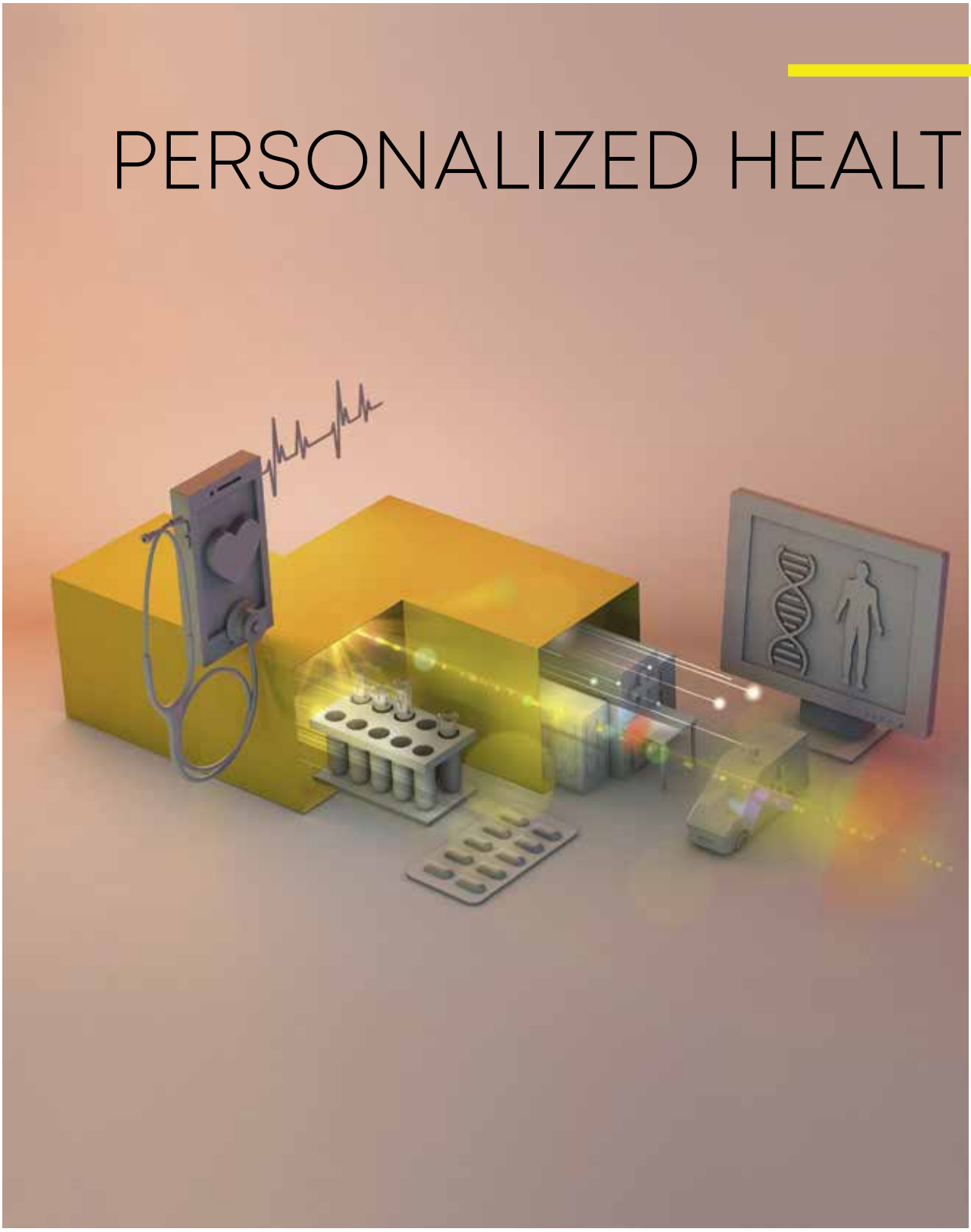
BRTA
BASQUE RESEARCH
& TECHNOLOGY
ALLIANCE

PERSONALIZED HEALTH



THE BRTA RESEARCH AGENDA

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CON-TENTS

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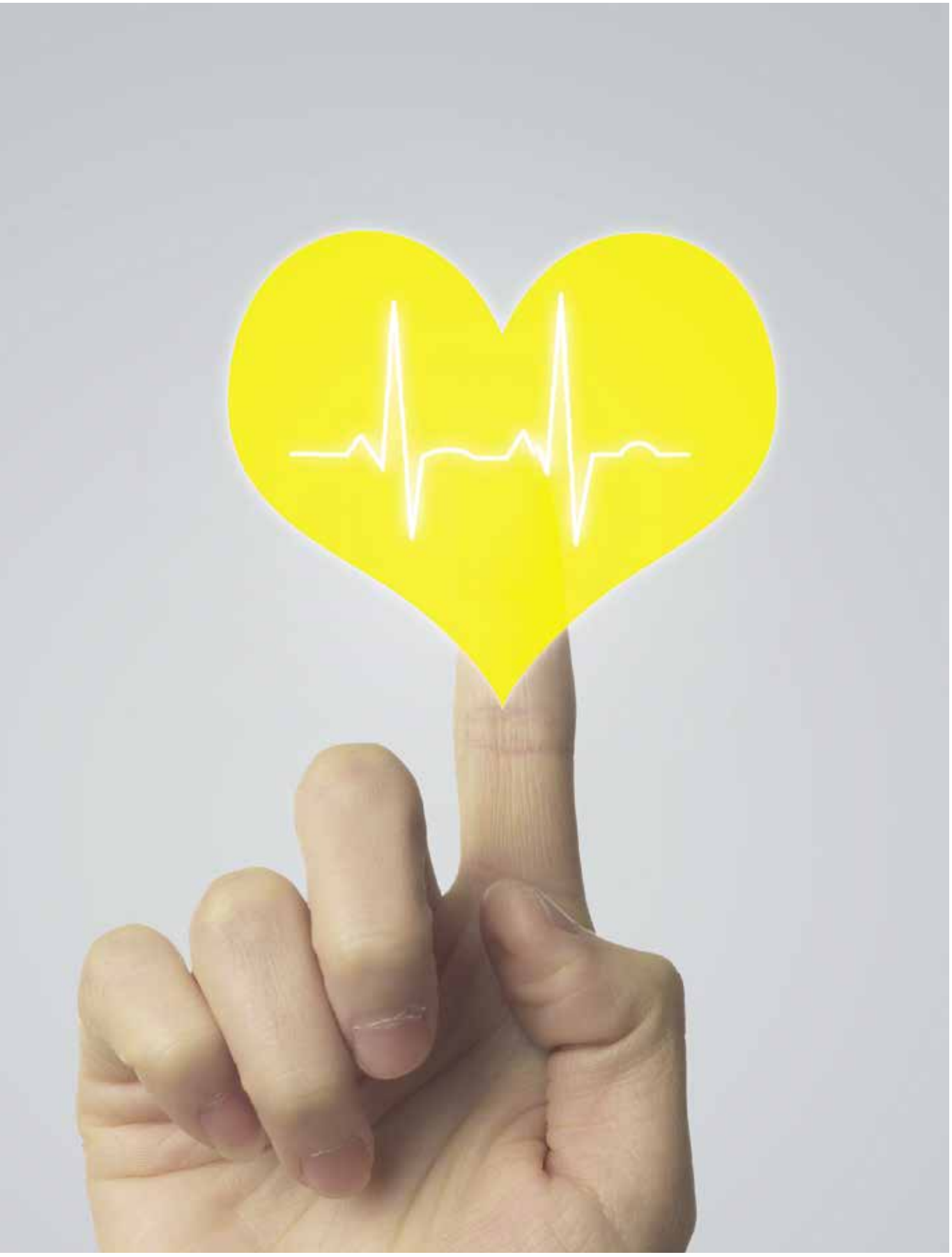
01

INTRODUCTION



HEALTHY
NUTRITION

01
INTRODUCTION

Personalized health may be defined as a focus aiming to maximize effectiveness in preventing and treating disease, by taking into account individual variability in terms of genes, environment and lifestyle.

Personalized health may be defined as a focus aiming to maximize effectiveness in preventing and treating disease, by taking into account individual variability in terms of genes, environment and lifestyle. Efforts are made to achieve and use the results drawn from measuring specific parameters connected with health, with the start and progression of the disease, and with the response to treatment. The aim is to ascertain the molecular, environmental, behavioural and any other factors contributing to health and the disease itself. This is destined to result in much more precise diagnoses, to design rational prevention strategies, appropriately select treatments, and develop novel therapies.

The success of a personalized health initiative is achieved by combining scientific and technological advances in different spheres of the life sciences and data science, with a change in the culture of clinical practice and health research. It is furthermore vital to involve people as active participants, and not just as research subjects or patients.

SAMPLES	DATA AND PARAMETERS	RESULTS
URINE	GENOMIC PROTEOMICS	**MATHEMATICS** Identification of random prediction patterns.
SERUM	METABOLOMIC MICROBIOTA	**BIOLOGY** Validation of diagnostic, prognostic and treatment models.
SALIVA	BIOCHEMISTRY	**BIOINFORMATICS** Identification of new biomarkers.
FAECES	LIFESTYLE	

PERSONALIZED HEALTH

01 INTRODUCTION

Precision medicine will serve to identify new predictive biomarkers, and to develop and validate non-invasive diagnostic tools.

Particular mention should be made of the digital aspect. Despite the efforts seen over recent years, the implementation of digitalization in the health sector is a process with its own difficulties, and where progress is slow. Unfortunately, some of the shortcomings in the digital transformation of healthcare systems became apparent during the Covid-19 crisis: lack of interoperability standards, lack of communication and of a clinical history shared by the healthcare system and the social healthcare side, lack of efficient tools for remote consultation and monitoring, lack of appropriate tools for data exploitation and epidemiology, etc. The shortcomings detected here must serve as the catalyst to achieve the required momentum, leading to a genuine digital transformation of the sector. This transformation involves not only transforming data into a standardized digital format, or including purely digital devices, but a profound transformation enabled by digitalization, including the transformation of clinical and management processes and digital skills training for staff. It would likewise seem clear that we need, directly or indirectly, to recruit staff with a range of profiles, such as biomedical engineers, scientists, data managers, analysts and experts in healthcare organization, in artificial intelligence, knowledge modelling or bioinformatics, evaluation of healthcare technologies, experts in data protection and security, etc.

From diagnosis to treatment.

In short, it is now clear that the combination of methods, techniques and protocols drawn from different spheres will allow precision medicine to identify new predictive biomarkers, and to develop and validate non-invasive diagnostic tools. This opens the way to the development of new therapies, and directed therapies capable of effectively treating disease, reducing side-effects, and identifying patients at stages when the treatments will be effective. One booming area is the development of advanced therapies, including such aspects as gene therapies, cell therapies, tissue engineering and digital therapies. The first pharmaceuticals are in fact already being brought to market. Nonetheless, there is a very broad window of opportunity in various spheres, despite the huge competition (immunotherapy, gene therapy, regenerative medicine). The challenge is to identify new targets, to develop new, effective drugs (Active Pharmaceutical Ingredients, or APIs) and to scale up and industrialise these processes, while also taking into account regulatory aspects.

In the case of regenerative medicine, one major challenge is to have appropriate cellular scaffolding in place, which can be printable, or which will activate the internal regeneration of the tissue to be treated.

