PIONEER

innovative medicines initiative

PIONEER

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Prostate Cancer DIagnOsis and TreatmeNt Enhancement through the Power of Big Data in EuRope

WP6 – HTA regulator – payer integration

D6.15 White paper presenting PIONEER policy strategy

Lessons learned from implementing PIONEER Big Data for Better Outcomes in Prostate Cancer to inform current and future policy making

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Publishable Summary

Deliverable 6.15 is a public deliverable and will be made available open access on the PIONEER website as well as being promoted via the projects communication and social media platforms.

Aim of the deliverable

The aim of this deliverable to inform regulators at EU, national and regional level of the PIONEER prostate cancer policy strategy and clearly outline how the PIONEER recommendations and research outputs can be translated into policy.

Title

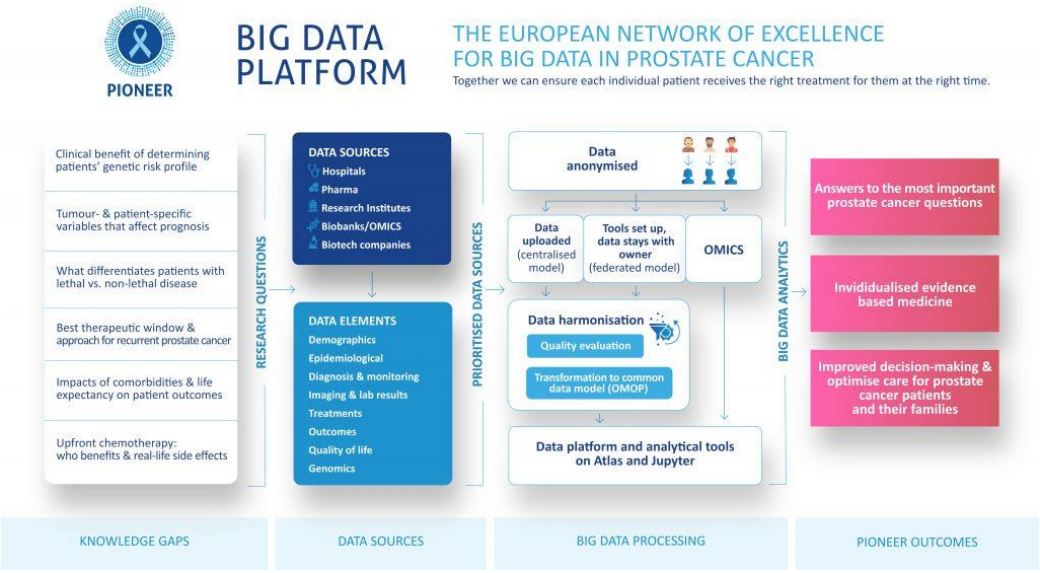
Lessons learned from implementing PIONEER Big Data for Better Outcomes in Prostate Cancer to inform current and future policy making

Introduction

PIONEER is a European Network of Excellence for Big Data in Prostate Cancer, consisting of 34 partners across 10 countries. Our goal is to ensure the optimal care for all European men living with prostate cancer by unlocking the potential of Big Data and Big Data analytics.

By applying advanced data analytics, and developing a data-driven platform of unparalleled scale, quality and diversity, PIONEER will empower meaningful improvement in clinical practice, prostate cancer disease-related outcomes, and health-economic outcomes across the European healthcare landscape.

PIONEER will assemble, standardise, harmonise and analyse high-quality big data from diverse populations of prostate cancer patients across different stages of the disease to provide evidence-based data for improving decision-making by key stakeholders.



The challenge facing PIONEER

Prostate cancer is the second most common cancer in men, 1 in 8 men will be diagnosed with prostate cancer during their lifetime, accounting for 9% of all cancer deaths among men in Europe. The socio-economic burden associated with prostate cancer is predicted to dramatically increase in the coming years due to our ageing population. Studies have reported a prevalence of 59% by the age of 79 years.

