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The use of molecular biomarker tests: an interview study with healthcare providers about a molecular biomarker test for prostate cancer

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Aim: Investigate why healthcare providers are not always willing to use molecular biomarker tests, even though they promise to personalize disease diagnosis and treatment. **Materials & methods:** We interviewed 20 Dutch urological healthcare providers to ascertain why they used or did not use SelectMDx, a biomarker test for prostate cancer. **Results:** Whether and how it was used differed from the developers' expectations, because users and nonusers disagreed about its perceived advantages; the scientific and clinical evidence; the advantages of MRI; and the value of PCA3 testing. Financial issues and the absence of SelectMDx in professional guidelines and hospital care pathways also hampered its use. **Conclusion:** Eliciting users' and nonusers' views is important to better understand how biomarker tests can be embedded in clinical practice.

Lay abstract: Molecular biomarkers are molecules, found in urine or blood, for instance, that help healthcare providers to diagnose a disease and provide a prognosis. This assists their clinical decision-making. However, not all healthcare providers use molecular biomarkers, and we wanted to find out why. We focused on a test for prostate cancer called the SelectMDx test. We interviewed 20 Dutch healthcare providers and found that whether they used the SelectMDx test and how they used it depended on things like their interpretation of the scientific evidence; how they valued other technologies; the financial disadvantages; and the test's absence in professional guidelines. By eliciting users' and nonusers' views, we have gained a better understanding of how biomarker tests can be embedded in clinical practice.

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In the shift from a 'one-size-fits-all' approach in healthcare to a more personalized one, the use of molecular biomarker tests is a key component of tailoring the diagnosis and treatment of a disease to the individual patient [1]. Molecular biomarkers are molecules that provide diagnostic or prognostic information about a disease and can therefore assist healthcare providers in their clinical decision-making [2]. Despite hopes and promises that molecular biomarker tests will improve the quality and efficiency of healthcare while decreasing costs, the use of these tests in clinical practice is still in its early phases, and only a small number of molecular biomarker tests have been widely adopted to the time of writing [1,3]. As research shows, even though there is compelling evidence of the benefits of new technologies, such as these tests, their use in clinical practice can be hampered by a dynamic interplay of factors at the individual level and at the level of the broader, organizational context [4–6]. Healthcare providers might be hesitant about using biomarker tests, for instance, because they do not want to change their professional routines or because they are not fully aware of or lack knowledge about molecular biomarkers [7–9]. Previous studies on a molecular biomarker test for breast cancer, for example, showed that the level of use of this test varied among oncologists [10,11]. Some were concerned about colleagues using the test for groups of patients who were unlikely to benefit or relying too heavily on the test [10]. Others were not confident that the evidence underpinning the test was robust enough [11]. Using molecular biomarker tests is also complicated by organizational factors such as a lack of

financial reimbursement from the government to the healthcare provider for the costs of molecular biomarker tests or clinical practice guidelines that are slow to be updated following the publication of new scientific evidence [1,9,12].

In this study, we focus on a specific molecular biomarker test for prostate cancer: the SelectMDx test, which was put on the market in mid-2016 by MDxHealth, an international company that specializes in producing molecular biomarker tests for urological cancers (www.mdxhealth.com). The SelectMDx test is an exemplary case of a molecular biomarker test that, despite encouraging evidence about its validity and cost-effectiveness [13–17], is difficult to implement evenly across the healthcare setting due to a combination of healthcare providers' individual perceptions and organizational dynamics. At the time of writing, the SelectMDx test is being used in hospitals all over the world. In The Netherlands, it is the most often used gene expression test in the diagnostic trajectory of prostate cancer. However, the value and appropriate use of the SelectMDx test and other novel molecular biomarker tests for prostate cancer is still under discussion [2,18–20]. Moreover, during our conversations with MDxHealth, it transpired that although some urologists are already using the SelectMDx test, others are hesitant about doing so. To the best of our knowledge, no prior research has been published on healthcare providers' opinions of novel molecular biomarker tests for prostate cancer, their motivation for using them and their doubts about them. To fill this knowledge gap, we conducted exploratory interviews with urological healthcare providers, that is, consultant urologists and specialist urological nurses, in The Netherlands to investigate the factors that enable and restrict the use of the SelectMDx test.

Prostate cancer & the SelectMDx test

Prostate cancer stands out from other forms of cancer as it is associated with substantial overdiagnosis and overtreatment [21,22]. This has to do with current screening for prostate cancer using the PSA blood test [2,21]. Increased PSA levels might be an indication of prostate cancer. However, because of the relatively low specificity of the PSA test, a substantial proportion of men with increased PSA levels in their blood undergo further diagnostic procedures unnecessarily, as they do not actually have prostate cancer [21]. These procedures often include prostate biopsies, which have a risk of complications, including bleeding, infection and sepsis, and can cause psychological distress [2]. Moreover, even if prostate cancer is detected following a biopsy, many men do not require treatment, as many forms of prostate cancer are clinically insignificant, that is, they are not life-threatening. Treating these forms increases the risk of complications such as urinary incontinence and impotence and does not improve survival rates [21,22].

Because of the overdiagnosis and overtreatment associated with PSA screening and prostate cancer in general, several technologies have been developed to make a more accurate selection of men who need prostate biopsies and to improve the distinction between men with a clinically significant form of prostate cancer and those with an insignificant form [21,23]. In addition to multi-parametric magnetic resonance imaging and risk calculators [23], novel molecular biomarker tests that use blood or urinary samples have been developed to reduce the overdiagnosis and overtreatment of prostate cancer [2,18–20].

