Perspectives

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The gaps between the new EU legislation on *in vitro* diagnostics and the on-the-ground reality

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Abstract: The background to this debate is now well-known: an EU policy decision to tighten controls on the devices and diagnostics sector led to the adoption of a regulation in 2017 with a schedule for implementation over coming years – a timetable extended still further by last-minute legislation in early 2022, to provide the sector and regulators with more time to adapt to the changes. Discussions among experts organised in April by the European Alliance for Personalized Medicine (EAPM) exposed continuing challenges that cannot be fully resolved by the recent deferral of implementation deadlines. One salient problem is that there is little awareness of the *In Vitro* Diagnostic Regulation (IVDR) across Europe, and only limited awareness of the different structures of national systems involved in implementing IVDR, with consequent risks for patient and consumer access to *in vitro* diagnostics (IVDs). The tentative conclusion from these consultations is that despite a will across the sector to seek workable solutions, the obstacles remain formidable, and the potential solutions so far proposed remain more a matter of aspirations than of clear pathways.

Keywords: devices; diagnostics; *in vitro* diagnostics; *In Vitro* Diagnostic Regulation; laboratory-developed tests; legislation; policy decisions; policy framework.

Introduction

The European Union aim "to establish a robust, transparent, predictable and sustainable regulatory framework for *in vitro* diagnostic medical devices which ensures a high level of safety and health whilst supporting innovation" [1] is widely supported. Achieving a positive trade-off between discontinuing obsolete diagnostic tests and increasing access to personalised medicine and associated companion diagnostics (CDx) can benefit patients, and open up better opportunities to innovation for clinicians, researchers, healthcare providers and technology developers. However,

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regulation depends on a sound framework if it is to operate successfully, as reflected in Box 1, and the framework for regulating *in vitro* diagnostics (IVDs) is still far from complete, even after the extended deadline for its implementation passed in May 2022 [2–8]. There are conspicuous gaps in the necessary infrastructure, inconsistencies and divergences in national supervision, multiple ambiguities, and uncertainties in the legislative provisions. Add to that the very variable levels of awareness of the new legislation across the sectors impacted by it, and divided opinions about how to remedy what is widely accepted as an unsatisfactory situation, and the stage is set for confusion to continue [9]. The supposed beneficiaries of the legislation – primarily patients, but also physicians, innovators in the diagnostic field, and manufacturers and labs – are unlikely to derive much profit from the change in the law until solutions effectively address neglected aspects of the regulation [10]. The 2017 regulation included a schedule for implementation over subsequent years, and the timetable was extended further by last-minute legislation in early 2022, to provide the IVD sector and regulators with more time to adapt to the changes. But there are continuing challenges. The pursuit of closer oversight, greater transparency, more demanding levels of clinical evidence and post market surveillance clash with the need for consistent and reliable supply of tests vital to much of modern medical care [9, 11]. This paper is based largely on an expert roundtable organised by European Alliance for Personalised Medicine (EAPM), which brought together clinicians, patient group advocates, EU and European Medicines Agency (EMA) officials, representatives of medical professional and research organisations, and executives from the devices and pharma industry.

Box: Implementation of *In Vitro* Diagnostic Regulation (IVDR) at the EU level.

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 of EU reference laboratories and/or expert panels (coordinated by the EMA) can be part of this procedure [12, 13].

The challenges

The challenges range from insufficiently clear legal texts to the absence of much of the regulatory or administrative or support infrastructure required for the new legislation to be effectively implemented. The consequences are already evident in terms of delays in approvals of existing products, carrying the risk of useful products being excluded from the market simply for administrative reasons – a phenomenon which is predicted to intensify as the flow of applications continues to grow. Equally severe longer-term consequences include the risk that valuable innovations in IVDs will not be developed – or will not be developed in Europe – because of the discouraging environment the new rules threaten to impose. The following examples identified in EAPM's investigation with experts and through literature review are illustrative, and by no means comprehensive. They are sufficiently dismaying, however, to suggest that without urgent action by the authorities to remedy the deficiencies, diagnosis and care in Europe will suffer.

