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ORIGINAL RESEARCH

Impact of the new European Union *In Vitro* Diagnostics Regulation on the practice of hospital diagnostic laboratories

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ABSTRACT

Objectives: The In Vitro Diagnostics Regulation 2017/746 (IVDR) coming into force from May 2022, creates the first European regulatory recognition for biomarker tests linked to medicinal products, so-called companion diagnostics (CDx). Since the introduction of the IVDR is associated with uncertainties about its impact on hospital practice, it is urgent and valuable to investigate how and why CDx are currently used in hospital practice, which factors influence the choice for applying in-house or commercial CDx, and what the expectations are about how the IVDR may affect current practice.

Methods: We investigated these questions using an interview-based approach and focused on 15 hospital laboratories in the Netherlands, including 7 academic and 8 general hospitals. All types of CDx were considered relevant for this research, including both genetic and protein-based biomarkers.

Results: Factors found included: costs and convenience, complexity of application, and compatibility with existing workflows. Next to in-house and commercial CDx, hospital laboratories addressed compatibility by tweaking existing CDx.

Conclusion: Although increased quality of CDx is welcomed, worries toward increased costs and administrative work, and decreased quality were expressed. Further, the IVDR might also hinder using optimized in-house and tweaked CDx. Additionally, increased administrative burden could decrease innovativeness toward CDx.

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In vitro Diagnostics Regulation; companion diagnostics; in vitro diagnostic medical devices; diagnostic testing; biomarker testing

1. Introduction

The field of precision medicine (PM) is gaining momentum and holds the promise to allow healthcare professionals to attune treatments to individual patients [1,2]. Biomarkers present in patients' blood or tissue may characterize how they will respond to therapeutic interventions. When these predictive biomarkers are tested in the context of medicinal treatments then these tests are called *companion diagnostics* (CDx). In the new Regulation 2017/746 on in vitro diagnostic medical devices (IVDR), a companion diagnostic is defined as: "device which is essential for the safe and effective use of a corresponding medicinal product to:

- identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- identify, before and/or during treatment, patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product".

CDx are thus diagnostic biomarker tests that are used to 'accompany' medicines to determine which patients will benefit most from those treatments [3].

In contrast to the situation in the US, CDx are not co-approved with the relevant medicinal product by the same regulatory authority, and the use of a specific approved CDx with a specific medicinal product is not mandatory in the European Union (EU). Until May 2022, CDx in the EU were not assessed by a regulatory authority, but instead were self-certified by manufacturers [4]. From May 2022, this changed as CDx in the EU are now assessed by Notified Bodies (NBs) prior to certification. This applies to CDx that newly enter the market as well as recertification of existing CDx. The NBs are appointed by EU countries and work independently from the medicine agencies in the EU. The requirements for assessment of CDx are laid down in the IVDR, which became fully effective on the 26th of May 2022 [5]. The IVDR covers tests that are used on biological samples to determine the status of a person's health, like CDx. The general aim of the IVDR is to reduce uncertainty and risks through standardization of CDx use. Two types of CDx can be identified: in-house tests that are developed and used by laboratories themselves and commercial tests that are developed by companies and subsequently sold to laboratories [6].

As part of the new IVDR, from May 2022 NBs consult the European Medicines Agency (EMA) and national medicine agencies (also known as national competent authorities), like the Medicines Evaluation Board (MEB) in the Netherlands.

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Usually, these agencies examine the balance between efficacy, risks, and adverse reactions of medicines and they assess whether medicines' quality is and remains satisfactory. With the IVDR having come into force, the national medicine agencies may also be consulted by NBs on the performance and safety of CDx.

The introduction of the IVDR, though principally welcomed due to the expected improved quality assurance of CDx, is associated with uncertainties about its impact on hospital practice and with how stakeholders should take the new legislation into account. Considering that the IVDR comes into effect soon, it is urgent and valuable to investigate how CDx are currently used in hospital practice. We studied why stakeholders who apply CDx in hospital practice in Dutch hospitals currently use either in-house or commercial CDx, and which factors influence this choice. Furthermore, we investigated expectations for how the new IVDR may affect the current practice with respect to CDx. All types of CDx were considered relevant for this research (e.g. for genetic and protein-based biomarkers).

