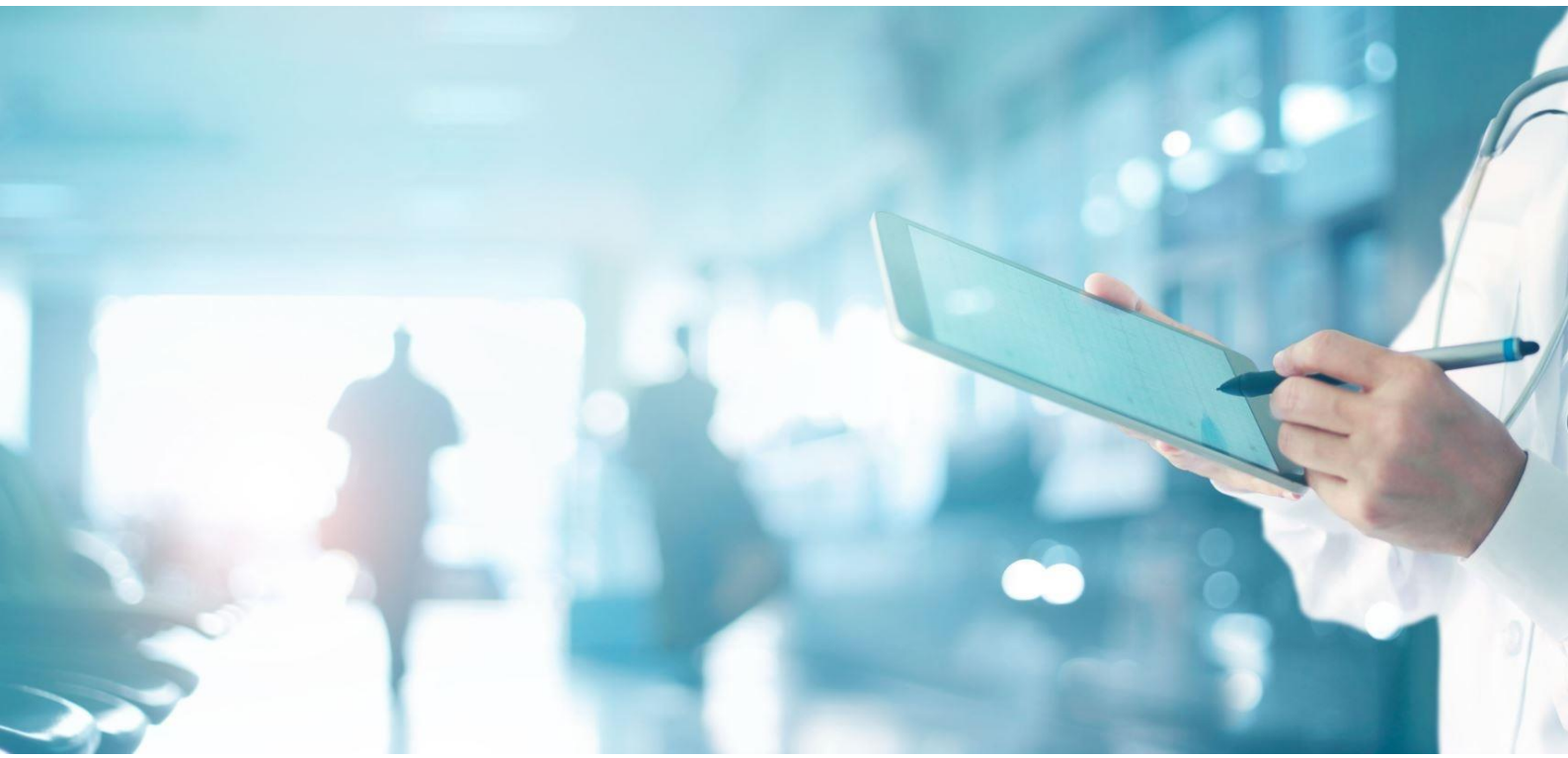
MEDICAL RESEARCH AGENCY

ANALYSIS OF THE NEEDS, TRENDS, AND OPPORTUNITIES IN BIOMEDICAL RESEARCH

Exploratory Report

Preparatory analysis for the development of MRA's Annual Agendas



Warsaw, November 2023
Science Division, Medical Research Agency
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Definitions and acronyms

MRA – Medical Research Agency

AI – artificial intelligence

AMD – age-related macular degeneration

OSC – Outpatient Specialist Care

AOTMiT – Agency for Health Technology Assessment and Tariff System

API – active pharmaceutical ingredient

ASCO – American Society of Clinical Oncology

ATMP – advanced therapy medicinal product

BMI – body mass index

CARG – compound annual growth rate, which defines the rate of return on investment over the period of that investment; used to compare investment strategies

CAR-T – chimeric antigenic receptor of T cells

CAWI – Computer Assisted Web Interview, an Internet surveying technique

CeZ – (Pol. *Centrum e-Zdrowia*) Polish e-health centre

DCT – decentralised clinical trial

DALY – disability-adjusted life year

EMA – European Medicine Agency

EPO – European Patent Office

FDA – U.S. Food and Drug Administration

GBD – Global Burden of Disease, a study by the Institute for Health Metrics and Evaluation, which analyses the level of disease burden in many countries around the world

GUS – (Pol. *Główny Urząd Statystyczny*) Statistics Poland, Polish central statistical office

GWAS – genome-wide association studies, cohort-based analyses using next-generation whole genome sequencing data and non-genetic data to find correlations between selected genetic variants and phenotypes

HIS – hospital information system

HIV – Human Immunodeficiency Virus

IAPB – International Agency for the Prevention of Blindness

ICD – International Classification of Diseases

IHME – Institute for Health Metrics and Evaluation, a US research institute which authors the Global Burden of Disease report/study

IKP – (Pol. *Internetowe Konto Pacjenta*) Internet Patient Account, an information platform of Centrum e-Zdrowia

KRN – (Pol. Krajowy Rejestr Nowotworów) National Cancer Registry, a registry of diagnosed cases of malignant neoplasms along with diagnostic descriptions, assessments of changes in time and space, analyses of experiences and prognoses, which supports the delivery of public services and public statistics, as well as epidemiological analysis

MoH – Ministry of Health

NCT – non-commercial clinical trials

NFZ – (Pol. *Narodowy Fundusz Zdrowia*) National Health Fund

NGS – next-generation sequencing, types of next-generation DNA or RNA sequencing used e.g. in oncological diagnostics to obtain and analyse whole-exome **(WES)** and whole-genome **(WGS)** sequences. NGS techniques are used e.g. for comparative analysis of healthy and cancerous tissues to predict potential disease progression, screen for rare diseases, and perform GWAS population analyses.

NMDA – N-methyl-D-aspartic acid, a methylated derivative of aspartic acid which affects neuronal activity

P1 – e-health system, the platform which underlies the digital ecosystem of e-health services

COPD – chronic obstructive pulmonary disease

PHC – primary healthcare

PZH – (Pol. *Narodowy Instytut Zdrowia Publicznego PZH – Państwowy Instytut Badawczy*) National Institute of Public Health – National Institute of Hygiene

REIDs – emerging and re-emerging infectious diseases, diseases that appear in a given population

RNA – ribonucleic acid

RWD – real-world data, health and/or healthcare data derived e.g. from patient registries that give insights on the effectiveness of a technology in actual clinical practice

RWE – real-world evidence, clinical evidence on the use and potential benefits or risks of a medical product, derived from real-world data (RWD).

WES – whole-exome sequencing, one of the types of NGS used to analyse the sequence of the coding regions of the genome (exome)

WGS – whole-genome sequencing, one of the types of NGS used to analyse both coding and non-coding sequences, i.e. the whole genome

WHO – World Health Organisation

ZUS – (Pol. *Zakład Ubezpieczeń Społecznych*) Social Insurance Institution

1. Introduction

1.1 Purpose of the report

The purpose of this report is to explore the current **opportunities and trends in the clinical trials market** from the perspective of the **needs of Polish patients** and the **healthcare system**, in order to define the **key areas** recommended to be included in Medical Research Agency Agenda for the coming years.

This analysis and its conclusions are meant to clarify the directions and areas of interest defined so far in the Strategic Documents of the MRA and provide a **substantive justification for the choice of the key areas and preferred items**.

The trends discussed in this report focus on several major **research and development priorities** and overlapping themes:

> **Translational medicine** – the development of innovative biomarkers and diagnostic tools as the basis for the implementation of targeted and personalised therapies;
> **Digital medicine** – based, among other things, on multi-omic diagnostics with particular emphasis on next-generation sequencing (NGS), telemedicine, digital therapies, RWE/RWD analyses, big data and AI algorithms;
> **Drug security** – having active substances, generics, biosimilars, and advanced therapies manufactured in Poland to build the resilience of the healthcare system to supranational crises and the demands of an ageing society;
> **Novel study designs** – e.g. decentralised, basket, umbrella, platform or N-of-1 research.

The report also maps the needs in the following **therapeutic areas**:

- **Cardiology** – characterised by low public awareness of the associated risks,
- **Oncology** – especially lung cancers,
- **Neurology, psychiatry and psychology** – with particular emphasis on neurodegenerative diseases,
- **Autoimmune diseases,**
- **Infectious diseases,**
- **Rare and ultra-rare diseases.**

The Agency's response to the emerging trends and needs is presented as **key non-commercial, commercial and strategic areas** outlined in Chapter 8 along with a detailed rationale, which synthesise the conclusions of this report and provide the basis for an extensive expert debate on the shape of the Agency's Agenda for the coming years.

1.2 The analytics team of the MRA's Science Department

This report was developed between March and September 2023 by the Division of Science Project Team composed of:

- Tymoteusz Iwańczuk – chapter 2
- Aleksandra Jakubiak – chapters 3 and 5
- Justyna Misiak – chapters 4 and 7
- Marzena Kucharczyk – chapter 6
- Wojciech Bodzan – barometer survey analyses, figures and infographics
- Katarzyna Kaczmarska, PhD – team organisation, scientific editing of the Report
- Marceli Ragan – project supervision, scientific editing of the Report

1.3 Methodology

The analysis was based on publicly available sources such as reports, summaries, statistics, and scientific publications originating from public institution websites, public databases and data published by commercial enterprises.

The analysis was supplemented with MRA's **own survey data**: between April and May 2023, the Project Team conducted a survey titled '**Clinical Trials Barometer**', which collected responses from representatives of patient associations, experts (including principal investigators carrying out clinical trial projects, national consultants and MRA expert reviewers) and representatives of businesses engaged in the manufacture of drugs, active substances and medical devices.

The survey was carried out using CAWI. Invitations to participate in the project were sent to a total of 1,065 representatives of patient associations, experts and companies operating in the medical sector. The Ministry of Health provided assistance in reaching the experts, while associations of drug and medical device manufacturers supported the distribution of questionnaires among businesses. Eventually, 210 questionnaires were collected and subjected to detailed analysis.

The following chapters provide a summary of the results obtained from open-source data and the survey, which were used to define the recommended key areas and preferred items for the Agency's Agendas for the coming years.

1.4. Existing strategic documents of the MRA

So far, the MRA has developed strategic documents that informed the implementation of calls for proposals for co-financing commercial and non-commercial projects to create an ecosystem of clinical research and biomedical sciences. A chronological list of the programmes along with their subsequent updates is presented below:

1. **Clinical Research Development Plan for the years 2020–2025 (2019, updated in 2022)**
2. **Governmental Plan for the Development of the Biomedical Sector for the years 2022–2031 (2022)**
3. **Epidemiological Research Development Plan for the years 2023–2033 (2022)**

The above documents delineate the framework for the operations of the Agency, whose main task is to develop and improve the quality of clinical trials and research experiments in Poland.

These documents define the directions, topics, objectives, activities, and funding sources and rates for the calls for proposals organised by the Agency.

This report provides a more detailed analysis of the measures outlined by the strategic documents, identifies the areas that are of paramount importance for improving the health of the nation and the quality of the Polish healthcare system, as well as defines and prioritises the objectives of the Agency.

In recent months, two new strategic documents of the Agency have been finalised:

4. **Medical Research Agency's Educational Strategy for the years 2023-2027 (04/2023)**

The document, developed in 2023, defines the objectives and thematic frameworks of education as a new responsibility for the Agency. It is a guide for developing the competence of research teams responsible for clinical trials in Poland, educating students in the field of biomedical research, instructing biomedical market innovators on how to commercialise research and implement it in clinical practice, as well as promoting the vital role of the patient in biomedical research with particular emphasis on clinical trials.

5. **Translational Medicine Development Plan for the Years 2024-2036 (09/2023)**

The document complements the above list and defines the areas of interest for the Agency to promote biomedical innovation in Poland, from fundamental application research, through preclinical and clinical research, to registration and implementation in clinical practice. The strategy focuses on supporting research and development (TransMED SEED calls), implementation (TransMED SPIN calls), and an education and training platform which provides learning opportunities and facilitates communication and collaboration within the Polish biomedical research and implementation community.

2. Needs of Polish patients – perspectives and perceptions of health risks

In order to support the development of the biomedical research sector, it is necessary to ensure access to reliable information on the health of the population, which would help allocate the limited resources as best as possible to the most essential needs. The tools necessary to identify the most pressing health problems in the population include demographic forecasts and epidemiological analysis, which are paired in this chapter with the opinions of experts and patient associations.