There are a number of critical questions that remain unresolved regarding the screening, diagnosis and treatment of prostate cancer patients, these questions relate to:

1. Disparities in the incidents of prostate cancer between different countries as well as unacceptable inequalities in prostate cancer survival rates across the EU. There is insufficient knowledge on risk factors for prostate cancer and on patient characteristics. This lack of knowledge means that prediction of which patients will have the best outcomes with specific treatments remains poor.
2. A lack of meaningful engagement of all key stakeholders (including patients) in the processes which define the most important prostate cancer research questions that urgently need answering.
3. Lack of effective implementation of knowledge gained in clinical practice (including knowledge informed by real-life data), with variability within and across European countries. This results in inequality in prostate cancer care, increased risk of short- and long-term harms to patients, as well as excess costs related to inappropriate management.

There is a need for an improved definition of prostate cancer across all stages of disease, improved stratification of patients at time of diagnosis, and improvement and standardisation of prostate cancer-related outcomes based on real-life data. Ultimately, such definitions and data need to be fed back and effectively implemented into prostate patients' care pathways to optimise screening, diagnostics and therapeutic management of these patients; therefore, providing them with the best possible care.

PIONEER's unique approach is to firstly identify critical evidence gaps in prostate cancer care through a detailed

prioritisation exercise including all stakeholders (i.e. clinicians, patients, researchers, industry etc.). PIONEER will then standardise and integrate existing 'big data' from high quality and multidisciplinary data sources from prostate cancer patients across different stages of the disease into a single innovative data platform. Based on a unique set of methodologies and advanced analytical methods, PIONEER will attempt to transform the field of prostate cancer care with particular focus on improving prostate cancer-related outcomes, health system efficiency and the quality of health and social care delivered to all prostate cancer patients and their families. In addition, PIONEER will aim to provide standardised care pathways for all clinical centres across Europe.

EU policy and legislative landscape

Numerous developments at the EU level are inter-related to PIONEER's aims and objectives. PIONEER's experience can help inform policy making on these issues. From the start of the project, PIONEER aimed at contributing to HTA assessments, but since the start of the programme new important policy and legislative dossiers have been developed, including Europe's Beating Cancer Plan, HTA Regulation, the European Health Data Space and EMA's DARWIN and the Pharmaceutical Legislation proposal.

This policy paper focuses on what has been learnt through PIONEER, and highlights key recommendations to policy makers to inform decisions.

Europe's Beating Cancer Plan

The urgency of addressing cancer is clear, and the European Union's Beating Cancer Plan (EBCP) can play a significant role in finding solutions. With over 4 billion EUR in funding and access to further financing through EU programs focused on research, regional development, and recovery, the EBCP has the potential to make a meaningful impact. The European Commission's Beating Cancer Plan is an ambitious cancer plan covering the whole spectrum of cancer care from prevention and early diagnosis, treatment and care to survivorship and quality of life. It is aligned with the Commission's research mission on Cancer. Ultimately, the Beating Cancer Plan and Research Mission will be the driving vision and force for all future actions on Prostate Cancer. The EU has the ability to assist Member States in implementing evidence-based policies that provide equal access to high-quality cancer prevention, screening, diagnosis, treatment, and aftercare for all EU citizens. However, it is important to recognize that cancer is not a singular disease, and each type of cancer presents unique challenges that should be considered in policy discussions. In addition to general actions that aid in the fight against cancer, specific needs must be addressed for individual types of cancer.

Quality of care and treatment and Quality of Life strategies will be strengthened by patient-reported outcome measures (PROMs) / patient-reported experience measures (PREMs) measures developed through PIONEER. As such, The PIONEER platform can give a unique contribution to the European Health Data Space governance framework, by contributing to their initiatives such as Cancer Knowledge Centre and UN.Can.

The EAU has also taken the lessons learned from PIONEER and data infrastructure and will apply these techniques to the Prostate Cancer Screening pilots co-funded by the EU4Health PRAISE U projects. Thus, informing Prostate Cancer screening practice across the EU.

