prognostic and predictive biomarkers seem to be critical in developing new therapies — prognostic biomarkers predict disease outcomes regardless of intervention (which is important e.g. from the point of view of identifying high-risk patients), while predictive biomarkers predict the response to a specific treatment.[12]

[6] van Gool, A. J., Bietrix, F., Caldenhoven, E., Zatloukal, K., Scherer, A., Litton, J. E., Meijer, G., Blomberg, N., Smith, A., Mons, B., Heringa, J., Koot, W. J., Smit, M. J., Hajduch, M., Rijnders, T., & Ussi, A. Bridging the translational innovation gap through good biomarker practice. Nature reviews. Drug discovery, 2017;16(9), 587–588. https://doi.org/10.1038/nrd.2017.72

[7] Hartl, D., de Luca, V., Kostikova, A., Laramie, J., Kennedy, S., Ferrero, E., Siegel, R., Fink, M., Ahmed, S., Millholland, J., Schuhmacher, A., Hinder, M., Piali, L., & Roth, A. Translational precision medicine: an industry perspective. Journal of translational medicine. 2021;19(1), 245. https://doi.org/10.1186/s12967-021-02910-6

[8] Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood). 2018 Feb;243(3):213-221. doi: 10.1177/1535370217750088

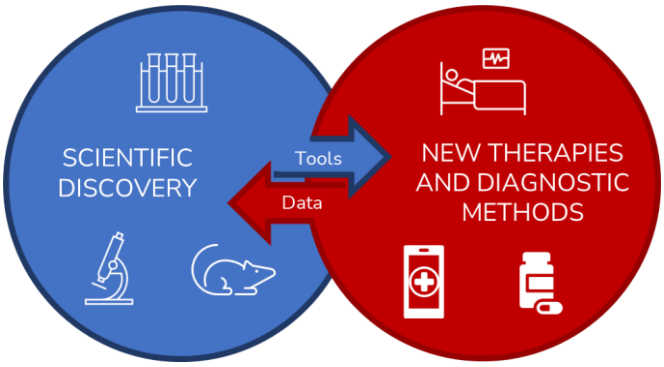
[9] Bravo-Merodio L, Williams JA, Gkoutos GV, Acharjee A. Omics biomarker identification pipeline for translational medicine. J Transl Med. 2019;17:155. doi: 10.1186/s12967-019-1912-5

[10] op. cit. 7

[11] Perez EA. Biomarkers and Precision Medicine in Oncology Practice and Clinical Trials. 2019 Dec 13. In: Ramirez AG, Trapido EJ, editors. Advancing the Science of Cancer in Latinos [Internet]. Cham (CH): Springer; 2020. Chapter 11. Available from: https://www.ncbi.nlm.nih.gov/books/NBK573223/ doi: 10.1007/978-3-030-29286-7_11

[12] Wallington-Beddoe, C.T., Mynott, R.L. Prognostic and predictive biomarker developments in multiple myeloma. J Hematol Oncol. 2021;14, 151 https://doi.org/10.1186/s13045-021-01162-7

The development of a new biomarker is a complex, multi-stage process that comprises discovery (often based on omic data), pre-analytical validation, assessment of utility and usability of various body fluids, analytical validation and ultimately clinical validation and qualification.[13] Well defined and validated biomarkers are invaluable in the development of new therapeutic approaches. Biomarkers should be highly sensitive and specific.



In general, the level of significance of a given biomarker depends on three key factors: its status of validation and eligibility, CoU, and the strength of evidence linking the biomarker to the CoU.[14] Regulatory agencies have worked together with the pharmaceutical industry to develop framework guidelines for the clinical validation of biomarkers, defined by both the Food and Drug Administration and the European Medicines Agency.[15,16]

In 2011, the European Medicines Agency released for public consultation the first qualifying opinion on a clinical biomarker, which aimed to identify pre-dementia patients to be recruited for clinical trials on Alzheimer's disease (AD).[17] Currently, biomarker-guided trial designs[18] are gaining popularity, especially in relation to basket trials and umbrella trials.[19] Biomarker-based stratification or stratified randomisation means that the biomarker level is measured in all patients before randomisation and the results obtained are used to ensure proportional distribution of patients in the study and control groups. As a result, patients are not excluded on the basis of the presence or absence of a given biomarker, and the results

[13] Kraus VB. Biomarkers as drug development tools: discovery, validation, qualification and use. Nat Rev Rheumatol. 2018;14(6):354–362. doi: 10.1038/s41584-018-0005-9.
[14] op. cit. 7
[15] https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification
[16] Berman S, Siegel J. Biomarker Qualification at the European Medicines Agency: A Look Under the Hood. Clin Pharmacol Ther. 2022 Jul;112(1):28-30
[17] Bakker E, Hendrikse NM, Ehmann F, van der Meer DS, Llinares Garcia J, Vetter T, Starokozhko V, Mol PGM. Biomarker Qualification at the European Medicines Agency: A Review of Biomarker Qualification Procedures From 2008 to 2020. Clin Pharmacol Ther. 2022 Jul;112(1):69-80. doi: 10.1002/cpt.2554
[18] Antoniou M, Kolamunnage-Dona R, Jorgensen AL. Biomarker-guided non-adaptive trial designs in phase II and phase III: a methodological review. J Pers Med. 2017;7(1):1
[19] Park, J. J. H., Siden, E., Zoratti, M. J., Dron, L., Harari, O., Singer, J., Lester, R. T., Thorlund, K., & Mills, E. J. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials, 2019;20(1), 572. https://doi.org/10.1186/s13063-019-3664-1

give a better picture of reality. Another way of using biomarkers in a clinical trial is enrichment[20], which means the decision to include/exclude a patient or to assign a specific protocol is based on the biomarker level and its anticipated effect on the efficacy or safety of treatment. In fact, biomarker-driven enrichment helps to prospectively use a given characteristic to better select the trial population in which the detection of drug effect (if any) is more likely than in an unselected population.

The translational success of biomarkers is most evident in the field of oncology.

The FDA's enrichment guidelines focus mainly on improving the detection of drug efficacy, but they can also be used for safety assessments.[21] An example of how biomarkers can be used in the translational process of searching for new medicinal products may be vemurafenib, a drug first used in the targeted treatment of melanoma, which inhibits the growth of BRAF V600E mutation-positive melanoma cells.[22] During the development of vemurafenib, researchers also looked for biomarkers that would help predict which patients are likely to positively respond to the drug.[23] Notably, oncology is the very therapeutic area in which translational success of biomarkers is the most evident; cancer treatment often involves innovative targeted therapies which have evolved from knowledge of specific gene mutations in a given type of neoplasm.[24] Recent advances in molecular genetics have made it possible to precisely characterise a tumour by stage and histological type, but also define heterogeneity between tumours according to their specific genetic or immunological subtype. This has allowed oncologists to better tailor the treatment to the needs of a specific patient and specific tumour subtype with highly targeted therapies. An example of this is one of the first clinically approved targeted therapies based on imatinib in the treatment of chronic myeloid leukaemia (CML). This treatment has been shown

[20] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products

[21] Ibidem

[22] Bollag, G., Tsai, J., Zhang, J., Zhang, C., Ibrahim, P., Nolop, K., & Hirth, P. Vemurafenib: the first drug approved for BRAF-mutant cancer. Nature reviews. Drug discovery. 2012; 11(11), 873–886. https://doi.org/10.1038/nrd3847

[23] Glutsch, V., Amaral, T., Garbe, C., Thoms, K.M., Mohr, P., Haushild, A., Schilling, B. Indirect Comparison of Combined BRAF and MEK Inhibition in Melanoma Patients with Elevated Baseline Lactate Dehydrogenase. Acta Derm Venereol. 2020;100: adv00174. doi: 10.2340/00015555-3526

[24] Liu D. Cancer biomarkers for targeted therapy. Biomark Res. 2019 Nov 15;7:25. doi: 10.1186/s40364-019-0178-7

to be associated with a significant improvement in 5-year survival rates.[25] Imatinib mesylate (Gleevec®) is a drug specifically designed to inhibit the Bcr-Abl protein kinase in Philadelphia chromosome-positive CML. It is a compound that affects the aberrant signalling pathway in cancer cells while largely sparing cells showing a non-cancerous phenotype. The discovery of cancer biomarkers with a potential for clinical utility, such as the aforementioned Bcr-Abl protein kinase in Philadelphia chromosome-positive cells, is usually the result of academic study. However, despite the ever-growing number of potential cancer biomarkers, very few biomarker-based diagnostic methods have emerged. The discrepancy between the pace of biomarker discovery and the implementation of new tests can be attributed to several challenges associated with the translation process,[26] e.g. the evident need for a multidisciplinary team, and some more complex issues, such as the scalability, standardisability and validatability of the methods used in research laboratories. In addition, the process requires a standardised operating procedure; approved standards; reference materials and calibrators; determination of the limit of detection; quantification; and verification of accuracy and potential interference from other substances present in the sample.[27] A good example demonstrating the legitimacy of searching for new biomarkers for the treatment of oncological patients are the high numbers of false positive biopsies and the increased rates of prostate cancer (PCa) overdiagnosis based on prostate-specific antigen (PSA).[28] Prostate cancer has been shown to follow a variable clinical course, and molecular characterisation revealed high heterogeneity of the mutation, which may underlie the unpredictable clinical course of the disease.[29,30] Algorithms analysing combined multimarker panels of 21- and 5-aminoacid proteins delivered high sensitivity

[25] Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood. 2005 Apr 1;105(7):2640-53. doi: 10.1182/blood-2004-08-3097

[26] Hristova, V. A., & Chan, D. W. Cancer biomarker discovery and translation: proteomics and beyond. Expert review of proteomics. 2019; 16(2), 93–103. https://doi.org/10.1080/14789450.2019.1559062

[27] Li D, Chan DW. Proteomic cancer biomarkers from discovery to approval: it's worth the effort. Expert Rev Proteomics. 2014. April;11 (2):135–136

[28] Filella X, Foj L. Novel Biomarkers for Prostate Cancer Detection and Prognosis. Adv Exp Med Biol. 2018;1095:15-39. doi: 10.1007/978-3-319-95693-0_2

[29] Barbieri CE, Tomlins SA. The prostate cancer genome: perspectives and potential. Urol Oncol. 2014 Jan;32(1):53.e15-22. doi: 10.1016/j.urolonc.2013.08.025

[30] Porzycki P, Ciszkowicz E. Modern biomarkers in prostate cancer diagnosis. Cent European J Urol. 2020;73(3):300-306. doi: 10.5173/ceju.2020.0067R

and specificity.[31] Other biomarkers are also being investigated for the detection and prognosis of PCa, including PCA3 (Prostate Cancer Gene 3), the TMPRSS2-ERG fusion gene and microRNA (miRNA).[32,33] Discussing the role of biomarkers in oncology, it is impossible not to mention immune checkpoint inhibitors, including PD-1/PD-L1 pathway inhibitors, which have transformed the paradigm of anticancer therapy.[34] PD-L1 expression in cancer cells enable the evasion of host immune response. Therapeutic management is guided by measuring the level of PD-L1 expression in cancer cells and testing for a mutation or rearrangement of these biomarkers. Immune checkpoint inhibitors such as pembrolizumab (anti-PD-1) and atezolizumab (anti-PD-L1) are approved for use alone or in combination with multi-drug chemotherapy. Recently, seven other anti-PD-1/PD-L1 inhibitors have been approved by the FDA.[35]

The development of new diagnostic and prognostic methods is still a challenge in cardiology. Attempts have been made to use biomarkers in various diseases, including arterial hypertension, atherosclerosis, or heart failure, and biomarkers are being sought that could help in early diagnosis of transplant rejection.[36] So far, the search for a marker of "heart failure" and the concept of surrogate markers (e.g. GDF-15, ST2 and Gal-3) have failed, which is why there is still an unmet need to develop early prognostic and diagnostic models in this field. In recent years, a number of discoveries have been made in psychiatry, including research into objective biomarkers

The development of new diagnostic and prognostic methods is still a challenge in cardiology.

[31] Neuhaus J, Yang B. Liquid Biopsy Potential Biomarkers in Prostate Cancer. Diagnostics (Basel). 2018 Sep 21;8(4):68. doi: 10.3390/diagnostics8040068

[32] Neuhaus J. Special Issue "Diagnostic Biomarkers in Prostate Cancer 2020". Diagnostics (Basel). 2021 Mar 12;11(3):505

[33] Scaravilli M, Koivukoski S, Latonen L. Androgen-Driven Fusion Genes and Chimeric Transcripts in Prostate Cancer. Front Cell Dev Biol. 2021 Feb 9;9:623809

[34] Sun C, Mezzadra R, Schumacher TN. Regulation and Function of the PD-L1 Checkpoint. Immunity. 2018 Mar 20;48(3):434-452

[35] https://www.cancerresearch.org/pd-1-pd-l1-landscape

[36] Zhou SS, Jin JP, Wang JQ, Zhang ZG, Freedman JH, Zheng Y, Cai L. miRNAS in cardiovascular diseases: potential biomarkers, therapeutic targets and challenges. Acta Pharmacol Sin. 2018 Jul;39(7):1073-1084

for schizophrenia, with a particular focus on genes, biochemical indicators, brain imaging, and electrophysiological, epigenetic, and transcriptional characteristics.[37,38]

The FDA and EMA have also approved a panel of 7 biomarkers that can be used to detect nephrotoxicity in drug research.[39] Other achievements include defining clinical biomarkers for the clinical management of transplant patients. New biomarkers are constantly emerging, among them imaging biomarkers or non-blood biomarkers such as liquid biopsy (which involves the measurement of circulating free tumour cells, ctDNA, miRNA, and exosomes). Introducing cerebrospinal fluid and imaging biomarkers in the diagnostic workup of Alzheimer's disease enabled the detection of early pathological changes at the preclinical stage and in patients with mild cognitive impairment, and to enrol such patients in clinical trials; it has also revolutionised the definition of the disease, which is now considered a biological continuum.[40]

Biomarkers are therefore necessary to enable the identification of new therapeutic targets, stratification of patients according to the expected treatment efficacy, and monitoring of the treatment response in order to ensure personalised and targeted treatment. However, before they can be used in clinical practice, they need to be adequately validated. There is an increasing interest in multimarker strategies to improve the early detection, diagnosis, prognosis, and monitoring of various human diseases. However, the process of developing and using biomarkers is associated with a number of challenges, such as high costs, validation according to the requirements of regulatory authorities, and the fact that only selected subgroups of patients can potentially benefit. The scope and complexity of the effort required

[37] Lin P, Sun J, Lou X, Li D, Shi Y, Li Z, Ma P, Li P, Chen S, Jin W, Liu S, Chen Q, Gao Q, Zhu L, Xu J, Zhu M, Wang M, Liang K, Zhao L, Xu H, Dong K, Li Q, Cheng X, Chen J, Guo X. Consensus on potential biomarkers developed for use in clinical tests for schizophrenia. Gen Psychiatr. 2022 Feb 23;35(1):e100685. doi: 10.1136/gpsych-2021-100685

[38] Kim S, Okazaki S, Otsuka I, Shinko Y, Horai T, Shimmyo N, Hirata T, Yamaki N, Tanifuji T, Boku S, Sora I, Hishimoto A. Searching for biomarkers in schizophrenia and psychosis: Case-control study using capillary electrophoresis and liquid chromatography time-of-flight mass spectrometry and systematic review for biofluid metabolites. Neuropsychopharmacol Rep. 2022 Mar;42(1):42-51. doi: 10.1002/npr2.12223

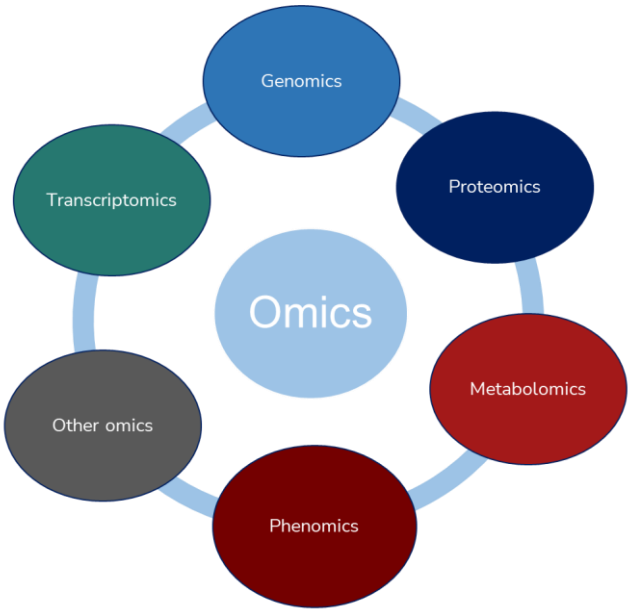
[39] Griffin BR, Faubel S, Edelstein CL. Biomarkers of Drug-Induced Kidney Toxicity. Ther Drug Monit. 2019 Apr;41(2):213-226

[40] Dubois, B., Villain, N., Frisoni, G. B., Rabinovici, G. D., Sabbagh, M., Cappa, S., Bejanin, A., Bombois, S., Epelbaum, S., Teichmann, M., Habert, M. O., Nordberg, A., Blennow, K., Galasko, D., Stern, Y., Rowe, C. C., Salloway, S., Schneider, L. S., Cummings, J. L., Feldman, H. H. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. The Lancet. Neurology, 2021;20(6), 484–496. https://doi.org/10.1016/S1474-4422(21)00066-1

to increase the availability of biomarkers call for a more efficient use of the existing infrastructure and cross-sector cooperation. Despite the measures taken by the EU to enhance the use of infrastructures such as BBMRI-ERIC and ELIXIR, their operational independence has only partially made it possible to address the demand in the field of biomarker development. In order to solve this problem structurally, it is essential to implement a long-term vision as presented in this document. The challenge lies not only in improving access to the existing infrastructure, but it is also necessary to involve allstakeholders, develop standards, ensure and enforce a certain quality of resources and, above all, promote the idea of knowledge sharing.