2.1 Demographic changes in the Polish population – ageing as a catalyst for an epidemic of chronic diseases and multimorbidity

In 2021, the average life expectancy for men stood at nearly 72 years, and for women – at 80 years. Life expectancy has been systematically rising from the early 90s to 2014. In the years 2014-2019, this increase halted in men, and between 2016 and 2019, there was even a downward trend in women. In the years 2020-2021, as a result of the **COVID-19** pandemic, an unprecedented reduction could be observed in the average lifespan of the Polish population. Compared to the 2019 value, life expectancy in 2021 was **2.3 years shorter** for men and **2.1 years shorter** for women. A study by the Ministry of Health titled Polityka Lekowa Państwa 2018-2022 [State Drug Policy 2018-2022] emphasised the following two key issues:

- an observable significant drop in the population of Poland,
- progressive ageing of the Polish society.

As a result, the MoH forecasts that in 2035, one in four, and in **2050, one in three Poles will be at least 65 years of age**.[1]

*One of the consequences of the changes in the demographic structure will be a significant increase in the incidence rates of **chronic diseases** in the 65+ age group.*

One of the consequences of the changes in the demographic structure will be a significant increase in the incidence and prevalence rates of **chronic diseases** in the 65+ age group — mainly **cardiovascular diseases** and **neoplasms**, as well as **diabetes mellitus**, **respiratory diseases**, and conditions of the central nervous system (**neurodegenerative and psychiatric disorders**). The growing incidence of chronic diseases will translate into increasing rates of **multimorbidity**.[2]

According to a study commissioned by the Polish Association of Pharmaceutical Industry Employers, the population aged 65+ is responsible for 40% of the total demand for prescription drugs in the European Union. Taking into account the above forecasts, it is to be expected that there will be a **growing demand for healthcare services**, including new effective and safe drug therapies.[3]

2.2 Epidemiological trends and perceptions of health threats in the Polish population – the dominance of cardiovascular, cancer, psychiatric and lifestyle diseases

The next step in identifying the most important health problems of the population is analysing selected **epidemiological parameters** and **input from the medical community**. The fundamental parameter that makes it possible to rank diseases according to burden is the share of deaths broken down by causes. According to GUS[4], in 2021, the main causes of death in Poland as a percentage of all deaths are:

1. cardiovascular diseases – 34.79%,
2. cancers – 19.61%,
3. COVID-19 – 17.35%,
4. other, not specified – 7.07%,
5. respiratory diseases – 5.42%,
6. external causes of illness and death – 4.17%,
7. gastrointestinal diseases – 3.98%,
8. endocrine, nutritional and metabolic disorders – 2.24%,
9. nervous system diseases – 1.66%
10. genitourinary diseases – 1.18%

It must be pointed out that the **COVID-19** pandemic has greatly affected the epidemiological situation in Poland, and the SARS-CoV-2 virus became **the fourth and third most common cause of death in 2020 and 2021, respectively**.
A more detailed analysis of cardiovascular diseases reveals that three indications had the greatest impact on the number of deaths in 2019:

1. ischaemic heart disease (97.2 thousand),
2. stroke (45.1 thousand) and
3. cardiomyopathies and myocarditis (11 thousand).

These health problems were responsible for 38% of deaths in 2019.[5]
After cardiovascular diseases, the second greatest cause of mortality is cancer. Reducing the incidence rate and premature mortality rate associated with cancer is one of the key health priorities postulated by the MoH.

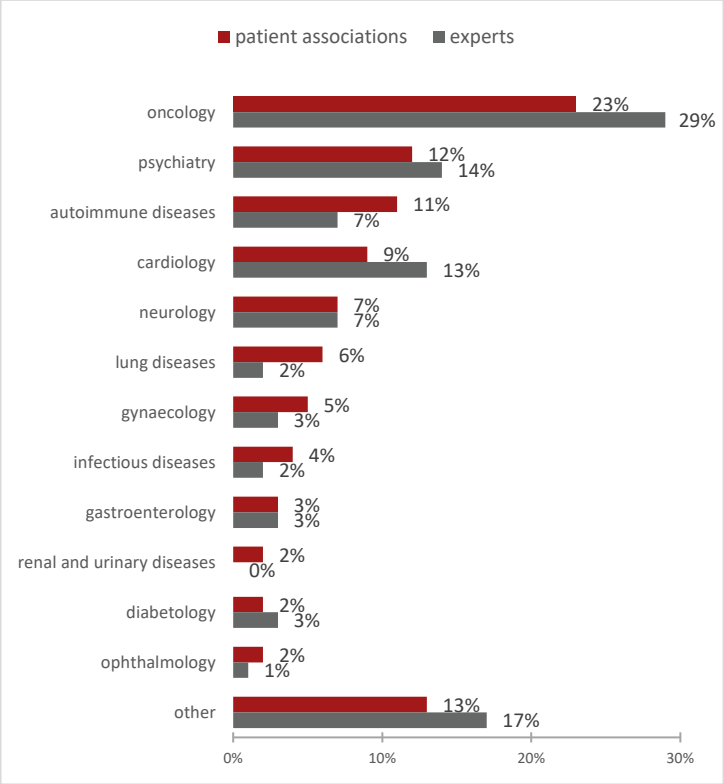

Figure 1 Medical fields that merit particular attention from the MRA to ensure the advancement of the healthcare system – survey responses of patient association representatives (N = 94 responses) and experts (N = 181 responses, methodology: CAWI). ***Oncology, psychiatry and autoimmune diseases*** *collectively account for nearly half the responses of both patient associations and experts, which illustrates the key importance of these areas from both perspectives. Experts, however, unlike patients, see a greater risk in* ***cancers*** *and* ***cardiac*** *diseases, while patient associations place greater emphasis on* ***autoimmune diseases, lung diseases, gynaecological disorders*** *and* ***infectious diseases****.*

The Ministry's priorities in this regard are fully aligned with the views expressed by patient associations and experts in the survey carried out by the MRA (Fig. 1).

There is a clear difference in how risks and needs are perceived by patient associations and experts – especially with regard to cardiology, psychiatry, lung diseases and autoimmune diseases. Nevertheless, despite these differences, oncology was almost twice as likely as its closest follower psychiatry to be indicated as a key area of medicine requiring financial support by representatives of patient associations and experts alike.

What is surprising, however, is the **relatively low perception of risk associated with cardiovascular diseases**, especially given their aforementioned top position in Poland in terms of mortality and morbidity, as well as the low score assigned to infectious diseases, which suggests a post-pandemic nature of risk perception.

In order to provide a detailed assessment of the risks of oncological diseases, an analysis was performed of the **morbidity and mortality structure** by type of cancer. According to the report based on data from the National Cancer Registry, the incidence rates of cancers vary by sex, and the most prevalent are cancers of the breast, prostate, lung, colon, and endometrium (Fig. 2).[6] Particularly striking is the **high mortality rate for lung cancers** compared to the incidence rate, which may result both from the ineffectiveness of the existing therapies and too late diagnosis. However, regardless of gender differences, there is a clear **fragmentation of morbidity and mortality rates for conditions classified as 'other',** which together account for nearly half of all events.

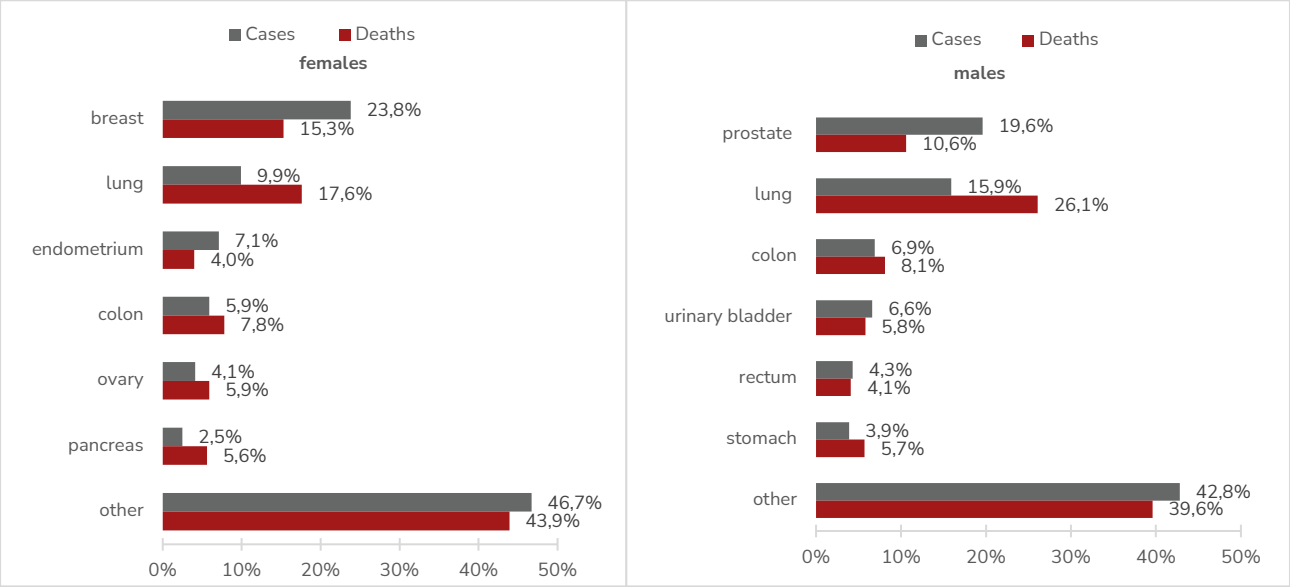

Figure 2 Morbidity and mortality structure of cancers by sex and organ; based on the data of the National Cancer Registry for 2020. In addition to the significant health burden resulting from breast and prostate cancers, a highly unfavourable morbidity to mortality balance in both sexes is observed e.g. for lung and colon cancers.

2.4 Analysis of the impact of diseases, injuries and risk factors on the Polish population – the importance of behavioural and metabolic factors as well as the risks associated with cancers, cardiac diseases and traumas

The most important epidemiological threats and needs of the Polish population can also be inferred from the *Global Burden of Disease* (GBD) report developed by the *Institute for Health Metrics and Evaluation* (IHME). The GBD study aimed to determine the magnitude of health loss due to diseases, injuries and risk factors. The study design involved the use of DALY (disability-adjusted life years) as the main measure of disease burden. DALY is the sum of two sub-indicators — years of life lost due to premature death (YLL) and years lived with disability (YLD). A DALY of one is therefore interpreted as one year of life in full health lost.[7] Based on the value of DALY, it was observed that in 2019, cardiovascular diseases, cancers, injuries and diseases of the musculoskeletal system were the most common causes of healthy life years lost in Poland[8] (Fig. 3).

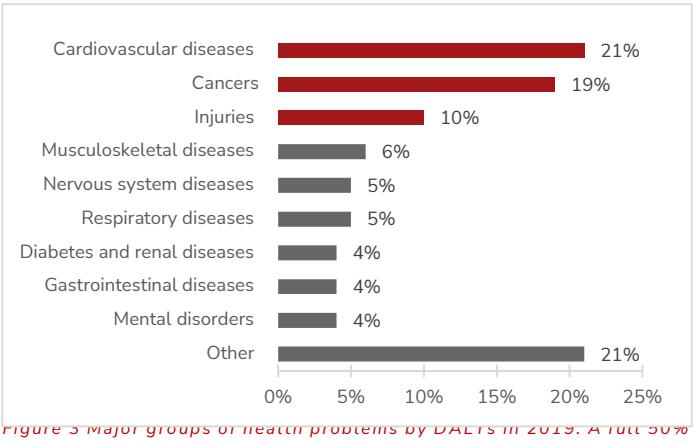

Figure 3 Major groups of health problems by DALYs in 2019. A full 50% of healthy life years lost are due to cardiovascular diseases, cancers and injuries put together.

Another parameter based on the GBD methodology that can accurately illustrate the health status of the population is the assessment of risk factors. Understanding the key risk factors makes it possible to adequately eliminate and reduce exposure to these factors through health policies, which in the long term may translate into lower incidence rates and, consequently,

prolonged life expectancy and quality of life. The impact of risk factors in Poland was expressed in DALYs and deaths (Fig. 4). The share of the main groups of risk factors in Poland in terms of **DALYs** and **deaths** is as follows:[9]

- behavioural risk factors – **48.5%** and **44.36%** (e.g. smoking, nutritional risks, alcohol consumption, malnutrition in pregnancy, low physical activity, risky sexual behaviours)
- Environmental and occupational risk factors – **14.16%** and **13.99%**, respectively (e.g. air pollution, occupational risks, unfavourable ambient temperature, other environmental risks)
- metabolic risk factors – **37.34%** and **41.65%** (e.g. high blood pressure, high BMI, high fasting plasma glucose, high cholesterol levels, impaired renal function).

These risk factors are aetiologically linked to the main health problems – cardiovascular diseases and cancers – which may illustrate the complex nature of the behavioural and metabolic causality of these diseases in the Polish population. In order, however, to confirm these relations of causality, it is necessary to conduct well-designed epidemiological studies, and in order to reduce these risks – to seek advanced diagnostic and preventive solutions and apply educational measures.