Another increasingly significant aspect is the study of the microbiome and its role in different pathologies. We could cite one nearby example developed in the Basque Country by the company Mikrobiomik, which is undertaking clinical trials on treatments with donors' faecal microbiota.

02

TRENDS

Current trends focus on integrating diagnostic information, detecting processes or information at the molecular level, linked to directed therapies.

PERSONALIZED HEALTH

02 TRENDS

Scientific research and omic techniques.

Scientific disciplines play a fundamental role here, such as genomics and the other 'omic' disciplines (transcriptomics, metabolomics, proteomics, epigenomics...).

Over recent years, metabolomics has been successfully narrowing a major gap in the post-genome era. Determining the flow of information from the genome to the transcriptome, proteome, and ultimately metabolome is for the first time granting us access to a complete description of living systems. However, to establish models and datasets to achieve the precise prediction of the physiological properties of cells, it is essential to progress in the development and application of different high-performance technologies to metabolic studies. The next logical step is to link data from the metabolites found with the metabolic flows and gene regulation, thereby covering the whole dynamic of living systems. Aside from these advances, the combination of data from mass spectrometry and ultra high field nuclear magnetic resonance is allowing remarkable progress in the search for new biomarkers to detect diseases or to monitor pharmacological intervention.

The current trend is based on the combination of omic data, serving to determine risk factors (pathological molecular variants) and/or to observe and quantify characteristic molecules of a disease in high resolution, known as biomarkers. The identification of these biomarkers is based on studying biological mechanisms, identifying maps or networks of

The current trend is based on the combination of omic data, serving to determine risk factors (pathological molecular variants) and/or to observe and quantify characteristic molecules of a disease with high resolution, known as biomarkers.

overall interactions, whether genetic, metabolic or proteomic, and identifying genes, metabolites or proteins associated with diseases.

This diagnostic and phenotypic information is supplemented by such other sources of information as diagnostic medical imaging, which is increasingly precise and capable of observing pathological processes and phenotypes in ever greater detail, clinical information held in an electronic clinical history, and information regarding lifestyle and exposure, which shape health to a great extent. Ultimately, precision medicine aims to determine the specificity of an individual, in accordance with their particular, defining phenotype and genotype based on lifestyle and exposure, so as to apply the best possible therapy from among those already in existence, or even at its greatest extent, to design a specific therapy. Given the level of data processing and computational modelling required, information and communication technologies prove essential for the complete development of precision medicine, and in this sense represent an evolution of digital health systems towards a new medical paradigm.

So far this century have seen the development of numerous successful international initiatives in Precision Medicine, which show the way forward. Various states have gathered highly extensive national cohorts of data with the aim of determining the factors shaping health and disease, establishing links between genotype, phenotype, lifestyle and exposure. Mention may be made of such initiatives as the UK Biobank, the US programmes *All of Us and Million Veteran* and the Finnish programme *FinnGen*, along with the incipient European initiative *One Million Genomes* (https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes). Data have thus been built up from huge populations, including genomic

information, biochemical and lifestyle data. In many cases, longitudinal monitoring of health outcomes has also been conducted over time.

The latest market trends tell us that society is increasingly aware of the importance of adopting healthy lifestyles, which include appropriate nutrition, physical exercise, good sleep hygiene, etc. These are non-omic data which nonetheless need to be linked up with the omic data described previously to generate digital or non-digital solutions capable of steering people towards healthy habits in terms of both the prevention and the treatment of disease. For example, *the trend towards healthier diet includes challenges such as progress towards personalized nutrition for active ageing or the development of ingredients in foods with nutritional and healthy properties, among others.*

Looking to the future, we see a vibrant horizon. Sources of information will be increasingly diverse, richer and more penetrating, raising the prospect of a Big Data horizon in precision medicine. Trends are focusing on the implementation of increasingly complex body sensors, implantable intra-corporeal devices, and multi-diagnostic systems integrating supplementary information of different kinds, using artificial intelligence approaches

The success of AI lies to a great extent in its capacity to model processes with multiple variables, learning from a large quantity of data, without too many prior hypotheses, and in general with fewer biases.

capable of learning from data and developing complex models based on diverse and complex information at the population level.

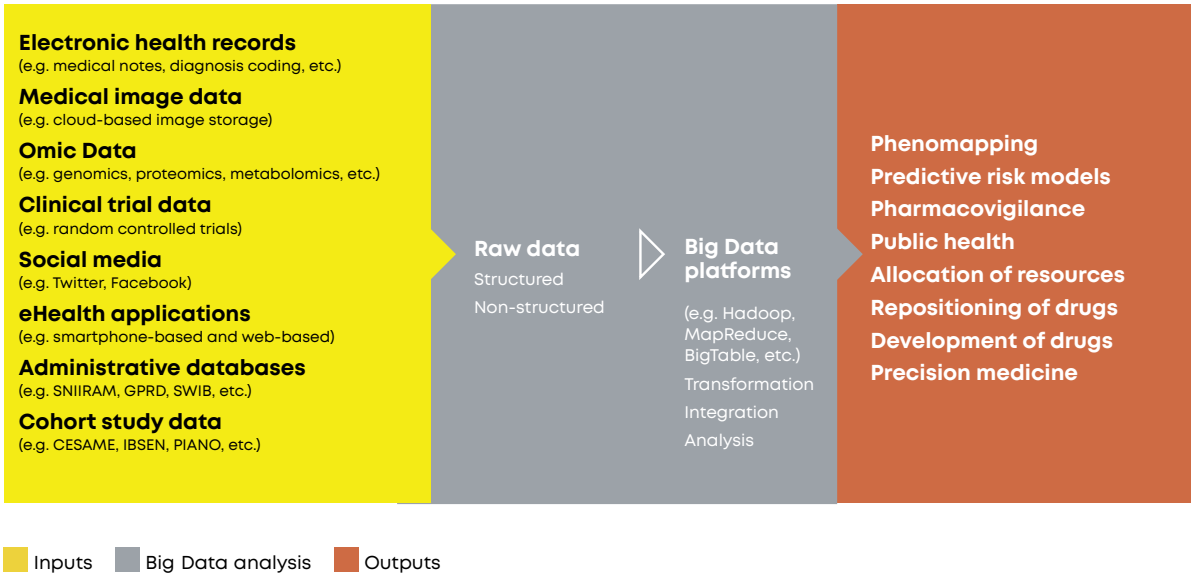
The digitalization of the health sector began through the computerization of certain services, such as the gradual transition towards generating electronic clinical histories, or the development of medical devices directly generating digital data as an output.

However, digitalization has moved more slowly in the health sector than in other sectors.

Meanwhile, artificial intelligence (AI) is one of the main drivers for the development of specialized digital health applications.

The success of AI is to a great extent rooted in its capacity to model processes with multiple variables, learning from a large quantity of data without too many prior hypotheses, and in general with fewer biases (provided that this is not incurred during the modelling and case selection process itself).

Current trends include the mass exploitation of electronic clinical histories and data from other sources which have built up information over years, allowing us to observe disease processes or pathways that evolve over the long term, with implications for prevention and prognosis.



PERSONALIZED HEALTH

02 TRENDS

AI is a fundamental component in digital diagnosis systems.

Mobility technologies.

Unfortunately, some apps are still not particularly rigorous, and so are inappropriate for use in clinical contexts. They nonetheless have huge potential, in particular when supported by criteria of scientific evidence, raising the need to amend the European regulatory framework in line with this new reality. This will mean many apps for medical use having to undergo clinical validation. The trend in this regard is to allow the validation of such applications to be performed in terms of efficacy and safety, and they in themselves represent authentic digital therapies, with the possibility of being prescribed if they demonstrate that they are beneficial and safe for use in healthcare.

The solutions currently being developed at the BRTA aim to incorporate a recommendations system based on the very latest AI, focused on giving patients a more prominent role in the self-management of the disease, thereby further improving their adherence to the treatment. The visible face of such AI normally takes the form of a virtual assistant, serving as a personal trainer. They are highly complex to develop, since they must take into account clinical data, information received in real time (symptoms, physiological signs...), the care or therapy plan, personal preferences and computational models trained with information from hundreds or thousands of other patients, to generate a dynamic and adaptive assistant capable of advising, encouraging or alerting health professionals when necessary.

Artificial intelligence (AI).

AI is a fundamental component in digital diagnosis systems. In accordance with approaches based on data from other patients, it is capable of learning from them, and issuing a diagnosis on the basis of what it has learned from information drawn from many other cases.

AI represents a paradigm shift in the field of health, driven by the huge availability of medical data and rapid progress in analytical techniques, with great potential to achieve better disease prevention, diagnosis and treatment.

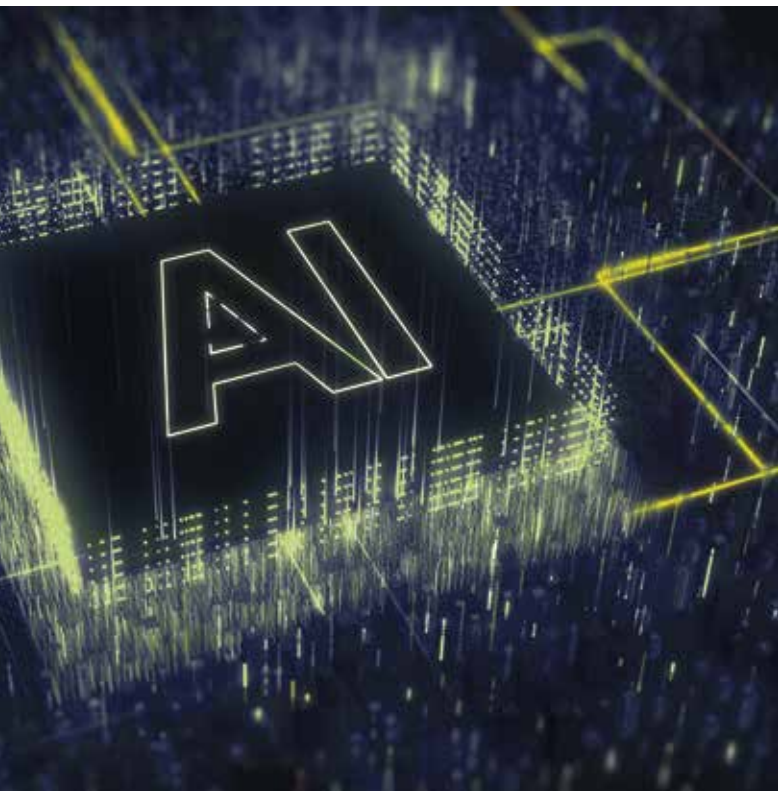
Examples of AI applications throughout human life

— Embryo selection for IVF (In Vitro Fertilization)

— Interpretation of the genome of sick newborn babies

— Medical assistant via a smart speaker (like Alexa)

Source: Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nature Med. 2019; 25(1), 44-56.



The following table shows some of the medical disciplines where AI has already been incorporated.

Artificial intelligence

- Cardiology (fibrillation, cardiovascular risk)
- Pulmonary medicine
- Endocrinology
- Nephrology
- Gastroenterology
- Neurology (epilepsy, Parkinson's)

Medical imaging

- Radiology
- Pathologies
- Dermatology
- Ophthalmology (diabetic retinopathy, macular degeneration)
- Cancer (computational diagnosis)

1. Topol E. Deep medicine: how artificial intelligence can make healthcare human again. Hachette UK; 2019 Mar 12.
2. Briganti G, Le Moine O. Artificial intelligence in medicine: today and tomorrow.
Frontiers in medicine. 2020 Feb 5;7:27.

