Access to Personalised Medicine for PDAC-patients

Report on the application of an EU-index for barriers to PM

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Executive summary

PDAC is one of the most lethal cancer types in the Western world. In order to be able to improve health outcomes, PM offers an interesting approach for PDAC-treatment and- care. However, implementation of PM-applications such as biomarkers is lacking in healthcare. To identify barriers in the field of PDAC that hamper access to PM for PDAC-patients, the current state of PM from scientific literature is compared to a recently developed EU-index of barriers.

The main barriers in the EU-index are in the fields of: 1. Stakeholder involvement; 2. Standardization; 3. Interoperable infrastructure; 4. EU-level policy making; 5. Funding; 6. Data and Research; and 7. Healthcare systems. In the field of PDAC, several initiatives exist to tackle some of the barriers from the index. Nevertheless, the implementation of PM-applications stagnates, and improvements are needed to translate scientific knowledge to PM-treatment and care for patients.

To be able to provide PM-treatment and –care to PDAC-patients, patients will need to be informed about PM, as well as healthcare professionals. In order to be able to provide clinical practice with relevant biomarkers and outcome measures, research has to progress to prospective point-of-care research in order to offer relevant and high-level evidence information. This information feeds into HTA-evaluation in order to make informed reimbursement decisions. Reimbursement will not only provide diagnostics and medicines to patients, but it can also offer innovative funding to stimulate relevant research designs focussing on translation of biomarkers to clinical practice.

Moreover, these approaches will need to be standardized across the EU to prevent health inequalities amongst PDAC-patients in different countries. Multidisciplinary platforms to harmonize feedback between research and clinical practice should be facilitated. Different stakeholders should be involved, not only in policy making, but also in research design. The results from research: data, information and evaluation (reimbursement decisions) should be shared across countries to provide a strong evidence base and streamline translation to clinical practice to offer PDAC-patient PM-treatment and care to improve their health outcomes.

Introduction

Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers currently, with a 5-year survival rate ranging from 2%-5% (Ansari, 2012; Hudson, 2013). PDAC is highly resistant to conventional treatment modalities such as systemic chemo- and radiation therapy (Braat, 2012). Early diagnosis and identifying markers for prognosis and response to therapy are important in PDAC, since the disease pathway is aggressive and it is often diagnosed at an advanced stage (Ansari, 2012).

Personalised medicine (PM) can improve the prognosis of patients with PDAC compared to current ineffective neo-adjuvant treatment protocols (Braat, 2012). Important molecular differences exist between various forms of pancreatic cancer, which can be used for the treatment of specific subsets of cancer types based on the gene expression profile of the cancer (Fang, 2013). Consequently, these differences should be addressed during diagnostic procedures in order to stratify patients and to tailor treatment accordingly (Braat, 2012; Hudson, 2013).

Personalised medicine

Personalised medicine (PM) focuses on individual patient outcomes. PM can be defined as: a targeted approach to the prevention, diagnosis and treatment of disease based on an individual's specific profile (EAPM, 2014[a]). Each person's unique clinical, genomic, and environmental information is mapped, and these factors are combined to adjust care and treatment to the specific patient (Chan, 2011). PM is increasingly under the attention of several stakeholders in healthcare, e.g. pharmaceutical companies as well as healthcare policy makers (Squassina, 2010).

A major, recently emerged aspect underpinning PM is genomics. Technology has become increasingly more able to analyse the human genome in an efficient way, and we can expect an increased implementation of this genomic information. Combining knowledge from a PM-point-of-view is needed to enhance the health outcomes of PDAC-patients, due to its high resistance to conventional treatment options and the late diagnosis. Biomarkers could offer valuable information for PDAC. Identification of biomarkers informs individualised

intervention regimens, to improve prevention, diagnosis or therapeutic outcome of a given disease (Staratschek, 2010). Biomarkers can - besides genes - also include proteins, metabolites and microRNAs (Ansari, 2012).

Biomarkers and Companion Diagnostics

Biomarkers are often translated into companion diagnostics (CDx) to aid treatment decisions and shape pharmacogenomics (PGx). PGx can be used to tailor treatment decisions with CDx. CDx is a molecular assay that, for instance, measures levels of specific mutations to stratify sub-populations, select appropriate medication and tailor dosages to a patient's specific needs (Cohen, 2012). Within PGx genomic biomarkers are often used for CDx: 'a measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes and/or response to therapeutic or other interventions' (Burt, 2013).

By making use of PGx, patients with the highest probability of therapeutic efficacy can be identified, ADRs can be reduced, and the most appropriate drug dosage – both for efficacy and safety - can be determined (Bakhouche, 2012; Scott, 2012). Differences between patients' responses to treatment can be partially explained by genotype, since genotype can influence drug metabolism, drug transport, and a person's sensitivity to a drug (Johnson, 2013).

Relevance

However, PM is not currently applied widely in practice. At the moment most treatments do not have CDx to assess the most appropriate dose, and healthcare providers lack relevant information to predict an individualised dose for a specific patient. If healthcare professionals can offer PM to patients, the benefits will be better patient outcomes, resulting in higher quality healthcare and a subsequent decrease in costs (Davis, 2009; Deverka, 2010; Cohen, 2012)

The lack of implementation of PM is caused by several barriers, it is well-documented that barriers to implement PM exist at several levels. The levels involved are for instance, education, regulation and reimbursement (Deverka, 2009; Gervasini, 2010; Chan, 2011; Cohen, 2012; Chadwell, 2013). A major bottleneck is the discrepancy between the ability to

sequence a genome, to a small amount of relevant genes for clinical practice (Mousses, 2009; Fiore, 2011). Causing for instance a barrier in the application of biomarkers: the process of biomarker discovery, validation, and clinical qualification is delayed considerably (Grossman, 2007; Deverka, 2009). (Abrahams, 2009; Bakhouche, 2012; Burt, 2013; Chadwell, 2013; Chan, 2011; Cohen, 2012; Davis, 2009; Deverka, 2010; Fiore, 2011; Gervasini, 2010; Johnson, 2013; Khoury, 2010; Mousses, 2009; Pirmohamed, 2010; Roden, 2013; Scott, 2012; Squassina, 2009; Staratschek-Jox, 2010; West, 2006)

Even though beneficial examples of PM are becoming more abundant, the uptake in healthcare in Europe is stagnant (Davis, 2009; Gervasini, 2010; Pirmohamed, 2010). Many challenges exist in moving from research data to translation into practice (Khoury, 2010; Johnson, 2013). In order to integrate PM in clinical practice, barriers must be lifted (Abrahams, 2009; Chan, 2011). Therefore, we need to be able to identify existing barriers in countries across Europe in order to benefit patients (Pirmohamed, 2010).

To be able to offer PDAC-patients the benefits of PM, the barriers that exist specifically to PDAC will need to be identified in order to address them. To assess the most relevant barriers in the field of PDAC, a recently developed EU-index will be used, combining information from different sources and viewpoints. The index targets patient access to PM and will focus on testing rather than disease prevention (Roden, 2013; Staratschek, 2010). A pilot study will be conducted including a general systematic literature review of scientific literature.