2.3 Omic Research in Translational Medicine

For more than a decade, advanced DNA and RNA sequencing techniques have been emerging to achieve much higher efficiency and lower cost than conventional Sanger sequencing. Next-generation sequencing (NGS) is used to obtain whole genome (Whole-Genome Sequencing, WGS) or whole exome sequences (Whole-Exome Sequencing, WES), as well as transcriptome sequences (RNA sequencing), enabling rapid and accurate analysis of genetic variability and gene expression in different tissues or organisms.



Precision medicine often uses the results of NGS to individualise therapy, effectively changing treatment perspectives. The genetic variants identified in whole genome studies have made it possible, for example, to characterise the interrelations between genomes and arterial hypertension.[41,42,43] In oncology, where clinical research is evolving from phenotypic analysis of cancers to targeting genes that differentiate types

[41] Xiao L, Zan G, Liu C, Xu X, Li L, Chen X, Zhang Z, Yang X. Associations Between Blood Pressure and Accelerated DNA Methylation Aging. J Am Heart Assoc. 2022 Feb;11(3):e022257
[42] Soler-Botija C, Gálvez-Montón C, Bayés-Genís A. Epigenetic Biomarkers in Cardiovascular Diseases. Front Genet. 2019 Oct 9;10:950
[43] Adua E. Decoding the mechanism of hypertension through multiomics profiling. J Hum Hypertens. 2023 Apr;37(4):253-264. doi: 10.1038/s41371-022-00769-8. Epub 2022 Nov 3. PMID: 36329155

of cancer, individual therapeutic approach is possible thanks to very precise methods of analysis, referred to as "omic" analysis. Of course, cancer is not the only area that benefits from omic analysis. This type of analysis comprehensively (holistically) describes: the genome (gene sequences), epigenome (factors regulating the structure of chromatin and genome functions, modulating the function of genes), transcriptome (gene expression), proteome (protein synthesis and signalling pathways), metabolome (concentrations and flows of cellular metabolites) and microbiome (the total population of microorganisms that live in the human body) of an individual. Research on cytomes (intracellular systems analysed on the basis of single cells) and the study of the flow and production of fatty acids (lipidomics) are also gaining popularity. Currently, omic technologies are used to capture static and temporal changes within chromosomes, transcriptomes, alternative splicing, or spatio-temporal protein dynamics, as well as post-translational modifications,[44] thus going far beyond standard genomic, transcriptomic or proteomic study. These types of analysis forming one omic family are rarely used in isolation; instead, they complement each other, giving a unique and extremely valuable biological image of an individual, in an approach referred to as a multiomics. Omics (as omic analyses) have become an integral part of translational research and are responsible for providing key information on the mechanism and course of many human diseases. In most cases, omic research is used at an intermediate stage in the treatment/product development process, which identifies mechanisms at the molecular level. However, especially in complex diseases, data on large sets of genes can be key in making therapeutic decisions. One instance of this is the diagnosis and treatment suggestions based on multiomic analysis of the cerebrospinal fluid (CSF) in patients with Alzheimer's disease. In this case, a combination of genomics, proteomics and metabolomics has been used to analyse the CSF of AD patients and healthy individuals. On this basis, a biomarker panel was identified that made it possible to distinguish between the two groups with high accuracy. These biomarkers included proteins involved in the immune response,

In complex diseases, data on large sets of genes can be key in making therapeutic decisions.

[44] Dai X, Shen L. Advances and Trends in Omics Technology Development. Front Med (Lausanne). 2022 Jul 1;9:911861. doi: 10.3389/fmed.2022.911861

as well as metabolites associated with energy metabolism and oxidative stress. The biomarkers were used to develop a diagnostic test that can distinguish AD from other neurodegenerative diseases with similar symptoms. Researchers have also proposed several potential therapeutic targets for AD.[45]

The development of omic techniques has also opened up a different approach to new drug development. In fact, out of the approximately 5,700 known human diseases, effective treatment is only available for about 500.[46] Extensive multiomic research and multidimensional analyses of publicly available big data in support of translational medicine are therefore an opportunity to develop treatments for more patients. Multiomics is now widely used in drug research, including on the use of existing drugs in new therapeutic areas.

Additional omics have emerged along the way, such as: phenomics (processes observed in the body that cause phenotypic changes during lifetime), exposomics (all environmental and lifestyle factors to which a person is exposed), cellomics (quantitative analysis of cells using bioimaging and computing methods), interactomics (study of the interactions and the consequences of these interactions between proteins and other molecules in a cell), kinomics (measurement of protein phosphorylation signature) and pregomics (study of drug repurposing in maternal-child health), significantly expanding the definitions of omic research.[47,48,49] Omic research conducted on large populations of patients from different ethnic groups do not take into account the characteristics of an individual, including genetic sensitivity. Therefore, despite the development of clinical practice guidelines for many common conditions on the basis of correct computational algorithms, some patients do not benefit from treatment. This problem is slowly being mitigated by the development

[45] Clark, C., Dayon, L., Masoodi, M., Bowman, G., L., Popp, J. (2021). An integrative multi-omics approach reveals new central nervous system pathway alterations in Alzheimer's disease. *Alz Res Therapy* 13, 71 https://doi.org/10.1186/s13195-021-00814-7

[46] Pulley JM, Rhoads JP, Jerome RN, Challa AP, Erreger KB, Joly MM, Lavieri RR, Perry KE, Zaleski NM, Shirey-Rice JK, Aronoff DM. Using What We Already Have: Uncovering New Drug Repurposing Strategies in Existing Omics Data. Annu Rev Pharmacol Toxicol. 2020 Jan 6;60:333-352. doi: 10.1146/annurev-pharmtox-010919-023537

[47]Kang M, Ko E, Mersha TB. A roadmap for multi-omics data integration using deep learning. Brief Bioinform. 2022 Jan 17;23(1):bbab454. doi:10.1093/bib/bbab454

[48] Hu X, Zhang B, Koeken VACM, Gupta MK, Li Y. Multi-Omics Approaches in Immunological Research. Front Immunol. 2021 Jun 11;12:668045. doi:10.3389/fimmu.2021.668045

[49] La Cognata V, Morello G, Cavallaro S. Omics Data and Their Integrative Analysis to Support Stratified Medicine in Neurodegenerative Diseases. Int J Mol Sci. 2021 May 1;22(9):4820. doi: 10.3390/ijms22094820

of precision medicine, whose main tools include omic research aimed at individuals with a specific disease. For example, multiomic approach has been used to classify types of multiple sclerosis, which helped identify specific gene variants responsible for unresponsiveness to interferon therapy or its toxic effects.[50]

Translational medicine is a holistic study of complex biological processes. To achieve its objectives, it is necessary to adopt an integrative approach that combines multiomic data to highlight the interrelations between biomolecules and their functions. There are a wide range of tools and methods available in public domain for integrating multiomic data sets. Currently, such repositories are created mainly on the basis of data derived from cancer research, due to the great involvement of omics in this branch of medicine.[51] However, as omics are being used more and more in biological research and pharmacology, new repositories are being established, and wide access to omic techniques and data will also have a considerable impact on the development of translational medicine. By combining different data such as copy number variation (CNV), genetic variants, DNA methylation data, transcriptomics (mRNA and miRNA expression) and proteomics, distinct molecular subtypes of breast cancer have been identified. Integrative analysis has created a comprehensive catalogue of genetic and epigenetic factors influencing breast cancer subtypes. Analysis of ChIP-Seq and RNA-Seq data in head and neck squamous cell carcinoma (HNSCC) revealed the presence of tumour-specific histone markers H3K4me3 and H3K27ac, which are associated with transcriptional changes in genes that control tumour development, such as epidermal growth factor receptor (EGFR), FGFR1 and FOXA1.[52]

Proteomics enables direct measurement of protein levels, thus facilitating translation into clinical practice, where protein biomarkers are most commonly used. Large-scale proteomic research of plasma proteins, which change progressively with age and may contribute to accelerated deterioration of health, are a promising direction of study. Circulating proteins are also perfectly suited as biomarkers for diagnosing, predicting and tracking treatment

[50] Lorefice, L., Pitzalis, M., Murgia, F., Fenu, G., Atzori, L., & Cocco, E. (2023). Omics approaches to understanding the efficacy and safety of disease-modifying treatments in multiple sclerosis. *Frontiers in genetics*, *14*, 1076421. https://doi.org/10.3389/fgene.2023.1076421

[51] Singer J, Irmisch A, Ruscheweyh HJ, Singer F, Toussaint NC, Levesque MP, Stekhoven DJ, Beerenwinkel N. Bioinformatics for precision oncology. Brief Bioinform. 2019 May 21;20(3):778-788. doi: 10.1093/bib/bbx143

[52] Subramanian I, Verma S, Kumar S, Jere A, Anamika K. Multi-omics Data Integration, Interpretation, and Its Application. Bioinform Biol Insights. 2020 Jan 31;14:1177932219899051. doi: 10.1177/1177932219899051

efficacy. Recent technological advances, e.g. mass spectrometry (MS), or protein testing platforms such as SomaScan or Proximity Extension Assay (PEA), have allowed to test thousands of plasma or other proteins as potential clinical biomarkers. The SomaScan platform has been used, for example, to create a molecular diagnostic test that distinguishes multiple sclerosis from other inflammatory and non-inflammatory diseases of the central nervous system, or a molecular test to distinguish relapsing-remitting MS from progressive MS (the SPINCOMS study).[53,54]

The integrability of protein data with genetic information plays an important role in selecting new therapeutic targets on the basis of disease-associated proteins.

While PEA has been applied primarily in blood protein screening, it is now also used for a variety of different samples and minimal sample volumes, including individual cells, exosomes, dried blood spots or fine needle biopsies.[55] The integrability of protein data with genetic information plays an important role in selecting new therapeutic targets on the basis of disease-associated proteins.[56]

However, there are a number of potential errors that can affect the analysis of omic data. For NGS data, reference material is required whose properties are sufficiently homogeneous and well-described to be used for sequencing calibration. The Centers for Disease Control and Prevention's Genetic Testing Reference Material Coordination Program (GeT-RM) is committed to creating renewable, publicly available, characterised genomic DNA (gDNA) reference materials that can be used for clinical NGS tests. The risk of using mismatched methods/algorithms or overfitting, as well as technological differences in how tests are performed, can also have a negative impact on the results. In addition to the reference materials, the CDC's Nex-StoCT II working group has published guidelines for laboratory

[53] Moaddel R, Ubaida-Mohien C, Tanaka T, Lyashkov A, Basisty N, Schilling B, Semba RD, Franceschi C, Gorospe M, Ferrucci L. Proteomics in aging research: A roadmap to clinical, translational research. Aging Cell. 2021 Apr;20(4):e13325. doi: 10.1111/acel.13325

[54] Amer B, Baidoo EEK. Omics-Driven Biotechnology for Industrial Applications. Front Bioeng Biotechnol. 2021 Feb 23;9:613307. doi: 10.3389/fbioe.2021.613307

[55] https://olink.com/our-platform/our-pea-technology/

[56] Wik L, Nordberg N, Broberg J, Björkesten J, Assarsson E, Henriksson S, Grundberg I, Pettersson E, Westerberg C, Liljeroth E, Falck A, Lundberg M. Proximity Extension Assay in Combination with Next-Generation Sequencing for High-throughput Proteome-wide Analysis. Mol Cell Proteomics. 2021;20:100168. doi: 10.1016/j.mcpro.2021.100168

practice. Still, as hardware and software are subject to frequent updates and NGS often involves complex, multi-stage processes, further guidance on quality control is needed, especially when sharing data between different laboratories.

Such guidance would help different laboratories validate their procedures, assess the quality of sequencing, evaluate the performance of new platforms and compare or share the results between them. Alternatively, to unify the analytical process, centralised reference sites could be created which would carry out these analyses as a service or as part of collaboration, and a list/catalogue of such analyses could be compiled. Omic analysis requires large sets of data to achieve sufficient statistical power. A small sample size can cause low statistical power, increased variability and a higher risk of false positives. Therefore, it is of paramount importance that omic data sets are shared. Careful experiment design, appropriate statistical methods and rigorous data validation within the platforms will be necessary to minimise errors in omic data analysis and ensure the results are accurate and reproducible.

2.4 Big Data Analyses in Translational Medicine

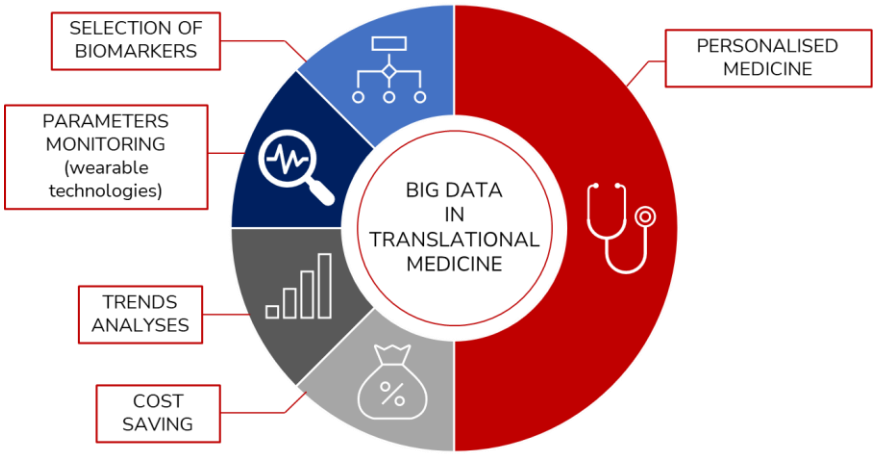
Translational data sets include e.g. omic, imaging, and clinical data, making them large and heterogeneous. Multiomic characterisation of a disease poses new challenges for disease course modelling,[57] but big sets of medical data have the potential to generate new information that is necessary not only for the patient but the healthcare system as a whole. As translational medical data become fuller and more complex, their informative potential increases. In 2022, the global market of big data in healthcare was worth $36.8 billion. Big data can be described by **five characteristics (the 5Vs): volume, velocity, variety, veracity and value. Volume** refers to the large scope of complex and heterogeneous data (data sets are too large to be stored and analysed using traditional database technology). **Velocity** is the pace at which new data is generated.[58] Currently, advanced technological solutions are able to generate health and medical data on an individual level, both in real time and in a real

The integration, analysis, and interpretation of large data sets pose a considerable challenge to researchers.

[57] Fosse V, Oldoni E, Gerardi C, Banzi R, Fratelli M, Bietrix F, Ussi A, Andreu AL, McCormack E, The Permit Group (2022) Evaluating Translational Methods for Personalized Medicine-A Scoping Review. J Pers Med. 12(7):1177

[58] Johnson KB, Wei WQ, Weeraratne D, Frisse ME, Misulis K, Rhee K, Zhao J, Snowdon JL (2021) Precision Medicine, AI, and the Future of Personalized Health Care. Clin Transl Sci.;14(1):86-93. doi: 10.1111/cts.12884

environment (e.g. measuring heart rate via a smartwatch). For this reason it is hoped they will contribute to improving medical practice, following the paradigm of personalised medicine based on real-world evidence. **Variety** refers to different types of structured, semi-structured, and unstructured data that often exist simultaneously. **Veracity** means the reliability, accuracy, relevance, and predictive value of data. Value refers to how convertible the results are into business insights. Volume, variety, velocity, and veracity of data contribute to the increasing complexity of data management and workloads, creating as a consequence a greater demand for advanced analytics.[59] It seems therefore essential to ensure that interpretability goes hand in hand with data generation. However, the definition of big data does not address the most important aspect of data use, which is data security. A critical issue in big data analyses is ensuring the safety and empowerment of the data subject, i.e. the patient.



