7. Cross-cutting themes

7.0 Introduction

This chapter reports on a number of issues which apply to all diseases and therapeutic approaches. The themes include the particular needs of special groups and the development of stratified medicine. The special groups highlighted in this chapter are the same as those covered in the 2004 Priority Medicines Report: children, women and the elderly. Although progress has been made in some areas, special attention for these populations is still warranted. Each of these groups have specific pharmaceutical needs due to their changing physiology, the spectrum of diseases they face, and the fact that these needs are under-represented in the pharmaceutical development process. While similar issues exist for these groups, particular needs have been identified and will be discussed below. An important cross-cutting theme that has been identified throughout this chapter is the need for better use of existing data (electronic health records) to provide insight into, and assess the implications of medicines use in these special patient groups (see also Chapter 8.4).

Stratified medicine is expected to play an increasingly important role in clinical treatment in the coming decades. Stratified medicine can be summarized as an approach targeting treatment specifically to subpopulations of patients who are more likely to benefit from, or less likely to be harmed by a particular treatment. Many different strata exist, including the special populations addressed in this chapter. New elements in stratified medicine, such as pharmacogenomics and other new technologies are rapidly evolving. Up until now, despite all the projected benefits of this approach, clinical implementation in health care systems has been limited, and various gaps remain at the level of basic research, translational studies and the establishment of societal and regulatory frameworks.

7.1 Priority medicines for children

See Background Paper 7.1 (BP7_1Children.pdf)

Children are entitled to safe, efficacious and age-appropriate medicines. However, the provision of optimal medicines for children is limited by the lack of commercial incentives, a dearth of clinical trials on children’s medicines, delays in licensing medicines for children and the absence of suitable formulations for children. Children are not small adults. They are a vulnerable population with specific needs as a result of changing physiology, and with a range of diseases and patterns of disease that differ
from those in adults. Unmet public health needs of children include, among others, paediatric oncology, pain, and neonatal morbidity. There is currently very little data on the appropriate delivery and use of medicines in children.

The 2004 Priority Medicines Report called for public investments to reverse the insufficient funding for research on children-specific medicine formulations. Such formulations need to take into account children’s body development, medicine related toxicity and children’s taste preference. In recent years, much progress has been made in the development of age-appropriate novel oral formulations with dose flexibility (mini-tablets, chewable and orodispersible tablets for younger children, and dosage forms dispersible into liquids or mixed with food). This development is in line with the global shift towards the use of solid oral dosage forms for children, as proposed by a WHO expert forum in 2008. Following recent studies on mini-tablets (see Figure 7.1.1), the age at which young children can safely swallow orally administered solid forms is decreasing. With the development of orally disintegrating mini-tablets, there are more promising results for infants younger than two years of age.

**Figure 7.1.1: Children’s ability to completely swallow mini-tablets and glucose syrup (n=10 children per age group; mean±95% CI).**


Despite the (ongoing) development of various innovative oral solid dosage forms and devices for use in children, there are continued research and development (R&D) gaps and further investments are needed. The research on children’s ability to swallow medicines needs to be accompanied by studies on children’s preferences and adherence to different dosage forms. In addition, alternative routes of administration
7. Cross-cutting themes

(such as oral-transmucosal (buccal strips), intra-nasal and transdermal routes) are ripe for future R&D efforts. For all formulations, methodologically sound data are needed on the impact of new technologies on patient-related outcomes such as clinical efficacy, side effects and administration errors. In view of the concerns about the toxicity of some excipients in formulations for children, more research is needed into the development of safe alternatives for children. An additional concern is the limited marketing of many newly developed drug delivery devices for children. Studies are needed on the implications of price and the need to improve access to innovative products that have tangible therapeutic benefit.

Another key recommendation of the 2004 Priority Medicines Report was the need to include more children in clinical trials. Progress since then includes the adoption by the European Union of the Paediatric Regulation in 2007, thereby combining requirements for paediatric drug development (Paediatric Investigation Plans – PIPs) with incentives for the pharmaceutical industry to, at least partly, cover the additional investment for testing new medicines in children.