Technologies such as MRI, risk calculators and novel molecular biomarker tests can be used when a man has slightly elevated PSA levels and there are doubts about whether or not to conduct a prostate biopsy. If it turns out that the risk of clinically significant prostate cancer is very low, a prostate biopsy might not be done, and clinical monitoring will be implemented instead. These technologies can also be applied postbiopsy as tools for selecting which patients need another biopsy because there is continuing suspicion after a negative prostate biopsy, i.e. when no prostate cancer was identified following the initial biopsy.

One of these novel molecular biomarker tests is the SelectMDx test, a urine-based test that provides a risk score for the chance of finding clinically significant prostate cancer following a biopsy. This risk score is based on the expression of two mRNA biomarkers (*HOXC6* and *DLX1*) in urine, combined with clinical parameters that include the PSA level, the prostate volume, family history and age [13–15]. The SelectMDx test is aimed at men with slightly elevated PSA levels, in other words, PSA of 4.0–10.0 ng/ml. MDxHealth envisages that urologists use this test prior to biopsy to help them decide which men should have prostate biopsies. The results of the SelectMDx test are presented as two percentages representing the risk that prostate cancer, in general, will be detected following biopsy and the risk that clinically significant prostate cancer will be detected following biopsy. MDxHealth does not provide explicit advice on whether or not biopsy should be considered based on test results, although its intention is that the test is used to avoid any prostate biopsies being performed where there is a very low risk (less than 10%)

of clinically significant prostate cancer. The developers of the SelectMDx test envisaged that a result of 10% or higher indicates that a biopsy may be needed.

Materials & methods

Data collection

To help us approach potential respondents easily, the sales department of the Dutch headquarters of MDxHealth provided us with a list of the contact details of urologists from Dutch hospitals that they had previously contacted. These urologists included both users and nonusers of the SelectMDx test. All of the urologists were approached by the first author, K Wendrich. Twenty two urologists from 22 hospitals declined the request or did not respond.

In the end, 20 urological healthcare providers were interviewed between July 2018 and May 2019: 16 urologists and four specialist nurses, from 13 different hospitals in The Netherlands. Two specialist nurses were interviewed together. From four hospitals two healthcare providers were interviewed, as we wanted to know whether there was variation in how urologists within the same hospital dealt with the SelectMDx test, as healthcare providers have some autonomy in how they shape the diagnostic trajectory.

Four interviews were conducted in person and 15 by telephone; the healthcare providers could choose which option they preferred to fit with their busy schedules. The interviews were audiotaped after the respondents had given verbal permission and ranged from 20 to 70 min, with an average duration of 40 min.

A semi-structured interview protocol was developed as this enabled us to ask follow-up questions and acquire a rich insight into the healthcare providers' perspectives. First, questions were asked about the healthcare providers' use of the SelectMDx test. The interviewees were asked to confirm the following: which patients the SelectMDx test was being used for and the effect of the SelectMDx test results on clinical decision-making. Second, the interview guide, inspired by the themes mentioned in the Introduction section of this paper, gave rise to questions that asked about the conditions that either enabled or constrained the use of the SelectMDx test, on the individual level and in the broader organizational context.

Data analysis

The interviews were transcribed verbatim. The transcripts were uploaded to the qualitative data analysis software ATLAS.ti 8 and subjected to thematic content analysis [24]. An initial deductive coding scheme, which was based on the interview guide, was developed by K Wendrich in discussion with L Krabbenborg. Both authors were familiar with the data. Codes were also inductively derived by K Wendrich from the interview data by iterative reading of the transcripts and discussion with L Krabbenborg. After coding the interview transcripts, K Wendrich gathered the codes into subthemes, meaning that overlapping individual codes were combined into overarching topics (Table 1). A consensus on these subthemes was reached through discussion with L Krabbenborg. Excerpts from the interviews, translated from Dutch by K Wendrich, are used throughout the Results section to illustrate our findings.

Results

All of the hospitals where the healthcare providers who were interviewed worked at at the time of the study had previously been approached by MDxHealth and invited to use the SelectMDx test. However, it was already clear prior to the interviews, based on our conversations with MDxHealth, that it was not common practice in all hospitals to use the test. Among the interview respondents, six urologists from six different hospitals said that they did not use the SelectMDx test (Table 2). Fourteen urological healthcare providers from nine different hospitals used the SelectMDx test. Four of them were specialist nurses and ten were urologists.

In the first part of the Results section, we will present how the SelectMDx test is used in clinical practice, that is, which patients the test is used for and how the test results are used in clinical decision-making. In the second part of the section, we will present the factors that influence the adoption of the SelectMDx test that emerged from the interview data.

Multiple uses of the SelectMDx test

The hospitals used the SelectMDx test in very different ways in their clinical practice. The SelectMDx test has been scientifically tested for use prior to prostate biopsy for all patients with slightly elevated PSA levels of between 4.0 and 10.0 ng/ml and, if the test reveals that the risk of clinically significant prostate cancer being found via biopsy is 10% or above, a biopsy may be carried out [13–15]. However, it turned out that in many hospitals the test was primarily applied postbiopsy and higher cut-off points were used for clinical decision-making regarding biopsies.

Table 1. Themes and subthemes that emerged from the interviews with urological healthcare providers regarding the multiple uses of the SelectMDx test and factors that influenced the use of this test.