Index of EU-barriers to PM[1]

Recently the EAPM has conducted a study to identify barriers in the access to PM for patient populations in the EU into an index (Figure 1). The study consisted of a literature review (scientific and policy papers), and stakeholder analyses (surveys and interviews) and focused on PM in the context of testing. Testing was defined as the use of biomarkers to tailor therapeutic decisions through e.g. companion diagnostics. Biomarkers include, but are not limited to, genomic factors. In the current report we use the background from the index and apply the knowledge to the current state of PM in the treatment and care for PDAC-patients. The background and content of the index are outlined in this section.

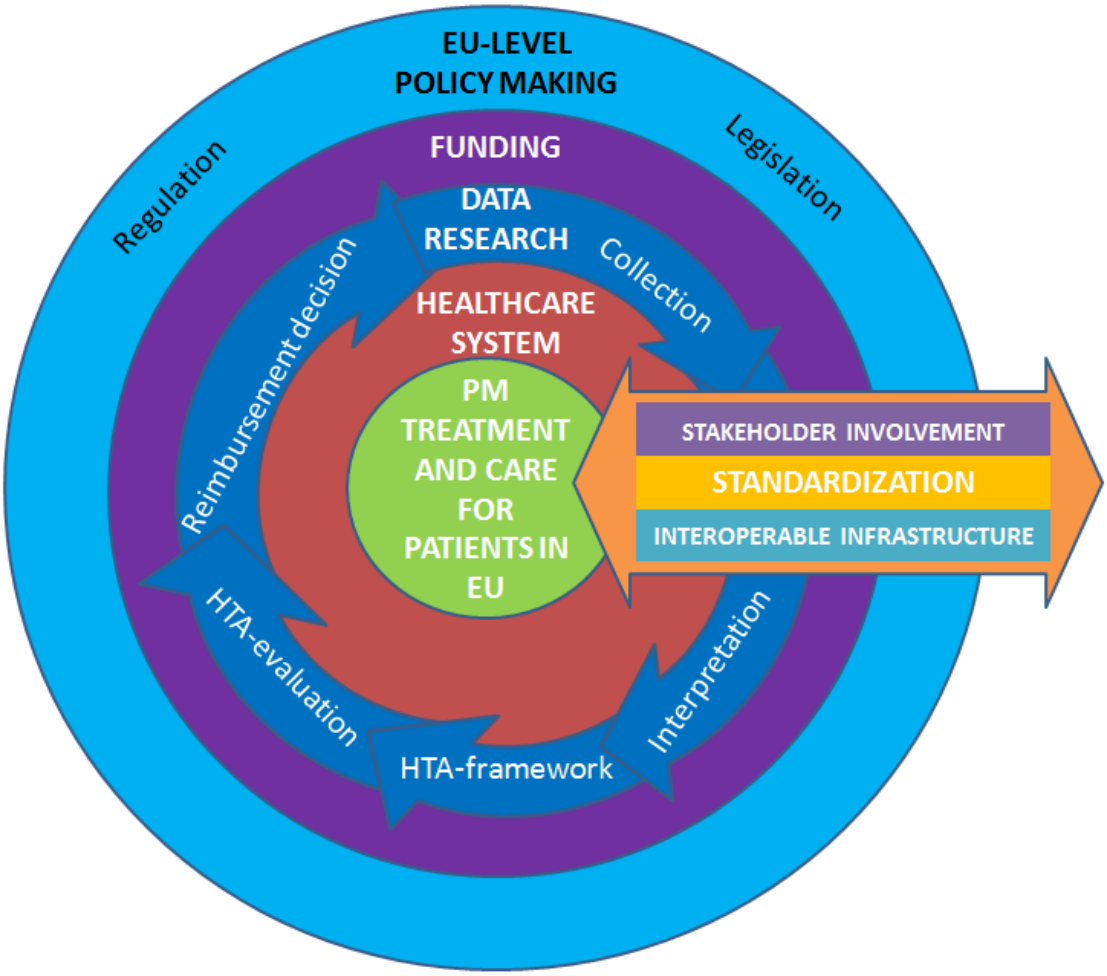


Figure 1. Index summarizing the areas that hold the main barriers in the context of access to PM for patients in the EU.

[1] Taken and adjusted with permission from EAPM, 2014.

PM is considered a complex approach to healthcare in the sense that it implies a change in information in clinical practice. The fact that healthcare professionals will be presented with new instruments to personalise care and treatment was not considered the complexity, since healthcare professionals are always trying to individualise healthcare for their patients (Abrahams, 2009; Squassina, 2010). The complexity lies in the characteristics of the additional data and the information delivery that healthcare professionals will need to employ to gain more access to PM for their patients.

Striving for PM delivered by healthcare professionals to patients will bring about benefits: better individual patient outcomes, resulting in higher quality healthcare, and a decrease in costs (Davis, 2009; Deverka, 2010; Cohen, 2012; iNNOVAHEALTH, 2012). To gain these benefits, the chain leading from PM-research to PM-care and -treatment needs to overcome barriers ranging from scientific (e.g. evidence, methodology), operational (e.g. regulations, information delivery), and economic (e.g. reimbursement, incentives) barriers. PM will require changes in healthcare infrastructure, diagnostic models, and a reimbursement policy (Squassina, 2010).

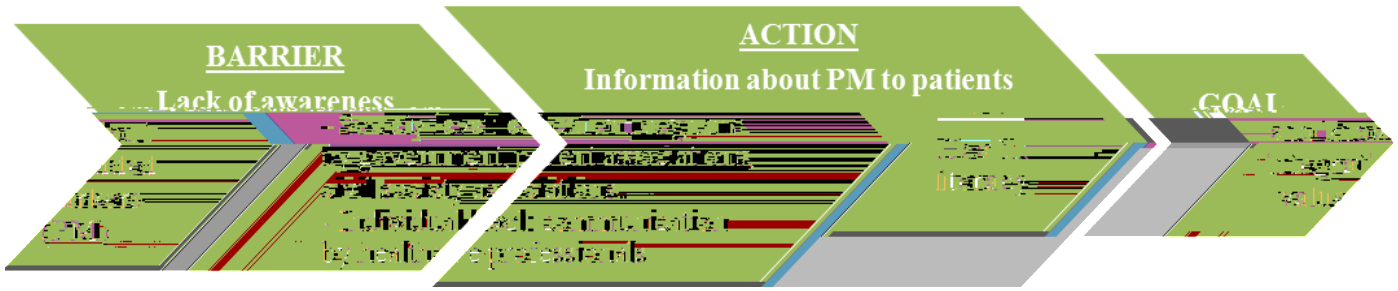
The index focuses on the access of patients in the EU to PM-treatment and –care. The access to PM-treatment and –care is supported by several layers of disciplines, depicted by 1. Healthcare systems, 2. Data and research, 3. Funding, and 4. EU-policy making. It should be facilitated that communication and harmonized approaches between these layers is enhanced by 1. Stakeholder involvement, 2. Standardization, and 3. an Interoperable infrastructure. Within these sections several barriers can be pointed out, that hamper the final access to PM-treatment and –care. The general barriers within each section are summarized below. Each sections includes a summary figure with the main barrier(s).

