Contents

Introduction...............................................................................................................................................................................................Page 4

Artificial intelligence..............................................................................................................................................................................Page 7

Digital health in Europe.......................................................................................................................................................................Page 10

Orphan drugs and rare diseases.......................................................................................................................................................Page 15

Prevention................................................................................................................................................................................................Page 19

Cost of medicines.................................................................................................................................................................................Page 23

Clinical research.....................................................................................................................................................................................Page 27

Working together...................................................................................................................................................................................Page 29

Moving forward with research.........................................................................................................................................................Page 32

Good companions..................................................................................................................................................................................Page 36

Cross-border healthcare......................................................................................................................................................................Page 39

Revolution and evolution...................................................................................................................................................................Page 43

Health literacy.........................................................................................................................................................................................Page 46

Interoperability.......................................................................................................................................................................................Page 49

It's all about the patient.......................................................................................................................................................................Page 52
Introduction

In healthcare, there is little doubt that game-changers such as personalised medicine have firmly placed a subject so close to the heart of citizens, namely healthcare, on the verge of one of its biggest evolutionary changes.

Politicians are coming aware of this, and are also acutely aware of the fact that 70% of Europeans place healthcare high up on their agendas.

The timing of this booklet could hardly be better because 2019 has seen the European Parliamentary elections take place at the end of May, which will be followed by the endorsement of a new European Commission under Ursula von der Leyen, as both institutions’ new five-year mandates begin.

This guide is designed to underline many of the issues facing healthcare stakeholders now and down the line, for the benefit of all MEPs, and especially those with a keen interest in healthcare.

EAPM will continue its ongoing engagement with deputies and DG officials, laying the groundwork for future dialogue with the new intake in both the Berlaymont and the Brussels and Strasbourg hemicycles.

Full and open discussion with stakeholders, dialogue with Member State decision makers in healthcare systems and the promotion of cooperation across borders are all key, and are all areas in which the European Parliament can have an impact.

In this year of change (not least the Brexit issue) now is the ideal time to evaluate where we are when it comes to healthcare across Europe, and where we need to be.

Given that healthcare is a Member State competence, there is only so much that Parliament and, indeed, the Commission, can do. But both have already had their say in areas such as in vitro diagnostics, clinical trials, data protection, cross-border healthcare and now the ongoing talks at Council level on EU-wide joint action on HTA.

Indeed, much has moved forward since the elections in 2014,
with the EU having acted in the burgeoning arena of personalised medicine in areas mentioned above.

Let us be clear, access to the best healthcare available for all is one of the key building blocks of the EU. The question is ‘can it do more?’ to facilitate this.

Obviously, many areas ripe for action instantly suggest themselves and these are covered in this booklet.

They include key and ongoing elements of the Alliance manifesto, the STEPs campaign and SMART Outreach programme, the MEGA+ initiative on healthcare data (more of which below and elsewhere in this publication), a solid new foundation for HTA going forward, and enhanced patient involvement in their own healthcare processes.

EAPM, as has been the case since its formation, is actively campaigning in many areas, not least for the introduction of lung-cancer screening programmes, with agreed guidelines, shared best practices and more.

Meanwhile, issues surrounding the sustainability of healthcare systems and what constitutes ‘value’ in this arena, won’t go away.

The ongoing training of healthcare professionals has also been identified as a key issue as science makes great leaps, as has health literacy among patients, citizens, journalists and our decision-makers.

MEGA+, mentioned above, is a new key initiative for EAPM, regions and Member States.

It is the inevitable and necessary response to a clearly demonstrated willingness on the part of many EU countries, and the highly innovative regions within them, to collaborate when it comes to comprehensive data sharing in healthcare.

The MEGA+ initiative includes all medial data, not just genomes, but imaging, eHealth apps, electronic health records, and more, all undertaken with the highest level of ethics and patient consent.

Europe’s regions are, of course, key to this process with their plethora of excellent universities and research bodies.

In recent times, the European Commission has been invited to pursue a dialogue with Member States’ authorities and stakeholders to facilitate step-by-step implementation of a public health genomics approach both at EU and national level on the basis of past initiatives.

This is to be praised. MEGA+ however, and as noted, will include all valuable healthcare data, with the activity having an emphasis on a ‘bottom-up’ strategy, using essential dialogue with the regions and healthcare actors who are the real drivers of innovation.

The field of healthcare data-sharing is just one example. Essentially, the goal of this publication is to ensure that we touch on all the bases in the many other fields in which the Parliament and Commission can make a difference.

Partly through this publication, it is EAPM’s aim that it will become abundantly clear to MEPs and Commission officials that
their involvement and engagement over the next five years will be vitally important in progressing healthcare in general, and personalised medicine in particular.

That involvement is vital. In this year of all years, one could argue that the Brexit vote occurred in great part due to the fact that UK citizens failed, down more than 40 years, to understand exactly what the EU has been doing for them. Many failed to grab the positives. Perhaps the concept is just too abstract, too far away, and this needs to be addressed.

Delivering the best possible healthcare is one way of doing just that (as the fallacy concerning an extra £350 million-per-week suddenly going to the NHS surely proved. Fact or fiction, the people cared) - citizens can see it, feel it, quantify it.

That could be in the form of access to necessary drugs that are affordably priced, more hospital beds, shorter waiting lists and a GP that isn’t too busy to see them until four-or-more weeks have elapsed.

It has never been more important for the EU to show the value of the ‘grand project’, and there is no better place to start this transformation than in the area of health.

And there are no better institutions to do this than the directly elected European Parliament, and the Commission it endorses and scrutinises.

The authors of this document and associated stakeholders are working hard to promote integration, collaboration and dialogue among each and every one involved in the field of personalised medicine.

They believe that legislation needs to be moulded to offer the right laws, in the right place, at the right time.

Once achieved, this will allow us all to work more quickly and more effectively towards creating a healthier – and thus wealthier – European Union.

Clearly, personalised medicine is here and here to stay. With the help of MEPs and a Commission that understands the needs of an ageing population and the challenges that this brings, Europe can benefit from its wider, quicker and more efficient introduction.

This can be made easier and more successful with a European Parliament, and its colleagues in the Commission, that is on message when it comes to the issues facing its citizenry.

Healthcare is key.

Denis Horgan
EAPM executive director
Artificial intelligence

Human intelligence set to explore aspects of the artificial version

Artificial intelligence, or AI, is a hot and ever-expanding topic in the world we now live in, and EAPM intends to set up a multi-stakeholder working group to explore AI’s potential and implications, to understand what is required to maintain momentum, and to create a workable ethical framework.

Key to this is to understand, appreciate and facilitate AI as part of ongoing innovations in healthcare, and particularly in personalised medicine.

The project will involve various Member States and regions, with initial target areas being core groups of stakeholders in Germany, France, Italy, Spain, Poland and the UK.

The goal would be to develop a common position alongside a framework document determining criteria, and hold an event to communicate the results in the second half of 2019.

A little background…

There’s no doubt that AI is changing the world around us. Not least in healthcare where, for example, algorithms can help dermatologists make better diagnosis by detecting 95% of skin cancers by learning from large sets of medical images.

AI improves products, processes and business models in many sectors, and we need to be sure to harness it to full effect here in Europe, where we are often under-resourced in this field and have to compete with the US and China, who are throwing vast sums of money at AI.

Artificial intelligence, or AI, covers systems that display intelligent behaviour by analysing their environment and then taking actions to achieve specific goals. This is done with some degree of autonomy.

Examples around us include using a virtual assistant to organise things, self-driving vehicles, and suggestions from a phone in respect of a restaurant you might enjoy, a song you might like, plus voice and face recognition and so on.

Advanced robots can use AI, as can ‘internet of things’ apps and drones.

The European Commission published a European strategy year ago, that put forward an approach that it says places people at the centre of the development of AI.

It also encourages the use of technology to tackle such issues as curing diseases, as well as climate change, anticipating natural disasters and improving cybersecurity.

Coordination at European level is essential for success, so there is a need to work with Member States to maximise the impact of investments at EU and national levels, encourage synergies and cooperation across the EU, exchange best practices and define the way forward.

Practical applications

Europe has such things as robotic urologists. Among machines being used by them are ones that are not exactly robots per se, but they allow the work of the surgeons to be miniaturised and very precise.

Many healthcare professionals say that surgery today is not good enough, and that there are too many complications. Going
A lot of the AI technologies rely on data in order to function better. Once performance is up to a high level they can help to improve and automate decision making in their particular domain.

Here in Europe we have a vast amount of data, a real wealth of information that can be pushed towards AI systems in a variety of fields, including healthcare.

AI is going to change our world. The promise has nowhere near been fulfilled yet and new applications will come along one-after-the-other. Therefore, the opportunities for Europe are huge. But we need a solid framework as the competition globally is, and will be, just as huge.

**Investment and regulation**

Unfortunately, Europe is behind on investment in AI. If we don’t have a big push in the arena we risk losing out on opportunities, losing a lot of clever people and being a consumer for solutions developed outside of the Union.

The Commission has increased investment in AI under the research and innovation framework programme to €1.5 billion in the period up to 2020. That’s a 70% increase compared to 2014-2017.

To help the development of AI, regulators have a part to play. One of the most important jobs they can do is work to eliminate obstacles caused by fragmented markets.

Products and services are becoming increasingly interlinked and digitised. So avoid market fragmentation must be avoided in areas such as artificial intelligence. What is required is a new research and innovation partnership in respect of AI. Ideally Europe needs cooperation among the best research teams in the EU. Working as a joint force should make tackling scientific and technological challenges in AI more efficient.

**Ethics and acceptance**

Humans should be at the centre of research, and this is as true in AI as any other area of healthcare. There may be robots, but there will always be humans.

Some people remain uncomfortable with the idea that robots are being used in everyday life and in medicine. So a human presence shows patients value, and often they feel better for it. But the robots are, for all that, here.

There are several major barriers to the use of robots in healthcare, including the actual appearance of robots, plus changes to healthcare work, and ethical and legal challenges.

There are perceived threats to professional roles among healthcare staff, especially against a backdrop where patient trust as an aspect of care is perceived to require human input. Putting a robot in a caring role causes problems sometimes.

Meanwhile, if a robot looks too ‘robotic’, then a fear arises But, on the other hand, if they look too human, perhaps expectations will be too high.

Changes to healthcare work also provides an obstacle in that this can cause tensions between standardisation through automation and the unpredictable nature of healthcare work. Essentially, the use of robotics can also be seen as impinging on human professionalism.

With regard to new ethical and legal challenges, there are currently no existing liability and ethical frameworks in what is a rapidly evolving field. Regulation is clearly key to promote routine use without stifling innovation.

There are other issues, too, specifically those that deal with data. These need transparency because the system used is based on certain principles and values and every stakeholder needs to understand and agree upon which ones those are.

And when it comes to accountability, there is the issue of responsibility. Clearly, responsibility and liability are with the humans and not the machines. This is an important issue that needs to be defined.

Overall, there are clearly significant social challenges, and experts, scientists, and lawyers need to be brought together to look at the practical questions which arise where AI is being used.

This is EAPM’s goal with this project.
Key recommendations

To prepare the healthcare systems in Europe to reap the benefits from AI and mitigate any unintended consequences of its use, we believe that a coherent strategy for AI in Healthcare must be put in place in Europe.

We suggest that policymakers and stakeholders should aim at achieving the triple aim of Innovation, Trust and Inclusiveness.

**Innovation:** Commit resources to the development, adoption and implementation of AI in Healthcare and foster its use to improve care, efficiencies and access.

- Setup programmes to safe test innovative AI solutions in healthcare settings;
- Invest in the interoperability of health data, its provenance and curation;
- Invest in research of explainable healthcare AI solutions.

**Trust:** Whilst AI needs data to function, autonomous determinations made by algorithms will affect individuals. More automation should not translate to less safety and less protection.

- Test-drive the large scale use of health data for research against the GDPR;
- Develop an healthcare specific AI ethical framework;
- Devise agile risk-based certification frameworks for AI based software medical devices.

**Inclusiveness:** As the use of AI in healthcare expands, its benefits should remain accessible to all, while the workforce and patients should be active in informing this transformation.