Themes	Subthemes
Use of the SelectMDx test	<ul style="list-style-type: none"> – Use prebiopsy – Use postbiopsy – Use combined with MRI – Frequency of use – Hospital policy on test use
Clinical decision-making based on SelectMDx test results	<ul style="list-style-type: none"> – Cut-off points for risk of prostate cancer – Other decision-making factors – Importance of test result in decision-making – Difficulties with interpretation of test results
Factors influencing the use of the SelectMDx test	
Themes	Subthemes
Perceptions of individual healthcare providers	<ul style="list-style-type: none"> – Perceived advantages of the SelectMDx test – Interpretation of the scientific and clinical evidence – The advantages of MRI – The value of the PCA3 test
Broader organizational context	<ul style="list-style-type: none"> – Relatively high costs of the tests – Lack of insurance coverage – Hospital budget for limited number of tests – Absence in professional guidelines – Absence in hospitals' care pathways – Resistance from urologists

Table 2. Overview of the number of urological healthcare providers (urologists and specialist nurses) that were interviewed, including both users and nonusers of the SelectMDx test.

Use of the SelectMDx test	Respondents
No use of the SelectMDx test	6 urologists (HP1–6)
Use of the SelectMDx test	
– Prebiopsy	2 urologists (HP9–10) 2 specialist nurses (HP12–13)
– Prebiopsy in combination with MRI	2 urologists (HP7–8) 1 specialist nurse (HP 11)
– Postbiopsy	6 urologists (HP14–19) 1 specialist nurse (HP20)

Users of the SelectMDx test have been categorized into three groups: prebiopsy, prebiopsy in combination with MRI and postbiopsy. Prebiopsy: using the SelectMDx test prior to biopsy to select patients for prostate biopsy. Postbiopsy: using the SelectMDx test to select patients who will have another biopsy when suspicion of prostate cancer remains after negative biopsy results, in other words, when no prostate cancer has been identified following an initial biopsy.
HP: Healthcare provider.

Use of the test

In three of the hospitals, the SelectMDx test was used prior to prostate biopsy for all patients with slightly elevated PSA levels, which is in line with what the test has been designed to do. One of these hospitals used the test in combination with an MRI scan. In six of the hospitals, the SelectMDx test was primarily used postbiopsy as a tool for selecting patients who needed another biopsy because there was continuing suspicion after negative prostate biopsy, in other words, when no prostate cancer had been identified during initial biopsy. In these cases, the urologists were using the SelectMDx test to confirm that the initial negative biopsies were indeed an indication of the absence of (a clinically significant form of) prostate cancer:

"You have done biopsies and they do not show anything. Then you check the PSA again. It stays high, it goes up. Then you think: should I perform biopsies again? You want to have confirmation that your first biopsies, that did not show cancer, were correct." – HP19

The frequency of postbiopsy use of the SelectMDx test varied between hospitals. Some urologists regularly used the test after negative biopsy whereas others only used it occasionally. Even in hospitals where the SelectMDx test

was used postbiopsy, it was common for not all urologists to use the test and there was no clear hospital policy on the use of the test:

"Some do not use the SelectMDx test at all. And then you see three tests go out of the door on one day. There is such fluctuation. Well, I do not have the idea that they really have a clear policy here." – HP20

In some of the hospitals, tasks that are linked with the SelectMDx test, such as patient counseling, performing the test and data interpretation, were performed by the urologist, whereas in the other hospitals some of these tasks were delegated to the specialist nurse.

Clinical decision-making

It became clear that urologists used different cut-off points regarding the SelectMDx test results when they were making decisions about prostate biopsies. Only urologists from two of the hospitals, which both used the SelectMDx test prior to biopsy, used the 10% cut-off point, which was the aim of the developers of the test.

In the other hospitals, the urologists mentioned higher cut-off points, ranging from 12 to 30% risk of clinically significant prostate cancer. In the three hospitals in which urologists applied the SelectMDx test prior to biopsy, the cut-off points were protocolized, whereas in the other hospitals, these were mostly picked at random by each urologist, as these two excerpts illustrate:

K Wendrich: *"How did you decide on that 20% cut-off point?"*

HP17: *"Guess work. Arbitrary. You have to agree on something. Then you still have 80% chance that you perform a biopsy for nothing, but that is much less than 99%."*

K Wendrich: *"How did you decide on that 15% cut-off point?"*

HP19: *"Well, that is just a feeling. It could just as well have been another value. I don't know."*

It was not only the arbitrary cut-off point that was relevant in urologists' decision-making regarding prostate biopsies. Several urologists explained that clinical decisions surrounding these biopsies were not only influenced by the results of the SelectMDx test but by a variety of factors, including the patient's attitude and desires, age, prostate volume, PSA course and the urologist's intuition. Urologists varied in terms of how much value they placed on the SelectMDx test in their clinical decision-making. Whereas for some urologists the SelectMDx test results were the primary indicator on which they based their decision, others saw the test results as a small piece of the puzzle when they were deciding whether or not to conduct a prostate biopsy. For instance, in the hospital that used the SelectMDx test prebiopsy in combination with MRI, decision-making was primarily based on MRI results. This hospital perceived the SelectMDx test as a safeguard that could capture clinically significant cases of prostate cancer that might have been missed by MRI.

Factors influencing the use of the SelectMDx test

Urological healthcare providers had different attitudes toward the SelectMDx test. Some mainly expressed enthusiasm and curiosity, but others were more skeptical and hesitant. The next sections consider the factors that play a role in the use or nonuse of the SelectMDx test.