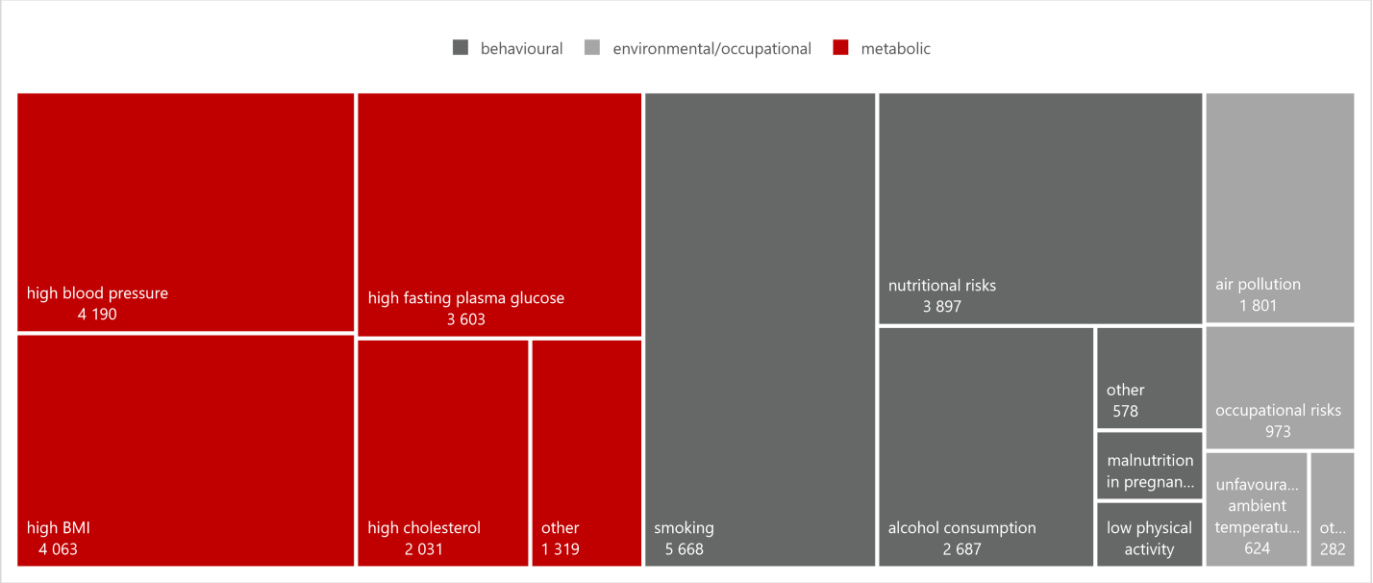

Figure 4 The share of risk factors in Poland in 2019 (DALY per 100,000 population). Behavioural factors (e.g. smoking, alcohol, diet) have the greatest impact on DALYs.

2.3 Summary and implementation takeaways

The analysis of Poland's epidemiological and demographic situation as well as the predominant perceptions of health risks shows that **cardiovascular diseases** and **cancers** are consistently the greatest challenges for the healthcare system; these two areas account for a total of **54% of all deaths and 40% of healthy life years lost (DALYs)**. A closer look into the area of oncology reveals, on the one hand, a **high granularity of risks** posed by the many types of oncological diseases (nearly 50% of all events were accounted for by relatively low proportional shares in the morbidity and mortality structure), and on the other hand, **a high risk associated with cancers of the lung, breast, prostate, endometrium and colon**. **Lung cancers are particularly important** given the much higher mortality-to-incidence ratio than is the case for other cancers.

Among cardiovascular diseases, the major risk contributors are **ischaemic heart disease, stroke, cardiomyopathies, and myocarditis**.

Demographic changes also suggest a growing need for medication and, consequently, for **active substances**.

The public **perception** of the risks in the field of oncology corresponds to the scale of the problem, while the **awareness of cardiological risks seems insufficient and requires educational support**.

A post-pandemic effect can be observed of a lowered perception of risks in the area of infectious diseases. The interest of both patients and experts in supporting **psychiatry, neurology** and **autoimmune diseases** is significantly higher compared to the respective positions of these areas among the direct causes of death and morbidity or DALYs.

The above conclusions can be used to inform decisions on the future implementation of measures in the following key areas:

1. **Development of non-commercial clinical trials on cancers,** incentivising the study of selected types of cancer, especially lung cancer, and focusing on **modern clinical trial protocols** — umbrella, basket, platform, and combination trials — given the multitude of different malignancies and the threat from several poor-prognosis cancers.
2. **Development of non-commercial clinical trials and research experiments,** incentivising research into **cardiovascular, autoimmune, psychiatric, and neurological** disorders, as well as **infectious** diseases. In addition, considering the low awareness of cardiovascular risks amongst the public and experts — which the Agency is also observing when recruiting for ongoing clinical trials in the field of cardiology — it will be necessary to develop educational strategies and build understanding in this area.
3. **Development of epidemiological research** aimed at studying the relationship between **behavioural and metabolic risk factors** and their impact on **cardiovascular and oncological risks**, especially on lung, breast and prostate cancers, as well as ischaemic heart disease, stroke, cardiomyopathy, and myocarditis.
4. **Supporting education** focused on the prevention of cardiovascular diseases, strategies to reduce the impact of the risk factors, and building awareness of the associated risks and preventive measures.
5. **Supporting the production of active substances**, as with the ageing society, the healthcare system will become increasingly dependent on stable access to medications, active substances and pharmaceutical raw materials. It will be necessary to build the domestic production capacity of selected APIs essential for the needs of people aged 65 and over.
6. **Preventive measures in case of potential future pandemics** — the experience of COVID-19, with the abrupt increase in mortality, and the subsequent rapid loss of awareness of the risks associated with infectious diseases among experts and patients are reasons to argue for early development of skeletal clinical trial protocols – Master Clinical Trials (MCTs) – to prepare for potential epidemics/pandemics of emerging and re-emerging infectious diseases (REIDs).

3. Directions of development of the Polish healthcare system

3.1 Map of needs — a clear and correct diagnostic and therapeutic path in response to the identified health problems and access to services barriers

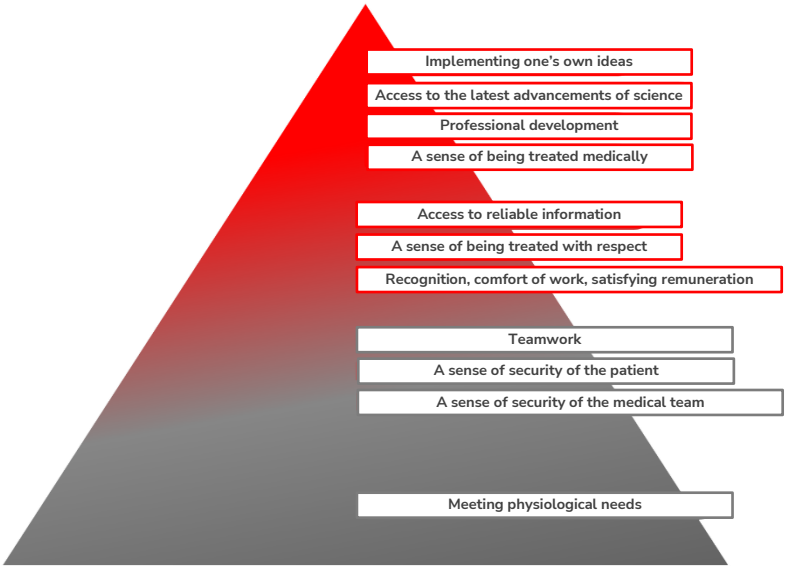

Figure 5. The pyramid of needs of the medical sector stakeholders — clinicians and patients — along the diagnostic and therapeutic path. [7-]

The Needs Pyramid (Fig. 5), while it was not designed specifically with the needs of patients and the healthcare system in mind, is often used to better understand different aspects of patient care and can guide the development of medical sectors.[10,11,12,13]

Experts and biomedical researchers, while focusing on high-tech solutions, should not disregard the more fundamental levels of the needs pyramid. According to our current state of knowledge, it is clear that the major barriers to the full use of the healthcare system apply at the level of basic needs.[7-10] Still, most of the unmet needs revolve around patient and doctor security during the diagnostic and therapeutic process: receiving a correct, confirmed diagnosis; efficient communication between the patient and medical staff (i.e. effective sharing of comprehensible, accurate, complete information); or using the right therapy and safe therapeutic solutions. The currently popular patient-centric approach in healthcare can also be considered in the context of **narrative medicine**, where emphasis is increasingly placed not just on the patient's perspective, but on the role of **communication and understanding between doctor and patient**, especially as the system is shifting from a model based on treating disease towards **prevention** and **personalised care**.[14,15]

In the current healthcare system, the costs of diagnostics are contained within the costs of comprehensive therapeutic procedures. This is why HCPs rarely use advanced, but more expensive diagnostic methods, ensuring instead that more funds are allocated to the treatment. Doctors are still bound by fixed budgets (capitation rate of PLN 191.88 per year). This is one of the reasons why 85% of laboratory diagnostics are performed in hospitals, at a point where the disease is already at an advanced stage. Only 3% of tests are ordered by primary care doctors, while approximately 10% of orders come from outpatient specialist care (OSC).[16]

Meanwhile, the results of the MRA's survey paint a very different picture of the most desirable healthcare system according to patients. Inpatient treatment was considered the optimal solution by **only 9% of respondents, while the preference was for outpatient and home treatment** (Fig. 6). These needs are very well recognised by the market — representatives of businesses engaged in the

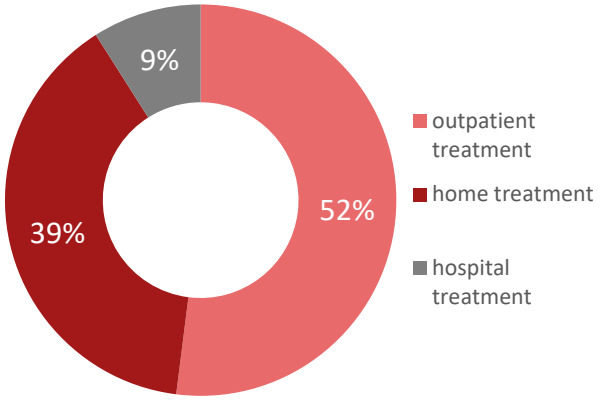

Figure 6. Healthcare system preferred by patients. Based on responses from representatives of patient associations. Methodology: CAWI, N = 82 responses. Patients favour outpatient and home treatment. The vast majority of patients would rather avoid hospital treatment.

manufacture of drugs, active substances and medical devices also acknowledged that the most desirable healthcare system would be based on **home treatment (45% of respondents)**, followed by **outpatient treatment (42% of respondents)** (Methodology: CAWI, N = 31 responses).

Access to more expensive diagnostic procedures and examinations is restricted, which is a strategic error, as the total cost of treating an advanced stage of disease is much higher from an economic and social perspective than investing in extended diagnostics and optimal treatment at an earlier stage. Therefore, it appears necessary to introduce a universal screening test panel for primary care visits, especially to test for cardiovascular, oncological and metabolic diseases. One option is procalcitonin, whose levels increase in the early stages of bacterial, inflammatory or neoplastic diseases well before the onset of clinical symptoms.[17,18]

In addition, it is necessary to **develop clear diagnostic pathways** leading to a correct diagnosis as soon as the patient presents to the doctor with clinical symptoms. Despite public funding for many procedures and therapies, the responsibility for achieving a final diagnosis rests largely with the patient. This is because the general practitioner or specialist orders certain tests in a conservative manner, taking into account the fact that diagnostics are included in the costs of the procedure. In addition, doctors usually lack access to their patients' full medical histories, which can lead to ineffective or redundant diagnostic testing or misdiagnosis based on fragmentary data without a broader medical context. Often, if a diagnosis cannot be reached, the process is interrupted, leaving room for disease progression, and in consequence, more difficult and expensive therapeutic methods become necessary at the later stages of treatment. Hence, an essential stage in the development of the healthcare system should be the **implementation of diagnostic algorithms** that would ensure making a final, confirmed diagnosis without losing sight of the patient within the system, even if they are consulted by different doctors. This applies both when the patient presents with clinical symptoms and when pathological symptoms are identified as part of screening. The most important types of interventions undergone by patients were addressed in the MRA survey (Fig. 7).