2. Participants and methods

2.1. Study design

To investigate the application of CDx in hospital practice, an interview-based research was conducted involving professionals who apply CDx in academic and general hospitals in the Netherlands. Due to COVID19, physical interviews were impossible, therefore video-calling tools were used to capture in-depth subjective experiences of participants. With semi-structured interviews, in-depth insights into expectations for the impact of the IVDR were clarified [7].

The interviews contained open-ended questions (Supplementary table 1), based on Rogers' theory on Diffusion of Innovations [8] (Supplementary material) to explore technology-related (e.g. relative advantage, compatibility, complexity, trialability, and observability). Previous research used Rogers' model to investigate how innovative decisions were made in healthcare [9], why and how innovations are implemented in healthcare [10], and the diffusion process of specific CDx into clinical practice in Italy [11]. The current research investigates similar elements, but in the context of CDx-use in the Netherlands.

Participants were asked about the CDx they work with, aspects that influence the decision to implement a specific CDx, and expectations for the impact of the IVDR on current practice. These topics functioned as a guidance for the interviews and ensured that all relevant topics were discussed while providing participants with the freedom to elaborate on opinions that they found important to share [7].

2.2. Participants

The Dutch healthcare system makes a distinction between eight academic and 70 general hospitals [12]. Academic hospitals employ a variety of researchers and medical specialists who can provide more specialized care. Specific for oncology, a field in which CDx features largely, Dutch academic hospitals have Molecular Tumor Boards (MTBs). Patients who have failed on standard therapy, or who have a cancer so rare that treatment options are limited, are discussed during MTB meetings [13]. Each MTB generally focuses on specific cancer types, such as colon, lung, or breast. MTBs usually have a multidisciplinary composition, consisting of molecular biologists, pathologists, and oncologists [13]. General hospitals provide more routine healthcare, which still may include the use of CDx. General hospitals can send patients or samples to academic hospitals with more experience with a specific condition or diagnostic test. Another option is that general hospitals receive help from academic hospitals through peer-to-peer consultation. This way of collaborating is also possible among academic hospitals.

In this study, both academic and general hospitals in the Netherlands were investigated regarding their use of CDx. Participants were selected based on their position as professionals working with CDx in Dutch academic and general hospitals. Representatives of all eight MTBs of academic centers in the Netherlands, as well as representatives of eight general hospitals were invited. One MTB was not available for an interview within the duration of this study. To find participants, all MTBs in the Netherlands and pathology departments of eight general hospitals were contacted, which referred us to the appropriate professionals. The selection of general hospitals was based on a list of 26 top clinical hospitals, which take part in scientific research [14]. Based on their participation in scientific research, these top clinical hospitals can be considered science-focused hospitals. Targeted participants consisted of currently active professionals working with CDx in academic and general hospitals and included pathologists, clinical chemists, molecular biologists, and oncologists. All of these professions have been included in the interviews. In total, fifteen interviews were conducted, of which seven involved professionals working with CDx in academic hospitals and participating in their MTB, and eight involved professionals working in general hospitals.

2.3. Data quality

To enhance validity of the research, raw interviews were transcribed within 7 days [15]. Furthermore, at the end of the interviews, a meeting for all interview respondents was held during which the results were presented, and participants could provide feedback. To increase reliability of the research, both the interviews and coding process followed a code book based on Rogers' theory on Diffusion of Innovations [16]. Coding was discussed during weekly meetings amongst the authors to enhance confirmability of data and thus data quality [17].

2.4. Analysis of the interview data

Qualitative data analysis software (Atlas.ti) was used to analyze the data. Since Rogers' theory on Diffusion of Innovations (Supplementary material) functioned as a guide for the interviews, analysis was structured using the theory's components: relative advantage, compatibility, observability, complexity, and trialability.

2.5. Ethical considerations

Informed consent forms were read by and explained to participants before interviews. Consent was given before conducting and recording interviews. Signed forms could only be viewed by the researchers, ensuring that names cannot be connected to results or quotes. Participants were made aware of anonymity and authority to withdraw from the research and skip questions at any time. Participants are referred to with a number they were assigned in an encrypted document to which only the researchers have access. In this way, transcripts, results, nor quotes can be traced back to participants.