Perceptions of individual healthcare providers

Healthcare providers' personal perceptions of the SelectMDx test and disagreements about its advantages and about other related issues were important deciding factors regarding their motivation for using or not using the test. The findings from our interviews highlight four factors that the users and nonusers of the test disagreed about and that affected whether the test was used and, if so, how it was used: the perceived advantages of the SelectMDx test, the scientific and clinical evidence, the advantages of MRI and the value of the *PCA3* test.

Perceived advantages of the SelectMDx test

When users of the SelectMDx test discussed their motivation for using it, they all referred to its perceived advantages. They liked the fact that this test is more specific than the PSA test and provides a high level of certainty about the absence of clinically significant prostate cancer. They also emphasized the user-friendliness of the test, both for the patient and for the healthcare provider. The test has a low level of invasiveness so the patient burden is limited, and it is easy for the healthcare provider to carry out the test:

"It is actually a very accessible test. You touch the prostate, you pee, you send it and then you have the result." – HP9

Another perceived advantage of the SelectMDx test was its potential to reduce unnecessary biopsies. At the time of our study, there was a high biopsy load at many of the hospitals, but a substantial proportion of the biopsies had negative results. As biopsies are unpleasant for the patient, expose him to potential complications and are expensive, there was a desire for technologies that can guide the selection of men for whom biopsy could be useful. One urologist described in detail his experience with a reduced biopsy load since the SelectMDx test had been implemented:

"The biggest group that gets the test can actually go straight back to the general practitioner. [...] And what we see in the group that remains. That we have much more positive biopsies. So less negative. And that also the level of aggressiveness has increased. [...] You just see that you catch more significant tumours. You see that our percentage of positive biopsies increases. And from that I conclude that the people we have sent away. Well, that for most part we were right to send them away." – HP10

Several users also saw value in the SelectMDx test being able to contribute to making a more accurate selection of patients needing a biopsy by distinguishing between clinically significant and insignificant forms of prostate cancer:

"Look, what we do now, is treat more and more people that we actually should not treat. Whereas our focus should be on the people who really need it. And this test could help with that." – HP14

Interpretation of the scientific & clinical evidence

Both users and nonusers of the SelectMDx test had doubts about its added value. Several criticisms were expressed about the current evidence, for instance, that longer follow-ups of study participants or larger sample sizes are needed to illustrate the added value of the test. Another criticism was that the added value of the SelectMDx test, compared with alternative technologies, has not been proven yet:

"It is not that I do not see the added value, but also that it has not been scientifically proven compared with other options. There is scientific evidence, but not for the added value, no. Not compared with MRI and risk stratification." – HP6

Moreover, several urologists believed that the SelectMDx test would be less reliable in clinical practice than has been found in research, as conditions in real life are more variable than in the context of a clinical study:

"We will have to see whether we will also find this 98% [negative predictive value] in the real-life population. It will definitely be somewhere between 90 and 98%. But 98, that would be astonishingly high. I expect that it will be lower." – HP8

The advantages of MRI

Healthcare providers disagreed about whether MRI has advantages over the SelectMDx test. Although we did not explicitly ask respondents to tell us about their experiences with other technologies, all of the healthcare providers, both the users and the nonusers of the SelectMDx test, made comparisons with MRI when discussing their motivation for using, not using or selective use of the SelectMDx test. MRIs and SelectMDx tests share the same diagnostic space and guide urologists when they are deciding whether or not to conduct a prostate biopsy. Users who preferred the SelectMDx test to MRI perceived MRI as more invasive and less accessible than the SelectMDx test:

"Well, because I find that [SelectMDx test] more charming. MRI is quite an invasive examination. People have to go in a noisy tunnel for half an hour. In general, that is not experienced as comfortable. And the people who come for a prostate examination, we already do an internal examination by means of a digital rectal exam. The only addition is that they also have to pee. It is more comfortable, I believe." – HP17

Nonusers believed that an MRI provides more value than the SelectMDx test for roughly the same price so was thought to be more cost effective:

"The MRI scan costs money. The SelectMDx also costs money. What do you think I am going to spend my money on if I have a limited budget? [...] I think that the MRI scan provides me with much more information than

a genetic test. It does not replace anything. The SelectMDx is an extra that does not provide me with clarity. It only indicates: in this group of patients you have a higher chance of finding something. Well, nice. I would rather have an examination that provides me with clarity whether or not there is prostate cancer. That is an MRI – that provides me with clarity." – HP3

Both users and nonusers acknowledged that the reliability of MRI scans is dependent on the quality of the scanning machine and the interpretations of the scans by radiologists. For the urologists who did a SelectMDx test prior to a biopsy but did not combine it with MRI, this was an important reason for preferring the SelectMDx test rather than MRI in the context of their own hospital:

"We do not yet trust the MRI sufficiently. Also today. The scan was handed in as normal, although I had the idea: well, there I see an abnormality that I believe is suspicious. Four of the six biopsies on that side were positive. In that sense I am not yet convinced that only the MRI is better than the MDx test. In our hands. Look, at [name hospital] they have a 3 Tesla MRI scan and a certain expertise. But that expertise cannot be extrapolated one to one to our practice." – HP10

The value of the PCA3 test

The PCA3 test is a urine-based molecular biomarker test that is manufactured by a company called Hologic and was developed prior to the SelectMDx test. Both tests originate from the same Dutch research group. Many of the respondents, both users and nonusers, therefore perceived the PCA3 test as a precursor of the SelectMDx test. Their experiences with the PCA3 test could act as either an enabling or a constraining factor regarding their use of the SelectMDx test.