This is a multidimensional issue which is associated with regulatory guidelines, anonymisation and pseudonymisation techniques, as well as building the general public's confidence in the security of the data used. An additional concern with regard to big data is enabling experts to efficiently use large data processing protocols. Machine learning (ML), deep learning (DL) and artificial intelligence (AI) in general seem to be a natural choice to aid analysis and interpretation. AI stands for obtaining output data generated by imitating (mimicking) human reasoning, without giving information on how the problem is solved. ML is a subtype of artificial intelligence consisting of algorithms that analyse data, learn from them, and consequently acquire the ability to perform typing and decision-making. These methods have improved knowledge management as regards both the investigational drug and the patient population, contributing to the optimisation of research

[59] Ibidem

and development across the three interdependent strategic pillars that are key to translational medicine: the right target, patient, and dose. These pillars are the foundations for generating translational hypotheses, and the data derived from them in preclinical and clinical studies are necessary to maximise the prospect of successful regulatory approval, and above all of therapeutic success of the medicinal product used at the right dose as part of relevant personalised medical strategies.[60]

Literature suggests that AI-assisted translational research will help solve the most difficult challenges faced by precision medicine, facilitating personalised diagnosis and prognosis of disease development and course on the basis of non-genomic and genomic determinants, symptoms, clinical history, lifestyle[61] or family history. Therefore, it seems advisable and even necessary to support ML algorithms based on big data, so that not only would it be possible to accurately identify patients who might benefit most from the available therapies (therapeutic recommendations based on computer-refined phenotypes), but also better manage population health, accelerate the identification of drug targets and increase the diagnostic capacity of clinicians.[62] However, harnessing the power of large amounts of diverse data comes with tremendous challenges. These include, for example, knowing what kinds of data are potentially available and what models of accessing these data exist (acquiring and responsible sharing of data). It is also critical to build and maintain public confidence in the use of medical data for analysis and to develop uniform standards for diagnosing diseases.[63] The use of big data in translational medicine is, of course, limited by information gaps. Gaps in data sets, especially non-random ones, may affect reasoning. Another challenge is linking multiple sources of data regarding the same individuals. Limited access to complete medical records is a result of the dispersed nature of data. In Poland, some data are reported to Centrum e-Zdrowia (CeZ) or to medical registries, some

[60] Terranova N, Venkatakrishnan K, Benincosa LJ (2021) Application of Machine Learning in Translational Medicine: Current Status and Future Opportunities. AAPS J. 2021 May 18;23(4):74

[61] op. cit. 58

[62] Weintraub WS, Fahed AC, Rumsfeld JS (2018) Translational Medicine in the Era of Big Data and Machine Learning. Circ Res. 123(11):1202-1204

[63] Hemingway H, Asselbergs FW, Danesh J, Dobson R, Maniadakis N, Maggioni A, van Thiel GJM, Cronin M, Brobert G, Vardas P, Anker SD, Grobbee DE, Denaxas S; Innovative Medicines Initiative 2nd programme, Big Data for Better Outcomes, BigData@Heart Consortium of 20 academic and industry partners including ESC (2018) Big data from electronic health records for early and late translational cardiovascular research: challenges and potential. Eur Heart J. 39(16):1481-1495

are stored in hospital information systems (HISs), other — in electronic Case Report Forms (eCRFs, if the patient is a clinical trial subject), and yet more are saved on medical devices. Ultimately, even the patients themselves do not have full access in one place to the entire information about their health. In addition, health data are very complex due to the presence of multiple data standards, and it is estimated that 80% of the information is unstructured.[64] Worse still, diagnoses and clinical decisions, such as histopathological interpretations, are often inherently biased and rely on the experience of the interpreters or the availability of standardised diagnostic nomenclature and taxonomy. This bias can cause interpretation errors and diagnostic discrepancies. ML-assisted biomedical research has recently been shown to be less reliable compared to other fields for the very reason of using data sets with missing, incomplete, or poor-quality data such as low-resolution histopathological images.[65]

In translational medicine, data from basic and preclinical research also come into play. In December 2020, a workshop was organised with the participation of the EMA, the European Network for Health Technology Assessment (EUnetHTA) and the Clinical Trials Coordination Group (CTCG-HMA), which led to identifying five main gaps in translational methods. One of them is still cooperation as part of preclinical and clinical research,[66] which of course affects the overall quality of resulting data. Creating a central repository of raw data in native format for future search, retrieval and analysis would be a great convenience in translational projects. **In 2023, the Medical Research Agency announced a call for proposals for establishment of Digital Medicine Centres Network with a goal of consolidating data from various sources, including HISs, eCRFs, and diagnostic devices, including sequencers.** It stands to reason that the next step should be to update the data repository with information from fundamental and preclinical research. There are considerable benefits in defining a framework for data management and mining, as it saves time and effort needed to collect data from different areas, integrate them and perform initial

[64] McPadden J, Durant TJ, Bunch DR, Coppi A, Price N, Rodgerson K, Torre CJ Jr, Byron W, Hsiao AL, Krumholz HM, Schulz WL (2019) Health Care and Precision Medicine Research: Analysis of a Scalable Data Science Platform. J Med Internet Res.21(4):e13043

[65] Jiang P, Sinha S, Aldape K, Hannenhalli S, Sahinalp C, Ruppin E. Big data in basic and translational cancer research. Nat Rev Cancer. 2022 Nov;22(11):625-639

[66] op. cit. 57

processing. Implementing data management standards and consistent APIs helps generate predictive algorithms that can be applied to a variety of bioinformatics systems. Increasingly, attention is drawn to the fact that the problem is not just data integration and analysis, but understanding the trends and causal relationships (not consequences), and then transforming these insights into meaningful information for patients and decision-makers.[67] The MRA plans further activities concerning the development of the Digital Medicine Centres Network.

One of the most important translational applications of big data is personalised medicine in oncology. A major objective of translational research in this field has been the development of genetic tests to help predict the risk of cancer, some of which have already been validated and made available for clinical use. The successful use of such tests depends on their high negative predictive value. Some of the selected large datasets include patients with breast cancer positive for oestrogen receptor (ER) or progesterone receptor (PR). These tests are particularly useful since adjuvant hormone therapy alone can provide sufficient clinical benefit to ER/PR-positive and HER2-negative patients with early-stage breast cancer. In this way, patients assigned into low-risk groups can avoid unnecessary additional chemotherapy.[68,69] The available and developed biomarkers are described in detail in Chapter 2.2. There are, however, several challenges to translating multiomic data into clinically meaningful biomarkers. First, pooling data will result in a large number of covariates which, combined with the high heterogeneity of different data types, can make integrative analysis very difficult. Many reduction techniques have been developed, such as multiple co-inertia analysis (mCIA) and multivariate analysis, with the aim to identify data that can be omitted from the analysis without significant loss of information.[70] Secondly, better standards of data generation and reporting are needed to facilitate data integration and reduce error (for example, the afore-mentioned data quality standards or diagnostic interpretation standards). Even the procedures for collecting and preparing samples intended for

[67] Jordan L (2015) The problem with Big Data in Translational Medicine. A review of where we've been and the possibilities ahead. Appl Transl Genom. 6:3-6

[68] Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet (London, England), 365(9472), 1687–1717. https://doi.org/10.1016/S0140-6736(05)66544-0

[69] You, Y. N., Rustin, R. B., & Sullivan, J. D. (2015). Oncotype DX(®) colon cancer assay for prediction of recurrence risk in patients with stage II and III colon cancer: A review of the evidence. Surgical oncology, 24(2), 61–66. https://doi.org/10.1016/j.suronc.2015.02.001

[70] op. cit. 65

sequencing must be well regulated.[71] In Poland, the best recommendations are contained in *Quality Standards for Polish Biobanks, v.2.0*, but few biobanks are certified to meet the quality objectives set out in that document.

Big data analysis and artificial intelligence are becoming more and more ubiquitous throughout the healthcare system, across service providers, decision-makers, patients and product manufacturers. However, attention should be paid to ensuring that patients demonstrate the right approach to the use of medical data in order to obtain information that reflects reality as best as possible, as learning models can only shorten the drug manufacturing pathway if they are fed real-world data (RWD), taking into account the disease process in the context of all the internal processes of the human body. Hence, it should be borne in mind that what we now refer to as big data is only a fraction of the future data volumes. Large and heterogeneous datasets typically associated with health care cannot be stored in conventional databases.[72] Moreover, medical data have become too complex for traditional data processing technologies.[73] The problem starts already at the stage of data collection, and it concerns both the resources (also financial) needed for storing large amounts of data, and the different data formats, sources and origins, which is also an indirect consequence of the absence of uniform standards for generating certain types of data and the lack of unified systems that could integrate information from different sources. The absence of standards at this stage may affect the final quality and therefore reliability of data.[74] Big data analytics is a type of advanced analytics supported by high-performance analytical systems, which makes it necessary to have personnel with appropriate qualifications. The main challenges associated with the use of big data analysis include structuring the data, ensuring data security and standardisation, storage and transmission, staff training in data analysis and management, as well as the issue of real-time analytics (health care units should be able

Big data analysis should consider many dimensions and variants of reliable top-quality data.

[71] Ibidem
[72] op. cit. 58
[73] https://itrexgroup.com/blog/big-data-in-healthcare-examples-problems-benefits/
[74] op. cit. 65

to use big data in real time).[75,76] All this means that most of the data are stored, not analysed, and seldom used to drive changes in healthcare.[77] The strategy aims to support the creation of platforms and IT systems enabling the compilation of preclinical and clinical data to be used for more efficient analysis of potential drug candidates and more productive modelling of diagnostic and therapeutic processes, with particular emphasis on AI-based solutions. Support for these type of actions has been planned, among others, within the establishment of the Digital Medicine Centres Network.

Deloitte conducted a study to explore how various organisations around the world use/plan to use artificial intelligence. The study shows that the costs of AI are still one of the biggest obstacles. In addition to costs, several other limitations were identified, such as the implementation of the solution and the risks associated with it. Moreover, a 2020 survey among U.S. physicians revealed that 69% of doctors are concerned about who will bear responsibility if AI-based solutions make a mistake.[78] It is therefore important to build trust on the part of healthcare professionals and patients alike. Apart from the implementation costs and the lack of trust, there are challenges related to data aggregation, cleansing, and security. To make matters worse, there are still unimplemented European regulations, such as The Data Act,[79] The AI Act,[80] whose continued absence leads to divergent legal interpretations in the area of data sharing.

2.5 The Role of Modelling and Simulation in Translational Research for Drug Development

The application of modelling and simulation starts from the early stages of fundamental research, where the potential utility of the drug candidate is first verified. Compound libraries

[75] Bainbridge, M. (2019). Big Data Challenges for Clinical and Precision Medicine. In: Househ, M., Kushniruk, A., Borycki, E. (eds) Big Data, Big Challenges: A Healthcare Perspective. Lecture Notes in Bioengineering. Springer, Cham. https://doi.org/10.1007/978-3-030-06109-8_2

[76] Ismail, A., Shehab, A., El-Henawy, I.M. (2019). Healthcare Analysis in Smart Big Data Analytics: Reviews, Challenges and Recommendations. In: Hassanien, A., Elhoseny, M., Ahmed, S., Singh, A. (eds) Security in Smart Cities: Models, Applications, and Challenges. Lecture Notes in Intelligent Transportation and Infrastructure. Springer, Cham. https://doi.org/10.1007/978-3-030-01560-2_2

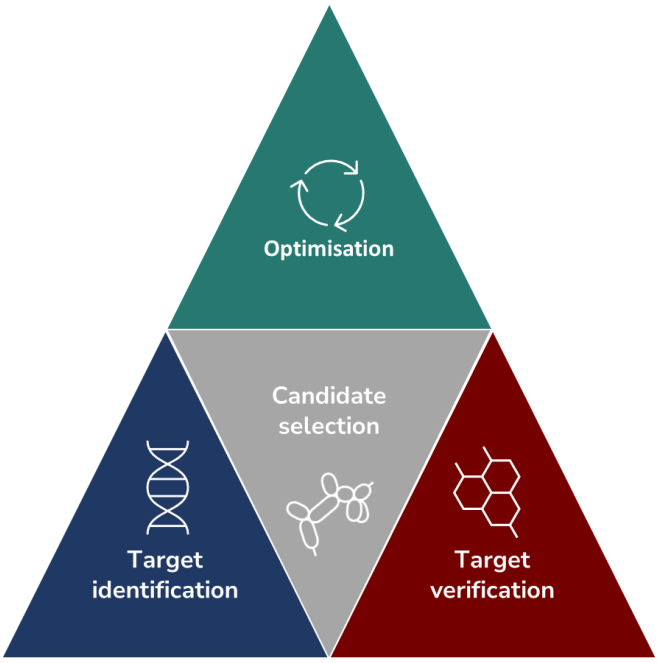
[77] Batko, K., Ślęzak, A (2022) The use of Big Data Analytics in healthcare. J Big Data 9, 3. https://doi.org/10.1186/s40537-021-00553-4

[78] https://www2.deloitte.com/us/en/insights/industry/health-care/artificial-intelligence-in-health-care.html

[79] https://digital-strategy.ec.europa.eu/en/library/data-act-factsheet

[80] https://artificialintelligenceact.eu/

are analysed to select the most promising substances for further biological screening using a variety of techniques and models to assess potency, affinity, and selectivity.



For example, the design of an active molecular structure that will match a selected receptor with a specific biological activity combines chemical expertise and application of *in silico* models, which together enable the chemical structure optimisation of the test substance, achieving the desired physicochemical properties. Modelling and simulation are important *in silico* tools for forecasting and formulating hypotheses from the already available data.[81] In the past, this technique was mainly used to predict the pharmacokinetic behaviour of a drug. Recently, pharmacodynamic assessments and even efficacy and safety endpoints have also been used in such models. Examples range from classic PK/PD modelling, through safety biomarker modelling or various *in silico* disease models, to even more complex models involving PK biomarkers, PD biomarkers and disease-specific biomarkers.[82] Information obtained from alternative studies conducted in conventional two-dimensional (2D) and spheroid (3D) cell cultures and then in animal models appears to be as much necessary as it is insufficient to unequivocally conclude if the study treatment is likely to succeed when translated into clinical practice.[83]

An example of the application of an *in silico* model in chronic inflammatory diseases is the paper by Jackson and Radivoyevitch (2013), who created a model of excessive activation of neutrophils to study the production of reactive oxygen species.[84] Based on the model,

[81] Shaker B, Ahmad S, Lee J, Jung C, Na D. In silico methods and tools for drug discovery. Comput Biol Med. 2021 Oct;137:104851

[82] Chang Y, Hawkins BA, Du JJ, Groundwater PW, Hibbs DE, Lai F. A Guide to In Silico Drug Design. Pharmaceutics. 2022 Dec 23;15(1):49

[83] Linder, S., Shoshan, M.C. (2006). Is translational research compatible with preclinical publication strategies?. RadiatOncol. 1, 4. https://doi.org/10.1186/1748-717X-1-4

[84] Jackson RC, Radivoyevitch T. Modelling c-Abl Signalling in Activated Neutrophils: the Anti-inflammatory Effect of Seliciclib. Biodiscovery. 2013 Mar 1;7(4):4. doi: 10.7750/BioDiscovery.2013.7.4. PMID: 24765523; PMCID: PMC3994723

The development of in silico models for a variety of diseases may help select the most promising biomarkers or therapeutic drug targets.

key biomarkers were selected, representing the main signalling pathways in neutrophils activating the release of reactive oxygen species.

Advances have lately been made in collecting data and developing models to assess and predict pharmacokinetic properties according to the sequence of absorption, distribution, metabolism, excretion, and toxicity (ADMETox) of bioactive compounds at the early stages of drug design. Drug discovery uses computer-aided drug design (CADD), which can help reduce the challenges of scale, time and cost faced by conventional experimental approaches.[85] CADD comprises computational identification of potential therapeutic drug targets, virtual screening of large chemical libraries in search of effective drug candidates, further optimisation of candidate compounds, and *in silico* assessment of their potential for toxicity. Following these computational processes, the drug candidates are subjected to *in vitro* or *in vivo* experiments to further verify and confirm their properties. This way, CADD can reduce the number of substances that need to be evaluated experimentally, while increasing the success rate by eliminating ineffective and toxic compounds. To date, CADD has successfully helped put on the market new medication for various diseases, including drugs against human immunodeficiency virus 1 (HIV-1; atazanavir, saquinavir, indinavir and ritonavir),[86] anticancer drugs (raltitrexed) and antibiotics (norfloxacin).[87]

Bioinformatics, systems pharmacology, structural biology, and cheminformatics are generating tools for creating translational models.

