HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

Big Data to enable better and faster treatment for Patients with Blood Cancer

The HARMONY Alliance:

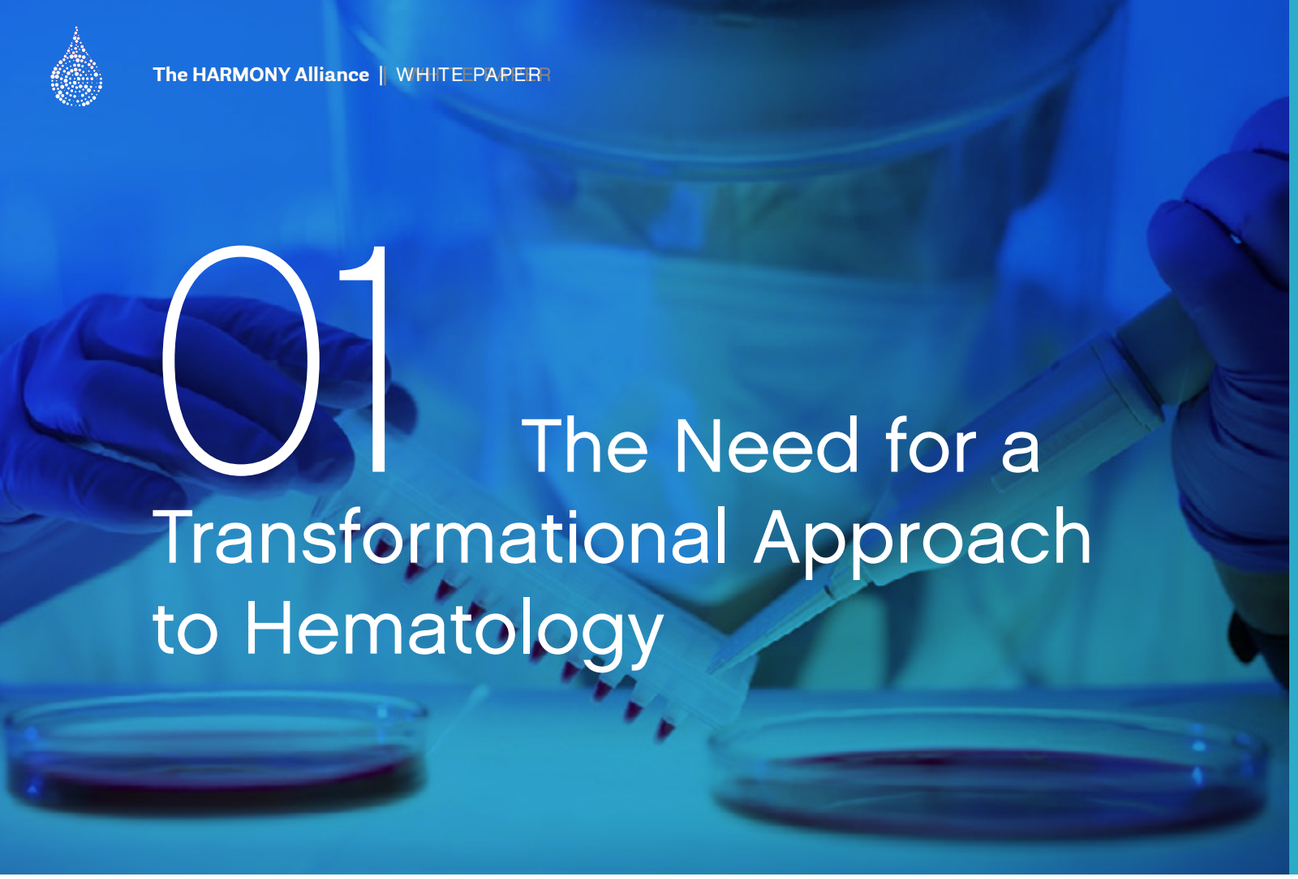
A Public-Private Partnership Transforming the Field of Hematology

- Is a pan-European Network of Excellence, consisting of HM experts seeking to transform the treatment of hematological malignancies (HMs).
- Maximizes the potential of Big Data, enabling information about HMs and intervention strategies to be shared, thus leading to innovations in the treatment of blood cancers.
- Is developing algorithms and other data-analysis mechanisms to more fully analyze and harmonize concepts of HM healthcare.
- Is built on the foundational principles of collaboration and communication, thus fostering enhanced medical interventions and the formulation of innovative strategies.
- Is creating a community that reflects the European HM landscape.
- Involves key stakeholders and decision-makers across the European continent.
- Ensures that patient perspectives and real-world data are included in any discussions about HM care.

WHITE PAPER

HARMONY

Uses Big Data to Transform the Treatment of Blood Cancers: Accelerating More Efficient Drug Development, Regulatory Evaluation, Access Appraisal, and Intervention Strategies



01 The Need for a Transformational Approach to Hematology

The HARMONY Alliance was launched in January 2017 with the primary purpose of capturing, integrating, analyzing, and harmonizing Big Data across the multidisciplinary spectrum of hematological malignancies (HMs), with a focus on areas with high unmet needs. All the partners in the Alliance recognized that, by making Big Data work harder to solve specific problems, drug development could be accelerated, and regulatory evaluation and access appraisal could be made more efficient —all of which would result in better and faster treatments for patients with HMs.

It is in this context that HARMONY is seeking nothing less than to fundamentally transform the treatment of HMs, the way information is gathered and analyzed in relation to blood cancers, and to facilitate the processes by which new drugs are developed and approved for use. All of these goals can be met through the exploitation of the potential of Big Data and by the development of mechanisms for collaboration and communication across the European Union, thus ensuring that medical information is shared, economic costs are reduced, and financial and other resources are optimally utilized. By feeding experiential data back into the process, HARMONY will increase efficiency and enhance the development of innovative strategies for the treatment of HMs.