Supply

Persistent delays in processing approvals are impeding supplies of existing IVDs [14]. Already a backlog has built up: 78% of manufacturers have reported difficulties getting their IVD tests approved [12]. There will be a massive increase in the number of IVD tests requiring certification, partly because one of the key differences in the new rules is that they extend beyond commercial IVDs. This means many products will need certification for the first time, taking the proportion of tests requiring certification from 15% to between 70 and 90% under IVDR [14, 15]. Even with the extended deadlines, this risk straining the regulatory system, with implications for delivery, because of question marks over the capacity of the notified bodies (NBs) on which the system in part depends. The number of NBs is still insufficient to cover overall requests by the companies. New submissions by diagnostic companies have been slowing down because of the delays. 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 [16]. Although certain exemptions from certification requirements are available (the requirements "shall not apply to devices manufactured and used only within health institutions

established in the Union," under specified conditions), the exemptions do not apply if the devices are manufactured on an industrial scale [17]. And the conditions for exemption are extensive: manufacture and use must occur under appropriate quality management systems, the laboratory must be compliant with International Organization for Standardization (ISO) or national standards, and there must be written justification that the target patient group's specific needs cannot be met at the appropriate level of performance by an equivalent device available on the market. The role of LDTs varies according to the context. In a typical hospital laboratory, with very little third level medicine, nearly all test results are non-LDT, while in genetics, nearly all tests will be LDT, and companion diagnostics are almost totally dependent on the pharmaceutical company [7, 18]. But LDTs are of pivotal importance in the ability to respond to emerging or neglected health problems such as pandemics and rare diseases [19]. The non-certified status of many of these tests is in part due to their complexity and the fact that they are typically used to support tertiary care, which often makes them commercially unattractive. Under IVDR, they face increased costs of development and operation, and the risk is that essential tests will not be available or will disappear [12, 14, 20]. This risk is particularly acute in countries where there has traditionally been a dependence on LDTs, such as Germany. The new obligation to use commercially available approved tests has serious cost implications, since these are often more expensive than a lab's own LDTs [21, 22]. It is also a limitation in that commercial tests are not always available – and attempts to ensure this are uncertain in outcome. This is a challenge to hundreds of producers of thousands of tests used today in routine clinical practice. Many labs using LDTs are required by IVDR either to switch to procurement of commercially-approved tests (often at higher cost) or to provide new justification for the authorities for continued use of their LDTs – but again in a situation of ambiguity over criteria and process [7, 12, 23]. There are direct implications for payers in terms of cost, but also in terms of planning. If fewer tests are available, pathologists may have to wait longer for results. LDTs can continue to be used for unmet needs – a term open to interpretation – but there is lack of clarity over whether or not a test manufactured in-house can be used when an equivalent test is available on the market [16, 19]. The regulation permits use of an in-house device if there is no appropriate certified device available – but agreement is still absent on interpretation of that limitation: should it have to provide better clinical performance, or does it apply if there is a shortage of a reliable device or that device has been discontinued? And does it apply where there are no safety issues and a lab can prove the efficacy and safety of its text in relation to the commercial CDx? Guidance has only just been published on what constitutes significant change in design and how to interpret the concept of a change in intended purpose under IVDR art. 110(3). Unsurprisingly, the European Commission MDCG says in this most recent publication that "it is important for manufacturers and notified bodies to have a clear understanding as to what changes to design or intended purpose would be considered 'significant'" under IVDR. Over 17 pages, it attempts to answer that question [24]. It remains to be seen how far it meets the concerns of the sector.

The outcome is that some medical devices will be taken off the European market because their manufacturers (often small and medium-sized companies) have decided recertification is not worth the cost and administration/management time. Many public labs may be unprepared to meet the new requirements. Research funded by Astellas Pharma Europe Ltd. has projected that if labs are no longer able to provide their LDT where a commercial CDx is available for a precision oncology treatment, a significant number of patients may not be able to access the biomarker test in countries where the LDT is by far the most commonly reimbursed tests for cost reasons – Germany and to a lesser extent France and Italy. The decision process for reimbursement is opaque and confused in Europe, leaving uncertain whether the qualification of an academic test will be enough to justify its use and to obtain the relative tariff of reimbursement. Italian laboratory professionals are still waiting for a specific official tariff for homologous recombination deficiency (HRD) assay covered by national health system (a situation that finds echoes in other European countries).