From 2007 to 2011, the number of clinical trials with a paediatric population (based on information from the EU clinical trials database, EudraCT) was relatively stable, with an average of 350 trials a year, while the proportion of paediatric trials among all trials increased from 7.4% to 9.9% (see Background Paper 7.1, Table 7.1.6). Of these paediatric trials, 109 were part of an agreed PIP. One effect was the inclusion of younger children in clinical trials for cholesterol-lowering and anti-hypertensive medicines, juvenile idiopathic arthritis, diabetes mellitus and haemophilia A and B. The Regulation may aid in preventing unnecessary trials since protocol-related information is made publicly available through EudraCT.

Since 2008, approximately 70% of all PIPs proposed or required the development of indications for the whole or subsets of the paediatric population. This indicates an increase in the development of medicines for children, as only approximately 30% of medicines applied for and obtained a paediatric indication before the EU Paediatric regulation came into force. Nevertheless, paediatric therapeutic areas addressed by the industry since 2007 seem more aligned with adult drug development than with the indicated unmet public health needs of children. The question as to whether the requirements and incentives system of the Regulation delivered what was expected needs to be answered. In addition, the awarding of SPC extensions to paediatric medicines may increase public expenditures for health care and have cost implications for public payers. Such effects have to be identified and studied.

Based on an EMA survey published in 2010, 45% to 60% of all medicines used in children in the EU27 countries were used outside their marketing authorization (off-label), especially in neonates, patients with serious conditions and in intensive care units. Preterm neonates were the most vulnerable patient group, exposed to high numbers of medicines (up to 90% unlicensed or off-label use), at higher risk of adverse drug reactions and with no information on safety and efficacy available in the Summary of Product Characteristics. Despite the risk of potential harm, off-label use
of medicines has become an accepted practice in health care for children. Off-label drug use can be medically appropriate if the benefits outweigh the potential risks, which calls for a systematic consideration of evidence for safety and efficacy. A priority list of studies into off-patent paediatric medicines has been produced by the EMA to serve as a basis for EU public sector research funding. In the absence of evidence obtained from robust clinical trials, other accessible data sources should be explored, such as existing electronic anonymized patient-level databases. The expanded availability and use of electronic medical records could allow researchers to link clinical treatments and outcomes with prescribing trends in off-label medication and better assess the implications of their use in children (see also Chapter 8.4).

Such data would also help facilitate other much needed research linked to medicines use in children. The collection of data on the use of medicines at country level could enable intercountry comparisons to be made over time in order to better understand the burden of childhood diseases within the EU and set priorities. The main challenges for a complete and comprehensive evaluation are the lack of systematic and continuous monitoring in all EU countries and the disparity between studies. To counter this, the methodological quality of data collection should be improved, and more multinational collaborative studies should be performed with EU support. Other essential studies include those that assess the effectiveness of interventions to improve treatment, and those that evaluate the impact of adherence-promoting interventions in children.

In summary, to further improve the development and use of medicines in children, investments are needed to: stimulate additional research into the development of age-appropriate medicines; study the impact of formulations development and paediatric regulations on patient and public health outcomes; increase the efficiency of the Regulation with a focus on genuine paediatric needs; facilitate the collection, linkage and use of data on medicines use in children Europe-wide; and improve (information on) the rational use of medicines in children.