Advanced Therapies.

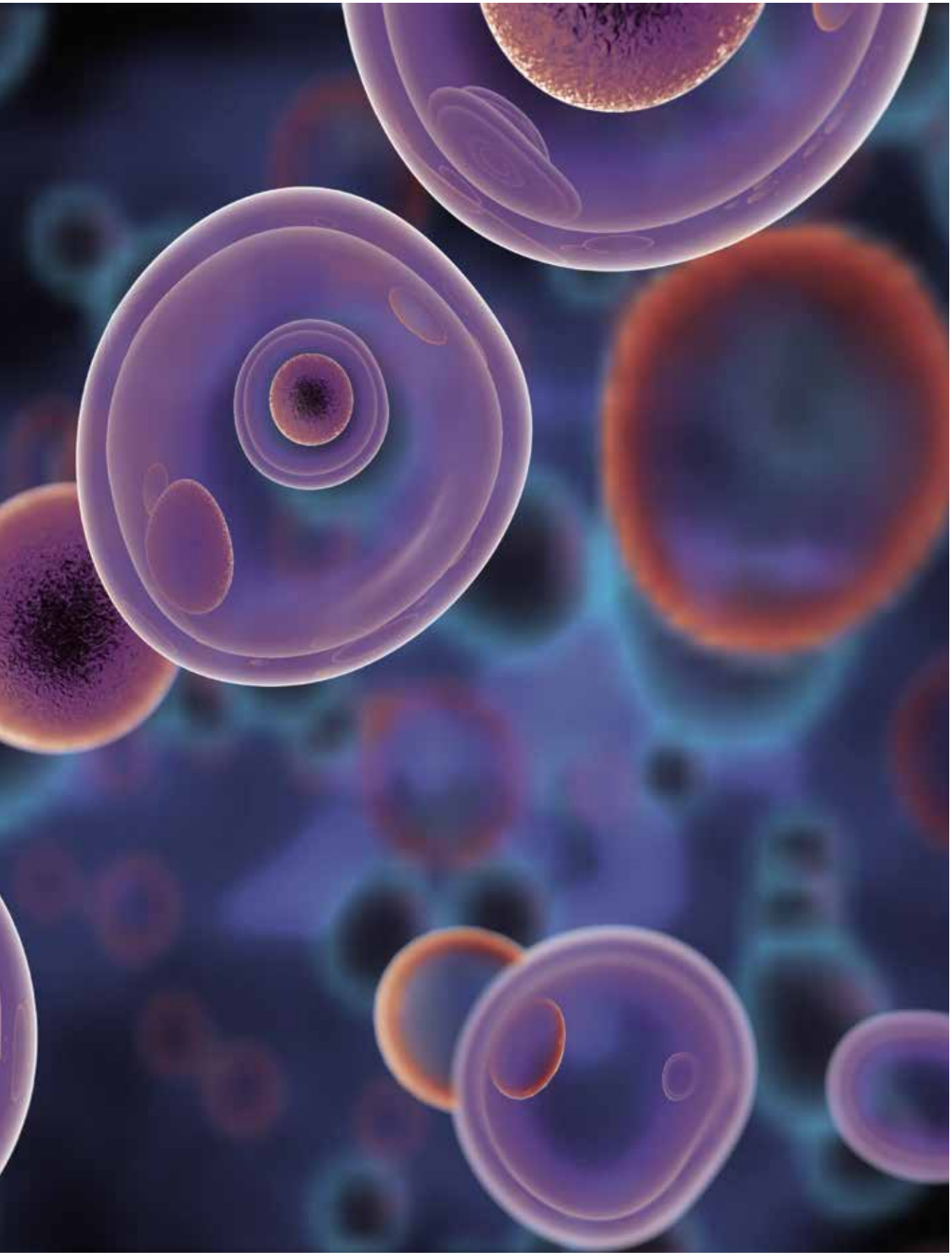
Advanced therapies refer to innovative medication based on the use of cells (cellular therapy), tissues (tissue engineering) or genes (gene therapy) to treat a range of conditions. Within our context, they have very considerable potential to implement personalized treatments. In fact, as new therapeutic strategies, they are revolutionizing medicine, being used to treat diseases for which no other effective treatments exist. One recent report is available via this link:

(https://www.institutoroche.es/static/archivos/Informes_anticipando_2020 TERAPIAS_AVANZADAS_RGB.pdf)

The current trend is to combine different advanced therapies in pursuit of synergy to develop personalized and effective treatments. One could here make mention of the use of "CAR-T cells" to treat cancer, which involves genetically modifying the patient's defence cells so they can more effectively combat tumour cells.

Another transformative scientific-technical advance still at the experimental stage is arising from gene editing, which has extraordinary potential for the medicine of the future. Unlike gene therapy, gene editing allows us directly to alter the target genes in the patient's genome. Other new technologies like nanotechnology have also recently emerged as Key Enabling Technologies (KET) for the development of advanced therapies. Nanomedicine is in this regard a translational science with the main goal of providing new therapies by using the enabling capacity of nanotechnology applied to medicine. Without aiming to set out a fully comprehensive list, we offer a brief description of some characteristics of these advanced therapies.

The current trend is to combine different advanced therapies in pursuit of synergy to develop personalized and effective treatments.

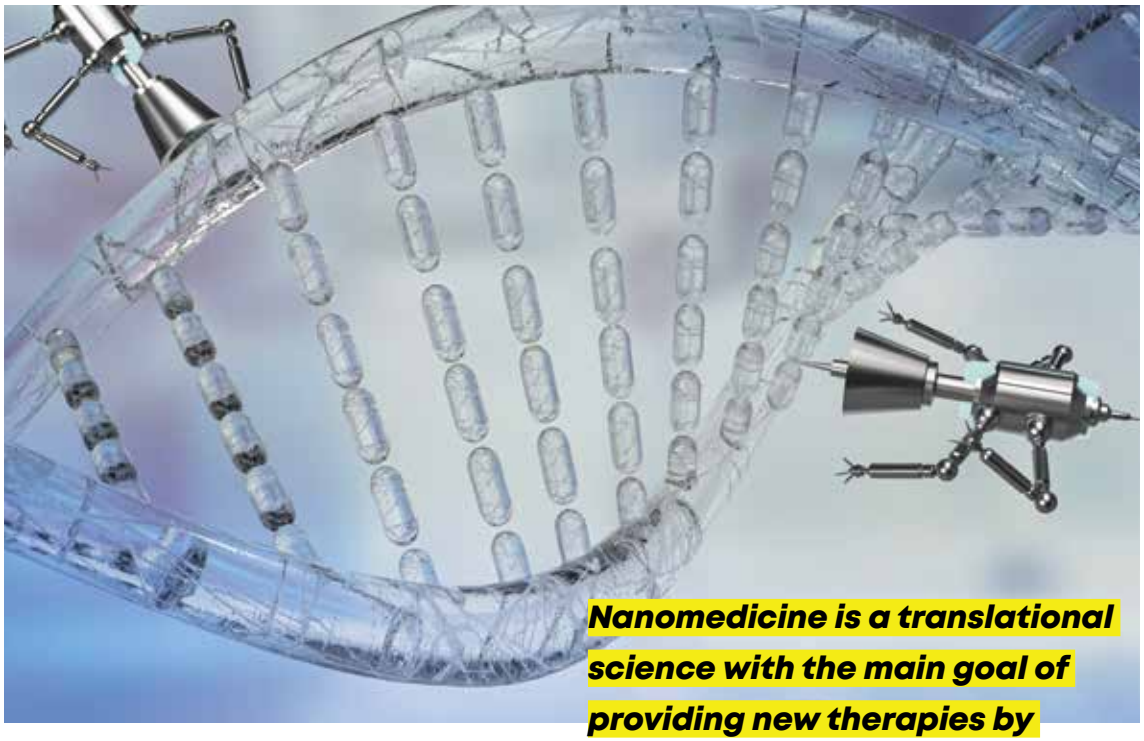


PERSONALIZED HEALTH

02 TRENDS

BIG DATA

The term 5P Medicine refers to the crossover between Health and Big Data.



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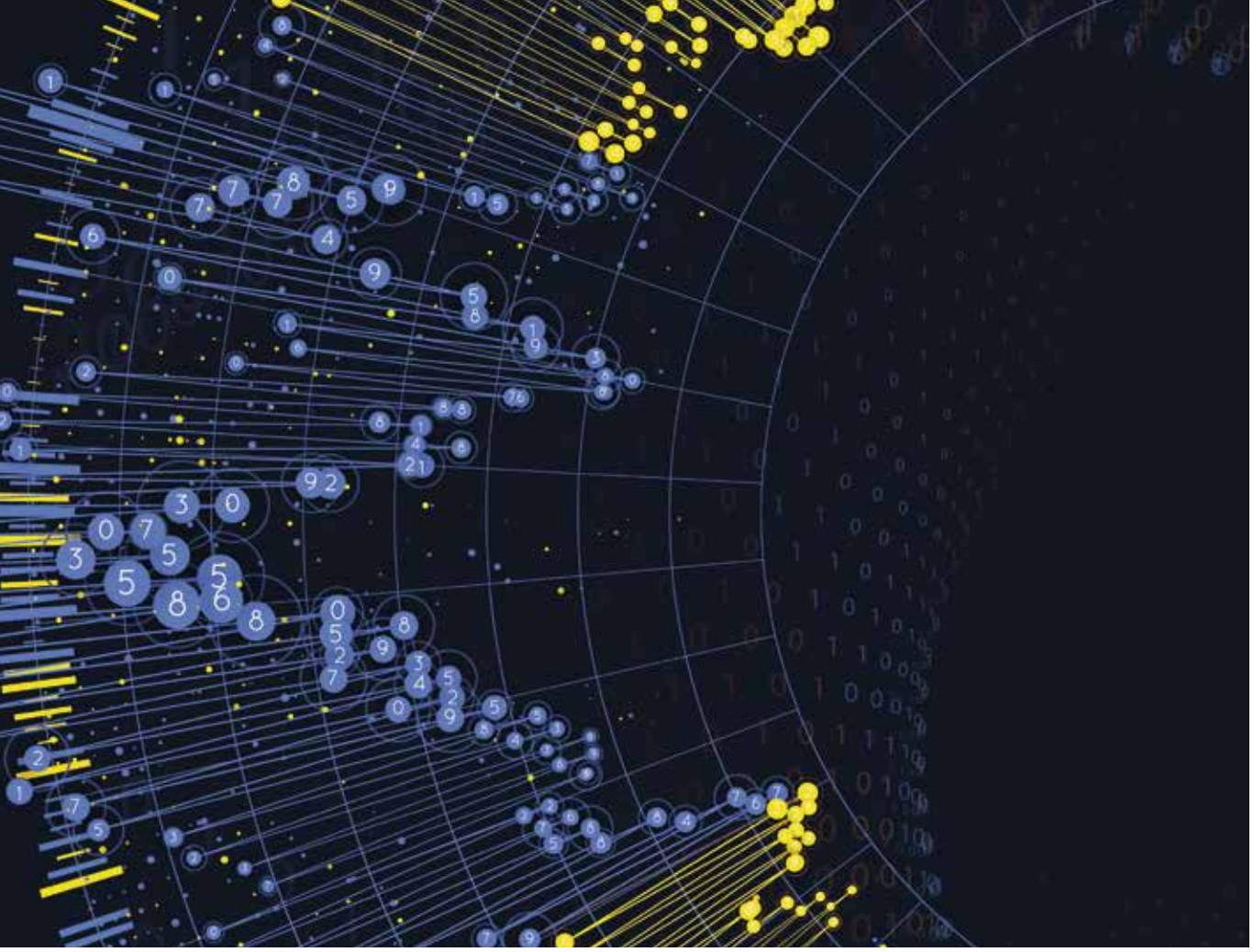


In short, the current trend is working towards 5P Medicine.