Meanwhile, some clarification emerged from MDCG on "first certification for that type of device" and corresponding procedures to be followed by NBs. For class D devices, the IVDR establishes the conditions to be applied by the NB to determine whether it has to consult the expert panel on the performance evaluation report of the manufacturer. This guidance provides clarification on the meaning of these conditions and on the corresponding procedures to be followed by the NB [25]. MDCG has also published a guidance document outlining the activities to be performed by NBs as part of the appropriate surveillance defined in IVDR, and covering requirements concerning certain manufacturers' obligations, especially in respect of their quality management system [26].

Infrastructure

Overall, the national regulatory apparatus is judged to be inefficient – and even ineffective – in some member states,

inconsistent across the EU, and lacking essential elements for effective implementation of the new legislation. By midsummer 2022 only seven NBs had been designated to operate under the terms of IVDR – recognized officially as insufficient to handle the acute growth in workload with thousands of certifications of existing IVDs, approvals of new IVDs and IVDD surveillance activities. In August 2022 the MDCG recognized in a position paper that "significant and urgent challenges remain in ensuring sufficient capacity of NBs and readiness of manufacturers in order to allow medical devices and *in vitro* diagnostic medical devices to be certified in accordance with the Medical Device Regulation (MDR) and the IVDR within the transition periods provided for in the regulations," and proposed a series of stop-gap measures to alleviate the pressure. This followed formal expressions of concern from an EU Council meeting of health ministers on 14 June that "these challenges, if left unaddressed, may lead to disruption of supply of devices needed for health systems and patients and may jeopardise the access of innovative medical devices to the European market" [27]. Also, in August MDCG issued new guidance on designation of NBs with the aim of increasing their availability for IVDR activity [28]. The process for designating further NBs can take as long as 30 months.

The lack of designated NBs is crucial, but the issue is not the number of NBs but the number of assessments that have to be conducted to allow the existing IVD to remain on the market. Insufficient capabilities have been created to ensure that can happen. NBs, even with the recent extension to the deadlines, admit there are still many challenges. NBs have significantly expanded their resources even though there is competition for personnel with the necessary knowledge and experienced persons are also in demand from other stakeholders in the IVD/MDR sector [29]. The lack of designated NBs could compromise product supply to patients and hospitals clearly threatening lives of patients, warn patient groups. Covid has shown that from the discovery of a pathogen to the introduction of the test can take as little as 6 weeks [30]; a conformity assessment will require longer and although the IVDR (article 54) includes the possibility for a derogation, this is only applicable at national level and expandable to the whole Union territory only in exceptional circumstances. Timelines for certification can be 12 months; longer timelines are expected for companion diagnostics for which the consultation with the EMA can add up to 4 months – and the EMA only recently provided an operational system to evaluate CDx [31]. In addition, the European Databank on Medical Devices (EUDAMED) database is not yet fully functioning to list all approved products, and the envisaged expert panels have not all been set up – with the IVDR panel in place only since September 2021. There is need for EC guidance for specific audiences, including payers, pathologists, and healthcare professionals. Manufacturers are already finding difficulty in identifying a NB for some of their products, and there are concerns over the availability of expert panels to provide certification for the more advanced class D IVDs, as well as over the sufficiency of EU reference laboratories – of which none exist at the time of writing [32]. And there are neither clear guidelines on many areas of decision-making, nor wide consensus on possible solutions to the challenges the regulation poses. There are disparities in approaches to accreditation, with some following ISO 15189 and others following parallel but distinct national requirements, and with organisations responsible for enforcing IVDR not always being the same as those responsible for certification, adding to the complexity. A European survey on the use of biomarkers showed wide inequalities among countries, with an absence of uniform regulations on safety and quality assurance of labs and a lack of methodology [33]. EU level guidance was issued by EMA on companion diagnostics in draft form in December 2021, and a consultation process is still underway.