3. Results

During the interviews, respondents described which factors influence the current practice of applying CDx in the Netherlands (Section 3.1), especially emphasizing: costs and convenience (relative advantage), complexity of application, and compatibility. Furthermore, we asked about the expected impact of IVDR for Dutch laboratories (Section 3.2).

3.1. Factors influencing current practice of applying CDx in the *Netherlands*

3.1.1. Reasons to use in-house versus commercial CDx

Three factors emerged as important and differing in their implications for in-house versus commercial CDx (Table 1): costs and convenience (relative advantage), complexity of application, and compatibility. First, since relevant new biomarkers are regularly identified, all 15 participants acknowledged that laboratories must stay up-to-date to ensure that they can test for all relevant biomarkers. In terms of costs and convenience, it was noted that in-house CDx are often cheaper than commercial CDx and could relatively easily be tailored to the specific laboratory needs and possibilities: *'we have developed a test ourselves, which just costs €3,- instead of €50,- … in that way, we now have the same test for all tumors, which is much more practical'* (Participant 2). Ten participants mentioned that it is more convenient to work with larger diagnostic test-panels (group of tests) that allow them to investigate multiple biomarkers simultaneously, instead of applying multiple single biomarker CDx. Such panels generally are developed and used in-house and are called home-brewed or Lab Developed Tests (LDTs). Furthermore, five participants mentioned that many commercial, dedicated CDx are considered to be of lower quality or miss important biomarkers, meaning that laboratories must buy additional tests.

Second, participants discussed complexity of applying CDx. Since the International Organization for Standardization sets strict requirements on quality and competence (ISO-15189:2012), all Dutch laboratories have qualified employees with necessary knowledge and skills for biomarker analysis using CDx. Therefore, according to all participants, application of CDx is not considered the most complex aspect of using CDx in a diagnostic laboratory. However, specifically the development of in-house CDx is complex for a diagnostic laboratory: *'if you get it commercially, yeah, then it's a bit easier … you don't have to come up with your own primers, you know that the region of that mutation is covered'* (Participant 9). Additionally, according to two participants a potential advantage of commercial CDx is that they are more straightforward to apply, resulting in less time-consuming processes.

A third factor that influences the current practice of CDx application is compatibility (Table 1). Costs and effort are made to adapt to working with new diagnostic tests: *'a new system must be integrated into the laboratory'* (Participant 2). This includes linking diagnostic tests to systems and servers, adapting request forms for clinicians, and collecting material. Furthermore, validation and verification processes must be completed before starting to work with new CDx. For in-house CDx these processes are completed by the laboratory. Commercial tests have been validated by the developer and must be verified by the laboratory before implementation. A participant described that validation processes by pharmaceutical companies are often conducted under ideal circumstances, e.g. with material containing plenty of tumor cells. However, in practice, circumstances are not always ideal. In addition, material can be saved in different ways after biopsies (e.g. freshly frozen, formalin embedded) and different CDx may require differently saved material. Of note, 11 participants explicitly mentioned that it is unfeasible to adapt material collection for each single CDx, due to the many people, departments, and resources involved in this process. Furthermore, processing times may be affected by such different preparation procedures per individual CDx. Due to the adaptations that must be made to work with a new CDx, all fifteen participants mentioned that the implementation of tests in the laboratory environment and diagnostic workflow require more effort. Since in-house CDx can be tailored to fit the needs of the individual laboratory, implementation of in-house CDx takes less effort compared to commercial CDx. Implementation of commercial CDx can take more effort depending on the level of compatibility of the specific CDx.

Table 1. Comparison of in-house and commercial CDx by professionals who apply CDx in academic or general hospitals in the Netherlands.