The term 5P Medicine describes the crossover between Health and Big Data, representing a new way of understanding medicine, so as to achieve a better society and the well-being of all. The designation is based on its five key characteristics:

Personalized: capable of offering a unique and distinctive treatment for the diagnosis, tailored to each patient. The use of Big Data allows this, given the need to "encode" into data clinical aspects and other factors such as mood, expression of pain, etc.

Predictive: switching from a reactive to a proactive healthcare model, thanks to the ability to predict situations which are harmful to patients.

Preventive: capable of anticipating and preventing the emergence of diseases, based on a set of medical actions and analysis of historical data and patterns.

Participatory: work with patients has an impact not only on aspects of treatment, but also management and processes.

Populational: for the whole population. Making the system more efficient could mean that the same resources can be used to address a larger volume of the population.

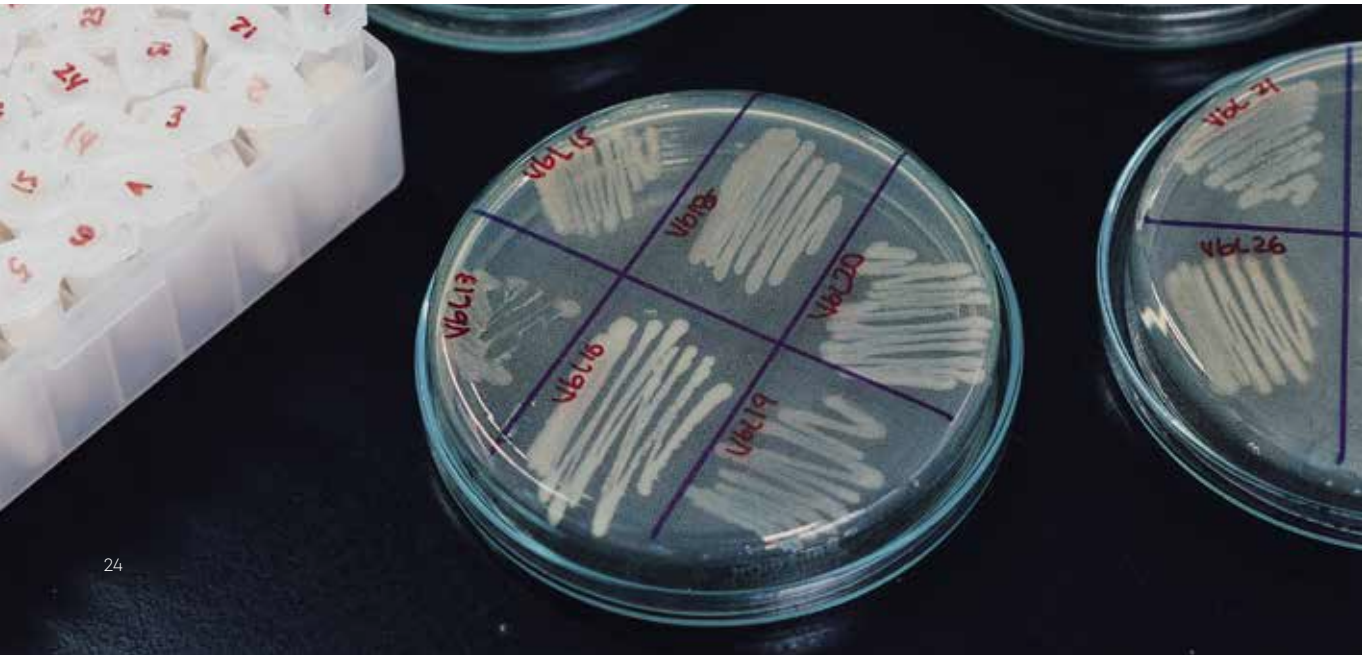
In summary, precision medicine is clearly destined to transform medical care over the coming decade, for both the prevention and the treatment of diseases, as it progressively expands into key areas: access to samples and data from very large cohorts of individuals, including diverse populations, artificial intelligence (AI), routine clinical genomics, phenomics and environment. We would over the coming decade expect to see a spectacular increase in the synergy between biomedical focuses, calculation algorithms, and the availability of high-resolution data. The ultimate aim is for this information, duly processed, to lay the foundations for a new predictive and therapeutic tool applied to personalized health with a focus on prevention, diagnosis, prognosis and the well-being of the population, as well as the treatment of diseases affecting a controlled population.

03

CHALLENGES AND PRIORITIES IN R&D

PERSONALIZED HEALTH

03 CHALLENGES AND PRIORITIES IN R&D



Challenge 1:
Samples and Data.

- Obtaining and initially processing biological samples.
- Biochemical information, general health and data gathered from individuals.
- Security, ethics, legality and privacy.
- Traceability.

Samples: Access, Storage, Generation and Data Analysis and Protection.

Samples must be drawn from very broad and interoperable longitudinal patient cohorts from the general population, with as great a diversity as possible.

The first challenge of a Personalized Health Programme lies in the need to gather a large variety of molecular and phenomic, lifestyle and environmental exposure data, with sufficient resolution for clinical and research use, serving to detect different types of molecule (biomarkers) which are unequivocally related to specific pathologies, so as to advance prevention, diagnosis, and ultimately therapy.

The gathering of health-related data, vital to, and the use of portable devices serves to determine activity, physical parameters and exposures to different types of environment.

Data.

Big data and artificial intelligence.

The gathering of health-related data, vital statistics and the use of portable devices serves to determine activity, physical parameters and exposures to different types of environment. Surveys can thus focus on those elements that are not covered by other methods.

The growth of clinical data (including images, histories and data in real time), scientific data (biochemical, omic) and the availability of portable devices to provide high-resolution data flows will expand the possibility of using phenotypic and environmental data to generate knowledge and apply it in prevention, diagnosis, prognosis and therapy.

In all aspects connected with samples and data, a genuine commitment to the community and complete transparency are needed so as to win trust in this programme.

The decades to come will see the continuous growth of research and clinical uses of different ways of measuring clinical phenotypes, environmental exposures and lifestyle. The links between data and declarations of healthy properties, national vital statistics and geospatial resources will become more common, as will the use of portable devices to measure activity, physical measurements and exposures. Surveys may thus focus more on ascertaining those elements that are not covered by other methods. In this regard, the challenge lies in ensuring that the data platform allows ***Access, Storage and Protection at the highest level and with full guarantees.***

Real World Data.

- Design and implementation.
- Design and implementation of the architecture to acquire data from patients on the move.
- Design and implementation of the mobile application to capture data on the move.
- Development of Real World Data (RWD) metrics and implementation of the logic of data preparation and Quality of Data (QoD).
- Legal aspects and data privacy.
- Search engines in the database.
- Regulation of access to data.

The necessary measures must be adopted to ensure that access to data is confined to registered researchers, and does not involve any risk of jeopardizing the privacy of participants. In principle, there may be two groups who access the data with various requirements:

1) Registered, for data that entail some risk for the participants (requiring a data usage agreement, identity verification, ethical training, approval).

2) Controlled, for data with a greater risk to the privacy of research participants (requiring registered access requirements + institutional signatory official).

Electronic Clinical Histories (ECH) as sources of research.

The key to success based on longitudinal analysis of any cohort is detailed evaluation of the phenotype, environmental exposure, and health outcomes. Many research cohorts at the local level use ECHs and other health data to provide information that has existed for decades about diseases and treatments, and which can be reused in research.

ECH-based studies have already proved fundamental in some genomic studies which have achieved clinically significant findings, some of which involve more than a million individuals. By providing a systematic compilation of health-related information, the ECHs provide phenotypes and data and allow the design of novel studies, which are often not available in conventional research projects. For example, a longitudinal study managed over the course of 8 years to generate an average of more than 190 clinical notes, 14 radiological studies and more than 700 laboratory tests. The power of discovering specific endophenotypes (e.g.: cardiac ejection fraction) or emerging phenotypes (e.g.: Covid-19), rare and specific phenotypes (e.g.: osteonecrosis

03
CHALLENGES AND PRIORITIES IN R&D

of the jaw), or an understanding of specific manifestations of a particular disease (e.g.: bronchiectasis) requires access to complete ECH data. These ECH data need to be cleaned up and harmonized, and may reflect different types of bias. Unstructured ECH data, such as narrative reports or image data, often require advanced methods, such as the processing of natural language or automatic learning, to make them useful at a populational scale. Fortunately, all these tools are increasingly available and applicable, providing access to data of a scale, depth and detail that are not feasible with data which are purely gathered for research purposes.

The ECH clinical data can also be combined with compilations of research data provided by the participants, thereby obtaining a more complete image of the patients' outcomes. Research cohorts such as UK Biobank and All of Us have integrated both sources of data.

Activity monitors taking a series of clinical measurements, such as single cable electrocardiograms and oxygen saturation, are increasingly inexpensive, and can be easily shared with the suppliers. As patients spend the vast majority of their life outside the medical care system, the integration of portable devices and other information provided by the patient would enhance the ECH and allow greater capabilities for remote health, as experienced at scale for the first time during Covid-19.

Lifestyle.

Despite the clear evidence of the impact of nutrition on health, diet is one environmental exposure which is often overlooked in much of clinical practice and in many research studies. When an evaluation takes place, it is often through episodic and laborious surveys (research) or superficial questions (in most clinical contexts). The challenge lies in obtaining reliable and objective data about dietary habits that can, in a swift, straightforward and cost-effective way, be used to evaluate the dietary pattern of an individual or a population. This can be done by working on the search for biomarkers for the ingestion of foods in biological fluids, or through recourse to digital tools providing us with access to data about habits, such as food purchases in grocery stores, digital restaurant uploads, or even automatic learning applied to images of food.

It would furthermore seem necessary to include other types of data in the analysis, such as physical activity and sleep hygiene.

Data privacy.

Participants also need to trust that their data will be secure and private. Public data breaches, the fear of re-identification and legal concerns as to the availability and exploitation of sensitive information, including its security, represent a challenge. To generate trust, it is essential that there be clear and honest communication with participants. An essential role is played in this regard by legal data protection mechanisms, technological focuses to guarantee secure information systems (such as anonymization or data disassociation, management of data and traceability through blockchain, pseudonymization of personal data by means of a range of techniques (hash identifiers) or analysis using advanced cryptography techniques, such as homomorphic encryption or multi-party computation).

One fundamental challenge is successfully to blend data drawn from different cohorts. This goal can only be achieved by means of minute manual adjudication of the phenotype, and access to extensive consortia capable of including experts for each cohort. It is vital here to develop and coordinate shared file formats and data models serving to facilitate interoperability and collaboration.

Participants also need to trust that their data will be secure and private. Public data breaches, the fear of re-identification and legal concerns as to the availability and exploitation of sensitive information, including its security, represent a challenge.