References


7. Cross-cutting themes


7.2 Priority medicines for women

See Background Paper 7.2 (BP7_2Women.pdf)

Over recent decades, female health, and especially maternal health, has been one of the top priorities for both health care decision makers and health researchers. Women have particular medicine needs. Not only do they use specific medicines related to reproduction and pregnancy, but they also differ from men in their overall medicines use, pharmacokinetics and pharmacodynamics. The 2004 Priority Medicines Report identified a number of key priorities for R&D in order to meet the particular medicine needs of women. They included the need for: the inclusion of more women in clinical trials; appropriate risk management strategies to monitor the long-term effects of female medicine therapies; and the global collection of data on birth defects and on women’s exposure to medicines during pregnancy.1
Some improvements in these areas have been observed over recent years. The most recent data (2007 to 2009) from the United States Food and Drug Administration (FDA) show that the participation of women in late-phase clinical trials was on average 44%. Of the new drug applications, 74% included exploratory or confirmative gender-specific efficacy and safety analyses. In early-phase clinical trials the participation of women was slightly lower. The need for gender-specific analyses was recently underlined when the FDA announced a recommendation to lower the dose for women of a medicine that had been on the market for decades. According to an EMA review, the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) do address gender. In particular, ICH guidelines M4E and E3 require adequate demographic (including gender) characterization, analysis and assessment of the patient population. The results of reviews and experience argue against stronger regulations and requirements for additional clinical trials, such as a separate ICH guideline on women as a special population in clinical trials. A better solution to obtain the necessary data would be to use existing (prescription or dispensing) data, especially since in many cases the need for knowledge relates to “old” medicines (see Chapter 8.4).

Therefore, use of existing data and the development of (innovative) methodological approaches for better use of existing data should be further explored. These data should be able to provide more insight into both the gender-specific benefit-risk profiles of medicines (also related to dosing), and the gender-specific underutilization of medicines. While the latter issue is of concern, with gender differences occurring, these are not consistently biased towards women.

Many pregnancy registries have been set up in addition to the already existing birth defect registries. These registries should be further strengthened and collaboration encouraged between registries (for example, in a research network) in order to harmonize strategies and definitions and thereby enhance the pooling of data. Particular attention should be paid to: the potential effect on children of paternal medicines use; the potential long-term effects on children (such as fertility and behavioural problems) of maternal medicines use during pregnancy; the effects of medicines use on fertility and very early spontaneous abortion in women; and opportunities to collect data on medicines use during lactation.

The World Bank estimates that contraceptive use worldwide increased from 58.1% in 1990 to 62.2% in 2010. In Europe, the two most popular forms of contraception among women are oral contraceptives (28%) and the male condom as a single method (17%), with the copper intrauterine device (5%) and other forms of hormonal contraception (such as implants and patches) being less popular. Access to (emergency) contraceptives is a major challenge in many parts of the world, but this issue is beyond the scope of this report. Another major challenge is the need to strengthen informed decision making among women. Women, but also doctors and pharmacists, need to be better informed about (emergency) contraceptive measures. Improving knowledge and attitudes towards contraceptives requires better patient counselling and aids, especially for young women and women with comorbidities. Strategies need to be
developed and evaluated for their impact, not only on the level of knowledge but also on important health outcomes such as unintended pregnancy rates.

In summary, the main recommendations to improve medicines use in women are:

- Use existing (real-life) data to their full potential (see Chapter 8.4) to provide better insight into: the gender-specific benefit-risk profiles; underutilization of medicines; and (through the use of pregnancy registries) the effects on children of parenteral medicines use. These pregnancy registries should be further strengthened and collaboration encouraged between these registries (for example, in a research network).
- Strengthen informed decision making among women, especially related to (emergency) contraception, by improving knowledge and attitudes and development and evaluation of better patient counselling and aids.

References


7.3 Priority medicines for the elderly

People aged 60 years and older are a growing part of both European and global communities (see also Chapter 5 Figures 5.2.1 and 5.2.2). The proportion of the global population aged 60 years and over is projected to increase from 11% in 2010 to more than 16% in 2030. In Europe, the growth of the elderly population is more pronounced, with an estimated proportion of 29% aged 60 and over by 2030. This rise poses challenges to health and social care systems. The incidence of diseases such as dementia, cancer and osteoporosis is increasing and the use of multiple medicines (polypharmacy) is common, often leading to medicine-related problems. In addition, the elderly reside in different care settings depending on the level of care needed—a trend that underlines the need for integration of care and for better self-management of medication. As with children, many medicines are prescribed off-label to the elderly. All of these issues require careful attention and analysis to guide future decision-making.