The potential for developing new drugs to treat HMs has never been greater, and so it is not surprising that research activity in this field is taking place at academic and corporate centers, and that physician experience and patient-centered data are being gathered at an increasing pace. But turning these resources into new treatments and then making them available to patients will require that a transformative approach to stakeholder collaboration be established. The long list of players in the hematology field include clinical and academic bodies; patient organizations; health technology assessment (HTA) agencies; regulatory bodies; experts in the fields of economics, ethics, information and communications technology (ICT); and pharmaceutical organizations. HARMONY, the Healthcare Alliance for Resourceful Medicine Offensive against Neoplasms in Hematology, is operating in the complex interface between these specialists and organizations, and is enhancing communication across a broad spectrum of experts.

HARMONY has grown to include 53 partners and 27 associated members from 22 countries, including 8 pharmaceutical companies from the European Federation of Pharmaceutical Industries and Associations (EFPIA).

This document describes the role of Big Data in hematology and the HARMONY Alliance in overcoming key obstacles to efficient treatment of HMs; our progress on relevant items so far; and our recommendations for the future.

Defining Blood Cancers and Hematological Malignancies

Blood cancers affect the production and function of your blood cells. Most of these cancers start in the bone marrow where blood is produced. Stem cells in the bone marrow mature and develop into three types of blood cells: red blood cells, white blood cells, or platelets. In most blood cancers, the normal blood cell development process is interrupted by the uncontrolled growth of an abnormal type of blood cell. These abnormal blood cells, or cancerous cells, prevent your blood from performing many of its functions, like fighting off infections or preventing serious bleeding. Hematological malignancies are cancers that affect the blood and lymph system. The cancer may begin in blood-forming tissue (e.g., bone marrow) or in the cells of the immune system.[1]

HARMONY will focus on the following seven hematologic malignancies:
Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Chronic Lymphocytic Leukemia, Myelodysplastic Syndromes, Non-Hodgkin's Lymphoma, Multiple Myeloma, and Pediatric Hematologic Malignancies.[2]

Defining Big Data

Big Data in medicine means massive quantities of healthcare data that is accumulated from patients and populations and the advanced analytics that can give it meaning. HARMONY will collect data from different sources (co-operative groups, hospitals, academic partners, industry partners, registries and other external projects) including patient history, treatments, clinical data, molecular data, demographics, etc.

1 www.harmony-alliance.eu/en/hematologic-malignancies
2 Read more about each of the 7 diseases www.harmony-alliance.eu/en/hematologic-malignancies.

02 Formulating and Implementing Strategies for Success

HARMONY has clearly defined its practical strategies for achieving the goals defined above, but recognizes that key, fundamental principles of operation must be put into place in order for the Alliance to comply with crucial ethical, medical, and legal standards; European law; and the criteria guaranteeing confidentiality and privacy.

Specifically, HARMONY is calling for:

- The setting up of a data place through a clinical data-sharing platform that provides a repository of relevant data, thus breaking down silos, and that works in concert with analytical tools aimed at predicting clinical outcomes.
- The creation of mechanisms to incentivize data contributors.
- A platform for public health infrastructures, while meeting the diversity of systems, data formats, and interoperability.
- Governance, including quality assurance, security, and patient confidentiality.
- Increased cooperation between healthcare systems across the European Union.
- Improved investment in research, thus driving innovation across the EU.
- The establishment of a community of expert academic institutions, national clinical disease networks, European organizations, patient advocacy groups, clinicians, the pharmaceutical industry, regulatory agencies, and other stakeholders.
- An effective and fit-for-purpose framework for legal, ethical, and governance issues.

All the stakeholders involved in the HARMONY Alliance are committed to working together to define, achieve, and implement the key objectives of the Alliance. The goal of establishing a more efficient process of treatment development and regulatory evaluation can only be realized by the concerted action of a multidisciplinary partnership like the HARMONY Alliance, which includes institutions, industry, hospitals, health-technology assessment, payers, and organizations, all of whom have a proven track-record of excellence and are a repository of the required expertise and experience. The platform will foster full cooperation and collaboration, thus leading to the establishment of a community of medical excellence.

HARMONY aims to assemble, assess, connect, and analyze heterogeneous data sources involving HM patients, all with the goal of defining sets of outcome indicators through the application of Big Data techniques that can be used for decision-making by key healthcare stakeholders.

In addition, HARMONY will establish a system to foster rapid decision-making in the interests of better therapy access and care for patients. This shared goal is the leading force behind the entire consortium, and everyone involved has pledged to use their combined know-how and extensive access to the relevant existing networks, data, and structures to ensure HARMONY's success.

Linked to the publication of this White Paper, a Policy Action Plan will be devised in order to continue and expand the existing dialogues with key targeted stakeholders and to maintain momentum to deliver on the objectives that have been stated in relation to this project.