Factors influencing application	In-house CDx	Commercial CDx
Costs and convenience (relative advantage)	Can be cheaper and tailored to be convenient for the specific diagnostic laboratory practices	Tend to be more expensive and are not always of sufficient quality/ convenience for diagnostic laboratory practice
Complexity of application	Application is not considered complex, but development can be complex	Application is not considered complex, but use of the CDx can be more straightforward than in case of in-house tests
Compatibility	Can be tailored to fit the needs of the individual laboratory and requiring less effort in implementation	Level of compatibility depends on how the diagnostic laboratory currently works, requiring more implementation efforts. However, a commercial test can be tweaked to fit the needs of the individual laboratory

3.1.2. Tweaked CDx

Eight participants mentioned on their own accord that in-house, multi-purpose CDx panels allow laboratories to update regularly, while commercial single biomarker CDx tend to lag in clinical developments after initial marketing. These eight participants also stated that they use in-house CDx. Likewise, and again unprompted, 12 participants mentioned that adaptations can be made for commercial CDx by 'tweaking' tests, meaning that commercial CDx are slightly adapted within the laboratory to better fit their needs. Such tweaks can be in components of the diagnostic test: *'we added certain targets that are not in the original CDx, because they are clinically relevant'* (Participant 6). Moreover, the execution conditions of the CDx can be tweaked: *'incubate a bit longer, or at a different temperature'* (Participant 8). Two participants expressed uncertainty about whether tweaked CDx are legally considered in-house CDx because they are adapted from a commercial CDx, or whether they should remain to be labeled as commercial CDx.

Besides the expressed uncertainty about the status of tweaked CDx, participants interpreted the definition of CDx in the IVDR in various ways. The IVDR defines CDx as: 'devices essential for the safe and effective use of a corresponding medicinal product' (Regulation 2017/746 on in vitro diagnostic medical devices). Seven participants interpret CDx as a specific kit offered by a manufacturer that is closely linked to a specific medicine. Those seven participants who interpret the definition as tests linked to single biomarkers prefer to use the term predictive tests instead of CDx. The other eight participants have a broader interpretation of the definition of CDx: *'I interpret CDx as finding targets for possible therapies'* (Participant 5). Nine participants explained that it is uncommon in the Netherlands for a CDx as a diagnostic test to only measure a single biomarker for the use of one specific medicine. Four participants mentioned that CDx linked to single biomarkers fit the US rather than Dutch way of working.

3.2. Expected impact of IVDR for Dutch laboratories

All participants agree that the IVDR will have an impact on the practice in Dutch diagnostic laboratories. Three participants described that the IVDR may lead to more standardization among laboratories, not only within the Netherlands but throughout Europe. However, many uncertainties in relation to the impact of the IVDR for laboratory activities were expressed as well. Five participants pointed out that the certification of CDx as required by the IVDR is not limited to CDx but also involves other components of the biomarker analysis process: *'it not only includes executing the tests or the panels that you use, but it is also about the software and devices'* (Participant 5). Three participants stated that they expect not to be able to uphold the future IVDR requirement to certify their complete process: *'we just bought two [sequencers] … we don't have a couple million lying around to replace those sequencers that are not depreciated'* [Participant 6]. Therefore, one participant suggested that there should be a longer transition phase, which *'must go very slowly, incorporating depreciation of devices and time for reorganization. Otherwise, it will be a mess'* (Participant 2).

All participants expressed uncertainties about the enforcement of the IVDR: *'I'm not really sure what that new regulation aims for, so I find that difficult'* (Participant 4). Nine participants indicated uncertainty on the enforcement of the IVDR on both European and national level. *'I don't know how strongly the European commission can demand that. And if there will also be some national freedom eventually. I'm afraid it won't work that way.'* (Participant 11). One participant mentioned that this unclarity may be caused by too little discussion between practice and policy on the CDx topic. Six participants mentioned that their laboratory is preparing for the IVDR, by inventorying which CDx they use, and which CDx are expected to become certified under the new IVDR. Three other participants expressed that they will wait for the IVDR to become fully effective in May 2022, as at the stage of interviewing (spring 2021) they are unsure what they should be doing to prepare for it.

