EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Personalised medicines

Report from a workshop on personalised medicines held by EMA on 14 March 2017

Introduction

Personalised medicine is a new paradigm in medicine and is a move away from traditional medicine, which applies the same treatment approach to all patients affected by a disease regardless of specific differences in their genetic make-up ('one size fits all'). Rapid advances in science are leading to an approach that puts the patient at the centre of healthcare by developing targeted diagnostic, treatment and prevention strategies, that take into account differences in patients' genetic make-up and environment. Personalised medicine uses our developing knowledge of how variability in gene expression leads to differences in susceptibility to disease and responses to medicines. This is combined with the collection of complex health-related data about an individual's genetic make-up, environment and lifestyle to group patients according to their likely response to a specific intervention, in order to better target treatment and prevention.

Personalised medicine does not only concern medicines. A better understanding of the biological mechanisms and environmental factors that lead to a disease will impact the entire health care continuum, from research to patient care. By targeting prevention and by making treatment more effective, personalised medicine aims to reduce the burden of disease. Improving the ability to better target treatment to patients who are likely to benefit from it and avoiding patients who may be at risk of being harmed would increase success rates of treatment, improve product development times and potentially reduce healthcare costs overall. However, changes and adjustments are needed from all parties involved in bringing medicines to the market and using them in order to ensure that the new tools provided by science can be applied to achieve the full benefits personalised medicine has to offer.

What do we mean by 'personalised medicine'?

- There is no universally agreed definition of personalised medicine, however a definition by the European Council[1] is now widely accepted in Europe:
  "Medical model using characterisation of individuals' phenotypes and genotypes or tailoring the right therapeutic strategy for the right person at the right time, and to determine the predisposition to disease and/or deliver timely and targeted prevention, and it relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs."

- The term **precision medicine** is also widely used,[2] often simply as a synonym for personalised medicine, although some prefer to reserve it for targeted treatment guided by use of biomarkers.

- **Stratified medicine** is another term that is used for the concept. This term emphasises the way patients' genes and physical characteristics are used to group them more precisely so that the right therapeutic strategy can be identified.

These concepts differ from the concept of **individualised medicine**, which refers to tailor-made medical treatment, for example with products based on the patient's own cells.

Why is this workshop needed?

”It is more important to know what sort of person has a disease than what disease a person has.”

Hippocrates of Cos,
ca. 460–ca. 370 BC

While personalised medicine provides promises for the future of patient care it also raises many challenges. They range from a need to adapt health outcomes research, the way clinical trials are designed and assessed, issues around the assessment by health technology assessment bodies to the way health care is delivered. The evidence to support personalised medicine may include so-called ‘big data’ and an additional challenge revolves around how data can be translated into knowledge. The approach to clinical care itself will need to change in order to fully implement personalised medicine.

There is increased interest in personalised medicine in the EU and around the world and the workshop was organised following specific requests from EMA working parties with patients, consumers and healthcare professionals to clarify perceived confusion around terminology and concepts. Education of patients and healthcare professionals is fundamental in order to make best use of personalised medicine. The very notion of personalised medicine implies that patients participate in the management of their own health.

The workshop tackled important questions from stakeholders, how European and global environments are shaping policy developments and how clinical practice and public participation can support personalised medicine in the context of EU regulatory activities. It was also intended to identify areas requiring attention from EU regulators, patients, healthcare professionals and civil society.

This report reflects the main issues discussed during the meeting.

Key messages

Personalised medicine is a new paradigm in medicine. It puts the patient at the centre of healthcare by developing targeted diagnostic, treatment and prevention strategies, while taking into account differences in patients’ genes and environments.