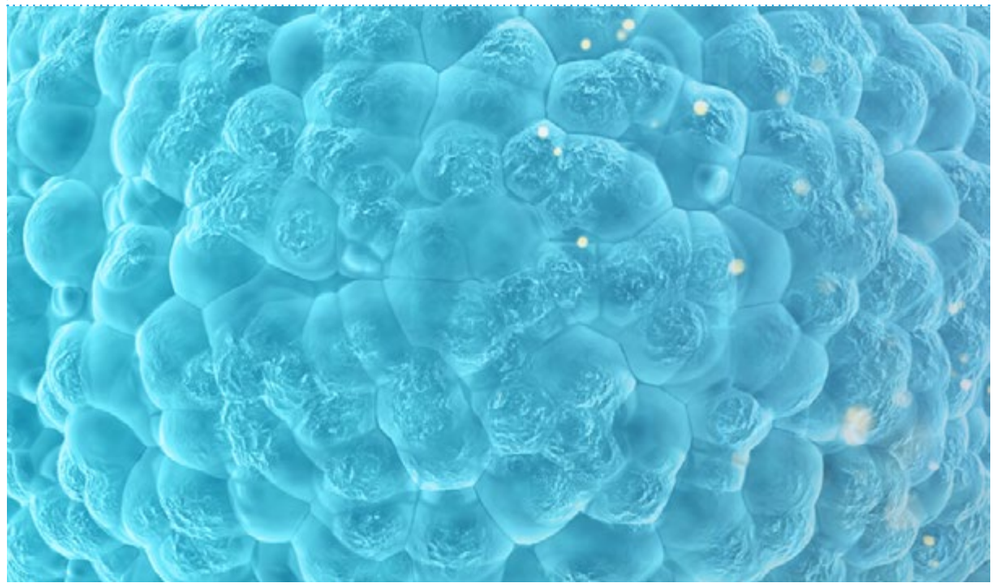
The Big Data platform developed by HARMONY will help define better treatment strategies at the level of the individual patients, leading to a reduction in the social and economic burden of hematological diseases on patients, caregivers, and the healthcare system—all of which will empower European and national policymakers to support funding for health and welfare initiatives.

Unique Public-Private Partnership

The HARMONY Alliance brings together key stakeholders from a broad spectrum of disciplines from 11 European countries. Expertise is drawn from academic institutions, national clinical disease networks, European organizations, patient advocacy groups, clinicians, and pharmaceutical companies, as well as regulatory agencies, experts in economics and ethics, and information and technology specialists.

HARMONY Alliance Strategic Objectives

- Demonstrate the importance of fast and accurate diagnosis via efficient use of standardized clinical data.
- Discuss how a specific characterization of HMs will help improve treatment strategies.
- Discuss the importance of the right use of data or the re-use of data.
- Establish a sustainable model for future work and development.
- Highlight the importance of supporting scientific research and innovation that will explore new potential treatment options.
- Communicate the benefits of data-driven personalized medicine and targeted healthcare on the economic and societal burden of HMs among policy-makers and secondary audiences, healthcare professionals, advocacy organizations, and others.



03 The HARMONY Alliance's Goals

Through the mechanisms for cooperation and collaboration it has set up and through the establishment of its Big Data platform, the HARMONY Alliance is seeking to collect and maximize the use of information related to HMs, increase the cost-effectiveness of treating blood cancers and HMs and, critically, to facilitate the process by which new HM treatment drugs are approved for use.

Collecting and Maximizing the Use of Information Related to HMs

The collection, dissemination, and analysis of information related to HMs is the linchpin of HARMONY's methods of operation and the key to its future success. It is in this context that the HARMONY Alliance's HM-specific Big Data platform is being developed. Current healthcare is data driven, and the Alliance recognizes that the acquisition, integration, harmonization, and communication of data related to HMs will radically transform patient diagnosis, treatment, and care, and will enhance their quality of life.

This platform will enhance the ability of medical professionals to rapidly identify and define promising treatment strategies and to predict any adverse effects likely to be associated with such interventions. In essence, the HARMONY platform, which will take into account demographic differences and which will foster greater patient engagement, will be an effective tool for determining therapeutic options for individual patients, thus "personalizing" patient care and treatment and ensuring that all approaches are patient- and outcome-oriented.

To improve the reliability and, therefore, the value of the data, HARMONY is assisting in creating models and algorithms for the effective analysis of the data that will be collected across Europe. In this context, the Alliance recognizes that there is a need to define standard sets of outcome measures that are relevant to all the stakeholders concerned, thus enhancing the monitoring of treatment strategies. The goal is to become a repository of invaluable information on HMs and to provide data on the current status of HM treatments and results.

Enhancing the Cost-Effectiveness of Treatments

It is accepted that incidence, the measure of the frequency with which a disease occurs over a specific time period, is a crucial and accurate measure of the economic costs borne by a population in relation to the treatment of specific medical conditions; understanding the incidence of these particular medical conditions serves as a vital guide as to how resources should be allocated.

Figures suggest that healthcare costs for each patient with a blood cancer are double the average for the treatment of other cancers. This is primarily due to the need for longer hospital stays, coupled with more complex treatments and diagnoses. The total cost of blood disorders to the European economy was in the region of €23 billion in 2012 and it is expected that expenditures will only increase.[3]

Blood cancers are in the top ten of the most common forms of cancer and are responsible for approximately 100,000 deaths in Europe every year. It is thus not surprising that the proportion of healthcare costs within the total economic burden is higher for malignant blood disorders than for other solid tumors. This means that blood disorders are not only an economic burden for patients, but also for society as a whole, with about 80 million people suffering from either malignant or non-malignant hematological disorders. Hence, it is urgent that the mechanisms for diagnosis and treatment be streamlined and improved.

There are, therefore, very strong arguments in favor of the need to raise public awareness about the effects of blood cancers/hematological malignancies in Europe, given that malignant blood disorders represent a leading cause of death, of increased use of healthcare services, and of costs. In a nutshell, the costs of hematological disease are already high and are rising all the time. As awareness of this has grown, calls for this challenge to be addressed have also increased.

The HARMONY Alliance was set up to overcome the boundaries and barriers that, in the past, have impeded progress in these areas.

Facilitating the Approval of New Drugs

Another critical issue that the HARMONY Alliance is tackling is facilitating the pathways to drug registration and the ability of patients to access novel agents. In short, HARMONY is seeking to overcome significant existing barriers to the registration of new drugs, a process that has become increasingly costly and time-consuming, especially when the pool of patients requiring these drugs is limited in number or when the treatments and therapies concerned can target only a very narrow patient population.