Due to the many uncertainties, all participants expressed worries about the impact of the IVDR. One concern that all 15 participants had, is that the IVDR will increase prices of CDx and administrative work: *'it shouldn't become a paper tiger … that's something that worries me'* (Participant 13). Since companies must pay for certification of their CDx, 10 participants expect that those costs will be reflected into increased prices of CDx: *'[pharmaceutical companies] can easily triple the price, or even more. Because I must show that the other one, the cheaper one … is better.'* (Participant 10). Additionally, some companies may discontinue their production of CDx as it is not financially interesting to continue under the IVDR: *'the danger is that the industry at some point says, it generates relatively little so I'm going to stop. You also see that with the medical devices'* (Participant 5). Especially the discontinuity of CDx of small companies for which CDx are not the main source of income is worrisome.

Furthermore, six participants expressed worry that commercial CDx certified under the IVDR do not uphold hospital-specific requirements or quality standards of currently used, often in-house, CDx. This worry is expressed against the background of high-quality standards in diagnostic laboratories in the Netherlands, largely using in-house CDx, as shown by an assessment of the Dutch National Institute for Public Health and the Environment [18]. Participants expressed that certification of CDx under the IVDR will not necessarily improve quality of CDx as compared to (multipurpose, in-house) CDx currently applied in the Netherlands. Additionally, participants worry that pharmaceutical companies will likely only certify their CDx on their own systems. *'if you're going to bake a cake, then it matters that you have a good mix of the ingredients. But whether you put it in an oven of Siemens or Bosch, or whatever, if they keep the right temperature, it will work out fine. And because one has a stamp saying, 'I'm the best according to the Consumer's guide, doesn't mean that the others aren't good'* (Participant 10). Considering that, according to the new IVDR, if laboratories want to use an uncertified CDx or own system that is believed to be of higher quality than a certified (commercial) CDx, they have to show that the in-house uncertified CDx/system is better than the certified CDx/system, eight participants feel that it will become more difficult to use in-house or tweaked CDx.

Another possible impact of the IVDR indicated by participants concerns innovativeness related to CDx. Five participants expressed that the IVDR will decrease flexibility of the individual diagnostic laboratories and the option to tweak CDx to fit their laboratory's individual specific needs. They feel that this may hold them back and the IVDR will be implemented at the expense of innovativeness. *'You want to continuously innovate. You must have the opportunity to do that and make those changes … Its [IVDR] disadvantage is that … innovation is slowed down.'* (Participant 11). Despite all the worries, three participants recognize that the general idea of expected standardization due to the IVDR is intended well. *'The IVDR goes beyond the point … The idea is well intended'* (Participant 2).

We also investigated to what extent academic and general hospitals showed any differences regarding the implications of the IVDR. They generally thought along the same lines regarding the use of CDx and the impact of the IVDR (Supplementary table 2). However, some differences were observed, e.g. academic hospitals had a more distinct worry about the use of in-house and tweaked CDx under the IVDR (six academic, two general hospitals), academic hospitals applied more in-house CDx than the interviewed general hospitals (seven academic, one general hospital), and academic hospitals more strongly articulated worries that commercial CDx certified under the IVDR do not have the same hospital-specific requirements or quality standards of currently used, often in-house CDx (five academic, one general hospital).

4. Discussion

Since the introduction of the IVDR is associated with uncertainties about its impact on hospital practice and with how stakeholders should take the new legislation into account, the aim of our research was to clarify the decision process for using in-house and commercial CDx, as well as expectations about how the IVDR may affect the current practice with respect to CDx. Below we discuss the most important scientific and practical contributions of our investigation.

4.1. Use of CDx and implications of the IVDR

Our study provides a unique perspective on implications of the IVDR from a professional user perspective. Following our investigation, it has become clear that stakeholders who apply CDx in practice in Dutch hospitals currently use in-house and commercial CDx, as well as tweaked versions of commercial CDx. The application of CDx in Dutch hospitals involves applying tests that go beyond testing for only one specific medicine, including whole-genome testing. While the results have provided valuable insights into what influences the choice for different forms of CDx, a key finding is that there is no straightforward answer as to why Dutch hospitals choose to use in-house or commercial CDx. This choice depends on the specific setting of the diagnostic laboratory in which CDx are needed.