- Ensure healthcare AI solutions cater for a diverse population by addressing data bias and promoting equitable access;
- Drive training and education on healthcare AI for patients, medical professionals, healthcare organisations, policymakers and government;
- Promote the engagement of all healthcare stakeholders to understand the technology, debate how it will impact healthcare and address concerns.
Digital health in Europe

Digital healthcare: The role of Member States and regions

There is plenty of innovation going on in the healthcare sector in Europe, although some - including EAPM - would argue that there should be even more. But huge a digital transformation is certainly underway and affects healthcare as much as any other arena.

The European Commission, for its part, has been working to identify specific aspects and tangible results necessary to make a noticeable change to health systems and investments at EU level. Other stakeholders are doing the same, including the Alliance.

We all know that silos can be counter-productive, certainly when it comes to digital healthcare, which is an arena which can only hope to reach its full potential if Member States and the regions found within them find ways to share their innovations for the benefit of European patients within and beyond their own borders.

Europe has fundamentally changed from an industrial to an information society. This can be seen everywhere, and in healthcare covers personal and societal aspects (not least with regards to data and data privacy) as well as the technological and scientific ones (healthcare apps, genomics et al).

Prevention is more to the fore, now, as is targeted care (the right treatment for the might patient at the right time) and leaps in the use of telemedicine have led to a shift in many cases from hospital-based care to outpatient-based care.

Of course, in this digital world, Europe must strive to have its healthcare digital systems as error-free as possible, as well as totally trustworthy. Not easy with so much information, but utterly essential.

Digital health and policy

Europe’s policymakers need to find ways to invest in systematic evaluation procedures, as well as in evidence informed policy measures and a robust evaluation methodology.

Lest we forget, a healthcare system should have two simple goals: efficiency, meaning to produce as much health as possible, and equity, meaning that health should be fairly distributed.
In line with its Digital Market Strategy, the EU adopted a set of conclusions on digital health in December 2017, inviting Member States and the Commission to work together to seize the potential of digital technologies in health and care.

The European Commission subsequently published a Communication on “enabling the digital transformation of health and care in the Digital Single Market; empowering citizens and building a healthier society”.

The vision outlined is to promote health, prevent and control disease, help address patients’ unmet needs and make it easier for citizens to have equal access to high quality care through the meaningful use of digital innovations. EAPM and its members and stakeholders have the same vision.

**MEGA+ and more**

Now has come the time for scaling up when it comes to digital solutions. EAPM is currently engaged in exactly that through its work with Member States and regions in respect of its own MEGA+ initiative, which seeks to make use - to ethical and optimal levels - of all the mass of relevant health data no out there, and theoretically usable.

A huge part of this will be encouraging EU countries, and the innovative regions within them, to share and co-develop innovative solutions to healthcare problems, on the back of the awesome power of Big Data.

Fortunately, over the years, EAPM has built upon its SMART initiative (SMART stands for Smaller Member states And Regions Together) to pull together a network of regions and Member States, not least through MEGA+.

Essentially, the Alliance is taking a three-pronged approach, through institutional engagement, Member State engagement and bringing MEGA+ ideas into practice through both Member State and regional cooperation and coordination.

**The aim and the way forward**

In pursuing the way forward in digital health, various data sets could and should be shared, from hospitals, electronic health records, digital phenotypes, wearables, other health apps, biobanks and many more resources available.

But of course effective data interpretation requires the rapid involvement of experts and organisations everywhere. The hurdles of healthcare data fragmentation, representation and organisational boundaries will need to be tackled for innovation in the field to succeed.

Also, the massive quantities of data involved from hundreds of different sources means that, to get the best out of it, networked environments will need to work together.

This is our goal as part of the digital health revolution.

A vital part of EAPM’s role has always been engagement with health-minded MEPs, as well as continuous involvement and ongoing discussions with expert groups in our arena.

For example, EAPM is working as part of the PIONEER (prostate
cancer) and HARMONY (haematology) projects, positioning MEGA+ (as well as the potential of and need for real-world evidence) front-and-centre in the problem statement for PIONEER, plus the policy paper strategy for HARMONY.

Other aspects being covered as EAPM cements itself firmly in the digital health age are ensuring the quality of genomic data, current gaps in data interoperability and whether EU standards for data sharing are being followed.

The big plus of MEGA+

These days, Big Data is everywhere and generated on a routine and daily basis.

Amid this explosion, Europe is trying hard to regulate its data-flows for solid privacy and ethical reasons, not least through the relatively recent entering into force of the General Data Protection Regulation.

At the same time, it and all stakeholders are trying to ensure that this wealth of valuable information can be freed-up for the public benefit, not least in the arena of health.

The enthusiasm resulting for the sharing of medical data has been clearly demonstrated on the part of many Member States, and the innovative regions within them, to collaborate when it comes to data sharing in healthcare.

Various data sets could and should be shared, from hospitals, electronic health records, digital phenotypes, wearables, biobanks, genomes and many more available resources.

Hence MEGA+, an initiative that aims to build and implement a coordinated, pan-European project in order to garner crucial medical information (genetic and more) that could have an immeasurable benefit when it comes to the health of current and future EU citizens.

Europe’s regions are, of course, key to this process with their excellent universities and research bodies.

MEGA+ will include all valuable healthcare data, with the activity having an emphasis on a ‘bottom-up’ strategy, using essential dialogue with the regions and healthcare actors who are the real drivers of innovation.

It extends to all medical data, to include imaging, eHealth apps, electronic health records, and more, all undertaken with the highest level of ethics and patient consent.

MEGA+ activity will place an emphasis on a ‘bottom-up’ strategy, using essential dialogue with the regions and healthcare actors who are the real drivers of innovation.

Such a project will achieve stronger cross-border research partnerships, the introduction of research results into clinical environment and practice, and vitally needed EU-wide research collaboration.

And it will build on existing national and regional personalised initiatives, strengthening cooperation amongst Member States and Regions of the EU and the European Economic Area.

It will provide the opportunity to bring about distributed, authorised and secure access to national and regional banks of Big Data relevant to the advancement of research, while promoting the use of open standards and data management systems to ensure interoperability of the information.

Underpinning this will be the setting-up of a pan-European networked infrastructure for health information and
undertaking the initiative as a coordinated effort across European countries with regions as the foundation.

Generating health data is no longer the limiting factor. The challenge lies in ensuring sufficient quality input and making sense of the output.

The MEGA+ project is geared towards securing country specific buy-ins to mobilising efforts around population-based health data - both within and across countries in the EU. Political sponsorship and commitment of resources will be critical.

Also, the identification of high-quality operational units acting at the interface to the healthcare system and a range of other stakeholders will help ensure delivery.

Meanwhile, the project will look to engage academics, plus pharmaceutical and biotech companies to ascertain what they consider to be valuable, and align the various stakeholders to facilitate delivery.

The latter would include research groups, commercial partners, clinical experts and more.

The EU's forward-looking regions need to coordinate in a smart fashion to help address Big Data's potential, working together, rather than singly - and this is at the heart of what MEGA+ is about.

More data on data

Data has often been referred to as ‘the fuel of the future’. But it’s also the fuel of the present as there is so much out there already, but we need to ensure that data flows as freely as possible across borders and between sectors.

Clinical data can be, and are, used in order to assess and monitor the effectiveness and safety of medical technologies, as well as the costs.

In this era of fast-moving science and the development of personalised medicine, Europe needs to put its hundreds-of-millions of potential patients across its Member States right at the heart of the revolution. And that means, in part, using the health data that the majority of them are willing to share (under the proper circumstances, of course).

You will have noticed that it is now possible to network pretty much anything ('the internet of things') – ‘smart’ wearables that pass data back to hospitals while we are at home and pill-boxes
that tell us that it’s time to take our medicines, are just a couple of examples in the field of health.

Gadgets that send back information are, of course, part of the gathering apparatus of Big Data – data that is stored, channeled and, theoretically at least, can be used for the greater good.

Increases in computing power and new technologies have very quickly brought down the price of using data in healthcare. But other aspects need to be optimised.

Effective data interpretation requires the rapid involvement of experts and organisations everywhere.

The hurdles of healthcare data fragmentation, representation and organisational boundaries will need to be tackled for innovation in the field to succeed.

The MEGA+ initiative aims to solve such issues although, realistically, we cannot assume that all Member States and regions will have the same capacity and resources, and thus ways need to be found to maximise on what already exists and look at enhancement possibilities.

Thus MEGA+ will take into account that every country has bigger or fewer resources. However, the concept will ideally see a linking together of the efforts of a coalition of the willing to gather and share routine data.

This would certainly represent a real breakthrough and allow the utilisation of the research across different health domains.

All the necessary pieces of the jigsaw need to be put in place to facilitate healthcare data sharing.

The appliance of science

Let us be clear, Europe’s scientists and researchers are among the best - but they all need access to up-to-the-minute data.

Making better use of Big Data in a medical sense will achieve several things, including reducing current inequalities in access to innovative technologies such as genetics.

The advances in science in recent years have been giant ones. The technology is out there, including in the amazing and exciting field of genomics, but there is a need for much better collaboration and more investment in research and innovation.

The European Union, Member State policy makers and regulators are critical in helping shape the landscape for the successful implementation of genomics and related technologies in healthcare.

We all know that EU Member States individually and as a group are facing multiple challenges in healthcare. With rising healthcare costs, Big Data has the potential to impact the health of all of us and provide diagnostic, economic and efficiency benefits, ensuring that patients receive the right information and the right treatment at the right time.

But the use of data sets needs to take into account underlying safety issues and any decisions need to be evidence based. Evidence from clinical practice, using the available routine data sets dovetailing with evidence from clinical trials (even smaller ones) can improve care quality, as well as improving HTA. Law- and policy-makers are critical in this regard.
Orphan drugs and rare diseases

A very personalised need

Orphan drugs are, according to Orphanet (supported by the European Commission and formed to gather knowledge on rare diseases), are intended to treat diseases so rare that pharmaceutical companies are reluctant to develop them under usual marketing conditions.

The process from the discovery of a new molecule to its marketing takes 10 years on average. It's, expensive and results are uncertain. From a financial point of view, developing a drug intended to treat a rare disease does not allow the recovery of the capital invested for its research.

Therefore, orphan drugs may be defined as those that are not developed by the pharmaceutical industry for economic reasons but which respond to public health need - a very personalised need, in fact.

On top of this, a drug may also be considered as ‘orphan’ when a substance is used in the treatment of a frequent disease but may not originally have been developed for a more rare disease.

Orphan products are developed to treat patients suffering from very serious diseases for which no treatment, or at least a satisfactory one, has so far been available. These diseases affect only a small proportion of the population (less than one person per 2,000 in Europe), most often at birth or in infancy.

The number of rare diseases for which no treatment is currently available is estimated to be between 4,000 and 5,000 world-wide. Twenty-five to 30 million people are thought to be affected by these diseases in Europe alone.

The EU’s Orphan Regulation of late 1999 was adopted to encourage the development and authorisation of medicinal products for rare diseases. Since then, there has certainly been progress, in particular as regards to generating significant activity by the pharmaceutical industry in this field.

It is estimated that 5,000 to 8,000 distinct rare diseases exist in the EU. Therefore, development of orphan medicinal products is an important consideration for public health policymakers.

Throughout the last decade of the 20th century, a number of Member States adopted specific measures to improve knowledge of rare diseases in respect of their detection, diagnosis, prevention and treatment.

Unfortunately, such initiatives were few and -significant progress in research on rare diseases didn’t really occur. So along came the Orphan Regulation…

What is the Orphan Regulation?

The Orphan Regulation came into being chiefly to ensure that patients suffering from rare conditions have the same quality of treatment as any other patient in the EU. Equitable access to the best treatment available is also a pre-requisite demanded by those who espouse the concept of personalised medicine.
The regulation established an EU procedure for designating orphan medicinal products (or OMPs) and put forward incentives for research in the field and the development and marketing of such products.

This occurred where the diseases are so rare that there is very little chance of development and marketing costs being covered by subsequent sales.

On top of this, the regulation encouraged Member States to adopt similar and/or complementary measures at national level.

Any incentives rely on the orphan drugs being designated as such before the marketing authorisation is granted.

The regulation’s processes involved the establishing of an expert committee for OMPs within the European Medicines Agency (EMA) with EMA protocol assistance for sponsors of medicinal products on the conduct of the tests and trials necessary to demonstrate their quality, safety and efficacy, or regulatory assistance.