For some urologists, how they used the PCA3 test explained their selective use of the SelectMDx test. While the SelectMDx test is intended to be used prior to biopsy and has also been clinically tested for this purpose, the PCA3 test is designed for postbiopsy application, meaning that it can be used to investigate further when a urologist is faced with an initial negative biopsy. Several of the urologists who had previously used the PCA3 test said they were therefore also using the SelectMDx test postbiopsy now:

"Look, that PCA3 test. That was just, that is also how it was launched. As a test that you do at the moment that you have negative biopsies and still an elevated PSA. And well, the Select is in fact the successor of that, so we still use it that way." – HP19

At the time of writing, the PCA3 test is barely used in The Netherlands anymore. Some respondents did not use the SelectMDx test partly because of their disappointment with the PCA3 test, as this quote illustrates:

"I think that is also a disadvantage of the SelectMDx. We used to have that PCA3. I know they are completely different tests. But I feel that it is a bit in the same niche. With the PCA3, I do not have the impression that we gained a lot of useful information from it back then." – HP2

Broader organizational context

The broader organizational context, such as financial aspects and clinical guidelines, appeared to be an important constraining condition for the use of the SelectMDx test. In The Netherlands, acts performed by medical specialists are covered by health insurance when they are part of the basic care package ('basispakket'). The content of this basic package is determined by the Dutch government, which is advised on this matter by the Dutch Care Institute ('Zorginstituut'). Decisions on this issue are made in line with whether or not a certain medical act is considered 'effective care', that is, whether it is deemed effective care according to current scientific knowledge and medical practice [25]. At the time of writing, the SelectMDx test is not covered by the Dutch health insurance system. This means that hospitals must pay for this test from their own budgets, so financial trade-offs have to be made by hospital departments. The relatively high cost of the SelectMDx test and the lack of insurance coverage turned out to be barriers to the adoption of the test. Although some nonusers were interested in using the SelectMDx test, they were hesitant because of the high costs:

"First of all, the price is quite high. A PSA test is 8 euros. I thought this test was something like 250 to 350 euros. That is quite a difference, so to say. That is a substantial disadvantage." – HP4

Similarly, some of the urologists who used the SelectMDx test postbiopsy said that they would like to use the test prebiopsy as well, but stated that agreements concerning hospital budgets only allowed for a limited number of SelectMDx tests to be performed. In other words, there was no budget available to test all men prior to biopsy:

"That is a limitation of the financing. We are not yet able to offer the test to everyone you would like to. That is just limited with respect to costs." – HP16

Professional guidelines and hospitals' care pathways were other institutional factors that influenced the adoption of the SelectMDx test. Professional guidelines play an important role in the practices of urological healthcare providers. These guidelines are established by teams of urologists based on clinical and scientific evidence and exist both on a national and a European level. At the time of the interviews, the SelectMDx test was not included in the Dutch guidelines [26], whereas it was included in the European guidelines [27]. The absence of the SelectMDx test in Dutch professional guidelines for urology turned out to be one of the reasons why some of the urologists did not use the test:

"I think the most remarkable [thing] is that it is not integrated in the guidelines. I think that that is a sign that you can apply it broadly and responsibly. That it is widely supported by colleagues. That it has been investigated and scientifically substantiated. And I think that that is the most important." – HP1

This urologist went on to say that once the SelectMDx test is integrated in guidelines, he expects the adoption of the test to increase:

"If you want such a thing to be broadly applied, you have to make sure that it gets included in a guideline. And once it gets included, well, then you will get a very fast application." - HP1

The respondents also discussed hospitals' care pathways, in other words, the organization of care processes for a well-defined group of patients [28]. Care pathways are established by the urological departments of one or more hospitals and provide guidance to individual urologists with regard to clinical workflows. Most hospitals have not yet included the SelectMDx test as part of their care pathway. Although individual urologists can decide to deviate from these care pathways, it is common for hospital departments to reach an agreement first before they allow new technologies to be used in clinical practice:

"We have not yet discussed this as a group and that is why it is not yet accepted policy. As leader of the group I believe that we should have good conversations with one another, reach agreements and act on that." - HP5

According to some urologists, the absence of the SelectMDx test in professional guidelines and hospital care pathways can at least partly be explained by resistance from other urologists. This was described by one urologist, who used the SelectMDx test postbiopsy but who would like to use the test prebiopsy too:

"Very recently we have set up prostate cancer guidelines for our region. Well, it [the SelectMDx test] is not in there. That will just not happen. You just notice: there is so much resistance among colleagues." – HP19

Another urologist explained that care pathways and professional guidelines often lag behind the scientific evidence by a few years, as these guidelines are only periodically reviewed and revised after thorough discussion between urologists, which can take months.

Discussion

Numerous novel molecular biomarker tests are being developed to personalize healthcare. However, such tests are not yet widely used in clinical practice [1,12]. In our study, we focused on Dutch healthcare providers' use or nonuse of the SelectMDx test, a novel molecular biomarker test for prostate cancer, and how it was used. This test is an exemplary case of a biomarker test that faces difficulties during the initial implementation period, despite evidence about its validity and cost-effectiveness [13–17]. We wanted to gain from the interviews a better understanding of the dynamic interplay between the individual perceptions of the healthcare providers and the broader organizational context when the SelectMDx test in The Netherlands was being implemented.

Regarding the individual perceptions of the healthcare providers, it was clear that the perceived added value of the SelectMDx test was important in terms of whether they used the test, and if they did, for what purposes. This is in line with technology adoption theories that are commonly used, such as the Technology Acceptance Model, in which perceived usefulness is one of the main factors that lead to the use of a particular technology [29].