Recommendation: Europe's Beating Cancer Plan has been an unprecedented strategic plan on cancer throughout the whole cancer pathway. The goal of EBCP is to offer screening to 90% of eligible EU population to ensure early detection and save lives. However, achieving this objective relies on the actions of individual member states since screening programmes are set up and managed by them. Policy developments should reflect the evident need to drive access, diagnosis, innovation, investment and research forward and redress the inequalities across Europe and among different populations and pathologies. An overall cancer plan—desirable in itself—is not sufficient, as a cancer plan is needed for each type of cancer. Nevertheless, at a general level, it is evident across the board that cancer registries are currently inadequate, non-standardised and lacking essential clinical data. There are vast differences in the incidence and survival of many cancers from state to state, and these differences are also reflected in screening and access to appropriate therapies and expertise. These regional variations are not cultural but the result of policy and political will to look beyond cost-benefit calculations. All countries should have the same objective of equal access to optimal care and equal outcomes. Moves are needed to systematically speed the process between early symptoms and diagnosis and between diagnosis and treatment. Uniform reporting standards, more comprehensive implementation of multidisciplinary teams and more excellent centralisation of specialised care in high-volume centres would assist. Measures are needed to overcome the lack of accurate data on costs, treatment modalities, outcomes—and the associated direct and indirect costs. It has enhanced coordination between the EU and Member States and also the departments in the Commission outside of DG Sante that have a role to play in the delivery of the cancer plan. This is the first time the Commission has implemented something of this scale and nature on a health theme and it has galvanized EU leadership, funds, policies, research and legislation. The ambition of the EU Cancer Plan should be maintained during the next Commission mandate, building on the success achieved so far, and building momentum. Prostate PIONEER is a key building block of quality data sets that can support action on Prostate Cancer into the next EU Commission mandate.

HTA Regulation

The PIONEER project was started in May 2018 and the EU Health Technology Assessment Regulation had been proposed by the European Commission in January of that same year. The EU Health Technology Assessment Regulation went on to be approved by the other EU institutions in December 2021 after. The EU Regulation on Health Technology Assessment will come into effect as of 2025 for new oncology medicines and therapies, including Prostate Cancer. This means that from 2025 there will a single joint scientific assessment for all EU member states.

Situation analysis of PCa HTA landscape and reason for inequalities

In 2021 PIONEER performed an analysis of the PCa HTA landscape and mapped HTA decisions across the EU, highlighting some of the inequalities in access which are explained in the image below.

PCa HTA Landscape

In the project timeframe (01 Jan 2019- 17Jul 2021), there were a total of 66 HTA decisions for PCa therapies (including 2018 Zytiga decisions).

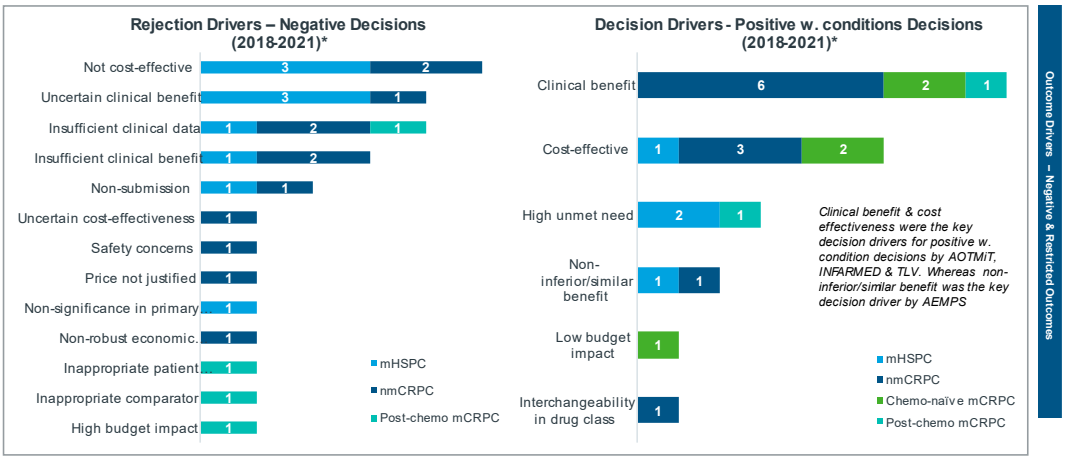
Current HTA Situation & Inequalities in Access