It is clear that the elderly often have difficulties with taking their medication, including opening packages, swallowing oral medication and/or reading leaflet information. For example, approximately 9% of people aged 65 years and up to 28% of people aged 85 years or over have problems with swallowing. Since many of the difficulties that the elderly have with medicine formulations are similar to the problems seen in children (e.g. swallowing medication), alignment is needed with the development of formulations for children, taking into account the differences between the two populations. When adapted formulations are developed in the near future, it will be necessary to evaluate these to determine whether these products have indeed led to better health in the elderly.

The elderly are still underrepresented in randomized clinical trials (RCTs), with age and (perceived) frailty being the predominant reasons for exclusion. A recent systematic review showed that in 38.5% of RCTs, people aged 65 years and over were excluded and in 81.3% of the RCTs people with comorbidities were also excluded. Furthermore, age and comorbidities were frequently categorized as poorly justified exclusion criteria (78.4% and 64.8%, respectively). There is a need to develop a consensus definition for frailty and tools to evaluate frailty, because these may enable the selection and inclusion of the elderly in RCTs as well as guide therapeutic decisions. Novel initiatives to increase the participation of the elderly in RCTs include the EU-funded development of a Charter in order to promote participation, and the launch by the European Medicines Agency (EMA) of a geriatric medicines strategy and the establishment of a Geriatric Expert Group. The geriatric medicines strategy promotes discussion concerning the anticipated effects of a medicine in geriatric patients, based on pharmacokinetics and other characteristics of the medicine. Investigation of population pharmacokinetics or specific pharmacokinetic studies (including those involving the very elderly) should be performed in order to recommend dose regimens...
and identify patients at risk. For these studies, modelling and simulation might be useful methods. The strategy recognizes the elderly as the main users of medicines and seeks to ensure that the development and evaluation of new medicines take into account specific safety and efficacy aspects related to ageing. In line with the recommendations for children and women, new approaches such as better use of electronic health records may be valuable in obtaining better data on medicine safety and effectiveness in the elderly (see also Chapter 8.4).

In addition, the strategy acknowledges the need to improve the availability of information for patients and prescribers on the use of medicines in the elderly. A recent study demonstrated that, while important information is often available in the European Public Assessment Reports (EPARs), this information is not sufficiently reflected in the Summary of Product Characteristics (SPC). For 53 new medicines, a maximum of 19 items derived from the ICH E7 guideline for studies involving geriatric populations were scored per new medicine. Of these items, 79% were included in the EPAR compared with only 56% in the SPC. Treatment guidelines appear to be more disease-driven than patient-centered, and specific guidance on the treatment of elderly patients is frequently lacking. This may not only cause overuse but also underuse of medicines in this population. Approaches to translate age-specific information on the benefits and risks of medicines into practical recommendations, in the SPC and/or treatment guidelines, should be further explored. Research should also focus on how physicians obtain the information needed to adequately treat elderly in daily practice, and how this information is updated on a regular basis.

Polypharmacy is very common in the elderly and inappropriate prescribing is often related to this. Medication reviewing, e.g. by pharmacists, is a structured evaluation and reconciliation of a patient’s medication and has become common practice in some countries. Although interventions to improve the appropriate use of polypharmacy lead to more appropriate prescribing and fewer medication-related problems, observed effects on important clinical outcomes such as hospital admissions or mortality are conflicting. This may at least partly be explained by methodological challenges. Due to a lack of robust research in this area, the cost-effectiveness of medication reviewing has not yet been established.