The iteration of criteria to measure the "success" of various treatments and agents is one issue that constitutes an important barrier to the development of drugs; for example, when the patient cohort is small, it is critical that any data-analysis mechanism is able to measure overall survival rates. As a result, the development of innovative treatments, their approval, and their eventual use are delayed, despite their potential to address the areas of malignancy where high unmet needs exist.

3 Link to recent study, supported by EHA: www.ehaweb.org/organization/newsroom/news-and-updates/eha-funded-study-in-the-lancet-haematology-economic-burden-of-blood-disorders-in-eu-is-23-billion/

It is, therefore, not surprising that complicated and lengthy development pathways mean that expensive treatments are not sufficiently cost-effective and that an increasing number of obstacles stand in the way of drug development. Solving this difficult problem is, in general, a critical issue, but is especially pertinent to drug development related to the treatment of HMs.

It is thus of paramount importance that a pan-European approach to the creation of new tools to refine HM outcome definitions is developed. To this end, HARMONY will utilize real-time, "real-life" hematology, an approach that will take into consideration the recent progress that has been made in the field of pharmacology.

The tools that will be developed and implemented will consider differences in national healthcare practice and policy. HARMONY will leverage this combined knowledge to support Medicine Adaptive Pathways to Patients (MAPPs) that aim to balance early patient access, public health, and social benefits within the boundaries of the current regulatory frameworks.

> "The HARMONY Alliance: only by applying Big Data Analytics we can enable better and faster treatments for patients with blood cancer."

04 The Foundational Principles Underpinning the Structures and Operation of the HARMONY Alliance

When European leaders, academics, medical experts, corporate leaders, representatives from the pharmaceutical industry, and all the other experts involved with HARMONY decided to launch this initiative, they did so with a clear vision of what they wanted to accomplish and of the principles upon which the HARMONY Alliance needed to be based so that future success could be guaranteed and outcomes could be concretely evaluated. To achieve maximum impact and efficient use of resources, they took steps to ensure that they established this Alliance on the basis of previous successful collaborative efforts, defined what mechanisms needed to be put into place to catalyze support and communication, and aligned strategic goals to create new business and health-funding models—all of which needed to be based on digital innovation, the free exchange of information, coordination and communication, and sound business and financial practices that were value-based and efficient.

Building on Previous Successful Collaborative Efforts

HARMONY seeks to build on pre-existing long-term collaborative initiatives and on successful HM projects previously carried out in partnership with the pharmaceutical industry. HARMONY will further advance HM management by improving on existing structures (European and national cooperative groups) and by including input from the consortium of clinical European key opinion leaders in HM, together with experts in health economics and "real-life" data management and analysis. This will ensure that all key stakeholders are engaged in fighting HMs.

This European Network of Excellence, which will build up a comprehensive relational database that will continuously integrate Big Data from high-quality multidisciplinary sources, will form the basis for value-based, outcome focused, sustainable, and efficient HM care across Europe.

Catalyzing Support and Communication to Achieve Better Outcomes

As the Innovative Medicines Initiative (IMI2) and other organizations have consistently stated, Europe needs to catalyze and support the evolution towards value-based, outcomes-focused, sustainable, and better-quality healthcare systems across the European Union (EU). This initiative involves exploiting the opportunities offered by the wealth of emerging data from many evolving sources and will generate methodologies and information that will inform policy debates.

It is acknowledged that there is a need to fully exploit the potential of large amounts of existing data from variable and quickly developing digital and non-digital sources. Thus, what is required is a platform to collect and analyze the data and sufficient resources to define the outcomes that will be required in order to enhance the evolution of transparency related to the treatment of HMs. For this to succeed, all stakeholders—patients, payers, physicians, regulators, academic researchers, healthcare decision-makers, governmental agencies, representatives from the pharmacological industry, and others—need to be involved. This type of approach, one that emphasizes transparency, collaboration, and communication, will work in the field of hematology as it has in other medical fields.

Aligning Strategic Goals to Create New Business and Health-Funding Models

A coordinated approach across projects will ensure the emergence of a strategic alignment of goals and outcomes and will assist in the definition of new business and health-funding models that will facilitate the transformation of healthcare systems.

In addition, the integration of areas of expertise (such as legal, ethics, data privacy, sustainability or collaboration with payers/HTAs) will yield higher-quality results, enhance consistency, and lead to increased efficiency by avoiding the duplication of work.

Europe needs to produce high-quality information that will provide decision-makers with the information on what enablers will enhance value-based healthcare systems that successfully and effectively focus on health-related outcomes. Healthcare-system transformation undertaken in this manner will help to bring about the goal of superior healthcare delivery based on high-quality data sharing.

What Will Ensure Success?

The key enablers that will ensure the success of HARMONY are whether:

- Outcome metrics are defined
- Protocols, processes, and tools to access high-quality data emerge
- Methodologies and analytics to drive improvements are iterated
- Digital and other solutions that increase patient engagement are created

Therefore, the engagement of patient organizations, regulators, payers, providers, and other public stakeholders is essential to ensure that the findings from those projects have appropriate buy-in and ultimately deliver real impact in transforming healthcare systems. Such a strategy will lead to the formulation of a comprehensive plan, based on the collection and analysis of data, which will ensure that key enablers are equipped to support the evolution towards value-based, outcomes-focused, and sustainable healthcare systems in Europe. As a result, research-and-development portfolios will be better managed and research methodologies will be refined as the focus shifts to the achievement of effective outcomes.

Progress and Success Are Tied to Digital Innovation

Arguably, because information is the main value asset of 21st century, Big Data and digital technologies are here to stay, and bring many benefits to the rapidly growing area of eHealth, mHealth, the treatment of rare diseases, and more. Considering these developments, the EU has noted that there is a need for policy measures that will promote digital innovation in improving people's health and that address systemic challenges to healthcare systems. Issues that arise in relation to these developments include the need to draft relevant legislation on data protection and on patient rights, and the necessity to enhance electronic identification. In addition, it is important to develop a European health record format that citizens can access from anywhere in the EU and that is more seamless.