- During 2011-20, seven PCa therapies received EMA approvals
- Access to these new PCa therapies varies widely across EU countries. France and Germany have the widest access to these therapies, whereas access is limited in countries like Belgium, Bulgaria, Finland & Ireland
- The majority of the HTA reviews focused on the earlier PCa indications (mHSPC and nmCRPC)
- HTA outcomes in PCa were generally in-line with other oncology assessments in Europe except for mHSPC where there was a higher percentage of negative outcomes (35% vs 24%, respectively)
- Time to positive recommendation varied from 93 to 3010 days post EMA authorization
- Also, there was resistance to accept surrogate endpoints like MFS and rPFS. For example, the G-BA did not accept rPFS as a surrogate for OS. G-BA will grant highest benefit rating based on a statistically significant benefit in OS, symptom improvement QoL, and better safety

Reasons for Access Inequalities

- The inequalities in access were either due to evidence-based challenges or economic/price-based challenges
- Immature data and lack of cost-effectiveness were unanimously critiqued by most European HTA bodies, especially Germany's G-BA and UK's NICE. Limited additional benefit to existing treatments was also a key clinical negative in Germany

Key decision drivers for negative recommendations lack of cost - effectiveness, uncertain clinical benefit & insufficient clinical data



The use of Big Data in HTA decisions

The IQVIA data validated the situation that we had already envisaged during the proposal writing phase and the top changes that we highlighted in a previous PIONEER policy paper, namely:

- HTA decisions are more likely to be successful around high unmet medical needs;
- Data are often lacking, including cost effectiveness;
- It is hard for Marketing Authorisation Holders to prove the clinical benefits, particularly around the traditional endpoint of Overall Survival (OS).

Realistic and achievable goals are both desirable and possible, particularly with the increasing recognition of real-world evidence (RWE) in healthcare. Those funding healthcare need proof of the effectiveness of these tests, but it's crucial to break the cycle of limited RWE availability and lack of reimbursement for tests. Big Data and RWE have the potential to unlock some of the challenges by allowing regulators to query diverse data sets in addition

to clinical trial data, including Electronic Health Records (EHR), reimbursement and registry data, etc., thus allowing regulators access to data on how certain treatments interact with and respond to health systems and daily life. In terms of prognostic data capture, the use of RWE is fertile ground for the integration and growth of PROMs and PREMs, allowing for a better understanding of what matters most to patients. The use of electronic health records (EHR) has the potential to provide timely and accurate information, which can improve digital healthcare. To achieve this, it's important to carefully consider and prepare for the implementation of EHRs. While it's possible to conduct research studies using data from entire hospital systems, it's important to gain experience in various settings to develop reliable scientific methods.

Different data models

When it comes to data, there are four main business models to consider. The simplest of these is a proprietary approach, where an individual or organization invests in owning or curating the data and charges others for access. For instance, trial data or Unicancer's Epidemiological, Strategy, and Medical Economics (ESME) cohorts, which use real-world data to enhance cancer patient management. A different method for obtaining curated data is through a "freemium" or channel-priced system of on-demand curation. Members within a group can provide data without any cost, with the expectation of receiving reciprocal data from other members. No money is exchanged in this system, and access to others' data is dependent on one's own contributions. Academics may choose to approach this differently by proposing an experiment, negotiating with interested parties, seeking funding together, and following any funding provider's rules without creating a specific club. A third approach might be termed capacity-rationed access. A government subsidises a certain amount of re-use by nominating representatives to the management of the data holder, and the data source chooses the projects (as in the UK cancer registry). The fourth model represents the direction of European policy, which is essentially open access. In this model, FAIR is considered equivalent to FREE. However, it is not in compliance with EU data protection rules, and it raises concerns from IP rights holders. Moreover, it is not economically sustainable.