Important implications of the IVDR that participants of our study described include worries about the possible unavailability of CDx, especially those of small pharmaceutical companies for which CDx are not the main source of income. Additionally, our participants regard unclarity around so-called 'tweaked CDx' as one of the biggest concerns of diagnostic laboratories. While the IVDR officially only distinguishes between in-house and commercial CDx, many laboratories also use tweaked versions of commercial CDx. It is uncertain if, once a commercial CDx has been tweaked, it is still 'original.' Clarification is needed regarding whether and how tweaked CDx fall into the scope of the IVDR. These implications of the IVDR found in our interview-based investigation for use of CDx in practice are in line with the findings of Lubbers et al. [19] who analyzed actions that laboratories can take to prepare for the IVDR based on close-reading the IVDR legislation texts. The variety of healthcare professionals' interpretations of CDx should lead policymakers to clarify what is expected of hospitals, e.g. by providing guidelines on what changes the IVDR requires of hospitals.

Despite these worries of respondents regarding uncertainty of the IVDR's scope, it should be recognized that the general aim of the IVDR is to reduce uncertainty and risk through standardization of CDx use. Standard setting ensures care provision of equal and sufficient quality, which may lead to improvement of healthcare provision across several countries and locations [20]. In the IVDR CDx are no longer considered as having a low-risk. Therefore, CDx will stop being self-certified by manufacturers. The IVDR classifies CDx as high individual risk or moderate public health risk (class C) and subsequently will require conformity assessment by NBs [21]. Considering this higher risk class for CDx, standardization poses benefits in terms of patient safety and quality of the tests [22]. Participants recognized this possible positive outcome of the IVDR, and Orellana García et al. [23] also found that the IVDR provides the opportunity for more consistent and transparent information on CDx to be provided in the evaluation of IVDs. However, such standardization can also limit innovation in specific, more advanced hospitals or laboratories. Participants, for example, worry that standardization can negatively impact tinkering and tailoring within hospitals to make implementation easier. The possible limitation of innovation due to the IVDR is a serious concern for practice. The use of in-house IVDs is allowed, however, stricter requirements apply than before the introduction of the IVDR with respect to their validation. Article 5 of the IVDR leaves room for innovation in the hospital setting, stating that *'the requirements of this legislation shall not apply to devices manufactured and used only within health institutions established in the Union,'* meaning that in-house IVD and tweaked CDx can still be used. However, this only applies when a total of nine conditions are met. An example of a condition that can be linked directly to worries of our participants, is having to prove that there is no commercial alternative available for the in-house CDx they want to use. Furthermore, raising regulatory barriers might lead to only large pharmaceutical or medical technology companies being able to comply, which results in monopoly power, reduction of available CDx, and raised costs.

In our research, we found that the answers of academic and general hospitals were in general similar with regard to the implications of the IVDR. However, Dutch academic hospitals seem to be more affected by the negative effects of standardization on

innovation, as they tend to apply more in-house CDx than the interviewed general hospitals do. Accordingly, this leads to a more distinct worry about the use of these in-house and tweaked CDx under the IVDR.

Here, we provided a first picture of the practice of applying CDx as well as the possible impact of the IVDR on that practice in a European country. This has not been previously described in literature, despite its relevance due to the shift in CDx-use following the IVDR. A limitation of our research is that we focused on the Netherlands. However, there are indications that the use of in-house or tweaked CDx are prevalent in hospitals in other countries as well, as Vermeersch, van Aelst and Dequeker [24] for instance showed for the use of In vitro Diagnostics (IVDs) in the laboratory of a large university hospital laboratory in Belgium: 47.1% of laboratory tests used by the academic hospital were in-house tests and 10.8% were modified or off-label IVDs. In accordance with our results, a main reason to use in-house tests was lacking certified commercial methods (71.9%). Additionally, Camajova et al. [25] sent a survey to 125 DNA diagnostic laboratories representing 20 EU countries about the use of IVDs for cystic fibrosis. They found that almost half of the respondents (43.6%) changed manufacturer-recommended protocols [25]. The German ad hoc Commission In-Vitro Diagnostics Medical Devices [26] even states that medical laboratories in a wide range of fields rely almost exclusively on in-house test methods, especially for diagnosing rare diseases.