In the area of diagnostics, particular attention should be paid to:

- cancer diagnostic algorithms, with particular emphasis on neuroendocrine cancers,[19] such as lymphoma and leukaemia (common use of flow cytometry), carcinoids (prevention of carcinoid crisis), neurofibromatosis, gliomas[20] and sarcomas;[21]
- neurodegenerative diseases, particularly dementias, and the development of diagnostic pathways to enable the identification of patients with pathological biomarker levels at a very early stage of the disease, possibly allowing to effectively prevent and slow down disease progression, which constitutes an objective of particular value in view of the ageing society;[22]

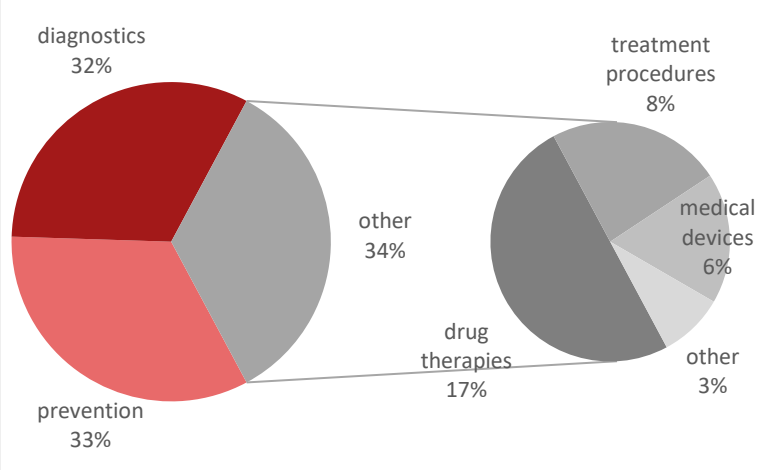

*Figure 7. Types of interventions considered most conducive to the improvement of the healthcare system according to experts. Methodology: CAWI, N = 117 responses. Prevention or diagnostics were mentioned by 65% of the respondents, which calls for developing innovative in vitro and imaging diagnostic methods, searching for **new biomarkers**, and advancing **digitisation**.*

- specialised diagnostic centres for patients with non-specific clinical symptoms or rare diseases whose diagnosis is difficult even for experienced clinicians,
- augmented reality (AR) and artificial intelligence (AI) tools to support medical professionals in managing the diagnostic workup.[23]

According to medical market experts, apart from diagnostic consultation and wider access to laboratory tests, it is necessary to ensure **access to comprehensive health information**. Individual online patient accounts (IKPs) proved successful during the COVID-19 pandemic, but there are still many unmet needs faced by individual healthcare units as regards **supporting data-based diagnostic and therapeutic processes**. For this purpose, it will be necessary for the Agency to keep **expanding the Digital Medicine Centres Network** and establishment of the **Central Omics Data Repository,** ultimately enabling central GWAS population analyses. This type of analyses, combined with data from other medical systems, will provide personalised treatments and precise preventive tools for all the stakeholders of the healthcare system in the future.

In the present context of dynamic international competition, it is necessary to develop a new strategy and systemic support to ensure **drug and biotech security**.[24] Over the last few decades, the United States and Europe have largely moved the production of APIs and drug intermediates to Asia for economic reasons, which has caused an unequal distribution of API production in different regions of the world. **Currently, about 50% of production is located in China, about 20% in India and the remaining 30% mainly in Europe and the United States.**[25] Asian countries control a decided majority of the production of active substances for critical diseases, such as diabetes mellitus, which affects over 2 million Poles. Should API supplies be reduced, Poland's drug security may be at risk. Medicines available on the Polish market are based on approx. 2,000 active substances, while the list of key medicines of the World Health Organisation (WHO) contains approx. 500–600 substances of critical importance for healthcare systems. Only about 100 active substances are manufactured in Poland, most of which are not even included on the WHO's list. Currently, only two types of APIs are produced in Europe. The first is innovative new molecules, whose owners earn high margins and keep the

production domestic to safeguard their technological secrets, but will probably also opt for Asian factories as soon as the relevant patent protection expires. The second is substances used in narrow product niches, e.g. orphan drugs, which are not attractive to Asian markets due to low sales volumes. These are the two main areas in which Europe can currently compete with China in terms of API production.

Another important trend from the point of view of the healthcare system is the growing popularity of **theranostics**, a domain which combines diagnostics and a personalised therapeutic approach. Currently, various types of radiopharmaceuticals are being explored for anti-cancer therapy, including peptide radiopharmaceuticals.[26] According to the forecasts by experts from the Polish Society of Nuclear Medicine, theranostic methods will gain popularity in the future. Theranostics makes use of the latest technological achievements, such as nanotechnology, nanomaterials, biomaterials and biomimetics, to simultaneously detect pathological processes and deliver medication directly to the affected areas. This type of targeted intervention allows for tailoring treatment methods (including drug doses) to the individual needs of the patient.[27] Theranostics as a combination of diagnostics and therapy at the molecular level is the basis of modern personalised precision medicine. Precision medicine often uses the results of NGS to individualise therapy, effectively changing treatment perspectives — especially in oncology, regardless of the dissemination stage. The results of genetic profiling with the use of NGS methods are also often used to characterise the neoplastic pathway and select the best therapeutic modality.[28]

While discussing theranostics and the diagnostic needs mentioned above, it is also worth addressing the importance of the **legal and regulatory environment**, which should correspond with the market situation and technological progress, allowing for the full allocation of procedures and resources. An example of this is the production of radiopharmaceuticals for hospitals' own needs, which is practised and allowed in other European countries.[29] However, the legal issues associated with theranostics are beyond the scope of this Report.

3.2 Summary and implementation takeaways

From the above analysis of the needs of the healthcare system in Poland, it follows that the principal issues to address in the coming years within the key areas are:

- **Development of non-commercial clinical trials** in the area of molecular/laboratory and imaging diagnostics — as early, as in-depth and as accessible as possible, with particular consideration of theranostics and nuclear medicine.[30,31]
- **Development of Clinical Trials Support Centres** — a clearly defined diagnostic pathway for patients to address any health problems quickly and comprehensively, which is of key importance for diagnosis, selection of therapy and optimised timing of treatment/hospitalisation. Healthcare professionals are expected to make a correct diagnosis, adapt the therapy to the individual patient's characteristics, obtain optimal results based on the patient's response to treatment, and provide patients with behavioural and metabolic (especially dietary) advice and support in order to maintain their physical health.[32] This is why the patient journey model requires organisational and systemic improvements that could reduce waiting times, make a diagnosis at an early stage of disease development and increase the effectiveness of therapy.
- **Expansion of production capacity in the field of digital medicine** – local production of medical devices of all classes, intermediates necessary to manufacture most used medicinal products

(e.g. new generation antidiabetic drugs, blood glucose monitoring systems, antihypertensive and cardiovascular drugs, class II-III medical devices for heart rate monitoring and stimulation), digital solutions supporting prevention, especially in oncology and cardiology, possibly including innovative systems of patient incentives and bonuses.[18-19]

- **Advancement of translational medicine and support of the dialogue and collaboration between the academia and business community** — persistent search for new more effective and/or less toxic anticancer therapies, as well as promoting personalised diagnostic and therapeutic approaches based on biomarkers.
- **Building public and expert awareness of the risks of cardiovascular diseases as well as behavioural and metabolic risk factors** — taking into account the complexity and specific nature of interactions between patients, doctors and the healthcare system. Possible implementation of patient reward systems as a preventive measure.

4. Directions of drug market development

4.1 Most researched drug technologies — increasing demand for new personalised treatments in oncology, rare diseases, or depression, and for antimicrobial technologies.

The European Medicines Agency has developed strategic goals to be achieved by 2025, which define key recommendations e.g. for the development of personalised medicine, biomarkers and omics, new advanced therapy medicinal products (ATMPs) that address the unmet needs of patients, and new antibacterial drugs and their alternatives.[33]

Oncology is expected to dominate the clinical research market. These predictions are fully consistent with the results of the MRA's survey study, where oncology was indicated as a priority by both representatives of patient associations and experts (Fig. 1). It is already very evident from the studies carried out by the parent institutions of principal investigators who receive MRA's funding. According to their reports, oncology comprises 35% of all researched indications, almost three times more than its immediate followers: infectious diseases and neurology (13% of indications each; methodology: CAWI, N = 23 responses).

*Continued research into **cancer treatment** and the growing demand for **precision medicine** contribute to the high focus on oncology in the developing drug market.*

Continued research into cancer treatment and the growing demand for precision medicine contribute to the high focus on oncology in the developing drug market. This segment is projected to record a 6.4% CAGR increase between 2022 and 2030.[34] The advancement of oncology focuses on the treatment of solid tumours with new-generation biotherapeutics including bispecific antibodies and other innovative solutions, such as antibody-drug conjugates, biotherapeutics for cell therapies, especially CAR-T therapies based on modified T cells used in haematological cancers. There is also a growing interest in mRNA vaccines, especially in solid tumours.[35]

There are more than 7,000 rare diseases, including rare cancers, and 95% of them have no treatment available. As a result, there is a growing need for new cell, gene, and RNA-based therapeutic options.[36,37] Cell and gene therapies are common in oncology, while RNA-based therapies are mostly used in infectious diseases.[39] Gene editing is gaining importance in the biotechnological development of medicinal products, particularly in rare diseases, neurology and oncology,[38] albeit the progress of this method as a cancer treatment has slowed down in recent years due to the significant rates of adverse events observed in clinical trials, which necessitated the implementation of proactive safety plans during product testing.[37]

There remains an unmet need for new antimicrobial drugs, treatments or vaccines to address the emerging health risks.[39] According to WHO, antibiotic resistance is one of the greatest threats to public health on a global scale, with an estimated nearly 10 million deaths annually worldwide. Particularly dangerous are multidrug-resistant *M. tuberculosis*, methicillin-resistant strains of *S. aureus*, vancomycin-resistant enterococci and *C. difficile*, carbapenem-resistant enterobacteria, and colistin-resistant gram-negative bacteria.[40] The emerging regulations and guidelines should support the development of vaccines, phage therapies, new biologically active molecules such as peptides or enzymes, non-specific immunomodulators, gene-editing technologies and photo-switchable antibiotics.[41]

According to WHO, ***antibiotic resistance is one of the greatest threats*** *to public health on a global scale, with an estimated nearly 10 million deaths annually worldwide.*

Options for age-related neurological disorders such as dementias and Parkinson's disease are currently limited. Given the ageing population and the increasing rates of Alzheimer's disease worldwide, it is necessary to develop effective therapies for these conditions.[38]

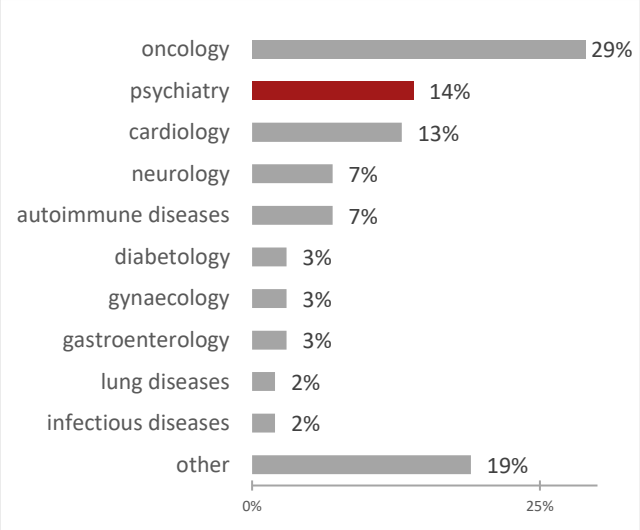

Figure 8. Medical fields that should be prioritised by the MRA in its efforts to improve the healthcare system in Poland. Responses from experts. Methodology: CAWI, N = 181 responses.

The demand for antidepressants has also been on the rise in recent years. There is increasing emphasis on targeted mechanisms of action, such as new serotonin reuptake inhibitors, neurotropic steroids, serotonergic psychedelics and NMDA psychedelics.[42], what has also been noticed by experts in MRA's survey study. Psychiatry, right after oncology, has been identified as an area of medicine that should be prioritised in the efforts to improve the healthcare system in Poland (Fig. 8).

In view of the increasing popularity of research on psychedelics such as psilocybin or MDMA, the US Food and Drug Administration (FDA) is currently working on guidelines to help standardise clinical research in this area.[43]

In addition, other medicinal products including plant-based vaccines (e.g. taliglucerase alfa produced in carrot cell cultures and used in the treatment of Gaucher disease) are an interesting option that may

have potential therapeutic benefits. Still, more evidence and research are needed to resolve the existing concerns.[43]

There are also no treatments available for patient groups that require a special therapeutic approach, such as children, pregnant women, breastfeeding women and the elderly.[41] Despite the effort undertaken in recent years in the area of paediatric drugs, there are still a lot of unmet needs in this respect, especially as regards oncology and neonatology.[35] EMA predicts that in 2024, the largest increases in assessment rates will pertain to new orphan drugs, ATMPs, and new non-orphan drugs, with slight increases for biosimilar, generic, and hybrid drugs.[44]

4.2 Innovative drug technologies with high development potential — dynamic development of advanced therapies and biotherapeutics

According to a report by IQVIA, an increase in the global drug technology market is expected to take place in the years 2023–2027, including the largest rise in spending on anticancer (13–16% CAGR), immune and antidiabetic drugs (3–6% CAGR each). In oncology, over a hundred new medicinal products are expected to be developed, including innovative cell therapies, RNA-based treatments, and immunotherapies targeting specific cancer-independent mutations. In immunology, which comprises small molecule and biological therapies, the highest rises are projected for new medicinal products, generics and biosimilars. With the expected increased prevalence of obesity (10–13%), the availability of highly effective therapies for this condition will also grow. The neuro market will also grow in importance, offering new anti-migraine agents, potential therapies for rare diseases, as well as for Alzheimer's and Parkinson's. The latest scientific advances in genomics, biomarkers, diagnostics, imaging techniques, and regenerative medicine, coupled with the emergence of breakthrough digital technologies, are transforming therapeutic innovation focused on the central nervous system.