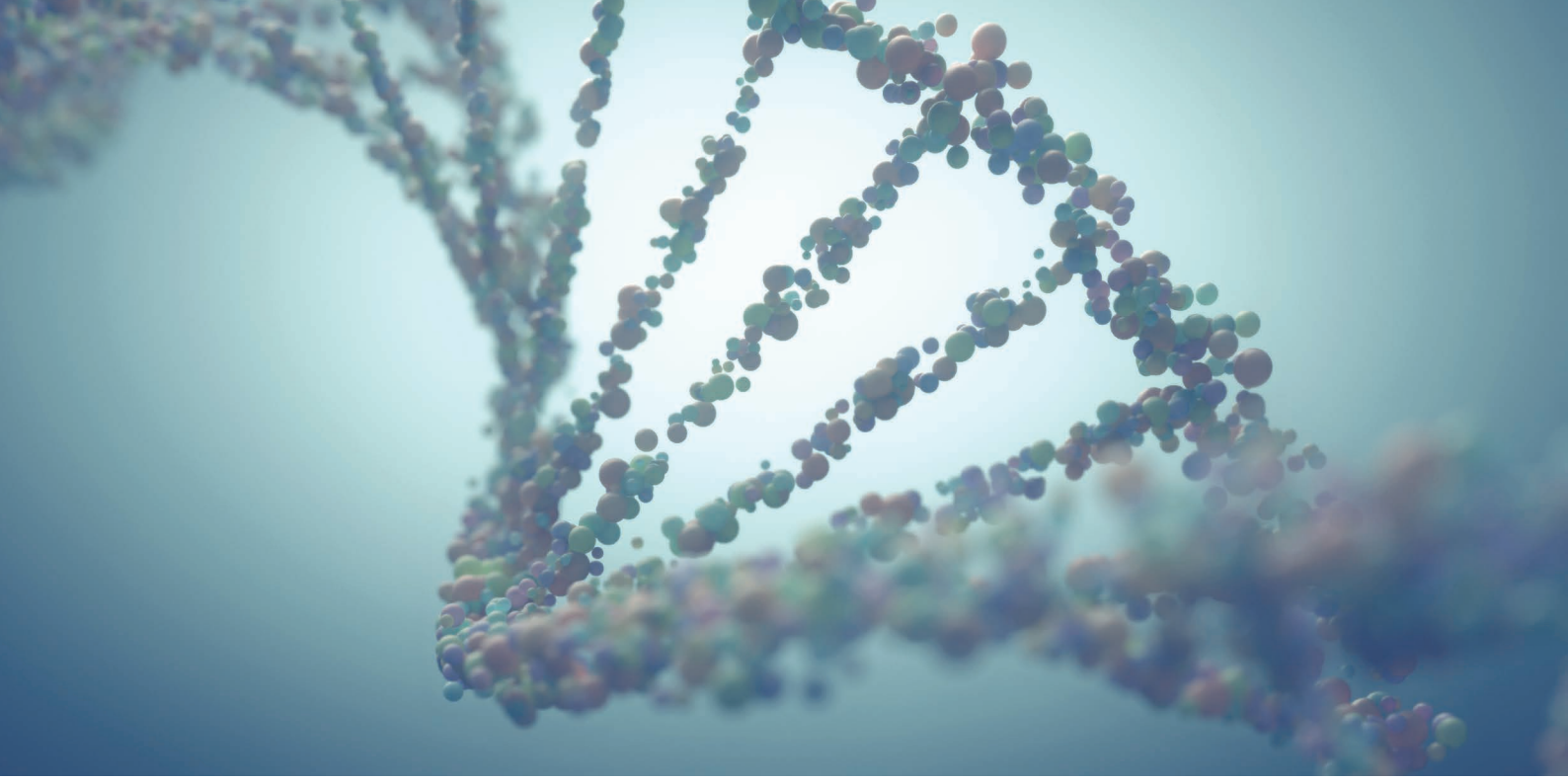
Personalised medicine has so far been largely confined to the fields of oncology and rare diseases. In order for personalised medicine to become mainstream, changes and adjustments are needed from all parties involved in bringing medicines to the market and using them.

In order to become patient-centred, personalised medicine requires a major change in the way medicines are tested and evaluated bringing together all stakeholders. Changes will also be needed in the way healthcare is delivered and healthcare systems are structured.

Personalised medicine requires that patients’ health literacy is improved to allow them to become the centre of healthcare.

Education is needed to help healthcare professionals support and serve their patients. In particular teaching curricula may need to change to provide healthcare professionals the tools needed to interpret the new data.

Personalised medicine implies the use of extensive patient and population data. This raises challenges in terms of integrating information and communication science technologies into clinical practice. It also raises challenges in terms of data protection and patient privacy.