One of the cornerstones of translational medicine is the search for candidate molecules. A key element in the validation of a therapeutic target is building trust in the therapeutic hypothesis, e.g.

[85] Wu F, Zhou Y, Li L, Shen X, Chen G, Wang X, Liang X, Tan M, Huang Z. Computational Approaches in Preclinical Studies on Drug Discovery and Development. Front Chem. 2020 Sep 11;8:726

[86] Robinson BS, Riccardi KA, Gong YF, Guo Q, Stock DA, Blair WS, Terry BJ, Deminie CA, Djang F, Colonno RJ, Lin PF. BMS-232632, a highly potent human immunodeficiency virus protease inhibitor that can be used in combination with other available antiretroviral agents. Antimicrob Agents Chemother. 2000 Aug;44(8):2093-9

[87] Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, Li B, Madabhushi A, Shah P, Spitzer M, Zhao S. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019 Jun;18(6):463-477. doi: 10.1038/s41573-019-0024-5. PMID: 30976107; PMCID: PMC6552674

with quantitative systems pharmacology (QSP) models. Such mechanistic models combine information on drug pharmacokinetics, target bonding, and biological processes derived from prior knowledge and available pre-clinical and clinical data in order to predict the efficacy and safety of a potential drug candidate. QSP provides a framework for the integration of large format data from different sources, including omics and imaging, whose dimensions can be reduced with machine learning. Once the target of interest has been properly identified, the next step in drug discovery and development is to design a compound that can elicit the intended effect on the target gene or protein, as well as to predict drug-target interactions. Using ML can help define the optimal dose, as well as determine the dosage regimen and the sequence of drug administration, depending on patient-specific factors.[88] The application of systemic pharmacology deserves particular attention where experimental models do not necessarily ascertain the clinical utility of the study molecules, which is the case e.g. in neurobiology, since there are significant differences in brain physiology and disease aetiologies between animals and humans. Magnetic resonance imaging (MRI), positron emission tomography (PET), and other visualisation techniques such as pharmaco-electroencephalography (Pharmaco-EEG) and pharmacological magnetic resonance imaging (phMRI) have made it possible to explore the biodistribution of molecules in the brain, among other things, helping to better understand the pharmacodynamics of how drugs affect brain activity and how a therapeutic target binds with the drug in the central nervous system. New preclinical *in vitro* models, such as microphysiological systems (MPS), more accurately illustrate tissue physiology and have the potential to improve the translation of results into the human body. The growing number of biomedical devices generate digital biomarkers that have a considerable potential in neurology as parameters complementary to the existing indicators of sleep quality, cognitive function, gait measurements, physical activity, voice abnormalities and behavioural changes.[89] One of the already existing QSP platforms has been developed and applied to study the underlying mechanisms of Alzheimer's disease, confirming that despite the potential interrelationship between the β amyloid and the tau protein, pathologies within the latter are usually not susceptible to

[88] op. cit. 60

[89] Bloomingdale P, Karelina T, Cirit M, Muldoon SF, Baker J, McCarty WJ, Geerts H, Macha S (2021). Quantitative systems pharmacology in neuroscience: Novel methodologies and technologies. CPT Pharmacometrics Syst Pharmacol. 10(5):412-419. doi: 10.1002/psp4.12607

amyloid-targeted therapy, as observed clinically in patients with mild to moderate Alzheimer's disease treated with a BACE inhibitor.[90]

Another study integrated mechanistic models with AI algorithms to predict treatment response and blood pressure control. High blood pressure increases the risk of cardiovascular diseases. Investigating treatment responses in patients with hypertension is essential, as about half of these patients do not achieve adequate blood pressure control after treatment. A QSP model of blood pressure control has been developed with a view to applying precision medicine to the treatment of hypertension. It featured a virtual population which accounted for the heterogeneity between the sexes and within the pathophysiology of hypertension. After developing the sex-specific QSP model incorporating the virtual population, the mechanistic model integrated with machine learning tools was used to study response to antihypertensive therapies. The authors then constructed a decision tree to identify the optimal drug class. The algorithm was trained to predict which class of drugs causes the greatest decrease in mean arterial pressure in the virtual population. The model was validated using five-fold cross-validation.[91] These results indicate the potential areas of application for precision medicine in primary arterial hypertension in humans. Continuous enrichment of models is their greatest strength and greatest limitation in terms of the amount of data required to be included and processed. Not only genetics, but the use of proteomics is also growing. Unlike mass spectrometry, next-generation proteomic technologies, such as aptamers, usually require smaller amounts of biological material, so they can be more easily implemented in large cohorts of patients to identify therapeutic targets.[92]

A major limitation of the QSP models in translational big data analysis has been their over-focus on specific pathological processes/cells,[93] and given their mechanistic nature, these models can also be used to understand the physiological behaviour of molecules and cells under non-pathological conditions. This problem was addressed by researchers

[90] Karelina T, Demin O Jr, Demin O, Duvvuri S, Nicholas T (2017). Studying the progression of amyloid pathology and its therapy using translational longitudinal model of accumulation and distribution of amyloid beta. CPT Pharmacometrics Syst Pharmacol. 6(10):676-685. doi: 10.1002/psp4.12249

[91] Ahmed S, Sullivan JC, Layton AT (2021). Impact of sex and pathophysiology on optimal drug choice in hypertensive rats: quantitative insights for precision medicine. iScience. 24:102341 doi: 10.1016/j.isci.2021.102341

[92] op. cit. 7

[93] op. cit. 89

who developed a model of T cell plasticity under physiological conditions, which made it possible to predict the circumstances that affect T cell function and responses.[94]

The Plan aims to support the development of existing IT platforms, adding new functionalities, and to stimulate the scientific community to create new platforms that will allow to model and simulate physiological and disease processes, and assess the impact of investigational substances and interventions on the human body.

3. Translational Research Centres and Areas of Interest in Poland

Polish translational medicine centres are institutions dedicated to conducting both fundamental research and early-phase clinical trials. The leading ones bring together scientists and clinicians to collaborate in research projects focusing on the development of new diagnostic tools, therapies and medical devices. Translational medicine centres established in Poland address the needs of general education. Study programmes in biomedical sciences have been launched at technical universities. Many opportunities have been created for young scientists to work on their ideas in practice, and there are implementation PhD programmes granting academic degree in recognition of work in the industry. Despite these measures, without enhancing the competencies of the stakeholders in this process and without a coordinated effort aimed at driving the implementation of innovations into clinical practice, the extent of translation of results into medicine will remain unsatisfactory. Responding to this need, the Medical Research Agency, as part of its Educational Strategy, announced a call for proposals for postgraduate study programmes in the field of biomedicine, where important bonus criteria include aspects related to translational medicine. The inclusion of translational medicine topics in postgraduate curricula will certainly contribute to a better understanding of the phenomenon, but may not be sufficient to provoke actions towards translation itself.

[94] Wertheim, K. Y., Puniya, B. L., La Fleur, A., Shah, A. R., Barberis, M., & Helikar, T. A multi-approach and multi-scale platform to model CD4+ T cells responding to infections. PLoS computational biology, 2021;17(8), e1009209. https://doi.org/10.1371/journal.pcbi.1009209

Polish translational medicine centres provide scientists with access to the state-of-the-art equipment and devices for preclinical research, such as *in vivo* imaging, genomics, proteomics and other types of omics. They also offer drug development services, including medical chemistry analyses and pharmacokinetic studies. These centres focus on developing innovative diagnostic and therapeutic approaches for oncology and cardiology, including immunotherapy and precision medicine, as well as innovation in regenerative medicine. Credit should be given to existing companies on the Polish market which can boast very capable R&D departments and a high potential for innovation in translational medicine. Studies show that most of these are biotech companies focusing mainly on oncology, immunology and neuropsychiatry. Medical biotechnology as a field has been included in the government's list of National Smart Specializations (KIS), i.e. industries prioritised in terms of research, development, and innovation, which increase added value and the economy's competitive advantage on foreign markets. Still, translational research in the field of biotechnology requires adequate funding and simplified, predefined pathways, since investors are reluctant to take long-term financial risks. So far, only large pharmaceutical companies in Poland have been able to fund research and development; this level of investment seems unattainable tomedium-sized companies. A helpful solution is the tax credit for research and development, available to both Polish companies and foreign enterprises that invest in Poland and take the risks associated with innovative research, also in the field of translational medicine. Although the R&D tax relief is a fairly simple instrument, entrepreneurs still rarely take advantage. An alternative is to promote Polish companies on the international level and create opportunities for joint venture solutions that would leave the ownership of the molecule in Polish hands in exchange for exclusivity in international commercialisation. The prospect of holding an exclusive licence or international distribution rights and returning a defined profit percentage to the state budget or to the enterprise could encourage foreign biotech

The existing Polish translational medicine centres mainly focus on oncology and immunology.

In order to ensure an agile development of medical technologies, it is necessary to create efficient multidisciplinary working groups.

corporations to invest in Polish translational research. Establishing working groups with representatives from biotech companies, biotech start-ups, national consultants, the Agency for Health Technology Assessment and Tariff System, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, the Medical Research Agency and the Ministry of Health could bring a breakthrough in the development of translational medicine in Poland by delivering clear and simplified research pathways. The educational aspect is also important, as well as cooperation with the Academy of Translational Medicine Professionals (ATMP) at the European Society for Translational Medicine, in order to teach translational medicine to medical professionals, employees of biotechnology companies, and decision-makers. One of the objectives of the strategy is to create intellectual property (IP) valuation guidelines/good practices in order to facilitate and accelerate the transfer of knowledge to the economy/clinical practice. In particular, an IP valuation guide will be developed, featuring methodologies and recommended forms of commercialisation developed as part of calls for proposals.

4. Technologies in Translational Medicine Research

Over the past decades, technological innovation has revolutionised medical science and healthcare.[95] Today, advanced technological solutions generate health and medical data at an individual level, in real time, and drive medical practice towards greater personalisation made possible by decision making based on real world data (RDW) and scientific evidence.

The main goal of translational medicine is to shorten the distance between discovery and implementation.

In recent years, research and development in the pharmaceutical industry have evolved into a very dynamic process, made possible by patient-oriented iterative translational approaches. Travelling from idea to application in medicine is becoming an increasingly multidisciplinary and interconnected process. An example of this new approach is the *Drug Discovery, Development, and Deployment Map*, which presents a web-based view of the process and the associated cross-sectoral ecosystem that challenges the usual linear

[95] Esteva, A., Robicquet, A., Ramsundar, B., Kuleshov, V., DePristo, M., Chou, K., Claire Cui, C., Corrado, G., Thrun, S., Dean, J. (2019). A guide to deep learning in healthcare. NatMed. 25(1), 24–9

and sequential path of implementation.[96] The Bayesian (*a posteriori*) approach to learning based on the entirety of data and evidence, which today often amount to informational chaos, is particularly important in delivering innovative solutions to potentially address the issue of over-fitting and provide a principled and automated method of selecting parameters. Applied to healthcare, it will meet health needs at an appropriate pace.[97,98,99]

One of the main objectives of translational research is to accelerate the development of medicine based on the transition from basic to applied sciences. In other words, it consists in shortening as much as possible the distance between discovery and implementation. Besides affecting different stages of research, this process also involves the need for legislative changes, new business models and transformed mentality of doctors and patients. The literature suggests that, like no other field, the dynamics of translation that drives new technologies require a synergy between many fields of technology and medicine, the collaboration of many scientific or research institutions and medical equipment manufacturers, as well as administrative support.[100] Currently in Europe, including Poland, work on biomedical innovations is highly dispersed, i.e. focused on own value chains, without interaction with the environment. The desired effect of synergy and interaction between individual value chains should be ensured by boundary spanning to catalyse changes in strategic cooperation and initiation of projects whose deliverables are defined in terms of measurable outcomes (patient health and wellbeing, cost of treatment, cost and social effect, economy). Establishing such boundary spanners — centres in which preclinical processes would run in parallel to clinical ones — would facilitate the transfer of knowledge between the scientific, medical and business communities, which could give rise

[96] Wagner, J., Dahlem, A.M., Hudson, L.D., Terry, S.F., Altman, R.B., Gilliland, C.T., DeFeo, C., Austin, C.P. (2018). A dynamic map for learning, communicating, navigating and improving therapeutic development. NatRevDrugDiscov. 17(2), 150–0

[97] Venkatakrishnan, K., Cook, J. (2018). Driving access to medicines with a totality of evidence mindset: an opportunity for Clinical Pharmacology. ClinPharmacolTher. 103(3), 373–5

[98] Venkatakrishnan, K., Yalkinoglu, O., Dong, J.Q., Benincosa, L.J. (2020). Challenges in Drug Development Posed by the COVID-19 Pandemic: an opportunity for Clinical Pharmacology. ClinPharmacolTher. 108(4), 699–702

[99] MacKenzie, R., Honig, P., Sewards, J., Goodwin, R., Hellio, M.P. (2020). COVID-19 must catalyse changes to clinical development. NatRevDrugDiscov. 19(10), 653–4

[100] Mayrink, N.N.V., Alcoforado, L., Chioro, A., Fernandes, F., Lima, T.S., Camargo, E.B., Valentim, R.A.M. (2022). Translational research in health technologies: A scoping review. FrontDigitHealth. 4, 957367

to an integrated understanding of patient care and orientation towards clinical practice, as well as tangible economic benefits.[101]

Broadly defined medical technologies applied to provide health services are a key element of healthcare, especially in the context of more dispersed and complex systems of service delivery. The development of medical technologies requires many diverse resources, from engineering design, through preclinical evaluation and clinical research, to production, marketing, distribution and post-market evaluation. Each of these areas is subject to unique regulatory requirements and commercialisation processes. This is the reason why the success rate of translating newly developed medical technologies into clinical practice is still very low.[102]

According to the GlobalData database, the number of planned and ongoing clinical investigations of (new) medical devices in the third quarter of 2022 increased by 31% worldwide compared to the average for the previous four quarters. By type of market, healthcare IT had the highest proportion of new studies (16%) in the third quarter of 2022, followed by cardiovascular science (12%) and neurology (11%).[103]

Key players in the medical device industry, along with sectoral decision-makers, will play a leading role in actively transforming this market and driving the development of translational medicine in Poland. There is a need to reevaluate some paradigms, address the existing needs and create good conditions for communication with customers, patients and consumers (end-users). This will require shifting from delivering the product, which has been the focus to date, to delivering value, and from treating advanced disease stages to prophylaxis and prevention, using integrated "smart" services and solutions that will reduce the costs of care and improve outcomes.[104]

[101] Nasir, L., Robert, G., Fischer, M., Norman, I., Murrells, T., Schofield, P. (2013). Facilitating knowledge exchange between health-care sectors, organisations and professions: a longitudinal mixed-methods study of boundary-spanning processes and their impact on health-care quality. Health Serv Deliv Res. 1(7). https://doi.org/10.3310/hsdr01070

[102] Brightman, A.O., Coffee, Jr. R.L., Garcia, K., Aaron, A.E., Sors, T.G., Moe, S.M., Wodicka, G.R. (2021). Advancing medical technology innovation and clinical translation via a model of industry enabled technical and educational support: Indiana Clinical and Translational Sciences Institute's Medical Technology Advance Program. JClinTranslSci. 5(1), e131. doi:10.1017/cts.2021.1

[103] https://www.medicaldevice-network.com/marketdata/new-medical-device-clinical-trials-q3-2022/

[104] https://assets.kpmg.com/content/dam/kpmg/cn/pdf/en/2018/04/medical-devices-2030.pdf

To get closer to the end user, now more than ever is it necessary to use data and build AI algorithms into new products — this is quickly becoming an important value of the proposed new devices. Artificial intelligence is an innovative technology with the potential to revolutionise clinical practice. The advancement of AI algorithms focuses on increasing their accuracy and effectiveness, which makes them a real help for medical professionals.

Research using AI algorithms has the largest share in R&D in healthcare. The global market of AI-powered clinical research solutions was valued at $1.6 billion in 2022 and is expected to grow at a compound annual growth rate (CAGR) of 22% between 2023 and 2030. What is driving the market is improving the productivity and effectiveness of various stages of research. This market growth is stimulated by the growing awareness of AI's potential and its wide variety of clinical research applications, including drug design, improved patient selection, or patient monitoring. The use of artificial intelligence in fields like drug research can be useful to drastically reduce costs, improve the quality of clinical outcomes and accelerate the process. For example, in January 2020, Recursion Pharma and Takeda joined forces to carry out a rare diseases research project that took less than 18 months to investigate molecules that were being studied by these companies in more than 60 indications.[105]

Research using AI and machine learning algorithms has the largest share in R&D in healthcare.

