Evaluation of New Tests and Interventions for Prostate Cancer Management- A Systematic Review

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TABLE OF CONTENTS

ABSTRACT ..... **IV**

RÉSUMÉ ..... **VI**

ACKNOWLEDGEMENTS ..... **IX**

CONTRIBUTION OF AUTHORS ..... **X**

LIST OF ABBREVIATIONS ..... **XII**

LIST OF TABLES ..... **XIII**

LIST OF FIGURES ..... **XIV**

1. INTRODUCTION **1**

2. LITERATURE REVIEW **3**

2.1. PROSTATE CANCER ANATOMY AND PATHOLOGY 3
2.2. EPIDEMIOLOGY OF PROSTATE CANCER 3
2.3. CURRENT ASSESSMENT TOOLS IN PROSTATE CANCER MANAGEMENT AND DIAGNOSIS 4
2.3.1. Prostate-specific antigen (PSA) 5
2.3.2. Digital Rectal Exam (DRE) 5
2.3.3. Biopsy, Gleason score, and Staging 6
2.4. RECENT CLINICAL GUIDELINES AND CONFUSION ASSOCIATING PCa SCREENING 7
2.5. POSSIBLE IMPACT OF UPDATED GUIDELINES ON CLINICAL PRACTICE 9
2.6. ACTIVE SURVEILLANCE (AS) –AN ALTERNATIVE TO RADICAL TREATMENT IN LOW RISK PATIENTS 10
2.7. RISK STRATIFICATION AND ACTIVE TREATMENT BY RISK GROUP 11
2.8. LOCALIZED PROSTATE CANCER 13
2.8.1. Radical Prostatectomy (RP) 13
2.8.2. Radiation Therapy 15
2.9. ADVANCED PROSTATE CANCER 16
2.10. COSTS OF DIAGNOSIS AND TREATMENT OF PROSTATE CANCER 18
2.11. PERSONALIZED MEDICINE ERA: NEW INTERVENTIONS IN PROSTATE CANCER 19
2.11.1. Progensa PCA3 assay 19
2.11.2. 4Kscore Prostate Cancer Test 20
2.11.3. ConfirmMDx 20
2.11.4. OncotypeDX 21
2.11.5. Prolaris 21
2.11.6. Magnetic Resonance Imaging (MRI) 22
2.11.7. Prostate Health Index (PHI) 23
2.11.8. ProMark 23
2.11.9. Prostarix 24
2.11.10. Prostate core mitomic test (PCMT) 24
2.11.11. Decipher 24
2.11.12. ProstaVysion 25
2.11.13. NaDIA ProsVue 25

3. OBJECTIVE **26**

4. METHODOLOGY **27**

4.1. STUDY DESIGN 27
4.2. LITERATURE SEARCH 27
4.3. TYPES OF STUDIES AND DATA EXTRACTION 28
4.4. QUALITY ASSESSMENT 30
4.5. TYPES OF INTERVENTIONS 30
4.6. STUDY POPULATION 36
4.7. DATA SYNTHESIS 38
4.8. OUTCOMES 38

5. RESULTS **40**

5.1. THE MANUSCRIPT 40
5.2. CONTRIBUTING AUTHORS *40*

6. DISCUSSION **80**

6.1. OVERVIEW 80
6.2. STUDY LIMITATIONS 82
6.3. IMPLEMENTATION OF OUR FINDINGS AND FUTURE DIRECTIONS 83

7. CONCLUSION **85**

REFERENCES **86**

APPENDIX **97**

Abstract

Introduction: In Canada, it is estimated that prostate cancer (PCa) will account for 21% of all new cancer cases in 2016. Inaccurate risk classification and the burden of unnecessary biopsies are a challenge due to the limited ability of current risk assessment tools and modalities in distinguishing indolent from aggressive disease. There is a need for evidence-based interventions that could improve stratification accuracy, and allow a decrease in overtreatment and overdiagnosis. Many new promising tools that could reduce the uncertainties accompanying treatment decision are now studied in PCa.

Objective: This systematic review assesses and identifies new developed tests and interventions with highest evidence of clinical utility, that might be adopted in clinical practice, throughout the PCa management: before initial and repeat biopsy, after positive or negative biopsy, and post radical treatment.

Methods: The Cochrane, Embase, Medline, and Web of Science databases were searched for studies of clinical utility evidence. The outcomes of interest were: a measure of the percentage of altered decision-making, decrease in number of unnecessary biopsies, decrease or increase in treatment intensity, and risk reclassification after test utilization.

Results: The search yielded 2,940 articles after duplicate removal, of which 46 met the inclusion criteria. We found clinical utility evidence on Prostate Health Index (PHI), 4Kscore,

Magnetic resonance imaging (MRI), Oncotype, Decipher, Prolaris, ConfirmMDx, Progensa PCA3, NadiaProsVue, and Promark. On the other hand, none was identified on Prostarix, Prostavysion, Prostate core mitomic test (PCMT), and Mi-Prostate Score (MiPs). The interventions demonstrated their clinical utility in terms of change in treatment recommendations, decrease/increase in interventional treatment, decrease in biopsy, and risk reclassification. Many of these interventions demonstrated to be good tools for pre-treatment and post-treatment risk stratification, in addition to elucidating aggressive versus indolent disease and enhancing an improved treatment allocation. At diagnosis after a positive biopsy, use of ProMark, Oncotype, Prolaris and MRI guide the use of active surveillance. The use of NaDIA ProsVue, Decipher, and Prolaris post-prostatectomy, aids in the decision of adding adjuvant therapy. Prior initial and repeat biopsies, PHI, 4Kscore, and MRI; and prior repeat biopsies ConfirmMDx, PHI, Progensa, 4Kscore, and MRI - improve prediction of biopsy outcome allowing a decrease in unnecessary biopsies.

Conclusion: Several tests might improve treatment decision-making for PCa patients. This review suggests that implementation of these tests in clinical practice could assist in the achievement of personalized treatment of PCa. Further clinical utility and economic studies are warranted to provide further guidance, knowing that this systematic review could provide evidence that allow accelerated use of such tests in the near future.

Résumé

Introduction : Au Canada, on estime que le cancer de la prostate (CaP) représentera 21% des nouveaux cas de cancer en 2016. La classification inexacte des niveaux de risques et le fardeau des biopsies inutiles sont un défi en raison de la capacité limitée des outils et des modalités actuels d'évaluation des risques de distinguer un cancer agressif d'un cancer indolent. Il existe ainsi un besoin d'interventions fondées sur des données probantes qui pourraient améliorer la précision de la stratification et permettre une diminution du taux de sur-traitement et sur-diagnostic. Plusieurs nouveaux outils qui pourraient diminuer les incertitudes qui accompagnent la décision de traitement sont maintenant étudiés dans le CaP.

Objectif: Cette revue systématique évalue les nouveaux tests et interventions et identifie ceux ayant le plus de preuves d'utilité clinique, qui pourraient donc être adoptés en pratique clinique tout au long de la prise en charge de la maladie du CaP: avant une biopsie initiale, avant une biopsie répétée, après une biopsie positive ou négative et après un traitement radical.

Méthodes: Les bases de données Cochrane, Embase, Medline et Web of Science ont été recherchées pour trouver des études sur les preuves d'utilité clinique. Les issues cliniques d'intérêt étaient: une mesure du pourcentage de l'altération de la prise de décision du traitement choisi, une diminution du nombre de biopsies inutiles, une diminution ou une augmentation de l'intensité du traitement et la reclassification du niveau de risque après

l'utilisation des tests.

Résultats: La recherche a répertoriée 2940 articles après la suppression des doublons, dont 46 satisfaisaient aux critères d'inclusion. Nous avons trouvé des preuves d'utilité clinique sur les tests Prostate Health Index (PHI), score 4K, imagerie par résonance magnétique (IRM), Oncotype, Decipher, Prolaris, ConfirmMDx, Progensa PCA3, NaDIA ProsVue et ProMark.

D'autre part, aucune preuve d'utilité clinique n'a été identifiée pour les tests Prostarix, ProstaVysion, Prostate Core Mitomic Test (PCMT) et Mi-Prostate score (MiPs).

Les premières interventions ont démontré leur utilité clinique en termes d'altération de recommandations de traitement, diminution/augmentation du traitement interventionnel, diminution du taux de biopsie inutiles et reclassification des niveaux de risques. Beaucoup de ces interventions pourront être de bons outils pour la stratification pré et post-traitement, en plus de différencier les maladies agressives des maladies indolentes et d'améliorer l'allocation du traitement. Au diagnostic du CaP après une biopsie positive, l'utilisation de ProMark, Oncotype, Prolaris et l'IRM guident l'utilisation de la surveillance active. Suivent une prostatectomie, l'utilisation de NadiaProsVue, Decipher et Prolaris contribuent à la prise de décision d'ajouter un traitement adjuvant un traitement adjuvant ou non. Dans le cas précédant une biopsie initiale ou répétée, PHI score 4K et IRM ; Et les cas précédents une biopsie répétée, ConfirmMDx, PHI, Progensa, 4Kscore et IRM - améliorent la prédiction des résultats de la biopsie permettant une diminution du nombre de biopsies inutiles.

Conclusion: Plusieurs tests pourraient aider à améliorer la prise de décision de traitement pour

les patients atteints de CaP. Cette revue systématique suggère que la mise en œuvre de ces tests dans la pratique clinique pourrait aider à la réalisation du traitement personnalisé du CaP. D'autres études d'utilité clinique et économique sont requises pour fournir de l'information supplémentaire, sachant que cette revue systématique pourrait fournir des preuves qui permettraient une utilisation accélérée de ces tests dans un avenir proche.

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List of abbreviations:

PSA	Prostate Specific Antigen
PCa	Prostate cancer
APC	Adenomatous polyposis coli
CCP	Cell cycle progression
BCR	Biochemical recurrence
PTEN	Phosphatase and tensin homolog
TRUS	Trans-rectal ultrasound
FDA	Food and drug administration
GS	Gleason score
DRE	Digital rectal exam
HGPIN	High-grade prostatic intraepithelial neoplasia
RP	Radical prostatectomy
ASAP	Atypical small acinar proliferation
PHI	Prostate Health Index
MRI	Magnetic resonance imaging
MiPS	Mi-Prostate Score
PHI	Prostate Health Index
PCMT	Prostate Core Mitomic Test

List of tables

Tables

Table 1. *Guidelines on Prostate cancer screening* *8*

Table 2. *Risk Stratification at diagnosis and management options* *12*

Table 3. *Inclusion and exclusion criteria for studies eligibility* *29*

Table 4. *Summary on Group 1 and 3 interventions* *31*

Table 5. *Summary on Group 2 and 4 interventions* *33*

Manuscript

Table 1. *Inclusion and exclusion criteria for studies eligibility* *68*

Table 2. *Summary on the interventions* *68*

Table 3. *Characteristics of studies on interventions included in the systematic review* *71*

Table 4. *Quality of publications for each intervention* *77*

Appendix

Table 5. *Medline Search Strategy* *97*

Table 6. *Data extraction sheet* *100*

Table 7. *Quality appraisal tool* *104*

List of figures

Figure 1. *Diagram of interventions grouped according to different stages of PCa*..... *36*

Manuscript

Figure 1. *Diagram of interventions grouped according to different stages of PCa*..... *77*

Figure 2. *Study flow Chart* *78*

Figure 3. *Retrieved articles after full text assessment*..... *79*

1. Introduction

Prostate cancer (PCa) is the second most frequent male malignancy worldwide (1). In Canada, it is estimated that prostate cancer (PCa) will account for 21% of all new cancer cases in 2016 (2). Canadian statistics estimated that in 2017 21,300 men will be diagnosed with PCa, and 4,100 will die from the disease (3). Likewise, in the US approximately 220,800 men are diagnosed with PCa and 27,000 men die from the disease per year (4).

Unlike when diagnosed at later stages, early detection of prostate cancer results in high cure rates, better outcomes, and lower costs (5, 6). Currently detection and clinical staging depend on digital rectal exam (DRE), serum prostate specific antigen test (PSA), Gleason score and T staging (7, 8). However, these assessment tools lack the ability of accurate stratification of PCa patients, leading to over-diagnosis and overtreatment (9). Although PSA screening was associated with declining disease specific mortality (10, 11), PSA use increased PCa incidence, leading to treatment of clinically insignificant tumours that could be alternatively not treated (11, 12). Other than PSA lack of specificity, clinicians are facing other major concerns. Biopsy under sampling is an important issue, mainly because it might lead to underestimation of the disease (13). Upgrading and downgrading Gleason score post prostatectomy (14, 15) is a clear reflection of biopsy sampling error (16), which will cause overtreatment of some cases and underestimation of others.

While some patients need immediate treatment, up to 60 % of diagnosed PCa patients by current practice can be safely managed by active surveillance (17). Thus, significant efforts have

been recruited to find new tests and interventions that are able to differentiate between indolent and aggressive cancer, to achieve better treatment decision.

Many new tests have demonstrated clinical utility and benefits in prostate cancer management. These tests are applied in four decision points: in screening, after positive biopsy, after negative biopsy and after radical treatment. To spare an indolent prostate cancer patient from an unnecessary biopsy after an elevated PSA, interventions as Prostate Health Index (PHI), 4Kscore, Magnetic resonance imaging (MRI), and Prostarix could be used for screening (18-24). Furthermore, Prolaris, Decipher, OncotypeDX, ProstaVysion, MRI, Mi-Prostate Score (MiPS), and ProMark are other interventions that could be used after prostate cancer diagnosis to distinguish aggressive cancers that need treatment from non-aggressive that could be safely observed such (13, 24-30). Another group of interventions that could help overcome false positive screening and sampling error are used after a negative biopsy to identify candidates for a repeat biopsy, such as Progensa PCA3, 4Kscore, PHI, MRI, Prostate Core Mitomic Test (PCMT), and ConfirmMDx (24, 31-36). Finally, after radical treatment, tests have been developed to assess if additional treatment is necessary depending on pathologic findings like Decipher, Nadia ProsVue, ProMark, and Prolaris (24, 37-43).