PM-treatment and –care for patients in EU

Since the focus of the index is the access of patients to PM-treatment and -care, these aspects form the centre of the index, because it is the goal to facilitate better access to PM for patients across Europe. If healthcare professionals can offer PM to patients, the benefits will be better patient outcomes, resulting in higher quality healthcare and a subsequent decrease in costs.

At the moment patients are not aware of the possibilities of PM, and they lack information tools, such as accessible websites or access to knowledgeable healthcare professionals, to inform themselves about PM. Therefore the barrier that needs to be overcome is their lack of awareness and knowledge of PM, which can be enhanced by e.g. providing information. Currently the public and patients are not informed about the integration and added value of biomarkers in health care.

When people enter a healthcare system, they start a care pathway that will become more and more individualized. By facilitating for instance stratified treatment options, PM offers opportunities to increase shared decision making between healthcare professionals and patients. However this also puts more emphasis on self-management from the patient to communicate their individual preferences and needs. In order to translate PM to the patient, the patient will need to be informed in the care pathway e.g. about 1. their disease, 2. their treatment options, 3. the added value of PM for their disease, and 4. the follow-up (in pharmaceutical and non-pharmaceutical interventions). The most central steps towards patient access will be increasing their health literacy (being able to understand consequences of CDx) with respect to PM, so they will be empowered and informed to handle PM and take away existing concerns about genomic-related tests, such as discrimination.

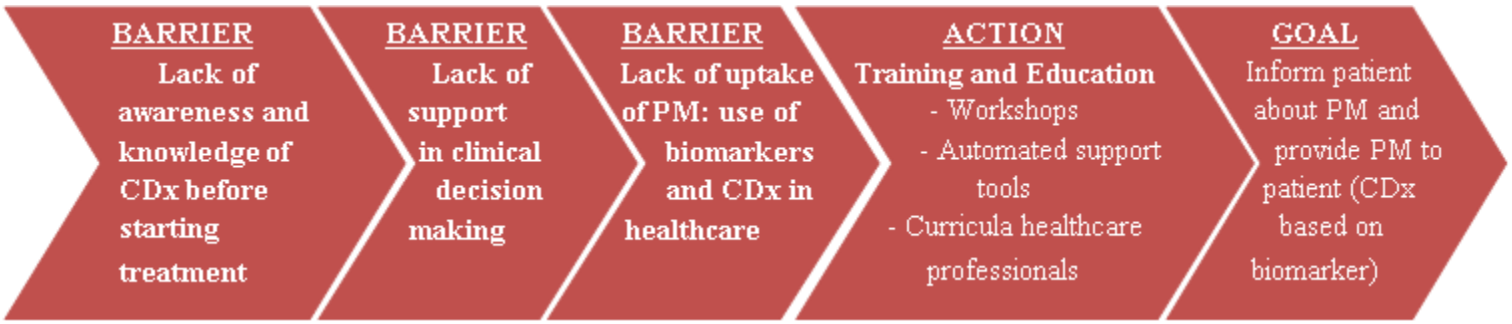


Information on PM can be e.g. communicated on an individual level by professionals in the healthcare system during the care pathway of an individual patient, but on a societal level information on PM can be provided by the government, patient organisations and civil society organisations, but it can also be provided by professionals in the healthcare system.

Furthermore on a society level, by involving representatives from patient associations in the different steps on the road to PM (e.g. policy making, communicating needs in research) via stakeholder involvement, the awareness and knowledge can be increased. This will be discussed under the section 'Stakeholder involvement'.

Healthcare system

The first layer around the patient is the healthcare system with healthcare professionals. The main barriers in this section are a. lack of awareness and knowledge of PM, and b. lack of support in clinical decision making based on CDx and c. the lack of uptake of PM i.e. using biomarkers and CDx in healthcare to provide PM-care and –treatment to patients. Healthcare professionals are not sufficiently informed about CDx and the added value the use of a biomarker test can offer before starting treatment, resulting in a lack of awareness and knowledge of PM. Furthermore, they feel not competent enough to use PM if they are aware of its application. Currently there is no sufficient support structure in making clinical decisions based on CDx, and how to adapt these technologies. These two barriers cause the lack of uptake of PM in healthcare.



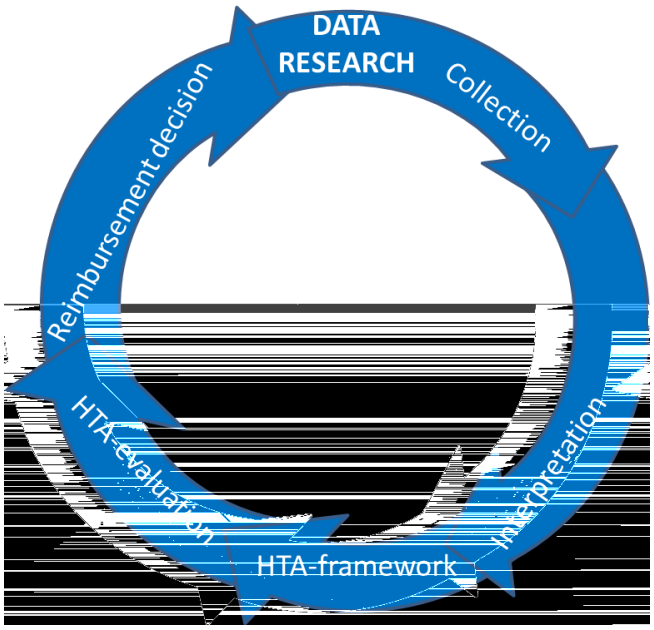
With respect to the implementation of new CDx, it is also important to involve stakeholders representing healthcare professionals such as members from specific associations focussing on the relevant disease area (e.g. associations of oncologists) early on in the development process. In the development process when the focus area of the biomarkers is determined the needs can be adapted to needs in healthcare, for instance to tailor a drug that has significant ADRs. The involvement of representatives from the healthcare perspective will also increase awareness of the development of relevant biomarkers for CDx in the context of PM, and provide relevant information from their point of view, increasing the probability of successful implementation of CDx. This will be discussed under the section 'Stakeholder involvement'.