Session 1—Setting the scene: the rise of personalised medicine

Although science and technology had provided new tools, it is not yet clear how these will be used in practice and what challenges come with them. The aim of the first session of the workshop was to give an overview of the current state of the field. The speakers in this session gave an insight into ongoing initiatives with personalised medicine in the EU and the United States and highlighted the challenges posed to society as a whole.

Irene Norstedt from the European Commission explained that personalised medicine has been on the agenda of the European Commission since 2011.[3] Challenges identified include patient awareness and empowerment, integrating 'big data' and information communication technologies, translating basic research into clinical research and implementation, bringing innovation to the market and shaping sustainable healthcare.

Since 2010 the EC has committed 2 billion Euros of health research funding to personalised medicine and this topic will continue to drive research and innovation agendas for years to come. However, partnerships between academia and industry such as the Innovative Medicines Initiative (IMI)[4] are deemed essential if a pipeline is to be developed from the lab bench to the bedside, allowing patients to benefit from new knowledge as soon as possible.

An initiative called the International Consortium for Personalised Medicine[5], or "IC PerMed", was highlighted. Maria Judit Molnar from this initiative described how it has been set up by several public health research funders and policy-making organisations to address the challenges facing the implementation of personalised medicine. It focuses on fostering and coordinating research and innovation actions to provide evidence of the benefits of personalised medicine and will support patient awareness to pave the way for a personalised approach for EU citizens. It will also look at the challenges involved, not least the cultural change needed to promote more patient-centred healthcare in all countries.

In the US, personalised medicine is also at its beginning and similar initiatives are underway. Sandra Kweder from the FDA informed the audience that,

in 2015, President Obama launched the Precision Medicine Initiative (PMI)[6] with the goal of bringing personalised medicine to all areas of healthcare. As in the EU, the translation of new scientific findings into safe and effective medicines remains a challenge. FDA is working to help the development of new medicines by developing regulatory standards and reference libraries which are based on large-scale patient-powered studies to gather genetic data, biological samples, and other information about their health. These data will be used by researchers to study a large range of diseases, with the goals of better predicting disease risk, understanding how diseases occur, and finding improved diagnosis and treatment strategies.

Luca Pani, an alternate member of Committee for Medicinal Products for Human Use (CHMP) who until 2016 was the director general of the Italian medicines agency (AIFA) described the massive volume of healthcare data ('big data') that has been generated so far and the need for healthcare to adapt to utilise this data, which will revolutionise the way healthcare is conceived and delivered, and which was the subject of a recent EMA workshop.[7] We now potentially have access to a vast amount of complex health-related data which requires innovative data analysis models to discover relationships and patterns within it and turn this data into knowledge.

One of the challenges that come with big data is the requirement to ensure confidentiality of sensitive personal information. In the discussions following the first session, participants emphasised the need for improving not only health literacy, so that patients can give truly informed consent to personalised medicine approaches, but also informatic literacy, so that they can understand the implications of sharing their data. Education is also needed to help healthcare professionals support and serve their patients better in the coming era of personalised medicine and big data. In particular teaching curricula may need to change to provide healthcare professionals the tools needed to interpret this data.

Session 2—Regulatory challenges and opportunities

The idea of adapting treatment to the patient's individual characteristics has long been a part of medicine. Concepts such as stratifying patients according to the way their bodies break down medicines (slow and fast metabolisers) are also not new, but implementation of these concepts in practice has proved challenging. For personalised medicine to become more widely applicable, the clinical research and regulatory paradigms need to be adapted.

"No matter how spectacular the technology, it is useless unless there is an underlying system able to make use of it."

Guido Rasi,
EMA Executive Director

Presenters from some of EMA's scientific committees, the CHMP, the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee for Orphan Medicinal Products (COMP), the Committee for Advanced Therapies (CAT) and the Paediatric Committee (PDCO), all of which can potentially get involved in the assessment of personalised medicines, gave the workshop some insights into the regulatory challenges in this field.

Among them, Rob Hemmings, CHMP member and Chair of EMA's Scientific Advice Working Party noted that the success of personalised medicines depends on the development of accurate and reliable diagnostics and on the identification of predictive biomarkers that help researchers identify patient groups that may be more responsive to treatment.