Unquestionably, we need to consider some of these interventions due to their potential role in improving risk stratification and outcomes prognostication. Unfortunately, in clinical practice most of these interventions are not used, mainly because we lack enough evidence on their clinical benefit, utility, and cost-effectiveness evidence. Many analytical validity and clinical

validity studies are published in literature; however, not many clinical utility studies are found, which actually reflect the interventions' usefulness in clinical practice.

The objective of this systematic review is to assess the clinical utility of new marketed tests for use in PCa management before initial and repeat biopsy (or after negative biopsy), after positive biopsy, and post-prostatectomy.

2. LITERATURE REVIEW

2.1 Prostate cancer anatomy and pathology

The prostate is a walnut sized exocrine gland present just under the bladder, in front of the rectum (44). While the testicles are responsible for sperm production, the prostate produces the fluid that provides the sperm with nourishment and protection (45, 46) . During orgasm, the prostate contracts producing the fluid into the urethra, that exits the penis while carrying the sperms, which are kept in the testicles.

While some tissue abnormalities that occur in the prostate are non-cancerous (such as benign prostatic hyperplasia), others are cancerous. Most cancers occur in the peripheral zone of the prostate. The alteration in prostatic tissue leads to PSA infiltration into blood, thus used as an indicator for prostate cancer.

2.2 Epidemiology of Prostate Cancer

As the male population grows older, the incidence of prostate cancer increases. Worldwide, more than one million patients are diagnosed, and over 300,000 patients die due to this disease every year (47). Prostate cancer mortality rates and incidence vary between countries, and constitute a huge burden worldwide. Canadian statistics show that one out of eight men can be diagnosed with prostate cancer during their lifetime (48). In 2016, reports estimates that prostate cancer will account for 21% of all new cancers in Canada (2). It is also expected that the number of new cases will triple to 76 379 in 2021 as compared to year 2009 (49). PCa is the third leading cause of death in men (50, 51).

This raised the interest of studying the economic burden of prostate cancer. Stokes et al used a model to estimate costs per patient from diagnosis until death (52). Lifetime costs per-patient were estimated to be $110,520 (95% CI 110,324-110,739) (52). Prostate-cancer-related costs varied between $26,078 and $39,182 based on patient's diagnosed stage. The lifetime prostate cancer costs approximated $4.0 billion in 2008 for incident cases ≥ 65 years old (52). In the early phase of the disease, costs in the first 12 months after diagnosis are approximately $12,000 per patient, while in high risk group direct costs might reach up to $83,418 per patient (5). Treatment and monitoring of PCa place a large burden on the health care system.

2.3 Current assessment tools used in prostate cancer management and diagnosis

The traditional diagnosis of Prostate cancer (PCa) is based on 12-core sampling by TRUS-guided biopsy after an abnormal DRE and elevated PSA. However, many challenges are encountered with conventional diagnosis tools.

2.3.1 Prostate specific antigen (PSA)

PSA is a protein produced by prostate tissues, and is elevated in several prostate conditions including PCa. Since 1986, this test is FDA approved to be used for prostate cancer monitoring. And since its introduction in Canada in the late 1980s, the incidence of PCa increased rapidly (53), mainly due to the extensive use of PSA testing as a screening method in the diagnosis of PCa. Although this allowed early detection of prostate cancer, PSA use led to over-diagnosis and overtreatment. This is due to the low specificity of PSA, knowing that this test is organ specific and not cancer specific. PSA cannot distinguish between aggressive and indolent disease, and is not directly linked to disease grade and stage. Although we are detecting PCa at an early stage, PSA also leads to diagnosing and treating insignificant cancer that could have been managed by active surveillance (AS) (54). An indolent disease has a low potential of progression, and thus treating it is now considered a major concern (9). Disease-specific-survival ranges between 97% and 100% for patients with indolent disease treated with conservative treatment (55), still radical treatment is given to insignificant PCa. Although PSA testing decreases mortality, PSA screening is accompanied with a high number needed to treat (NNT). In the European Randomized study of Screening for Prostate Cancer (ERSPC) trial, the NNT for each cancer death avoided was 48 (12). This was further assured by several studies that emphasized the need to control overtreatment (56, 57).

2.3.2 Digital rectal exam (DRE)

Digital rectal exam is an examination that consists of palpating the prostate by introducing a lubricated gloved-finger into the rectum. Abnormalities can be detected by this procedure; however, the tumour can be located away from rectal wall, thus missed (58).

2.3.3 Biopsy, Gleason Score, and Staging

Biopsy and radical prostatectomy (RP) tissue are assessed for aggressiveness and extent of spread. To evaluate aggressiveness and differentiation pathologists use Gleason score grading. Gleason score is a score that reflects the degree of differentiation and extent of growth by tumour cells after examining prostate tissue under a microscope. The score ranges between 1 and 5, and two grades are given for each tumour for the most dominant and second most common pattern of cancer. The score is obtained by summing the most dominant cell pattern and the second most prevalent pattern. The higher the Gleason score is, the worse the prognosis (59, 60). Also, to assess the extent of tumour spreading, the followed staging classification is the TNM (Tumour, Node, and Metastasis) system from the American Joint Committee on Cancer (AJCC) system. TNM is used to evaluate the extent of tumour growth within and outside prostate.

Biopsy is usually done after an elevated PSA and a suspicious DRE; however, the false negative rate of a biopsy is prominent. Many regions of prostate are miss-sampled leading to under-diagnosis (14). Due to sampling errors, 66% of patients diagnosed with PCa and treated have indolent disease that could only be on AS (61). This suggests that in addition to the biopsy cost

and the economic burden of overtreatment, patients will be suffering from biopsy associated-complications, such as bleeding, urinary retention, and infection (62, 63). Treating a nonlife-threatening disease with invasive treatment is also accompanied with treatment associated-side effects that could highly impact patients' lives (57, 64, 65). The main side effects of primary therapies are described later in the thesis at the treatment section.

2.4 Recent Clinical Guidelines and Confusion Associating PCa Screening

The incidence of PCa diagnosis markedly increased after adopting PSA as a screening method (66). This peak in PCa incidence is due to the overdiagnosis of insignificant disease (67-70), thus raising concerns on the diagnostic accuracy of PSA. Although mortality decreased in some countries with high screening, it also decreased in others who do not widely screen (66). Two important studies further raised the controversy, and could be used to evaluate PSA screening. The first study, the Prostate, Lung, Colorectal and Ovary (PLCO) trial, which is designed to explain the effect of screening on PCa death (71), showed that after 7 years of follow-up there was no reduction in mortality in the screened group. On the other hand, the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that after 13 years of follow up, the risk of PCa death declined by 21% after screening (rate ratio, 0.79; p=0.001) (70). However, since prostate cancer is a long-term disease, studying mortality after 7 to 10 years will probably show different results when compared to longer follow-up. This could explain the difference in results between PLCO trial and ERSPC study, where patients were followed for 7 and 13 years, respectively. After 7 years of follow-up, the risk of PCa death might not be precisely detected.

Despite of the decrease in mortality, confusion concerning PSA screening remains unresolved, since it is leading to overdiagnosis and overtreatment (72). Currently, patients with insignificant, unthreatening disease are treated aggressively. This further enhances the debate on PSA benefits and harms, and whether its use is justifiable. Overdiagnosis is associated with high costs, since latent disease is treated knowing that this disease would not have been diagnosed in an absence of screening. Screening is not able to differentiate between diseases that need treatment and those that do not; hence clinicians end up giving curative treatment to most diagnosed patients. Overdiagnosis ranged from 25% to 84% of screened cancers (72-74), and is accompanied with significant costs and side-effects (75).

In an attempt to reduce over detection and overtreatment associated with PSA screening, many guidelines were updated to try to resolve the controversy associated with prostate cancer screening (76). However, the variation between these guidelines created more controversy and confusion. Contemporary guidelines are presented in the following table:

Table 1: Guidelines on Prostate Cancer screening

Guideline	Recommendations
The Canadian Task Force on Preventive Health Care (2014) (67)	• For men aged less than 55 years, it is recommended not to screen for prostate cancer with PSA. (Strong recommendation; low quality evidence) • For men aged 55–69 years, it is recommended not to screen for prostate cancer with PSA. (Weak recommendation; moderate quality evidence) • For men 70 years of age and older, it is recommended not to screen for prostate cancer with PSA (Strong recommendation; low quality evidence)

Canadian Urological Association (2011)(8)	• PSA screening recommended: For men aged 50-70 with average risk and life expectancy of at least 10 years /for men aged 40 years at high risk
United States Preventive Services Task Force (USPSTF) (2012) (77)	• Routine PSA screening is not recommended • Recommendations are being revised (78)
American Urological Association (2013) (79)	• Men aged less than 55 are not recommended to routinely screen, and those aged between 55 and 69 should discuss with their physicians
European Association of Urology (2013) (80)	• Routine screening is not recommended • Discussion should take place with physicians (In favor for opportunistic screening)

2.5 Possible Impact of Updated Guidelines on Clinical Practice

Since guidelines conflict concerning PSA screening, studies attempt to understand effect of guidelines' new recommendations on patients' and physicians' attitudes about screening. Fleshner et al, demonstrated a 3-10 percentage points decrease in PSA screening rates, accompanied by a decrease in biopsy rates (81). After the USPSTF elucidated on the harms of PSA screening, many conducted studies demonstrated a decrease in screening rates. Jemal et al, reported a drop from 37.8% to 30.8% in 2010 and 2013 (82). Similarly, this was seen in Li et al, where a decrease from 31.8% to 24.2% was demonstrated in 2008 and 2013, respectively (83). Furthermore, this uncertainty led to further testing, rescreening, and more concerns about PCa assessment. Perez et al for instance (84), noted that patients received significantly more PCA3 and repeat PSA testing. PCA3 test calculates the ratio between Prostate cancer antigen

gene (PCA3) and PSA mRNA found in urine samples post DRE, and is used guide treatment decisions (85, 86). After the USPSTF statement, PCA3 increased by 16% ($P<0.01$) and repeat PSA testing by 10% ($P=0.02$). This is further assured by Moul et al (87), who expected a rise in physician consultations and further testing. Thus the uncertainty concerning PSA screening resulted in clinicians' employment of more testing, hence even more costs.

2.6 Active Surveillance (AS) – An Alternative to Radical Treatment (RT) in Low Risk Patients

Treatment options vary from active surveillance (AS), to radical prostatectomy (RP), to radiation therapy (RT). The treatment decision depends on several factors that are mainly related to patient's age, Gleason score, stage of disease, and life expectancy. Watchful waiting (WW) is often confused with AS, however those two interventions are different. WW allows monitoring of the disease, but involves less testing and systematic check-ups than AS. Lately, AS replaced WW because it allows better control and monitoring of the tumor. When compared to WW, AS extends life of a prostate cancer patient more than WW (88). Life time risk of prostate cancer-specific death is higher when WW is used instead of AS (88).

Men with insignificant disease might be diagnosed with cancer when screened; however, this cancer will not affect their survival (89). Clinically insignificant prostate cancer is an organ confined, low grade, and low volume cancer that will not likely progress to aggressive disease (90). Those patients should be put under active surveillance, in which they are followed and monitored without treatment. They will be assessed effectively and most likely die from other

causes (91, 92). AS candidates are actively monitored with an intention to start curative treatment if disease progresses.

Many studies reported that using AS will not negatively affect survival or disease curability in men with low-grade, low-volume disease, who have little or no metastatic potential (93-95). Interventional treatment did not show additional survival benefit over observation (93, 96). In addition to the fact that AS is a safe option (97, 98), it will avoid men from suffering many treatment related-side effects, including urinary, sexual, and bowel dysfunction (54, 99-103). Today, AS is considered an important alternative to radical treatment in low risk patients, and a solution for overtreatment. Yet, some patients might experience some psychological distress while living with cancer, and thus affecting their quality of life.

2.7 Risk Stratification and Active Treatment by Risk Group

Other than AS, there are a variety of treatment options, and deciding which treatment depends on many factors. In addition to grade, stage, and PSA levels; other elements such as age and family history are taken into account. Many contemporary stratification systems are found to classify the patients and give treatment accordingly. Although those systems are similar, some differences exist. Introduced in 1998, D'Amico stratification system divides prostate cancer patients into three groups (104). Low risk group that include patients with T1- T2a, and PSA ≤ 10 ng/ml, and Gleason score ≤ 6 that is obtained by summing the most dominant cell pattern and the second most prevalent pattern. Patients with T2b stage, and/or PSA 10-20 ng/ml,

and/or Gleason score 7 are identified as Intermediate. While, high risk group is defined as ≥T2c, PSA ≥ 20 ng/ml or Gleason score 8-10 (104). Other systems are also present, such as National Comprehensive Cancer Network (NCCN), National Institute for Health and Clinical Excellence (NICE), American Urological Association (AUA), and the European Association of Urology (EAU). The AUA and EAU agree with D'Amico classification, while the NCCN added very low-risk group to its classification (105, 106). Risk stratification is an important aspect in clinical decision, and based on those systems, prostate cancer is managed.

For instance according to NCCN guideline which is commonly used worldwide, men are classified into (i) very low risk, (ii) low risk, (iii) intermediate risk, or (iv) high risk, to identify optimal treatment. Staging, treatment possibilities, and life-expectancy are presented in Table2.