Data and research

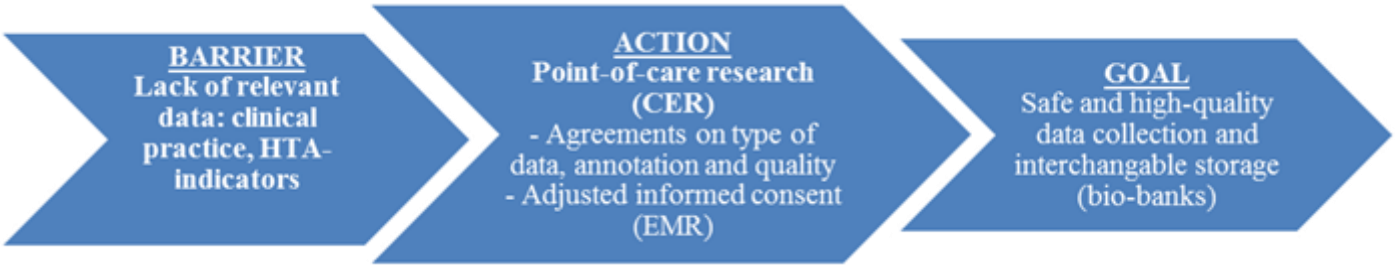
The information that feeds into the healthcare system will be provided from research. Researchers in industry and academia will need to be able to provide the needed information to the healthcare system to ensure implementation of relevant biomarkers in CDx with a proof of concept of PM in this context. This group is therefore also important to involve in stakeholder pools throughout the development process (section 'Stakeholder involvement'). The storage and dissemination of the data will require interoperable infrastructure supported by ICT-tools for instance in bio-banks. This will be further explained in the section 'interoperable infrastructure'.

Since PM calls for a new approach to healthcare (preventive rather than reactive), new research approaches will also be needed, for instance comparative effectiveness research (CER). These changes imply several hurdles to be taken in the field of data collection, interpretation, and evaluation (HTA-indicators, reimbursement decisions). To be able to

gather relevant information, research will need to be changed, and guidelines will need to be developed to ensure quality of data and information.

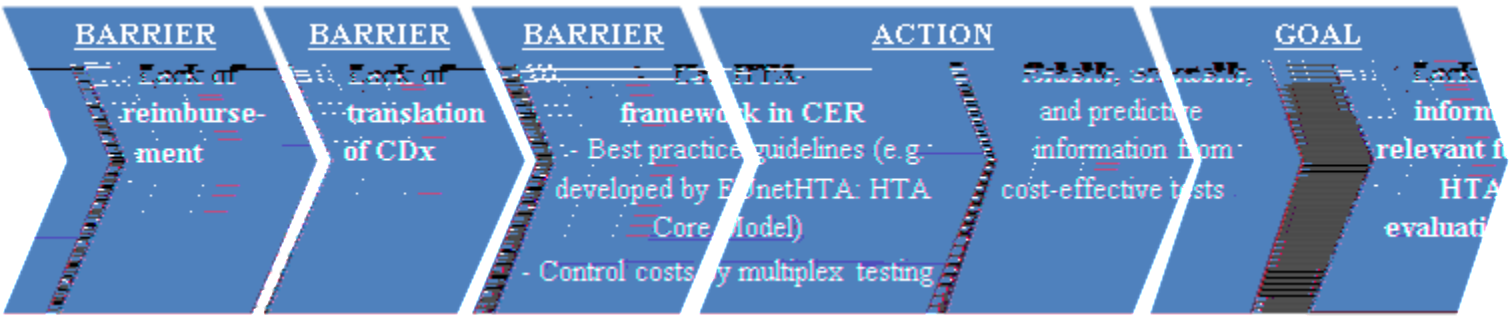


The idea of clinical trials as currently known will need to progress to a prospective point-of-care research, such as CER, in which patient data is gathered in research via EMRs. In order to enable this type of data collection, agreements need be established on data collection: type of data, annotation and quality assurance. Furthermore, informed consent will need to be adjusted to be able to gather the relevant data, while ensuring patients' privacy through data protection and ownership.



To be able to interpret data, several sources will need to be integrated, to ensure informational models of all relevant health data. Incorporating information on relevant biomarkers, other omic-profiles, clinical data and environmental data can provide information to enhance informed clinical decision making. In order to provide interpretation of the data to clinical decisions on treatment, disease models will need to be updated to account for the interaction between the different aspects of health data.

There appears to be a discrepancy between the information currently provided by science, and the information needed to streamline CDx translation to clinical practice, which delays the implementation. A barrier that is relevant in this translation, is the lack of use of the indicators of HTA-framework, such as societal impact, cost-effectiveness, but also clinical utility. When these outcome values are included as endpoints early on in research, the information relevant for decision makers in healthcare are gathered. A test can be implemented if it provides reliable, actionable and predictive information to imply an alternative drug-dosage regimen based on genetic information in a cost-effective and timely way. Currently these frameworks are not always applied, which delays the evaluation of HTA-aspects of biomarkers. Methodologies for reliable detection of biomarkers should be developed and distributed, such as statistical designs.

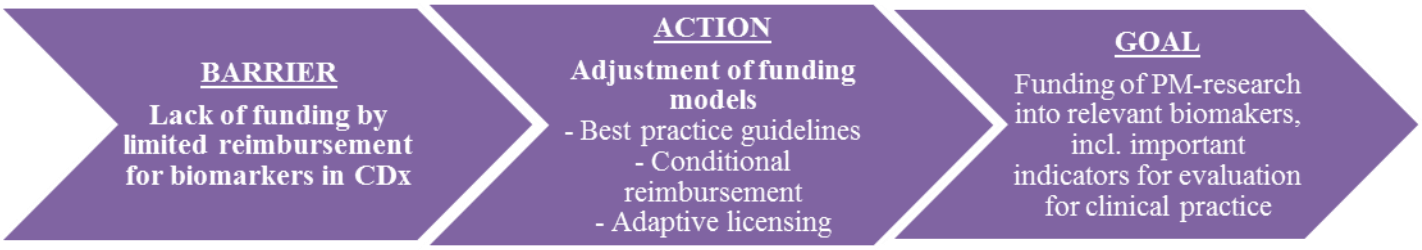


The information from HTA-framework flows into a HTA-evaluation, incorporating the impact on several levels: economic, clinical practice and patient health outcomes. This information is needed to make a sensible reimbursement decision. The lack of reimbursement is considered an important barrier, since a financial incentive is important to be able to apply a new test. Besides trying to control the costs by pre-emptively testing a

large amount of people on a broad panel of common relevant genotypes (multiplex testing), innovative reimbursement procedures can be used to increase the implementation of CDx, based on relevant information and a thorough evaluation according to HTA-indicators. Taking these aspects together (HTA-indicators, evaluation by HTA-experts and reimbursement decisions) will streamline the implementation of relevant biomarkers. Moreover, it will provide healthcare professionals with information to support them in their clinical decision making in order to provide patients with the optimal care and treatment.