The use of multiple data sources can also help to develop and validate surrogate endpoints, shifting away from the complexities of proving impact on OS. These complexities have been described in our previous policy paper. Big Data assists researchers to risk stratifying certain sub-groups of patient populations so that we become more aware of the patients that will and won't benefit from a certain medicine or treatment strategy. This, in turn, can assist with cost-effectiveness assessments because it allows health systems and clinical practitioners to become smarter at making treatment decisions, and only prescribing medicines to those that will really benefit. Subgroups of patient populations who will not benefit from certain treatments are, therefore, saved from the potential side effects and toxicity of ineffective treatments, while health systems and payers are spared costs of these ineffective treatments, and the costs of managing side effects and complications. To effectively use Machine Learning (ML) and AI for diagnostic interpretation and decision-making, a significant amount of data is required for training, validation, and ongoing learning. The quality and relevance of the data can vary depending on its source, with data from countries with strong Health Technology Assessment (HTA) bodies and large markets being more valuable than those from smaller markets or weaker HTA systems.

Use case example PIONEER Big Data Platform
Observational health data analysis on the adverse events of systemic treatment in patients with metastatic

hormone-sensitive prostate cancer (mHSPC).

Background

The treatment of mHSPC has evolved over time with the introduction of combination systemic therapies, which are more effective than androgen deprivation therapy (ADT) alone. These combination therapies include ADT in addition to either chemotherapy (docetaxel) or androgen receptor signalling inhibitor (ARSI) (enzalutamide, apalutamide, abiraterone acetate, darolutamide) or both (triplet). Combination therapies have been shown to improve survival rates and delay disease progression; however, each of the novel therapies come with their own set of toxicities and adverse events. Therefore, the selection of drugs for each patient must be specific and personalised to provide maximum safety and maintain quality of life. Published randomised prospective studies have reported on the toxicities and oncologic outcomes of mHSPC patients treated with combination therapy, but the patient populations are highly selective and data on the patient characteristics and adverse events within a large cohort of "real-life" patients is lacking.

Objective

To characterise and report the incidence of drug related adverse events in real-world patients treated for mHSPC in four cohorts: ADT monotherapy, ARSI, docetaxel, and ARSI plus docetaxel in real-world patients treated for mHSPC.

Methods

Analysis of routinely collected observational health data converted to OMOP CDM. Characterisation analysis will be performed using code developed and adapted from the OHDSI Methods library. Estimation analysis will be performed to estimate the crude incidence rates (per 1,000 person-years) and incidence proportions (per 1,000 persons) of adverse events across all four cohorts. Sensitivity analysis to understand the risk of misclassification of metastatic castration-resistant prostate cancer (mCRPC) patients as metastatic hormone-sensitive prostate cancer (mHSPC) and to describe baseline characteristics and outcomes of cohorts when restrictions are placed to define time periods where agents have received regulatory approval for mHSPC.

Strengths

- The study is anticipated to be the largest patient-level cohort of mHSPC patients, allowing for the characterisation of relatively uncommon outcomes, otherwise not identifiable in smaller datasets.
- Data will be obtained from multiple sources and diverse settings across numerous countries maximising the external validity and generalisability of the findings.

Limitations

- Patient records may be incomplete or have incorrect entries, leading to misclassification of study variables.
- Data regarding diagnosis of metastatic PCa, treatments, pathology, imaging and laboratory results or baseline covariates prior to enrolment within the database may not be available.
- PCa specific characteristics such as stage, grade at diagnosis or the extent of the disease are not readily available in most EHR and claims databases.
- Selection bias cannot be ruled out as patient factors such as age, comorbidities and clinical characteristics may influence treatment choice and subsequent outcomes.
- Medical conditions may be underestimated as they will be based on the presence of condition codes, with the absence of such a record taken to indicate the absence of a disease.
- Medication records indicate that an individual was prescribed or dispensed a particular drug, but this does not necessarily mean that an individual took the drug as originally prescribed or dispensed.
- Cohorts have not been matched or weighted to ensure comparable groups at baseline.

What has PIONEER learned about use of Big Data and HTA?

PIONEER has some important lessons learned with regard to methodologies and technical arrangements that will facilitate the use of RWE and Big Data going forward in HTA decisions. This will, in turn, assist HTA decisions by either supporting marketing authorisation holders to close the gap in evidence required by regulatory and HTA bodies, for example by providing clinical evidence acceptable to both, or by improving HTA certainty in clinical benefit by supplementing the evidence package with complementary data.

On the basis of PIONEER use cases, we have learned that there are a number of technical, operational and governance issues that will need to be addressed before real-world evidence can be fully exploited by HTA assessment agencies.