Spending on next-generation biotherapeutics is also expected to swell, mostly on cellular and RNA-based therapies, and to a lesser extent on gene therapies (which partly feature under oncology).[45] Over the past decade, new active substances have been introduced with varying intensity in the field of infectious diseases, including anti-COVID-19, antibacterial, antiviral, antifungal and antiparasitic therapies or new drugs for HIV, Ebola, and monkeypox.[44]

4.3 Factors determining the development of innovative medicines — reduction of costs and risks through interinstitutional collaboration and combined research

Currently, investments in drug technologies do not necessarily focus on the greatest unmet needs of patients due to insufficient commercial interest or the existence of scientific constraints[41] (e.g. the complexity of diseases and the scarcity of reliable biomarkers[38]). Developing a new drug is a long-lasting, costly and risky process. It is becoming increasingly reliant on modern technologies, such as artificial intelligence and machine learning. The problem is the underfunding of the initial phases of product development. The high costs of developing medicinal products have forced biopharmaceutical companies to form alliances to increase resources and share the risks associated with the expense. The trend towards combined trials and clinical trial collaborations is expected to continue.[36]

Extremely important for the development of innovation are: multidisciplinary collaboration (of scientists, clinicians, patients, biotech and pharma businesses) to ensure new technologies are adapted to the actual patient needs; specialist knowledge, including technical and regulatory know-how; and effective communication.[46]

4.4 Summary and implementation takeaways

The analysis of the drug technology market has revealed a dominance of **anticancer products**, including cellular, RNA-based, and immune therapies. A rise can be expected in expenditure on immunological drugs: small-molecule drugs, biologicals, including new and — to a lesser extent — generic and biosimilar drugs, as well as antidiabetics and biotherapeutics. There is a growing need for **new personalised treatment options** for rare diseases, for targeted treatment of depression, as well as **new antimicrobial agents, particularly antibiotics**.

The identified lack of effective treatments for neurological disorders (dementia, Alzheimer's, Parkinson's) and paediatric diseases (especially in paediatric oncology and neonatology) indicates the need for more effort in these areas. In the surveys, experts emphasised the need for extensive support of cardiology. Much attention has also been paid to psychiatry. This area requires a multifaceted approach, especially to improve the mental and physical health of **children and adolescents**.

Based on the above considerations, the following solutions might be implemented in the future:

- **Development of advanced therapy medicinal products**, with a focus on rare diseases, cancers and neurological conditions, as well as infrastructural support and adaptation of already existing ATMP manufacturing plants in Poland.
- **Development of generic and biosimilar medicines** and support of immunology in collaboration with patient organisations to create technologies adapted to the needs of target recipients.
- **Advancement of translational medicine**, personalised medicine, biomarkers and omic techniques; promoting collaboration with patients (in order to create technologies adapted to the needs of target recipients); taking advantage of state-of-the-art data analysis technologies, such as artificial intelligence and machine learning, as well as combined research and interinstitutional collaboration to reduce costs and risks.
- **Development of epidemiological research** — promoting omic research and analysis in oncology, old age neurology, psychiatry, paediatrics and neonatology (especially cancer therapies), and research on sensitive populations: pregnant women, breastfeeding women, the elderly, and children; taking advantage of state-of-the-art data analysis technologies, such as artificial intelligence and machine learning.
- **Development of non-commercial clinical trials on cancers** — promoting omic research and analysis, solid tumour research, and mRNA vaccines, with particular attention to paediatric oncology.
- **Development of non-commercial open-label clinical trials and research experiments** — promoting omic research and analysis in the therapeutic areas of oncology, old age neurology, psychiatry (with particular emphasis on antidepressant technologies), paediatrics, and neonatology.

5. Directions of development of the medical devices market and other medical technologies

There are a variety of categories of medical devices. Their number on the global market is estimated at approximately 2 million, and on the Polish market at 300,000.[47] Innovation in this industry often takes the form of continuous improvement of effectiveness, exploration of new methods of use,

or reduction of side effects associated with existing solutions. This is evidenced by the fact that medical devices typically have a life cycle of a mere **18–24 months**[48] before an improved version enters the market. In this respect, the rate of innovation in medical devices, if measured by the number of patents, significantly exceeds that of the pharmaceutical industry.

When analysing global and national trends, as well as the unmet needs of patients and the challenges of the medical sectors, it is to be expected that the development will follow a matrix approach. There are easily recognizable trends towards **extensive digitisation** of existing devices, making improvements and adding functionalities; **re-orientation of the business and operating models** of medical device manufacturers and expanding their offer to include diagnostic and logistic services; as well as the **development of new products** in response to the unmet clinical, logistic and functional needs.

5.1 Digitisation of the medical device industry — mobile devices and applications as a response to patient needs

Currently, becoming more and more popular are medical devices which, apart from their main functions, bring added value, e.g. collect data, monitor patient compliance or vital signs, or minimise invasive procedures. There is also a growing demand for modern wearables equipped with e.g. health data management applications and services.

The manufacturer's relationship with the end-users is changing and is reinforced mainly by the continued use of the technology (in the case of wearables) and a shift in focus from the hospital/clinic to the home. Using these technologies, clinicians gain access to data that make it possible to accurately diagnose diseases, monitor patient parameters and prevent deterioration of health. Whereas patients avoid unnecessary medical visits and have access to a number of solutions to support building good habits. However, the development of this type of technology requires departing from producing devices that only serve diagnosis or treatment and focusing instead on providing integrated, comprehensive services and solutions that will not only boost the therapeutic/diagnostic effectiveness but also reduce the costs of care.

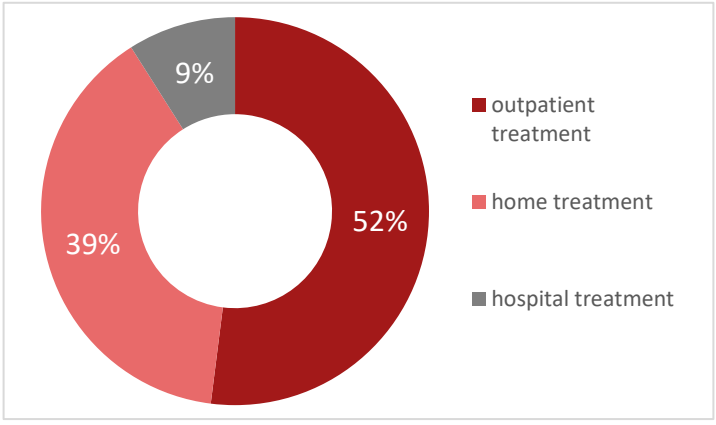

Figure 9. Treatment modalities considered most desirable by patients. Based on responses from representatives of patient associations. Methodology: CAWI, N = 82 responses.

In the survey conducted as part of the Clinical Trials Barometer, **only 9% of the respondents from patient associations considered hospital treatment as the most desirable type of patient care**. The treatment modalities most often regarded optimal were outpatient (52%) or home treatment (39%) (Fig. 9)

These expectations were recognised by respondents representing businesses engaged in the manufacture of drugs, active substances and medical devices, who also cited home treatment (45% of responses) as the most desirable modality, followed by outpatient

treatment (42% of responses) (Methodology: CAWI, N = 31 responses).

Intelligent drug delivery and patient monitoring systems will personalise and minimise invasive therapies thanks to innovative devices such as wearable drug delivery systems (Biostamp) and smart inhalers. These smart devices will not only send patients reminders of their medications (to improve compliance), but also forward feedback to their doctors, enabling more personalised and preventive care. For example, Novartis has teamed up with Qualcomm Life to develop a web-connected inhaler that can send information to a cloud-based analytical platform that uses large volumes of data to support the treatment of patients with chronic obstructive pulmonary disease (COPD).[49]

5.2 Examples of digital solutions implemented in healthcare systems — reduced costs and increased efficiency

The economic and legislative reality is forcing medical device manufacturers to revise their traditional business and operation models to support a heterogeneous base of business customers and patients (existing and prospective). The growing involvement of businesses in prevention, diagnostics, delivery logistics, hospital waste management, and post-intervention patient monitoring contributes to the overall reduction of healthcare costs, e.g. through shorter, cheaper and fewer hospital visits.

This trend is illustrated by the emergence of solutions created by device manufacturers in collaboration with technology or IT providers, such as the Zimmer Biomet + HealthLoop platform supporting patients awaiting alloplastic surgery.[50] The HealthLoop app educates patients about pre- and postoperative protocols and collects data on postoperative outcomes and therapies to help estimate reimbursement costs. Meanwhile, Siemens Healthineers has forged a strategic alliance with IBM Watson Health, focusing on population health management and value-based healthcare solutions for hospitals.[51] This partnership will make it possible to use clinical imaging services to analyse data generated by medical technologies to better understand the underlying causes of diseases. Google and Ethicon have co-founded Verb Surgical, a company that develops surgical robots powered by artificial intelligence, image data analysis software and machine vision.[52]

5.3 Innovation in medical devices — dynamic progress in robotics, nanotechnology, and biomaterials

- **Nanotechnology, microsystems and biosensors in the medical device sector**

Both in the design of individual devices and in the intervention procedures themselves, a prevailing trend is miniaturisation. The reason is the need for minimal invasiveness, lower risk of complications, lower costs of hospitalisation and faster recovery.

This trend is supported by the advancement of BioMEMS technologies, microflow and nanoscale systems, including microanalysis, arrays and biochips for the detection and quantification of clinically relevant analytes in complex matrices. Applications include biomedical research, clinical laboratory diagnostics, high-throughput screening and implantation devices, to mention just a few. Noticeable progress has been made in nano-solutions, e.g. nanocapsules, nanodiamond-based drug delivery systems, nanoendoscopes, micro- and nanosystems for diagnostics and targeted therapy, or DNA nanobots.

Currently, there is skyrocketing interest in hyperbolic metamaterials. The design, production and development of new nanomaterials for optical biosensors is an extremely important challenge for

modern science and sophisticated technologies, owing to the attractiveness of these solutions and the need for miniaturisation, weight reduction, and mobility of biosensors. In addition, these types of materials do not require electrical power and provide high accuracy and precision of detection.

- **Bioresorbable, bionic and biodegradable medical devices and packaging**

Both clinical demand and concern for environmental protection call for research and development of new biomaterials, especially in the area of tissue engineering, implantable devices, biosensors and actuators. Particularly high hopes are placed in the **engineering of new carriers**, which can include biomimetic materials, liposomes, micelles, nanoparticles and dendrimers. An unquestionable advantage of biomaterials is their biocompatibility and bioresorption potential, making it possible to produce biodegradable stents, prostheses and scaffolds, implantable bionic lenses, absorbable threads and other surgical closure devices, biodegradable packaging, 3D-printed organs and bones, or absorbable catheters, also for paediatric applications.

Projects such as the bio-hybrid kidney will minimise the need for certain services (e.g. dialysis) and reduce many of the risks associated with current systems. Researchers at the University of California have developed a prototype of an artificial, implantable kidney the size of a coffee cup. It contains filters developed with silicon-based nanotechnology and living kidney cells that will be nourished by the patient's body, further preventing rejection of the artificial organ.[53]

- **New-generation surgical tools, techniques and systems**

The progress made in this category of solutions is exemplified by surgical robotics and minimally invasive surgical devices applied to improve the outcomes of surgical interventions, as well as to increase patient safety and reduce recovery time. Innovative surgical solutions such as autonomous surgical robots and smart balloon catheters will improve the outcomes of complex surgeries and enable new forms of minimally invasive surgery. An example of this type of solution is the Mako robotic arm for total knee replacement developed by Stryker. Such advanced technologies also make it possible to design medical simulator systems for the training of surgical staff. Conventional biopsies are also being improved to obtain better results with less invasive methods.

There is still a high demand for robotics in eye surgery, augmented reality solutions, and remote surgery solutions.

- **Modern rehabilitation engineering**

Effective holistic rehabilitation and physiotherapy methods in neuromuscular diseases, deep brain stimulation with imaging and electrophysiological targeting, neuroprosthetics for hearing, sight and movement, and spine lengthening devices are in high demand, also in physical medicine. In response to these needs, works are underway to create smart equipment with software controls to operate it and predict physiological signals and human behaviours. It is to be expected that they will bring tangible results that will go on to become part of medical and rehabilitation practice. Currently, also in Poland, projects are being carried out on smart exoskeletons, as well as muscle and nerve stimulators, which is a promising prospect in this area.

- **Innovative diagnostics — higher sensitivity and specificity with less test material**

Accurate and early diagnostics is a sine qua non of a successful treatment process. Unfortunately, in this respect, there are two types of challenges:

- a systemic challenge — the pricing of therapeutic procedures, which include diagnostics, often makes the latter a target for cost-cutting efforts of medical facilities. Less expensive methods are preferred, and their numbers strictly limited; as a result, patients are at risk of being misdiagnosed, receiving the wrong therapy, and ultimately getting worse;
- a technical challenge — improving existing methods to make them more sensitive, specific and perform better on small sample volumes can reduce costs and make the diagnostic procedures less invasive.

The second challenge is persistently undertaken by engineers in the medical device industry; progress is being made in ultrasound devices (including echocardiography), in order to obtain higher sensitivity and resolution, as well as in eye imaging systems such as small retinal scanners. Flow cytometry methods are being enhanced, as well as imaging methods, such as dynamic magnetic resonance. Perfecting imaging diagnostic methods also includes equipping devices with artificial intelligence (AI) in order to accelerate diagnosis and improve accuracy.