Guidance is still missing, particularly on critical issues, although a document [24] has just appeared on how to manage (and what is) "a significant change" under IVDR art. 110(3) and there is a lack of standard documents, templates and examples, and of training and familiarisation workshops. Reference laboratories for high-risk products are not in place and relevant specifications emerged only at midsummer, when the European Commission adopted two implementing acts to lay the groundwork, with rules on tasks and criteria for the labs, and on the fees they can levy from NBs and Member States [34]. In July 2022, the European Commission sent a call for EU reference laboratories for high-risk IVDs to the EU Member States, as well as Iceland, Norway, Liechtenstein and Turkey, but the deadline to submit nominations is not until 31 March 2023. The high-quality pathology and laboratory medicine services that are an integral part of health systems are also not available evenly across Europe, despite the fact that new molecular diagnostic techniques, advances in precision cancer treatments, and population-based screening programs for disease prevention or early detection have made these services an even more important part of modern medicine and health care [35, 36]. For the most sensitive 'class D' diagnostic products, evaluation by Expamed, a panel board of laboratory medicine experts, ceased immediately after the deferred deadline was announced, and

the recent transfer of many of the responsibilities to the EMA has created new confusion and misalignment. Reimbursement and procurement arrangements across Europe, already complex, are futher complicated by the new legislation. In general, it will be required for priority to be given to companion diagnostics rather than LDTs when both are available – and safe [12]. There is also significant variation in the public procurement of IVDs [5], and wide variation in IVD reimbursement practices across Europe. Some countries, including Germany, reimburse only the LDT, for cost-saving reasons, creating a potential access gap. Germany's refined regulatory framework splits healthcare responsibility between the federal level in Berlin and the 16 regional governments, the Länder, with trade regulated from Berlin [37]. As a result, allege critics, appointment of responsible authorities to implement the IVDR has been delayed. It is uncertain who is in charge of dealing with IVDR and raising awareness of its impact on labs. One disturbing consequence is inconsistency in the marketing of some Covid tests, leaving some of them available without any assessment of its quality and efficacy [38]. There is also a degree of confusion about accreditation, with parallel systems perceived as an unsatisfactory overlap of responsibilities. France's centralized regulatory system has yet to prompt conversations on the implementation of the IVDR and on its implications – particularly for in-house testing, and parts of the diagnostic sector claim to lack formal representation. Italian regulation is national but accreditation is devolved to the region's leading to some labs following ISO and others only a regional law. The results are a low awareness among laboratory professionals with only few scientific societies aware of the new obligations created by the IVDR implementation [39]. Bulgaria's health system faces serious funding shortages for the supply of tests, and gaps in the infrastructure and skills for the development and use of tests. The problems include lack of sufficient funding to conduct additional molecular genetic tests and the lack of reimbursement of certain targeted drugs. In general, it is also the case that the deficiencies in infrastructure have left many businesses that are subject to the IVDR in the dark. They are often not well-informed of the changed legal context and their obligations, further raising uncertainties over consistent supplies and to future access to IVD technologies in the EU. A factor in the challenging situation is a classic European Union ambiguity on policy and management: legislation is in the hands of the European Parliament and Council, and implementation is in the hands of national competent authorities and other para-statal bodies such as standards agencies. These are in turn assisted – but not in any binding fashion, the EC makes clear – by a medical devices coordination group (MDCG) that involves national authorities [24, 40, 41]. To complicate the arrangements still further, the EMA has been given the duty to progress reflections on companion diagnostics [42–44].