In order to facilitate appropriate prescribing and conduct medication reviewing more efficiently, there is a need to improve the supporting role of electronic health records. A computerized decision support system (CDSS) can be incorporated into a computerized physician order entry. When combined with other data such as laboratory values, this system can generate more advanced advice to provide clinical guidance that is based on clinical rules and aligned with treatment guidelines. These electronic solutions could make reviewing less time-consuming and help the reviewer to systematically select those patients who might benefit most from a review. In a hospital pharmacy in the Netherlands, the implementation of an alert system for adverse events involving medicines, with about 121 clinical rules, resulted in the selection of different patients and additional interventions performed by the pharmacist, compared with those of the conventional medication surveillance
method. The hospital setting, with more shared data between health care professionals, could serve as an example for primary care. In addition, the added value of fast and extensive data sharing with the aid of computerized systems needs to be established.

Finally, the integration and continuity of care in elderly patients is essential, especially when an elderly patient is living with several co-existing diseases, as many are. A Cochrane Review of follow-up studies involving older patients admitted to hospital who underwent a comprehensive geriatric assessment (a multidimensional interdisciplinary approach), indicated that they were more likely to be alive and to live at home, and less likely to live in residential care, to experience deterioration or to die. Similar approaches in other settings should be further explored. The elderly live in different care settings and each transfer introduces potential risks, such as the unintentional discontinuation of medicines or the re-prescribing of medication that was recently stopped. More extensive sharing of data could play a crucial role in preventing such errors. In addition, while effort is put into ensuring accurate medication taking (for example, through medication reviews), little effort is invested in ensuring effective communication between first and second-line care. Better interface management, both at a policy level and the health care professional level, is therefore needed.

There is a current trend for the elderly to live independently for a longer period of time. However, medication management becomes more complex as they age. Many elderly people have cognitive, physical and/or visual difficulties that may hamper accurate medication management. Tools have been developed to assess their ability to manage their medication at home, but further evaluation of these is needed.

In summary, improvement in the development and use of medicines in the elderly needs investments in:

- The development and evaluation of adapted formulations and packaging for the elderly and alignment with formulations for children where appropriate;
- Better use of electronic health records to obtain data on safety and effectiveness in the elderly, and approaches to translate age-specific information on the benefits and risks of medicines into practical age-specific recommendations;
- Evaluation of the (cost-)effectiveness of interventions to increase appropriate prescribing and use with a focus on important clinical outcomes;
- Approaches that support further integration of care, sharing of information and communication between health care professionals, and the role of electronic solutions, and other tools to assess and improve medication self-management among elderly people living independently in the community.
7. Cross-cutting themes

References


7.4 Stratified medicine and pharmacogenomics

See Background Paper 7.4 (BP7_4Stratified.pdf)

Stratified medicine is a rapidly developing field that is likely to have an important impact on clinical practice in the coming decades. Personalized medicine has been defined as ‘a medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention’. However, the term ‘stratified medicine’ is more accurate than the still popular term ‘personalized medicine’. The term ‘stratified medicine’ reflects the realistic effects of medicines at population level, while the term ‘personalized medicine’ reflects the possibly overambitious promise of individualized unique drug targeting and development. The population approach aligns with the public health approach of this cross-cutting chapter and with the overall aim of the Priority Medicines Report.

Figure 7.4.1: The concept of stratified medicine.

Historically, human disease has been treated on a ‘one-size-fits-all’ basis. One medicine should suit all patients, and the choice of a medicine has been guided by evidence-based information, professional guidelines and a ‘trial-and-error’ approach. Without applying the concept of stratified medicine, a particular treatment is targeted to the whole patient group, without being able to predict the treatment response in patients. When a patient does not respond adequately to a prescribed medicine or shows substantial adverse drug reactions, the dosage can be adjusted or the medicine may be replaced by another medicine. The availability of genomic and non-genomic biomarkers and other characteristics may enable physicians to increasingly target treatment specifically to sub-populations of patients who are more likely to benefit
from a particular treatment or less likely to develop adverse drug reactions (see Figure 7.4.1). In this way, the benefit-risk profile of the medicine can be assessed per population stratum, and unnecessary (in case of non-response) or harmful (in case of toxic effects) use of medicines may be prevented. In this sense the other cross-cutting themes in this chapter (children, women and the elderly) are also examples of stratified medicine.