Table 2: Risk stratification at diagnosis and management options (107)

Risk Group	Management options
Very low	Life expectancy 10 or ≥ 20 years (i) Active surveillance (ii) Radical prostatectomy ± pelvic lymph node dissection (iii) External beam radiation therapy/ brachytherapy
Low	Life expectancy ≥ 10 years (i) Active surveillance (ii) Radical prostatectomy ± pelvic lymph node dissection (iii) External beam radiation therapy/ brachytherapy
Intermediate	Life expectancy ≥ 10 years (i) Radical prostatectomy ± pelvic lymph node dissection (ii) External radiation therapy ± androgen deprivation therapy (ADT) (4-6 months) ± brachytherapy (iii) Brachytherapy alone
High	(i) External beam radiation therapy + androgen deprivation therapy (2-3 years) (ii) External beam radiation therapy + brachytherapy ± androgen deprivation therapy (2-3 years) (iii) Radical prostatectomy + pelvic lymph node dissection

Very high	(i) External beam radiation therapy + androgen deprivation therapy (2-3 years) (ii) External beam radiation therapy + brachytherapy ± androgen deprivation therapy (2-3 years) (iii) Radical prostatectomy + pelvic lymph node dissection (iv) Androgen deprivation therapy (ADT) when cure is not possible

2.8 Localized Prostate Cancer

Cancer not affecting any other organ nor spreading outside the prostate is called localized prostate cancer. Patients with localized prostate cancer can have a localized tumour with a low potential of malignancy, or a curable cancer that could be treated by one treatment modality, or a high risk cancer that has a high likelihood of recurrence. The proportion of men with localized prostate cancer is increasing. In 2010, 90% of patients diagnosed with prostate cancer had localized disease (108). Radiation therapy, radical prostatectomy, and active surveillance are all reasonable treatment options. One study reported that radiation therapy and prostatectomy were used in 76% of patients diagnosed with localized prostate cancer (108). In Canada for instance, the number of radical prostatectomies increased from 3 per 100,000 in 1980/81, to 71 per 100,000 in 1998/99 (109).

2.8.1 Radical Prostatectomy (RP)

This is the actual removal of the prostate in a surgical procedure. Usually, the seminal vesicles and vas deferens are also removed. RP is used in patients with clinically localized cancer who are not contraindicated to surgery (80). Risk stratification and staging exclude men who will

not be disease-free post-RP. Thus, any assumption of lymph node metastases, systematic metastases, or seminal vesicle invasions will raise questions on whether RP would be an appropriate treatment decision. Usually at the time of RP, lymphadenectomy is used to decide whether to proceed or switch to other treatment plans. The majority of patients doing RP are under 70 years with life expectancies exceeding 10 years (110). If performed at early stages, RP provides the patient with a long-term control of cancer.

A study conducted to analyse the effect of RP on the survival of prostate cancer patients showed that RP was associated with significantly longer mean survival time when compared to non-interventional treatment (111). Similarly, this was demonstrated in several other studies that assured the excellent survival outcomes that accompany RP (112, 113). The 10 year survival rate post RP ranged between 96% and 97.6%, in several studies (112, 114, 115). The 5 and 10-year biochemical progression-free survival estimates were 80% and 68%, respectively (112).

Many long-term complications arise after RP including erectile dysfunction (ED) and urinary incontinence. The most common complication is ED that occurs after damaging the erectile nerves during surgery. Although there is a nerve-sparing technique, nothing is assured especially if it is a large volume tumour. Haahr et al (116) stated that RP caused ED in 67.9% of the patients. Another important complication is incontinence, and its rates range between 5% and 31% (110).

2.8.2 Radiation Therapy

Radiation therapy allows the gradual and cumulative destruction of cancerous tissue. With an intention to cure prostate cancer, radiation is used when tumour is confined to the prostate. Radiation could be given through two approaches: the external beam radiation therapy (EBRT) and brachytherapy. When using EBRT, thin radiation beams are directed to the prostate, and it is usually administered every day, 5 days a week (79). On the other hand brachytherapy or Seed Implant Therapy involves introducing small radioactive pellets into the prostate(117). Brachytherapy will cause a temporary prostate swelling, and the seeds remain radioactive for a limited period of time. Choosing between EBRT and brachytherapy usually depends on cancer aggressiveness. For instance brachytherapy alone is not used in higher grade cancer, thus PSA should be < 10 ng/ml, stage should be T1 or T2 , and Gleason score should not be above 6 (3+3) (118).

Many studies compared radiation to other treatments; for instance, Boorjian et al compared radiation to RP. It included 1,238 patients undergoing radical prostatectomy and 609 patients undergoing EBRT. Results showed that there was no significant difference in 10-year cancer-specific survival rates or in distant metastasis for patients receiving either treatment (119). Another study also comparing radiation therapy to RP demonstrated better biochemical-failure free survival with radiation after 3 years of follow up (86.8% vs. 69.8%; p=0.001) (120).

Fatigue, cutaneous reactions in the pubic area, frequent need to urinate, blood in urine, diarrhea, rectal bleeding are side effects that may accompany EBRT. Most of the side effects

gradually disappear over a year (121, 122). However EBRT is also associated with long term complications, such as, cystitis, urinary incontinence, hematuria urethral strictures, and permanent erectile dysfunction (65, 123, 124). Above 40 % of patients who have EBRT could have erectile dysfunction (125, 126). Brachytherapy is also associated with side effects such as, increased frequency of urination, nocturia, and sexual dysfunction(127).

Furthermore, many articles studied outcomes for patients using hormone therapy with radiation therapy. A Scandinavian randomised phase III trial showed that combining radiation to hormone therapy yielded improved survival rates, thus recommending this combination as a new standard in locally advanced or high-risk local prostate cancer (128). Similarly, this was demonstrated in another trial, overall survival improved significantly at 7 years (74% vs 66%, p=0.033). Thus, for men with locally advanced disease, combined EBRT and hormone therapy is recommended.

2.9 Advanced Prostate cancer

Hormonal therapy or Androgen deprivation therapy (ADT) is the mainstay treatment in advanced cases (129). This treatment option aims to limit cancer progression, control symptoms, and extend survival (130). Hormone therapy prevents the testicles from producing testosterone, since testosterone enhances prostate cancer growth. This is achieved by two ways: either by Orchiectomy (surgical castration) or by Luteinizing hormone releasing hormone (LH-RH) analog therapy (chemical castration).

Orchiectomy is the permanent removal of the testicles, thus causing shrinkage of prostate cancer. Although it is considered a simple procedure, not all men accept the change in physical appearance.

On the other hand, chemical castration is an option. LH-RH analogs over stimulate the pituitary gland until it stops producing LH, and thus an inhibition of testosterone production. Leuprolide, Goserelin, Buserelin, and Triptorelin are all examples of LH-RH analogs. They are given as regular injections that could last few months and up to life time. Current evidence favors long-term ADT over short term ADT. A study randomizing 970 men to six months (short-term) verses 3 years (long term) of same hormonal treatment demonstrated the inferiority of short-term ADT concerning survival. A higher prostate cancer specific mortality was reported after 6 months of ADT relative to 3 years (4.7% vs 3.2%, corresponding to HR 1.71, p=0.002) (131). However, ADT is associated with toxicities. Treatment-related- complications such as hot flashes, loss of sexual drive, fatigue, mood swings, loss of bone and muscle mass could affect patients' quality of life (53).

The majority of men respond to treatment; yet the resistance to castration occurs, and thus those patients are considered castration-resistant. Despite taken treatment, PSA rises, disease worsens, or metastasis appears. Docetaxel, Mitoxantrone, Cabazitaxel, are chemotherapies studied in resistant and metastatic cancers (132-134). In addition to that, abiraterone and enzalutamide are two new hormonal agents effective in castration resistant disease.

Abiraterone, is an androgen synthesis inhibitor, and enzalutamide is a second generation antiandrogen that could be used prior or post docetaxel (135, 136).

In advanced PCa, multiple agents could be used as supportive treatment, such as bone-targeted therapies. Until 2012, Zoledronic acid was the main bisphosphonate used due to its important role in preventing bone complications (137). Another drug that proved to be superior to zolendronic acid is denosumab. This agent is a monoclonal antibody that not only prevents skeletal side effects , but also delays bone metastasis (138, 139). This was approved for public reimbursement in 2012 in Quebec and elsewhere in Canada.

2.10 Costs of diagnosis and treatment of prostate cancer

Studies are showing that patient's risk group influences total costs, knowing that high risk groups accrue the maximum costs (140). For instance, it is estimated that the total life-time costs per patient increased from $18,503 at 5 years to $28,032 and $39,143 at 10 and 15 years, respectively. Sanyal et al (5) further detailed the total cost per patient according to risk group stratification. The study demonstrated a total cost per patient at 5 years ranging from $12,814, to $17,944, and $33,559 for low, intermediate, and high risk, respectively. This was also analysed at 10 and 15 years, where it reached $17,265, $46,090, and $83,418 at 15 years for low, intermediate, and high risk, respectively (5). Furthermore, in that study costs were more detailed. For instance, for high risk group patients, the cost per patient for RP, IMRT+ADT and IMRT+ADT+BT reached $74,702, $85,206, and $86,566, respectively at 15 years (5).

2.11 Personalized Medicine Era : New Interventions in Prostate cancer

To overcome PSA lack of specificity, under-sampling of performed biopsy, and overtreatment, new tests and interventions are assessed today as alternative methods to achieve better prognosis, facilitate treatment decisions, detect aggressive cancer, and improve risk stratification. The clinical utility and effectiveness of these new interventions are studied in prostate cancer treatment, diagnosis, and screening. Some interventions are developed for screening in order to reduce the number of unnecessary (negative) biopsies in patients with elevated PSA levels, such as MRI, Prostate Health Index, 4Kscore, and Prostarix. Others are used in patients who previously had a positive biopsy, to distinguish aggressive cancers that need treatment from those who do not, such as OncotypeDX, Decipher, MRI, Prolaris, Prostavysion, ProMark, and MiPs tests. In addition, to allow the identification of patients in whom a repeated biopsy is needed, ConfirmMDx, Progensa, 4Kscore, PHI, MRI, and Prostate Core Mitomic are developed to be used in patients post a negative biopsy. Finally, to assess if additional treatment is necessary depending on pathologic findings, some tests were studied post-radical treatment, such as Decipher, ProMark, Prolaris, and Nadia ProsVue.

Hence, employing these new interventions that could help differentiate aggressive from indolent cancer, would provide guidance on treatment decisions; thus avoiding overtreatment and allowing earlier treatment of possibly metastatic cancer. Available interventions are discussed below to give an overview of what could be implemented in clinical practice.

2.11.1 Progensa PCA3 assay

Progensa is a test that calculates the ratio between Prostate cancer antigen gene (PCA3) and PSA mRNA found in urine samples post DRE. PCA3 score increases the probability of a positive biopsy, since cancer tissues over-express PCA3 (85). Progensa is a valuable predictor of insignificant cancer and low volume disease (86, 141). A low PCA3 score predicts a low PCa volume, thus helping clinicians find an insignificant disease that could avoid treatment (86). In many studies, this FDA approved test showed a good correlation with biopsy outcome, thus guiding a repeat biopsy decision (142-147). Many studies noted that PCA3 outperformed PSA, and is superior in detecting early PCa (141, 148, 149) especially after demonstrating a 3-5% accuracy gain (85).

2.11.2 4Kscore Prostate Cancer Test

A 4K test is a widely evaluated blood test measuring a panel of kallikrein markers: total PSA, free PSA, intact PSA, and human kallikrein 2 (KLK2). Many published studies indicate 4Kscore's ability to detect insignificant cancer and predict metastatic disease when compared to PSA alone (150). The test demonstrated its capability of predicting the occurrence of metastatic and aggressive disease (35, 151-158), thus enhancing PCa detection. By eliminating an important number of unnecessary biopsies, 4kscore benefits are also reflected in decreased health care expenses (159).

2.11.3 ConfirmMDx

This intervention is a biopsy based test that measures methylation levels of three genes (160). ConfirmMDx effectively predicts repeat biopsy outcome with a negative predictive value (NPV) of 88-90% (32). A reduced rate of repeated biopsies would result from the use of ConfirmMDx

(161), since it is an independent predictor of PCa capable of distinguishing disease free patients from those that are more likely to have the disease (162). This quantitative assay can confirm based on methylation ratios of GSTP1, APC and RASSF1 genes whether there is cancer surrounding noncancerous tissues or not, taking into consideration that needle biopsy can miss cancer. Thus, confirming that a negative biopsy truly indicates the absence of cancer, in addition to identifying high-risk patients (32, 163). Thus, even if a microscope biopsy sample appears normal, using this assay will allow finding patients at risk of false negative results.

2.11.4 OncotypeDX

This is another genomic test that is considered a significant predictor of grade and stage of prostate cancer. It can be used after a positive biopsy on tissue sample as little as 1 mm of prostate tumour (24, 164). Based on prostate biopsy, the genomic prostate score (GPS) predicts recurrence and adverse pathology post –RP (13). This score ranges between 0 and 100, knowing that high scores indicate aggressive disease. Due to its ability to discriminate high grade from low-grade cancer, OncotypeDx could be used to guide treatment decisions (165, 166). Every 20 point increase in GPS is accompanied by approximately a two fold increase in risk of have high-grade disease (13). This test enables clinicians to re-stratify patients, and thus detecting candidates for immediate treatment (163).

2.11.5 Prolaris

This is a genomic test that measures cell cycle progression (CCP) signature consisting of 46 genes to predict disease mortality and progression. This tissue based test measures directly

tumour growth since it reflects proliferation. It could be used after a positive biopsy to identify active surveillance candidates and post radical prostatectomy providing risk of adverse pathology (167). Several validation studies demonstrated this test's ability to predict biochemical recurrence (BCR), metastasis, and prostate cancer specific mortality (43, 167-169). The incidence of death increases when CCP score is above 2 (168). Freeland et al, showed that the hazard of BCR increases by two folds approximately with every unit increase in CCP score (170). Many studies assessed reclassification by Prolaris, and others noted the ability of this prognostic test to change therapy (43, 171-175). For instance, Crawford et al (171) showed that Prolaris altered 64.9% of the treatment recommendations, 37.2% had a reduction of interventional treatment and 23.4% had an increase. Notably, radical prostatectomy and radiation decreased by 49.5% and 29.6% respectively. CCP is a good prognosticator of PCa, and including it in current prediction models could help avoid many long-term complications that accompany unnecessary treatment (176).