Innovation

Persistent delays in processing approvals are not just impeding supplies of existing IVDs, but are also inhibiting the development and marketing of new and better products [14]. This is a challenge to hundreds of producers of thousands of tests used today in routine clinical practice, and whose work also constitutes a valuable test-bed for potential breakthrough testing innovations. This has implications for patients today and in the near future, because of how the new rules for LDTs could impact access to precision medicine where a companion diagnostic is required [7, 38]. The loss of many LDTs is seen by some specialists as the potential loss of innovation in human genetics. Specialty tests – the area where labs will continue to develop – are particularly vulnerable as they are not commercially attractive and will not be prioritized, leading to a lack of personalized, flexible approaches and diminished translation of innovations. And novel devices that are non-LDT commercialised tests, such as those containing artificial intelligence algorithms, will require certification. The needs for an efficient system are going to grow. Greater innovation is forecast in tests linked to companion diagnostics, particularly for cancer and other areas of personalised medicine, and in the use of digital health and diagnostics, with next generation sequencing (NGS) and artificial intelligence systems [45]. Among academics, whose aim is to protect the translational research value chain from basic research to clinical treatment, there is genuine concern for the innovative diagnostic sector in the wake of IVDR. There are fears that over-rigid requirements on new tests could impede development and lead to the abandonment of some promising projects. Even where big multinational companies may be able to transfer their development activities outside EU and register the products elsewhere, possibly under less demanding rules, small national companies and start-ups will continue to face many constraints, as well as economic obstacles, with negative impacts on their capacity to develop. At the same time, the diagnostic sector fears that over-rigid insistence on the use of approved tests could lead into a trap which would allow manufacturers to exercise effective monopolies. If labs, health institutions and even companies developing their own tests in novel areas are required to obtain certification through what is currently uncertain – they may be discouraged from pursuing their investigations, and

innovation will be negatively impacted [46]. Assays with higher complexity are more difficult to commercialize. Experts in the field suggest that molecular oncology itself is at risk. In what is a varied landscape for approval of testing in Europe, NGS testing for certain cancers is becoming broadly available, but validated in ways that would not meet IVDR requirements. In the meanwhile, many comprehensive genomic assays are provided on demand and these tests have been developed in line with standards that are not completely compliant with IVDR. Nevertheless, some hospitals or patients are using these assays aimed to profile cancers – as is the case of Foundation one or Myriad myChoice which are routinely used in both translational research and routine diagnostics. Clinical trials involving IVDs also face new difficulties, as manufacturers must comply with IVDR's performance evaluation requirements. Clinical trial applications now require approval by national authorities and Ethics Committees in each Member State where the trial is to take place – a more onerous procedure than under the previous legislation, when a process of coordinated assessment was possible via EUDAMED. Here too, there is delay, with additional guidance published in July 2022 on stop-gap measures [47]. A further barrier is that the necessary coordinated process, infrastructure, and guidance are not yet available, risking delays to trial initiation. In addition, many novel devices developed by European companies are being introduced in the US first rather than in Europe – arguably because the United States Food and Drug Administration (FDA) provides greater clarity and easier feedback about necessary testing than European regulators [48]. There has been a steady increase in the number of new cancer treatments which require a biomarker test [49–51]. In Europe, 37 precision medicines which require a biomarker test have been EMA approved by the end of 2021 [34]. However, access to treatment and biomarker tests varies. In prostate cancer the need for innovation is evident. Large scale introduction of prostate-specific antigen (PSA) testing is associated with overtreatment, and with early detection of prostate cancer coming into scope after the recent recommendations of Science Advice for Policy by European Academies (SAPEA), the overdiagnosis is already significantly decreased by the use of risk calculators and magnetic resonance imaging (MRI) before biopsy. New biomarkers that can identify with clinically significant prostate cancer using a liquid diagnostic substrate obtained non-invasively [52, 53] will in the end make it possible to reduce to a minimum the detection (and eventual overtreatment) of insignificant cancers [54, 55]. Another example can be given by the HRD assessment where, despite the large use of surrogate LDTs capable to predict possible genome instability, the lack of an academic validated test obliges oncologists to request such tests in outsourcing. All these outsourced tests cannot be completely replaced by LDTs, since the commercial ones involve complicated algorithms and molecular platforms that require a high level of laboratory infrastructure to determine the HRD. Finally, the definition of a unique HRD score still remains challenging, limiting the implementation of in house HRD assays in clinical setting. The major issues regarding this test are the following: (a) both FDA and EMA (AIFA in Italy) have approved use of new PARP-inhibitors for patients who are HRD-positive and this means that these patients must be tested; (b) the reimbursement of assay is not covered by country health systems and patients have to pay on their own. The implementation of LDTs in this specific setting will continue in the near future to facilitate the access to these drugs for thousands of patients within EC [12], particularly when the cost for the outsourced HRD tests is considered.