Important to pharmaceutical companies is the provision of ten years of market exclusivity (which period disallows other industry operators from entering the market with a similar product for the same medical condition).

According to the European Commission, market exclusivity is regarded as crucial to any system of incentives for R&D on such products. The protection thus granted prevents the EU or individual Member State from subsequently issuing or varying a marketing authorisation for a similar product (for example, one with the same active substance) and for the same indication.

It is worth noting that a section of the regulation dealing with medicinal products for paediatric use allows that market exclusivity may be extended to 12 years if a paediatric investigation plan is completed.

The regulation also allows for access to a centralised procedure allowing immediate marketing authorisation in all Member States, thereby facilitating the availability of medicines to all patients in the EU.

It allows offers a system of reduced fees for regulatory procedures, and a repository of all designated and authorised orphan medicinal products.

So...is it an orphan drug?

It is if its producer can establish that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five-in-10 thousand persons “in the Community when the application is made”.

Either that, or it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition but, without incentives, it is unlikely that the marketing of the medicinal product would generate sufficient return to justify the necessary investment.

On top of this, there must exist no satisfactory method of diagnosis, prevention or treatment of the condition already authorised or, if such a method does exist, the new product will be of significant benefit to those affected by that condition.
More on incentives

The main direct incentives introduced by the Orphan Regulation allow for companies to apply to the EMA to have a product designated as an OMP. The process is free. The EU says manufacturers benefit from incentives such as protocol assistance to make development easier and authorisation of innovative medicines for the benefit of patients.

The products can also more easily attract public or private funding, with the EU’s research framework programme allowing companies to secure R&D financing. This, in turn, creates opportunities for scientists to make important advances in treating the rare diseases in question.

Since the introduction of the Orphan Regulation there has been a steady increase in the number of requests, which suggests that at least to some extent the incentives have proved to be attractive.

For the record, up to 2015, the most frequently designated orphan conditions have included acute myeloid leukaemia, cystic fibrosis, glioma, pancreatic carcinoma ovarian cancer, multiple myeloma, and chronic lymphoblastic leukaemia. About one-third of all applications have concerned some form of cancer.

Member States and OMPs

Some Member States have introduced reduced fees for registration and academic clinical trials, tax reductions or waivers, public funding for research and free scientific advice.

Meanwhile, many Member States have confirmed that they are implementing ‘compassionate use’ programmes to bring unauthorised medicinal products to market, thereby speeding up their delivery to patients in need.

These programmes are designed for individual patients on the basis of a healthcare professional’s statement or, alternatively, the manufacturer can make products available to a group of patients. Personalised medicine in action. The cost of the product may or may not be reimbursed, and this depends on the Member State in question.

The impact of reimbursement on the availability of orphan medicinal products already looks to be a matter of concern in the EU, with the budgetary impact of OMPs expected to rise due to newly authorised products down the line.

As a result of anticipating this, some EU Member States have adopted specific measures for the reimbursement of OMPs.

Taking Germany as one example, by 2015 the country had introduced fee reductions for activities involving medicinal products targeting rare diseases or under its national research programme.

Regarding the compassionate use of medicinal products, no marketing authorisation is required products made available free of charge to patients with a seriously debilitating or life-threatening disease that cannot be treated satisfactorily with an authorised product.

The German system means also that, once authorised at European level, all OMPs are fully reimbursed by statutory health insurance.

In Ireland, meanwhile, between 2010-2015, almost €7 million had been invested in research on a number of rare conditions and diseases, such as retinal degeneration, Battens Disease and Epidermolysis Bullosa. The country’s Health Products Regulatory
Authority advises and supports pharmaceutical companies as appropriate and operates a system of fee reductions or waivers for clinical trial applications.

Access to unauthorised medicines is given in accordance with the specifications of a practitioner for individual patients, or through participation in an approved clinical trial.

And in Italy, fees for national scientific advice procedures relating to OMPs are subject to a 50% reduction, while access to treatment for patients suffering from a rare disease is guaranteed through various legislative instruments, in particular the compassionate use programme.

As a further example of Member State policy, Spain has measures to support R&D on OMPs, including independent clinical research projects, a platform of clinical trials formed by 30 research groups; and a biomedical research network centre for rare diseases.

*Note: Orphanet was established in France in 1997 to gather what was then scarce knowledge on rare diseases so as to improve the diagnosis, care and treatment of patients with rare diseases.

The initiative became a European endeavour from 2000, supported by grants from the European Commission.

Orphanet has gradually grown to a network of 37 countries, within Europe and across the globe.

Over the past 20 years, Orphanet has become the reference source of information on rare diseases. As such, it is committed to meeting new challenges that arise from a rapidly evolving political, scientific, and informatics landscape.
**Prevention**

We share the burden of disease, and we share the responsibility for disease prevention

Preventative care saves lives (and let’s be absolutely honest, much-needed money) and part of this should be an onus on policy- and law-makers and part of it an onus on members of the public taking better care of themselves.

Civil society and certainly patient groups can help to emphasise this. The public can be part of the solution, as well as their health obviously being the problem.

Prevention in a public health sense has been called ‘the science and art of preventing disease, prolonging life and promoting human health through organised efforts and informed choices of society, organisations, public and private, communities and individuals’.

The public can be as small as a handful of people, the population of a region, as large as an entire Member State or even larger, encompassing the entirety of Europe and beyond. It takes into account physical, psychological and social well-being.

The simple facts are that, in a Europe whose Member State healthcare systems are creaking under the weight of fiscal pressure - due to an ageing population which, ironically, is living longer due to healthcare improvements - keeping the population as healthy as possible is a two-way street.

From one direction comes the public itself, while from the other direction comes the policies and laws put in place by those that make and implement decisions.

**Time to get personal**

Science is moving quickly in healthcare - often too quickly for politicians, patients and front-line healthcare professionals to grasp and keep up with. The rise of genetic sciences, improved imaging, the ubiquity of data, and the emergence of personalised medicine are not single reason, they merge as one.

But taking one of those aspects, there is a need to underline the ‘personalised’ nature of healthcare in the modern world.

Millions of individualised citizens, often in smaller groups (such as those with rare diseases), alongside those who would treat them, need to be imbued with the knowledge of personalised healthcare options, including the new medical ‘pot of gold’ that is genetic profiling.

In the same way that, say, vaccination is widely accepted (at least by the majority) as a cost-effective preventative healthcare measure, it needs to be highlighted and emphasised that personalised and genetic treatments show that resources can be used more efficiently.

Screening is a part of this, and in the case of lung cancer it just isn’t happening, despite the success of breast-cancer screening programmes and a proof that screening for lung cancer works.

**Money, money, money**

Ah, but what about the cost of all this preventative stuff? Well, the maths is pretty simple...

Assuming that society doesn't throw away its core values as suddenly say ‘let’s just let the old and the sick die, as we can’t afford the pensions or the treatments’ the best plan is to keep people as healthy as possible for as long as possible.
Health means wealth, as has often been demonstrated. Keep people healthy and they can work longer, pay taxes longer and put more and more in to society before the time comes to take something back out.

Waiting times will be shorter, expensive hospital beds will be taken up for less time, and fewer people will anyway need to even be admitted to hospital or even head to the doctor once a week, given the advances in health apps, for example.

**Live and learn**

As well as policy decisions and laws covering, say, ethical use of Big Data, electronic health records, IVDs and cross-border healthcare, there also needs to be ongoing education for healthcare professionals in modern methods coupled with input from ‘ordinary people’.

In the latter case, given that prevention is better than cure, individuals need to take up a responsibility to live healthy lifestyles by, for example, cutting down alcohol consumption, giving up tobacco products, taking more exercise and re-thinking their diets. For preventative purposes they can even, these days, undertake genetic sequencing as a further measure.

**Getting smart on healthcare**

You don’t have to be a genius to realise that, if every disease could be prevented before it began, the improvements in the long-term health of citizens would be assured and the savings for healthcare services would be enormous.

Personalised medicine can go some way to achieving this, with genome sequencing (as mentioned above) having the ability to spot a tendency to develop a certain disease down the line. Vaccinations and screening for breast, prostate and lung cancer, for example, can also bring this about.

Resources are of course limited - every healthcare system in each Member State is struggling to keep pace with the new demographics - and there needs to be a substantial, ‘smart’ shift in the way these services spend what money they have.

Putting more emphasis on preventative measures is a rock-solid way to do this.

Currently Europe is under-using its ‘cash for care’. Each EU country should be looking at ways in which every euro spent has a higher-value impact on the health of its citizens.

MEPs, representing these Member States, should be actively campaigning and working towards better preventative processes for the benefit of each and every citizen.

This means that the European Parliament, through its deputies, could have a significant role to play in any programmes geared towards ramping up preventative health measures.

At the start of the new five-year term, MEPs will have countless opportunities going forward to change things for the better.

When it comes to a preventative measure such as screening, to make it optimal we need to ensure best use of efficient risk-assessment methods, top-of-the-range imaging technology, and guidelines that encourage the minimisation of invasive procedures and risk to the patient.

Overall, we have an ageing population in which many patients
suffer from more than one chronic disease, at high human and financial cost, so we are clearly missing prevention opportunities at every turn.

There will certainly be an increase in the prevalence of chronic diseases, which brings both great cause for concern and an opportunity for more and better prevention. Europe must look to somehow preventing the growing number of chronic diseases.

Surely the case for prevention as treatment – as well as treatment as prevention – is now here, if it wasn't already. That would be the smart way to go about things.

**Diagnosis: the sooner the better**

Early diagnostics, obviously, also have a major part to play in healthcare and there has never been a better time to grasp the opportunities in, for example, cancer prevention using the latest discoveries in “omics” – including genomic science.

Due to these advances, our knowledge of common variants related to cancer risks has leaped from five to more than 450 and, genetically, we know a great deal more about what makes individuals susceptible.

As many will know, personalised medicine utilises research, data and up-to-the-minute technology to provide better diagnostics and follow-up for citizens than is currently the case. It uses genetic information to discern whether a particular drug or regime will work for a particular patient and assists clinicians in deciding which treatment will be the most effective. It can also have a huge impact in a preventative sense.

Earlier diagnostics and earlier treatment has many benefits, among them fiscal, as mentioned above, because while cost is a major issue – and there are key questions about the cost-effectiveness of new and even existing treatments – better diagnostics will ease the burden on healthcare systems.

Not least, it will allow a more preventative approach in that gene technology will flag up the likelihood of a particular individual developing a particular disease and provide a good idea of how it will develop, thereby encouraging early intervention.

**Genetics - the gene genie**

You will read plenty about EAPM’s MEGA+ initiative in this document. It has its own section but, to sum up briefly, the Alliance has been involved in the one-million genomes project (which it initially dubbed MEGA - for Million European Genomes Alliance) since its inception and helped pave the way for a multi-Member State sign-up in April 2018.
The Declaration of Cooperation “Towards access to at least one million sequenced genomes in the European Union by 2022” was signed in Brussels on 10 April 2018 during Digital Day.

The cast majority of Member States have either signed up to the voluntary agreement or are watching closely as observers.

In the last year, EAPM has expanded the idea from only genomes to any data deemed suitable for medical purposes (under all agreed standards and ethical constraints), which the Alliance calls ‘MEGA+’.

Essentially, the Alliance is taking a three-pronged approach, through institutional engagement, Member State engagement and bringing MEGA+ ideas into practice through both Member State and regional cooperation and coordination.

Moving forward…

Various data sets could and should be shared, from hospitals, electronic health records, digital phenotypes, wearables (and other health apps), biobanks and many more resources that are already out there.

Effective data interpretation requires the rapid involvement of experts and organisations everywhere. The hurdles of healthcare data fragmentation, representation and organisational boundaries will need to be tackled for innovation in the field to succeed.

Also, the massive quantities of data involved from hundreds of different sources means that, to get the best out of it, networked environments will need to work together.

What this will all add up to is not only knowledge of how to cure or control a disease once it has developed, but also to understand a particular disease’s development which allows it to be halted at an earlier stage.

Key elements of prevention

In a nutshell, there are several aspects key to prevention that need to be addressed during the forthcoming legislative period.