The perceived value of the SelectMDx test was influenced by several factors. One of these factors was how the healthcare providers interpreted the current evidence about the validity of the SelectMDx test. Interestingly, some of the urologists were convinced by that evidence and therefore used the test, but others were waiting for more scientific proof. The healthcare providers, therefore, disagreed about what counts as sufficient evidence. There were similar findings in a study on oncologists' views of a molecular biomarker test for breast cancer [11]. These findings echo the current discussion about what evidence healthcare providers need to convince them to adopt molecular biomarker tests [9,12]. The different interpretations of the scientific and clinical evidence by healthcare providers signal that evidence alone is not a magic bullet that will lead to the acceptance of a new medical technology [30,31].

Healthcare providers' attitudes to other technologies, MRI and the *PCA3* test in particular, influenced their valuation of the SelectMDx test and thus their motivation for using or not using the test. Our findings show that the healthcare providers had mixed experiences with the *PCA3* test, and this influenced their valuation of the SelectMDx test. This is in line with other studies on the adoption of new medical technologies [4,5], which suggest that although previous events do not completely determine technological innovation trajectories, they can influence the route that a new technological innovation is taking [32].

Moreover, it became clear during our study that urological healthcare providers are used to working with visual data, such as MRI scans, and are less used to working with molecular data that provide results via measurements and numbers in relation to the actual molecules, which are invisible to the naked eye (cf. 33). The belief that MRIs are objective and neutral sources of knowledge is dominant in the daily practices of healthcare providers, where medical images are the 'gold standard' in diagnostics [34]. This complicates the implementation of nonvisual diagnostic tools, such as molecular biomarker tests, in clinical practice. In fact, as Joyce [34] shows, the use of visual tools dominates the entire healthcare system, for example, the professional routines and daily practices, and it is therefore more difficult for an individual healthcare provider to deviate from this system because it is so entrenched.

In line with previous literature on the adoption of new medical technologies [4–6], we found that other organizational issues, such as hospital policies and professional guidelines, also enable or constrain the choices that individual healthcare providers can make [35]. Even when an individual urologist is interested in using the SelectMDx test, he or she might be constrained by, for example, a limited hospital budget, a lack of insurance coverage or resistance from colleagues. This shows that implementation strategies should focus on multiple 'levels' [36,37]: they should not only focus on the adoption of a technology by individual healthcare providers but should also explore the extent to which there are opportunities to include new technologies at the institutional level or barriers that prevent this.

It is important to note that these multiple levels influence each other. If most urologists are not convinced of the value of the SelectMDx test, for instance because of a perceived lack of evidence, it will not be included in professional guidelines and hospital care pathways. Additionally, if the cost of the SelectMDx test is not reimbursed by health insurance and the test is not included in professional guidelines, healthcare providers might get the impression that the test is not sufficiently validated, which negatively influences their perceptions of its value. This might result in vicious circles that are difficult to break, which could slow down the adoption of molecular biomarker tests.

A complex and varied picture emerged with regard to the use of the SelectMDx test by some of the healthcare providers. We were able to reveal that the actual use in practice often differed from the envisaged use of the test. First, although the SelectMDx test was designed for use prior to a prostate biopsy for all men with slightly elevated PSA levels, many hospitals applied the test postbiopsy instead where there was a continuing suspicion that prostate cancer was present despite initial negative biopsy. Second, the SelectMDx test has been scientifically and clinically tested based on a cut-off point of 10% risk of clinically significant prostate cancer. Nevertheless, most urologists used higher percentages as cut-off points in clinical decision-making that were based on SelectMDx test results.

This phenomenon, which involves users selectively integrating technologies into their daily practices and selecting which functions of the technology they will use and for which purposes, is already known from previous studies [38,39]. Healthcare providers try to fit new technologies into their practices and routines in a way that is meaningful and useful for them [40]. They compare the new technologies with alternatives and decide whether they will use a particular technology and if so, how they will use it [41]. These emerging use practices can differ from the expectations and intentions of the technology developers, despite the implicit and explicit directions they supply with their products, for instance via user manuals and instructions that are clear from the design of the technology [40].

This is the first qualitative study on the factors that lead to healthcare providers choosing to use or not use novel molecular biomarker tests for prostate cancer in their clinical practice. Although our study has provided a rich insight into the enabling and constraining conditions that affect the use or nonuse of biomarker tests, we would

like to highlight some of the limitations of the study and provide some directions for future research. First, because we focused on a single case study, we cannot generalize our findings statistically [42]. However, our findings are in line with previous studies and can be generalized analytically in relation to the broader context of the study, as we have shown that the factors that can facilitate or hinder the adoption of a technology also play a role in other studies [4–6,10,11] and will probably play a role in the adoption processes relating to other molecular biomarker tests in the future. To uncover similarities in and differences between the adoption dynamics of different molecular biomarker tests, it would be interesting to compare the adoption processes relating to multiple tests in future research.

Second, although we interviewed a variety of urological healthcare providers, we only talked to healthcare providers from 13 hospitals. Therefore, we might not have discovered additional relevant information that would have helped us to gain an even better understanding of the use of the SelectMDx test. Third, to really grasp the adoption dynamics of the SelectMDx test, and that of similar molecular biomarker tests, longitudinal studies are required as they allow the study of the considerations that healthcare providers bear in mind and the actions they take, and those of other actors, over time. We see our current research as a first step that provides building blocks for further research on the enabling and constraining factors that affect the adoption of novel molecular biomarker tests. Fourth, in this study we only focused on healthcare providers, but we acknowledge that there are other important actors that are involved in the adoption process, such as health insurance companies and hospital boards, which might enable or constrain healthcare providers regarding using a new technology. Although examining these actors was beyond the scope of our current research, we recommend that they are considered in future research endeavors so that a more complete understanding of adoption dynamics can be reached. Finally, in this study we only focused on The Netherlands. To take into account the country-specific political, cultural and social context, it would be highly valuable to compare the adoption of the SelectMDx test, or another molecular biomarker test, in multiple countries.