The advancement of research, disease prevention, and personalized healthcare can now become a reality and is unfolding across borders, although cross-border healthcare is not yet optimal. Hence, there is a need for what the European Commission has termed "large-scale implementation of interoperable digital services that support health system reforms and capacity-building towards more patient-centered and integrated care".

HARMONY recognizes the need for a multi-location digital infrastructure and data-exchange platform, an initiative that will be especially (but not exclusively) useful when it comes to addressing the diagnosis and treatment of rare diseases.

Not only does a digital single market using Big Data offer the potential to revolutionize the effectiveness of health interventions, it may also help ensure that resources are more effectively managed in what are increasingly cash-strapped public healthcare systems. The elimination of the existing fragmentation in relation to the sharing of information and the enhancement of cross-border collaboration can assist in addressing these challenges. This lack of transparency and the inconsistency in terms of the information are unacceptable in the 21st century. As defined by the EU treaties, health is a national competence and the ability of the European Commission to address the complex issues involved and to meet demand are limited. In light of this, the authors would strongly recommend that all Member States, as a matter of urgency, find a way to agree recommended guidelines in relevant areas. The authors of this White Paper have thus consistently called for better pathways to the collection, storage, and dissemination of key health data and will continue to do so.

05 Transcending the Local, Expanding Involvement, and Harmonizing Evidence

HARMONY has sought not only to introduce innovations in terms of how data is collected, analyzed, and utilized, but is also seeking to expand the definitions of what data is relevant, how it is shared and communicated, and how patient information can form the key component to improving concrete patient outcomes. Thus, it will not only combine information from clinical and pre-clinical trials, but will also include evidence-based information from “real-life”, “real-world” HM-treatment scenarios.

> “Only by sharing Big Data we can improve patient outcomes.”

The Need for Data to Transcend National Borders

HARMONY feels that it is important to note that, without the involvement of all Member States, much data and research will be needlessly duplicated or will not be shared and/or properly analyzed. This is a critical issue that the HARMONY Alliance is striving to address as it seeks to ensure that mechanisms, procedures, and tools are put into place to enhance the sharing, analysis, and interpretation of data in a manner that transcends the borders of individual countries.

It is a truism that information systems in the health sector have historically concentrated on the local collection of data, often with an administrative and financial purpose as the focus of primary activity. Therefore, a detailed assessment of participating systems needs to be carried out in order to understand what the existing gaps in capabilities are that are preventing the delivery of a multinational genomics program, thus facilitating the alignment and integration of regional, national, and supranational eHealth programs and the establishment of appropriate international standards.

The authors strongly believe that the above will significantly improve healthcare, but that more is required. They are of the view that healthcare is also enhanced when patients are more involved in their own treatment. Thus, anything that facilitates the sharing of information among all the groups involved in the treatment of diseases will not only empower patients but will fundamentally transform healthcare systems.
It is clear that in the case of medicines and treatments, one size definitely does not fit all. It is known that certain treatments or combinations may produce excellent results for some patients, yet fail miserably for others. Side-effects can also vary. This can lead to unnecessary suffering and has a huge impact on costs.

Personalized medicine in hematology and elsewhere offers the promise of seeing healthcare move away from “trial-and-error” therapies to evidence-based individual ones, removing that outdated “one-size-fits-all” philosophy. It will help tailor healthcare solutions to the individual patient.

Down the line, healthcare services will increasingly deliver the right intervention when appropriate, thus improving the outcomes for patients and cutting down on unnecessary treatments. Healthcare data, including its collection, storage, dissemination, and analysis is, therefore, vital.

To make the most of all the massive amount of invaluable information flowing into super computers and biobanks, a shared vocabulary needs to be created, as do data-set standards and agreed universal protocols for sending, receiving, and querying information.
In addition, data-storage formats need to be interoperable. Finally, all of this information needs to be interpreted properly and accurately, and not just by clinicians working on the front line.

Personalized Medicine: Translating Research Promise into Medical Innovation

Personalized medicine has advanced hugely in recent years, not least through developments in such scientific areas as genetics which, for example, have had a profound effect on

the treatment of cancers. The right tools to make clinical decisions; the development and introduction of innovative medicines; better diagnostics and prevention; and the creation of proper regulations to keep up with giant leaps in health-related sciences will all contribute to the new era of personalized medicine and all that it promises. At the center of personalized medicine lies the aim of giving the right patient the right treatment at the right time. But, of course, the tools need to be in place in order to achieve what amounts to individualized clinical decisions geared towards the individual patient. Evidence-based medicines and treatments are crucial in this context, and the conjoining of these two processes needs to take place for this to be brought about.

Experts agree that identifying the relevant strands of evidence, which may be many and varied, and tying them together will enable researchers and medical personnel to predict the probability that a particular drug or treatment will be the best option for a particular individual. The one-size-fits-all method is no longer valid, as there really is no such thing as the "average patient" and the time has come to stop prescribing treatments according to the group and the population being treated. The wherewithal currently exists to transcend such approaches.

Personalized medicine has always been and always will be about both patients and doctors jointly deciding what steps need to take place during treatment, and always in the context of a consideration of individual factors. A multidisciplinary effort is required, involving clinicians, methodologists, and others, but truly personalized decision-making can only occur if the patients are on board during the decision-making process.

Given the new understanding of disease at the molecular level (especially in cancers), the promise of personalized and/or precision medicine is real. New therapeutic and diagnostic methods have been designed, which can specifically target and treat mechanisms that drive the disease process. However, obstacles currently exist in science hindering the development of innovative medicines that can address unmet medical needs.