The size of the global clinical research market in neuroscience was valued at $5.23 billion in 2022 and is expected to grow at a CAGR of 5.6% in the years 2023–2030. This is largely due to the increasing incidence of neurological diseases such as dementia, stroke and peripheral neuropathy, as well as the growing investments in neurology. A considerable number of neurology studies began in 2022, among them a neurooncology study titled: "*SGT-53 in Children with Recurrent or Progressive CNS Malignancies*",[106] which aims to evaluate the safety and feasibility of SGT-53 administration in conjunction with conventional radiotherapy and/or chemotherapy in children with recurrent or refractory CNS malignancies. Another study, "*GB5121 in Adult Patients with Relapsed/Refractory CNS Lymphoma (STAR CNS),*"[107] investigates the anti-tumour activity of GB5121 and evaluates

[105] https://www.clinicaltrialsarena.com/comment/big-pharma-ai-partnerships/
[106] https://clinicaltrials.gov/ct2/show/NCT03554707
[107] https://clinicaltrials.gov/ct2/show/NCT05242146

its safety, tolerability and toxicity. The high burden of neurological diseases worldwide has increased the interest of sponsors and investors in neurological clinical trials. For example, in March 2022, a team of researchers from Brown University, New York University and University of Rochester received funding of $16.0 million to develop research on Alzheimer's disease.[108]

The pace at which innovative solutions keep emerging in the field of medical devices often far surpasses the speed of transformation of the applicable procedures, legal regulations, and mentalities. This process should be stimulated by more international collaboration and a favourable regulatory environment.

The largest venture capital deals for medical devices in 2022 predominantly featured broadly defined non-invasive diagnostics, precision drug delivery solutions and several major medical fields such as neurology, cardiology, orthopaedics and surgery.[109] Table 1 presents some examples by selected fields.

Table 1. Examples of the largest venture capital deals for medical devices in 2022.

Field	Company	Solution
Neurology	Nalu Medical	A system designed to deliver gentle electrical impulses to the nervous system in order to modulate pain signals travelling to the brain. The system uses a miniaturised implantable pulse generator (IPG) controlled by a smartphone app. The neurostimulation device has been approved by the FDA.
Cardiology	Orchestra BioMed, Terumo partnership	Virtue Sirolimus AngioInfusion Balloon (SAB) for patients with coronary in-stent restenosis, designed to dilate the artery and restore blood flow without leaving a permanent implant. In 2019, Virtue SAB was granted Breakthrough Device designation by the FDA.
Orthopaedics	THINK Surgica	TSolution One Total Knee Application featuring a preoperative planning workstation and a robotic surgical device for bone preparation with submillimetre precision. The workstation contains an open library of knee implants and surgical plans

[108] https://www.brown.edu/news/2022-03-10/retrotransposon
[109] https://www.medicaldesignandoutsourcing.com/biggest-medical-device-vc-venture-capital-deals-2022/

		from different manufacturers, allowing surgeons to consider different options and select the best personalised solution for a given patient. The application has been approved by the FDA.
Non-invasive diagnostics	Ceribell	A portable electroencephalography (EEG) device for the rapid assessment of brain waves to diagnose epileptic seizures in emergency and intensive care settings. The cloud-connected system based on artificial intelligence offers 24/7 monitoring of brain activity and delivers results within minutes.

Medical devices for early detection of diseases and for remote and non-invasive monitoring of patient health will have a key impact on increasing the effectiveness of health systems and therapeutic processes. Equally important will be solutions associated with telemedicine and transferring the point of patient care from the hospital to the home. The Internet of Medical Things (IoMT), wearables, biosensors and home-based digital point-of-care are setting trends for medical devices and solutions.[110]

Strategic challenges in translational research of new medical technologies include support at the prototyping stage — ideas and innovative medical technologies at early stages of development should be quickly prototyped and tested in frequent iterations in order to verify their functionality and quality in meeting clinical needs.

5. Internationalisation of Translational Medicine Research

The traditional process of developing new drugs or interventions is considered not fast enough,[111] which ultimately affects end users, namely patients and the National Health Fund. Translational medicine should therefore not only connect medicine silos by building interdisciplinary bridges, but also develop strategies for early implementation of effective solutions into clinical practice. It is worth noting that translational medicine is advancing through the effective collaboration of multiple scientific disciplines, as well as regulatory

[110] Mutunhu, B., Chipangura, B., Twinomurinzi, H. (2023). A Systematized Literature Review: Internet of Things (IoT) in the Remote Monitoring of Diabetes. In: Yang, XS., Sherratt, S., Dey, N., Joshi, A. (eds) Proceedings of Seventh International Congress on Information and Communication Technology. Lecture Notes in Networks and Systems, 448. https://doi.org/10.1007/978-981-19-1610-6_57

[111] Sun D., Gao W., Hu H., Zhou S. Why 90% of clinical drug development fails and how to improve it? Acta Pharmaceutica Sinica B,2022;12(7),3049-3062. https://doi.org/10.1016/j.apsb.2022.02.002

bodies such as the EMA, the FDA, competent Member State national authorities, research funding bodies and decision-makers. Governments can play an important role in creating a favourable ecosystem, providing critical infrastructure and removing cross-sectoral barriers. The success of translational medicine is ultimately defined by how the system can adopt an innovation with an acceptable cost-benefit ratio.[112] Importantly, this approach benefits patients as much as pharmaceutical companies. In 2011, AstraZeneca began a major overhaul of its R&D strategy to improve the efficiency of research and development. The revised strategy focused the decision-making process on five technical considerations (right target, right tissue, right safety, right patient and right commercial potential). Owing to the new approach, the success rates for drug candidates by the end of Phase 3 improved from 4% in 2005–2010 to 19% in 2012–2016.[113] This approach has become extremely popular and is now a milestone in the transformation of the pharmaceutical market. The imposed standards made it a necessity before initiating clinical research to have a good understanding of the molecular effects and disease progression, as well as to identify biomarkers, the expected response to therapy, and prognosis, e.g. by means of defining specific therapeutic targets.

Providing opportunities for a wide variety of stakeholders to work together requires unconventional and innovative collaborative models that prioritise the achievement of common goals, with the needs of patients as the overriding objective. Examples of organisations involved in the field of translational medicine in Europe are the European Infrastructure for Translational Medicine (EATRIS, established in 2014), the European Alliance of Biomedical Research Infrastructures (AMRI, established in 2021), and the Innovative Medicines Initiative (IMI). IMI1 ran from 2008 to 2013, IMI2 until 2020,

[112] https://toolbox.eupati.eu/resources/translational-medicine/
[113] Morgan P, Brown DG, Lennard S, Anderton MJ, Barrett JC, Eriksson U, Fidock M, Hamrén B, Johnson A, March RE, Matcham J, Mettetal J, Nicholls DJ, Platz S, Rees S, Snowden MA, Pangalos MN (2018) Impact of a five-dimensional framework on R&D productivity at AstraZeneca. Nat Rev Drug Discov. 17(3):167-181

and since 2021 it has proceeded as the Innovative Health Initiative.[114] The Innovative Medicines Initiative[115] is the largest public-private translational medicine initiative in Europe which aims to accelerate drug development, promote collaborative research projects, and support active industrial and academic networking to foster pharmaceutical innovation. EATRIS[116] is an initiative undertaken by the European Strategy Forum on Research Infrastructures (ESFRI) responsible for the planning and operation of translational research infrastructure in Europe. ESFRI's objective is to promote a coherent and strategic approach to European policy making in this regard. ESFRI has established an ad hoc working group to monitor the performance of research infrastructures. It is organised as an expert group of the European Commission, and membership in it is limited to the EU Member States, countries affiliated as part of the framework research programme and the European Commission.[117] With its programmes, EATRIS provides access to preclinical and clinical expertise, as well as facilities available in more than 144 top-class academic centres across Europe, even taking into account the need for the entire production and development process of advanced therapy medicinal products (ATMPs).[118]

In 2018, 22 EU countries, the United Kingdom and Norway signed a Member State declaration to step up efforts to establish a European infrastructure for genomic data and implement common national rules for accessing data, which is part of the EU's Digital Transformation of Health and Care[119] programme and complies with the objectives of the European Health Data Space.[120] The "1+ Million Genomes" (1 + MG) initiative, later referred to as "Beyond 1+ Million Genomes" (B1MG), and then as "Genomic Data Infrastructure" (GDI), aims to provide secure access to genomics and clinical data across Europe in order to ensure better quality research, personalised healthcare and health policy making.[121]

[114] op. cit. 112
[115] http://www.imi.europa.eu
[116] http://www.eatris.eu
[117] www.esfri.eu
[118] op. cit. 116
[119] https://www.fairshareinitiative.eu/
[120] https://health.ec.europa.eu/
[121] https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes

Since 2018, work has been underway to establish a European framework for genomic data in line with the objectives of the European Health Data Space.

Of no lesser importance are organisations such as the European Society for Translational Medicine (EUSTM), whose main goal is to improve global healthcare by facilitating the rapid translation of scientific discoveries into therapies. Another institution is the Academy of Translational Medicine Professionals run by the EUSTM, which works to set standards of excellence in translational medicine and implements certification programmes aimed at promoting and maintaining high quality clinical research by verifying competence in translational medicine and related specialisations. These certification programmes are accredited by the EUSTM and the Global Translational Medicine Consortium (GTMC).

There are also many scattered thematic groups and initiatives, for example the Epigenetics, Metabolism and Aging group which is part of the Translational Medicine Centre at the International Clinical Research Centre of St. Anne's University Hospital in Brno (FNUSA-ICRC).

The EMA's Human Medicines Division oversees medicines for human use throughout their life cycles. This includes providing guidance and advice during drug development and approval processes, as well as monitoring of the safety of the medicines already on the market. The Department also works to facilitate access to drugs and their optimal use. Clearly, the EMA is not alone in promoting translational medicine.

As regards America, it should be mentioned that in 2017, the Center for Drug Evaluation and Research (CDER) at the FDA took the initiative to modernise the New Medicines Regulation Programme.[122] The Critical Path Initiative (CPI) is the FDA's strategy aimed at transforming the way FDA-regulated medical products are developed, evaluated and manufactured.[123] Of note is also the Office of Translational Sciences (OTS), which consists of five offices and 22 divisions.[124] The OTS Immediate Office supports

[122] https://www.fda.gov/science-research/science-and-research-special-topics/advancing-regulatory-science
[123] https://www.fda.gov/science-research/science-and-research-special-topics/critical-path-initiative
[124] https://www.fda.gov/drugs/regulatory-science-research-and-education/reorganization-office-new-drugs-corresponding-changes-office-translational-sciences-and-office

translational medicine efforts for CDER and leads the areas of technology transfer, data mining, health information technology, research oversight, and knowledge management. The FDA receives an immense amount of data from a variety of sources, including product reports, details of adverse events, anonymised patient data, and fundamental research results. The FDA's Sentinel Initiative holds data derived from the medical billing records of more than 170 million Americans.[125] These data are being used on a regular basis to understand drug safety issues, among other things. The integration and interpretation of such large volumes of data draw a much broader picture than any individual entity such as university or pharmaceutical company could provide, which is one of the foundations of translational medicine that can bring about discoveries, for example, of new biomarkers or therapeutic strategies for orphan diseases, or special groups of patients, e.g. immunocompromised patients diagnosed with cancer. In the United States, there are translational medicine centres which constitute the first institutionalised approach to translational research, namely the National Institutes of Health (NIH), the Harvard Clinical and Translational Science Center and the National Center for Advancing Translational Sciences (NCATS) established in 2011. A joint project of the NIH and the Defense Advanced Research Projects Agency (DARPA) envisages spending 140 million dollars to develop a chip with specific types of human cells representing human biology whose readings will indicate the suitability of the drug in humans.[126] NCATS initiatives also include the National COVID Cohort Collaborative (N3C), a platform that uses real-world data (RWD) to rapidly explore and test key research questions about the pandemic. Other projects include the Platform Vector Gene Therapy (PaVeGT) and the Bespoke Gene Therapy Consortium (BGTC), which work on developing gene therapies.[127]

On the global level, there are Translation Together, an institution established to facilitate cooperation between NCATS (USA), EATRIS

Institutions around the world take measures to support the transfer of technologies in medical practice.

[125] Califf RM., Ostroff S. FDA as a catalyst for translation. Sci. Transl. Med. 2015;7,296ed9-296ed9. doi:10.1126/scitranslmed.aab2404

[126] https://www.pharma-iq.com/pre-clinical-discovery-and-development/articles/translational-medicine-2020-what-does-the-future

[127] https://ncats.nih.gov/files/NCATS_Speeding-Treatments-Fact-Sheet_508.pdf

(Europe), LifeArc (UK), Admare (Canada), TIA (Australia), FIOCRUZ (Brazil), and AMED (Japan).[128]

Another initiative, Global Alliance for Genomics and Health (GA4GH), was established to develop standards and policies for sharing genomes and related health data on a global scale.[129] For example, Data Connect API is a biomedical data mining standard developed by GA4GH Discovery Work Stream.[130] Last but not least, one should mention the Global Genomic Medicine Collaborative (G2MC), an independent non-profit charity organisation dedicated to implementing genomic medicine in clinical care.[131]

There is a tendency to expand cooperation in the field of translational medicine, and growing numbers of stakeholders and initiatives in this area should be viewed as a global change in medicine which follows from understanding the importance of sharing data and resources. Considering the foregoing, an important objective of this strategy will be to strengthen international collaborations in the field of translational medicine and promote awareness of the availability of European research infrastructure among the Polish scientific community.

[128] https://translationtogether.org/
[129] https://www.ga4gh.org
[130] Ibidem
[131] https://g2mc.org/

6. Principal Obstacles to the Progress of Translational Research

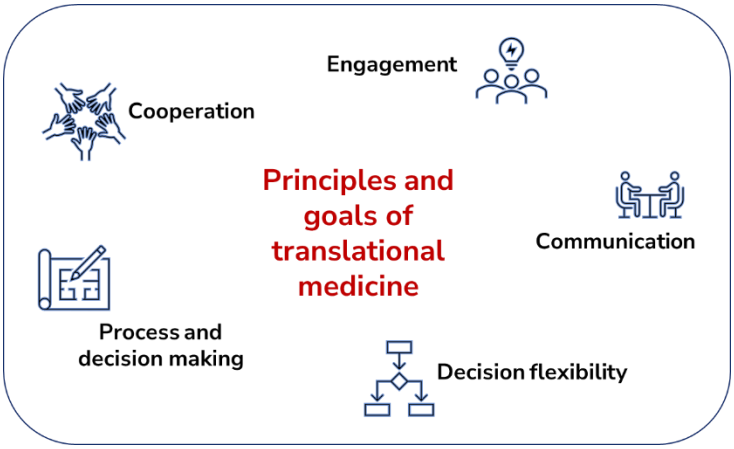
Translational medicine is a process of applying laboratory-based medical discoveries in clinical practice to improve patient outcomes. The main barriers to achieving this goal can be divided into the following categories:

- **Organisational:** Translational research often spans across many disciplines, including basic sciences, clinical research, and industry. Lack of cooperation between these disciplines can hinder the progress of discoveries.
- **Regulatory:** Having a new technology approved for human use can be a lengthy and complicated process involving many stages of research and approval, which can result in significant delays in making it available to patients.
- **Legal:** Scientists and companies may be reluctant to share information about their findings for fear of losing control of their intellectual property. This can create barriers to collaboration and slow down the progress of translational research.
- **Financial:** Translational research can be costly, and the funding limited, especially for projects that are unlikely to bring an immediate return on investment. This can make it difficult to carry out research necessary to transfer a discovery from bench to bedside and to bring together interdisciplinary teams (combining scientific and business competencies) capable of setting up companies to implement translation projects at the early stages of development (TLR1–4).
- **Ethical:** Translational research often involves testing new treatments or interventions in humans. Ensuring that this research is conducted in an ethical and responsible manner can be challenging, especially as regards sensitive populations.
- **Social:** Patient recruitment for clinical trials can be difficult, especially when it comes to rare diseases or conditions that affect specific populations. This can slow the progress of translational research and limit the number of patients who benefit from new medical technologies.

The discovery and development of a new medical technology is a complex process accompanied by uncertainty. Most will fail at the later stages of the process. Many of

the problems described in the previous chapters deepen the translation gap referred to as the "valley of death".