2.11.6 Magnetic resonance imaging (MRI)

After the emergence of MRI-targeted biopsy, and its ability to accurately target suspicious lesions, studies are suggesting MRI use in screening and diagnosis due to its potential role in detecting aggressive cancer. Thus, MRI helps to achieve more targeted treatment. Studies on MRI showed high specificity and sensitivity in predicting post-operative pathology (177), in addition to high detection rates (178, 179). In one study including patients after initial biopsy, MRI use upgraded Gleason score of 20% of patients (180). Another study noted that using MRI prior RP improved significantly prediction of tumour of Gleason score ≥ 4 (181). Hence, MRI

demonstrated an important role in reclassification and staging (182, 183), which would enable a physician to directly monitor the disease and identify a high-grade disease that really needs treatment (184).

2.11.7 Prostate Health Index (PHI)

PHI test combines the measurement of PSA, free PSA, and pro PSA (p2PSA). This test enables better cancer detection since its levels are correlated to malignancy. The usefulness of PHI was investigated in several other studies (185, 186). Lazzeri, et al. (187), which prospectively evaluated 646 patients who were subjected to initial biopsy, showed that the PHI cut-off of 27.6 would allow avoiding 15.5% biopsies while missing 9.8%. The same group of authors (188) also reported a 16.5% reduction in biopsies if using a cut-off of 25.5, while missing 8.5%. Thus, better specificity in cancer detection is achieved when using PHI along PSA (189).

2.11.8 ProMark

ProMark is a biopsy based prognostic test detecting 8 protein biopsy markers to predict both aggressiveness and outcome in PCa patients (190). The test was developed in a study of 381 patient biopsies matched with prostatectomy tissues, then validated in another part of the same study consisting of 256 men to distinguish between favourable and non-favourable pathology at RP (191). Results showed that frequency of favourable pathology decreases with increasing ProMark scores. Furthermore, the cost-effectiveness of this assay was studied, showing that using the 8–protein assay would cause a gain of 0.04 more QALY, accompanied with $700 less in costs (192).

2.11.9 Prostarix

Performed on urine post DRE exam, Prostarix measures the concentrations of four amino acids, knowing that metabolic abnormalities associate with malignancy. This test predicts the likelihood of having a positive biopsy in men with elevated PSA and normal DRE. No validation studies were found on this test.

2.11.10 Prostate core mitomic test (PCMT)

The Prostate core mitomic test (PCMT) is a quantitative assay measuring mitochondrial DNA deletions, thus allowing clinicians to differentiate between aggressive and indolent disease. These deletions are very common in PCa (193). Even when used on normal biopsy specimen adjacent to malignant biopsies, this test can predict cancer. This test helps clinicians decide whether a repeat biopsy is indicated. PCMT predicts outcome of repeat biopsy with a negative predictive value of 91% (34). Additional validation studies are needed for this test.

2.11.11 Decipher

Decipher or Genomic classifier (GC) is a genomic test which uses the expression of 22 RNA markers (coding and noncoding) to predict metastasis and prostate cancer-specific mortality, outperforming currently used assessment tools. Moreover, it allows risk stratification of PCa patients post radical prostatectomy (RP) and guides the treatment decision for adjuvant therapy (38, 194-197). Decipher is a good predictor of metastasis, knowing that for every 10% increase in score, the HR for metastasis is 1.26 ($p<0.01$) (198). Furthermore, lower scores are

associated with better survival rates (38). Many studies also explain the effect of decipher on decision making and risk classification (37, 197, 199). For instance, one study reported that treatment was de-intensified to observation for 40% of patients who were recommended for adjuvant radiation therapy, and was intensified for 13% of patient recommended for observation (199). Likewise, Ross et al (197), showed that decipher reclassified 71%, 52% and 19% of patients in CAPRA-S low-, intermediate- and high-risk groups, respectively. This test was validated in several studies that include RP treated PCa patients.

2.11.12 ProstaVysion

This is a tissue based genomic tests that measures ERG gene fusion/translocation and loss of PTEN suppressor gene. It gives an overview on cancer aggressiveness and risk of metastasis. Although we can find lots of literature discussing the link between these genes and cancer, no validation studies were published on this assay.

2.11.13 NaDIA ProsVue

This blood based test, predicts risk of clinical recurrence post-RP. It measures the rate of total PSA change over a period of time by detecting extremely low concentrations of PSA from 3 blood samples taken after RP (200). NaDIA helps identify patients with low risk of recurrence post RP (40, 200). It is seen as a cost-effective method if used in patients of intermediate risk CAPRA, to relieve the ambiguity accompanying treatment decisions (201).

3. OBJECTIVES

The primary objective of this systematic review is to assess and identify new developed tests and interventions with highest evidence of clinical utility, that might be adopted in clinical practice, throughout the PCa management: before initial and repeat biopsy (or after negative biopsy), after positive biopsy, and post radical treatment. Thus our specific objectives are:

1. To determine the clinical utility of MRI, PHI, 4K, and Prostarix tests aiming at improving the detection and diagnosis of prostate cancer in male patients with suspicion of having prostate cancer (PCa) in whom screening is indicated (men > 50 years or > 45 years with PCa family history or African Americans; without previous prostate cancer treatment or previous biopsy, with PSA 2-10 ng/ml or suspicious digital rectal exam (DRE)).
2. To determine the clinical utility of OncotypeDx, Decipher, Prolaris, Prostavysion, ProMark, MRI, and MiPs tests aiming at improving the diagnosis and treatment of prostate cancer in male patients with prostate cancer (PCa) to guide treatment choice and decision after a positive biopsy (men with previous positive biopsy)
3. To determine the clinical utility of ConfirmMdx, MRI, Progensa, 4K, PHI, and Prostate Core Mitomic tests aiming at improving the diagnosis and treatment of prostate cancer in male patients with suspicion of having PCa (elevated PSA, suspicious DRE), and previous initial or more negative biopsies or an indeterminate biopsy result by guiding repeat biopsy decision.
4. To determine the clinical utility of Decipher, Prolaris, ProMark, and Nadia ProsVue tests aiming at guiding post-operative treatment decisions in men at risk for recurrence or

PCSM (men with adverse post RP pathology, pT3, rising PSA or positive surgical margins) in whom treatment amelioration/ addition is suggested.

4. METHODOLOGY

4.1 Study design

We conducted a systematic review. Hence, we assessed all research studies related to the usefulness of new tests and interventions in prostate cancer management. A protocol was established and followed for each phase of the systematic review.

4.2 Literature Search

The bibliographic databases Cochrane, Embase, Medline, and Web of Science were systematically searched by an experienced librarian at McGill University. All search strategies were peer-reviewed by a second experienced librarian at the same institution. The search strategy included vocabulary and text built around the research question according to PICO (patient, intervention, comparators, outcomes) framework. The search was conducted on November 22, 2016 and updated on February 24, 2017 to identify studies on clinical utility of the new tests in prostate cancer. The appropriate strategy was employed to perform the study using selected MeSH terms and keywords. The Medline search strategy (see Appendix I) was adapted for Cochrane, Embase, and Web of Science.

All published studies written in English or French were considered. The search was not restricted by year of publication to include all articles about the issue of concern. After

screening reference lists of the included articles retrieved by our database search, we were able to have additional articles we found eligible. Search terms included “prostate cancer” , “Prostatic Neoplasms”, “4KScore”,“ Progensa” ,“PCMT”, “ConfirmMDx” ,“Decipher”, “Nadia ProsVue”, “Prostarix”, “Oncotype”, “ProMark”, “MRI”, “MiPS”, “Prolaris”, “Prostate health index”, “ProstaVysion”, as well as acronyms or other terms for these words. Duplicates were identified and excluded using EndNote’s Author/Title/Year duplicate checker, followed by a manual verification. Truncation and wild cards were used to avoid missing any article that might include tests of interest. We included all possible study types that could include clinical utility evidence.

4.3 Types of studies and Data extraction

In our systematic review, we included articles that have clinical utility evidence. Clinical utility studies assess the ability of the test to affect patient outcomes and treatment decisions. The best way to demonstrate the clinical utility of a test is by showing its ability of decreasing PCa specific mortality (PCSM) or metastasis. Other important outcomes are overtreatment and over-diagnosis in contemporary management of prostate cancer, and showing how testing affects them would be essential. However, since prostate cancer is a long-term disease, present studies might not have the ability to demonstrate these outcomes. Thus, clinical utility evidence concerning prostate cancer will logically focus on short-term outcomes such as change in treatment decision or patient stratification or the amount of decrease in interventional treatment. These outcomes will clarify the ability of each test to change treatment decision at each phase of the disease.

After duplicate removal, two reviewers screened independently all the titles and abstracts as a first step to exclude all irrelevant studies as part of step 1 of the systematic review. The screening procedure then continued as part of step 2; however, full texts were now assessed for relevancy by using predetermined eligibility criteria presented in Table 1.

Table 3: Inclusion and exclusion criteria for studies eligibility

Inclusion Criteria	Exclusion Criteria
• Any article related to PCa treatment, screening, diagnosis	• Conference abstracts
• Any article related to test of interest	• Unrelated and Untraceable articles
• Any article with clinical utility evidence	• Animal or in vitro studies
	• Commentaries, Letters, and editorials
	• Review papers and case reports
	• Articles with no clinical utility evidence (not including our outcomes of interest)
	• Studies in languages other than English and French

The studies included had clinical utility evidence. Clinical utility studies included tests that demonstrate: a measure of the percent of altered clinical decision making after addition of the tests (how many patients had a change in treatment), a measure of patients' reclassification into risk groups, a quantification of the decrease/increase of interventional treatment after employing these tests, or an evaluation of the number of unnecessary prostate biopsies and number of missed PCa diagnosis (before initial biopsy and after a negative biopsy). Long-term outcomes such as the effect of test use on morbidity and mortality were included if available. Any study that does not tackle one of these issues was excluded. The reviewers assessing the

studies were initially blinded to each other's results. Each reviewer worked on the collected database on his own, and at each step discussion occurred. At step 3, data extraction of the eligible full text articles that were included in the systematic review occurred using a prepared Data Extraction Sheet (Appendix II). Each reviewer completed this stage independently, and then results were discussed afterwards to solve any disagreement.

4.4 Quality Assessment

Eligible studies were assessed for quality using a modified version of the scale developed in Rector et al (Appendix III). The modified checklist is composed of 17 questions evaluating study design, methodology, intervention, bias risk, and outcomes (202, 203).

An ordinal scale was used to give values for each question, 0 if ''not clear'' or ''not a relevant item'' or "not good quality", 1 for ''good quality'', 2 for ''excellent quality''. This scoring procedure was done by two reviewers independently, and a discussion was carried out at the end. Based on the overall score, the studies were categorized as excellent quality if scoring >75%; good quality if scoring between 50% and 75%; and poor quality if scoring <50% (202).

4.5 Types of interventions

The interventions are grouped into 4 groups based on what is published in the literature and by manufacturers' websites (Table 2 and 3).

1. Group 1: MRI, PHI, 4K, Prostarix
2. Group 2: OncotypeDx, Decipher, Prolaris, Prostavysion, ProMark, MRI, and MiPs
3. Group 3: ConfirmMdx, MRI, Progensa, 4K, PHI, and Prostate Core Mitomic

4. Group 4: Decipher, Prolaris, ProMark, and Nadia ProsVue

Table 4: Summary on Group 1 and 3 interventions

Intervention	Type of intervention/ markers measured	About the intervention	Indication	Group
Prostate Health Index (PHI) Beckman Coulter	Blood based immunoassay PSA, freePSA, p2PSA	-The phi score is a continuous measure. -Categorizes patients into: 0–20.9 (low risk); 21–39.9 (moderate risk); and >=40 (high risk). - Estimates of the risk of cancer being detected at biopsy are: 8.7% for men with a phi score in the low-risk category, 20.6% for men in the moderate-risk category and 43.8% for men in the high-risk category.	-used if PSA between 2-10ng/ ml (4-10ng/ml FDA) + negative DRE+ age more or = to 50 (FDA approved for this indication) -After a negative biopsy and continuous suspicion -Not for patients receiving 5-α-reductase inhibitors medication	1 /3
4Kscore Prostate Cancer Test OPKO Health, Inc.	Blood based immunoassay 4 kallikrein markers: Total PSA , free PSA, intact PSA, hK2	-4Kscore>7.5% → predicted probabilities of 2.5, 5.6, 9.9, 16.4% of distant metastasis in 5, 10, 15, 20 years respectively. -4Kscore< or =7.5% → predicted probabilities of 0, 0.2, 1, 1.8% of distant metastasis in 5, 10, 15, 20 years respectively. - Gives probability of finding high grade PCa (GS > =7) on biopsy	-Men with an abnormal PSA or DRE or clinical suspicion -Patients who have had a prior negative biopsy and want to do repeat biopsy - Not to patients who received 5-α-reductase inhibitors medication in past 6 months	1/3
Prostarix Metabolon Inc.	Urine based 4 metabolites: sarcosine alanine glycine glutamate	-Prostarix-PLUS Risk Score: Prostarix + PSA + TRUS-determined prostate volume -Score (1-100) = predicted likelihood of having 5 year recurrence	-Men with an abnormal PSA or DRE or clinical suspicion -No validation studies	1
MRI	Magnetic resonance imaging (imaging of lesions)	-To decide who to biopsy, re-biopsy , treat - Identify men with insignificant disease and are ideal for AS -Early detection of PCa -Patients diagnosed with cancer→ who need treatment, adjuvant , dose (PCa staging)	-Men with no previous biopsy, with a previous negative biopsy, after positive biopsy	1/ 2/3

		-Improving accuracy of biopsies		
ConfirmMDx MDx Health	Biopsy tissue based genomic test Monitors the methylation states of APC, GSTP1 and RASSF1 genes	-Negative result: avoid repeat biopsy and monitor with routine screening -Positive: suspicious areas marked as positive providing repeat biopsy guidance on prostate map	- Prior negative or high-grade prostatic intraepithelial neoplasia (HGPIN) biopsy result (12-core biopsy within 24 months)	3
Progensa PCA3 Assay Gene-Probe Inc	urine-based biomarker assay : Post DRE first urine catch PSA+ PCA3 mRNAs	-The PCA3 is a ratio of the PCA3 mRNA copies/ml to PSA mRNA copies/ml multiplied by 1000 -Predicts the likelihood of positive biopsy -Recommended threshold score: 25, with values 25 and higher suggesting the presence of cancer	-Patients 50 or older with a negative diagnosis of prostate cancer on analysis of the biopsy sample (one or more previous biopsies) and elevated serum PSA+ and a repeat biopsy is recommended (FDA approved) -Not for patients who are taking medications known to affect serum PSA levels	3
Prostate core mitomic test Mitomics	Tissue based genomic test mtDNA deletions	-PCMT negative outcome: Patient is currently at a low risk of undiagnosed prostate cancer. -PCMT positive outcome: Patient is at a high risk of undiagnosed prostate cancer.	- Patients who have had a prior negative biopsy and show PSA > 4.0 ng/ml, PSADT < 3 months PSAV > 0.4 ng/ml/year or Irregular DRE, Family history African American Life expectancy > 10 years - Patients who have had a prior indeterminate biopsy (ASAP, HGPIN, Atypia)	3

Group1: Screening (before initial biopsy): Decide who to biopsy
Group3: Tests after negative (or indeterminate) biopsy: To decide when to re-biopsy
Abbreviations: Atypical small acinar proliferation (ASAP), High-grade prostatic intraepithelial neoplasia (HGPIN), Prostate-specific antigen(PSA), Digital rectal exam (DRE), Gleason score (GS), Food and drug administration (FDA), Transrectal ultrasound (TRUS), biochemical recurrence (BCR), cell cycle progression (CCP), Prostate cancer (PCa), mitochondrial (mtDNA), Adenomatous polyposis coli (APC), glutathione S-transferase (GSTP1) , Ras Association Domain Family Member 1 (RASSF1), PSA Doubling time (PSADT), PSA velocity (PSAV).