Some of these are the need to ensure, in the context of financial pressures on healthcare budgets, that innovative medicines are taken up by health systems and are made available to patients, and the need to adapt regulatory cooperation so that this medical sector and its supply chain can be globalized.

One positive aspect related to the sphere of personalized medicine is that selection markers have been identified that can help doctors match a drug and its mechanism to patients in a manner that can predict a response, thus bringing about greater clinical benefits. Some of those clinical benefits are obviously derived from medicines and, in that context, the pharmaceutical industry, recognizing the potential involved, is tackling the core challenges of discovering and developing more effective medicines, of reducing rates of attrition, and of addressing the issue of rising costs—all necessary to ensure the sustainability of future healthcare systems. One problem, however, is that Europe's current healthcare systems are out of date and personalized medicine is struggling to be embedded into those systems. Collaboration, innovation, deliverability, a solid evidence base, and sustainability are all required. The field of regulatory affairs in the European Union (EU) is by its very nature a complex one, and nowhere is it more complicated than in the arena of health; the issue of regulation is especially difficult when it comes to legislating the introduction of exciting advances and the growing expectations being brought about by personalized medicine.

Once Brexit takes place, there will still be 27 Member States and the welfare of more than 400 million citizens to consider. There are so many disciplines, industries, and other stakeholders involved in healthcare that it is often a struggle for legislators, despite their best efforts, to formulate regulations that are satisfactory for all, are up-to-date and progressive, and do the job they are supposed to do.

There are certainly ways to make things easier and more efficient. One of the key issues is the lack of collaboration between all stakeholders, some of whom are currently operating within their own "silos". This is a major problem in many areas of health generally, and is particularly troublesome in terms of personalized medicine in particular, and affects a number of issues, including education and information-sharing; how authorities take decisions involving patient access; the need to ensure that there is one, clear message being communicated to legislators and other stakeholders; and much more. It is also a fact that much legislation tends to be reactive rather than proactive. Again, with the enhancement of better collaboration between all the stakeholders involved, it will be possible for all the participants to foresee potential problems that could occur down the line, rather than their acting in an ad hoc manner if and when these problems do occur.

There is undoubtedly a need for extensive common European health legislation, but it must be the right legislation. Experience has shown that having separate rules in every Member State does not work for a variety of reasons. This often leads to a research-and-development environment that is not competitive, slows the innovative dynamic, and ultimately represents a barrier to the emergence of effective therapies for untreated diseases. On top of this, duplication in health technology assessment agencies (HTAs) can slow down the delivery of novel and effective therapies offered to the patient. There is no time like the present for all those involved to come together with the shared aim of focusing on Member States and regional collaboration in order to enable innovation to find its way swiftly into healthcare systems.

MEGA (Million European Genomes Alliance)

The MEGA Initiative has been adopted by a considerable number of countries since a joint declaration was made on 13 April 2018 by 13 European countries. MEGA constitutes a major commitment on the part of a coalition of willing Member States, alongside the Commission, to join genomic databanks at an EU level for medical research. The signatories agreed to work together "towards building a research cohort of at least one million genomes accessible in the EU by 2022" .

That is a tight deadline, yet within Europe, the United Kingdom has already led the way with the 100,000 Genomes Project, which is looking at the genome sequences of patients with rare diseases or cancer. The time has come to broaden this initiative to an EU-wide level: A coordinated, pan European project would garner crucial genetic information that could have an immeasurable benefit when it comes to the health of current and future citizens. It was reported that, by the end of 2000, the majority of the genomes had been sequenced as part of the Human Genome Project. Since that time, research has greatly furthered the understanding of the genome and its implications for health. But although genome sequencing is starting to be introduced into clinical care; is improving the diagnosis and care of patients with rare genetic diseases; and is starting to have an impact on cancer diagnosis and on the stratification of therapies, there remain a number of key challenges that must be tackled in order to ensure that genomics and related technologies are applied in such a way that, over the next few years, the potential of personalized medicine can be fully realized.

Digital Innovation and HARMONY

MEGA is one example of digital innovation and, in the Nordic countries (namely, Denmark, Iceland, Norway, Sweden, and Finland), personalized health programs that are focusing on the convergence of genomics-based and data-driven cure-and-care are being deployed. They are coordinated, united in terms of their strategic approach, and are striving to be consistent in relation to the quality and level of their data and in their organizational structure.

Such a cooperation-based strategy and the involvement of both the public and private sectors should form a vital building block underpinning the EU's position as a frontrunner in innovative healthcare. The fundamental principles guiding these strategies are the need to understand the present, overcome challenges, and develop agreed EU-wide standards.

If successfully delivered to its optimum potential, the project emerging from the MEGA initiative will achieve stronger cross-border research partnerships; facilitate the introduction of research results into clinical environment and practice; and improve vitally needed EU-wide research collaboration on personalized medicine. In addition, it will build on existing national and regional personalized medicine initiatives, thus strengthening cooperation among Member States and regions of the EU and of the European economic area.[4]

Indeed, the MEGA signatories have committed themselves to developing common approaches that will support the establishment of a decentralized, connected European health data infrastructure. This will provide distributed, authorized, and secure access to national and regional banks of genetic data and to other data relevant to the advancement of research on personalized medicine. Such an infrastructure will promote the use of open standards and of data-management systems to ensure the interoperability of genomic data.

4 www.ec.europa.eu/digital-single-market/en/news/eu-countries-will-cooperate-linking-genomic-databases-across-borders

> "Regulation will help overcome disparities, reduce barriers to accessing innovative treatment, recognize the true value of new therapies, and improve the sustainability of national healthcare systems."