Among them are the following, which all feature in this publication:

• Screening programmes, guidelines and best practices

• The improvement of health literacy in respect of personalised medicine

• Best use of Big Data (example MEGA+ and including health apps)

• Education for HCPs in respect of preventative aspects of personalised medicine

• Public health - responsibility split between patient own-initiatives and law/policymakers
**Cost of medicines**

The affordability or otherwise of medicines in the EU

Earlier in 2019, none other than the European Parliament produced a report looking at the current pharmaceutical system in the EU, something the Commission has done regularly, so here on these pages EAPM will try to provide and overview.

According to the EP, the pharmaceutical system we currently have in the developed world dates back to the 1970s, when it was set up with the principal aim of improving and ensuring patients’ healthcare safety.

This came on the back of the thalidomide tragedy, which was one of the deciding factors behind what is now the EU’s pharmacovigilance system.

Subsequently, the World Trade Organisation greatly encouraged the inclusion of medicines in the patent system and the protection of intellectual property rights in the industrial sector in connection with the development of new drugs.

That may be so, but (says the report) the pharmaceutical market differs significantly from other markets in that the protection of intellectual property in the medicines market could conflict with the fundamental right to health protection, whereby governments must guarantee access to medicines.

Down the years and decades, a number of parliamentary resolutions and Council conclusions have drawn attention to the specific nature of the pharmaceutical market, highlighting the need for debate and for measures to be taken in this regard.

The pharmaceutical market in Europe has generally faced high levels of safety regulation but looser control over financial matters and innovation quality.

This, the Parliament says, can be seen in the way the pharmaceutical industry decides which research areas to prioritise: it bases its decisions on the size of the market, whilst setting the price based on the market value, and choosing the market according to the highest price that the buyer is willing to pay and on the greatest financial gain possible.

The report adds that “This practice has called into question the sustainability of healthcare systems and provoked a reaction from health care authorities, which are advocating the rebalancing of public and private interests.”

It certainly hasn’t solved the issue of the prices of so-called orphan drugs for use in rare diseases.

The 2019 report notes that prices of new medicines have increased during the past few decades to the point of being unaffordable for many European citizens and of creating an unsustainable situation for healthcare systems. It’s a fact that, in Europe, 20% of Member States’ average health budgets is spent on medicines.
Another factor distorting the medicines market is the generics industry. These drugs are one of the main ways of increasing competitiveness. However, misusing and abusing the system of intellectual property leads to a large number of litigation cases which delay a generic drug’s entry onto the market, as well as many strategies and ploys whereby companies reach agreements aimed at achieving this purpose.

Parliament pulls no punches when it says that “individual Member States and the Commission have taken timid measures without any kind of coordination, which has fragmented the market even more and generated inequality in access to medicines for European citizens”.

“Likewise, they have missed the opportunity to achieve greater efficiency,” the report adds. Ouch!

The pharmaceutical industry is one of the most competitive sectors in Europe with a 20% return on investment, generating 800,000 jobs and producing an output of approximately €200 billion annually.

But it is up against big competitors, such as the US and Asia, which calls for the implementation of key strategies, such as innovation (disruptive or otherwise) to up its competitiveness.

Parliament in its report has concluded that, after being in place for four decades, the system needs to be reviewed, as does its regulation.

This is in order to “strike a balance between public and private interests, the sustainability of health care systems and the right everyone has to health protection, guaranteeing research incentives as well as individuals’ interests and their right to better healthcare standards”.

Each Member State and all EU institutions, as well as the private sector, should be aware of the role they have to play going forward.

**The sector itself**

The pharmaceutical sector accounts for more than 17% of EU R&D expenditure. With the population ageing globally, health-related services and products are growth markets and offer a potential for Europe’s pharmaceutical industry.

We all know that Europe faces major health, economic and scientific challenges: and has been losing ground in pharma innovation - especially to the aforementioned US and Asia.

We are seeing shortcomings in the availability of medicines. European patients still suffer from inequalities in availability and affordability of medicines. Treatments are becoming more personalised, when those treatments are actually available.

As we all do, the European Commission believes that “European citizens need to increasingly benefit from a competitive industry that generates safe, innovative and accessible medicines.”

The institution has supported eHealth measures, as well as attempting to help create a single and sustainable market in pharmaceuticals.

It notes, however, that stakeholders (not least EAPM, members and partners) continue to raise concerns “with regard to the market fragmentation linked to disparities in national pricing and reimbursement schemes, unnecessary regulatory burdens caused by divergences in the implementation of Community legislation, and a lack of commercial interest in national markets which are economically less attractive”.

This situation may create important inequalities between patients in the access to medicines while the growth potential of the EU industry is hampered. Completing the single market in pharmaceuticals remains an important objective of the Commission. (This, of course, includes cross-border healthcare, which is covered in another section of this publication.)

**Access, or lack thereof**

The lack of available of medicines is particularly striking in those Member States where the national market is small and
the expected return on investment for companies is low. Ditto orphan drugs for rare diseases. Orphanet has this to say about the latter: “So-called orphan drugs are intended to treat diseases so rare that sponsors are reluctant to develop them under usual marketing conditions.

“The process from the discovery of a new molecule to its marketing is long (10 years in average), expensive (several tens of millions of euros) and very uncertain (among ten molecules tested, only one may have a therapeutic effect). Developing a drug intended to treat a rare disease does not allow the recovery of the capital invested for its research.”

Orphan drugs may be defined as those that are not developed by the pharmaceutical industry for economic reasons but which respond to public health need.

In the case of products intended to treat rare diseases, these are developed to treat patients suffering from very serious diseases for which no treatment, or at least a satisfactory one, has so far been available.

These diseases affect only a small proportion of the population (less than one person per 2,000 in Europe), most often at birth or in infancy. The number of rare diseases for which no treatment is currently available is estimated to be between 4,000 and 5,000 world-wide. Twenty-five to 30 million people are reported to be affected by these diseases in Europe.

Obviously, the effectiveness of data in the orphan medicines framework is of vital importance.

Orphan drugs are just one part of the picture, but generally speaking access as a whole is seen as a real problem, especially in terms of innovative medicines and maintaining the innovative environment.

Affordability is an old problem, it is not a new one and there are still no solutions. EAPM has argued that value should be clearly identified and that it should be a Member State responsibility.

It is also important to look at barriers to access from a broader perspective, with more focus on early detection, early prevention and early diagnosis. There should also be an assessment from the economic point of view - not only looking at drugs.

Price is not the only problem in access to medicines - although different economic situations often arise in different Member States. Regardless, there is a need to increase cooperation between Member States as regards price-setting procedures, and there needs to be a common position on the importance of individual member states proceeding in this direction and acting at the national level, before creating cooperation between them.

Any serious discussion on access should consider not only access itself but rational use. Quality of use is important, while also optimising individual drug therapies and poly-pharmacy, especially in the ever-growing cases of multi-morbidity as the population ages.
Cooperation on price negotiation and HTA

Various groups have been set up to try to jointly do deals over drug prices but have met with only limited success thus far.

The BeNeLuxA group, comprising Belgium, Netherlands, Luxembourg and Austria, has been attempting to jointly negotiate prices of innovative drugs, aiming for more affordable access to innovation.

The cooperation here extends to horizon scanning, joint analysis of health technology assessment (a subject close to the Commission’s heart)) and the sharing of information. It has, to date, achieved one success.

Finland, Norway and Sweden, meanwhile, the FINOSE group of countries, aims to harmonise and share health economic analyses of new products, providing a joint assessment by the three agencies. It began in March 2018 and it will run as a pilot project for two years.

Meanwhile, the Valletta Group is made up of Croatia, Cyprus, Greece, Ireland, Italy, Malta, Portugal, Romania, Slovenia and Spain.

The objectives again include joint clinical assessment plus economic evaluation. Joint work has already begun (it started late 2018) on several pharmaceutical products.

As well as these Hungary, Lithuania, Poland, Slovakia, Czech Republic (with observer status) and Latvia (as an invited guest) form the Fair And Affordable Pricing (FAAP) group. The difference here is that pricing decisions are kept at national level, with no current joint negotiation.

Finally, the Nordic Pharmaceuticals Forum (NLF), made-up of Norway, Iceland and Denmark, and with Sweden as an observer, began life as an informal space for cooperation among Nordic nations, concerned with security of supply.

Begun in 2015, it is looking into joint tendering procedures in respect of pharmaceuticals, and driven by Amgros, which is the pharma procurement office Denmark’s five regional health authorities in Denmark.

The Visegrad, (or V4) initiative, which has as its partners Czech Republic, Hungary, Poland and Slovakia, is active in joint procurement but collaboration has not extended to other areas thus far.
Clinical research

Co-ordination and co-operation key factors in modern-day clinical research

There’s no denying that we’ve seen major breakthroughs in our knowledge of molecular biology in recent times, alongside many other aspects of 21st century healthcare.

There’s also no denying that this has led to changes in the design and methodology of innovative clinical research, for example.

All to the good. But there’s no denying either that Europe needs much-better co-operation at the highest level. That means at the top of the EU as well as between Member States.

In doesn’t help that, within the European Commission, the legal changes that the Union can actually effect in healthcare (given that it’s a Member State competence under the treaties), are dealt with by different Directorates-General, or DGs, in the Berlaymont and beyond.

Hardly ideal. This type of fragmentation of legal frameworks, coupled with national laws, can obviously bring about inconsistencies, repetition and the wasting of scarce resources.

There is an argument for bring all aspects of healthcare that the EU is empowered to affect under one roof. IVDs, health data, eHealth, clinical trial rules, health research, research incentives, cross-border healthcare and so on.

On the whole, policy- and law-making becomes extremely complicated when legislating for the exciting advances and growing expectations being brought about by personalised medicine.

Side-by-side with genomic-related matters, other areas are clinical trials, in-vitro devices, national market access and data protection.

The issues are labyrinthine. Yet all have to be addressed swiftly, effectively and in a fully coordinated manner if we are to be able to give the right treatment to the right patient at the right time, while offering every European equal access to the best treatment available.

There is the welfare of 100s of millions of citizens to consider, plus so many disciplines, industries and other stakeholders involved that, to be fair, it is often a struggle for legislators to formulate regulations that are satisfactory for all, are up-to-date and progressive, and do the job they are supposed to do. This despite the best efforts from all involved.

And it should go beyond Brussels - the competitiveness of
European research is arguably at stake and a new-born and more-comprehensive coordination between all partners is crucial for the benefit of EU citizens.

As EORTC has put it: “With the rapid development of new technologies and the massive call for personalised treatments, the biomarkers, gene signatures and other advances in diagnostic development became of the utmost importance…”

It is discussed and opined elsewhere in this publication that the regulatory environment is not keeping up with the rapid advances in science and technology - despite best and well-meaning efforts. This slows down the capacity of researchers to radically move towards co-developments.

Focusing on the field of cancer, in which genetic advances have proven ultra-valuable, in this era of personalised medicines, the rise of biomarker-based clinical trials, performed internationally to access molecularly defined patient populations in the EU, would fall simultaneously under clinical trial and IVD regulations, with the additional need to comply simultaneously with the general data protection regulation.

This surely emphasises the need for frictionless coordination between all regulations.

During discussions on the text and throughout the ongoing implementation phase, multiple events brought all relevant stakeholders together. This, in turn, encouraged productive and detailed discussions that ended up by finding acceptable solutions to most of the identified issues.

During that time, and specifically, representatives of the European Commission and and the European Medicines Agency (EMA) were receptive to detailed descriptions of practical issues. These were sometimes less relevant to the higher level text of the regulation itself, but essential to ensure the appropriate implementation.

EAPM, alongside its partners and fellow stakeholders, believes that the EU needs to strive for better integration of healthcare and research, not least via more-effective coordination for health research within the EU commission, including, but not limited to a cross-DG’s dialogue.

Simply taking the clinical trial directive as an example, it is clear that the best (and possible only) way to insure a smooth implementation of related healthcare regulations going forward is through a multi-stakeholder and multi-DG dialogue that is open and silo-free.

As EORTC has noted, the legislation on clinical trials acted as “a great example of open multi-stakeholder dialogue”.
Working together

More collaboration, please - despite Member State competence on healthcare

In this publication, we’ve already highlighted cross-border healthcare in its own section. But let’s touch upon it again here as, alongside joint HTA, it’s an ideal example of how cooperation and coordination across Member States could and should be working - and where it simply isn’t happening.