Funding

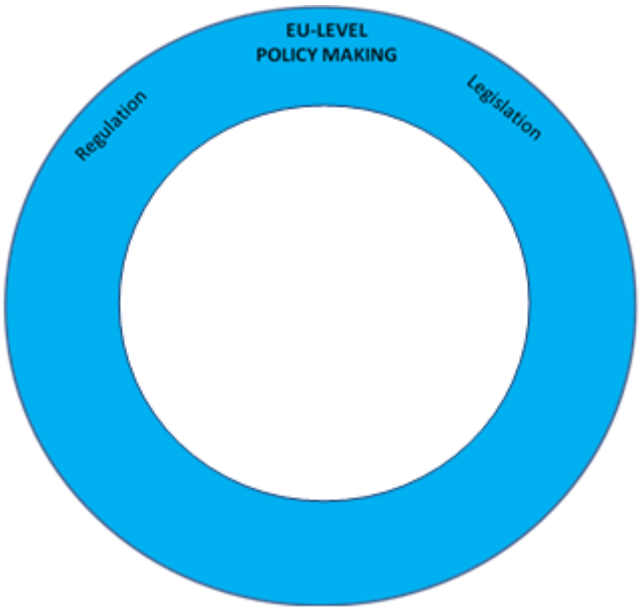
A major barrier in general is lack of harmonized funding procedures among EU-countries. The lack of funding is partially due to the limited uptake of reimbursed CDx in healthcare, which make the financial and health outcome return on investment a limiting factor. The uptake in healthcare, as mentioned before in the section, is dependent on several indicators (e.g. provided information on clinical utility, cost-effectiveness, analytical validity etc.), not the least being the final reimbursement decisions. Therefore it was suggested to develop innovative payment mechanisms, and to focus funding on allocation to relevant research in important indicators.



Besides these changes on the translation from research to healthcare, the basis for research also needs adaption. As discussed in the previous section, approaches to research need to be adjusted to provide relevant information to clinical practice. Stimulating research with a PM-approach, looking at relevant biomarkers and taking into account indicators important

for HTA-evaluation, will also boost the development of useful CDx. In order to achieve funding for relevant biomarker research, funding procedures will need to be adapted towards PM, starting with CDx. Funding can for instance be financed with adaptive licensing, and conditional reimbursement is another suggestion to stimulate CDx-research.

EU-level policy making



In the previous sections, several suggestions included adjustment of current practices to improve the final access to PM for patients, not only for clinical practice (sections on , and), but also for research activities financed by funding (sections on , and). To ensure harmonized developments in PM and the implementation of PM starting with CDx across the EU, EU-level policy making will need to be employed. By employing EU-level policy making, inequalities in availability for patients across the EU can be prevented, since implementation will be more synergized, and hence more equality in health outcomes is ensured.

On one hand regulations for the different sections (and) will need to be developed on EU-level, such as best practice guidelines for research approaches, since one of the main barriers is the fact that policies in guidelines are still scattered across the EU. The EU-policy should account for differences in national and regional healthcare systems, and take notice of quality assurance in data. Furthermore interdisciplinary clinical teams and biomedicine skills under one roof are needed, for instance in centres of excellence.

On the other hand, legislation will need to be evaluated to assess the differences across the EU and address them in order to facilitate research in CDx. The main barrier in this area lies in the difference between legislation for diagnostic tests and treatment. Currently only legislation exists for in vitro diagnostics. These differences make it difficult to harmonize

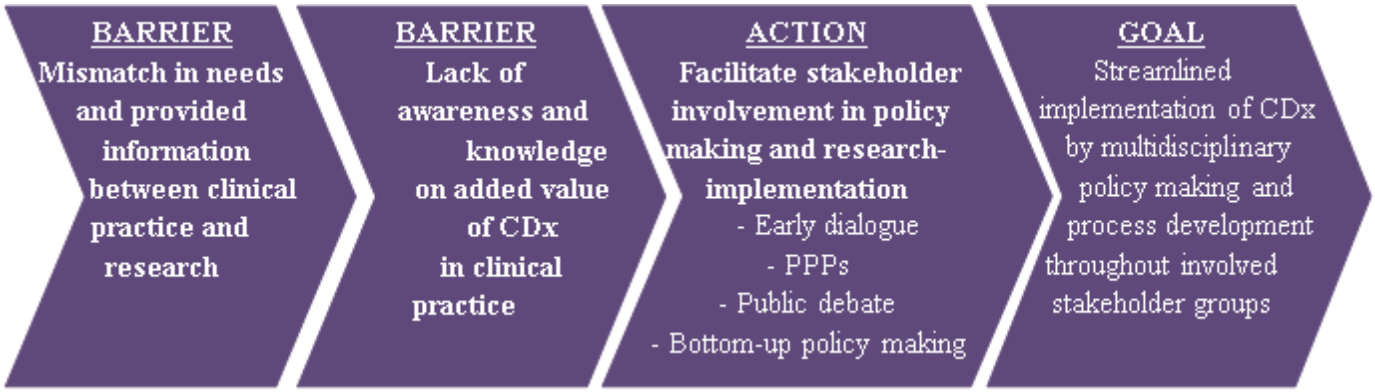
the diagnostic test and drug development process between diagnostic companies and pharmaceutical companies, also leading to different business models and business environments in the two industries.

Stakeholder involvement

Since the field of PM influences a wide range of stakeholders (basic science, translational research, regulation, health systems and patient perspective), it is important to involve representatives of the different stakeholder groups within the developments in the sections presented in the EU-index (figure 1). As mentioned before in the sections on and , the information needs from patients and healthcare professionals in clinical practice (e.g. clinical utility) should be harmonized with the data gathered in research. Currently there is a mismatch between the needs and the provided research. As was mentioned in the sections on and , research should focus more on outcomes included within e.g. HTA-framework. The type of health outcomes relevant for patients should be considered, but also factors such utility i.e. different treatment regimens based on the outcome of the biomarker-test.

By facilitating early dialogue between e.g. patient organizations, healthcare professionals' associations and industry the needs from clinical practice can be harmonized with research approaches. Needs in the areas of policy on e.g. data handling should be discussed in such multi-stakeholder platforms, to ensure it is a feasible approach for research in industry and academia, and can be communicated in an effective way to the population. Adjusting policy

regulations in best practice guidelines to the needs of the several groups of stakeholders will streamline the process from biomarker development to CDx and implementation in clinical practice to provide PM in the healthcare system to the patient.



Furthermore, by involving stakeholders in early in the development process (starting at research), the awareness on PM will increase. Information on the benefits and the safeguards of for instance genetic testing and bio-banking will be tailored to the target populations, also increasing the skills and willingness to apply CDx. Taking together these aspects of involving stakeholders in e.g. early dialogue will harmonize the direction of policies within research and information delivery, and increase awareness and knowledge on PM, resulting in a more streamlined implementation of CDx. The streamlined implementation of CDx will enhance the possibilities to offer PM to patients.