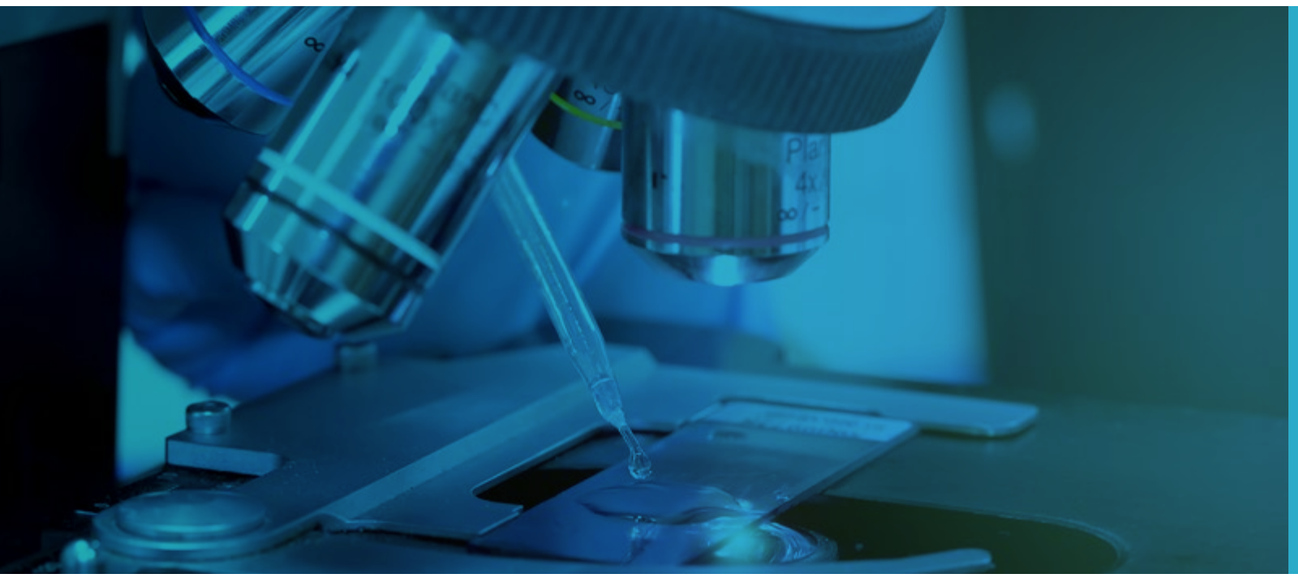
Using Real-World Data to Revolutionize HM Patient Care

According to the European Medicines Agency's update on real-world evidence data collection, real-world data is a term used to describe healthcare-related data that is collected outside of randomized clinical trials. It describes "real-world evidence" as evidence coming from registries, electronic health records, and insurance data. The term has been used to describe different types of healthcare data that are not collected in conventional, randomized controlled trials; it includes such information as patient data, data from clinicians, hospital data, data from payers, and social data.

The European Commission has recognized the importance of this evidence and has summarized it as consisting of specifics not collected under experimental conditions, but as information that emerges from routine patient care (and found in patient registries, electronic health records, insurance data, web/social media content, and on mobile phones). Research using real-world data has been used during comparative-effectiveness investigations; patient-adherence studies; and drug-development initiatives. Sometimes real-world evidence emerges from data collected for other purposes (secondary data). This data is crucial for the implementation of the results of adaptive clinical experiments; is invaluable during drug development (feasibility) trials; and is used to detect patient responses to new therapies in real time. Its potential is enormous, but given that the necessary data infrastructure is currently not European-wide and given the lack of harmonization among systems and regulations, it is perhaps not surprising that the potential of real-world data has not yet been exploited. In this context, regulators need to facilitate health IT according to best practices, support new projects, and listen to patients.

Patient Access and Health Technology Assessment

All stakeholders involved in HARMONY and in personalized medicine aim to improve access to health technology in the EU, not only in terms of ensuring quality, but also in choosing research projects according to medical needs, all of which contribute added value for patients and public health systems. What Europe needs is a regulation on how health-technology assessments are carried out in order to allow Member States to make the most reasonable choices for patients and for the public budget; regulation will help overcome disparities, reduce barriers to accessing innovative treatment, recognize the true value of new therapies, and improve the sustainability of national healthcare systems.



Outcomes:

It is hoped that with the HARMONY BigData Platform containing over 45.000 data sets for example the knowledge of the gene–gene interactions that occur will improve, and means are provided to predict the likely response and outcome of patients following treatment with specific therapies. In addition, improved knowledge of the patient's disease may assist in the move towards more personalized treatment approaches and novel combination regimens. By gathering this knowledge, it is hoped that it will be possible to further refine the molecular landscape and classification of Hematological Malignancies.

There is no doubt that personalized medicine has the potential to improve outcomes for Europe's patients, but its promise must be balanced against a number of highly relevant challenges that may limit its positive impact. There are issues such as increasing costs and the need for the fostering of a relevant ethical, regulatory, and reimbursement environment. These are some of the barriers to implement such innovative treatment at European and national levels.

Personalized medicine approaches have already been particularly effective in terms of treating certain cancers, and have brought practice-changing clinical benefits to patients. However, the spiralling costs associated with personalized or precision cancer medicine, even for new standard medicines, highlight the need to address the cost-value dilemma.

Europe needs to move beyond a simplistic "what the market can bear" approach to a more nuanced, value-based pricing philosophy. Employing this approach and embedding this philosophy into cancer care pathways, for example, can help reward innovation that has truly transformative potential and allow the benefits of a value-centered strategy to accrue for patients and for society in general. Research has shown that patient-centered care models are cost-effective and lead to better outcomes and to patient satisfaction. Patient empowerment can be a vital element of high-quality, sustainable, equitable, and cost-effective health systems. There is a need to secure access to, and affordability of, healthcare, so technological and social innovations are needed to empower the health system, the citizen, and the patient.