A report released in early June 2019 by the Luxembourg-based Court of Auditors underlined that while cross-border healthcare remains marginal in comparison to healthcare delivered domestically, in some situations, the most accessible or appropriate care for a patient is available in a Member State other than their home country.

The report noted that the Cross-Border Healthcare Directive “facilitates closer cooperation in a number of areas: notably the cross-border exchange of patients’ data and access to healthcare for patients with rare diseases”.

Approximately 200,000 patients annually take advantage of the system to receive healthcare treatments abroad. That sounds a hefty number, but it’s worth bearing in mind that this represents less than 0.05 % of EU citizens.

No records are being broken here, and there’s no dancing in the streets outside the EAPM offices, or any other stakeholder’s offices either.

It appears that while EU actions in cross-border healthcare have to a degree enhanced cooperation between Member States, the impact on patients is limited. According to the understated remark of the report “there remains some scope for improvement” when it comes to giving citizens more information. No kidding…

Is the Commission getting optimal results? No, but it’s not just the EU Executive’s fault.

The Court’s report noted that “the concept of European Reference Networks for rare disease is widely supported by EU stakeholders (patients’ organisations, doctors and healthcare providers)".

No denying that it’s a great idea.

However, “the Commission has not provided a clear vision for their future financing and how to develop and integrate them into national healthcare systems”.

Rare diseases

When it comes to cross-border initiatives for rare-disease patients, the specificities of such diseases led the Council of the European Union to single out cooperation in this field as “as a unique domain of very high added value of action at Community level”.

For its part, the Commission put forward a specific policy framework to tackle rare diseases, notably through the creation of the European Reference Networks (ERNs). It supports Member States in the development of ERNs, which are intended to reduce time to diagnosis and improve access to appropriate care for rare disease patients, while providing platforms for the development of guidelines, training and knowledge sharing.
Networks were launched in 2017 for different classes of rare diseases. Each receives €1 million funding over five years from the EU Health Programme.

The Commission also finances patient registries and support activities for the ERNs as well as the development of IT tools, notably through the Connecting Europe Facility (known as CEF).

The Commission is, of course, working towards better cross-border exchanges of health data as well as the exchanges of ePrescriptions across the EU's Member States - not least as part of its digital market strategy, but it all varies from country-to-country.

The problem is that there is not enough cooperation happening between Member States and there’s only so much that the Commission can do about it in reality, given Member State competence in respect of healthcare.

The majority of Member States were late in the adoption of the national transposition measures for the cross-border project and this is not one-off.

On top of this, there's the issue of non-comparable data between countries in this and other areas of healthcare.

It’s a fact that, when it comes to exchanging patients’ health data across borders, high expectations have not been matched by results.

As the report notes, “creating mechanisms to exchange patients’ health data within the EU requires a clear strategic and governance framework, supported by the Member States. Clear objectives should be set and performance monitored regularly”.

Member States have a responsibility. But the news is good and bad, really. The work on cross-border exchanges of health data has at least resulted in the creation of interoperability standards.

The Commission, in cooperation with Member States, is building EU-wide infrastructure for these exchanges. However, it seems that the Commission did not estimate the likely numbers of users of the EU-wide eHealth infrastructure.

**A better EU strategy?**

The over-arching 2018 eHealth strategy refers to new challenges such as the introduction of the General Data Protection Regulation and cybersecurity threats.

However, this strategy did not include an implementation plan with timelines for expected results and outputs that would show the Commission’s approach to implementing the eHealth strategy. And, as it turns out, the Commission underestimated the difficulties involved in deploying EU-wide eHealth Infrastructure.

Meanwhile, the auditors’ report makes clear that the Commission overestimated the likely take-up of the eHealth Digital Service Infrastructure with its announcements on the likely level of health data exchanges across borders proving to be over-optimistic.

There is some good news regarding Member State cooperation, though, at least in respect of some ePrescriptions programmes (namely Finland and Estonia).

As the report states: “When a patient with an ePrescription issued in Finland goes to an Estonian pharmacy to get their medicine, the pharmacy should register the patient’s ID. The pharmacy should then send the prescription data, provided patient consent is available, to the Estonian eHealth portal which should forward it to the Finnish eHealth portal.

“After the medicine is dispensed to the patient by the Estonian pharmacy, the Finnish eHealth portal should be informed that the ePrescription has been processed.”
It’s one happy example showing that collaboration key. It’s all about the teamwork.

But there clearly is not enough teamwork and collaboration happening in a healthcare sense.

**Time to get our act together**

Given the problems that beset our ageing society, which include under-resourced health services, an age spent getting new drugs to market, an increase in chronic diseases, et al, Europe definitely needs to do better.

Healthcare needs modernising and, while top-down legislation on clinical trials, IVDs and data protection and sharing has helped in recent times, arguably the EU should be doing more from a centralised point, at the very least in encouraging Member states to share more information on health from data banks, cooperate way-more effectively, work to avoid research duplication and so on, for the benefit of the citizenry.

We know all about a lot of these issues through the ongoing debate on HTA.

Several have been highlighted, including differences in methodology and procedures across Member States, while it is noted that limitations to current systems - despite a couple of decades of a certain level of cooperation - include low uptake of joint work and no sustainability of the current co-operative model.

However, on the plus-side, achievements thus far include the development of trust between HTA bodies, capacity building, the development of joint tools and earlier dialogues.

After all, we do say that ‘sharing is caring’ and that’s a great excuse - if one were needed - for much more collaboration.

With more and better sharing of data, for example, Europe’s undeniably excellent researchers would potentially be able to access millions of genetic markers and accelerate science towards better understanding of diseases and specific patients.

Crucially, this would guide choice of therapy, prevention and screening programmes, increasing overall healthcare efficiency and patient outcomes.

Important among EAPM’s aims has always been the fostering of partnerships between Member States, the health stakeholder community and, of course, those at the absolute centre of healthcare - Europe’s patients.

Ultimately, when it comes to the health of the EU’s citizens, we need more Europe, not less. And that means stepping up collaboration in all areas.
Moving forward with research

In the past few years, clinical research has evolved dramatically. It’s also played a huge part in the emergence of personalised medicine.

But has regulation kept up, or is the pace of science proving too fast? Sadly, the latter is often the case.

Paradigm shifts have occurred in the way treatment is assessed and delivered, not least through the huge advances in genetics and dramatic improvements in imaging, which have had a profound affect, not least on the treatment of some cancers.

Cancer clinical research is often referred to as a model for personalised medicine, as new understandings of the biology of tumours and more, allows for more rational drug development.

There is a view nowadays, shared by EAPM, that such advances have rendered current models for medicine development less suitable as we now live in an era of ageing populations, increased co-morbidities and the challenges of managing chronic diseases.

As Denis Lacombe of EORTC and colleagues have put it, there is now a need to develop a different framework in which patient management and care, rather than drug development, is the centre of the process as we move into patient-centric clinical research.

“Patients must remain the focus throughout the process as streamlined solutions from research into healthcare are developed. Patient needs are multiple and most commonly do not depend on a single drug at any point in time and certainly not along the evolution of the disease,” said Lacombe and his co-authors.

“Therefore, the concept that drugs are developed with the sole purpose of market access, not anticipating the open questions beyond registration, needs to be revisited,” they added.

The art of bringing up-to-date science to the patient, while taking into account his-or-her priorities such as quality of life needs to be developed further.

Unfortunately, regulatory agencies, funding agencies and even Member State governments do not often do not do enough to boost the integration of cutting edge, innovative research into the healthcare arena.
At the same time: “The pharmaceutical drug development process remains protected during the competitive phase, placing drug development priorities before public health issues when the continuum of care would require early consideration, a broader view and a more comprehensive approach.”

**Relevance of regulation to shape personalised medicine**

In the medical arena, personalised medicine is the wave of the future. But it has already emerged in the here-and-now, and its influence is growing everyday.

It relies today on new technologies, Big Data and better-targeted clinical trials, among other aspects, in order to deliver the right treatment to the right patient at the right time.

However, there are many practical barriers to be overcome and stakeholders believe that regulators have a vital role to play if the potential of personalised medicine is to be fully realised sooner rather than later.

These areas include the need for more promotion for research, (but we can also add a need for education programmes, incentives for innovators and, not least, better regulation and commonly accepted, widely implemented, best practices).

While it is true that healthcare remains a Member State competence, the EU as a whole is becoming more involved in various aspects (legislation on IVDs, clinical trials, cross-border healthcare, data protection and more) which, theoretically at least, span all EU countries.

It is evident that the EU, in tandem with Member States, needs to ensure the proper transposition of its legislation and policies regulation at national level. More work needs to be done on agreeing treatment guidelines, and encouraging their implementation, quickly and effectively.

Innovation is key to progress and, currently, there are a lack of incentives - increasingly post-economic crisis, a time during which payers pulled up the drawbridge thus adding to a scenario in which Europe's healthcare systems have struggled.

As things stand, there is a surfeit of incentives to promote investment in developing diagnostics. Experts say that coordinated timing when it comes to reimbursement and approval of a companion diagnostic is essential. On top of this, the transferring of technology and public health assessments differ from state-to-state.

The translation of research is another key issue. This affects
both treatment once a disease has been discovered and, importantly, prevention - with all the cost savings that go along with the latter, not to mention continuation of the best quality of life.

Translating cutting-edge research effectively in the arena of personalised medicine will save lives and lower costs.

Policymakers at both EU and national level (Commission, Parliament, Council and Member State health care payers) have a significant role to play in bringing about a Europe in which personalised medicine, in all its forms, can be integrated into national healthcare systems, via the sharing of data, cross-border collaboration in research projects, exchanging of best practices, and a seismic shift from a silo mentality, not only in the main cross-disciplinary fields but within single disciplines.

Optimising knowledge, not wasting it

There’s plenty of knowledge out there. But are we using it properly? Not always.

The latest proposals from the Commission, subsequently backed by Parliament, in health technology assessment (HTA) have been in the news non-stop at the moment as Member States wrangle over the idea of mandatory joint action.

HTA has been defined as a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner.

A well-working system of HTA is extremely important when it comes to access for patients to the best treatments out there. The new proposals represent a step towards guaranteeing the fundamental right of access to health, while cutting down on duplication and therefore a waste of time and resources, across Member States.

EU countries need to make the best choices for patients and the cash that health systems have. This is vital when looking at value, especially when times are tough with increasingly cash-strapped healthcare systems coming under the cosh.

The Commission’s proposal contains provisions covering the sharing of data, among others, and many Member States have been loosely collaborating on HTA for two decades. The results have been mixed and unnecessary duplication has been rife, but a nudge in the direction of mandatory cooperation could be the logical next step.

As EORTC’s Lacombe and his colleagues put it: “Focusing on the patient and the disease evolution is closer to the art of
medicine. It requires that questions central to patient care are being addressed early on to optimise the use of treatments in real life. A number of questions central to patients and healthcare providers are not addressed during the drug development process, inadequately feeding into health technology assessment.

“Efficient comparative effectiveness research which could be referred to as applied clinical research is needed to bridge drug development and real life, offering a tighter link into real life as well as ensuring long-term patient safety and monitoring long-term outcome.”

Innovative mechanisms are required to ensure that the patient dimension becomes one of the key drivers. Arguably, innovation per se is no longer the issue, instead access to innovation is the next challenge and there is a need for new rules and frameworks.

Patient-centric solutions will lead to patient empowerment which is recognised as an asset for both the therapeutic progress and the evolution of the regulatory framework.

Innovative modern trial designs are emerging as a patient-centric approach to drug development. Also, the rise in public-private partnerships and other collaborations is bringing about complex clinical trial designs, which poses significant challenges for healthcare systems and regulatory approval.

There are now loud calls for a major evolution of policy and processes, particularly regulatory requirements for approval for new therapeutics.

Given the new understanding of disease at molecular level, the promise of personalised and/or precision medicine is real, but we're still a way off, and the challenges are also all too real, as his publication attempts to explain.

We have new therapeutics and diagnostic methods designed to specifically target and treat mechanisms that drive the disease process. This type of innovation is key, but it's not as easy as it may seem.

There are obstacles in science to develop innovative medicines for unmet medical needs, a need to ensure, in a context of financial pressure on healthcare budgets, that innovative medicines are taken up by health systems and made available to patients, and a need to adapt regulatory cooperation to the globalisation of the sector and of its supply chain.