To prepare for this significant step change, PIONEER has learned that it is of utmost importance to include a broad range of stakeholders in the HTA-related research questions. This range of stakeholders should be strongly involved in all aspects including prioritisation, scoping and engagement of the new data contributors; technical and operational infrastructure development; implementation and analysis of data; and the setting of relevant standards and governance practices through to the implementation phase, including in the technical. Obtaining trust and broad engagement will be essential for the general acceptance, effectiveness, endorsement, and rapid adoption of real-world evidence in healthcare.

Our key recommendations on the HTA Regulation and application of real-world evidence would be as follows:

1. The European Commission's HTA Stakeholder Group should be developed and resourced as a dynamic outreach and coordination mechanism to garner necessary support, expertise and involvement, particularly in terms of developing new methodology on the adoption of real-world evidence for HTA assessments.
2. The Commission should ensure synergies with the Data Analysis and Real-World Interrogation Network (DARWIN EU) as much as possible, and learn lessons from their approach.
3. Investment in consistent standards and use of a common data model will be essential. PIONEER has used the OHDSI OMOP model and our use case testing on a specific research question, we found that even though the whole platform was aligned to OMOP, that improvement in the consistency of OMOP mapping of datasets currently available in the PIONEER platform would be required. The resource necessary for mapping data should not be underestimated and future EU funding programmes may need to see further investment in this area.
4. Investment in a shift towards prospective data capture of pre-defined key variables for prostate cancer including PROMs/PREMs. Over the lifetime of PIONEER, it has become apparent that different datasets collect a wide and diverse number of variables in numerous ways. Solely mapping to OMOP does not overcome the problem of missing variables or lack of PROMs. PIONEER has developed a core outcome set for localised and metastatic prostate cancer as well as core outcome sets (COSs) for PROMs and PREMs for the different stages of the disease. PIONEER has learned that development of a federated prospective data capture platform for PIONEER COSs which is automatically mapped to OMOP would allow effectively streamline data capture to fill the current data gaps.

EU Pharmaceutical Legislation

Improving our understanding of the consequences of policy decisions and therapeutic choices can lead to significant advancements. The creation of databases that track resource usage and outcomes would enable us to compare the efficiency of healthcare systems in different countries, regions, and populations. These studies could also shed light on how much money countries spend on cost-effective medicines, which currently lacks investigation. Furthermore, there is a lack of information on how much money is wasted in healthcare spending, which means that there is little incentive to reduce it. Lastly, new prevention, diagnosis, and treatment options are only useful if there is data available on how to implement them in the healthcare system. In the last 20 years, various channels for innovation have evolved tremendously. Patients and citizens now play a more active role, and the use of data has significantly progressed. Patient groups anticipate innovative developments in diagnosis, medication, devices, and the integration of medicine and medical devices. The European Commission views the prospect of revised legislation as a thrilling opportunity for innovation. It acknowledges that Europe is lagging behind and may be losing its competitive edge in this field. Despite significant technological advancements, Europe has yet to address gaps and maximize its potential in accommodating and leveraging these developments. For new technologies when the first (later-line) indication may have the greatest uncertainty but also the highest unmet need: new prostate cancer treatments are typically initially introduced in last-line metastatic disease where there is the highest perceived unmet need. Regulatory pathways currently open the opportunity to launch 'breakthrough' cancer medicines based on single-arm Phase II data in populations with a lack of effective options.

EU proposal Art 83 on unmet medical need (UMN)

"A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following conditions are met: (a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality; (b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population"

A proper definition of UMN plays a fundamental role in the entire pharma legislation strategy. There is a considerable lack of agreement regarding the concept of unmet medical need, which has resulted in tension among stakeholders and decision-makers across different contexts. Patients who do not have satisfactory treatment options tend to view their situation as an example of an unmet need. Limiting the definition of unmet need to cases where no existing treatment is available is not in the best interest of the patient. What we read in Article 83 of the proposed legislation proposes a very narrow definition. The disease must be life-threatening or seriously debilitating, and any new products (if there is something already on the market) must show a meaningful reduction in mortality and/or morbidity over existing treatments. We are afraid that this definition will lead to the opposite of what the EU Pharmaceutical Legislation intends to achieve, which is less R&D investment in the EU and fewer treatments for patients, as it will increase uncertainty. When it comes to UMNs, people have different aspirations regarding patient rights and access to treatment. These aspirations are influenced by broader healthcare-related issues like data protection, patient empowerment, and return on investment. While it's easy to declare these rights, it's important to remember that some requests may seem good on paper but are difficult to implement in reality. Proclaiming a right is not the same as making it happen, and the necessary mechanisms must be put in place for these aspirations to become a reality.