Table 5: Summary on Group 2 and 4 interventions

Intervention	Type of intervention/ markers measured	About the intervention	Indication	Group
OncotypeDX Genomic Health	Tissue based genomic test 17 genes (12 cancer- related +5 reference genes)	-Genomic Prostate Score (GPS) from 0 to 100 providing a likelihood of favorable pathology. -Can be used on cancer as small as 1 mm	- Very Low, Low & Intermediate Risk PCa patients	2
MRI	Magnetic resonance imaging (imaging of lesions)	-To decide who to biopsy, re-biopsy , treat - Identify men with insignificant disease and are ideal for AS -Early detection of PCa -Patients diagnosed with cancer→ who need treatment, adjuvant, dose (PCa staging) -Improving accuracy of biopsies	-Men with no previous biopsy, with a previous negative biopsy, after positive biopsy	1/2/3
Prolaris Myriad Genetics	Tissue based genomic test 46 genes (31 CCP + 15 housekeeping genes)	- Estimates 10 year PCa specific mortality risk and BCR - Stratifies patients according to aggressiveness	-On biopsy: In low/very low → candidates of AS - Post RP: Patients that may benefit from aggressive intervention /at high risk of recurrence -FDA approved	2/4
ProMark Metamark Genetics	Tissue based proteomic test 8proteins	-Predicts probability of adverse pathology at RP based on biopsy -High score independently predict unfavourable pathology at RP -Predict BCR in patients after RP -Score bet 0 and 1	-Biopsy tissue based prognostic assay for patients with biopsy Gleason Scores 3+3 and 3+4 -In patients with low, low - intermediate risk	2/4
Mi-Prostate Score (MiPS)	Urine based biomarker	-According to levels of TMPRSS2: ERG and PCA3 in their urine: patients	-high specificity in detecting high grade (Gleason >6) in	2

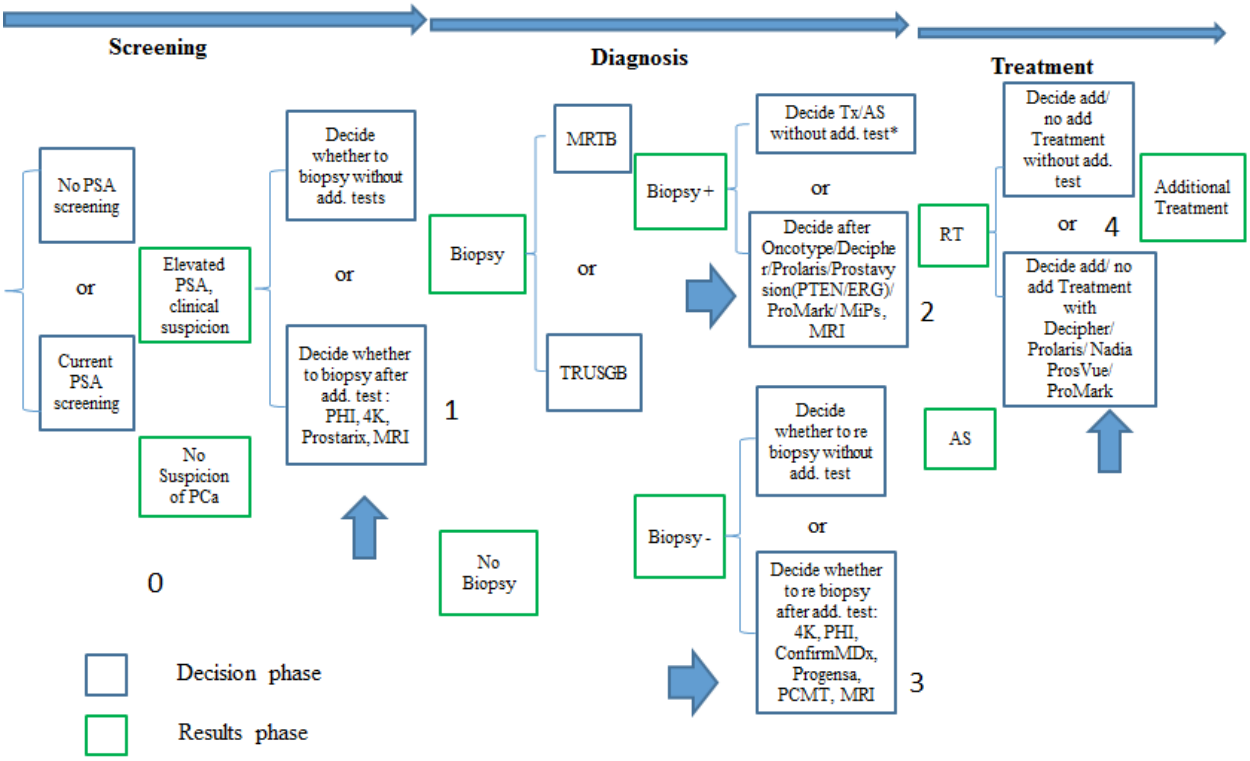
MLabs	Post DRE first urine catch PSA,PCA3, TMPRSS2:ERG mRNAs	classified to low, intermediate and high levels, or scores→ Cancer was diagnosed in each of the groups respectively: 21%, 43%, and 69%. -Probability of cancer based on biopsy	low risk patients	
ProstaVysion Botswick Laboratories	Tissue based genomic test ERG gene fusion/translocation and the loss of the PTEN tumour suppressor gene	- Predicts PCa related death in low risk patients/ future metastasis after RP -PTEN loss linked with higher risk of BCR -ERG associated with more aggressive phenotype	-No validation studies	2
NaDIA ProsVue IRIS International	Blood based Calculate PSA slope	- PSA < or =2 pg/mL/mo → reduced risk of clinical recurrence within 8 years post RP	-useful for intermediate risk patients that are candidates to adjuvant radiotherapy (ART) post RP	4
Decipher Genome DX Biosciences	Tissue based genomic test 22 coding and noncoding RNAs	-reports probability of metastasis at 5 years after surgery and 3 years after PSA recurrence -Decipher high risk (>0.6) men may benefit from adjuvant radiation -Decipher low risk men (<0.45) can be safely observed with PSA monitoring	- Patients with adverse pathology post-surgery: pT3 or positive surgical margin or rising PSA -Candidates for radiation	2/4

Group2: After a positive biopsy: Indolent vs. Aggressive: Who to treat
Group4: After an intervention: To decide who needs additional treatment
Abbreviations: Prostate-specific antigen(PSA), Digital rectal exam (DRE), Gleason score (GS), Food and drug administration (FDA), Transrectal ultrasound (TRUS), Phosphatase and tensin homolog (PTEN), biochemical recurrence (BCR), cell cycle progression (CCP), Prostate cancer (PCa)

Group 1 is developed for screening in order to reduce the number of unnecessary (negative) biopsies in patients with elevated PSA levels, such as MRI, Prostate Health Index, 4Kscore, and

Prostarix. Those are usually used in male patients with suspicion of having prostate cancer (PCa) in whom screening is indicated (men > 50 years or > 45 years with PCa family history or African Americans; without previous prostate cancer treatment or previous biopsy, with PSA 2-10 ng/ml or suspicious digital rectal exam (DRE)). Group 2 is used in patients who previously had a positive biopsy, to distinguish aggressive cancers that need treatment from those who do not, such as OncotypeDX, Decipher, Prolaris, Prostavysion, ProMark, and MiPs tests. The third group includes ConfirmMDx, Progensa, 4Kscore, PHI, MRI, and Prostate Core Mitomic used in patients post a negative biopsy, to allow identification of patients in whom a repeated biopsy is needed. Usually, Group 3 is used in male patients with suspicion of having PCa (elevated PSA, suspicious DRE, and previous initial or more negative biopsies or an indeterminate biopsy result) to guide the repeat biopsy decision. Finally, Group 4 includes the tests that are used in post-radical treatment, to assess if additional treatment is necessary depending on pathologic findings, such as Decipher, ProMark, Prolaris, and Nadia ProsVue. Those patients are men at risk for recurrence or PCSM (men with adverse post RP pathology, pT3, rising PSA or positive surgical margins) in whom treatment amelioration is suggested.

These interventions are showed in a diagram that allows correlation of each intervention with the different stages of prostate cancer throughout screening, diagnosis, and treatment of prostate cancer (Figure 1).



Prostate specific antigen(PSA), prostate cancer (PCa), prostate health index (PHI), 4Kscore (4K), magnetic resonance imaging (MRI), phosphatase and tensin homolog/ERG gene (PTEN/ERG), mi-prostate score (MiPs), radical treatment (RT), active surveillance (AS), prostate core mitomic test (PCMT), magnetic resonance imaging-targeted biopsy (MRTB), transrectal ultrasound-guided biopsy (TRUSGB) ;1) Tests before 1st biopsy; 2) Tests after a positive biopsy; 3) Tests after a negative biopsy; 4) Tests after Radical treatment (RT)

Fig. 1: Diagram of interventions grouped according to different stages of PCa

4.6 Study Population

The selected studies evaluate the clinical utility of interventions used in improving screening, diagnosis, and treatment of prostate cancer in prostate cancer patients.

Group 1: Screening: are used for patients with suspicion of having prostate cancer with a life expectancy of at least 10 years (with no previous biopsy / without previous prostate cancer treatment)

- men aged = or >50; or

- men aged > 45 years with PCa family history; or
- after elevated PSA or suspicious DRE

Group 2: After a positive biopsy: are for patients diagnosed with prostate cancer (with previous positive biopsy /without previous prostate cancer treatment)

- men with rising PSA; or
- candidates for active surveillance
- men with Gleason Scores 3+3 and 3+4; or
- men with pT3 cancer

Group 3: after negative (or indeterminate) biopsy: are for patients with suspicion of having prostate cancer with a life expectancy of at least 10 years (with previous negative biopsy)

- men aged = or >50; or
- men aged > 45 years with PCa family history; or
- after elevated PSA or suspicious DRE; or
- men having HGPIN biopsy, Atypia, ASA

Group 4: After an intervention: used in patients diagnosed with prostate cancer (with previous prostate cancer treatment)

- men with pT3 cancer; or
- men with rising PSA; or
- men with Gleason Scores 3+3 and 3+4; or
- men with adverse post RP pathology

4.7 Data synthesis

The flow chart is reflective of the different stages of the systematic review. The number of screened articles, abstracts, screened full texts, and excluded ones are clearly mapped in the study flow chart (figure 2).

Outcomes studied varied depending on the used intervention and when it is used, in screening, diagnosis, or treatment phase. The change in decision to perform a biopsy was assessed as an important outcome for tests categorized as Group 1. Similarly, this was studied for Group 3, to see the change in deciding whom to rebiopsy. On the other hand, the percentage of treatment change, decrease/increase in interventional treatment, and patient reclassification were assessed to quantify the importance of the used tests of Group 2 and 4.

4.8 Outcomes

Primary outcomes (short term outcomes):

<u>Group 1:</u>

1. Measure the proportion of altered clinical decision-making after the addition of the tests (how many patients had a change in decision to perform biopsy.)
2. Evaluate the number of unnecessary prostate biopsies and the number of missed PCa diagnosis

<u>Group 2:</u>

1. Measure the proportion of altered clinical decision-making after the addition of the tests (how many patients had a change in treatment)
2. Quantification of the decrease of interventional treatment* after employing these tests

3. Quantification of the increase of interventional treatment* after employing these tests

Group 3:

1. Measure the proportion of altered clinical decision-making after the addition of the tests (how many patients had a change in decision to repeat biopsy.)
2. Evaluate the number of unnecessary prostate biopsies and the number of missed PCa diagnosis

Group 4:

1. Measure the proportion of altered clinical decision-making after the addition of the tests (how many patients had a change in treatment)
2. Quantification of the decrease of interventional treatment after employing these tests
3. Quantification of the increase of interventional treatment after employing these tests

*Note: Interventional treatment includes: Radical prostatectomy, radiation therapy, or some combination of treatment. The burden of the treatment options are ranked as follows: radical prostatectomy> radiation therapy> other therapy (brachytherapy/cryotherapy, etc.)> androgen deprivation therapy> active surveillance> watchful waiting. Hence the quantification of the decrease or increase in interventional therapy will include both a shift from an interventional to a non-interventional therapy and shift from one interventional option to another.