Standardization

Throughout the processes standardization is needed, to e.g. ensure national databases gather the same type of data EU-wide, and assess its quality according to the same criteria. There will be a greater pool of data that can be used for research if the quality and methodology for interpretation of a data sample are aligned between regions and EU Member States. Not only data collection, but also data interpretation and evaluation should be standardized, so the same information on HTA-indicators and reimbursement decisions is stored. Furthermore, the evaluation of research grant applications should be

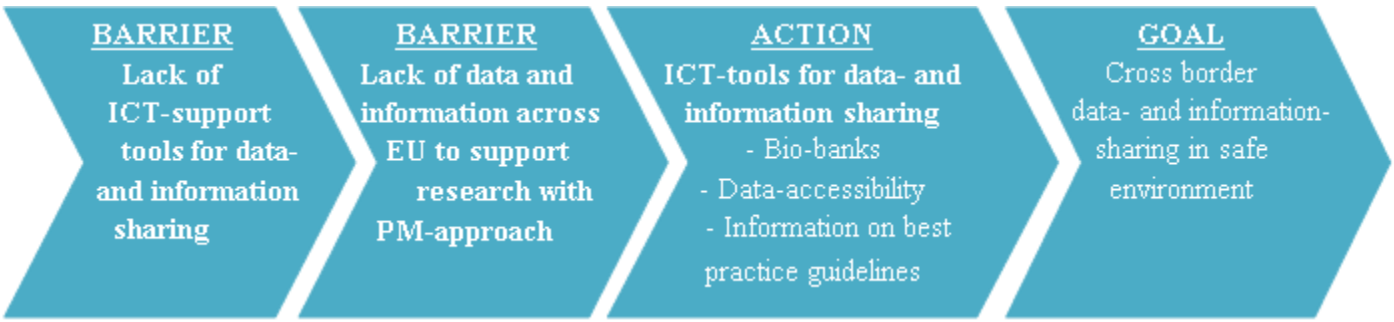
standardized in order to facilitate uniform funding procedures on national level across EU-funding countries procedures. When data collection, interpretation and evaluation is standardized and the funding is harmonized to provide comparable information, the amount of relevant data for PM-applications will be increased. This process would lay a basis for relevant data and information in databases (e.g. bio-banks) that can be shared cross-border while protecting privacy of patients and IP of research.

Moreover, standardizing evaluation of biomarkers, i.e. the reimbursement process and the clinical decision making, will enhance equality in the access to PM for patients across the EU. When the reimbursement processes and clinical decision making is standardized, patients will receive the same care at the same moment throughout the EU. The information to conduct these decisions effectively should be harmonized between stakeholders, as mentioned in the section , in order to ensure relevant data is delivered to base e.g. the reimbursement decision on.

Interoperable infrastructure

As mentioned in the previous section, standardized data collection and interpretation can offer information for data-sharing. This information on all relevant health data (-omics, but also imaging and environmental factors) can for example be stored in bio-banks, and it is also possible to share the information in these bio-banks. Especially across Europe different approaches are used for bio-banking, which hampers the European and at the more broad international level the interoperability. In order to facilitate bio-banking the infrastructure should be efficient, so also international trials can be conducted and the results can be stored in a safe environment. Merging several databases in bio-banks, increases the complexity and therefore the safety risks. The risks should be evaluated and prevented by effective management of bio-banks.

However, to be able to share data in a safe environment, interoperable infrastructure will need to be developed. ICT-tools throughout policy-making, research and healthcare systems should facilitate data-sharing. For instance support systems to dissemination policy decisions of best practice guidelines on research (data collection; informed consent in EMR) can be developed to share across the EU. Also for research practice, attention is paid within the ICT-field to translate PM to healthcare, however the applications are still in test phases. Currently, the application of PM in ICT focuses around DNA sequencing, bioinformatics and statistical analysis. ICT-solutions to include new research outcomes within CDS as part of point-of-care research need to be developed. The accessibility of data across the EU will need to be ensured for research, while protecting IP.



In summary, an effective European policy on PM is needed, facilitating harmonisation of data across the EU. By harmonising data in bio-banks, international interoperability between bio-banks can aid research towards effective PM. Such bio-banks will offer standardised information on relevant biomarkers for CDx regarding factors in HTA and provide input for CDS for healthcare professionals across Europe, within legal and reimbursement frameworks, and will enable a patient-centred and timely implementation of PM.

Methods

In order to identify key indicators and factors contributing to the use and access of PM for PDAC-patients across the EU a literature review has been carried out (Figure 2). The goal of the study is to explore the barriers in access to PM treatment and care in the field of PDAC. The identification of the barriers will help to evaluate access to PM according to a Personalised Medicine EU Access index. The index will be described in the , and focuses on evaluating access from multidisciplinary literature and stakeholder viewpoints, from basic science, translational research, regulation, health systems and patient perspective.

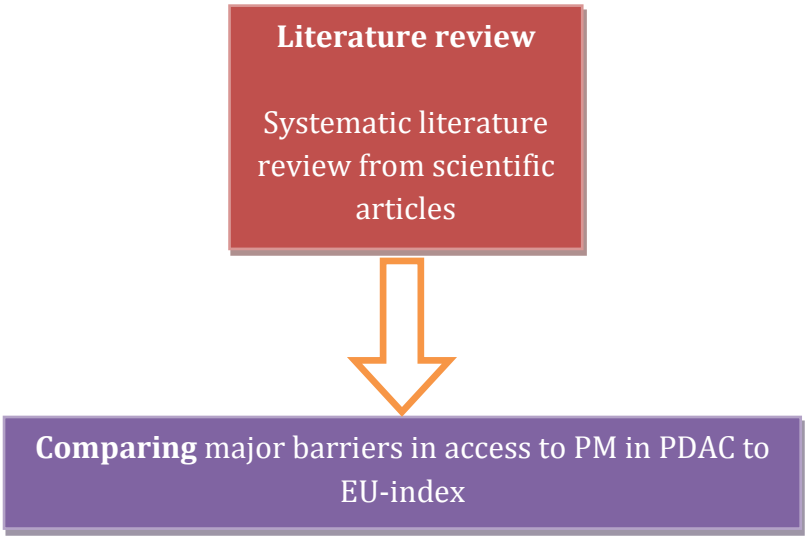


Figure 2. Summary of the research methods to analyze the access to PM for PDAC patients in the EU according to the EU-index

Systematic literature review

A literature review was undertaken to establish the current state of publications addressing the issues included in the EU-index. For the systematic review of scientific literature PubMed, Web of Science, and Medline were searched. Search terms focused on the sections of the EU-index and enclosed (synonyms of): 'personalised medicine', 'bio-bank', 'research', 'reimbursement', 'funding', 'HTA', 'stakeholder', 'policy', 'legislation', 'ICT', 'clinical practice', 'health literacy', 'companion diagnostics', 'biomarker', 'patient', 'treatment', and 'care' (Figure 3). Only documents in English were included in the review.