The individualized monitoring inherent in any precision medicine initiative must be conducted constantly and in the long term, so as to identify at a very early stage any possible biological alterations with significance for clinical practice. In parallel, all available data are compiled from yearly medical checkups (blood pressure, body mass index, heart rate, height, hip circumference, waist circumference and weight), periodic lifestyle surveys (drawn up under the supervision of experts in epidemiological data analysis) for each participant, and data derived from the use of ancillary sensors and devices.

The ultimate goal is that this information, once duly processed, would lay the foundations for a new predictive and therapeutic tool applicable in personalized health with a focus on the diagnosis, prognosis and treatment of diseases, affecting a controlled population to improve their well-being.

Surveys.

The need is to generate surveys to monitor lifestyle, biochemical data and the general state of health of the participants. It is essential that questionnaires gathering data connected with lifestyle (nutritional, physical activity, quality-of-life…) are validated for the population to which they apply (by age or by culture, e.g. types of food consumed, etc.) so as to extract precise information, and furthermore to allow a comparison with other studies, in other countries.

03
CHALLENGES AND PRIORITIES IN R&D

Ethical-Legal Aspects.

It is vital to take into account and to follow the rules set out below:

- Quality and security standards for the donation, obtaining, evaluation, processing, preservation, storage and distribution of human tissues and cells, and the coordination and functional rules for their use in humans.
- Personal Data Protection standards.
- Basic standards governing patient autonomy and rights and obligations with regard to information and clinical documentation.

Devices: sampling, portable devices.

One essential aspect to develop this challenge is the need to have effective devices to collect samples and perform sampling, and to gather lifestyle data. This aspect is covered in greater depth in the subsection referring to Challenge 4.

Challenge 2:
Scientific-technological methodologies and tools.

Challenge 2 requires that we maintain the continuous development of science and technology in the state of the art, in order to use the data generated through the application of omic technologies to samples from the different cohorts, associated with existing phenotypic data, to identify biomarkers linked to specific pathologies.

From a scientific perspective, then, it is essential to maintain the state of the art in research in cellular, molecular, chemical and genetic biology, as well as in the development and application of high-performance technologies on a synergistic basis (integromics). An integrated precision medicine programme must include data and parameters from a range of sources, including genomics and epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, glycomics and microbiome data. This combination must serve to obtain the detailed molecular composition of the biological processes taking place within an individual. For example, clinical genomic analysis is at present typically used only when evaluating certain cancers, or when a rare genetic disease is suspected.

We may envisage that in the very near future various genetic causes and directed therapies will be discovered for numerous common diseases, which could lead onto specific treatment and prevention for the patient and their relatives. We will probably also discover that many genetic diseases occur across a spectrum of severity, penetrance and expressivity, guided by the presence of different genetic variants, lifestyle and environmental interactions.

In general, the routine use of sequencing will generate valuable data sets for secondary research, driving a more complete understanding of diseases, including the factors that influence

An integrated precision medicine programme must include data and parameters from a range of sources, including genomics and epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, glycomics and microbiome data.

the variable expressivity of certain genetic variants. More patients revealing incidental pathogenic variants will likewise be detected. As our genomic knowledge increases, there will also be a significant increase in the number of actionable genes and the fraction of the population affected.

In parallel, pharmacogenomics will improve the efficacy of drugs, reducing adverse incidents and cutting costs. We may in principle expect that if the DNA sequence of each person is already in their medical record and a simple click provides access to all the information needed, there will be a much lower barrier to incorporating all this information when prescribing drugs.

PERSONALIZED HEALTH

03 CHALLENGES AND PRIORITIES IN R&D

Challenge 2:
Scientific-Technological Aspects.

Scientific Aspects.

- At the boundary of cellular, molecular, chemical and genetic biology.
- Omic methodologies and analysis and detection tools.

Precision medicine has become particularly prominent because of the growing need to develop personalized strategies for the diagnosis, treatment and prediction of diseases. The methodologies, technologies and tools on which precision medicine is based are transforming medical care. For example, we have recently seen the development of transformative molecular treatments for low prevalence (rare) diseases, such as spinal muscular atrophy and cystic fibrosis. Research in the omic sciences, in particular in genomics, has brought about new drugs for hyperlipidaemia. In this pandemic era, science provided an immediate response to the huge threat that Covid-19 meant for medical care.

Biomedical focuses, calculation algorithms and the availability of high-resolution data will continue to expand hugely over the next 10 years. It would seem clear that we need to implement a bold and decisive plan, committed to cross-cutting collaboration among different institutions, at the broadest level possible, to allow collaboration among different specialists, doctors, scientists, engineers, mathematicians, etc., serving to combine the clinical and research data that they have available in a broad sense, to generate knowledge, and to implement the knowledge generated in clinical practice, so as to reach the horizon of precision medicine for all.

It is essential in this context to maintain the state of the art in the development and application of high-performance technologies in a synergistic manner (integromics), including genomics and epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, glycomics and microbiome data, to obtain the detailed molecular composition of the biological processes taking place in an individual. Different BRTA agents specialise in these spheres, in particular the CIC bioGUNE NMR platform, which is the State ICTS, or Scientific and Technical Infrastructure of Excellence, and a European flagship in the use of Magnetic Resonance in metabolomic studies. The high sensitivity and specificity of these technologies must serve to identify the markers associated with a particular pathological process. These biomarkers may comprise one single molecule or the combination of various molecules constituting molecular signatures of the process, giving a high degree of specificity in the stage of diagnosing and classifying the pathology. Furthermore, the combination of the molecular knowledge of an individual and their lifestyle

The methodologies, technologies and tools on which precision medicine is based are transforming medical care.

covers most of the causes for failure in biological systems resulting in disease. In short, as well as providing effective tools for prevention, diagnosis and prognosis, one additional goal is to predict how an individual will respond to therapeutic intervention.

The identification of these molecules and the corresponding biochemical pathways must be accompanied by basic research of excellence, at the boundary of cellular biology, molecular biology, chemical biology and genetics, so as to understand the mechanisms of action underlying the pathologies, and thereby obtain the necessary knowledge to modify the existing therapies and diagnostic methods, or design other new ones, improving early detection and increasing therapeutic efficacy against a particular pathology. In this regard, the application of new materials and technologies, including nanotechnology, must play an essential role in terms of designing new therapy and diagnosis technologies, including point-of-care devices that are sensitive enough but also simple to apply, allowing sufficiently broad monitoring of the biomarkers of interest, which is of particular value in the event of epidemics and pandemics.

INTEGROME

Genomics / Transcriptomics / Proteomics / Metabolomics / Lipidomics / Glycomics / Microbiome data

PERSONALIZED HEALTH

03 CHALLENGES AND PRIORITIES IN R&D

Artificial intelligence as technological challenge. Big Data methodologies and tools in Personalized Health.

It is essential to apply AI to structured information so as to extract connections and nodes influencing certain biological effects, and thereby achieve the required precision in making a prognosis.

Overall, molecular knowledge and an understanding of mechanisms of action will allow us better to diagnose and classify patients, and will help to increase the efficacy of therapeutic interventions, thereby achieving considerable socio-economic impact.

A)

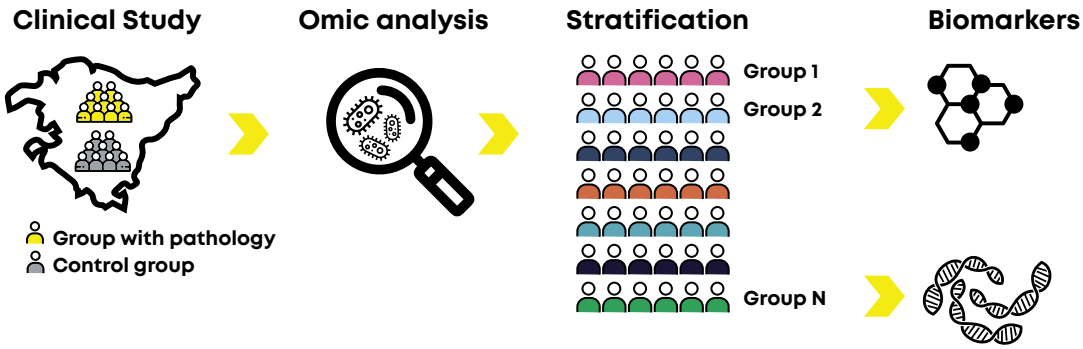


Illustration of how the analysis of macrodata obtained on the basis of detailed omic analyses of patient cohorts can result in detailed phenotyping, and hence lead to the stratification of patients into different groups. We can within this context identify a set of biomarkers that can be used for stratification in clinical practice. These biomarkers are single molecules (or combinations of molecules), such as genes, metabolites or proteins, which cross a certain threshold when specific cellular processes are modified in connection with the onset or progression of the disease.

Big Data and artificial intelligence (AI) are transforming our society. One fundamental challenge for the application of AI in personalized health is the need to have access to very large data sets that are appropriately structured. In other words, it is essential that the available data sets be increasingly prepared for analysis. Given the expected growth of clinical data, then (including images, histories and activity data in real time), molecular (omic) technologies, and the use of portable devices providing continuous high-resolution data flows, this will hugely increase the availability of detailed phenotypic and environmental data.

The application of machine learning methods must result in the generation of new omic, phenomic and environmental predictors for the different pathologies.

As the healthcare sector becomes increasingly connected, greater risks arise for data and information security and privacy, making it vital to define and implement a robust strategy at the level of data chain cybersecurity.

B)

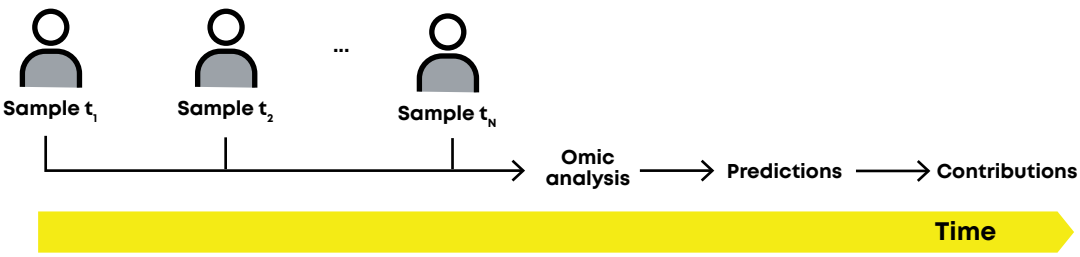


Illustration of the concept for N-of-1 trials. Each individual in the cohort is monitored over time, with samples being taken at different moments. This detailed phenotyping over time serves to identify deviations from the norm, which could suggest the development of the disease.

PERSONALIZED HEALTH

03

CHALLENGES AND PRIORITIES IN R&D

The methodologies, technologies and tools on which precision medicine is based are transforming medical care.

Challenge 3:

Applications for prevention, diagnosis, prognosis and treatment.

The next general challenge in a personalized health programme focuses on the clinical application of the achievements made in the first two, so as to intervene in terms of prevention, diagnosis, prognosis and therapy. Nanomedicine plays a notable role in this sphere.

Biomarkers in Precision Medicine.

On the basis of the data generated through the application of omic technologies to samples from the different cohorts, associated with the existing phenotypic data, biomarkers connected with the specific pathologies have been identified, allowing us to detect their presence or evaluate their progression. The challenge to be addressed is that of developing technologies and applying methods to achieve the greatest possible sensitivity for their detection and/or unequivocal stratification.