Parliament has always had a role to play in what has been an increase in EU-wide regulations of late in the healthcare arena.

It is sure to have a role to play as we move forward.
**Good companions**

*The value of diagnostics in modern healthcare*

First, a little recent history: The European Council issued its General Approach on the Proposal for a Regulation on in vitro diagnostic medical devices in September 2015.

The text aimed to overhaul the regulation of these specific types of diagnostic devices, knowing that this would have a significant impact on personalised healthcare.

At the time, EAPM stated that “the way in which companion diagnostics are defined, in-house assay exemptions applied, clinical evidence gathered, highly specialised distance-sales regulated, and a transition period decided will profoundly change the structures within which IVDs reach patients in the application of personalised healthcare”.

The IVD discussions had been ongoing since 2012 and, in fact, these eventual 2016 medical device regulations updated existing EU legislation going back to the last millennium.

In essence, the new deal secured further, more up-to-date, health and safety protection for patients.

EAPM's key asks on the In Vitro Diagnostic legislation were originally outlined in a 'call to action' document which included: ensuring patients have access to safe and reliable IVDs in a timely manner; defining companion diagnostics appropriately to reflect the small number of IVDs that play a unique role in choosing patients that are suitable or unsuitable for a specific therapy; accounting for the specificities of companion diagnostics and other IVDs to ensure appropriate and proportionate requirements on clinical evidence, transparency, and the transition period; and; maintaining an attractive and competitive environment for innovation in the diagnostic area…

*What exactly are companion diagnostics?*

A companion diagnostic (often called a CDx) is a diagnostic test used as a companion to a therapeutic drug to determine its applicability to a specific person.

Within personalised healthcare, companion diagnostics have emerged as what has been called "a very specific and special group of in vitro diagnostics among the different technologies shaping the personalised healthcare spectrum".

In a paper entitled 'The value of companion diagnostics: overcoming access barriers to transform personalised healthcare into an affordable reality in Europe', Victoria Wurcela and her...
co-authors state that such diagnostics “provide highly valuable information, allowing patients, health practitioners and payers to decide with a higher level of certainty about the potential benefits of a treatment or care pathway”.

Such extra certainty is geared towards ensuring a more efficient selection of treatments and care, targeted at sub-populations that are most likely to benefit.

From a cost point of view, companion diagnostics account for what Wurcela and colleagues call “a minimal portion of the already small expenditure on in vitro diagnostics”, which is far less than 1% of total healthcare expenditure.

And yet they “provide the means to limit inefficient use of healthcare resources while optimising patient outcomes”.

This comes against a backdrop showing that equal access to personalised healthcare remains an issue in Europe.

There is almost a discussion, of course, about affordability. Proponents argue that investment in companion diagnostics can provide long-term value for patients and healthcare systems, which in turn allows the shifting of resources to areas of need.

But do health systems recognise the value of CDx? It seems not.

The ‘value’ argument

It is argued that the value that companion diagnostics bring to make personalised healthcare more affordable across the EU is not fully appreciated. Such a lack of acknowledgement can (and does) lead to less patient access to personalised treatments and care, which in turn prevents improved outcomes.

In many EU Member States it is clear that market access frameworks for diagnostic tests are fragmented. They are not aligned with specific funding and reimbursement mechanisms, which acts as a disincentive to using the tests.

Allowing patients, healthcare professionals and payers to decide with a higher level of certainty about the potential benefits of a treatment and care pathway, is clearly desirable, but there is evidence to strongly suggest that patients are missing out on appropriate tests and treatments.

As Wurcela’s article states: “Major changes are taking place in the way healthcare is conceived, applied and paid for. Healthcare providers and decision makers are starting to prioritise management strategies based on their potential to improve results for patients (health outcomes, quality of healthcare), ensuring that healthcare resources are wisely spent” and will be sustained for future generations.

The authors argue that “intelligent management strategies” refer not only to treatments (medicines and medical devices), but also to in vitro diagnostics, including tests to predict evolution of disease and treatment response, among others.

The dual objectives of advancing health and ensuring sustainable use of resources - more and more necessary as our population ages and puts health systems under the financial cosh - are often complementary “and comprise the basis of the value of healthcare and healthcare interventions”.

Among the technologies shaping the personalised healthcare spectrum developing before our eyes, companion diagnostics have emerged as a one-off group of in vitro diagnostics.

Companion diagnostics provide information influencing the benefit-risk ratio of a specific treatment. The information gleaned helps to segment patients according to the presence or absence of a specific characteristic that will determine the individual patient’s response to a targeted therapy.
This is about as ‘personalised’ as it is possible to get today.

Since the value of companion diagnostics as enablers of better patient outcomes, while facilitating affordable selection of medicines and efficient use of resources, is not yet fully recognised by EU health systems, equal access to affordable personalised healthcare remains an issue across the EU.

The article’s authors say that: “There is an emerging body of evidence,” they say, “that patients are missing out on the appropriate tests and treatments while reduction of inefficient use of healthcare resources is not realised”.

**Challenging times…**

Equal access to personalised healthcare is a challenge, spot smart use of resources is vital.

Health technologies such as companion diagnostics, that can limit ineffective medication use, prevent unnecessary consultations and hospitalisations, should help to contain overall healthcare costs which, in turn, should help to make personalised healthcare more affordable across the EU.

There are several moves that can be made to drive the process, including developing clear, transparent and timely market access processes for CDx in all European health systems, by establishing reimbursement processes, with associated specific funding streams and uptake mechanisms. Improving the efficiency, clarity and speed of the existing reimbursement processes for diagnostic tests would also help.

On top of this, recognition and rewarding of the value of diagnostic information should be key in the assessment, reimbursement and funding decisions of diagnostic-medicine combinations.

Fit-for-purpose HTA, processes would help, too. Especially those can sure that we don’t limit access to valuable diagnostic innovation and personalised healthcare in Europe.

The authors of the article conclude by saying that: “For a successful and affordable personalised healthcare strategy that is able to reach all European patients who will benefit from it, challenges around effective market access to companion diagnostics need to be addressed by most Member States.

“National health systems and European initiatives should ensure that an innovation-friendly environment exists, uptake of valuable diagnostic innovation is encouraged, and patient access to diagnostics is improved,” they say.

EAPM agrees that for such objectives to be reached, clear, transparent and timely market access processes based on the value of the information provided by the diagnostic test need to be in place.

Once these crucial pieces of the jigsaw are put in place, alongside improved collaboration between health systems, patients, healthcare professionals and in vitro diagnostic manufacturers, then the big picture will emerge - one that allows personalised healthcare to enhance healthcare now and into the future.
Cross-border healthcare: What it is and where we are

It's safe to say that, despite the excellent intentions of all concerned, the Cross-Border Health Care Directive has so far failed to deliver fully on its promise, as the Commission itself has noted.

First of all, let's give the original idea the once-over.

Back in 2013, EAPM was of the view that the directive on patients' rights in cross-border care "offers a graphic demonstration of just how far Europe remains from any real coherence on health policy and on innovation".

The rule was brought in to clarify and reinforce citizens' rights to choose where to seek medical treatment, and in what circumstances. But when it came into effect, even the then European commissioner for health, Toni Borg, was unable to announce anything more than a theoretical achievement.

"From today, all EU countries should have transposed" the directive into their national law, Borg said. The reality, as his officials were obliged to admit, is that very few of the Member States had actually done so, 30 months after the EU agreed it (in early 2011).

For cross-border healthcare to work optimally, it relies on collaboration between Member States at EU level - arguably a tough ask given that each EU country has a jealously guarded competence for its own healthcare.

As it stands, Member States are currently struggling to reach agreement on health technology assessment, so little appears to have changed.

The legislation provided for what could have been real shifts away from national isolationism in health, with the new rules intended to slot nicely into the EU’s internal market. This should have happened by strengthening the freedoms relating to the movement of goods, persons and services.

The vision is, and remains, of patients moving around Europe to access safe and high-quality cross-border healthcare, accompanied by the freer flow of their health data from one country to another.

The directive might have triggered cooperation to overcome some deep-rooted divergences in healthcare across the EU.

Certainly, for personalised medicine, proper implementation of the measure is crucial to progress. Freer movement of patients and data around Europe, closer collaboration on reference networks and data banks, wider access to information, institutionalised cross-fertilisation between providers, payers and regulators, and enhanced common understanding on health technology assessment are all preconditions to the successful evolution of personalised medicine.

In essence, cross-border healthcare is a test case for Europe's ability to seize opportunity, as well as a crucial determinant of how far and fast Europe can develop valuable new therapeutic approaches.

With 2019's new European Parliament and Commission, EAPM is determined to push for the creation of a more conducive environment, for patients, for science, and for innovation.

Europe has an opportunity to generate more coherent management of care and wider access for patients. But if the opportunity is missed – or muffed – the damage will be felt not only by today's patients, but by tomorrow's too.
Years go by...

In 2018, a report was prepared to analyse the current shortcomings in the implementation of the Directive and to make recommendations for its improvement.

The report noted that under the Treaty on the Functioning of the European Union (TFEU), a high level of human health protection is to be ensured albeit while the organisation, management, financing and delivery of healthcare remains the responsibility of Member States.

Case law over the years, it noted, has acknowledged that patients have, under specific conditions, the right to access healthcare in other Member States than their own.

The main goal of the Directive is to originate an EU framework and set of rights to ensure the access of Europe’s citizens to care abroad, “with the intention to facilitate closer cooperation in a number of areas of medicine and healthcare such as eHealth and rare disease treatment”.

The report’s rapporteur tells that particular aspects of healthcare abroad have improved significantly following the Directive. However, on the grounds of late or incomplete implementation, infringement procedures were launched against 26 Member States. Currently, all Member States notified their complete transposition measures.

Funding

Funding for cross-border healthcare comes in the main rom the 2008-2013 and 2014-2020 Health Programmes which foresaw a combined total of approximately €64 million per year for health-related issues.

The Commission has proposed that the funding continues under the European Social Fund Plus (ESF+) which will have, among its operational objectives, to support the implementation of legislation in the area of cross-border healthcare.

Patient Mobility

Cross-border patient mobility is an important policy issue. Even though the levels of patient mobility are still relatively low, for certain groups of patients, due to rare diseases or due to geographical proximity of healthcare services, cross-border healthcare is the most appropriate and accessible care.

Cross-border patient mobility involves certain issues such as the continuity of care and the exchange of information between health professionals on different sides of a border.

Next to this, there are also logistical and administrative barriers, which can affect the cross-border care for patients in a negative way.

There have also been issues surrounding electronic health records (EHRs), but more of that later.

In general, the Commission has identified four areas, which it sees as having the greatest potential to act as barriers to patients if left unaddressed. These are systems of reimbursement, use of prior authorisation, administrative requirements and charging of incoming patients.

Although Member States are obliged to notify the Commission of any decision to introduce limitations - and some Member States have transposed in ways that could be considered as limiting - the Commission has received no specific notifications from the Member States.
**National Contact Points**

For the Directive to be truly successful it is crucial that patients, healthcare professionals and other stakeholders are well informed. Unfortunately, this has not been the case.

The Eurobarometer survey in May 2015 indicated that fewer than 20% of citizens feel well informed about their cross-border healthcare rights.

Although each Member State has at least one National Contact Point (NCP) to provide patients and health professionals with information concerning their rights regarding a cross-border healthcare service or product, the message is clearly not getting across.

Across the 29 NCPs in Europe, Norway and other EEA countries providing data, 74,589 enquiries were made in 2017, but most Member States received fewer than 1,000 requests.

The number of enquiries differs strongly between the NCPs. Overall, patients are not aware of the existence of their national NCP. A broad and lasting information-campaign on NCPs and on patients' rights with regard cross-border care is vital.

It has become clear that in-depth information on patients' rights is generally lacking on the NCPs websites. Insight into what to do in case of undue delay, information on complaint procedures and settlement of dispute, as well as information on the duration to process reimbursement or prior authorisation requests is scarce.

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**European Reference Networks**

Meanwhile, the European Commission has supported Member States in the development of European Reference Networks (known as ERNs) between healthcare providers and centres of expertise.

The first 24 European Reference Networks officially got going in early 2017, based on a framework provided by the Commission, driven by the involved healthcare providers and national health authorities.