Real-world data, for example, promises to substantially increase the effectiveness and efficiency of all the processes central to the development and utilization of medicines, including research and development, regulatory decision-making, pricing and reimbursement decisions, and use in medical practice.

Healthcare systems must be ready in terms of technology to collect data and to use a methodology that analyses information in a way that takes into account aspects such as the protection of personal data, consent, ethics, and data access. The digital market in the healthcare sector needs to be ready and able to take up the challenge.

Transcending Barriers to HM Innovation and Treatment

HARMONY, through its Big Data platform, will not only collect, analyze, and share this real-world data, but will seek to overcome the major hurdles that currently exist and that prevent the successful use and implementation of this source of invaluable information related to HMs.

06

Increasing Knowledge about Hematological Malignancies: Educating All the Stakeholders Involved

Raising awareness about HMs, the treatments that are emerging, and the findings that have come about because of the research carried out by the partners and stakeholders that are involved in this initiative are key to ensuring HARMONY's success and future viability. An important issue is the need to inform key stakeholders on the benefits of and barriers to targeted medicine and treatment in the arena of hematology and in other medical fields. However, it should be borne in mind that there are key deficiencies in the knowledge and the awareness of the benefits among healthcare professionals and policy-makers. Thus, there is a need to increase literacy by developing educational materials and tools tailored for healthcare professionals, healthcare policy-makers, healthcare payers (including insurance agencies), regulatory agencies, and other relevant stakeholders. Approaches that enhance the development of personalized medicine include:

- Enabling patient participation in personalized medicine research, development, decision-making, and health delivery models.
- Developing an educational tool-kit to inform stakeholders on the benefits and challenges of personalized medicine.
- Defining best-practice guidelines for integrating personalized medicine into health systems.
- Making progress in developing personalized medicine across all HMs.
- Assessing the health, economic, and societal benefits of personalized medicine.
- Identifying and validating appropriate models for effective integration of personalized medicine into health systems.
- Influencing policy developments and funding decisions that will advance personalized medicine integration in Europe.

Crucial to the successful implementation of any research agenda in Europe is the active engagement with patients, patient advocates, policy-makers, and regulators at European and national levels.

07 Evaluating the Impact of the Harmony Alliance

The success of HARMONY will eventually be assessed in terms of whether it has succeeded in reaching the following specific objectives:

- The establishment of a clinical data-sharing platform that empowers clinicians, patients, and policy stakeholders to improve decision-making procedures and identify appropriate treatments for patients with HMs.

- The creation of a community that reflects the European HM landscape and that is made up of key expert academic institutions, national clinical disease networks, and European organizations, and includes the active involvement of patient advocacy groups, clinicians, the pharmaceutical industry, regulatory agencies, and other stakeholders from beyond the HARMONY consortium.

- The improvement of access and management of Big Data series from HM patients through the development of a data platform that harmonizes data capture and provides a repository of representative relevant HM data.

- The definition of meaningful and harmonized clinical endpoints and outcomes in HMs in order to facilitate clinical decision-making and allow a more rapid development and evaluation of MAPPs, while at the same time taking into account patient needs.

- The provision of tools for analyzing complex data sets comprised of different layers of information so that molecular and clinical data can be linked to predict clinical outcomes. Small and medium-sized enterprises (SMEs) will participate in the development of novel algorithms to collect, analyze, and distribute large-scale data.

- The identification of specific biomarkers that better define outcome parameters. Through a better understanding of predictive and/or prognostic biomarkers, HARMONY will contribute to the development of specific treatments.

- The setting-up of mechanisms facilitating the sharing of relevant information and knowledge on HMs: The HARMONY Alliance has demonstrated that it has broken down existing silos that restricted access to data between relevant stakeholders both within and outside HARMONY. This will provide a refined role model for Big Data collection, linkage, and usage.

- The provision of a framework for legal, ethical, and governance issues.

08 Conclusions

Ultimately, HARMONY, which will map out the current European landscape of hematological malignancies, facilitate knowledge-sharing, identify trends and correlations, define endpoints, align outcomes, and enhance stakeholders' decision-making and diagnostic skills, will transform patient care for rare blood malignancies—all of which will be done in a cost-effective manner that makes optimum use of European human and economic resources.

Applying the strategies outlined in this White Paper, including harnessing Big Data through the HARMONY Alliance; implementing personalized medicine approaches; seeking out real world evidence; and ensuring education in hematology among healthcare professions will reduce the immense challenges and economic burden of HMs.

This will have a significant and positive effect not only on costs, but also on the quality of life of patients suffering from these diseases; it will also enhance welfare support for individuals with hematological diseases.

What the HARMONY Alliance is seeking to accomplish is nothing less than the radical transformation of HM patient care. The way forward is clear and is attainable.

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The Innovative Medicines Initiative (IMI) is a partnership between the European Union and the European pharmaceutical industry. IMI facilitates open collaboration in research to advance the development of, and accelerate patient access to, personalised medicines for the health and wellbeing of all, especially in areas of unmet medical need.

www.imi.europa.eu

The Horizon 2020 Research and Innovation Programme of the European Union is the largest EU Research and Innovation programme ever with nearly €80 billion of funding available over 7 years (2014 to 2020), in addition to the private investment that this money will attract. It promises more breakthroughs, discoveries and world-firsts by taking great ideas from the lab to the market.

https://ec.europa.eu/programmes/horizon2020/

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 36 national associations and 40 leading pharmaceutical companies, EFPIA's mission is to create a collaborative environment that enables our members to innovate, discover, develop and deliver new therapies and vaccines for people across Europe, as well as contribute to the European economy.

www.efpia.eu

HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

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About HARMONY

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