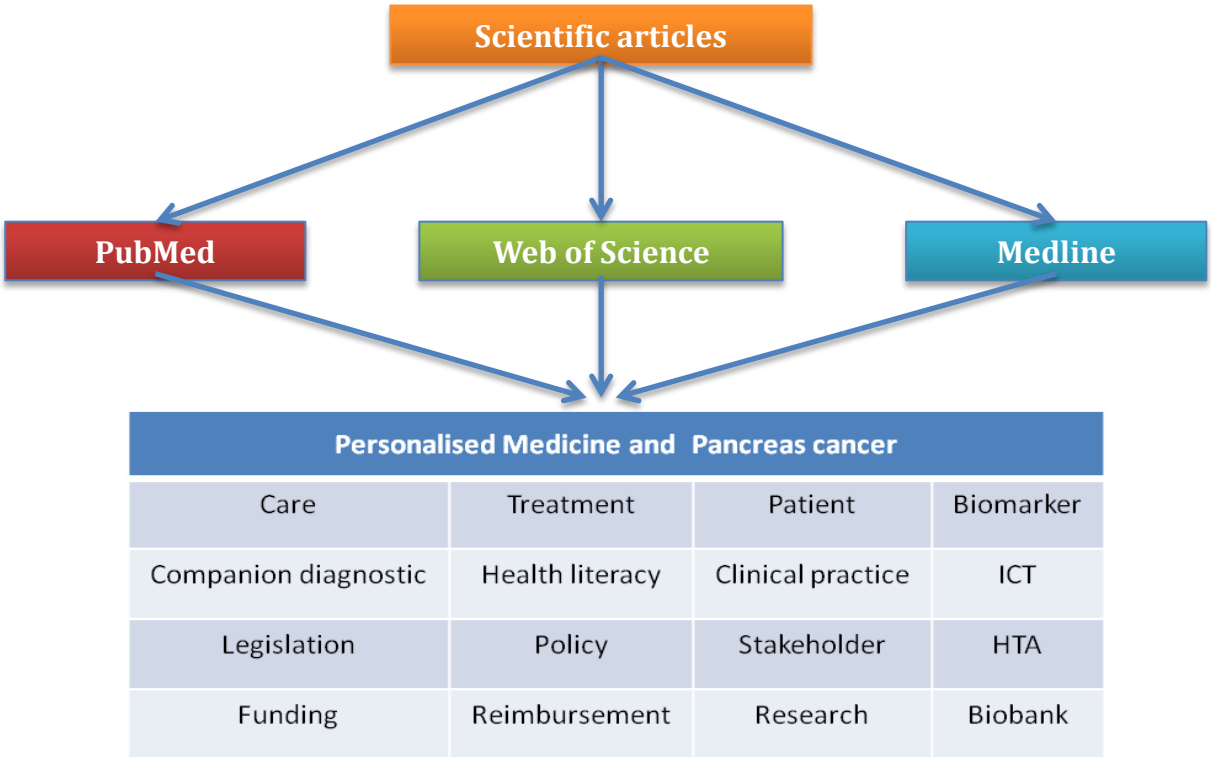


Figure 3. Search terms for systematic literature review.

Comparison to EU-index

After summarizing the results from the literature review the outcomes were compared to the factors in the index to analyse the most relevant barriers in the context of PDAC. The index consists of relevant barriers translated into criteria to improve access to PM for patients.

PDAC and PM

Applications

Several aspects of PM have been mentioned in the with respect to PGx and CDx, facilitated by e.g. genomic biomarker analysis. Since PM could affect various areas of healthcare, the barriers to implementation are numerous, and a wide range of stakeholders is involved. Analysing the barriers to PM is relevant for policymakers (government and health technology assessment bodies), industry (pharmaceutical, diagnostic, and ICT), healthcare professionals, patients, and insurance companies (Davis, 2009; Deverka, 2009). It is expected from PM that is new therapies will be developed that will target specific alterations in disease processes, reducing the need for treatments with undesirable ADRs (Hudson, 2013).

The full advantages and potential of PM can only be achieved when it is used in clinical decision making in an informational, structured framework and benefits all stakeholders (West, 2006; Squassina, 2010). In the area of PDAC translation of biomarkers into routine clinical practice still experiences major hurdles, while a multitude of investigational biomarkers have been identified (Ansari, 2012). Improvement of the diagnostic work-up through de identification of novel biomarkers will help to improve treatment results in patients (Braat, 2012). Examples are KRAS or SMAD4, and biomarkers of DNA damage response, to identify subsets of patients (Braat, 2012; Hudson, 2013).

PM offers an attractive treatment option for PDAC, however the approach is limited due to the complex nature of the disease, e.g. interactions with the microenvironment and the limited knowledge regarding the biological processes. These hamper the ability to translate treatments from cell lines and animal models passed phase III clinical trials (Fisher, 2011: Braat, 2012). Specific gene profiles in blood, pancreas tissue, and pancreas juice can potentially be used as new biomarkers for diagnosis, prognosis, and to assess the response to treatment (Fang, 2013). It may take decades to unravel the mechanisms by which this complex mutational profile results in tumour progression and devise strategies to interfere with these mechanisms (Hudson, 2013).

The process of discovery to translation into clinical routine is complex (Ansari, 2012; Hudson, 2013). Still tailored therapy should be strived for, since better clinical results are feasible for PDAC-patients (Ansari, 2012; Braat, 2012). Data suggests a large detection interval of potential curable disease exists: PDAC is the end-stage of a multi-step progression model resulting from cumulative genetic mutations and the metastatic lesions show more mutations than the original tumour (Braat, 2012; Iacobuzio-Donahue, 2012). Even if patients with PDAC could be identified early in the course of the disease, localizing the disease and treating it in a minimally invasive fashion will remain problematic (Fisher, 2011). New methods to improve diagnostic accuracy are urgently needed to improve clinical decisions and to develop new therapies, such as well-designed clinical trials (Braat, 2012; Hudson, 2013).

Barriers

More attention is paid to PM due to the increase in knowledge of the human genome, for instance the Genomic and Personalized Medicine Act was proposed in 2006 (Fang, 2013). Furthermore in the field of cancer, several guidelines have been developed, such as methodological reporting for biomarkers: Standards for Reporting Diagnostic accuracy (STARD). And guidelines are available addressing the Reporting Recommendations for Tumour Marker Prognostic Studies (REMARK) (Ansari, 2012). Besides these policy interventions, also several consortia and platforms have been developed for cancer and genomic information, such as the International Cancer Genome Consortium (ICGC) (Hudson, 2013). And specifically for PDAC the EU Pancreas has been facilitated (Milne, 2013).

Even though these developments have risen the past years, difficulties remain in the application of PM in PCAD. Barriers exist in effective demonstration of clinical utility of biomarkers, while this is the key to gaining widespread acceptance. How new information will be validated and proven to be clinical useful prior to clinical application is currently uncertain (Fisher, 2011). These barriers are also increased due to regulatory issues and budgetary constraints of the biomarker industry (Ansari, 2012). To be able to prove outcome measures relevant for clinical practice, such as diagnostic accuracy and other important factors from HTA-frameworks, time-consuming, large population-based

systematic prospective studies will need to be developed to provide highest levels of evidence (Fisher, 2011; Braat, 2012; Hudson, 2013).