The process of new drug development is lengthy (more than 13 years from invention to approval), costly (about $2.6 billion) and risky (almost 95% of drugs tested in clinical trials ultimately fail). According to the NIH, 80–90% of research projects fail before they are even tested in humans, and for every drug approved by the FDA, more than 1,000 others are unsuccessful. Nearly 50% of all investigational drugs fail in phase 3 trials. Consequently, bringing new drug candidates from preclinical studies to human trials and registration only succeeds in 0.1% of cases. The main reasons why a drug candidate is dropped are lack of efficacy and insufficient safety that could not have been predicted at the earlier stages.[132]



According to a 2020 survey conducted in 68 doctors, nurses, social workers, physiotherapists and non-clinical researchers in Canada (University of Windsor, Windsor-Essex), the biggest barriers to conducting translational research were managing competing interests and lack of time, funding, infrastructure, networks, organisational support, and mentoring. Attention was also drawn to the lower research experience of clinicians compared to other specialists in publishing the results and applying for funding. The main barriers to interdisciplinary cooperation included: lack of time/schedule incompatibility, funding issues, difficulties in identifying interested collaborators, absence of common infrastructure, lack of organisational support, and overlapping interests of colleagues.[133]

A systematic review by Mayrink et al. (2022), which covered 33 publications (from the U.S., England, France, Canada, Ireland, Belgium, India and Japan), identified the following barriers

[132] Fernandez-Moure J. S. Lost in Translation: The Gap in Scientific Advancements and Clinical Application. Frontiers in bioengineering and biotechnology, 2016;4, 43. https://doi.org/10.3389/fbioe.2016.00043
[133] Senecal, J. B., Metcalfe, K., Wilson, K., Woldie, I., Porter, L. A. (2021). Barriers to translational research in Windsor Ontario: a survey of clinical care providers and health researchers. Journal of translational medicine, 19(1), 479. https://doi.org/10.1186/s12967-021-03097-6

faced by university laboratories when carrying out translational research in medical devices: deficient training of personnel (73%), lack of organisational support for the research team (64%), inadequate funding (60%), public policy and institutional model adapted to the linear process of innovation (57%), difficulties interacting with the industry and associations (54%), communication difficulties (48%), investigator training programmes (45%), high costs of the translational research process and patent maintenance (33%), long duration of the translation process (36%), lack of interest from the industry (15%) and lack of agility in university administrative processes (9%).[134]

An umbrella review by Aguilera-Cobos et al. (2022), which covered 71 publications, found that the most commonly reported barriers to the assessment and translation of results for advanced therapy medicinal products were associated with clinical efficacy, e.g. insufficient number of studies to draw conclusions (84.5%), low quality of trials, i.e. small cohorts, single-centre, single-arm, non-randomised trials (53.5%), and no follow-up to evaluate long-term outcomes (13%). Another commonly reported barrier was associated with the characteristics of the technology: lack of standardisation (51%), uncertainty about the mechanisms of action (32%), and lack of databases of clinical and preclinical studies (3%). Also pointed out were: safety concerns (25%), concerns about costs, budgetary impact and cost-effectiveness (20%), organisational aspects including uncertainty about translation T1 (from preclinical to human studies) and T2 (from clinical trials to clinical practice) (32%), concerns about logistics and manufacturing (4%), and profitability of business models (4%). Also voiced were concerns about patient perspective (8%) and regulation and legislation (8%).[135] Cousin et al. (2016) reported that the high failure rate in translating outcomes from the pre-clinical to the clinical phase was due to the lack of a commercial partner, insufficient financial resources, a research program not involved in translation, and lack of expertise in regulatory affairs.[136] Goldberg et al. (2017) noted the lack of links between pre-clinical and clinical research.

[134] op. cit. 100

[135] Aguilera-Cobos, L., Rosario-Lozano, M. P., Ponce-Polo, A., Blasco-Amaro, J. A., & Epstein, D. (2022). Barriers for the evaluation of advanced therapy medicines and their translation to clinical practice: Umbrella review. Health policy (Amsterdam, Netherlands), 126(12), 1248–1255. https://doi.org/10.1016/j.healthpol.2022.10.007

[136] Cousin M.A., Greenberg A.J., Koep T.H., Angius D., Yaszemski M.J., Spinner R.J., Windebank A.J. The value of systematic reviews in estimating the cost and barriers to translation in tissue engineering Tissue Eng Part B Rev, 2016;22 (6), 430-437, 10.1089/ten.TEB.2016.0060

Not one study group was found that would participate in both types of research.[137] In a systematic review by Smith and Johnson (2023), which covered 13 publications (from Australia, Saudi Arabia, China, Denmark and Canada), the most commonly reported barriers to the transfer of clinical trial results into clinical practice in public hospitals according to the nursing and similar staff were: lack of time, lack of ability (including poor self-confidence and skill in evaluating scientific evidence), clinical priorities limiting the time to study research papers or implement evidence-based practices, lack of education in evidence-based clinical practice and scientific strategies, research and translational knowledge. Also mentioned were no sense of empowerment (to upskill or teach clinicians of other disciplines about new guidelines or evidence-based practices and to change patient care practices), personal values (little benefit in evidence-based improvements of practice, no interest/willingness to drive change according to current recommendations), lack of trained leaders at intensive care units promoting the use of translational research in patient care, high staff turnover, and working in silos.[138]

[137] Goldberg A., Mitchell K., Soans J., Kim L., Zaidi R. The use of mesenchymal stem cells for cartilage repair and regeneration: a systematic review J OrthopSurg Res, 2017;12 (1), 39, 10.1186/s13018-017-0534-y

[138] Smith S, Johnson G (2023) A systematic review of the barriers, enablers and strategies to embedding translational research within the public hospital system focusing on nursing and allied health professions. PLoS ONE 18(2): e0281819

6.1 Organisational Factors

Organisational barriers constitute the most important and the largest group of factors hindering translational research in Poland.

Translational research is complex and requires a variety of skills. Although organisations invest in educational programmes, various types of facilities and advanced infrastructure, creating a sustainable, multidisciplinary team remains a challenge. Collaboration between specialists from various fields, e.g. researchers, statisticians, clinicians, provides opportunities to share knowledge and use it as effectively as possible in practice. Teamwork produces more and better ideas, and involving the team in the decision-making process optimises breakthroughs and reduces failure compared to individual work. Increasingly, research teams require not only technology development skills, but also competence in negotiation, organisation, project management and driving competitive advantage.[139]

Currently, in order to translate a discovery into an intervention that can be applied to a patient, and then in clinical practice, experts from more than 20 distinct fields of science need to be involved.[140] It is extremely important to enjoy assistance from experts in regulatory matters and commercialisation, as well as the support of financial, regulatory, and patient organisations, the industry and the press.[141] Collaboration between pharmaceutical companies and public organisations integrates resources and reduces duplication of efforts. The support of a commercial partner also increases the chances of success in translational research, especially the transition from the pre-clinical to the clinical phase.[142] On the other hand, involving patients and communities helps adapt new technologies to real-life needs. This is why the U.S. National Center for Advancing Translational Sciences (NCATS) engages patients in every project that it runs or supports. What is more, every NCATS project involves collaboration with at least one partner from the public, private and non-profit sectors, making it possible to develop more effective and productive solutions.[143]

[139] op. cit. 132
[140] Austin CP., Opportunities and challenges in translational science, Clin Transl Sci. 2021;14:1629–1647
[141] op. cit. 135
[142] Ibidem
[143] op. cit. 140

In their systematic review, Mayrink et al. (2022) list the following as the factors most commonly contributing to faster development of technology, lower risks and reduced uncertainty in healthcare innovation: interdisciplinary, transdisciplinary, collaborative and networked work, including with the industry; technical and regulatory expertise of team members; effective communication; valuing the perspective of the patient and the user of the technology; and clinical immersion to identify and assess unmet needs and clinical problems.[144]

In Poland, the challenge lies in recruiting qualified personnel, especially capable of developing an innovation pathway in the field of translational medicine, including managerial medicine. There are no effective mechanisms for building large interdisciplinary teams led by a scientist-inventor that would feature both scientific and business competencies capable of setting up companies to carry out translation projects. A significant proportion of currently available forms of financing translational research do not allow for the creation of interdisciplinary teams of sufficient size, which makes it necessary for the inventor-scientist to also act as an entrepreneur (no funding available to create positions for team members with expertise in technology transfer). Few people in the scientific community are willing to take the time to develop additional business/translational skills at the expense of improving their scientific technique, especially in view of the existing challenges and intense competition in science. The existing system of evaluation of scientists and scientific units does not enable or encourage a departure from the standard career path in favour of translational research, which would require, among other things, transforming the publication strategy. Reducing their publication activity is not beneficial for scientists, on the one hand due to the evaluation requirements and the need to maintain publication activity in the short term (4 years), and on the other due to the necessity to publish in prestigious international journals in order to gain recognition and credibility with potential

In Poland, there is a shortage of highly qualified personnel capable of driving the development of translational medicine with innovation and implementation.

[144] op. cit. 100

commercial partners. As a result, many studies with high implementation potential do not even enter the translation path.

Conversely, the necessity to acquire a business partner for grants for products or services that are at the early stages of development (TRL 2–4) reduces the chance of acquiring funding due to the high risk associated with such projects and the reluctance of potential business partners to bear that risk. This advocates for a paradigm shift to enable the formation of multidisciplinary project teams led by scientist-inventors with competent support in translation matters.

Another issue is limited opportunity for obtaining grants for early-stage projects (TRL 2–4) that would take into account the high costs of biological research and its long-term, unique nature. The unavailability of grants ensuring formal and organisational flexibility makes it difficult to undertake high-risk translational medicine research.

Another important barrier is that there is little cooperation between scientists and clinicians. One of the main reasons for this is the low priority given to this type of study by clinicians due to unattractive financial remuneration associated with R&D projects compared to commercial clinical trials. The situation is not helped by the horizontal structure of biomedical organisations, which are arranged according to areas of expertise into so-called “silos” centred around a discovery, often accidental. This can cause communication problems, especially when information has to be exchanged between the silos. Early discoveries are not being developed towards product utility, possibly due to duplication of effort across disciplines. The National Cancer Institute's Early Detection Research Network (NCI EDRN) promotes a vertical approach. It consists in the development, enhancement, and analytical and clinical validation of biomarkers within one organisation, in which several experts coordinate a number of disciplines, using shared resources and information flows.

Translational medicine has to take into account the uncertainty and risk associated with drug development due to complex logistics, requiring continuous and repeated decision-making by a wide range of specialists in various fields. Decisions on whether to continue research are commonly intuitive rather than based on a structured approach. Risk analysis is very important in project management. So is compliance and making decisions on the basis of exhaustive information, without personal bias. Selecting projects with a high translation

potential or adapting innovation to institutional and local priorities have been named among the factors accelerating the development of technology and reducing the risk and uncertainty in healthcare innovation.[145]

The cooperation process is not facilitated if research centres limit third-party access to their results.[146] Even though special biobanks are created all over the world to which access is made available to researchers working on new projects (e.g. the MINDACT study),[147] Poland falls behind in this respect. Admittedly, however, in recent years a network of biobanks has been established within the European Biobanking and BioMolecular Resources Research Infrastructure (BBMRI-ERI), and Biobank Łódź is one of the cooperating facilities that makes their collections of biological material available to other research units.

Transparency of research is of paramount importance. It is a problem when study data, the protocol or other activities are not available for verification or further use by other scientists. Several changes should be made to research practices that would allow for greater transparency, such as making available the detailed methodologies, the protocol, results (also raw data), software and code that enable re-analysis or replication of results. Currently, most study results cannot be replicated, and many do not have immediate utility when repeated (although they may lead to new discoveries and future benefits). Non-replicability of results may be caused by poor study design, inadequate analysis or questionable research practices. Ideally, the results of biomedical research should be clinically useful regardless of the final outcome. Negative outcomes can also have value, but are often neglected or unpublished. This is a known error in science called publication bias, which is defined as a propensity to only publish positive study results. Transparency aimed at improving the quality of research, avoiding duplication of effort, and sustainable development is considered one of the factors associated with faster development of technology and reduced risk and uncertainty in healthcare innovation.[148]

Barriers hindering translational research result not only from scientific, design and financial reasons, but also from knowledge gaps and inadequate remuneration and recognition

[145] op. cit. 100
[146] https://poradnik-naukowy.gumed.edu.pl/42023.html
[147] Ibidem
[148] op. cit. 100

of researchers. Translational research should be part of scientific education and development, and researchers should be trained to consider the practical applications of their results and seek collaborations with stakeholders. Shifting the educational paradigm towards meeting future needs of the healthcare system has been discussed as another factor accelerating the development of technology and reducing the risk and uncertainty in healthcare innovation.[149]

In order to integrate knowledge from various areas, it is necessary to create multidisciplinary study programmes that will be carried out simultaneously in a number of institutions. From the very first stages of the process of translating new technology into clinical practice, it is important to ensure cross-industry cooperation and a wide perspective incorporating many points of view, including that of the scientist/discoverer/researcher, clinician, market (manufacturer), and regulator. Each of these perspectives should have a say in the final study design and further development path of a given technology. For this to happen, communication between these groups must be efficient, and the language used by each of them must be understandable to the others rather than constitute an obstacle already at the beginning of the translation process. Better preparation and an extensive interdisciplinary knowledge of researchers potentially increase the chance of success.

Cultural factors are also not without significance, and among them high competitiveness in the research community (e.g. striving for priority in publication or patenting), prioritising novelties and publishing them in prestigious journals. Ranking researchers depending on the number of grants won and publications written, while it is a fairly objective indicator of success, raises some controversy. For clinicians, on the other hand, success is measured by the number of patients treated, which dampens their ambition to do research and seek the necessary funding. This state of affairs increases the communication distance between professionals in fundamental and applied sciences. There are no mechanisms to support the scientific process. No incentives or rewards are offered to the authors of meaningful research.[150]

[149] Ibidem
[150] op. cit. 132

Nor are structural and educational initiatives sufficient to support the expansion of IT infrastructure and the necessary research facilities for biological material repositories, computational biology, and biostatistics. Preclinical research needs to be supported with appropriate IT solutions and tools.[151] Solutions based on artificial intelligence can support the discovery process and development of medical technologies. Some companies use them, for example, to search for new targeted drugs, new mechanisms of action or innovative first-in-class medicinal products. However, this technology is limited by the quality of available data. Errors in data lead to incorrect results.

In translation, data interoperability and integration are extremely important, and so is the availability of national and international platforms. The challenges associated with data platforms, especially for sites that do not have extensive resources to collect and manage data, may include integration of technical data (e.g. due to their different formats and structures), quality of data (collected from different institutions), data sharing (e.g. due to constantly evolving data sharing agreements), liability (e.g. for data security breaches, also by foreign partners), privacy (resulting from the complexity of national and international regulations), discovery (resulting from intellectual property agreements), and sustainable financing (e.g. differences in profits and returns between government and industry actors).[152]

The available data (pertaining to all aspects of disease and treatment) are limited, as are the time and resources, which are always the limiting factors for extensive research. In Poland, there are 3 researchers per million population, which ranks our country as 18th among the European Union Member States. In 2019, only 9 Polish research institutions initiated projects as part of international biomedical research (the corresponding figure for Germany was 200, for France — 127).[153]

Another important issue is accelerating the process of adaptation of new medical technologies. It has been estimated that an average of 17 years elapses between the moment an intervention is proven effective and the time it is provided to all patients who may benefit

[151] Governmental Plan for the Development of the Biomedical Sector for the years 2022–2031, Annex to Resolution No. 141/2022 of the Council of Ministers dated 21 June 2022.
[152] Quintana Y., Challenges to Implementation of Global Translational Collaboration Platforms, MOJ Proteom Bioinform. 2015 ; 2(6): 65
[153] op. cit. 151

from it.[154] Therefore, systemic solutions are needed that would make it easier for new technologies to reach the patient.

There is also a need for new methods that use data from patient registries and historical group studies based on the natural course of the disease, e.g. in rare diseases, to identify common features of diseases and speed up the process of finding new indications for a medicine. The increasing number and variety of therapeutic agents and diseases to be tested, as well as the need for cheaper and more convenient solutions, call for additional study designs that would deliver reliable results from fewer patients or allow for multiple interventions or indications to be tested at the same time. It is necessary to develop and implement more projects based on adaptive, pragmatic, basket and umbrella research.[155]

Translational medicine centres recently established in Poland, e.g. at medical universities, will make it possible to shorten the time from discovery to medical practice and overcome mental and organisational barriers. They will enable the optimal use of the research potential (e.g. integration of dispersed teams and research groups) and infrastructure (e.g. available equipment and apparatus), as well as increase the competitiveness of the parent institution, improve cooperation with other scientific facilities and help acquire funds for research and implementation projects from various sources, both domestic and foreign.[156]

A systematic review by Smith and Johnson (2023) identified ways to facilitate translational research focused on nursing and allied staff in public hospitals. Leadership (including the roles of leaders and mentors), education, and access to educational resources and educators were identified as the three most important factors that help transfer results from research into clinical practice. Also mentioned were motivation, time, multidisciplinary cooperation, research-oriented work culture and evidence-based practice. Other factors included: financial incentives to conduct research, training in the implementation of clinical guidelines, access to patients after the end of the study to see how it has affected patient care, and student internships as a source of new evidence-based knowledge as part of university curricula. The authors concluded that the three overarching themes in translational research were: leadership (from mentors, experts and leaders in a given field

[154] op. cit. 140
[155] Ibidem
[156] https://gdansk.naszemiasto.pl/gumed-otworzyl-centrum-medycyny-translacyjnej-zdjecia/ar/c1-5115793

of research), capabilities (knowledge and skills, the value in conducting, understanding and interpreting research) and organisational culture (time, support from management, work culture and teamwork).[157]

6.2 Financial Factors

On average, pharmaceutical companies spend over 14% of their profits on research and development. It takes approximately 12 years and more than €1 billion to bring a new drug to the market.[158] As the development progresses, studies become relatively less risky but exponentially more expensive, especially in the later phases of in-human testing. It is estimated that clinical trials consume 60–80% of the costs of introducing a new drug to the market.[159]

Current funding mechanisms for biomedical research often only support small, short-term studies, since they take less time to complete and publish the results. Although the results of such studies usually require validation in larger cohorts of patients with longer follow-up, it is rarely undertaken due to unavailability of funding.[160] One of the reasons for the high rate of translation failure between the preclinical and clinical phase is lack of sufficient sources of financing.[161]

Risk aversion is prevalent in both the public and private sectors, and investigators, funding agencies and businesses prefer to work with small subsets of diseases and targets rather than bear the risks associated with new targets and treatment areas.