During the COVID-19 pandemic, diagnostic tests of all kinds gained importance. These methods have evolved significantly, which has translated into an increased range of parameters tested. For example, new metabolomic and predictive tests are emerging which use e.g. proteomic biomarkers. New devices for cell separation are also being developed, as well as more sensitive, more specific, faster and cheaper genetic assays based on WES and WGS methods. There is increasing talk about the needs and works towards non-invasive diagnostics, including methods of measuring ventricular refractory period and intraventricular conduction time or non-invasive monitoring of intracranial pressure.

- **New, device- and/or biotechnology-based approach to combating bacterial infections**

According to the available data, each year in Europe there are 4.5 million cases of nosocomial infections. An increasing threat comes from multiresistant bacteria, e.g. the ESKAPE group, which are able to evade drugs as much as the body's defence mechanisms. That is why numerous research teams around the world are looking for new methods to eradicate these microorganisms, which is one of the major challenges for healthcare systems globally.

One alternative to new antibiotics is antimicrobial photodynamic inactivation developed by the Intercollegiate Faculty of Biotechnology of the University of Gdańsk and the Medical University of Gdańsk in collaboration with experts from Tianjin University, China. It involves the administration of a haem-mimetic gallium porphyrin photosensitiser to sensitise bacteria to light, which is then used to inactivate them. Antimicrobial photodynamic inactivation can be used against multidrug-resistant microorganisms to combat antibiotic resistance and enhance photodynamic antibacterial activity. Another promising area is innovative diagnostic devices that can automatically and comprehensively test bacteria isolated from clinical samples for susceptibility to clinically available antibiotics and their combinations.[54] High hopes are also placed in phage therapies, new gene-editing technologies and photoactivated antibiotics.

- **Medical devices for the diagnosis and treatment of rare diseases**

Rare diseases can take years to be diagnosed due to the non-specific nature of the symptoms and the unavailability of case comparisons. According to the NIH, even 80% of rare diseases are of genetic origin, which means genetic testing is necessary to confirm a diagnosis.[55] Delaying the diagnosis, and hence effective treatment, often leads to progression or even premature death.

From the perspective of the patients, their families and the public system, fast and accurate diagnosis is key. On the other hand, when it comes to treatment of rare diseases, it is considered necessary to improve measuring methods, e.g. of glomerular filtration rate (GFR) or systemic blood flow (e.g. in Guillain-Barré syndrome and dopamine beta-hydroxylase deficiency), as well as prognostic tools (e.g. in Huntington's disease). Clinicians call for improving drug delivery control systems based on data from physiological sensors, which would find applications in virtually any disease with a known dose-response relationship.

A particular challenge is the reluctance of businesses to invest in rare diseases, motivated by the small size of the market and concerns about return on investment.

- **Trends in the development of nuclear diagnostics**

Nuclear medicine has the necessary tools to implement the concept of 'magic bullet', which refers to the targeted application of medication.

Radioisotope techniques make it possible to assess functional disorders at a very early stage of the disease, even before any structural changes occur. Examples of morphological tests include computed tomography, magnetic resonance, or ultrasound, while radioisotope methods are functional tests which consist in administering a radiopharmaceutical whose distribution in the body reflects a specific function, e.g. blood flow, receptor activity, metabolic changes of amino acids, or production and release of certain chemicals. These methods make it possible to diagnose a tumour focus that contains only 10^6-10^7 cells and determine whether a lesion visible on CT or MRI is malignant or benign. The alpha radiation emitted by radiolabelled drugs, which penetrates specifically into cancer cells, damages both DNA strands, ensuring higher effectiveness of the treatment. Owing to the different metabolic features of cancerous and normal cells, PET with ^{18}F-fluorodeoxyglucose (FDG) can be used to distinguish between the two types of cells with high accuracy. Other radiopharmaceuticals are able to distinguish between these two types of cells based on intensified proliferative processes (^{18}F-choline). Advances in the application of radiolabelled antibodies in precision diagnostics make for earlier detection and consequently more effective treatment of malignant tumours.[56]

5.4 Summary and implementation takeaways

The above analysis of market trends and reports from the medical device sector calls for giving consideration to the following key areas:

- **Supporting the development of digital medicine**, expanding the functionality of existing medical devices, e.g. with AI algorithms that enable continuous monitoring, data collection, and integration with other medical systems/technologies.
- Supporting the implementation of **innovative diagnostic medical devices that incorporate nanotechnologies and microsystems, including high-throughput screening tests**. This will enable diagnostics in an outpatient setting or at home with high precision even on small volumes of sample material.
- Support for projects aimed at **developing technologies to assist antibiotic therapies**. Biologically safe methods based on photodynamic inactivation will provide more effective methods of combatting microorganisms and possibly slow down the rise of drug resistance.
- **Expansion of production capacity for radiopharmaceuticals**. Enhancing of the precision of cancer cell detection will significantly advance precision medicine.

- Support for **new-generation surgical tools, techniques and systems, including rehabilitation devices**. Smart equipment or software to control devices and predict physiological signals and human behaviours will provide opportunities for less invasive and more precise procedures and rehabilitation activities, which will shorten the recovery period.

6. Directions of scientific research development (fundamental and pre-clinical)

6.1 Genetic and epigenetic research as a priority for patients and the healthcare system in Poland.

Research in the field of medical genetics is an integral part of **personalised medicine**, whose unquestionable and rapid progress has been observed for several years. The paradigm of medical care is shifting from 'one size fits all' to 'one size fits one' (tailored treatment). Using a person's genotype to make decisions about prevention, diagnosis and treatment has a good chance of perfecting the available diagnostic and therapeutic methods. Personalised medicine gives the greatest hope for **oncology**, **cardiology**, **rare diseases** and **neurodegenerative conditions**. **These areas were also named by experts as the highest priorities for the advancement of medical sciences in Poland (Fig. 11).** One field of science which has a high potential to make a difference in medicine is **epigenetics**, which focuses on the relationship between the environment and genetics. Epigenetic changes can influence e.g. how a patient responds to treatment. In addition to cancers, epigenetic research focuses on **mental disorders**, **cardiovascular diseases**, **rheumatic diseases**, **metabolic diseases** (for instance, epigenetic modifications seem to play a role in the development of type 2 diabetes mellitus) or **non-alcoholic fatty liver disease**.[57]

6.2 Comprehensive research on immunotherapeutics in oncology.

Cancer immunotherapy (an approach based on using the patient's own immune system to fight cancer), or immuno-oncology, is one of the most innovative and promising areas of biotechnology. It seems to be what antibiotics and preventive vaccinations used to be for the treatment of infectious diseases. The first of these types of drugs was approved in 2011 for the treatment of melanoma, and currently, over a dozen immuno-oncological therapies are fully tested and approved.

Nowadays, immunotherapy is a two-pronged approach:

- therapies based on **immune checkpoint inhibitors** (e.g. ipilimumab, pembrolizumab and nivolumab), which activate the immune system to fight a specific cancer the same way in all patients with that cancer, have been used successfully in the treatment of melanoma and lung cancers;
- personalised therapies based on **therapeutic cancer vaccines**, which mobilise the immune system to fight a specific cancer in a specific patient. These require the identification of neoantigens — proteins which are only present in a particular growing tumour and are dependent on a unique combination of genetic mutations carried by the cancerous cells in an individual patient.

A number of studies are underway to assess the use of new therapies in the treatment of renal cancer, colorectal cancer, prostate cancer, breast cancer, head and neck cancers and other malignancies.

Neoantigen identification requires the application of the latest achievements in **genetics and molecular biology**: NGS, **bioinformatic algorithms,** and **computer modelling**. Enormous funds are currently being allocated all over the world to expand our understanding of cancer immunology and to bring new immune therapies to the market.[58,59] **Oncology was named by experts as the highest priority for the advancement of medical sciences in Poland (Fig. 10).**

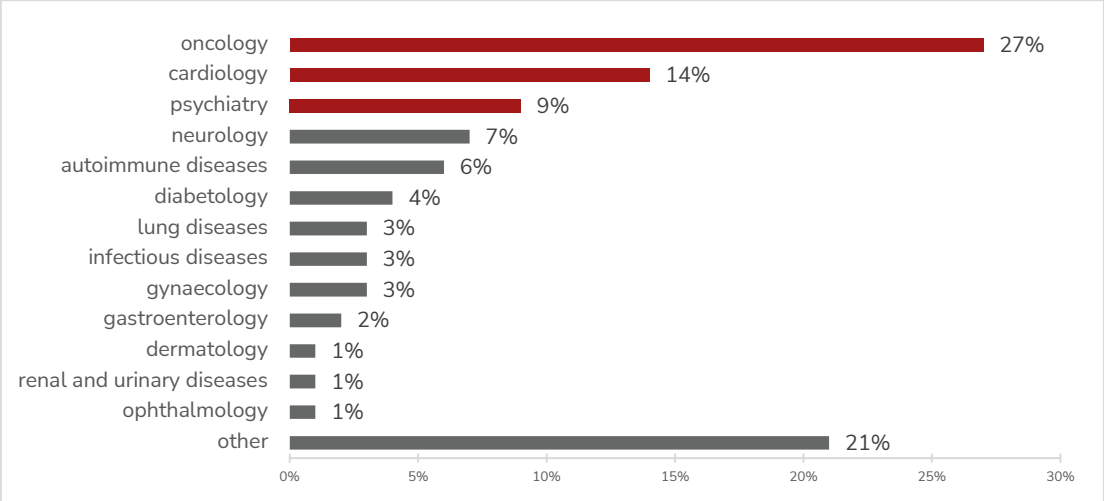

Figure 10. Medical fields that should be prioritised in order to advance medical sciences in Poland. Responses from experts. Methodology: CAWI, N = 188 responses. Oncology, cardiology and psychiatry together account for half of all responses.

6.3 Comprehensive research on the complexities of brain plasticity — development of new solutions improving the prevention, diagnostics, monitoring and treatment of brain diseases.

Brain neuroplasticity, i.e. the ability of the brain to constantly and permanently reorganise the network of nerve cells under the influence of various stimuli, is crucial for the processes of learning, memory and regeneration after damage resulting from injuries or diseases. It makes it possible to reduce the effects of e.g. multiple sclerosis, Alzheimer's disease or Parkinson's disease. On the other hand, neuroplasticity disorders can lead to a number of conditions such as addictions, autism spectrum disorders, depression, schizophrenia, and bipolar disorder. Our understanding of neurobiology and brain function has grown tremendously in recent years. Revolutionary advancements have been made in: 1) **biomolecular methods** of highly efficient gene and protein analysis and manipulation, 2) **precision imaging and visualisation** of individual cells or synapses and the activity of neural networks throughout the brain, 3) **novel research modelling techniques** such as brain organoids derived from induced pluripotent stem cells; and 4) **bioinformatics** to analyse the resulting enormous data sets. Research on **the mechanisms of neuroplasticity** creates new opportunities for exploring **the aetiopathogenesis of many neurological, neurodegenerative and psychiatric disorders.** Brain conditions generate the highest social costs (up to EUR 800 billion in the EU). The burden of nervous system disorders has increased in recent years and is likely to increase in the future as the population ages. Hence, there is an urgent need to improve the prevention, diagnosis

*Research on the **mechanisms of neuroplasticity** creates new opportunities for exploring the aetiopathogenesis of many **neurological**, **neurodegenerative** and **psychiatric disorders**.*

and treatment of these disorders.[60,61] **Psychiatry was named by experts as the third highest priority for the advancement of medical sciences in Poland (Fig. 11).**

6.4 Digital medicine — a marriage of medicine and information technology to develop new diagnostic and therapeutic solutions for personalised healthcare.

DIGITAL MEDICINE
Artificial intelligence, machine learning, advanced algorithms, computer modelling and simulations, large-scale high-performance computing, big data analysis, augmented reality *can be used to* ***prevent, accurately diagnose and treat*** *diseases.*

Personalised medicine is based on the recognition and understanding of the differences between patients suffering from the same disease, and tailoring the treatment to the needs of individuals. Adding to the challenge of personalised healthcare is our growing understanding of the complexity of the disease process and the multiplicity of physiological mechanisms involved in it. **Digital medicine**, also known as *in silico* medicine or computational medicine, is a new field of knowledge that has emerged thanks to the advances in computer technologies. **Artificial intelligence, machine learning, advanced algorithms, computer modelling and simulations, large-scale high-performance computing, big data analysis, and augmented reality** – all these can be used to **prevent diseases, ensure accurate diagnosis, and plan and support effective treatment with minimal side effects**. The aim and challenge for modern medicine is to combine medical knowledge and computational capabilities to provide patients with the best possible quality of life, which can be achieved through individualised treatment.[62]

6.5 Summary and implementation takeaways

Based on the above analyses, the following solutions can be implemented in the future:

- **Expansion of production capacity for advanced therapy medicinal products (ATMP) -** elaboration of new cancer immunotherapies and personalised therapeutic cancer vaccines
- **Advancement of translational medicine**
  - Research on the mechanisms of neuroplasticity may produce effective diagnostic and therapeutic methods for neurological, neurodegenerative and psychiatric conditions
  - New methods of precision imaging and visualisation — nervous system disorders (neurological, neurodegenerative and psychiatric conditions)
  - Creating new research models — nervous system disorders (neurological, neurodegenerative and psychiatric conditions)
- **Advancement of epidemiological research –** supporting research in elderly populations involving neurodegenerative and other age-related conditions.
- **Development of the Digital Medicine Development Plan**
  - Using artificial intelligence, machine learning, advanced algorithms, computer modelling and simulations, large-scale high-performance computing, big data analysis, and augmented reality to prevent, accurately diagnose and effectively treat diseases
  - Using individual genetic profiles to make decisions about disease prevention, diagnosis and treatment or employing genetic tests and molecular markers to guide the selection of the right therapeutic strategies for the right patient at the right time

and/or detect molecular factors predisposing a person to a specific disease in order to take well-timed preventive measures (personalised medicine).