The idea behind ERNs is that they will tackle complex or rare diseases, which obviously require specialised treatment and knowledge.

In total, the ERNs bring together more than 900 highly specialised healthcare units located in more than 300 hospitals across the EU, Norway and the EEA countries.

**eHealth**

The objective of what we have come to call eHealth is to work towards sustainable economic and social benefits of European eHealth systems and services and interoperable applications, to achieve a high level of trust and security, to improve the continuity of care and to ensure access to safe and high-quality healthcare.

Maximising the potential of eHealth in the EU would allow health professionals to share patients' summaries and data across borders.
The transferability of data will facilitate cross-border healthcare with less barriers but is also crucial for further research, especially in the field of rare diseases.

**Electronic health records (EHR)**

The ability to exchange health records across borders is certain to benefit citizens seeking treatment anywhere in the EU.

In the Commission’s own words: “Today in Europe, there is a clear need for well-functioning access to existing data and the right infrastructure to provide timely information on existing health conditions, such as allergies and existing health conditions, and also, where needed, to an individual’s recent laboratory or medical imaging results.

“This would help health practitioners and hospitals in another Member State to avoid repeating such tests, which can save patients’ time and reduce hospital costs.”

Of course, developing the secure exchange of EHRs across the EU is complex, and systems that will transfer such data have to consider into cybersecurity and data protection, in order to provide full trust to the European citizens.

In latest developments, at the start of this year, the exchange of ePrescriptions became possible between Estonia and Finland, using the eHealth Digital Service Infrastructure.

A further 20 Member States are expected to be able to exchange this kind of information by the end of 2021. The Commission has recommended that work on interoperability be further extended to laboratory results, medical images and hospital discharge reports, and has put forward recommended technical specifications for the exchange of this data.

A Commission Communication on enabling the digital transformation of health and care in the Digital Single market, adopted last April, identified three areas for action.

These cover citizens’ secure access to, and sharing of, health data across borders, better data to advance research, disease prevention and personalised health and care, and digital tools for citizen empowerment and patient-centric care.

**Regional cooperation at the border**

Cross-border regions represent 40% of the EU’s territory and more than 1-in-3 EU citizens live in a border region. In total, there are 37 cross-border urban areas in Europe.

Cross-border healthcare initiatives in border regions have generally worked well. The similarity of factors such as the geographical context, habits, culture, language and the political and administrative constellation have a large impact on the sustainability of the cooperation.

**And so to Brexit…**

Every year, an estimated 1,000 UK citizens are reimbursed for treatment under the Directive. France, Poland and Latvia are among the most popular destinations for Brits to head to for treatment.

On top of this, the UK treats an estimated 1,500 EU patients coming the other way. Apparently, because not all Member States are able to present relevant patient mobility data, this number is slightly larger than the estimate. On top of this, some 40 National Health Service Hospitals are involved in the ERNs.

It remains to be seen what effect the UK leaving the EU will affect the above.
The emergence of personalised medicine has had a huge impact on oncology and immuno-oncology, so let’s take a look at where we are right now, and what we can expect down the line.

Leaps in science and an ageing population have combined to mean that personalised medicine is not only here, but here to stay, and advances in genetic sciences, the emergence of Big Data, improvements in imaging and so much more, have brought us to the cusp of a true revolution in healthcare.

The aim is to deliver the right treatment to the right patient at the right time in general healthcare, of course. But here we look at particular aspects which require patient information, biomarker information and human bio-sample information.

From the perspective of the pharmaceutical and diagnostic industry, the objective is to develop innovative therapeutic ‘concepts’ with increased value for patients – including in the area of orphan drugs, which brings its own issues, discussed elsewhere in this publication.

According to experts connected to EAPM, there is a need today to develop rational-based combination strategies, optimised monitoring systems and treatment regimens, as well as biomarker-based patient selection.

What is a biomarker, and what is immuno-oncology?

A biomarker can be described as a naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, and so on can be identified.

Emerging clinical evidence shows that indication-agnostic biomarkers are paving the way for fewer barriers between various different clinical disciplines. Personalised and precision medicine has been fostered and elevated to the next level by recent successes in immuno-oncology.

Immuno-oncology is a revolutionary development whereby we can take advantage of the body’s own immune system to fight cancer.

Indeed, thanks to our deeper understanding of cancer and its interaction with the immune system, industry for its part is currently moving away from an over-simplistic single-hypothesis approach towards a medicine’s development strategy based on a hybrid hypothesis-free and hypothesis based model.

Pus simply, immuno-therapies target the interaction of the immune-system and cancer. Anticancer immunity in humans can be segregated into three main phenotypes: the immune-desert phenotype, the immune–excluded phenotype and the inflamed phenotype.

Each of these is associated with specific underlying biological
mechanisms that may prevent the host’s immune response from eradicating the cancer. They have been defined based on current understanding of the disease biology.

However, it is expected that future studies may suggest a number of intermittent phenotypes, which would require different, individualised therapeutic concepts.

Some immuno-therapies have been designed to target specific biological mechanism within these cancer phenotypes. However, response rates have so far differed between high and relatively low.

Given the mode of action of immuno-oncology therapies, it has been assumed that the general immune status will be relevant in many clinical settings.

We don’t intend to get too technical here, but an important consequence of personalised cancer immunotherapy is that newly discovered biomarkers often have to compete for limited amounts of biomarker samples.

In essence, this means that improved sample processing and alternative testing strategies will be required. In this context, the addition of new biomarkers for testing has the greatest effect on small-biopsy specimens, partly due to the limited amount of tissue material per specimen and to the unavoidable loss of tissue during processes.

Many diagnostic companies, in tandem with pharmaceutical partners, are currently trying hard to overcome the “hierarchical sequential testing approach” which creates a disadvantage for less prevalent markers.

Combining strategies

Cancer immunotherapy is today a key element of clinical development strategies. Due to the multifactorial nature of cancer-immune interactions, combinations of biomarker assays will - by definition - be required.

A high number of these studies conducted so far involve chemotherapy combinations and to a lower extent targeted therapies.

It is envisaged that the large number of chemo-based strategies to increase the benefit of immune-oncology combos will dominate safety and tolerability aspects. This view is possibly due to the fact that immuno-oncology is currently considered as a “substitution market” from a pharmaceutical perspective.

Some of the advanced biomarker technologies in use today include digital pathology as a novel tool in precision medicine to help drive drug development.

This empowers biomarker intense assessments in standardised fashion, at short turn-around times, as requested by immuno-therapy and combination strategy.

Liquid biopsy-based biomarker assessments are more
convenient and have the potential to foster longitudinal generation of clinically actionable insights. This makes sense from a systems pharmacology perspective.

**Regulation in Europe**

In terms of health technology assessment (HTA), approval procedures covering the marketing of medicinal products and IVD medical devices are consistently linked across EU.

In conjunction with the in vitro diagnostic medical devices regulation, it is becoming more urgent to develop a precision medicine enabling EMA guidance. But in order to lower the risk that the harmonisation of IVD regulation may slow down the approval of new technology platforms, a dedicated accelerated path needs to be formally installed where relevant.

Given that we have reached an impasses on HTA coordination and cooperation although it is moving in the right direction, slowly), it is well-worth repeating that harmonisation in HTA needs to speed up in Europe.

HTA represents a hurdle for many reasons, but in particular because it refers to clinical guidelines which are not consistently updated on a regular basis. Better synergy is required now between regulatory, clinical guidelines and HTA if we are to move forward at the required pace.

**Going forward**

Given already cash-strapped healthcare systems taking on increasing burdens, new therapies, which address multiple unmet medical needs, and outcome-based or value-based pricing from the pharma industry, are vitally important. Meanwhile EU healthcare systems must work harder to assess the accuracy of outcome measurements.

Generally speaking, the impact of predictive biomarker identification in cancer immuno-therapies in clinical practice remains relatively low.

Although emerging scientific data suggest multiple promising predictive biomarker candidates in a number of cancer indications, robust clinical evidence is still lagging somewhat behind. In addition, a subsequent change of the testing landscape appears to be challenging.

The complex and highly diverse reimbursement situation around companion diagnostics further complicates the efficient introduction of personalised or precision medicine into healthcare systems.

Stakeholders within and outside healthcare systems need to combine their efforts in order to turn scientific insights about predictive biomarkers into superior and affordable therapeutic concepts.

European policymakers are asked to help to make this happen by ensuring that a suitable regulatory framework and, of course, incentive system are in place.

These are prerequisites to encouraging the kind of ground-breaking innovation required to improve the availability of new treatment options for Europe's patients.
Health literacy: Knowledge is power

As we prepare to enter the third decade of the 21st century, many citizens expect to be more-involved in their own healthcare. They are more knowledgeable than ever before and have a right to dialogue with their doctors, nurses and surgeons for the important purpose of co-decision making.

Patients know more, doctors know more, regulators know more… yet it is the case that in this age of personalised medicine neither patients nor healthcare professionals know quite enough.

That’s unsurprising as science is advancing so swiftly. The same ‘knowledge gap’ also exists for regulators and policymakers.

All are linked as more understanding at every level will bring about greater awareness of stakeholder issues and will inevitably lead to better regulation and legislation from on high.

Personalised medicine is now at the centre of most, if not all, aspects of patient care. It is not limited to rare diseases or cancer, but spans all medical specialties. This exciting new way of treating patients is, however, based on specific concepts or biological pathways in a field which is continuously moving and undeniably complex in some areas.

This means that all HCPs in close contact with patients or their families need to possess a solid knowledge of the current aspects of personalised medicine and its latest breakthroughs, in order to better understand patients’ concerns.

Clearly our HCPs are trained to be experts in diagnosing conditions and suggesting treatments, but better health literacy among all stakeholders - including those serving in the Commission and Parliament - need to get up to speed.

It’s pretty obvious that the patient obviously knows more about his or her own lifestyle, work environment and how much he or she can rely on family-care resources, for example, so co-decision is a growing part of modern-day medicine and we need to facilitate more of it.

Such co-decision can only work if both ‘sides’ have a good degree of health literacy. To recap: All healthcare professionals in close contact with patients need a solid knowledge of current aspects of medicine and its latest breakthroughs.

To complement this, patients need to be as literate as possible (and that goes for potential patients).

The power of health literacy

Citizens can change their lifestyles by, for example, lowering the risk of lung cancer by giving up smoking, and lowering the risks of contracting diabetes by making changes to how they eat, how they exercise, how much alcohol they drink and so on.

Staying healthy longer not only benefits the patient on a
personal level, but it makes sense for society in general, not least financially. Health means wealth, as we all keep saying and hearing.

All this fast-moving science undoubtedly makes life more complicated. And no matter how good the HCP is, it’s difficult to keep abreast with all developments. Nobody is born understanding difficult topics such as a patient’s genetic profile, for example.

On the other hand, patients are growing more-and-more knowledgable about their conditions. This is often achieved via the internet which, of course, can pose its own problems in respect of misinformation or the misinterpretation of information. Care is needed.

What is key, or should be, is communication between HCPs and patients, based on knowledge, or in other words literacy.

Of course health literacy has various aspects. Within the medical profession itself there is often a lack of understanding between different silos, which is to be expected in part given the different areas of expertise. This also extends to different stakeholder groups, even before we consider the patient.

Evidence has shown that strengthening health literacy builds individual and community resilience, helps to address health inequities and improves health and well-being.

Indeed, a European Health Literacy Survey found that nearly 50% of adults tested in eight EU countries have inadequate or problematic skills “that adversely affect their health literacy”.

This tends to lead to the individual making less healthy choices, indulging in riskier behaviour, and, in patients already diagnosed with a disease, it brings about poor self-management of chronic diseases and lower adherence to medicine regimes.

The end result, inevitably, is more time spent in hospitals and doctors’ waiting rooms, leading to further draining of resources in what we can see are already-stretched healthcare systems.

And as a WHO report has pointed out, health literacy is an important form of social capital, an asset for individuals and communities. High literacy rates benefit societies, with the more-literate individuals active in economic prosperity.

For the benefit of all, it clearly needs to be better promoted, and politicians, the media, civil society and employers can all play a part in addressing the challenges of health literacy and health promotion.
The latter has been described as the process of enabling people to increase control over, and to improve, their health. To reach a state of complete physical, mental and social well-being, an individual or group must be able to identify and to realise aspirations, to satisfy needs, and to change or cope with the environment.