Different studies require different levels of investment, and their potential return can vary. Clinical trials are very costly. In most cases, the benefits of biomedical research offset the costs incurred. This suggests that streamlining research by adopting a patient-oriented approach (rather than focusing on the needs of investigators, clinicians or sponsors) may help ensure better execution, eliminating trials that lack the power to prove a hypothesis,

[157] op. cit. 138
[158] Wpływ na gospodarkę i potencjał rozwoju branży innowacyjnych firm farmaceutycznych w Polsce [Impact on the economy and development potential of the industry of innovative pharmaceutical companies in Poland], INFARMA, Warsaw, June 2017, version 1.0
[159] Ibidem
[160] op. cit. 140
[161] op. cit. 135

are inaccurate, or have inadequate follow-up periods or endpoints.[162] The development of technologies, knowledge and paradigms that reduce the risks arising from the exploration of new targets and diseases will encourage funding institutions to finance them.

Financial barriers arise mainly from limited access to funds for research and development (e.g. if they do not fit the industry in terms of risk profile and length of investment cycles), mismatch between financing and the nature of the activity (e.g. inability for start-ups or large enterprises to obtain funds) and high operating and development costs (e.g. lack of subsidies for the installation of renewable energy sources at the national level). Funding is the greatest development need for 65% of start-ups in the healthcare sector.[163]

In 2017, despite the enormous potential of the biotechnology sector supported by numerous scientific and research institutions, spending on biotechnology-related R&D was far behind the leading European markets. The 2022 European Industrial Research and Development Scoreboard (IRI) did not list any Polish company from the biotechnology and pharmacy sector. The available sector-specific reports indicate that Poland lacks funds for the early stages of innovation, while companies and private investors are unwilling to take risks.[164]

The systematic review paper by Mayrink et al. (2022) listed regular availability of funds to support the research team as one of the factors accelerating the development of technology and reducing the risk and uncertainty in healthcare innovation.[165] In particular, significant factors inhibiting the development of translational medicine in Poland include the very limited opportunities for financing proof-of-concept translational research and the lack of dedicated mechanisms to fund early stage medical technologies before a business is established or a commercial partner acquired. Such studies are key to lowering the risk of product development. In R&D, building interdisciplinary teams with high competence cannot be achieved with uncompetitive remuneration, no other incentives to conduct translational research, and high costs of obtaining and maintaining patent protection during the long process of medicinal product development and commercialisation.

[162] op. cit. 132
[163] op. cit. 151
[164] Ibidem
[165] op. cit. 100

6.3 Legal Factors

A major problem is the lack of a comprehensive and coherent legal regulation on translational medicine. The legal provisions in this area are dispersed. There are no clear regulations to take full advantage of the potential of the clinical research market, which in turn has an impact on the implementation of innovations.

In addition, Poland does not implement EU solutions that would be beneficial for the patients and for the system, e.g. procedures for individual post-trial use of a medicinal product (compassionate use).

There is no systemic legal solution in Poland that would make it possible to fully tap into the potential of translational medicine. This can be considered to inhibit the development of this field to some extent: an uncertain, unclear legal environment may discourage researchers, hinder the operations of research or clinical centres, and constitute an obstacle preventing potential sponsors from undertaking complex, multi-stage activities.

Legal regulations on personal data can be perceived as a kind of limitation to the full development of translational medicine, since they restrict the exchange of information between different entities and may prevent data use after the completion of the research.

In the context of personal data processing in clinical trials, the following legal documents are important: Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ L 119, 4.5.2016 [GDPR] and Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014 [Regulation 536/2014]. Since both these acts apply simultaneously, in order to provide guidelines for a consistent approach to data protection in clinical trials in the EU, the European Data Protection Board (EDPB) issued Opinion No. 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR).

According to the EDPB, all processing operations related to a specific clinical trial protocol during its whole lifecycle should be understood as primary use of clinical trial data [Recitals 156 and 161 of the GDPR].

In its Opinion, the EDPB makes a clear distinction between two main categories of processing activities — in particular, processing operations related solely to research activities must be distinguished from processing operations for the purpose of healthcare. Depending on the category, the following legal bases for the processing of personal data may apply:

- Article 6(1)(c) of the GDPR in conjunction with Article 9(2)(i) or (j) of the GDPR — processing activities related to reliability and security that result directly from the legal obligations of the controller — "*processing is necessary for compliance with a legal obligation to which the controller is subject*", and in the case of special categories of data — when it is necessary for reasons of public interest in the area of public health, if processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes, and as regards processing activities other than those mentioned above (processing operations related only to research activities), there are three alternative grounds for processing personal data (all circumstances of the investigation and the specific processing activity should be considered before choosing a specific basis):
- Article 6(1)(e) in conjunction with Article 9(2)(i) or (j) of the GDPR — a task carried out in the public interest,
- Article 6(1)(f) in conjunction with Article 9(2)(j) of the GDPR — a task carried out in the legitimate interest of the controller,
- Article 6(1)(a) and Article 9(2)(a) of the GDPR — in specific circumstances, if all the conditions are met, the data subject's express consent.

The processing of personal data on the basis of informed consent requires meeting special requirements.

Considering the conditions for obtaining informed consent within the meaning of the GDPR and the possible consequences of relying on consent as the basis for the processing of personal data (e.g. in case of consent withdrawal), it should be concluded that the application of this legal basis may adversely affect the way applicable rules of personal

data processing are understood by data subjects, and ultimately have a negative impact on the security of the research and the integrity of the results obtained. It is recommended to rely on legal bases other than consent.

If consent has been obtained from a patient/subject for the processing of his/her personal data for a specific, predefined purpose (a specific study, experiment), the data must only be processed for that purpose covered by the original consent. In practice, this may turn out to be a barrier that slows down data exchange between centres or even between centres and patients. The use of patient data for purposes other than those indicated in the original consent is theoretically possible, provided, however, that certain conditions are met,[166] which may not be feasible in practice. In order to change the purpose of data processing, the controller must notify the data subject of the intention to do so and obtain a new consent for the processing of personal data for a new purpose other than the original purpose.[167] In practice, doing so may prove impracticable. Sometimes it will be impossible to reach a specific patient or even identify him/her, and even if not impossible, it will be extremely time-consuming, which — considering the amount of data processed in translational medicine — may paralyse the entire research effort.

For the above reasons, it is desirable to rely on grounds other than consent when processing personal data, as well as to take the opportunity to have the subjects of clinical trial/medical experiment sign a broad consent pursuant to Article 28(2) of Regulation 536/2014 (outside the protocol of a clinical trial/medical experiment, as part of scientific research projects):

"*Without prejudice to Directive 95/46/EC* [now GDPR], *the sponsor may ask the subject or, where the subject is not able to give informed consent, his or her legally designated representative at the time when the subject or the legally designated representative gives his or her informed consent to participate in the clinical trial to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject or his or her legally designated representative.*

[166] Article 5(1)(b) of the GDPR: "*(...) further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes shall, in accordance with Article 89(1), not be considered to be incompatible with the initial purposes*." It is therefore permissible to further process personal data for the purposes indicated in this provision. However, this does not exempt the data controller from its information obligations.

[167] Article 13(3) of the GDPR.

The scientific research making use of the data outside the protocol of the clinical trial shall be conducted in accordance with the applicable law on data protection."

It is therefore about having the patient or subject in a clinical trial/medical experiment (or his/her statutory representative) give consent to the use of his/her data for broadly defined future scientific research, but without naming any specific projects where the data would be used or any specific entity that will carry out the research, or the title and duration of the trial.

The possibility of using broad consent is also provided for in Recital 33 of the GDPR, which reads: *"It is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognised ethical standards for scientific research. Data subjects should have the opportunity to give their consent only to certain areas of research or parts of research projects to the extent allowed by the intended purpose."*

A broad consent can be the basis to obtain data from clinical trials, medical experiments and medical records (the option of sharing medical records on the basis of a patient consent results directly from Article 26(1) et seq. of the Patient Rights Act). It is reasonable to assume that it may constitute a legal basis for the collection and processing of personal data of subjects in clinical trials/medical experiments outside the protocol, as part of scientific and research projects, both by the entity that conducted the original study/experiment and obtained the broad consent, and by other entities who receive the data on the basis of the broad consent. This type of consent should be subject to the same requirements as informed consent to participate in a clinical trial/medical experiment.

The Act of 9 March 2023 on Clinical Trials of Medicinal Products for Human Use introduced (in Article 8) the option of limiting the application of certain provisions of GDPR, if it is likely that these provisions will prevent or seriously impede the achievement of the objectives of the clinical trial that is a scientific research project, and if such limitation is necessary to meet these objectives. This will undoubtedly, to some extent, simplify the conduct of clinical trials and help avoid certain risks, for example those resulting from patient consent withdrawals or deletion of their data. The option applies to the following rights: right to information

and access to personal data (Article 15), right to rectification (Article 16), right to restriction of data processing (Article 18), and right to object (Article 21). As mentioned above, the limitation of the personal data protection rights may only be used if the rights set out in these laws make it impossible or extremely difficult to achieve the objectives of the clinical trial that is a scientific research project and if such exemptions are necessary to achieve these purposes.

Another challenge for translational medicine is the lack of legal solutions regulating the use of big data. It is necessary to establish a framework for the management and mining of such data at the organisational level, as well as to provide for audit trails and data security.

Funding is a considerable barrier to the development of translational medicine. Among other things, a desirable move would be to create more public funding opportunities and define the rules of co-financing. At the same time, it should be noted that the Polish tax law provides for a tax relief for enterprises that undertake research and development activities. Importantly, the tax relief is available to both Polish companies and foreign enterprises that invest in Poland and take the risks associated with innovative research, also in the field of translational medicine. This instrument is extremely attractive, but still rarely used in practice. Perhaps it would be advisable to promote the awareness of this R&D tax relief among entrepreneurs by means of information campaigns and training.

Important issues for translational medicine include intellectual property rights to research results and commercialisation of these results. Regulations in this area are scattered and mostly focus on non-commercial research; for example, the Act on Clinical Trials of Medicinal Products for Human Use addresses the topic in Articles 5–7. On the other hand, according to the Pharmaceutical Law Act of 6 September 2001 and the Regulation of the Minister of Health of 2 May 2012 on Good Clinical Practice, the ownership of both commercial and non-commercial clinical trial results belongs to the sponsor, who may transfer the ownership or assign rights to dispose of all or some of the study data to another entity by way of a written agreement. Restrictions on the use and disposition apply to data obtained in non-commercial clinical trials, i.e. when the sponsor and owner of the study data is a university or other scientific institution, investigator, or investigator organisation. In principle, such research and its results serve exploratory, scientific and non-commercial

purposes and can be disseminated, e.g. in scientific publications. They cannot, however, be used for marketing purposes or for the purpose of amending an existing medicinal product marketing authorisation. Problems may arise where study results are derived from joint research activities. These problems may include issues such as priority of publication, joint commercialisation, or further research use. This makes it necessary to undertake specific legal measures, which in practice may slow down the progress of research work. In addition, disputes are certainly not beneficial to translational medicine and should be avoided.

The principles of management and commercialisation of academic research carried out at universities are set out in the Act of 20 July 2018 — Law on Higher Education and Science, and in the Act of 30 April 2010 on Research Institutes (which applies to research institutes supervised by the Minister of Health). However, these regulations do not apply if the results originate from scientific activities carried out by entities that are not subject to the above-mentioned acts, or if they were funded from external sources. In such cases, commercialisation is usually negotiated between the interested parties. It is conceivable that standardising these issues as part of translational medicine procedures/processes would simplify the formalities and make it possible to focus on scientific problems.

As already mentioned, the legal regulations on issues important from the point of view of translational medicine are dispersed. It would be advisable to create a systemic, structured solution, and build an organisational structure with clear legal principles.

6.4 SWOT Analysis

Table 2 illustrates the strengths, weaknesses, opportunities, and threats of translational research.

Strengths	• Better understanding of the mechanisms of diseases. • Searching for ways to apply new knowledge in preclinical and clinical research. • Producing meaningful and useful results. • Development of new diagnostic and therapeutic methods. • Potential to introduce new technologies into clinical guidelines and clinical practice. • Assessment of the outcomes and clinical efficacy of technologies in the population (e.g., in cost-benefit analyses, observational studies, and evaluation programmes). • Patient access to state-of-the-art medical technologies. • Interdisciplinary collaboration between professionals and stakeholders. • Faster and more effective discovery and development of new medical technologies owing to the use of modern solutions.
Weaknesses	• Highly uncertain success of translational research (especially in terms of translating preclinical results into clinical ones). • High costs and long waiting times for final results. • Methodological irregularities in designing and conducting translational research. • Lack of transparency in conducting translational research. • Reluctance to share research results with others. • Unfavourable organisational structure. • Non-agile project management and organisation. • High competition in the research community. • No mentoring, no leadership. • Difficulties in communication and interdisciplinary cooperation, e.g. due to insufficient time and commitment. • Not enough financial and human resources and no optimisation of available resources and infrastructure. • Available financing mechanisms not adapted to the actual needs of inventors, producers and recipients. • Absence of an educational and training system that would support the actual needs of the healthcare system, including the patients.

	• Insufficient knowledge (e.g. in the field of legal regulations and commercialisation of results) and lack of continued participation of the research team in the entire translation process.
Opportunities	• More effective and safer patient diagnostics and treatment. • Access to state-of-the-art medical technologies. • Improved public health (in terms of life expectancy and quality of life). • Clinical optimisation of medical technologies in clinical guidelines and practice. • Cost-effective optimisation of technologies in the healthcare system. • Reduction of indirect costs of disease (e.g. due to improved productivity as a result of effective treatment). • Opportunity to share information and cooperate with experts from various fields. • Development of modern methods and technologies to accelerate and optimise the translation process. • Improved transparency in conducting translational research. • Development of national and international biological material repositories and data sharing platforms. • Creating a research-oriented work culture. • Promoting high-quality research with a significant impact on the healthcare system. • Organisational and systemic support in conducting translational research. • Development of innovative training and education programmes. • Adaptation of existing and new translational research co-funding programmes to the actual needs of the market. • Development of national and international centres for translational medicine (including basic and pre-clinical research). • Development of international cooperation.
Threats	• Limited funds to continue translational research. • Limited human and material resources necessary for the development of translational research. • High costs and risk of failure. • Inadequate management, insufficient financial resources and uncompetitive salaries to keep trained employees. • Difficulties in conducting research due to economic crises or pandemics.

7. Strategic and Specific Objectives of the Translational Medicine Development Plan

As part of the Translational Medicine Strategy for the years 2024–2036, the MRA creates organisational and financial conditions for the implementation of a modern and targeted translational research programme, in accordance with the following objectives:

1. **Strategic Objective: Development of the high-quality nationwide translational research**

The Medical Research Agency undertakes to fund applied, preclinical and early phase clinical trials (including experiments) presented in a forward-looking manner, namely incorporating a plan for the development of a medical technology, a diagnostic test, or a new panel of prognostic markers to the extent corresponding to the level of technological readiness of the innovation declared in the project, i.e. projects meeting the criteria of translational research according to the adopted definition.