7. Clinical trials in Poland and worldwide

7.1 Biomedical research in Poland and worldwide — a growing dominance of cancer clinical research

According to the ClinicalTrials database, as at 8 May 2023, there were 451,373 trials registered globally, of which 77% (347,993) were interventional trials and most investigated medicinal or biological products, behavioural interventions, medical devices and treatment procedures. There were 129,648 trials registered in Europe, of which 8,844 in Poland, including 7,927 interventional ones.[63] The European database ClinicalTrialsRegister registered 42,304 clinical trials, of which 4,218 in Poland.[64]

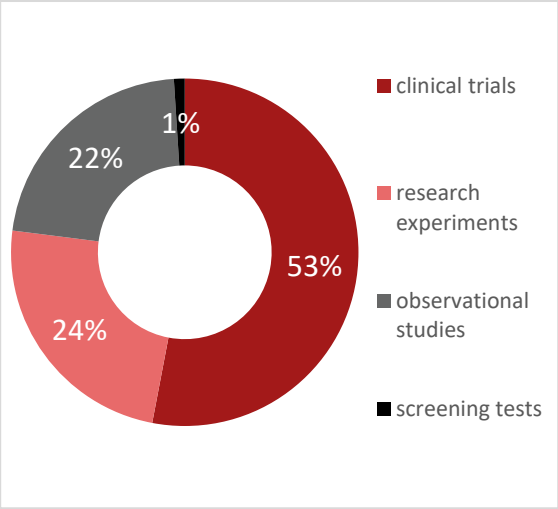

Figure 11. Types of research considered most conducive to the improvement of the healthcare system. Responses from experts. Methodology: CAWI, N = 68 responses. Clinical trials were indicated by over half of the respondents.

Interventional research is expected to dominate the clinical trials market,[34] and **oncology will likely remain the most investigated therapeutic area**.[65] This opinion is shared by experts surveyed by the MRA, who emphasised the key role of clinical trials in improving the healthcare system in Poland (Fig. 11).

Clinical trials related to COVID-19 have contributed to increased interest in the study of other infectious diseases, particularly bacterial infections, HIV, hepatitis, and influenza. Between 2021 and 2022, great progress has been made in mRNA vaccines, which has spread to many diseases unrelated to COVID-19, e.g. influenza and respiratory infections, other infectious diseases, cardio-metabolic disorders and cancers. Clinical trials in oncology reached historically high levels in 2022 (a growth of 22% compared to 2018) and focused mainly on rare cancers. In 2022, research initiated in other important therapeutic areas returned to pre-pandemic levels, with the exception of studies related to ophthalmology and women's health, whose levels increased during the pandemic and returned to or slightly exceeded the 2021 levels. The number of initiated clinical trials grew by 68% compared to the period before the pandemic, and psychedelic drugs were tested in nearly 25% of all trials initiated in 2022.[44]

7.2. Dominant research trends in new drug and biomedical technologies — the advent of next-generation research patterns

EMA's strategic goals and core recommendations for human medicine by 2025 include driving collaborative evidence generation to improve the scientific quality of evaluations, e.g. by fostering innovation in clinical trials through the use of novel designs and new clinical endpoints, especially related to quality of life, data collection techniques or the use of new methods such as 'omics' and real-world data to stratify populations or disease taxonomy, as well as promoting the inclusion of hitherto

neglected populations such as pregnant women, the elderly and those of diverse ethnicity in clinical trials.[35]

The number of **clinical trials with novel designs**, including umbrella, basket and adaptive platform trials, is systematically growing (from 7.5% in 2010 to 17% in 2022).[44,66] Research of this type has been dominating in oncology, and in the last three years also in infectious diseases, including COVID-19,[44] and autoimmune diseases.[67] In 2022, the FDA developed guidelines for the use of master protocols in clinical trials of oncology drugs and biologics,[68] and in 2019 it published guidance for adaptive study designs.[69] In addition, the FDA is planning to harmonise its guidelines for adaptive clinical trials with foreign regulatory agencies.[43] Experts say phase 0 trials (used to identify the patient-specific activity of a drug before phase 1 trials) and master protocol trials (which use the same protocol for multiple drugs or trials) may become particularly popular. Meanwhile, non-traditional trial designs: N-of-1, basket and umbrella trials, are gaining momentum[70] (Fig. 12).

Major changes are also happening in survival analysis studies. Clinical trials are expected to become **increasingly patient-oriented** (e.g., matching the drug to the patient based on their tumour biomarkers) rather than drug-oriented (matching subjects to the characteristics of the clinical trial).[78] Another trend in the drug technology market can be observed in data collection. RWD/RWE is increasingly used to design trials or supplement clinical trial data.[71]

Trial design	Description	Trials by year (2013-2022)	Most common therapy areas
Phase 0 trial	Microdose in patients prior to Phase I		Oncology, central nervous system diseases
Master protocol trial	Employ same design for multiple studies/drugs		Oncology, infectious diseases
N-of-1 trial	Intervention personalised for one patient		Central nervous system diseases, cardioavascular diseases
Basket trial	One intervention, multiple indications		Oncology, genetic disorders
Umbrella trial	Multiple interventions, one indication		Oncology, infectious diseases

Fig. 12 Trends in most common non-traditional clinical trial designs [83].

Both commercial and non-commercial sponsors are showing increasing interest in using **RWE** not only in phase 4 trials but also in pre-marketing (phase 3 and 2) trials, e.g. in the form of synthetic (external/concurrent) control arms that can include a combination of RWD and historical data. Data collected by patients with a variety of biosensors, wearables, and mobile phone trackers, are an important form of RWD. According to GlobalData, in 2022, RWE was most used in newly initiated trials on cancers, infectious diseases and central nervous system disorders.[72]

Remote, virtual or decentralised clinical trials have been growing in popularity among those initiated by the industry, with a slight drop in 2022.[44] Similarly, **digitisation** is on the rise (e.g. the use of cloud

computing, online platforms or other advanced tools) to help recruit patients and ensure the effectiveness of research.[84] **Decentralised clinical trials** (DCTs) are a patient-oriented approach offering maximum flexibility and convenience through the use of wearables/sensors, personal applications (electronic diaries used remotely), patient-reported outcomes, telephone follow-up, home visits, home drug delivery, electronic consent, or remote data monitoring.[73,74] Currently, these types of solutions are most often used in clinical trials investigating central nervous system disorders, metabolic, endocrine, autoimmune, and inflammatory conditions,[87] as well as infectious diseases.[44] In December 2022, the EMA issued recommendations on DCTs,[75] and the FDA is currently working on theirs.[82]

The use of **artificial intelligence and machine learning** is growing in research design (e.g. to select the most optimal endpoints), recruitment (e.g. to identify sites and strategies), and analysis, as well as in supporting the diagnostic process, generating evidence from real-world practice, and performing predictive analysis.[76,44]

Drug developers consider new technologies (including mRNA and drug discovery platforms) as one of the greatest opportunities in clinical research. According to the survey, the leading therapeutic area is haematology/oncology (59%), followed by rare diseases (39%) and immunology/rheumatology (38%). These areas are focused on cell, gene and nucleic acid therapies and more advancements are to be expected in these methods.[84]

7.3 Factors determining clinical research in individual medical fields — the need to stimulate the European clinical research ecosystem

In recent years, there have been fewer and fewer clinical trials conducted in Europe. The reasons behind it may include an insufficient pool of eligible patients, a long approval process for medical technologies, the attractiveness of other regions, and high costs. Despite many emerging initiatives, implementation of digital health technologies progresses more slowly in Europe compared to other regions, such as the United States, which causes the Old Continent to lag behind in attracting clinical research. The most important factors accelerating the development of clinical trials on new ATMPs or digital technologies are pricing and market access policies, the location of major hospitals and specialists, and a flexible regulatory environment.[77]

The key drivers of the growth of the clinical research market are the adaptation of new technologies in clinical trials, the increasing incidence of chronic diseases, and the demand from developing countries.[78] This market is also stimulated by the increasing rates of new diseases. There is growing interest in combined and collaborative trials, which will further strengthen the global clinical trials market.[76]

Patient recruitment, including patient retention and patient diversity, is of greatest concern for the biotechnology and biopharmaceutical industry. Meanwhile, the development of more targeted therapies is associated with increasing complexity of trial designs, regulatory obstacles,[84] and the challenges of data management and access to appropriate infrastructure.[79]

7.4 Summary and implementation takeaways

The clinical trials market is dominated by interventional trials (mainly on conventional and biological medicinal products) focusing on oncology, especially rare indications. Research is also intensifying in the fields of infectious diseases and psychiatry. Clinical trials are increasingly taking advantage of

modern patient-oriented designs (e.g., phase 0, umbrella, basket, N-of-1, master protocol, adaptive protocol), and decentralised and digitised solutions. The conclusions of this chapter give grounds for supporting the following key areas:

Development of non-commercial clinical trials — favouring: the therapeutic areas of oncology, immunology, infectious diseases, and psychiatry; clinical endpoints of overall survival, quality of life; underrepresented study populations such as the elderly, pregnant and breastfeeding women; decentralisation and digitisation solutions such as wearables, e-diaries, home visits, home drug deliveries.

Development of non-commercial clinical trials on cancers — favouring: studies on rare cancers; clinical endpoints of overall survival, quality of life; underrepresented study populations such as the elderly, diverse ethnicities; application of new research designs such as umbrella or basket designs.

Development of epidemiological research — favouring research on underrepresented populations: pregnant women, breastfeeding women, the elderly, ethnically diverse populations; using new technologies for data collection (e.g., wearables) and analysis (e.g., artificial intelligence, machine learning).

Advancement of translational medicine — using new technologies to analyse data (e.g. artificial intelligence, machine learning).

Expansion of production capacity for advanced therapy medicinal products (ATMP) — support in the therapeutic areas of haematology, oncology, rare diseases, immunology.

8. Summary and exploratory diagnosis for future MRA Agendas

In Poland, **cardiovascular diseases and cancers** have consistently been the greatest challenges for the healthcare system for many years. The changes in the demographic structure will bring a significant increase in the incidence rates of **chronic diseases** in the 65+ age group. The growing incidence of chronic diseases will translate into increasing rates of multimorbidity. In addition to cardiovascular diseases and cancers, also on the rise are **metabolic diseases, respiratory diseases, and central nervous system disorders** (neurodegenerative and psychiatric conditions), which is a consequence of both the COVID-19 pandemic and the impact of environmental factors.

The dangers of **multimorbidity in an ageing population** call for more epidemiological research into the relationship between **behavioural and metabolic risk factors** and the development of **cardiovascular and oncological diseases**. Identifying the most important epidemiological threats and the needs of the Polish population will allow for more effective distribution of the limited resources or planning ahead in terms of resource structure.

All these contributors: the ageing of the population, the effects of the pandemic, and the environmental factors, are major challenges to the key areas of **prevention, diagnostics and effective treatment**. From the point of view of the Polish healthcare system, a fundamental measure for a healthy society is an effective response to all of the above-mentioned challenges.

Diagnostics based on **advanced molecular and imaging analysis, supported by AI algorithms** to provide **personalised therapy**, will be the key to faster and comprehensive resolution of health issues and will be of strategic importance for accurate diagnosis, selection of therapy and optimisation of treatment and hospitalization time. Due to the very rapid development of medical technologies and the ever-growing volumes of medical data, we need to support the **responsible use of AI in the healthcare system**, both in epidemiological research and in improving the entire diagnostic and therapeutic process.

Increased efficiency of **diagnostic systems combined with education** aimed at encouraging the public to **actively participate in prevention programmes** has a chance to accelerate the patient journey towards treatment. **Accurate and fast diagnostics** means not only well-established **biomarkers** but also efficient and accurate devices for **outpatient or home testing** offering high precision of measurement even from a small volume of the tested material. Supporting the implementation of **innovative medical devices** that incorporate **nanotechnologies and microsystems**, including high-throughput screening tests, seems to be a key aspect that defines the **personalised therapeutic journey**.

Putting the patient on a well-defined healthcare path is of key importance in increasing the effectiveness of the diagnostic and therapeutic process. This path should be defined for individual areas, and the patient, regardless of their disease, should be under continuous care every step of the way. Establishing a **clear patient path** requires organisational and systemic changes to significantly reduce the time between **initial diagnosis** and initiation of **effective therapy**. In defining optimal patient management, attention should also be paid to **fostering communication and understanding between the doctor and the patient**.

Extremely important for the development of biomedical innovation are: **interdisciplinary collaboration** (of scientists, clinicians, patients, biotech and pharma businesses) to ensure new technologies are adapted to the actual patient needs; **specialist knowledge**, including technical and regulatory know-how; and **effective information flows** within the innovation ecosystem. The development of **translational medicine**, whose aim is to directly translate scientific discoveries made in the laboratory into practical clinical applications that will benefit patient health, in addition to financial and organisational support, will also require promoting **education** and **building clinical, business and regulatory competence**, and consequently, **sharing knowledge** in these areas among **experienced scientists, business representatives, as well as PhD students and undergraduates majoring in biomedical sciences**.