We should emphasise the development of bionanosensors, electrochemical biosensors, microfluidic platforms, lab-on-a-chip methodology, optic and photonic methods, and bioimaging, depending on the type of sample and biomarker. Clearly, these methods are associated with a range of scientific-technological

developments, with various BRTA agents specializing in these spheres.

In terms of prevention, research focuses on the pursuit of molecular biomarkers as referred to in the previous section.

In Vitro Diagnosis technologies.

The recent Covid-19 crisis represented a challenge for the development of this type of diagnostic technology, where aside from mass PCR testing, often using conventional laboratory diagnosis techniques, there was widespread use of diagnosis using new generation rapid testing, capable of detecting antibodies in the sample. The development of Micro-Electro-Mechanical Systems and micro-fluidics, linked to biological reactions and components, is giving rise to a new generation of point-of-care diagnostic devices. The qualities of these devices include the possibility of a rapid diagnosis and universal access, based on a small biological sample. As the capacity for miniaturization and diagnosis increases, systems are evolving towards the possibility of diagnosing more than one biomarker or disease, and performing other processes beyond diagnosis, evolving towards the concept of miniaturized laboratory, or lab-on-a-chip.

Another technological development of particular interest is liquid biopsy, thanks to its non-invasive capacity compared with other techniques such as conventional biopsy, which means that the process can be performed and monitored more frequently on the basis of the results. These developments include the capacity to detect circulating tumour cells, circulating tumour DNA, circulating endothelial cells (e.g. in myocardial infarctions) or foetal DNA, among other possibilities.

At CIC nanoGUNE various lines of research are being undertaken with a focus on rapid medical diagnosis by means of photonic and plasmonic techniques. We are specifically seeing the development of technologies that combine various spectroscopic methods, such as Raman, SERS, FTIR and fluorescence for in vitro diagnosis. Examples would include the early diagnosis and classification of the stage of Alzheimer's disease, the detection of infectious diseases and the differentiation of specific tumours. These techniques gather complementary spectral information which is studied by means of an analysis of multiple variables and machine learning algorithms. Plasmonic methods have also been developed, such as liquid biopsy, to detect bacteria and exosomes.

Within this sphere, the TECNALIA biomaterials group develops technologies in biosensors to integrate into lab-on-a-chip diagnostic devices, specializing in the development of immuno sensors with optical and photo-electrochemical technology.

In Vivo Diagnosis Techniques.

Medical imaging technologies represent the main approach for in vivo diagnosis. The most established techniques, such as computerized tomography and magnetic resonance, use well-known physical principles along with mathematical reconstructions serving to generate the final image, sometimes in three dimensions.

Aside from the improvement in the modalities themselves, and their combination, imaging techniques are evolving towards the observation of molecular processes in vivo, thanks to advances in the development of new contrast agents, tracer nanoparticles and new molecular imaging techniques. In this regard, and within the context of precision medicine, this type of technology allows the in vivo observation of physiological processes linked to specific biomarkers or molecular entities.

Particular mention should be made in this area of the capacities of CIC biomaGUNE, which has a unique research infrastructure equipped with the most advanced Nanoscience, Biomaterials and Molecular Imaging installations. To begin with, the functional nanomaterials area develops a broad spectrum of bio-nanomaterials and nanosensors for optical diagnosis, by techniques such as MRI or nuclear imaging. We would highlight the Molecular and Functional Imaging Unit, which represents one

03
CHALLENGES AND PRIORITIES IN R&D

of the best examples of research infrastructure in pre-clinical imaging in Europe, and offers cutting-edge capacities and equipment for: (i) the production of a broad spectrum of radioisotopes and their inclusion in radiolabelled species (small molecules, peptides, proteins, antibodies, polymers, DNA/RNA, nanoparticles and cells); (ii) preclinical nuclear image studies, including Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT), both in a hybrid modality with Computed Tomography (CT); and (iii) high-field Magnetic Resonance Imaging (MRI) studies (7 and 11.7T). The facility also has an exclusively dedicated animal house accredited by AAALAC, a private organization promoting the humanitarian use of experimental animals, whose accreditation represents an international seal of excellence in animal experimentation.

CIC nanoGUNE develops photonic methods, with a particular emphasis on spectroscopic methods for in vivo medical diagnosis. Within this context, Raman spectroscopy assisted by machine learning are used for the in vivo monitoring of physiological changes connected with conditions of hypoxaemia.

The TECNALIA biomaterials group develops biosensor technologies applicable in the development of wearable devices for continuous monitoring and the diagnosis of biomarkers through the skin. This group has in particular developed its own lab-on-a-patch platform.

Advanced Therapies.

Advanced therapies, including cell therapy and gene therapy, face the challenges common to all therapies, along with others which are specific and inherent to each of them.

In general, without aiming to set out a fully comprehensive list, the shared challenges would include:

- The need for facilities with GMP (good manufacturing practice) accreditation at a large scale and with affordable costs.
- The need for specialist training for all the staff involved.
- At the scientific scale, and in connection with Challenge 2, it is vital to continue exploring in greater depth the underlying elements and mechanisms of the different pathologies, using synergies between basic research and clinical practice.
- The need is to adapt the existing regulations in line with the particular necessities of specific advanced therapy applications.

Within this sphere, the TECNALIA biomaterials group is researching the use of biomaterials in regenerative medicine, designing and developing biotint formulations based on cellular and acellular hydrogels with properties of printability, structural integrity, biocompatibility and potential to create new tissue, as well as processing technologies for the bioprinting of functional tissues including regenerative elements.

Cell therapies.

The specific challenges faced by cell therapies would include the following needs:

. Continue researching to establish an in-depth understanding of the mechanisms of action. It is vital to increase the depth of our knowledge of how cells behave, so that they can be used as a therapeutic entity.

. Improved therapeutic efficacy and definition, validation and application of specific criteria to evaluate the efficacy of cell therapy.

We are now seeing spectacular developments in the treatment of diseases (which depend on one single gene) through undirected gene therapy, both in vitro and in vivo.

PERSONALIZED HEALTH

03 CHALLENGES AND PRIORITIES IN R&D

Gene therapies.

The challenge lies in increasing the applications of such methods. In undirected gene therapy, the desired genetic material is transferred to the target cells, and once there may remain within the cells without integrating into the genome, or inserting itself in an undirected manner into the cellular genome.

We are now seeing spectacular developments in the treatment of diseases (which depend on one single gene) through undirected gene therapy, both in vitro and in vivo. There are numerous single-gene diseases where this type of therapy can have a very high impact: haematological, metabolic, degenerative muscular, ophthalmological conditions, etc.

Since many types of cancer have substantial genetic components, there are significant challenges in the application of gene therapy strategies to address specific genetic targets. One could here cite the use of oncolytic viruses, modified in the laboratory specifically to infect tumour cells, and as far as possible to stimulate the natural immune response. Another very important aspect is the application of gene therapy methods based on CAR-T or CAR-NK cellules. The challenge in this regard lies in the development of new gene editing tools, the effective use of bioinformatics and enhanced knowledge based on synthetic biology. We are in fact on the way to designing powerful, safe and inexpensive CAR medication for solid tumours. The ultimate challenge lies in the design of CARs for other targets, in infectious or autoimmune diseases.

Alternatively, in directed gene therapy (gene editing), the genetic material used for therapy must be specifically directed to a particular location of the genome. Specifically, the DNA is modified in situ by inserting a designer gene sequence in the target region of the genome.

On the basis of current results, essentially using different nucleases, such as CRISPR/Cas, ZFN or TALEN to modify genes in vitro, the essential challenge lies in achieving in vivo modification. One desirable goal is to allow many degenerative diseases to be treated in the near future through gene editing therapies.

The specific challenges in the development and application of gene therapies would thus include:

- Improved processes to generate viral vectors and reduce the immunogenicity of the therapeutic vectors.
- Improved efficacy and reduced toxicity of non-viral vectors.
- Increased efficacy of in vitro gene modification in the target cells.
- Continue researching to achieve optimization of "directed gene therapy" methods (gene editing) as an alternative to "undirected gene therapy".

Facilitating technologies.
Nanomedicine: Drug Delivery systems.

One particular field of great interest in the context of advanced therapies is the development of systems for the controlled release of drugs, or drug delivery systems. The low in vivo stability of many of the active ingredients that make these therapies possible means they have to be protected and effectively directed.

Researchers are therefore looking for new delivery systems to improve stability and transfection. One typical case, which is widely utilized in the Basque Country, is the use of viral vectors employing non-pathogenic viruses. However, their use in vivo is limited, and in some cases they activate the patient's immune response, making a second treatment impossible. Furthermore, each type of virus is limited by the type of API and its size. Meanwhile, manufacturing processes are not easy, and scaling is limited. One alternative to overcome the limitations of viral vectors comes courtesy of the development of new biomaterials with specific properties, designed for a particular purpose. For example, lipid nanoparticles came to prominence during the pandemic, as they were used as the delivery system allowing various of the Covid-19 vaccines to be brought to market, specifically those based on mRNA.

Delivery systems must be easily adaptable, which represents a great technological challenge.

The use of nanoparticles (NP) to develop precision drug delivery systems is a novel concept. There are various types of NP. We could cite such examples as those based on lipids (liposomes, LNPs, emulsions), polymers, of both natural and synthetic origin (polymersomes, nanospheres, nanoemulsions, polymer micelles, dendrimers) and inorganic nanoparticles of different compositions.

In some cases, the different nanoparticles have not taken into account certain essential aspects of medicine for their development. However, there is an increasing volume of data about how they behave and how these systems need to be designed to cross through biological barriers, improve their circulation in the bloodstream, improve their stability, take advantage of the micro-environmental conditions in the tissue or organ to be treated, local distribution, cell barriers and the location of the target within the cells. In other words, delivery systems must be easily adaptable, which represents a great technological challenge. A different design is required, for example, depending on whether the APIs will be administered intravenously or through an inhaler, whether they need to be directed to the immune system cells, or some other type of cell, whether they act at the membrane level or in the cytoplasm, or whether a gene editing system is being used. Furthermore, though, the micro-environment faced by the drugs differs considerably in a healthy or sick organ (for example, the lungs of patients with cystic fibrosis have much denser mucus, laden with DNA and immune system cells, while the skin of a patient with psoriasis has a much thicker stratum corneum, which makes topical treatment more difficult).

The structure of the nanopharmaceuticals ultimately used is therefore of vital importance.

PERSONALIZED HEALTH

03 CHALLENGES AND PRIORITIES IN R&D

In addition, the characteristics of many bio-nanomaterials used as delivery systems (optical and magnetic properties) open up the opportunity of manufacturing multifunctional systems to monitor the nanopharmaceuticals and how treatment is progressing. This added value of nano-biotechnological approaches is fundamental for the progress of advanced therapies and personalized medicine.

Meanwhile, another technological challenge involves the development of advanced characterization systems that can subsequently be validated in accordance with good manufacturing practice (GMP), as well as safety control and regulatory systems for the product manufactured in accordance with good laboratory practice (GLP).

In short, controlled drug release through drug delivery systems, and the design of such precision systems, involves such specific challenges as:

- Directing drugs to improve their efficacy and reduce side-effects.
- Drug delivery systems with response to stimuli capable of delivering the drug in the medium of action.
- Drug delivery systems for immunotherapy.
- Patches for transdermal delivery and monitoring of active ingredients.
- Combination of delivery systems with drug monitoring and treatment tracking.