These are worthy goals, of course, but difficult to achieve across all countries and socio-economic groups.

However, Europe must strive to do this, as around 350 million working days are lost in the EU every year, which is bound to rise as the number of workers over-65 continues to grow rapidly.

There is also obviously a very strong case for businesses to invest in health literacy.

Updating the institutions

EAPM is of the view that key personnel at the Commission should undergo ‘awareness training’ in fields that are moving swiftly, such as personalised and precision medicine.

Updating regulators and policymakers would allow them that all-important insider view, which should help to ensure that any ensuing policies (or recommendations to Member States) would reflect the current and future needs of our modern-day society. It would also make it more likely that grass-roots health literacy is stimulated at national level and pan-national level.

The health, research, legal, policymaking and regulatory contingent are in clear need of more focus on health literacy in a top-down way that will complement the bottom-up knowledge being gained by patients. This knowledge could include the new models for clinical trials, pharmacovigilance, data sharing and cross-border healthcare.

Europe is currently lacking adequate frameworks that support collaboration between health professionals across Member States, and often within a single Member State. Meanwhile there are many issues around pricing, reimbursement, incentives and access for all patients, regardless of location, to the right treatment at the right time and the best care available.

Improving health literacy

Health information is often inaccessible because, says the WHO, the literacy demands of health systems and the literacy skills of average adults are mismatched.

Then there’s eHealth literacy. This means the ability to seek, find, understand and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem.

The problem is that it combines six types of literacy, which are traditional, health, information, scientific, media and computer. That’s a lot of ‘literacy’ for anyone to handle.

But in the end, at the core of the ideal, modern relationship between healthcare providers and their patients is increased communication to facilitate co-decision making. And that can’t be done unless the knowledge is there.
Fixing the interoperability connection

OK, so we have Big Data. Yes! And we're even getting closer to the best ways of sharing it in a medical sense - including privacy, guidelines and ethical considerations. Double yes!

One big problem we do still have, however, is interoperability of systems in this arena. Big oops!

Interoperability has been described as the ability of two or more devices, including software, from the same manufacturer or from different manufacturers, to exchange information and use the information that has been exchanged for the correct execution of a specified function, without changing the content of the data, and/or communicate with each other, and/or work together as intended.

Sometimes machines just can’t ‘talk’ to each other, across borders or even within regions of countries, or sometimes we don’t have a pan-European system in place - a language, if you will.

The medical technology (or medtech) sector obviously has plenty to say about this, and its members are well aware that interoperability is an issue that won’t go away. It’s a huge barrier to the deployment of digital health technologies services.

But it’s not just about this industry, there are issues with the transfer of important data in every area of health (one of the reasons for the slow take-up of electronic healthcare records and e-prescriptions, for example).

On this topic, Mariya Gabriel, above, the European Commissioner for Digital Economy and Society, said in February this year that the Commission has adopted a recommendation on a European Electronic Health Record exchange format seeking to facilitate cross-border interoperability of health data.

She said: “It can also contribute to further develop the e-Health Digital Service Infrastructure that allows the exchanging e-prescriptions and summaries of patient health records between Member States.”

On top of this, she said that the Commission “expects the review of Commission Implementing Decision to be adopted before the end of 2019, in order to clarify the role of the eHealth Network in the governance of this infrastructure and its operational requirements”.

The Commissioner pointed out that the digital transformation is supported under the Horizon 2020 programme, and through initiatives various programmes, adding that, until next year, the European Regional Development Fund invests more than €1 billion in Information and Communications Technologies solutions. This addresses healthy active ageing and e-Health.

Commissioner Gabriel pointed to the continued support for the digital transformation of health and care, “including interoperability”.
Where to next?

So aside from the Commission’s efforts, what can and must the EU and industry do about it? The answer to the last question is clear - if we want to share important health data then we MUST find a solution.

The first question is tougher: what can we do?

Industry certainly believes that European publicly funded healthcare systems have the chance to address the issue. But it will need key stakeholders to take action to advance an interoperable ecosystem for digital health in Europe, they say.

According to MedTech Europe: “Governments and healthcare authorities need to develop guidance, recommendations and mandates (in the form of digital health strategies, action plans, or other indicative statements) that raise awareness about the benefits of interoperable data ecosystems, and advance these ecosystems on the regional, national and European level.

They add that: “In accordance with these digital health strategies and their technical specifications, payers and providers to adopt common standards and mandate adherence to these in their procurements to ensure digital health interoperability. The demands from payers and procurers will ultimately affect the supply side of the digital health market.”

OK, that’s an industry point of view, but perhaps we also need to hear from patients groups and those patients who wish to share their data for the benefit of others, and who also want to benefit themselves from data from other citizens.

It is a fact that most patients are willing to share their data, but it has to be under proper privacy and ethical circumstances, plus transparent and understandable pan-EU and international standards, before interoperability truly opens the floodgates.

In any case we need a more interoperable digital health ecosystem in which data flows freely but securely, systems communicate properly, and information empowers citizens, patients and carers, as well as healthcare professionals, providers, payers and authorities, science and research.

Only connect

There’s plenty of information available that suggests that digital health technologies and services have the potential to make our health and care systems safer, better and more efficient.
Most stakeholders agree that readily available data and information can reduce medical errors, support care coordination and workflow, and assist HCPs in diagnostic and treatment decisions.

MedTech Europe says that: “Connected devices and sensors can empower citizens and patients with information and enable remote monitoring and self-management of chronic conditions or prevent them in the first place.

“Sharing of health information among patients, carers, and health professionals enables integrated, patient-centred care.”

EAPM is in full agreement with all of this, of course, but we can see that despite the rapidly evolving and expanding field of digital health innovations and a growing body of evidence that data and digital solutions can transform healthcare, digital health models are still not being widely adopted.

The lack of interoperability is a key factor. And this is holding back investment in, and deployment of, digital health.

In typically stodgy and long-winded fashion, the European Council of late 2017 noted:

“Barriers to scaling up the potential in digital health and connected care, such as dominance of data silos, lack of interoperability and of common standards for measuring clinical and patient reported outcomes, limited access and use of large databases for research and innovation purposes, lack of funding and financial incentives, fragmented markets across the EU and across the spectrum of services, still exist and progress in implementing the data-driven digital solutions in the health sector remains limited.”

Phew! OK. We’ve still a long way to go, clearly.

But instead of simply telling us what we already know, perhaps it’s time for all major stakeholders – including the institutions of Europe and big-big-money tech industries - to look to themselves just a little bit more and move faster in finding solutions.

Maybe addressing the “lack of funding and financial incentives” would be a start?
It's all about the patient, right?

So, wasn't healthcare always personalised? No, not totally. And that's the truth.

Yes, your GP had your family records and may well have known you since birth, but doctors have historically prescribed medicines and treatment largely by population.

This means that if a medicine or treatment works for 75% of people then it's the default option. Just ask an oncologist whether chemotherapy and/or radiotherapy works the same for everyone, and you'll get an idea of what we mean.

As often-genetics-based personalised medicine becomes ever-more mainstream it’s worth remembering that its many proponents espouse the goal of giving ‘the right treatment to the right patient at the right time’. And you can't guarantee to do that using a percentage base and occasional ‘guessmology’.

Of late we have been blessed with great leaps in our understanding of genetics, and how diseases work plus what we can do to stop them. But it’s not only new technologies that change societies. It’s the response new technology that causes change.

Clearly, in healthcare, technology is in constant and rapid transition. But in a field as complex as personalised medicine, involving so many disciplines, dimensions and stakeholders, questions are numerous.

Like how do we ensure the interests of the person are taken into account amid all the competing and conflicting priorities of multiple stakeholder/shareholders with their particular interests, each imparting a distinct dynamic?

And how do we establish effective governance concerning a process where there is the ebulition of tens of thousands of simultaneous contributions?

These are among today’s key questions as we take stock of where personalised medicine is now, and where it can go. The patient being put at the centre and being kept at the centre is vitally important.

The promise of personalised medicine

Personalised medicine offers should see 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, improving the outcomes for patients and cutting down on unnecessary treatments.

Personalised medicine can also reduce percentage-based prescribing, minimise adverse reactions to drugs and cut down on invasive testing methods.

Meanwhile, the emergence of immunotherapy will allow us to use a patient’s own immune system to combat diseases such as cancer, while the cost of gene sequencing is falling on an annual basis. Gene therapy is allowing researchers to look for ways to place genetic material directly into a patient’s cells, replacing a disease-causing mutated gene.
It is important to note that personalised medicine is not just another addition to the understanding and practice of medicine - the art that concerns itself with the prevention, diagnosis and treatment of disease. It has the potential to significantly alter medicine itself.

Modern technology and the information highway have created new ways to put the patient at the centre of medicine. Giant leaps in genetics have advanced certain key areas in healthcare. If people with serious diseases are to make informed decisions about their health, it is vital for them to have the necessary knowledge and support.

DNA tests, for example, can show in advance the likelihoods of major illnesses happening in an individual, although of course not everybody wants to know that they may have more chance of getting breast or colon cancer than their neighbour.

Genetics has opened new doors for patients via personalised medicine. It has often changed the ‘patient journey’, with new treatments available and better communication between doctors and patients.

Diagnosis of a disease based on its molecular image will allow clinicians to select the most effective pharmaceutical, for example, while pharmacogenetic assays will make predicting the patient’s response to treatment much easier.

**Decision-making with the patient**

Proponents of personalised medicine, in all fields, are aware of the duty to talk about better medicine, giving not only hope but leading to longer survival rates of more patients with better quality of life.

These days, there is more co-decision as lifestyle, work and personal preferences come into play – or should do, especially with those front-line healthcare professionals who are up-to-speed with developments, or know where suitable clinical trials are taking place and actually pass this on to their patients.

Patients are pushing to play a bigger role. These stakeholders in personalised medicine are carrying the message “Involve me!”, and it is never the best policy to ‘shoot the messenger’.

**Big Data**

Big Data is here and here to stay and its power cannot be over-emphasised. We are sharing more and more information in more and more different ways and the trick, clearly, is how to use these data superhighways for the benefit of mankind.

It is clear that patients, researchers and industry all need information. And there’s no doubt that there are ever-more new ways of collecting it. Clinical trials, screening programmes and the subsequent sharing of related data across borders is crucial. Yet data needs not only to be shared but the knowledge to interpret it must be increased.

There is a wealth of data out there now, more than ever before and growing by the day. EAPM believes that we must remember that, in health, this information should revolve around, and give benefit to, the patient.

**The legislative responsibility**

The EU is well-placed to find the right mechanisms and balances to keep the person at the centre of personalised healthcare.

Some of its laws and its governance structures already tend in that direction, and democratic principles are embedded in the Member States themselves and underpin systems that offer frameworks for collaboration, cooperation and coordination.

In the EU, legislators, healthcare professionals, HTA experts, and payer organisations all have social principles at their core.

But for this have any real impact, adequate governance frameworks need to exist, alongside education in the intricacies of healthcare provision, from an earlier age.

Better education will raise the level of understanding between different groupings, and help in establishing common goals and visions that take account of the other’s perspective.

If the EU puts the right frameworks in place, it can act as a hub for personalised medicine in the years ahead.

One key focus now should be investment in guidelines for governance to ensure that the person is the principal in shaping the use of innovative technology, so that technology remains at all times subservient to the person. And that means the patient!
About EAPM

The European Alliance for Personalised Medicine was launched in March 2012, with the aim of improving patient care by speeding development, delivery and uptake of personalised medicine and earlier diagnostics, through consensus.

EAPM began as a response to the need for a wider understanding of priorities in personalised medicine and a more integrated approach among stakeholders. It continues to fulfil that role, often via regular major events and media interaction.

Our stakeholders focus not just on the delivery of the right treatment for the right patient at the right time, but also on the right preventative measures to ensure reliable and sustainable healthcare.

The mix of EAPM members and its broader outreach, provides extensive scientific, clinical, caring and training expertise in personalised medicine and diagnostics, across patient groups, academia, health professionals and industry.

Relevant departments of the European Commission have observer status, as does the EMA, and our engagement with MEPs and Member State health ministries in key policy areas is a crucial part of our ongoing work.

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