4.2. Need for clarity: guiding transition

Our results show that there is a need for clarity on multiple aspects of the IVDR. To get a first understanding of what is needed to guide the transition toward the IVDR, we organized a validation workshop in the Netherlands. During this workshop preliminary results of this study were shared with Dutch healthcare professionals that apply CDx, representatives of Dutch governmental organizations and policy makers. Attendants were given the opportunity to discuss and respond to the reported results. It was expressed that there is a need for clarity on which roles should be fulfilled by which stakeholders. For example, who will enforce the IVDR and to whom will diagnostic laboratories have to answer and justify the choice to use in-house CDx?

Currently, many stakeholders have explored implications of the IVDR for their organization or operations within their network. They formed working groups and organized workshops around different aspects important for the use of CDx, including legislation, reimbursement, and the development of hospital practice. An overall picture has not emerged, and lessons learnt remain rather siloed. It would therefore be valuable to conduct additional research on this topic aimed at bringing together the various stakeholders' perspectives and activities. This could also involve other stakeholder groups than the currently interviewed group of CDx users in hospital practice, like governmental organizations, policy makers, pharmaceutical/CDx producing companies.

Additionally, the transition that is advanced by the IVDR would be most efficient when facilitated by change agents [27,28]. Such change agents can be groups with insights into practice and connections to policy, who can facilitate and guide the transition [27]. In fact, from the European Commission, several groups, e.g. the Medical Device Coordination Group (MDCG), the Notified Body Operations Group (NBOG), the Competent Authorities for Medical Devices (CAMD), Team-NB of the European Association for Medical devices of Notified Bodies, as well as the EMA, take part in this process. Further, at a national level, the Ministry of Health and National Inspectorate, as well as the Dutch Commission Evaluation Oncological Diagnostics are involved in national implementation of the IVDR. However, despite involvement of different groups, the consequences of the new IVDR still appear unclear to CDx users, and apparently this group is not sufficiently reached as of yet. It seems that there is a gap between policy implementation and practice, as our participants were also unaware of all the different groups that are involved in facilitating the implementation of the IVDR. For a smooth transition into a fully effective IVDR, more attention to the CDx users in this respect is considered advisable.

In light of the complexity of the issue and the lack of certification capacity, on October 14th, 2021 the European Commission proposed a progressive roll-out of the IVDR with an extended transition period for CDx [29]. The reason for the proposed extended transition period is a serious shortage of NB capacity which would cause disruption of the supply of IVDs. The length of the transition period differs per IVD risk class. Higher risk devices (class C or D) such as CDx will have a transition period until May 2025 or 2026. For new IVDs that do not have a NB certificate nor a declaration of conformity as under the Directive 98/79/EC of before May 2022, the IVDR will apply from May 26th, 2022 as planned. The commission also proposed postponing the requirements for in-house devices, which would give everyone more time to prepare and ideally also discuss the previously mentioned unclarities regarding the implementation of the IVDR legislation, as well as understanding of the nine conditions for using in-house IVDs.

5. Conclusion

We studied which factors influence the choice of Dutch hospitals to use in-house or commercial CDx. The decision for in-house or commercial CDx is mainly influenced by costs and convenience (relative advantage), complexity of application, and compatibility. Furthermore, we investigated expectations for how the new IVDR may affect the current practice with respect to CDx. The expected impact of the IVDR on current practice in relation to CDx use remains unclear. Generally, the positive intention of the IVDR is recognized as well as the possible beneficial effects due to the classification of CDx in a higher risk class. However, worries were expressed about the impact related to increases in costs and administrative work, and decreased quality, especially if laboratories want to work with home-brewed and tweaked CDx, optimized to meet local laboratory and clinical requirements. Worries exist that due to the IVDR it may become more difficult to work with in-house and tweaked CDx. Additionally, increased administration could decrease innovativeness, as laboratories will be less inclined to innovate and develop new in-house CDx or tweak commercial CDx.

Author Contributions

All authors contributed to the design of the study. Data collection and analysis was done by the corresponding author. All authors contributed to drafting the article and approve of the final version. All authors agree to be accountable for all aspects of the work.

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