With the **ageing society**, the healthcare system will become increasingly dependent on stable access to medications, active substances and pharmaceutical raw materials. It will be necessary to **expand the domestic production capacity of selected APIs**, especially those of key importance for the elderly. Defining these APIs for the purposes of future annual Agendas will be the subject of a **separate Report of the MRA's Science Department**.

A country's drug security is not only dependent on the growth of domestic active substance production capacities. The **development of generics and biosimilars** is also an important factor ensuring the **availability and stable pricing of medication**, which is particularly important in view of the high potential of the Polish drug market and the domestic biopharmaceutical sector.

The growing need for new **personalised treatment options** in oncology, rare diseases, targeted treatment of depression and advanced antimicrobial treatments is **driving the progress of advanced therapy medicinal products**. To take full advantage of the domestic capabilities, it would be advisable to provide infrastructural support aimed at building new and **adapting the existing ATMP manufacturing facilities in Poland**, with a particular focus on blood cell therapies and personalised cancer treatments based on nucleic acids.

In addition to medicinal products, an extremely important element of therapeutic processes are **new generation surgical techniques and systems** which significantly reduce the invasiveness of interventions, ensuring faster recovery. The speed of recovery also depends on appropriately selected **innovative rehabilitation solutions**, for example biomaterials.

The arguments and conclusions presented above will be used as a foundation for proposing key areas to be addressed in **future annual Agendas of the Agency** for the coming years and **subsequent periodic updates of the Exploratory Report**. The table below contains a summary of these **key areas divided into major non-commercial, commercial and strategic areas,** listing preferred elements as well as source and reference documentation.

KEY NON-COMMERCIAL AREAS			
1.	**Development of non-commercial clinical trials and research experiments with particular emphasis on cardiovascular diseases** **Objectives and targets:** • Continued advancement of non-commercial clinical trials and research experiments in all research areas, with particular emphasis on cardiovascular diseases • Requiring a detailed plan for clinical trial promotion, patient recruitment support and patient education as part of cardiovascular research	**Preferred items:** • Cardiology and cardiovascular diseases • Infectious diseases • Autoimmune diseases • Neurology and psychiatry — especially anti-depressant therapies • Application of digitisation and decentralisation solutions • Head-to-head comparative studies • Application of theranostic solutions • Targetting priority populations — children, the elderly, pregnant and breastfeeding women. • Early diagnosis and prevention • Advanced clinical trial protocols — umbrella, basket and platform trials, and combinations thereof • Application of digital medicine solutions — AI algorithms, telemedicine, RWE/RWD-based analysis • A detailed plan for the promotion of clinical trials and building patient awareness — a necessary criterion for cardiology projects • Quality of life assessment as a primary endpoint	**Source documents:** Clinical Research Development Plan Exploratory Report ○ Chapter 2 ○ Chapter 3 ○ Chapter 4 ○ Chapter 7
2.	**Development of non-commercial clinical trials on cancers** **Objectives and targets:**	**Preferred items:** • Lung, breast, prostate, colorectal, and uterine cancers • Rare cancers • Paediatric population	**Source documents:** Clinical Research Development Plan

	• Development of non-commercial clinical trials focused on new cancer therapies and diagnostics • Promoting modern research protocols which address a wide range of indications rather than one — in view of the presence of several high-risk types of cancer in the Polish population, as well as the fragmentation of other oncological risks	• Additional support for patients using digital solutions, with particular emphasis on telemedicine and digital therapies, e.g. compliance analysis or psychological support • Advanced clinical trial protocols — umbrella, basket and platform trials, and combinations thereof • Targeted treatments (with well-defined molecular targets) and personalised therapies (molecular profiling/stratification of patients) • Advanced treatments/diagnostics for more than one oncological indication • Innovative diagnostic and therapeutic methods with particular emphasis on theranostics • Overall survival or quality of life as primary endpoints	Exploratory Report ○ Chapter 2 ○ Chapter 4 ○ Chapter 7

3.	**Development of epidemiological research, especially to address cardiovascular, oncological, psychological and neurological risks** **Objectives and targets:** Development of high-quality epidemiological research, with particular emphasis on: • studying the relationship between behavioural and metabolic risk factors and their impact on cardiovascular and oncological risks, especially on lung, breast and prostate cancers, as well as ischaemic heart disease, stroke, cardiomyopathy, and myocarditis. • assessing risk factors (e.g. behavioural, environmental, emerging) associated with the emergence and prevalence of neurological diseases and mental disorders, in particular neurodegenerative, age-related, and neurodevelopmental conditions.	**Preferred items:** • Cardiovascular diseases • Cancers • Paediatric diseases, especially cancers and neonatal conditions • Autoimmune diseases • Neurological and mental disorders, with particular emphasis on neurodegenerative and age-related diseases • Targetting specific patient populations — children, pregnant or breastfeeding women, the elderly • Digital medicine solutions — omics, AI algorithms, and telemedicine solutions, especially for testing the effectiveness of patient and doctor reward systems as part of early diagnosis and prevention	**Source documents:** Epidemiological Research Development Plan Exploratory Report ○ Chapter 2 ○ Chapter 3 ○ Chapter 4 ○ Chapter 6 ○ Chapter 7

4.	**<u>Advancement of translational medicine and support of the dialogue and colalboration between the academia and business community</u>** **<u>Objectives and targets:</u>** • Creation of the TransMED platform along with an acceleration programme for potential beneficiaries (pre-TransMED) • Performing and developing non-commercial fundamental application and preclinical research in the field of translational medicine to establish innovative biomarkers, *in vitro* diagnostics and medical device solutions to be potentially funded as part of TransMED SEED calls • Detailed verification of project objectives in the four pillars of innovation: technological, clinical, business, and regulatory, at each of the required TRL levels and their components. • Iterative verification of projects during their lifetime with the potential for adapting the approach • Continued funding of innovation as part of future commercial TransMED SPIN calls • Creation of a comprehensive training programme on innovations for PhD students and undergraduates as part of the TransMED platform	**<u>Preferred items:</u>** • Cardiovascular diseases, cancers, rare and ultra-rare diseases, neurological and psychiatric conditions, eye disorders • Targetting priority populations — children, the elderly, pregnant and breastfeeding women • Innovative paths of personalisation in medicine • Digital medicine solutions, including telemedicine, multi-omics, RWE/RWD analysis, AI algorithms • Involving patients and patient associations to develop technologies best suited to their needs • Reward systems for patients and doctors as part of developing solutions for early diagnosis and prevention	**<u>Source documents:</u>** Translational Medicine Development Plan Medical Research Agency's Educational Strategy Exploratory Report ○ Chapter 4 ○ Chapter 6 ○ Chapter 7

5.	**<u>Development of Clinical Trials Support Centres as regards advanced diagnostics and prevention</u>** **<u>Objectives and targets:</u>** • Building competence at Clinical Trials Support Centres in advancing early diagnosis and prevention technologies, with particular emphasis on conditions with non-specific clinical symptoms or rare diseases. • Supporting clinical trials and digital medical solutions, especially in priority populations	**<u>Preferred items:</u>** • Application of biomarkers for diagnostic and prognostic purposes • Reward systems for patients and doctors as part of developing solutions for early diagnosis and prevention	**<u>Source documents:</u>** Clinical Research Development Plan Exploratory Report ○ Chapter 3 ○ Chapter 6 ○ Chapter 7

6.	**Expansion of production capacity for advanced therapy medicinal products (ATMP)** **Objectives and targets:** • Continued growth of capacities for targeted and personalised medicine in Poland • Expansion and adaptation of the existing ATMP manufacturing infrastructure to cater for specific advanced therapy medicinal products — both CAR and other cell therapy products • Continued growth of domestic capabilities in RNA technology, with particular emphasis on personalised anticancer therapies	**Preferred items:** • Haematology and oncology • Rare and ultra-rare diseases • Autoimmune diseases • Neurological diseases	**Source documents:** Plan for the Development of the Biomedical Sector Exploratory Report ○ Chapter 4 ○ Chapter 6 ○ Chapter 7
7.	**Expansion of production capacity for active pharmaceutical ingredients (APIs)** **Objectives and targets:** • Expansion and maintenance of Poland's existing API production capacity • Development of new antimicrobial options, particularly antibiotics • Development of personalised therapies for rare diseases, neurological diseases (dementia, Alzheimer's, Parkinson's) and targeted treatment of depression	**Preferred items:** • Rare diseases • Neurological diseases (dementia, Alzheimer's, Parkinson's) • Oncology • Immunology	**Source documents:** Plan for the Development of the Biomedical Sector Exploratory Report ○ Chapter 2 ○ Chapter 3 ○ Chapter 4

8.	**Building public and expert awareness of the risks of cardiovascular diseases and the associated behavioural or metabolic risk factors** **Objectives and targets:** • Development of a training programme for practitioners as well as social and educational campaigns for the public focused on prevention and building awareness of cardiovascular diseases • Development of methods to increase awareness and effectively manage risk factors, with particular attention to behavioural and metabolic ones • Promoting personalised therapeutic, diagnostic and preventive modalities among clinicians and patients	**Preferred items:** • Remote interactive educational activities • Selective targeting of critical groups, including the elderly, people at high risk of developing cardiovascular diseases • Using digital medicine, especially telemedicine, to build awareness and prevent cardiovascular diseases • Elements of narrative medicine focusing on the relationship between the patient, doctor, and healthcare system • Consideration of reward systems for patients and doctors as part of early diagnosis and prevention	**Source documents:** Medical Research Agency's Educational Strategy Exploratory Report 2023 ○ Chapter 2 ○ Chapter 3

9.	**Defining a clear patient diagnostics path** **Objectives and targets:** • Creating an algorithm for an uninterrupted diagnostic path from first consultation to final diagnosis without the patient being lost to the healthcare system after a number of separate consultations with different specialists • Automatic access to comprehensive information on one's health, test results and therapies used (consultation = access to IKP) • Early final diagnosis means less aggressive treatment and savings for the system (less advanced disease process, less aggressive = cheaper therapy, fewer side effects; misdiagnosis = ineffective treatment) • Interdisciplinary consulting teams (also online) to be involved in diagnostics at the level of primary care, OHC, and inpatient care	**Preferred items:** • Interdisciplinary team of clinicians and diagnosticians • Interconnection of various medical data systems with P1/IKP — insight into all procedures for a given individual • Collaboration with the NFZ, MoH, and the AOTMiT • Collaboration with patient associations, especially in the area of rare diseases	**Source documents:** Epidemiological Research Development Plan Exploratory Report 2023 ○ Chapter 3

KEY COMMERCIAL AREAS			
1.	**Expansion of production capacity for generics and biosimilars** **Objectives and targets:** • Creation and development of innovative solutions in the area of new pharmaceutical forms and active substances of authorised medicinal products (generic drugs) and biosimilars	**Preferred items:** • Immunology • Personalisation of treatment • Patient-friendly solutions, e.g. new administration modes, sustained release forms • Environmentally-friendly solutions, e.g. biodegradable packaging • Generic or biosimilar medicines in key therapeutic areas: oncology, cardiology, rare diseases, autoimmune, neurological, or psychiatric diseases	**Source documents:** Plan for the Development of the Biomedical Sector Exploratory Report 2023 ○ Chapter 4 ○ Chapter 5

2.	**Expansion of production capacity for digital medicine** **Objectives and targets:** • Development of digital diagnostics, digital therapies and telemedicine • Reducing waiting times and optimising costs (fewer 'empty' consultations just to get a referral, transferring some patients to the outpatient setting without compromising on quality) • More data collected about an individual patient in various clinical situations	**Preferred items:** • Data format compliant with the CMC Network Standard • Collaboration with OHC and primary healthcare facilities, as well as hospitals as part of product development • Validation of solutions in a public clinical environment • Key therapeutic areas — oncology, cardiology, rare diseases, autoimmune, neurological, or psychiatric diseases	**Source documents:** Plan for the Development of the Biomedical Sector Exploratory Report 2023 ○ Chapter 1 ○ Chapter 5 ○ Chapter 6 ○ Chapter 7

KEY STRATEGIC AREAS			
1.	**Creation of the Digital Medicine Development Plan** **Objectives and targets:** • A detailed plan for the development of the RDMC network under the supervision of the MRA's Digital Medicine Head Office and the Central Repository of Omic Data, which will drive the implementation of evidence-based personalised medicine, with particular emphasis on multi-omic data • Building an economy based on medical data at the level of public-private partnerships and EU legislation • International collaboration with other sites engaged in projects based on medical data analysis, with particular emphasis on multi-omic data.	**Preferred items:** • Personalisation of therapy (adapting treatment to individual genetic profiles, targeting specific molecular targets) • Optimisation of the diagnostic and therapeutic process • Streamlining preventive, diagnostic and therapeutic processes • Predictions of treatment response • Prevention programmes • Screening programmes	**Source documents:** Exploratory Report ○ Chapter 5 ○ Chapter 6 ○ Chapter 7 **Related documents:** ○ Translational Medicine Development Plan ○ Plan for the Development of the Biomedical Sector ○ Educational Strategy ○ Programme for e-health development in Poland for the years 2022–2027 ○ Mobile technologies in modern Poland — responsible development and equal opportunities, report ○ Patient in the digital world, or how new technologies are changing the medical services market in Central and Eastern Europe, report