The use of biomarkers in early drug development requires new development models. Genomic data submission is needed early on in the product

development, which means that the early stage of clinical research (which aims to determine who will be studied in confirmatory trials) becomes more important than in traditional clinical trials. A significant challenge in the development of personalised medicine is the setting of the diagnostic cut-off values that represent significant results. Choosing a conservative cut-off may improve results, however this would be at the expense of potentially losing data for a population that might benefit from the medicine.

Once clinical trials begin, different designs from the classical randomised controlled trial may be needed, since stratification may imply studying much smaller populations, in whom the epidemiology of the disease might potentially be different. New clinical trial designs that may be considered for personalised medicines include:

- Basket studies, which recruits patients on the basis of their molecular characteristics irrespective of the diseased organ.
- Umbrella studies, where patients with the same type of disease are screened for a series of hypothesised predictive biomarkers. They are then allocated to appropriate therapies.
- Platform trials, where multiple treatments are evaluated simultaneously.

However, these new innovative clinical trials throw up new questions in terms of assessment, labelling and post-authorisation commitments. The speaker illustrated this point by discussing some of the questions that had arisen in the licensing of the oncology medicines Opdivo and Vectibix.

Together with oncology, it could be argued that the orphan medicines industry is leading in the field of personalised medicine. In many ways rare diseases paved the way for some of the modern approaches to personalised medicine. Personalised medicine and orphan medicine development have many similarities. Both are developed for a small population and they often link therapy with a biomarker.

The point was made throughout the day that the taxonomy of diseases based on signs and symptoms may need to be revisited in favour of a system which is based on genomics, to better support personalised medicine. However this may also have an impact on the way orphan medicines are designated. Bruno Sepodes, chair of EMA's COMP highlighted that for some clinical conditions interpretation of the orphan legislation may need further discussion, to uphold its spirit and to avoid applying the orphan regulation to artificial subpopulations of broader patient groups. This is to ensure that true innovation in rare diseases with clear unmet medical needs continues to be rewarded with incentives for drug development.

Margarida Menezes of EMA's CAT and Dirk Mentzer, chair of EMA's PDCO highlighted the relevance of personalised medicine for the development of advanced therapies and medicines for children, including the use of a risk-based approach and the importance of registries as a source of information.

Part of the workshop focused on how genomics have been used in the field of medicine safety. More than 6% of acute hospital admissions are caused by serious adverse reactions to medicines. Personalised medicine and genetic testing can not only help to determine which medicine is most effective for a particular patient, but will also help to predict the safety of a medicine. June Raine, chair of EMA's PRAC gave the example of the investigation of hypersensitivy to the HIV medicine abacavir, which was found to be linked to a particular genetic variant (allele HLA-B5701). Requiring a test to ensure this allele is absent before giving abacavir has greatly reduced the incidence of hypersensitivity for abacavir. Another well-known example is codeine, the efficacy and safety of which is influenced by genetic variations that affect the speed with which it is converted to morphine in the body, explaining why slow metabolisers lack an analgesic effect with therapeutic doses while ultra-rapid metabolisers may experience adverse effects with the same doses. June Raine questioned whether more needs to be done to make better use of genetic testing in pharmacovigilance, whether existing guidelines are used optimally, whether PRAC activities on pharmacogenomics are sufficiently systematic and whether PRAC should take a more proactive role in stimulating research in this area.

Personalised medicine raises challenges not only for regulators but for researchers, developers and payers.

Denis Lacombe of the European Organisation for Research and Treatment of Cancer (EORTC) made the case that clinical trials need to become more patient-centred and need to answer real life questions that are central to patient care. He suggested new models of clinical research and improvements throughout the lifecycle of a medicine, from the planning and development stages through to product launch and post-marketing monitoring. Any transformation of clinical research must not be driven exclusively by industry but should be achieved through better collaboration between all stakeholders.

Personalised medicines tend to be expensive since, by definition, they are suitable for only a limited number of patients. From the perspective of payers, this may raise the question of affordability in a context of strained public health budgets. Speaker Anna Bucsics highlighted the problems that payers and health technology assessment (HTA) bodies face, most notably a need for convincing evidence of real, patient-relevant benefit to support reimbursement of personalised medicines. When these are coupled with a diagnostic device, one difficulty is that the reimbursement of devices and medicines may be handled by different authorities and communication between them is often insufficient. She also highlighted the need for privacy and data protection and the need to continue cooperation between payers and HTA bodies at European level.