Furthermore, the whole line of research and the challenge indicated requires consideration of the 3R philosophy, with the aim of developing in vitro, ex vivo and in silico experimental systems capable as far as possible of developing methods that avoid or replace the use of animals (Replacement), strategies to facilitate the Reduction of animal experimentation (maximizing the information obtained per animal), as well as Refinement, to improve the well-being of the animals used.

Bio-electronic medicine uses devices to modulate the electrical activity of the nervous system.

Challenge 4:

Digital health: towards digital medicine.

Lastly, we bring in digital medicine as a challenge extending the applications presented under the previous challenge and completing the Personalized Health programme. Digital health exploits the benefits of digital technologies and data to develop digital medicine applications.

Smart medical devices

The role of medical devices and digital health has become an essential element in the health of citizens in all countries. As mentioned previously, this sector has huge potential for growth in the Basque Country, with notable research and technology capacities in various areas. The consolidation of a Personalized Health programme would be expected to achieve advances in:

Neurotechnology: bioelectronic medicine uses devices to modulate the electrical activity of the nervous system. Positioned at a point of convergence of molecular medicine, neuroscience and bioengineering, this opens up new treatment pathways without the use of medication.

Medical robotics: robotics is transforming medicine in various spheres of application: robotic devices for neuro-rehabilitation, robotic surgery tools and systems, exoskeletons, and automated robotic systems for hospitals.

Point of care: wearable devices to conduct diagnostic tests in the vicinity of patients, which are faster than centralized, conventional laboratory tests.

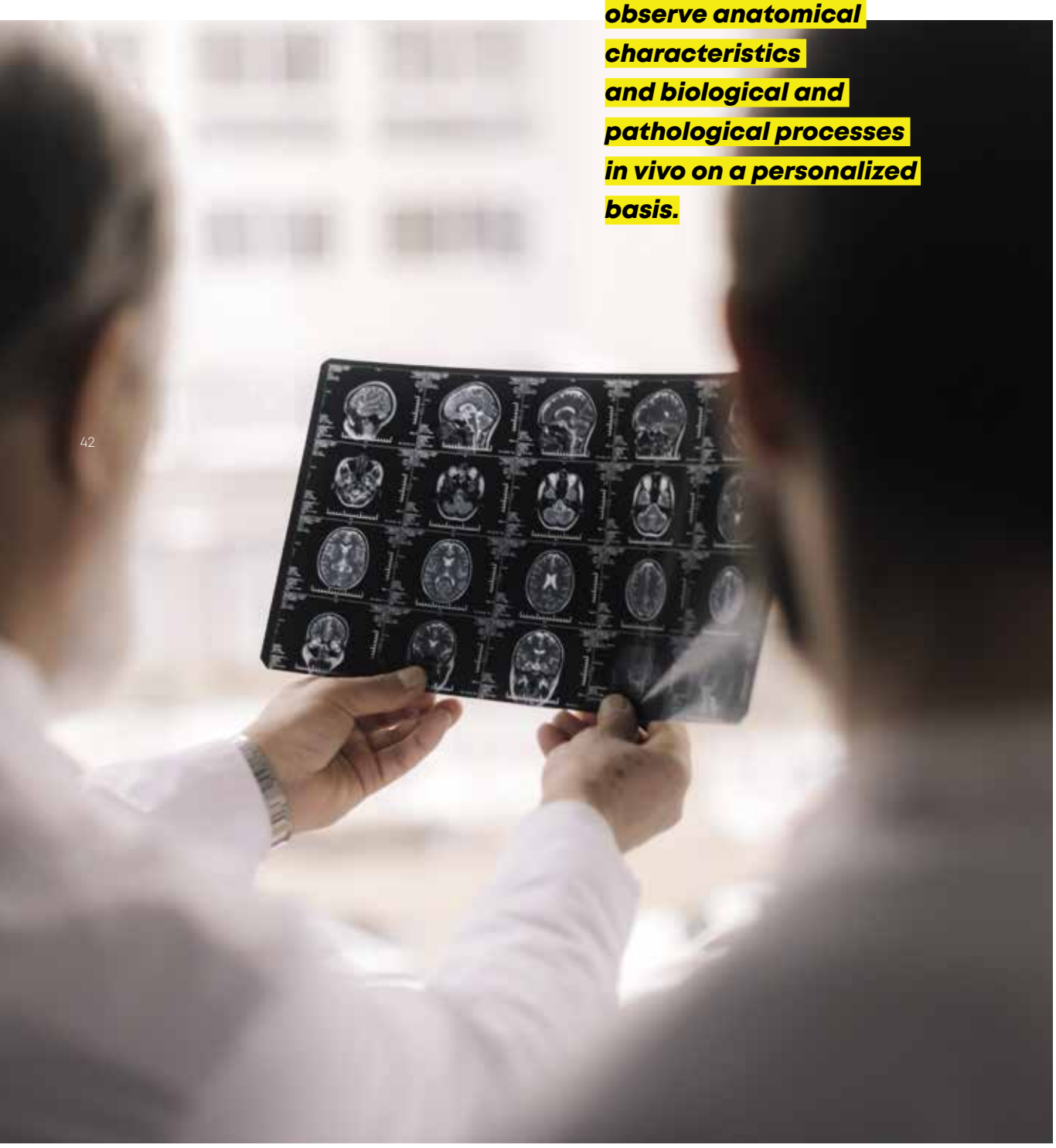
Wearables & monitoring devices: devices to monitor healthy lifestyles and users in domestic settings, including devices to monitor patients in professional contexts.

Particular mention should be made in this area of the capacities of TECNALIA, which has 3 research groups in place focused on the development of medical devices. The TECNALIA neuroengineering group develops medical devices for the diagnosis and treatment of neuromotor pathologies based on knowledge of robotics, electrical stimulation and biomechanics. More than a decade of research has achieved a high level of international recognition in the spheres of robotics for rehabilitation, functional electrical stimulation and brain-computer interfaces, serving to transfer technology to Basque industry, as in the success story of the company Fesia Technology, which is marketing 2 new products. The TECNALIA Biomaterials group develops biomaterials for biomedical applications. With extensive experience in the processing, modification and bio-functionalization of materials, over the last 5 years it has focused on consumables for in vitro diagnosis, from the development of sensory systems, integrated into a Lab on a Chip with the associated reading devices, to advanced laboratory consumables. The TECNALIA medical robotics group, specializing in perception technologies and human sensorimotor physiology and robotic engineering, researches new modes of human-robot interaction, for the development of exoskeletons, and new medical devices for robotic surgery.

PERSONALIZED HEALTH

03 CHALLENGES AND PRIORITIES IN R&D

Medical imaging technologies have seen great advances, allowing us to observe anatomical characteristics and biological and pathological processes in vivo on a personalized basis.



Medical Image Analysis.

Medical imaging technologies have seen considerable progress, allowing us to observe anatomical characteristics and biological and pathological processes in vivo in a personalized manner, as an important technology for the development of the new Precision Medicine. The growth of these technologies goes hand-in-hand with the generation of a huge quantity of high-quality information, which although it is difficult to exploit, has in parallel led to significant progress in capacities for the automated analysis of such images, in particular courtesy of artificial intelligence through deep learning.

Within this context, the CAPV has a very powerful ecosystem in place for the development of this field: it has a healthcare network which is firmly committed to digitalization and continuous improvement, an emerging and growing business sector and a leading R&D network in the field of health.

The TECNALIA Computer Vision group, with experience in image processing and smart systems development, photonic technology development and deep learning applied to the development of diagnostic support systems and digital pathology solutions, received European recognition in the form of the EARTO award in 2014.

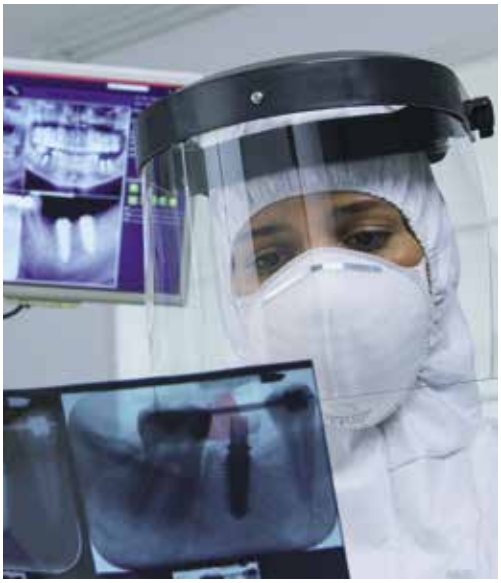
The areas with the greatest potential in this field are:

Radiological Diagnosis support systems: automatic processing of medical images and integration of other clinical data. This is in the spotlight in particular in screening programmes and applications for the early detection of diseases of the central nervous system, circulatory and locomotive apparatus. Digital Pathology: as a new source of valuable information at the level of precision medicine imaging. Recent advances in image analysis with artificial intelligence allow us to characterize these complex and extensive images of biological samples, helping to characterize carcinogenic zones.

Optical biopsy: the new in situ tissue analysis techniques require advanced processing systems for two reasons: first because they generate signals which require complex interpretation without prior training, and secondly because the quantity of data they generate is difficult for a person to interpret during the time spent examining a patient.

Medical robotic support systems: including the use of intra-operative imaging, the combination with pre-operative imaging, with greater definition and used for planning, and the merger with visualization techniques such as augmented reality.

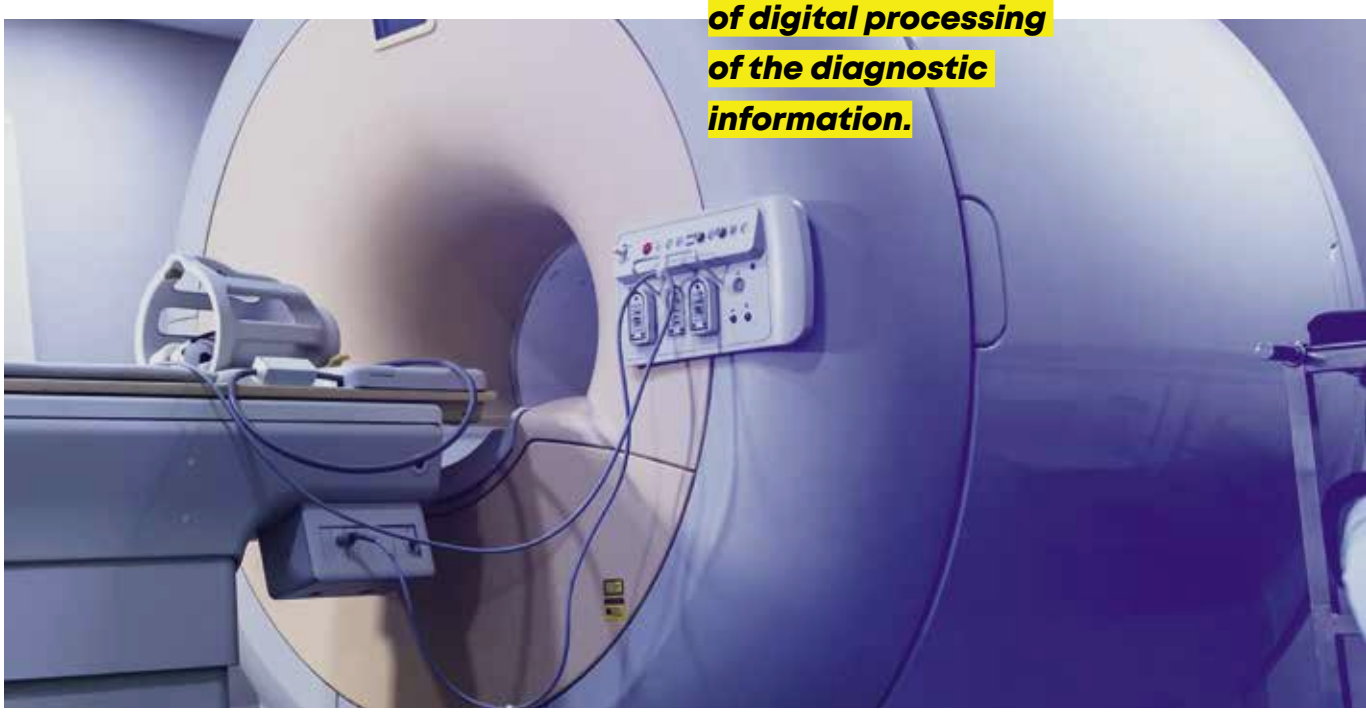
Generative models: the latest artificial intelligence techniques can recreate realistic artificial images with a variety of applications, including image correction or restoration, synthetic image generation for simulation or training, and the virtual generation of images in one modality, based on those from another.