Conclusion

Urological healthcare providers varied in whether and how they used the SelectMDx test, a molecular biomarker test for prostate cancer. This depended on factors such as urological healthcare providers' interpretation of the scientific evidence; how they valued other technologies; the financial disadvantages; and the test's absence in professional guidelines. By eliciting users' and nonusers' views in this exemplary case study, we have gained a better understanding of how biomarker tests can be embedded in clinical practice.

Summary points

- We studied the SelectMDx test, a novel molecular biomarker test for prostate cancer, as an exemplary case of a molecular biomarker test that, despite encouraging evidence about its validity and cost-effectiveness, is difficult to implement evenly across the healthcare setting due to a combination of factors that concern healthcare providers' individual perceptions and organizational dynamics.
- Healthcare providers often used the SelectMDx test in a different way to that envisioned by the developers and also used the test in different ways during clinical decision-making processes.
- Users and nonusers of the SelectMDx test disagreed about the perceived advantages of the test; the scientific and clinical evidence; the advantages of MRI; and the value of the *PCA3* test.
- A lack of financial reimbursement for the cost of the test via the Dutch national health insurance scheme and the absence of the SelectMDx test in professional guidelines and hospital care pathways restricted the adoption of this test in clinical practice.
- Eliciting (non)users' views, which we did in our study, is a valuable step toward understanding how molecular biomarker tests can be embedded in clinical practice.

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Ethical conduct of research

The authors state that for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

- Chong HY, Allotey PA, Chaiyakunapruk N. Current landscape of personalized medicine adoption and implementation in Southeast Asia. *BMC Medical Genom.* 11, 94 (2018).
- **Provides a nice overview of the current state of personalized medicine adoption and implementation.**
- Alford AV, Brito JM, Yadav KK, Yadav SS, Tewari AK, Renzulli J. The use of biomarkers in prostate cancer screening and treatment. *Rev. Urol.* 19(4), 221–234 (2017).
- Bangash H, Kullo IJ. Implementation science to increase adoption of genomic medicine: an urgent need. *J. Pers. Med.* 11, 19 (2021).
- Strohm L, Hehakya C, Ranschaert ER, Boon WPC, Moors EHM. Implementation of artificial intelligence (AI) applications in radiology: hindering and facilitating factors. *Eur. Radiol.* 30, 5525–5532 (2020).
- Greenhalgh T, Wherton J, Papoutsis C *et al.* Beyond adoption: a new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies. *J. Med. Internet. Res.* 19(11), e367 (2017).
- **Provides a thorough and elaborate overview of factors that play a role in the adoption of healthcare technologies.**
- Abrishami P, Boer A, Horstman K. Understanding the adoption dynamics of medical innovations: affordances of the da Vinci robot in the Netherlands. *Soc. Sci. Med.* 117, 125–133 (2014).
- Manolio TA, Chisholm RL, Ozenberger B *et al.* Implementing genomic medicine in the clinic: the future is here. *Genet. Med.* 15(4), 258–267 (2013).
- Delaney SK, Christman MF. Encouraging physician adoption of genetic testing for precision medicine. *Per. Med.* 13(3), 201–204 (2016).
- Pritchard DE, Moeckel F, Villa MS, Housman LT, McCarty CA, McLeod HL. Strategies for integrating personalized medicine into healthcare practice. *Per. Med.* 14(2), 141–152 (2017).
- **Discusses some important considerations for the integration of personalized medicine in clinical practice.**
- Bombard Y, Rozmovits L, Trudeau M, Leigh N, Deal K, Marshall D. The value of personalizing medicine: medical oncologists' views on gene expression profiling in breast cancer treatment. *Oncologist* 20, 351–356 (2015).
- O'Brien MA, Dhesy-Thind S, Charles C, Hammond Mobilio M, Leigh NB, Grunfeld E. Uptake of a 21-gene expression assay in breast cancer practice: views of academic and community-based oncologists. *Curr. Oncol.* 24(2), e138–e145 (2017).
- Pirmohamed M. Acceptance of biomarker-based tests for application in clinical practice: criteria and obstacles. *Trans. Med.* 88(6), 862–866 (2010).
- **Discusses some important barriers for the adoption of molecular biomarker tests in clinical practice.**
- Haese A, Trooskens G, Steyaert S *et al.* Multicenter optimization and validation of a 2-gene mRNA urine test for detection of clinically significant prostate cancer before initial prostate biopsy. *J. Urol.* 202, 256–263 (2019).
- Hendriks RJ, Van der Leest MMG, Dijkstra S *et al.* A urinary biomarker-based risk score correlates with multiparametric MRI for prostate cancer detection. *Prostate* 77, 1401–1407 (2017).
- Van Neste L, Hendriks RJ, Dijkstra S *et al.* Detection of high-grade prostate cancer using a urinary molecular biomarker-based risk score. *Eur. Urol.* 70, 740–748 (2016).
- Govers TM, Hessels D, Vlaeminck-Guillem V *et al.* Cost-effectiveness of SelectMDx for prostate cancer in four European countries: a comparative modeling study. *Prostatic Dis.* 22(1), 101–109 (2018).
- Dijkstra S, Govers TM, Hendriks RJ *et al.* Cost-effectiveness of a new urinary biomarker-based risk score compared to standard of care in prostate cancer diagnostics – a decision analytical model. *BJU Int.* 120(5), 659–665 (2017).
- Filella X, Fernández-Galan E, Fernández Bonifacio R, Foj L. Emerging biomarkers in the diagnosis of prostate cancer. *Pharmacogenom. Per. Med.* 11, 83–94 (2018).
- Kornberg Z, Cooperberg MR, Spratt DE, Feng FY. Genomic biomarkers in prostate cancer. *Transl. Androl. Urol.* 7(3), 459–471 (2018).
- McGrath S, Christidis D, Perera M *et al.* Prostate cancer biomarkers: are we hitting the mark? *Prostate Int.* 4, 130–135 (2016).