1.1 Specific Objective: Financing and support for the research and development projects (TransMED SEED)

1.2 Specific Objective: Stimulation of the new medical technologies development, with particular emphasis on non-drug technologies, through periodic verification of progress in the following areas: clinical, technological, business, and regulatory

2. **Strategic Objective: Support for the transfer of the intellectual property and new medical technologies from Polish research centres to the economy**

In focusing on the translation of fundamental research into clinical practice, the MRA will pursue the following specific objectives:

2.1 Specific Objective**:** Co-funding and support for the implementation projects (TransMED SPIN)

2.2 Specific Objective**:** Stimulation of registration and implementation of medical technologies through the periodic verification of progress in the following areas: clinical, technological, business, and regulatory

3. **Strategic Objective: Fostering the collaboration and education in translational medicine**

The objective assumes building broadly defined mechanisms for the development of translational medicine through the following:

3.1 Specific Objective**:** Creation of an interdisciplinary TransMED Platform for communication and training purposes

3.2 Specific Objective**:** Implementation of the acceleration programmes for the potential applicants of the TransMED SEED and TransMED SPIN calls

3.3 Specific Objective: Supporting the wide-ranging national and international collaboration to disseminate the results of translational research and good practices, and to promote a culture of openness, sharing, and transparency

8. Implementation and Monitoring of The Plan

The Translational Medicine Development Plan for the Years 2024–2036 aims above all to incorporate into a the health care system a pathway for the efficient implementation of innovative diagnostic and therapeutic discoveries.

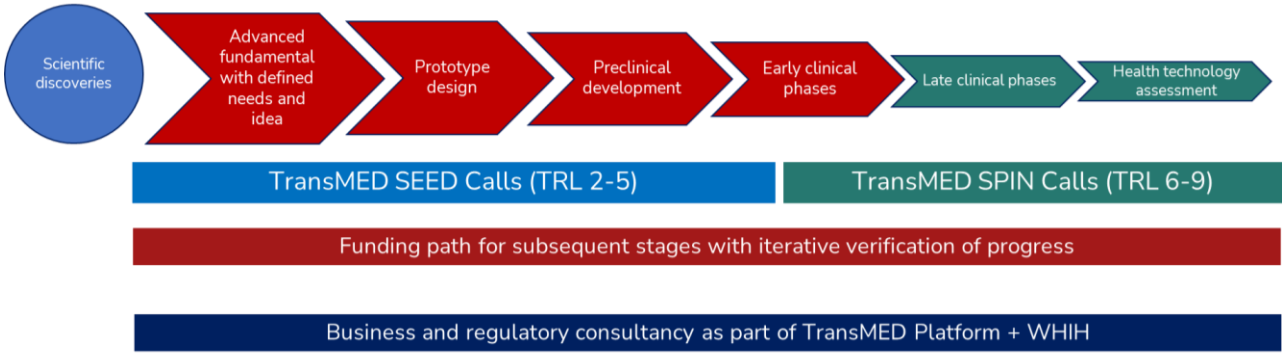


Figure 1 Illustrative diagram of the implementation of the Plan from the perspective of the life cycle of a translation project

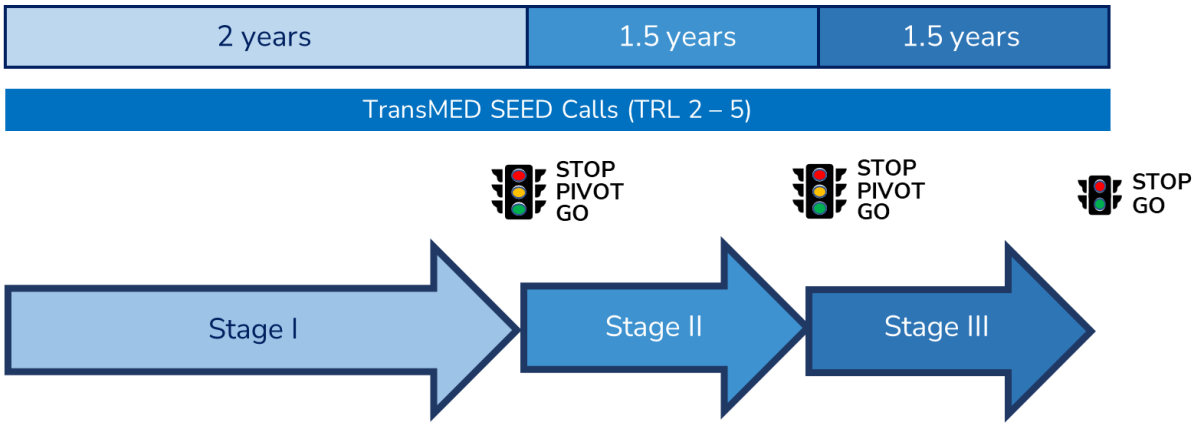
8.1 Activities Defining Strategic Objective No. 1

In order to address the unmet medical needs and solve the greatest challenges currently faced by healthcare, the MRA will support projects with particular emphasis on neoplastic, neurodegenerative, cardiovascular, and metabolic diseases, as well as rare diseases of other types.

This objective will be achieved by announcing calls for proposals for research and development projects (**TransMED SEED**). This phase will involve the funding of applied, preclinical and early phase clinical trials (**TRL2 to TRL5; applied — preclinical — clinical trials up to phase 2a**). Trials conducted as part of the TransMED SEED calls will be non-commercial.

In the calls for proposals, the MRA will impose requirements regarding risk analysis at the prototyping stage; ideas and innovative medical technologies at early stages of development will need to be prototyped and tested in frequent iterations in order to verify their functionality and quality in meeting clinical needs. The system will require collaboration with clinical practitioners already at an early stage of research.

Projects in the area of non-drug medical technologies will be able to apply for 10-year funding. During this period, projects under TransMED SEED are envisaged to be funded for a maximum of 5 years. **The projects will be subject to periodic viability verification at intervals of 2 and 1.5 years.** Project activities will be subject to revision versus the development plan adopted/created for a given technology, and as a result decisions will be made on further implementation and financing. In view of the longer time perspectives and higher budgets necessary for the effective implementation of medicinal products from the early stages of technological readiness compared to other medical technologies, **project proposals concerning drug technologies will be subject to more restrictive requirements as part of the TransMED SEED calls**. Beneficiaries of the TransMED SEED calls who successfully pass all stages of project implementation will be invited to participate in the TransMED SPIN calls, as an opportunity to ensure continued funding for the implementation and commercialisation of their technologies.



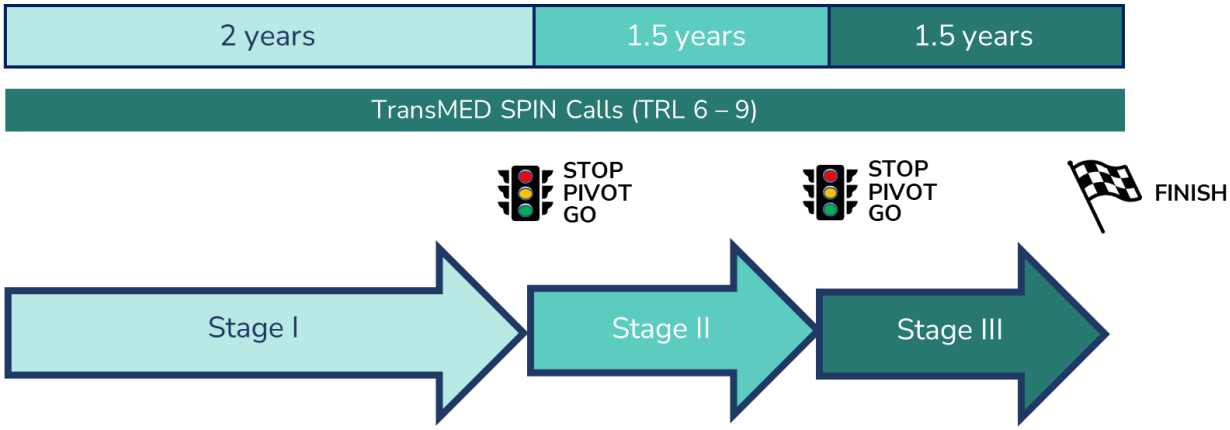
An important aspect of project implementation as part of TransMED SEED will be the use of existing national and international data platforms, including those developed by the Digital Medicine Centres Network, which will help overcome the problem of potential data shortage. Adding new functionalities to the platforms will make it possible to model and simulate physiological and disease processes, and assess the impact of investigational substances and interventions on the human body. An equally important factor, aside from using common data platforms, will be tapping into the dispersed infrastructural potential by creating multicentre collaborative systems to build common technical facilities (in the sense of performing specific research at existing, well-equipped sites), as well as provide and maintain high-quality infrastructure enabling the conduct of multicentre trials taking into account the division of competence and technical possibilities. Research carried out in an extensive collaborative setting will have a better chance of developing the technologies of interest. The MRA intends to further develop the infrastructural and research potential in the field of medical data analysis and collection, with particular emphasis on multiomic data, as part of a dedicated Digital Medicine Development Plan.

8.2 Activities Defining Strategic Objective No. 2

In keeping with the idea of 10-year funding granted by the MRA for the development of translational medicine products, Beneficiaries of the SEED calls and other entities with comparable organisational and technological readiness will be able to apply for co-financing of further stages of development as part of **TransMED SPIN** implementation calls. Theimplementation phase will include funding of high-tech innovations (**TRL6 to TRL9; phase 2b to 4 clinical trials**). Beneficiaries of commercial TransMED SPIN calls will be obliged

to implement their medical technology, and the clinical trials performed to this end will be commercial trials.

Improvement of the implementation pathway will depend on the development of guidelines/good practices for cooperation of scientific, clinical, and business communities, valuation of intellectual property, and transfer of knowledge obtained at subsequent stages into clinical practice. Developing effective models of collaboration with private sector partners as part of the Plan in order to advance translational technologies may potentially bring significant benefits to patients in terms of faster diagnostics, more accurate and less invasive therapies, and greater personalisation of treatment. TransMED SPIN projects will be funded for a maximum of 5 years. **The projects will be subject to periodic verification at intervals of 2 and 1.5 years.** At each predefined interval, project activities will be subject to verification to possibly enhance the development plan adopted for a given technology, and as a result decisions will be made on further financing.



The creation of intellectual property valuation guidelines/good practices as part of TransMED SPIN projects, as well as facilitating and accelerating the transfer of knowledge to the economy/clinical practice will open an effective implementation pathway for future translational medicine products.

8.3 Activities Defining Strategic Objective No. 3

The deliverables of the Translational Medicine Development Plan will contribute to a significant increase in international initiatives, and consequently improve the prestige of national centres for translational medicine, both in terms of fundamental research and R&D.

In order to comprehensively support cooperation and education in the field of translational medicine, the MRA will establish and coordinate the **TransMED Communication and Education Platform**. The Platform will feature a network of human and technological resources created by institutions open to collaboration in multidisciplinary projects. It will also serve as a source of information on translational medicine and related topics in connection with the activities undertaken internationally and domestically.

The platform will be a **communication space** available to a large group of stakeholders, including:

- representatives of Polish and foreign scientific units engaged in translational research,
- experts in translational medicine, business development, regulatory matters, and intellectual property law,
- representatives of investment funds, business angels, private investors,
- young scientists and clinicians with translational aspirations,
- representatives of patient organisations,
- representatives of companies and start-ups willing to develop in the area of translational research.

In addition, winners of the calls announced under the TransMED Strategy will form a special group on the platform, bringing together people with unique knowledge and experience. This will help improve subsequent editions of MRA's calls for proposals and provide opportunities to share experience between stakeholders, consolidating the domestic translational medicine community and providing space for effective translation of technical and clinical knowledge into real solutions and implementations.

The platform will also be a space for **organising and financing education in the field of translational medicine** — trainings, workshops, educational programmes

(e.g. foreign postgraduate courses, internships, study trips) — for the Beneficiaries of translational medicine calls.

Communication and educational initiatives of the platform will be either **virtual** (website, online meetings/workshops/symposia) or **face-to-face** (on-site meetings/workshops/symposia).

In order to increase the chance of success of projects at the early stages of technological readiness and reduce the concerns about cooperation with consulting firms, the TransMED Platform will also be used by the MRA to carry out preparatory programmes (referred to as Accelerators) for potential applicants of the SEED calls. The main objective of the programme will be to teach potential applicants to develop suitable project design for the SEED calls, in particular in terms of business and legal aspects related to product registration or clinical trials (depending on the level of knowledge of the potential applicant). The Platform will also offer mentoring cycles before the SPIN calls commence. Mentoring will be organised jointly with individuals/entities involved in the Warsaw Health Innovation Hub. The aim of these meetings will be to share experiences on the commercialisation and implementation of medical technologies.

8.4 Monitoring of the Plan

Plan implementation monitoring relies on indicators focused on strategic objectives and project implementation. Monitoring will be carried out on the basis of qualitative and quantitative indicators (basic and prospective) listed in Tables 3, 4, and 5.

Table 3. Quantitative indicators – basic

No.	Indicator	Strategic objective	Outcome measure
1	Number of translational research hypotheses generated and evaluated	1	min. 30
2	Number of validated medical technologies (technologies that successfully passed early phase clinical trials)	1	min. 10
3	Number of translational research publications measured by the success rate, i.e. number of citations in clinical journals	1	min. 30
4	Number of innovative medical technology projects implemented	1; 2	min. 60
5	Number of multidisciplinary consortia established for the benefit of translational research	1; 2	min. 30
6	Number of clinical trials or medical experiments based on or validating translational research	1; 2	min. 30
7	Number of subjects enrolled in clinical trials or medical experiments based on or validating translational research	1; 2	min. 5 000
8	Number of patents and patent applications	1; 2	min. 30
9	Number of treatment protocols, guidelines or recommendations developed in clinical practice as a result of TransMED projects	1; 2	min 10
10	Total number of spin-offs/start-ups established as a result of TransMED projects	2	min 20
11	Number of participants of acceleration and mentoring programmes on the TransMED Platform	3	min 200
12	Number of events (domestic and international) organised as part of the educational activities of the TransMED Platform	3	min 24

Table 4. Quantitative indicators — prospective, evaluated until 2042[168]

No.	Indicator
1	Number of registered medical technologies covered by public funding
2	Total improvement of the quality of life of Polish citizens benefiting from the solutions developed under the TransMED Programme
3	Total value of IPRs transferred at a charge to third parties by the Beneficiaries of the TransMED Plan
4	Total number of licences/patents transferred at a charge to third parties by the Beneficiaries of the TransMED Plan
5	Number of new jobs created by the Beneficiaries as a result of TransMED projects
6	Total years of operation of spin-offs/start-ups established as a result of TransMED projects
7	Total valuation of companies established as a result of translational medicine projects
8	Total state budget revenues from the enterprises that are Beneficiaries of the TransMED Plan
9	Average market share, in Poland and globally, of medical technologies created as a result of TransMED projects

[168] Duda, G. N., et al. Measuring translational research impact requires reaching beyond current metrics Science Translational Medicine; 2023;2;15(707) https://doi.org/10.1126/scitranslmed.abp8258

Table 5. Qualitative indicators

No.	Indicator	Category	Description
1	Development of and collaboration between translational medicine groups in a given research area	1; 2; 3	As part of this criterion, verification will be performed of the collaboration between Polish and foreign translational medicine institutions that results in the development of new tools to be used in joint analyses.
2	Successful application activities in the field of translational medicine	1	The success of application activities will be measured by the Ts score,[169] which is the quotient of the number of citations resulting from SEED calls in clinical journals and the total of all citations.
3	Development of a commercialisation strategy in the context of the resultant economic benefits	2	As part of the development of the commercialisation strategy, the following will be verified: - activities related to the valuation of intellectual property, - assessment of technological readiness, - market analysis, - compliance assessment, - analysis of the scope of industrial property protection, - sales plan or licensing scenario analysis and business plan including funding, outcome forecasts and necessary investments.
4	Development of good practices for effective certification pathways taking into account the necessary guidance from regulatory authorities	2	The strategy will involve verification of the development and implementation of a well-defined certification pathway and approvals from regulatory authorities with respect to clinical trials and marketing of medicinal products based on the technologies developed (e.g. approvals from the Chief Pharmaceutical Inspectorate and permissions to use GMMs);

In addition, during project implementation, relevant indicators will be continuously monitored, such as:

- Number of TransMED SEED projects being implemented,
- Number of TransMED SPIN projects being implemented,
- Number of investigated subject areas.

[169] Kim, Y. H., Levine, A. D., Nehl, E. J., & Walsh, J. P. A Bibliometric Measure of Translational Science. Scientometrics, 2020;125(3), 2349–2382. https://doi.org/10.1007/s11192-020-03668-2

8.5 Financial Projection of the Plan

Strategic objective	Estimated allocation value (PLN)
1. Development of the high-quality nationwide translational research	900,000,000.00
2. Support for the transfer of the intellectual property and new medical technologies from Polish research centres to the economy	1,350,000,000.00
3. Fostering the collaboration and education in translational medicine	36,000,000.00
TOTAL ALLOCATION OF THE PLAN	**2,286,000,000.00**

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