Discussion: the way ahead?

Agreement still has to be found across the sector on the best way to manage the evident diversity and consequent ambiguity and even confusion across Europe over IVDR. There are those who favour more binding EU-level decision-making to avoid regulatory differences across countries – "with 20 different flavours of a single opinion" – and those who claim that no group of officials can satisfactorily deliver the detailed rules for processes as complex as diagnostic testing, so legislators should set broad frameworks and the diagnostic sector should develop and evolve standardised practices on matters of operational detail. This could apply to questions such as what constitutes an LDT, how to define equivalence or how to justify maintaining LDTs when there is a commercial approved kit on the market, so that patients' access to IVDs is not jeopardised. In this scenario, out of long discussions and via engagement with the EC, the national competent authorities would dictate what must be done, but diagnostic specialists would define how it is to be done. It also seems vital that labs continue to be able to make their tests so that specialists can use them. This approach is based on the obvious reality that clinical decisions take account of a complex interplay of clinical presentation, laboratory and other testing results, patient and family p, often involving multidisciplinary care and surveillance. There is not a regulation that can cover every clinical scenario, it is argued. The genetics and rare disease fields and haematology are particularly insistent on the need for flexibility since these patients have very diverse needs, which can be met only

by decisions at the most appropriate level. There is a perceptible will to seek constructive compromises. Desirable arrangements are sketched out that would see cooperation between the diagnostics sector and manufacturers in the interests of patient access, so that diagnostics are transferred to the manufacturing sector when they are commercially viable, and diagnostic laboratories continue to contribute to healthcare with products not commercially viable. As tests become more specialised and more complicated, they become less interesting for the manufacturing sector. The optimistic scenario envisages closer interplay between NBs and scientific societies and governments, and among standards and certification bodies. The EU approach might helpfully be modified to take into account possibilities of closer partnerships between public and private sectors: "we can only start working together once we understand each other" is the rationale [33]. There is the hope that closer communication within the sector – among all stakeholders, from end-users and patients, authorities and the devices, diagnostics and pharma industries – could provide longer term benefits, even providing a regulatory pathway that could generate European harmonisation. The new transition periods provide a breathing space until 2028 to work out the best methods for ensuring that innovative diagnostics continue to be vibrant in the dynamic European environment.

Conclusions

Recommendations from the EAPM expert panel – summarised and discussed in this paper – are aimed at offering guidance to policymakers at EU and national level that could make it more likely to avert supply interruptions, encourage continued innovation, and assure the best possible conditions now and in the future for the development and use of IVDs that will increasingly safeguard and improve the health status of EU citizens. 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. Clarification on EUDAMED as to which IVDs will be available could also help. But in the longer term, a solution depends on agree of a hierarchy of guidance, with a collaborative approach with the authorities' determining objectives, and the diagnostic community collaborating to deliver guidance on how objectives are to be achieved. This would be conducted in alliance with medical societies who would agree and publish detailed guidelines. Guidelines should also be developed for health technology assessment and for certification, to provide a reference for common understanding at national, EU and international level. And specifications for reference labs will have to be completed. Overall, there is an obvious need to boost awareness about IVDR, which could involve holding guidance workshops at European level with national competent authorities. The need to train both lab directors and professionals is equally important. And within the diagnostic specialties 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. But for all the merits of the plan, it is now increasingly clear that the update is imperfectly adapted to the complex realities of IVD supply and development. Success depends on a functioning regulatory system being in place, and that is far from guaranteed. The unintended consequences of IVDR could therefore be a reduction, rather than an increase, in the quality and scope of patient care. It is also likely to be an impediment to the innovation on which improved diagnosis and treatments depend. The need is urgent for wide stakeholder engagement with relevant policy circles and decision-makers at EU and national level.

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