Secondary outcomes (long term outcomes):

1. Evaluate morbidity and mortality from treatment of diagnosed cancer after adopting such tests.

2. Clinical outcomes, such as progression free survival, overall survival, and relapse-free survival.
3. Detect adverse events from false test results including treatment of clinically insignificant prostate cancer.

These outcomes will most likely not be demonstrated in current clinical utility studies since prostate cancer is a long-term disease. And since these tests are not associated with direct harms or adverse effects, such criteria will not be included in the systematic review.

5. RESULTS

The results of the study done as part of the master's degree are presented in the form of a manuscript.

5.1 The Manuscript

Ghadeer Olleik, Wassim Kassouf, Armen Aprikian, Jason Hu, Marie Vanhuyse, Fabio Cury, Stuart Peacock, Elin Bonnevier, Ebba Palenius, Abdel-Rahman Tarifi, Alice Dragomir. **Evaluation of new tests and Interventions for prostate cancer management – A systematic review**. (Currently being revised for submission)

5.2 Contributing authors

I wrote all the sections of the manuscript (abstract, introduction, methods, results, and conclusion). I generated the results written in this manuscript. I was always working with a student at each stage of the systematic review. Each student was working independently, and

then discussion took place afterwards, thus respecting the rules of performing a systematic review.

Roles of co-authors:

- Dr. Aprikian and Dr. Kassouf are urologists, Dr. Cury, a radiation specialist, Dr. Vanhuyse, a medical oncologist.
- The medical team at the McGill University Health Center (Dr. Aprikian, Dr. Vanhuyse, Dr. Cury, and Dr. Kassouf) participated in the design of the project with Dr. Dragomir, my supervisor. These physicians validated the project on a clinical level, participating in putting the objectives of this project. They reviewed the manuscript.
- Dr. Peacock is a health economist and Co-Director of the Canadian Centre for Applied Research in Cancer Control. He contributed to the objectives protocol and reviewed the manuscript.
- Elin Bonnevier, Ebba Palenius, and Abdel-Rahman Tarifi are the students who participated in the project. Elin and Ebba worked on groups 1 and 3, while Abdel worked on groups 2 and 4. Meanwhile, I worked on Groups 1, 2, 3, and 4. At each stage, we met to discuss, knowing that the different stages of a systematic review should be done by two reviewers.
- Jason Hu is a doctoral student under the supervision of Dr. Dragomir. He contributed to protocol revision and he reviewed the manuscript.
- Dr. Dragomir is my supervisor. She is the principal investigator of this study. She wrote the research protocol. She led the team and the whole project. She has also reviewed my work at different phases and this manuscript.

EVALUATION OF NEW TESTS AND INTERVENTIONS FOR PROSTATE CANCER MANAGEMENT – A SYSTEMATIC REVIEW

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Keywords: Prolaris, Decipher, PHI, 4Kscore, Prostavysion, Prostarix, Oncotype, Promark, Progensa, PCMT, ConfirmMdx, Nadia ProsVue, MiPs, and MRI screening, Clinical utility, Prostate Cancer, systematic review

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ABSTRACT

BACKGROUND:

In Canada, it is estimated that prostate cancer (PCa) will account for 21% of all new cancer cases in 2016. Inaccurate risk classification and the burden of unnecessary biopsies are a challenge due to the limited ability of current risk assessment tools and modalities in distinguishing indolent from aggressive disease. There is a need for evidence-based interventions that could improve stratification accuracy, and allow a decrease in overtreatment and overdiagnosis. Many new promising tools that could reduce the uncertainties accompanying treatment decision are now studied in PCa.

OBJECTIVE:

This systematic review assesses and identifies new developed tests and interventions with highest evidence of clinical utility, that might be adopted in clinical practice, throughout the PCa management: before initial and repeat biopsy, after positive biopsy, and post radical treatment.

METHODS:

The Cochrane, Embase, Medline, and Web of Science databases were searched for studies of clinical utility evidence. The outcomes of interest were: a measure of the percentage of altered decision-making, decrease in number of unnecessary biopsies, decrease or increase in treatment intensity, and risk reclassification after test utilization.

RESULTS:

The search yielded 2,940 articles after duplicate removal, of which 46 met the inclusion criteria. We found clinical utility evidence on Prostate Health Index (PHI), 4Kscore, Magnetic resonance imaging (MRI), Oncotype, Decipher, Prolaris, ConfirmMDx, Progensa PCA3, NadiaProsVue, and Promark. On the other hand, none was identified on Prostarix, Prostavysion, Prostate core mitomic test (PCMT), and Mi-Prostate Score (MiPs). The interventions demonstrated their clinical utility in terms of change in treatment recommendations, decrease/increase in interventional treatment, decrease in biopsy, and risk reclassification. Many of these interventions demonstrated to be good tools for pre-treatment and post-treatment risk stratification, in addition to elucidating aggressive versus indolent disease and enhancing an improved treatment allocation. At diagnosis after a positive biopsy, use of ProMark, Oncotype, Prolaris and MRI guide the use of active surveillance. Post-prostatectomy, the use of NadiaProsVue, Decipher, and Prolaris aid in the decision of adding adjuvant therapy. Prior initial and repeat biopsies, PHI, 4Kscore, and MRI; and prior repeat biopsies ConfirmMDx, PHI, Progensa, 4Kscore, and MRI - improve prediction of biopsy outcome allowing a decrease in unnecessary biopsies.

CONCLUSION:

Several tests might help to improve treatment decision-making for PCa patients. This review suggests that implementation of these tests in clinical practice could assist in the achievement of personalized treatment of PCa. Further clinical utility and economic studies are warranted to provide further guidance, knowing that this systematic review could provide evidence that allow accelerated use of such tests in the near future.

1. INTRODUCTION

Prostate cancer (PCa) is the second most frequent male malignancy worldwide (1). In Canada, it is estimated that prostate cancer (PCa) will account for 21% of all new cancer cases in 2016. It is expected that 21,600 new prostate cancer cases will be diagnosed (2). Likewise, in the US approximately 220,800 men are diagnosed with PCa and 27,000 men die from the disease per year (3).

Unlike when diagnosed at later stages, early detection of prostate cancer results in high cure rates, better outcomes, and lower costs (4, 5). Currently detection and clinical staging depend on digital rectal exam (DRE), serum prostate specific antigen (PSA), Gleason score, and T staging (6, 7). However, these assessment tools lack the ability of accurate stratification of PCa patients, leading to overdiagnosis and overtreatment (8). Although PSA screening was associated with declining disease specific mortality (9, 10), PSA use increased PCa incidence, leading to treatment of clinically insignificant tumours that could be alternatively not treated (10, 11). In addition to PSA lack of specificity, biopsy under-sampling raised more concerns (12). Upgrading and downgrading Gleason score post prostatectomy (13, 14) is a clear reflection of biopsy sampling error (15), which causes overtreatment of some cases and under treatment of others.

While some patients need immediate treatment, up to 60 % of diagnosed PCa patients by current practice can be safely managed by active surveillance (16). Thus, significant efforts have been engaged to find new tests and interventions that are able to differentiate between

indolent and aggressive cancer, to optimize the use of biopsy and to achieve better treatment decision.

Many new tests have demonstrated clinical utility and benefits in prostate cancer management. These tests are applied in four main decision points: for screening, after positive biopsy, after negative biopsy and after radical treatment. To spare an indolent prostate cancer patient from an unnecessary biopsy after an elevated PSA, interventions as Prostate Health Index (PHI), 4Kscore, Magnetic resonance imaging (MRI), and Prostarix could be used for screening (17-23). Furthermore, once diagnosed with prostate cancer, patients might benefit from a group of interventions that have been developed to distinguish aggressive cancers that need treatment, from non-aggressive that could be safely observed. Such interventions are Prolaris, Decipher, OncotypeDX, ProstaVysion, MRI, Mi-Prostate Score (MiPS), and ProMark (12, 23-29). Another group of interventions that could help overcome false positive screening and sampling error are used after a negative biopsy to identify candidates for a repeat biopsy, such as Progensa PCA3, 4Kscore, PHI, MRI, Prostate Core Mitomic Test (PCMT), and ConfirmMDx (23, 30-35). Finally, after radical treatment, tests have been developed to assess if additional treatment is necessary depending on pathologic findings like Decipher, Nadia ProsVue, ProMark, and Prolaris (23, 36-42).

Unquestionably, clinicians would like to consider some of these interventions due to their potential role in improving risk stratification and outcomes prognostication. Unfortunately, in clinical practice, most of these interventions are not used, mainly because we lack enough evidence on their clinical benefit, clinical utility, and cost-effectiveness analysis. Many analytical

validity and clinical validity studies are published in literature; however, not many clinical utility studies are found, which actually reflect the interventions' usefulness in clinical practice.

The objective of this systematic review is to assess the clinical utility of new marketed tests for use in PCa management before initial or repeat biopsy (after negative biopsy), after positive biopsy, and post-prostatectomy.

2. METHODS

2.1 Literature Search

The bibliographic databases Cochrane, Embase, Medline, and Web of Science were systematically searched by an experienced librarian at McGill University. All search strategies were peer-reviewed by a second experienced librarian at the same institution. The search strategy included vocabulary and text built around the research question according to PICO (patient, intervention, comparators, outcomes) framework. The search was conducted on November 22, 2016 and updated on February 24, 2017 to identify studies on clinical utility of the new tests in prostate cancer. A research protocol was established and followed for each steps of the systematic review. The appropriate strategy was employed to perform the study using selected MeSH terms and keywords. The Medline search strategy (see **Appendix I**) was adapted for Cochrane, Embase, and Web of Science.

All published studies written in English or French were considered. The search was not restricted by year of publication to include all articles about the issue of concern. After screening reference lists of the included articles retrieved by our database search, we were

able to have additional articles we found eligible. Search terms included: “prostate cancer”, “Prostatic Neoplasms”, “4KScore”,“ Progensa” ,“PCMT”, “ConfirmMDx” ,“Decipher”, “Nadia ProsVue”, “Prostarix”, “Oncotype”, “ProMark”, “MRI”, “MiPS”, “Prolaris”, “Prostate health index”, “ProstaVysion”, as well as acronyms or other terms for these words. Duplicates were identified and excluded using EndNote’s Author/Title/Year duplicate checker, followed by a manual verification. Truncation and wild cards were used to avoid missing any article that might include tests of interest. We included all possible study types that could include clinical utility evidence.

2.2 Study selection and Data extraction

In our systematic review, we included articles that have clinical utility evidence. Clinical utility studies assess the ability of the test to affect patient outcomes and treatment decisions. The best way to demonstrate the clinical utility of a test is by showing its ability of decreasing PCa specific mortality (PCSM) or metastasis. Other important outcomes are overtreatment and overdiagnosis in contemporary management of prostate cancer, and showing how testing affects them would be essential. However, since prostate cancer is a long-term disease, present studies might not have the ability to demonstrate these outcomes over such follow-up period. Thus, clinical utility evidence concerning prostate cancer will logically focus on short-term outcomes such as change in treatment decision or patient stratification or the amount of decrease in interventional treatment. These outcomes will clarify the ability of each test to change treatment decision at each phase of the disease.

After duplicate removal, two reviewers screened independently all the titles and abstracts as a first step to exclude all irrelevant studies as part of step 1 of the systematic review. Then the screening procedure continued as part of step 2; however, now full texts were assessed for relevancy by using predetermined eligibility criteria presented in Table 1. The studies included should have clinical utility evidence. Clinical utility studies should include tests that demonstrate: a measure of the percent of altered clinical decision making after addition of the tests (how many patients had a change in treatment), a measure of patients' reclassification into risk groups, a quantification of the decrease/increase of interventional treatment after employing these tests, or an evaluation of the number of unnecessary prostate biopsies and number of missed PCa diagnosis (before initial biopsy and after a negative biopsy). Long-term outcomes such as the effect of test use on morbidity and mortality were included if available. Any study that does not tackle one of these issues was excluded. The reviewers assessing the studies were initially blinded to each other's results. Each student worked on the collected database on his own, and at each step discussion occurred. At step 3, data extraction of the eligible full text articles that were included in the systematic review occurred using a prepared Data Extraction Sheet (Appendix II). Each reviewer completed this stage independently. The results were then discussed afterwards to solve any disagreement.

2.3 Quality Assessment

Eligible studies were assessed for quality using a modified version of scale developed in Rector et al (Appendix III). The modified checklist is composed of 17 questions evaluating study design, methodology, intervention, bias risk, and outcomes (43, 44).

An ordinal scale was used to give values for each question, 0 if ‘‘not clear’’ or ‘‘not a relevant item’’ or “not good quality”, 1 for ‘‘good quality’’, 2 for ‘‘excellent quality’’. This scoring procedure was done by two reviewers independently, and a discussion was carried out at the end. Based on the overall score the studies were categorized as excellent quality if scoring >75%; good quality if scoring between 50% and 75%; and poor quality if scoring <50% (43).

2.4 Types of interventions

The interventions were grouped into four groups (Table 2). Group 1, which is developed for screening, is used in order to reduce the number of unnecessary (negative) biopsies in patients with elevated PSA levels, such as MRI, Prostate Health Index, 4Kscore, and Prostarix. Those are usually used in male patients with suspicion of having prostate cancer (PCa) in whom screening is indicated (men > 50 years or > 45 years with PCa family history or African Americans; without previous prostate cancer treatment or previous biopsy, with PSA 2-10 ng/ml or suspicious digital rectal exam (DRE)). Group 2 is used in patients who previously had a positive biopsy, to distinguish aggressive cancers that need treatment from non-aggressive ones that do not, such as OncotypeDX, Decipher, Prolaris, Prostavysion, ProMark, and MiPs tests. The third group includes ConfirmMDx, Progensa, 4Kscore, PHI, MRI, and Prostate Core Mitomic used in patients following a negative biopsy, to allow identification of patients in whom a repeated biopsy is needed. Usually, Group 3 is used in male patients with suspicion of having PCa (elevated PSA, suspicious DRE, and previous initial or more negative biopsies or an indeterminate biopsy result) to guide a repeat biopsy decision. Finally, Group 4 includes the tests that are used post-

radical treatment, to assess if additional treatment is necessary depending on pathologic findings, such as Decipher, ProMark, Prolaris, and Nadia ProsVue. Those patients are men at risk for recurrence or PCSM (men with adverse post RP pathology, pT3, rising PSA or positive surgical margins) in whom treatment amelioration/addition is suggested.