When effective biomarkers will be available, PM can be increased in care. These applications will need to be supported by bioinformatics, such as automated decision support, which will include a wide range of data (Fisher, 2011). The development of such infrastructures will pose a challenge towards healthcare in general, and also in the care for PDAC to pinpoint which data is relevant for this disease area. Furthermore, a personalised medicine program usually takes pace in multidisciplinary clinics, where physicians and scientists tailor medical decision to the individual patient based on the clinical and bioinformatics databases, so this type of multidisciplinary facilities should be developed and managed, e.g. centres of excellence (Fang, 2013; EAPM, 2014).

A considerable amount of the barriers lie in the field of (the application of) guidelines and research, but a gap remains within funding moving from focusing on promising biomarkers towards translational research. Remarkable improvement in clinical treatments based on promising biomarkers have yet to be realized (Fisher, 2011). Moreover, education of clinicians and patients is important. The education should include information on patient discrimination and access to care for patients and for clinicians the application of rapidly evolving information base will be particularly important (Fisher, 2011).

Conclusions

In this study we explained a recently developed EU-index with barriers in access to PM. Furthermore, we shortly mapped the current state of PDAC-treatment and -care with regard to PM. From literature several barriers were provided, however limited information was available on most of them. The possibility to compare the barriers in PDAC to PM-treatment and –care to the barriers in the EU-index therefore sometimes provides general recommendations (EAPM, 2014).

Patients

For patients information on PM is lacking, so within this barriers it would be advisable to develop an implementation and dissemination plan to inform patients to increase awareness and knowledge on PM. Such an implementation plan should account for user-friendly communication tools, and inform the public about PM and its purpose. The information provided should prevent misunderstanding about PM, and take away concerns about genetic tests, e.g. discrimination and limited access to care.

Healthcare system

Not only patients will need additional information to be able to deal with PM, also healthcare professionals in the healthcare system will need to be educated. The education can be implemented for instance by providing information through associations, but also by organizing workshops to explain ICT-tools that can support healthcare professional in clinical decision making. Not only the current workforce should be educated, also future healthcare professionals should learn about PM and decision making tools by adjusting the curricula of healthcare education programs. To ensure comparability across the EU, these programs can be harmonized among countries as much as possible.

Data and research

Complexity of PDAC and lacking knowledge about the biological processes and interactions also hampers the application of relevant biomarkers. To be able to provide relevant biomarkers, research will need to be innovative. Prospective study designs using point-of-care research can facilitate needed evidence on treatment procedures. Structures to communicate between clinical practice and laboratory medicine will need to be planned.

This circle of research needs to be closed in order to plan improvements. Clinical exome sequences is necessary to target mechanisms underlying disease and be able to provide a target for modern drugs.

The translation of these drugs should be tailored, which implies that pharmaceutical and diagnostic companies will need to work in close relation to keep developments in pace. Furthermore, the turnaround time for a test needs to be applicable for clinical practice, i.e. the results of a test should be available before the clinical decision needs to be made. Combining these types of expertise calls for multidisciplinary centres to be able to integrate knowledge together with clinical practice and translate it to the patient in a timely fashion.

Funding

Funding for PDAC research has increased the past years, however the implementation of promising biomarkers stagnates. This could be due to the fact that translational research is not funded sufficiently. Funders, such as the European Committee, national funding bodies and charities, should focus on generating evidence that shows a link between specific tests and outcomes of treatment. Furthermore, by employing innovative funding procedures, such as adaptive licensing, point-of-care research will also be stimulated.

EU-level policy making

Several initiatives already exist on the level of policy making in research, it seems however the focus on guidelines to incorporate relevant outcomes for clinical practice can be increased. Harmonization should focus on HTA aspects, e.g. cost-effectiveness should be harmonized. Increasing the focus on relevant outcomes for clinical practice can also enhance positive reimbursement decisions, making PM-treatment and –care more available to PDAC-patients.

Stakeholder involvement

Involving stakeholder throughout PDAC-care processes can for instance be facilitated by setting up multidisciplinary teams with basic researchers and clinicians. These teams can for instance focus on implementation of biomarkers in the field by harmonizing research agendas to the needs in clinical practice. Furthermore, working together in centres of

excellence also provides interactions between lab-based diagnostics and clinicians. The education of patients can also be enhanced by systematic patient involvement in processes surrounding PDAC. Not only in clinical practice, but also in clinical trials from design to implementation and regulatory affairs patients should be involved. This type of involvement can be facilitated by EU-wide platforms.

Standardization

In order to provide equality among PDAC-patients across the EU, synergies should be further developed. The standardization can focus on EU-wide funding programs for research, but also an EU-wide catalogue of biomarkers including information on access to biomarkers is needed. Focusing on EU-research programs will enhance standardization of gathered evidence in e.g. bio-banks and provide a stronger evidence base for relevant biomarkers for clinical practice.

Interoperable infrastructure

To be able to communicate amongst countries in the EU and provide information on data and research, funding, reimbursement decision, but also relevant clinical decision making support, interoperable infrastructures will be needed. This interoperability can be enhanced by consolidation of European infrastructures in bioinformatics.

Future developments

From scientific literature, the specific needs for PM in PDAC were not always stated clearly. However, possibilities to tailor treatments more and perhaps improve diagnostics are studied, and healthcare research and systems should develop towards a more PM-approach. In order to facilitate PM, the way research is approached and conducted for drug development needs updating, e.g. by involving biomarkers and cooperation between pharmaceutical and diagnostic companies. However, to be able to change research, the chain before and after research also needs to be adapted.

Development of best practice guidelines is helpful to both direct research, and to evaluate results from new research. Harmonisation on gathered information from research to implement PM in healthcare is also needed to be able to ensure interoperability between bio-banks by providing the same type of data and interpretation. The evaluation and

information availability will need to be translated to healthcare by ICT-tools to support healthcare professionals in giving information to the patient, but also to standardize reimbursement information across the EU. Stakeholder groups need to be involved more in the development and implementation of PM, not only through education and training, but also for bottom-up policymaking.

Taking into account the different barriers from this research, the access to PM has numerous barriers, on EU-level most of them exist on the harmonisation of approaches to research, finance and information delivery. To be able to facilitate such harmonisation, platforms bringing together the stakeholders should focus on developing standardised legislation and best-practice guidelines for these factors.

However to be able to provide evidence based strategies; more research is needed in feasible methods to increase the access to PM for patients, such as implementation and dissemination strategies how to design information delivery to patients in user-friendly methods. For instance, our study did not show results for the payment strategies if healthcare becomes more cross-border because of increased collaborations across the EU, or how patient-support should be organized when patients use cross-border healthcare.

Furthermore, the feasibility and available resources to be able to achieve the end goal of accessible PM and changing and applying new policies remain unclear and should be assessed in an overview. To facilitate efficient stakeholder involvement in order to harmonize practices throughout the different stakeholder sections within the index (basic science, translational research, regulation, health systems and patient perspective) undertaking a mapping is advisable to analyse the different stakeholders that engage in the process and the different ways that they interact. Realising the promise of cost savings under the PM-approach will first require cost-investment at EU-level. However, initiatives exist on stakeholders working together to realise new research approaches in order to facilitate PM by CDx with relevant biomarkers.

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