As a core principle, any application of a definition of unmet medical need should be sure that it commands the

confidence of patient communities as representing what is most important to them.

In Vitro Diagnostic Regulation (IVDR)

There is widespread support for the European Union's goal of creating a strong, transparent, predictable, and sustainable regulatory framework for in vitro diagnostic medical devices. This framework is designed to ensure high levels of safety and health while also promoting innovation. By discontinuing outdated diagnostic tests and increasing access to personalized medicine and companion diagnostics (CDx), patients can benefit, and new opportunities for innovation can open up for clinicians, researchers, healthcare providers, and technology developers. However, access to treatment and biomarker tests can vary depending on the disease. For example, in the case of prostate cancer, there is a clear need for innovation. The widespread use of prostate-specific antigen (PSA) testing has led to overtreatment, but recent recommendations from the European Academies' Science Advice for Policy (SAPEA) have helped to reduce overdiagnosis by using risk calculators and magnetic resonance imaging (MRI) before biopsy to detect prostate cancer earlier. EU-level implementation of the In Vitro Diagnostic Regulation (IVDR) is executed by the European Commission (EC) and the Medical Device Coordination Group (MDCG), which is chaired by the EC and a representative of the member state competent authorities.
Market surveillance of notified bodies (NBs), health institutions, and economic operators such as IVD manufacturers is the primary task of each of the member state competent authorities. For some high-risk devices, consultation with EU reference laboratories and/or expert panels (coordinated by the EMA) can be part of this procedure. Particular challenges over availability are being encountered specifically for laboratory-developed tests (LDTs), which play a vital role in diagnostics, and which may find themselves for the first time under stringent new requirements. Overall, there is an obvious need to boost awareness about IVDR, which could involve holding guidance workshops at the European level with national competent authorities. The need to train both lab directors and professionals is equally important. Within the diagnostic specialities sector, it would be helpful to build more effective advocacy and to obtain financial support for collective activities in the sector. It is essential that health legislation is up to date, to ensure above all the safety of patients, but also to maximise the chances of patients and health systems benefiting from the best possible care options. The purpose of the IVDR, to update decades-old legislation to current conditions, is admirable: to bring EU legislation up to date with medical advances and to ensure better protection of public health and patient safety. Top of the list is for the EU and national authorities to speed up the certification process since this is where the immediate threat to supply lies. This means providing greater capacity for NBs and accelerating the designation process for NBs. Immediate supply problems could be eased by clarifying and possibly extending the exemptions available for LDTs that are shown as safe and efficacious.

There is a strong societal component to be taken into consideration when thinking about unmet medical needs. This includes how the burden of treatment on patients, their families and carers can be reduced, as well as reducing the burden on health systems by, for example, making therapies simpler and easier to administer. There should be a place for societal considerations within the definition structure of unmet medical needs.

As a core principle, any application of a definition of unmet medical need should be sure that it commands the confidence of patient communities as representing what is most important to them.

European Health Data Space

In May 2022, the European commission proposed a "European Health Data Space" that aims to benefit health by utilizing the increasing amount of health data in Europe. EHDS is part of the EU's overall data policy strategy, which includes the Data Governance Act, draft Data Act, and global data. EHDS is designed to complement other