During the subsequent discussions, participants reiterated the need for patient involvement right from the planning stages of any initiatives in the field of personalised medicine, and discussed potential barriers to patient and clinician involvement. The importance of real world evidence and existing difficulties in collecting this evidence were also highlighted. One problem is the lack of a common forum for stakeholders to address these issues, as well as the financial barriers many patients' organisations face, and the reluctance of all parties to step outside their comfort zones. Nonetheless, broader involvement, particularly from patients, was seen as key to ensuring implementation of personalised medicine on a wider scale.

Session 3—What are the priorities for patients and healthcare professionals?

The workshop's third session looked at the priorities of patients and healthcare professionals, and discussed ways to capture their input and apply it in practice.

Julian Isla, chair of the European Dravet Syndrome Federation, gave the patient perspective. In order to make the best use of personalised medicine, and arrive at medical treatment that is both accurate and precise, treatment should be centred on patients and their involvement and incorporate feedback loops that allow learning and adaptation. Patients are in a unique position to collect and provide data, but partnerships with healthcare professionals continue to be essential in helping to ensure the quality of the data and supporting patients in interpreting it to make the best decision.

Ulrich Jaeger gave the perspective of healthcare professionals. There are many challenges for the application of personalised medicine to day-to-day practice: one of the challenges can be current disease classifications which define diseases on the basis of signs and symptoms rather than the molecular causes and do not accommodate new information about disease mechanisms. There is also a certain reluctance to use new diagnostics, which is partly due to the fact that biomarker utility remains a moving target. Clinicians also face the problem of information overload making it difficult to consider, communicate and implement information during a consultation, often lasting not more than 10 minutes. A future of personalised medicine will almost certainly require a team approach to making treatment decisions, involving patients and a range of healthcare professionals and perhaps informatics specialists, but we are not there yet in most cases, even in specialised treatment centres.

In the facilitated discussions, participants highlighted that personalised medicine needs to go beyond the disease areas of oncology and rare diseases. Using small populations as a starting point may lead to better understanding of methodologies and treatment avenues that may pave the way for broader use in the future. However, barriers to a broader use are the variability in patients' ability and willingness to contribute to treatment decisions, which may also vary for the individual patient over time. Patients need to be able to make informed decisions about health-related issues, in other words be empowered in their healthcare. In order to do this it will be vital for them to have the necessary knowledge. Health literacy – the ability to access, understand, appraise and apply health information to make sound health decisions – is an important tool to ensure patient empowerment. It is important to ensure that less empowered patients do not have worse outcomes, and patients' organisations can have an important role in supporting them, although funding could be an issue. It was reiterated that training for both, representatives of patients' organisations (through initiatives such as EUPATI or the Eurordis summer school) and healthcare professionals (through medical curricula supporting a shift in medical culture) is crucial in preparing both groups for this new era and helping them to support patients.

Participants agreed that EMA could also help by continuing its engagement with both patients' and healthcare professional groups, by providing a common platform for discussion and perhaps for data access, by ensuring that relevant stakeholders had access to clear, unbiased information, guidance and product information, and by extending its networks to incorporate new stakeholders such as academic researchers.[8]

Conclusions

The workshop illustrated how the concept of personalised medicine is both challenging and exciting for the future. It provided the wide range of views among patients, healthcare professionals and payers and was as much a forum to clarify current concepts as a forum to share ideas for initiatives to move forward.

Although it was agreed that many issues will require wider discussion, the following actions were agreed:

- Assist relevant stakeholders to gather and discuss information that is already available on personalised medicines, positions, guidelines, etc.
- Consider a joint subgroup of the patients, consumers' and the healthcare professionals' working parties (PCWP and HCPWP) as a common platform to pursue the topic.
- Ensure close collaboration between this subgroup and all EMA human scientific committees, Scientific Advice Working Party and Pharmacogenomics Working Party.
- Already existing initiatives should be followed up on (such as registries and ongoing work on Product Information).
- Ensure that EMA contributes where possible to initiatives on personalised medicine led by the European Commission.
- Pursue links with the European Reference Networks and European Research Infrastructures.
- Organise a follow-up workshop also involving industry stakeholders.
- Work on defining the role different actors (i.e. patients, healthcare professionals, industry and regulators) can play in personalised medicine.