We grouped the interventions into these 4 groups based on what was published in the literature and manufacturers' websites.

These interventions are showed in a diagram that allows correlation of each intervention with the different stages of prostate cancer throughout screening, diagnosis and treatment of prostate cancer (Figure 1).

2.5 Data synthesis

The flow chart is reflective of the different stages of the systematic review. The number of screened articles, abstracts, screened full texts, and excluded ones are mapped in the flow chart clearly.

Outcomes studied varied depending on the used intervention and when it is used, in screening, diagnosis, or treatment phase. The change in decision to perform a biopsy was assessed as an important outcome for tests categorized as Group 1. Similarly, this was studied for Group 3, to see the change in deciding whom to rebiopsy. On the other hand, the percentage of treatment change, decrease/increase in interventional treatment, and patient reclassification were assessed to quantify the importance of the used tests of Group 2 and 4.

3. RESULTS

We identified a total of 2,940 citations, after duplicate removal. After screening citations for relevance, 170 were selected for full text assessment (Figure 2). All in all, after full-text review, 41 articles were included in the systematic review. After reviewing the bibliography, we further identified five more articles, thus ending up with 46 articles.

3.1 Study Characteristics

Articles that were included in the systematic review were either clinical utility articles (34-36, 45-57) or articles that include some clinical utility evidence (22, 42, 58-85). We further categorized the articles retrieved based on whether the intervention was used during screening, after negative biopsy, after positive biopsy, or after radical treatment which is clarified in table 2. The included articles were published between 2001-2016. Sample sizes ranged between 11 and 2914 patients (56, 63). There were five articles on MRI screening, seven on PHI, ten on 4Kscore, two on OncotypeDx, seven on Decipher, six on Prolaris, one on ConfirmMDx, six on Progensa, one on NaDIA ProsVue, and one on Promark. There was no clinical utility evidence on Prostarix, Prostavysion, and MiPs (Figure 3).

3.2 Outcomes

The clinical utility outcomes studied were different based on which intervention is used and how it affects those outcomes. Twenty four articles studied the reduction in unnecessary biopsy, either considering initial or repeat biopsy (22, 34, 51-53, 58, 59, 61-67, 69-72, 75-78, 83, 85), one studied avoided overtreatment (60), one studied likelihood of risk reclassification between groups (35), eighteen considered change in treatment recommendations,

increase/decrease in interventional treatment, ten considered risk re-stratification (22, 36, 42, 45, 47-50, 54-57, 68, 73, 74, 79-81, 84), and one considered reduction of under- and over-staging (82).

4Kscore Prostate Cancer Test

The 4Kscore is a blood test measuring a panel of kallikrein markers: total PSA, free PSA, intact PSA, and human kallikrein 2. Many published studies indicated 4Kscore's ability to detect insignificant cancer and predict metastatic disease when compared to PSA alone (86). Our literature search detected ten publications of clinical utility evidence on 4Kscore. Nine publications (34, 58-61, 63-66) demonstrated the capability of reducing unnecessary biopsies by prediction of biopsy histopathology and occurrence of metastatic and aggressive disease. The first publication on 4kscore (64) consisting of 740 unscreened men who underwent biopsy for an elevated PSA, demonstrated that application of this test would result in a 60 % reduction in unnecessary biopsies at a threshold > 20%. Similarly, this was seen with all the other articles. A reduction of biopsies of 49%, 51%, 82%, 41%, 64%, 36%, and 25% were reported in Benchikh et al. (58), Vickers, et al. (63), Gupta, et al. (61), Vickers, et al. (65), Konety, et al. (34), Vickers, et al. (66), and Lin, et al. (62), respectively. In addition, Braun et al (59) reported a 25% reduction, however at a threshold of >= 8%. Hence, reduction of unnecessary biopsies ranged between 25 and 82%.

Another study (60), that includes 392 men who were diagnosed with prostate cancer and underwent RP, showed that the use of 4Kscore would allow a 14% reduction of unnecessary surgeries, thus avoiding overtreatment.

Prostate Health Index (PHI)

Seven studies have investigated the utility of PHI, and the main results are found in Table 3. Lazzeri, et al. (71), which prospectively evaluated 646 patients who were subjected to initial biopsy, showed that the PHI cut-off of 27.6 would allow avoiding 15.5% biopsies while missing 9.8%. The same group of authors (70) also reported a 16.5% reduction in biopsies if using a cut-off of 25.5, while missing 8.5%. Furthermore, another two studies evaluated the decrease in biopsy number, which reported a 19% and 45.2% reduction in biopsy in Filella, et al. (67) (Cut-off 31.94) and Ng, et al. (72) (cut-off 27.6), respectively, while missing 9.8 % of cases.

Magnetic resonance imaging (MRI)

Studies on MRI showed high specificity and sensitivity in predicting post-operative pathology (87), in addition to high detection rates (88, 89). Five articles were included in our study on MRI use in screening (Table 3). Three articles studied the effect of MRI use on number of biopsies performed (22, 83, 85). These studies reported a decrease in biopsies ranging between 51% and 70%. Confirming other previous publication results, MRI demonstrated a role in reclassification and staging (84, 90). MRI would enable physicians to directly monitor the disease and identify high-grade disease that really needs treatment (91).

Progensa PCA3 Assay

Six identified studies investigated clinical utility evidence on Progensa, a test that calculates the ratio between Prostate cancer antigen gene (PCA3) and PSA mRNA found in urine samples post

DRE. All the publications recovered and kept for this systematic review correlated PCA3 to reduced repeat biopsy outcome (51, 52, 75-78). Malavaud et al. (77) estimated a 37% reduction in repeat biopsy if PCA3 is used. Similarly, a 63% and a 49.51% reduction were reported at a cut-off of 25 by Tombal et al. (78) and Gittelman,et al. (52), respectively. Crawford, et al. (51) confirmed previous publication results by reporting a reduction by 77.1% at a cut-off 35; however, PCA3 missed 21.6% cancer patients. Likewise, de la Taille, et al. (75) and Haese, et al. (76) reported approximately a 60% and a 40% reduction at a cut-off of 35 and 20, while missing between 9 and 21% patients.

ConfirmMDx

We found one clinical utility study (53) on Confirm MDX, a biopsy based test that measures methylation levels of three genes (92). Wonjo et al. reported a reduced rate of repeated biopsies in patients at risk for malignancy and with a previous negative biopsy. Only 6 of the 138 (4.3%) men with a ConfirmMDx negative result performed a repeat biopsy. A 10-fold decrease in repeat biopsies was observed.

Prolaris

This intervention is a genomic test that measures cell cycle progression (CCP) signature consisting of 46 genes to predict disease mortality and progression. This tissue-based test could be used after a positive biopsy and post radical prostatectomy (93). Five articles showed clinical utility evidence on Prolaris after a positive biopsy and one post RP (Table 3, Fig. 3).

Two observational prospective studies (45, 47) were conducted to evaluate the change in treatment recommendations pre- and post- Prolaris. Crawford et al. (45) showed that Prolaris

altered 64.9% of the treatment recommendations, 37.2% had a reduction of interventional treatment and 23.4% had an increase. Notably, radical prostatectomy and radiation decreased by 49.5% and 29.6% respectively. While, Shore, et al. (47) reported a 47.8% change in treatment recommendations, noting that 72.1% of the change was a decrease in interventional treatment and 26.9% was an increase.

Also, another study, Shore et al. (46), consisting of 294 prostate cancer patients studied effect of Prolaris on treatment decisions. In this study, "possible" change of treatment was evaluated by sending physicians biopsy results with and without the test results of patients who were already treated. Test results would lead to definite or possible change in 32% of patients.

The remaining three articles assessed reclassification by Prolaris (42, 48, 73). Two were after a positive biopsy (48, 73), and one after radical prostatectomy (42), and the results of the studies scored as high quality are explained. Cuzick, et al. (73) reported reclassification of 14% of low CAPRA and 44% of intermediate CAPRA to higher risk and lower risk, respectively. Cooperberg et al (42) reported the reclassification of 56% of low risk CAPRA by the test.

ProMark

ProMark is a biopsy based prognostic test detecting 8 protein biopsy markers to predict both aggressiveness and outcome in PCa patients (94). The test was developed in a study of 381 patient biopsies matched with prostatectomy tissues, then validated in another part of the same study consisting of 256 men to distinguish between favourable and non-favourable pathology at RP (74). The primary goal of this study was to demonstrate a model able to distinguish candidates for active surveillance (AS) from those who need prostatectomy, in

addition to identifying favourable versus non-favourable pathology. Results showed that frequency of favourable pathology decreases with increasing ProMark scores. This study also had clinical utility evidence on ProMark, showing that the Net reclassification Improvement (NRI) was 0.34 ($P < 0.00001$; 95% CI, 0.20–0.48) and 0.24 ($P < 0.0001$; 95% CI, 0.12–0.35) for NCCN and D'Amico respectively.

OncotypeDX

This is another genomic test, which can be used after a positive biopsy on tissue sample as little as 1 mm of prostate tumor (23). Two studies were found to have clinical utility evidence on Oncotype in which both studied effect of the test on treatment patterns. Albala et al. (49) reported a 21% reduction in interventional treatment, mainly a 13% decrease in radiation and 10 % in RP. In addition to that, Oncotype reclassified 4.3% very low and 35.7% low NCCN patients into intermediate risk. Similarly, a 24% reduction in interventional treatment is observed in Dall'era et al. (50).

Decipher

Decipher, or Genomic classifier (GC), is a genomic test which uses the expression of 22 RNA markers (coding and noncoding) to predict metastasis and prostate cancer-specific mortality. Moreover, it allows risk stratification of PCa patients post radical prostatectomy (RP) and guides the treatment decision for adjuvant therapy (37, 95). Seven studies were found to have clinical utility evidence (Table 3, Fig. 3) on Decipher after prostatectomy, and none were found after a positive biopsy.

The effect of decipher on decision making was studied in most of these articles. The first article, which employed 24 pathologically high-risk patients (36), studied the effect of Decipher use on salvage and adjuvant treatment recommendations. The urologic oncologists gave their treatment recommendations for each patient pre- and post- decipher testing results. The treatment recommendations changed in 43% of the cases in the adjuvant group among, which 27% was a reduction in interventional treatment and 37% increase. In the salvage group, there was 53% change in treatment recommendations with a 16% reduction in interventional treatment and a 61% increase. In a similar context and with a larger number of urologists (54), this study reported that treatment was de-intensified to observation for 40% of patients who were recommended for adjuvant radiation therapy, and was intensified for 13% of patient recommended for observation. In addition to that, Decipher reclassified 51% of the patients as low risk. Similarly, Michalopoulos et al. (55), reported that Decipher caused a change in treatment recommendations of 30.8% of patients, of whom 42.5% had a reduction in treatment intensity and 17.6% had an increase. That agrees with Nguyen et al. (56) findings showing that GC results modified 35% and 45% of the treatment recommendations by oncologists and urologists, respectively.

Risk reclassification was also an important outcome in the remaining three articles. Cooperberg et al. (79), test reclassified 49 out of 185 men as low to intermediate risk who were high risk according to CAPRA-S score > = 6. Among those men, three CSM events were observed, while 17 CSM were observed in those who were classified as high risk by GC. Den et al. (80), which includes 2342 patients, is another study showing that GC reclassified 52%, 76% and 40% of patients in CAPRA-S low-, intermediate- and high-risk groups, respectively. Likewise, Ross et al

(81) showed that decipher reclassified 71%, 52% and 19% of patients in CAPRA-S low-, intermediate- and high-risk groups, respectively. In addition to that, GC correlated with increased cumulative incidence of BCR, metastasis, and PCSM after RP ($p<0.01$). Metastasis was 47% in those classified as high risk by GC versus 12% in those with low GC score.

NaDIA ProsVue

This test is a blood based test that determines the rate of total PSA change over a period of time by measuring extremely low concentrations of PSA from 3 blood samples taken after RP (96). This test helps identify patients with low risk of recurrence post RP (39, 96). Only one study found to show clinical utility evidence on this test. Moul et al. (57) is a prospective, multicentre clinical trial that enrolled 598 men treated by RP; 225 completed the study. A score <= to 2 pg/ml/month reduced secondary treatment recommendation in 63.4% of patients who were initially referred for secondary treatment. After ProsVue results, only 11.7% of the men were referred to secondary treatment.

ProstaVysion, Mi-Prostate Score (MiPS), Prostarix, and Prostate core mitomic test (PCMT)

No clinical utility evidence was found on these tests.

3.3 Quality Assessment

Table 3 presents the quality assessment scores. Sixteen articles were of excellent quality scoring >75 (22, 52, 54, 61, 63-65, 72, 74, 77, 79-84), while most of the others were of good quality (26 articles) scoring between 50 and 75 (34-36, 42, 45-47, 49, 51, 53, 55, 57-60, 62, 66-

71, 73, 75, 76, 78). Additionally, table 4 presents the summary of the quality assessment score in term of number of studies in each category (high-, good- and low- quality) as well as median score and range when this number is higher than 3.

4. DISCUSSION

Although tools used in current practice lack precision to guide treatment decisions, Gleason score, T staging, PSA, and DRE continue to be important in risk stratification, diagnosis, and management of PCa patients. Finding and developing new prognostic tests and interventions won't be enough to directly improve treatment decisions. After validating these interventions, they should be integrated into clinical practice to provide insight on their benefits and applicability. This depends on the ability to access the interventions, which mainly depends on their ability to understand intervention's results and scores, to link all these to patient's outcomes, and their cost. After effective access to an intervention and adoption in real life, clinical utility can be evaluated, which demonstrates the usefulness of this test, and the value this intervention adds to clinical management (97).