21. Gandaglia G, Albers P, Abrahamsson PA *et al*. Structured population-based prostate-specific antigen screening for prostate cancer: The European Association of Urology Position in 2019. *Eur. Urol.* 76(2), 142–150 (2019).
- **Discusses the various technologies that currently exist to improve the diagnostics of prostate cancer.**
22. Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Penson DF, Carter HB. Overdiagnosis and overtreatment of prostate cancer. *Eur. Urol.* 65(6), 1046–1055 (2014).
23. Van Poppel H, Hogenhout R, Albers P *et al*. Early detection of prostate cancer in 2020 and beyond: facts and recommendations for the European Union and the European Commission. *Eur. Urol.* 79(3), 327–329 (2020).
24. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: implications for conducting a qualitative descriptive study. *Nurs. Health Sci.* 15, 398–405 (2013).
25. Zorginstituut Nederland. Medisch Specialistische Zorg (Zvw) (2021).
<http://www.zorginstituutnederland.nl/Verzekerde+zorg/medisch-specialistische-zorg-zvw>
26. Nederlandse Vereniging voor Urologie. Prostaatacarcinoom – Diagnostiek (2014).
<https://richtlijnendatabase.nl/richtlijn/prostaatacarcinoom/diagnostiek.html>
27. Mottet N, Van den Bergh RCN, De Santis M *et al*. EAU Guidelines Prostate Cancer (2019).
<https://uroweb.org/guideline/prostate-cancer/#5>
28. Schrijvers G, Van Hoorn A, Huiskes N. The care pathway: concepts and theories: an introduction. *Int. J. Integr. Care.* 12, e192 (2012).
29. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. *MIS Q* 13(3), 318–340 (1989).
30. Urquhart R, Kendell C, Geldenhuys L *et al*. The role of scientific evidence in decisions to adopt complex innovations in cancer care settings: a multiple case study in Nova Scotia, Canada. *Implement. Sci.* 14, Article Number 14 (2019).
<https://implementationscience.biomedcentral.com/articles/10.1186/s13012-019-0859-5>
31. Turner S, D'Lima D, Hudson E *et al*. Evidence use in decision-making on introducing innovations: a systematic scoping review with stakeholder feedback. *Implement. Sci.* 12, Article number 145 (2017).
<https://implementationscience.biomedcentral.com/articles/10.1186/s13012-017-0669-6>
32. Rycroft RW, Kash DE. Path dependence in innovation of complex technologies. *Technol. Anal. Strateg. Manag.* 14(1), 21–35 (2002).
33. Bell K. Biomarkers, the molecular gaze and the transformation of cancer survivorship. *Biosocieties* 8(2), 124–143 (2013).
34. Joyce KA. Painting by numbers: the development of magnetic resonance imaging and the visual turn in medicine. In: *Magnetic Appeal: MRI and the Myth of Transparency*. Magnetic Appeal: MRI and the Myth of Transparency. Cornell University Press, NY, USA, 24–46 (2008).
35. Krabbenborg L. Dramatic rehearsal on the societal embedding of the lithium chip. In: *Ethics on the Laboratory Floor*. Van der Burg S, Swierstra T (Eds). Palgrave Macmillan, London, UK, 168–187 (2013).
36. Geels FW. From sectoral systems of innovation to sociotechnical systems: insights about dynamics and change from sociology and institutional theory. *Res. Policy* 33(6–7), 897–920 (2004).
37. Moors EM, Rip A, Wiskerke H. The dynamics of innovation: a multilevel co-evolutionary perspective. In: *Seeds of Transition. Essays on Novelty Production, Niches and Regimes in Agriculture*. Wiskerke JSC, Van der Ploeg JD (Eds). Van Gorcum, Assen, The Netherlands, 31–56 (2004).
38. Oudshoorn N. Diagnosis at a distance: the invisible work of patients and healthcare professionals in cardiac telemonitoring technology. *Soc. Health Ill.* 30(2), 272–288 (2008).
39. Piras EM, Miele F. Clinical self-tracking and monitoring technologies: negotiations in the ICT-mediated patient–provider relationship. *Health Soc. Rev.* 26(1), 38–53 (2017).
40. Pols J, Willems D. Innovation and evaluation: taming and unleashing telecare technology. *Soc. of Health Illn.* 33(3), 484–498 (2011).
- **Acknowledges the complex use practices that emerge when new technologies are introduced in healthcare.**
41. Garud R, Ahlstrom D. Technology assessment: a socio-cognitive perspective. *J. Eng. Technol. Manag.* 14(1), 25–48 (1997).
42. Yin RK. Case study methods. In: *APA Handbook of Research Methods in Psychology: Vol. 2 Research Designs*. Cooper H (Ed.). American Psychological Association, MA, USA, 141–155 (2012).