EU legislation, including the EU General Data Protection Regulation ("GDPR"), the Medical Device Regulation ("MDR"), and the In Vitro Diagnostics Regulation ("IVDR"). There is a significant difference between the EHDS and other EU data legislations as it specifically applies to the healthcare sector. Other EU data legislations are more generic with horizontal provisions and may be supplemented with legislation on artificial intelligence and cybersecurity. The EHDS is solely focused on healthcare and is considered a potential game-changer in EU health policy by legislators and various stakeholders, including patient groups, academics, civil society organizations, and the healthcare industry. To enable the free flow of data and cross artificial borders, traditional silos must be eliminated. In addition, extensive engagement is required among healthcare professionals, researchers, patients, and citizens who will benefit the most. Winning their trust is crucial for them to allow the use or transfer of their data. If approved, this will provide a legal basis at the EU level for the creation of electronic health records (EHR) in each EU member state which can be used by EU citizens across the EU for primary healthcare purposes. It also provides a mechanism for the use of health data for 'secondary purposes', which include research, regulatory purposes and evidence-based policy making.

The IMI BD4BO projects look forward to engaging with the European Health Data Space in the future and to learning how the platforms developed can contribute to the EHDS infrastructure for secondary use.
Our experience from PIONEER is that the different interpretations of GDPR across EU member states are a challenge when it comes to sharing data cross borders, and that most time and resource are spent on mitigating the patchwork of approaches across the EU. We highly value the aims of the EHDS to streamline and align these processes to allow cross border research with a genuine ambition to learn more so that better health outcomes can be achieved.

In October 2022, PIONEER joined forces with 35 other health stakeholders to highlight 7 key recommendations:

The consensus statement encourages decision-makers to strongly support this Regulation and to engage with stakeholders to ensure the final Regulation optimises its potential. The statement also formulates several recommendations to consider when developing the more specific implementation plans to put this Regulation into practice across the Member States:

1. A broad range of stakeholders must be strongly involved from the outset of the process to guarantee the success of the EHDS.
2. The EHDS must align with all relevant horizontal and sectoral European laws.
3. There must be harmonised interpretation and implementation of the Regulation across the EU.

   For this, in particular, PIONEER would recommend the use of the OMOP common data model, plus the prospective application of PROMS and PREMS (both recommendations are mentioned in more detail at the section on the HTA regulation)

4. Approvals for secondary use of health data must be consistent and harmonised across Europe.
5. The scope of EHR systems must be defined clearly within the Regulation.
6. The successful implementation of the EHDS must be adequately resourced.

7. Existing health data infrastructures must be leveraged to allow continuity and build on existing expertise. Here, the PIONEER network would particularly like to highlight the willingness for the achievements of PIONEER to be sustainably accessed through the European Health Data Space infrastructure.

In June 2023 as negotiations with the EU Council and European Parliament progressed, PIONEER again joined 31 stakeholders to support the approach taken in the Commission's original legislative proposal from May 2022 (Proposal for a regulation - The European Health Data Space (europa.eu)) on the issue of consent and opt-out, as it strikes a sensible balance between protection of personal data while enabling the use of data for research and innovation to create tangible benefits for patients and citizens.

The stakeholders raise concerns about the real risk that data bias will form part of the EHDS from its inception and thus undermine its principal value for secondary use research purposes if an opt-out or opt-in mechanism is approved, and call for an impact assessment that will inform implementation of this policy option.

If the proposals for opt-out are approved in the final EHDS legislation, the collective group make six recommendations. They believe the opt-out mechanism should:

- be **applicable across all Health Data Access Bodies in EU Member States**, limiting the scope of national derogation and ensuring that the technical specifications are aligned
- **consider the impact on health and care professionals and for other data holders**
- be **capable of implementation across the EU, without limiting lawful and ethical data sharing** for secondary purposes
- be **routinely monitored** as part of a regularly updated HealthData@EU data governance framework
- have a **limited, but well-defined, consistent and transparent scope**
- have necessary investment, infrastructure and budget to **ensure sufficient transparency** so that **citizens are well informed** of the opt-out

Finally, the current debate on enabling secondary use of health data in Europe highlights the need to achieve **stakeholder alignment** where possible on the implementation journey ahead for the EHDS. It also speaks to the need for implementation decisions to be highly informed by those with experience and responsibilities for **on-the-ground implementation**. This reiterates a need for strong, balanced and inclusive stakeholder representation within the governance model of the EHDS such as its Board of Directors.

Repository for primary data

Not applicable

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