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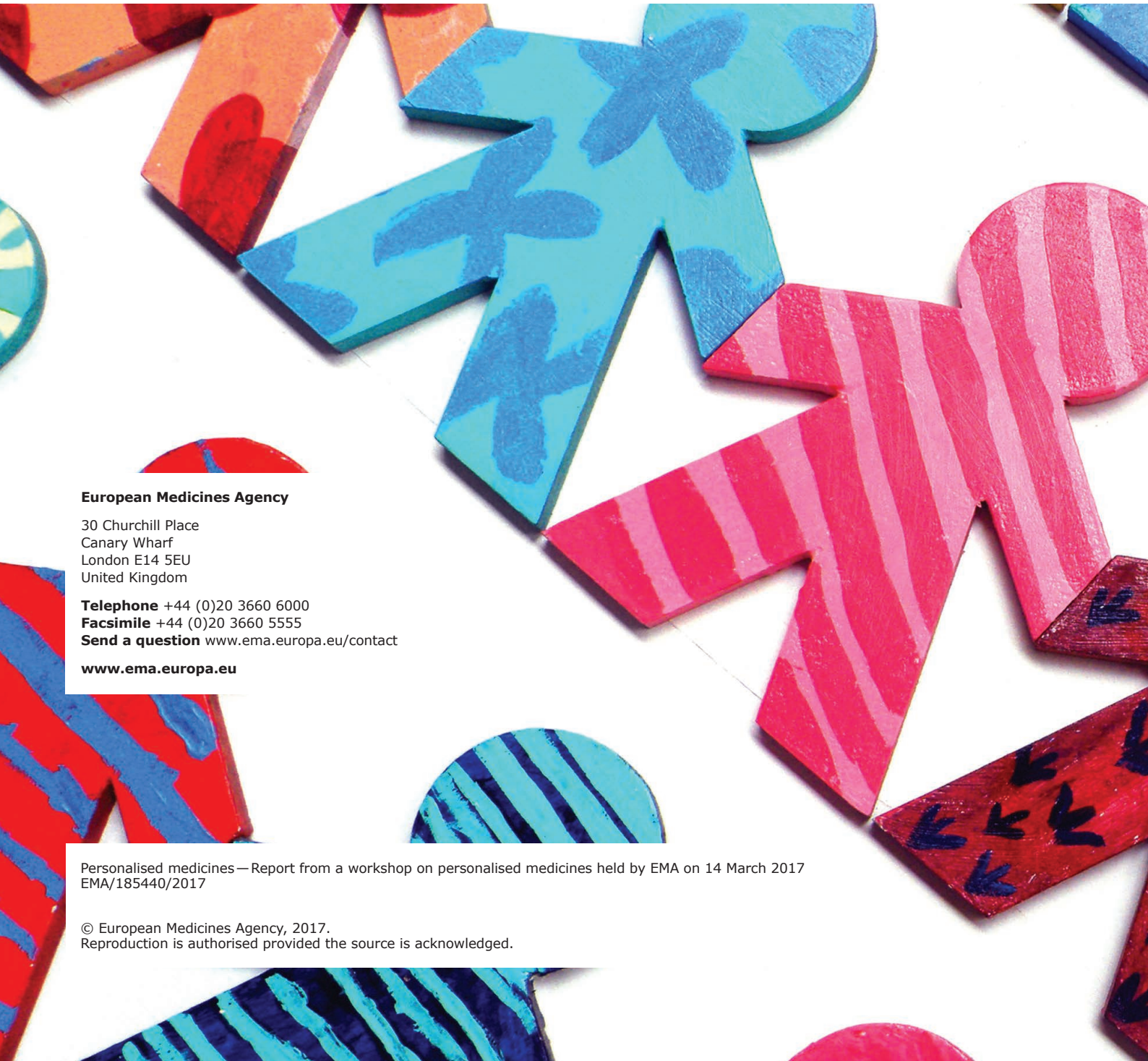

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