Pharmacogenomics study the influence of genomic variation on treatment response. Two successful pharmacogenomics examples include HLA-B*5701 genotyping and the risk of hypersensitivity to the antiretroviral treatment abacavir and HER2 testing in breast tumour biopsies and clinical response to the antineoplastic agent trastuzumab.

The first example illustrates the importance of stratified medicine for the safer use of existing medicines. Abacavir was approved in the late 1990s by regulatory authorities. It was well tolerated in the majority of patients, but caused a life-threatening hypersensitivity reaction in a small group of patients (5% to 8%). From 2001 onwards, there was increasing evidence for the relation between a genetic variation in the HLA-B*5701 gene and the risk of hypersensitivity to abacavir. Sales of abacavir-containing medicines subsequently declined. A shift took place after the development of a genetic test that was shown to be valid across patient populations (different regions and genetic ancestry) and have a very high negative predictive value, and the development of a skin patch test to immunologically confirm the genetic test. HLA-B*5701 testing was rapidly adopted by HIV practitioners and the test was incorporated in clinical guidelines. Genetic testing of HLA-B*5701 kept abacavir on the market because it is now possible to target the drug to a patient population with almost no risk for developing the severe hypersensitivity reaction.

The second example is related to medicines effectiveness. Trastuzumab is used to block human epidermal growth factor receptor 2 (HER2). This protein is encoded by the ERBB2 gene and the gene is overexpressed in approximately 15% to 30% of patients with breast cancer. Only patients with high levels of HER2 are likely to respond to trastuzumab. Regulatory agencies have approved trastuzumab for the treatment of HER2 overexpressing breast cancer (and in other HER2-overexpressing carcinoma) and HER2 testing has been imbedded in clinical guidelines. The classic example of trastuzumab and HER2 highlights the potential of stratified medicine in the targeted use of expensive medicines, thus ensuring that (public) expenditures are not wasted on ineffective pharmaceutical care.

Despite these and similar examples, clinical implementation of stratified medicine has been limited. However, it holds promise for better and safer use of existing medicines in all settings, as well as for the identification of new medicines, drug targets and the development of innovative diagnostic tools. Science is shifting from monogenic (assessing one single gene, e.g. many orphan diseases) to polygenic (assessing multiple genes at the same time, e.g. many chronic diseases such as diabetes mellitus, cancer and depression) diseases and approaches. Pharmacogenomics is only one of the many –omics technologies that have emerged. All of these technologies (e.g. transcriptomics,
proteomics and metabonomics) hold promise, to a greater or lesser extent, to improve the prediction of the incidence and course of disease, phenotyping of disease and prediction of drug response.\(^5\) This chapter focuses mainly on the role of pharmacogenomics in stratified medicine as this particular field has been most successfully translated into clinical practice in comparison to the other -omics fields. Although technologies develop rapidly and collaborations emerge, there remain major gaps related to the development, translation and implementation of this new knowledge.

Currently, stratified medicine mainly focuses on the development of new medicines, drug targets and diagnostics. This is also reflected in the guidelines of the different regulatory agencies on the use of pharmacogenetic methodologies in assessing drug pharmacokinetics, which primarily concentrate on medicines that are currently under development.\(^6\) In addition, pharmaceutical companies may be less interested in assessing stratified medicine post-approval, due to pricing inflexibility and possible loss of market share.\(^7\) Several genomics initiatives are emerging in low-resource settings, but stratified medicine approaches are still rare and should be encouraged.\(^8\) In countries where resources are limited, stratified medicine could be very successful in ensuring that limited health care resources are used as efficiently as possible. In addition, efforts should be made to stimulate the use of stratified medicine in vulnerable groups. Research should be funded to allow biomarker-based prescribing during pregnancy and childhood.