PERSONALIZED HEALTH

03 CHALLENGES AND PRIORITIES IN R&D

Digital diagnosis refers to approaches with a substantial component of digital processing of the diagnostic information.



Digital Diagnosis.

Digital diagnosis refers to approaches that contain a substantial component of digital processing of the diagnostic information. For example, one specific detection method (e.g. medical imaging, molecular data, biophysical or biochemical sensors…) produces a signal or series of complex signals requiring analysis by digital means. However, beyond mere digitalization and processing of the data, digital diagnosis systems allow for further possibilities:

Integration of multiple diagnostic sources: the digitalization of information serves to integrate complementary diagnostic sources, to issue one single diagnosis in a more reliable manner. For example, integrating different image modalities or complementing molecular or genetic information (e.g. about a tumour) with information drawn from radiology or pathology.

Remote diagnosis: the digital component serves to separate out signal capture and analysis, allowing for remote diagnosis, with approaches such as tele-radiology, domestic or mobile diagnosis (e.g. during an emergency), etc.

Artificial intelligence: artificial intelligence is an important component of digital diagnosis systems. By integrating multiple sources of information (imaging, molecular information, clinical data) and developing a predictive or classification model based on a multi-variable approach and an extensive series of training data, AI constitutes a diagnostic system in itself. This type of system is now beginning to receive approval from the regulatory authority for medical use, provided that it is clinically validated, as with other software-type medical devices. This type of validation must take into account not only results of the required

precision (sensitivity, specificity), but also aspects such as the possible existence of undesirable biases or the necessary explicability in certain approaches.

The TECNALIA Digital Health group develops Big Data architectures and technologies for data analysis and optimization, prediction, classification and learning, specializing in validated algorithms and models incorporated within healthcare products. The group has a scientific computation centre specializing in Artificial Intelligence and Big Data, to develop, test and validate artificial intelligence model developments.

Clinical Decision Support Systems.

From the clinical perspective, health applications providing advanced data analysis concepts, recommendations with regard to decision-making and approaches to artificial intelligence for a disease, process (e.g. emergency triage) or specific clinical problem constitute what are known as Clinical Decision Support Systems, or CDSS. An electronic clinical history, covering all clinical dimensions of a person's health, is used to build up an application focused on the interpretation and exploitation of data and decision-making in different medical specialisms and with specific fields of application. For example, the European DESIREE project has proposed a decision support system for the tumour committee, made up of multi-disciplinary clinical specialists (oncology, gynaecology, radiology, radio-oncology, pathology…) who decide as to the treatment approach in cases of breast cancer. The various elements required in the development of CDSS systems include:

- The modelling of the clinical knowledge domain, the consistent representation of cases and modelling of evidence (e.g. clinical practice guides).
- The integration of different sources of information to provide a comprehensive view of the patient, of relevance for decision-making.
- The usage of biological, physiological or computational models capable of providing important information based on established models with diagnostic or predictive capacity (prognosis, response to therapy…).
- The exploitation of information from actual cases, or Real World Data, using exploratory visualization or data analysis tools.
- The incorporation of artificial intelligence paradigms capable of learning from cases and detecting relevant patterns and variables based on information from numerous cases.

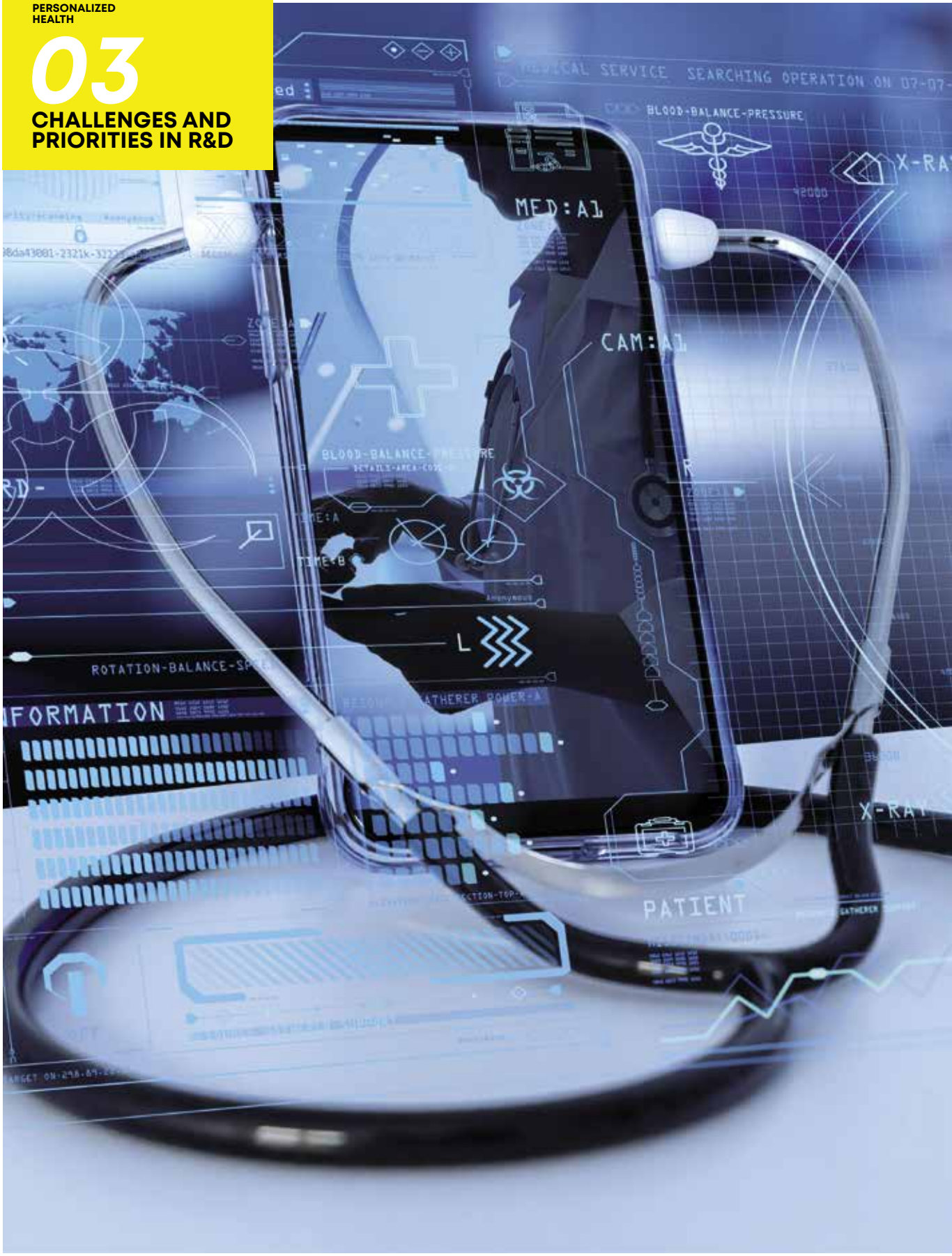
Some of these concepts are already current trends. For example, the Covid-19 pandemic taught us the importance of having interoperable and integrated systems capable of learning quickly from real cases in the absence of better evidence, both on clinical scenarios (case treatment) and in epidemiology (contagion). There had never previously been such a large-scale scenario involving the need to analyse real cases (Real World Data) in the absence of medical evidence. In fact, the pandemic revealed the existing shortcomings in the effective exploitation of current health information systems, and served to show the way forward, as an unprecedented exercise in sharing data for research purposes.

CDSSs are naturally evolving into systems based on precision medicine, incorporating all the data complexity of this scenario (e.g. multiple scales of molecular data, medical images…) together with the respective approaches to data analysis and biological or computational models. CDSS are thus based on prior developments in precision medicine with a view to clinical decision-making in diagnosis, therapy or patient monitoring.

PERSONALIZED HEALTH

03

CHALLENGES AND PRIORITIES IN R&D



Digital Therapies.

Health apps are evolving towards personalization, taking into account clinical and diagnostic parameters, personalized care plans and monitoring information, whether through questionnaires, assistants or through point-of-care and, more recently, wearable devices. The incorporation of artificial intelligence paradigms may cover two fundamental aspects:

- From the perspective of clinical professionals, it serves to automate certain monitoring tasks, flagging up alerts, prioritizing risk situations or offering assistance as with any CDSS, based on monitoring information.
- From the perspective of patients, the development of AI models often incorporated into personal assistants or recommenders focuses on gathering personalized monitoring information, or coaching, to improve the patient's self-management and adherence.

Thanks to these technological advances, health apps are evolving into what are known as digital therapies. A digital therapy is a whole digital system (e.g. app) to help in managing a disease, which improves health outcomes, and delivers demonstrable efficacy and safety as an assistant therapy or a therapy in itself, through the corresponding clinical trials. This vision is compatible with the EU's new MDR (Medical Device Regulation), under which all decision support systems for medical use must have the corresponding clinical validation tests (device class IIa or higher). We are now therefore beginning to speak of the possibility of prescribing duly validated health apps, which would in many cases accompany conventional care plans or treatments.

Health apps are evolving towards personalization, taking into account clinical and diagnostic parameters, personalized care plans and monitoring information.

BRTA AGENT CAPACITIES

DIVIDED INTO TECHNOLOGICAL CHALLENGES

	AZTI	CEIT	CICBIOGUNE
CHALLENGE 1. Samples. Access, storage, generation, analysis and protection of data.			
Access and management of samples.	●		●
Data.	●		●
CHALLENGE 2. Scientific-technological methodologies and tools.			
At the boundary of cellular, molecular, chemical and genetic biology.	●		●
Omic methodologies and analysis and detection tools.	●	●	●
Big Data methodologies and tools in Personalized Health.	●		●
CHALLENGE 3. Applications for prevention, diagnosis, prognosis and treatment.			
Biomarkers in precision medicine.	●		●
In vitro diagnosis technologies.			●
In vivo diagnosis techniques.	●		●
Advanced therapies.			●
CHALLENGE 4. Digital health: towards digital medicine.			
Analysis of medical images.			
Digital diagnosis.			
Smart medical devices.		●	
Clinical decision support systems.			
Digital therapies.			

CICBIOMAGUNE	CICNANOGUNE	CIDETEC	GAIKER	IKERLAN	LEARTIKER	TECNALIA	TEKNIKER	VICOMTECH
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