It should be acknowledged that a large part of variability in treatment response cannot be explained by genomic variations.\(^9\) Patient characteristics (such as age, gender, severity of disease), gene-environment interactions, patient compliance, and also epigenomic regulation and protein modification may also play an important role and should not be underestimated. Therefore, the use of multi-dimensional analyses in which biomarkers generated from different technologies are combined with clinical parameters should be stimulated.

Several scientific limitations currently hamper efforts to exploit the full potential of stratified medicine. For example, the lack of standardization of response outcomes, including adverse drug reactions complicates the comparability of studies.\(^10\) Successful replication is generally low, and there is as yet no global or European pharmacogenomic database with a thorough inventory of available knowledge and biological specimens. A European catalogue of pharmacogenomic datasets and a harmonization programme should therefore be established. To validate pharmacogenomic findings, there is a need for replication studies in different cohorts and for harmonization of outcome measures. An electronic platform that will enable data sharing is therefore essential. Finally, a funded EU research network could function as a partner for the European Union in identifying opportunities in research, strengthening collaborations within Europe, contributing to standardization processes, and organizing educational and scientific conferences.
Ideally, medicines and diagnostics should be developed simultaneously and stratification of patients should be taken into account during the drug development process, market authorization and reimbursement procedures. However, in the EU introducing stratification prior to registration has been complicated due to the different regulatory frameworks for diagnostics and therapeutics. The EC recently submitted a proposal for a new regulation to replace the current Directive 98/79/EC on in vitro medical devices, which includes clinical genetic tests.\textsuperscript{11} However, other regulatory guidelines and reimbursement procedures might need to be adapted. There is a need to align regulatory processes between different regulatory agencies, but also on the evidence required to assess clinical utility. A randomized clinical trial might not always be feasible because of ethical reasons, lack of resources or small populations. Clear guidelines are needed to assess when a randomized clinical trial is necessary in order to test a stratified medicine approach. Furthermore, an adaptive trial design, which enables the researcher to implement prior knowledge to optimize the remainder of the trial might be a cheaper and faster alternative to test observational findings.\textsuperscript{12} Assessment of the added clinical value of a test or a marker calls for the development of a framework in which clinical utility and cost-effectiveness are assessed and compared to current clinical practice.

There is a need for a well-organized technology infrastructure, professional training and an internationally aligned ethical, legal and regulatory framework. At present, only a low proportion of health care providers have received training in stratified medicine and pharmacogenomics.\textsuperscript{13} They should be better prepared for clinical decision making by having adequate knowledge about the medicines for which patients should be tested and how test outcomes should be interpreted and acted upon. Patients and the public need to be informed about stratified medicine in order to understand the possibilities and limitations of this approach. The new genomic era brings with it new ethical and social issues such as genomic data sharing, consent, ownership and liability.\textsuperscript{14} These issues should be further studied in order to guide the implementation of stratified medicine in global health.

In summary, this chapter recommends investments in the following areas to further strengthen research in and knowledge of stratified medicine and pharmacogenomics:

- Stimulate pharmacogenomic approaches to existing drugs, with a particular emphasis on the use of stratified medicine approaches for vulnerable groups.
- Stimulate the use of multi-dimensional analyses in which biomarkers generated from different technologies are combined with clinical parameters.
- Establish a European research network and establish a European catalogue of pharmacogenomic datasets with a harmonization programme.
- Adapt regulatory guidelines and pricing and reimbursement procedures. For pricing and reimbursement, develop a framework in which clinical utility and the cost-effectiveness of new approaches are assessed and compared to current clinical practice (clinical added value) and, where needed, refined.
- Develop and evaluate harmonized training and education programmes, not only for researchers, but also for clinical specialists, pharmacists and the public.
Investigate the ethical, legal, economic and social implications of stratified medicine.

References