Our systematic review was performed to assess clinical utility evidence on available interventions, hoping this will influence their utilization to achieve a better personalized treatment in prostate cancer management. Choosing the appropriate intervention where it is applicable, throughout the states of the disease from screening to treatment, is important to reduce the uncertainty related to diagnosis and treatment. Hence, we divided all the interventions into groups where each intervention could be employed, and interventions with the highest evidence of clinical utility are identified.

Our results showed that some interventions might have as many as 10 publications that have clinical utility evidence such as 4Kscore, whereas others might have none. The quality of the articles also differed between interventions. The interventions with highest clinical utility evidence were 4Kscore, PHI, MRI, PCA3, Prolaris, and Decipher.

4Kscore and PHI are two tests that could be used for screening and after a negative biopsy. These tests proved their ability in decreasing unnecessary biopsies ranging between 15% and 64 % at varying thresholds and cut-offs, while missing some cancers (34, 60, 71, 72). This agrees with many publications that correlate PHI to GS (98, 99) and its ability of avoiding unnecessary biopsies. MRI is an intervention that can accurately identify significant cancer, even tumours missed in anterior region (87). Retrieved articles showed clinical utility evidence on MRI at different disease stages (82, 83). PCA3, is able to identify men with higher risk of cancer. This test demonstrated a reduction of repeat biopsy up to 77% at cut-off 35 (51). Although we had these findings on PCA3, we found difficulty choosing the most appropriate PCA3 cut-off that is useful in predicting PCa aggressiveness. The literature search yielded articles talking about PCA3 ability to reduce biopsies; however, at different cut-offs. This agrees with Roobol et al. that concludes that PCA3 cannot replace PSA, underlining that it could be used along with other assessment tools (100).

Decipher, for instance, is one test that has potential ability to identify who has a higher risk of metastasis and death post RP, thus resolving uncertainties on who will benefit from adjuvant therapy. Clinical utility evidence showed that 31% to 53% of post RP treatment recommendations were changed, with 16% to 43% of recommendations changing from any to no treatment (36, 54, 55). In addition, GC reclassified up to 60% of high-risk patients to low-risk.

Similarly, Prolaris was associated with post-operative adverse outcome prediction (42). In addition to that, Prolaris showed a change in treatment ranging between 48% and 65%, while reclassifying up to 56% of low risk CAPRA patients (42, 45, 47).

Our study has some limitations related to the studies selected in the final step of the systematic review. Some studies were not blinded and others had potential biases. However, all of these issues were taken into consideration in the quality appraisal score, and this is reflected in the final score. Secondly, we didn't assess grey literature; however, this won't significantly affect our results especially since these tests were recently developed.

On the other hand, our study has important strengths. Many articles in the systematic review were clinical utility studies designed primarily to evaluate the new interventions of prostate cancer. And after organizing a protocol, we were able to assess the articles by two interpreters at each step, thus assuring our results. Most articles included in our review were of good and excellent quality, thus yielding important evidence on the new interventions that could be employed in PCa management.

5. CONCLUSION

This study provides an overview of clinical utility evidence on many interventions that could have significant potential to impact personalized treatment decisions and to improve clinical outcomes and quality of life of men with prostate cancer, if adopted in clinical practice. Yet, their cost-effectiveness should be proved before public access to these interventions. This review suggests that the use of these tests in clinical practice could help achieve personalized

treatment of PCa by adding meaningful new information for better risk assessment and disease prognostication. Further clinical utility and economic evaluation studies are warranted to provide further guidance.

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Conflicts of interest:

There is no conflict of interest.

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Table 1: Inclusion and exclusion criteria for studies eligibility

Inclusion Criteria	Exclusion Criteria
• Any article related to PCa treatment, screening, diagnosis	• Conference abstracts
• Any article related to test of interest	• Unrelated and Untraceable articles
• Any article with clinical utility evidence	• Animal or in vitro studies
	• Commentaries, Letters, and editorials
	• Review papers and case reports
	• Articles with no clinical utility evidence (not including our outcomes of interest)
	• Studies in languages other than English and French

Table 2: Summary on the interventions

Intervention	**Type of intervention/ markers**	**About the intervention**	**Indication**	**Group**

	measured			
Prostate Health Index (PHI) Beckman Coulter	Blood based immunoassay PSA, freePSA, p2PSA PHI score= (p2PSA/fPSA) ×√tPSA	-The phi score is a continuous measure. -Categorizes patients into: 0–20.9 (low risk); 21–39.9 (moderate risk); and >=40 (high risk). - Estimates of the risk of cancer being detected at biopsy are: 8.7% for men with a phi score in the low-risk category, 20.6% for men in the moderate-risk category and 43.8% for men in the high-risk category.	-used if PSA between 2-10ng/ml (4-10ng/ml FDA) + negative DRE+ age more or = to 50 (FDA approved for this indication) -After a negative biopsy and continuous suspicion -Not for patients receiving 5-α-reductase inhibitors medication	1 /3
4Kscore Prostate Cancer Test OPKO Health, Inc.	Blood based immunoassay 4 kallikrein markers: Total PSA , free PSA, intact PSA, hK2	-4Kscore>7.5% → predicted probabilities of 2.5, 5.6, 9.9,16.4% of distant metastasis in 5, 10, 15, 20 years respectively. -4Kscore< or =7.5% → predicted probabilities of 0, 0.2, 1, 1.8% of distant metastasis in 5, 10, 15, 20 years respectively. - Gives probability of finding high grade PCa (GS > =7) on biopsy	-Men with an abnormal PSA or DRE or clinical suspicion -Patients who have had a prior negative biopsy and want to do repeat biopsy - Not to patients who received 5-α-reductase inhibitors medication in past 6 months	1/3
Prostarix Metabolon Inc.	Urine based 4 metabolites: sarcosine alanine glycine glutamate	-Prostarix-PLUS Risk Score: Prostarix + PSA + TRUS-determined prostate volume -Score (1-100) = predicted likelihood of having 5 year recurrence	-Men with an abnormal PSA or DRE or clinical suspicion -No validation studies	1
MRI	Magnetic resonance imaging (imaging of lesions)	-To decide who to biopsy, re-biopsy , treat - Identify men with insignificant disease and are ideal for AS -Early detection of PCa -Patients diagnosed with cancer→ who need treatment , adjuvant , dose (PCa staging) -Improving accuracy of biopsies	-Men with no previous biopsy, with a previous negative biopsy, after positive biopsy	1/ 2/3
OncotypeDX Genomic Health	Tissue based genomic test 17 genes (12 cancer- related +5 reference genes)	-Genomic Prostate Score (GPS) from 0 to 100 providing a likelihood of favorable pathology. -Can be used on cancer as small as 1 mm	- Very Low, Low & Intermediate Risk PCa patients	2
Prolaris Myriad Genetics	Tissue based genomic test 46 genes (31 CCP + 15 housekeeping genes)	- Estimates 10 year PCa specific mortality risk and BCR - Stratifies patients according to aggressiveness	-On biopsy: In low/very low → candidates of AS - Post RP: Patients that may benefit from aggressive intervention /at high risk of recurrence -FDA approved	2/4
ProMark Metamark	Tissue based proteomic test	-Predicts probability of adverse pathology at RP based on biopsy	-Biopsy tissue based prognostic assay for patients with biopsy	2/4

Genetics	8proteins	-High score independently predict unfavorable pathology at RP -Predict BCR in patients after RP -Score bet 0 and 1	Gleason Scores 3+3 and 3+4 -In patients with low, low - intermediate risk	
Mi-Prostate Score (MiPS) MLabs	Urine based biomarker Post DRE first urine catch PSA,PCA3, TMPRSS2:ERG mRNAs	-According to levels of TMPRSS2:ERG and PCA3 in their urine: patients classified to low, intermediate and high levels, or scores→ Cancer was diagnosed in each of the groups respectively: 21%, 43%, and 69%. -Probability of cancer based on biopsy	-high specificity in detecting high grade (gleason >6) in low risk patients	2
ProstaVysion Botswick Laboratories	Tissue based genomic test ERG gene fusion/translocation and the loss of the PTEN tumor suppressor gene	- Predicts PCa related death in low risk patients/ future metastasis after RP -PTEN loss linked with higher risk of BCR -ERG associated with more aggressive phenotype	-No validation studies	2
ConfirmMDx MDx Health	Biopsy tissue based genomic test Monitors the methylation states of APC, GSTP1 and RASSF1 genes	-Negative result: avoid repeat biopsy and monitor with routine screening -Positive: suspicious areas marked as positive providing repeat biopsy guidance on prostate map	- Prior negative or high-grade prostatic intraepithelial neoplasia (HGPIN) biopsy result (12-core biopsy within 24 months)	3
Progensa PCA3 Assay Gene-Probe Inc	urine-based biomarker assay : Post DRE first urine catch PSA+ PCA3 mRNAs	-The PCA3 is a ratio of the PCA3 mRNA copies/ml to PSA mRNA copies/ml multiplied by 1000 -Predicts the likelihood of positive biopsy -Recommended threshold score : 25, with values 25 and higher suggesting the presence of cancer	-Patients 50 or older with a negative diagnosis of prostate cancer on analysis of the biopsy sample (one or more previous biopsies) and elevated serum PSA+ and a repeat biopsy is recommended (FDA approved) -Not for patients who are taking medications known to affect serum PSA levels	3
Prostate core mitomic test Mitomics	Tissue based genomic test mtDNA deletions	-PCMT negative outcome: Patient is currently at a low risk of undiagnosed prostate cancer. -PCMT positive outcome: Patient is at a high risk of undiagnosed prostate cancer.	- Patients who have had a prior negative biopsy and show PSA > 4.0 ng/ml, PSADT < 3 months PSAV > 0.4 ng/ml/year or Irregular DRE, Family history African American Life	3

			expectancy > 10 years - Patients who have had a prior indeterminate biopsy (ASAP, HGPIN, Atypia)	
NaDIA ProsVue IRIS International	Blood based Calculate PSA slope	- PSA < or =2 pg/mL/mo → reduced risk of clinical recurrence within 8 years post RP	-useful for intermediate risk patients that are candidates to adjuvant radiotherapy (ART) post RP	4
Decipher Genome DX Biosciences	Tissue based genomic test 22 coding and noncoding RNAs	-reports probability of metastasis at 5 years after surgery and 3 years after PSA recurrence -Decipher high risk (>0.6) men may benefit from adjuvant radiation -Decipher low risk men (<0.45) can be safely observed with PSA monitoring	- Patients with adverse pathology post-surgery: pT3 or positive surgical margin or rising PSA -Candidates for radiation	2/4

Group1: Screening (before initial biopsy): Decide who to Biopsy
Group2: After a positive biopsy: Indolent vs. Aggressive: Who to treat
Group3: Tests after negative (or indeterminate) biopsy: To decide when to re-biopsy
Group4: After an intervention: To decide who needs additional treatment

Abbreviations: Atypical small acinar proliferation (ASAP), High-grade prostatic intraepithelial neoplasia (HGPIN), Prostate-specific antigen(PSA), Digital rectal exam (DRE), Gleason score (GS), Food and drug administration (FDA), Transrectal ultrasound (TRUS), Phosphatase and tensin homolog (PTEN), biochemical recurrence (BCR), cell cycle progression (CCP), Prostate cancer (PCa), mitochondrial (mtDNA), Adenomatous polyposis coli (APC), glutathione S-transferase (GSTP1) , Ras Association Domain Family Member 1 (RASSF1),), PSA Doubling time (PSADT), PSA velocity (PSAV).

Table 3: Characteristics of studies on interventions included in the systematic review

	Study	**Type of study**	**n**	**Outcomes**	**Results**	**Gr.**	**Score**
4Kscore	Benchikh , et al. 2010(58)	Validation study	269	Reduction in biopsy number	Reduction in biopsy= 492 biopsy avoided (49.2%) for every 1000 man with elevated PSA using of threshold= > 20% -Miss= 61 advised against biopsy (majority low risk-:163/ high risk:12)	1	63
	Carlsson, et al. 2013(60)	Cohort of men from a randomized trial	392	Avoided overtreatme nt	-Overtreatment avoided: in 110 patients for every 1000 men but delay treatment for 26 patients with aggressive disease using of threshold= > 30%	*	73
	Vickers, et al. 2010(63)	Population based cohort	2914	Decrease in unnecessary biospy	-Reduction in biopsy= 513 per 1000 men using of threshold= > 20% -Miss= 12/100 high grade	1	82
	Vickers, et al.	Cohort of men from a	740	Reduction in biopsy	-Reduction in biopsy= 443 /740 (60%) using of threshold= > 20%	1	83

	2008(64)	randomized trial		number	-Miss= 31/152 low grade + 3/40 high grade		
	Vickers, et al. 2010 (65)	Cohort of men from a randomized trial	1241	Reduction in biopsy number	-Reduction in biopsy= 41% (1000 patient) using of threshold= > 20% -Miss= 60 patient /259 cancer cases	1	80
	Braun et al, 2016(59)	Randomized study	749	-Reduction of Biopsy	-Reduction in biopsy= 25% avoided -delayed treatment = 13 high grade cancer -Threshold= >8% risk for cancer	1	62
	Vickers, et al. 2010 (66)	Clinical utility	1501	Reduction in biopsy number	-Reduction in biopsy= 363/1000 (36%) -Missed = 47 patients (of which 4 high grade cancer)	1	68
	Lin, et al. 2010 (62)	Clinical utility study, data from trial	718	-Reduction in biopsy number	-Reduction in biopsy= 252 biopsy avoided (25.2%) for every 1000 man with elevated PSA using of threshold= > 20% -Miss= 19 advised against biopsy but need it(high grade)	*	68
	Konety, et al. 2015 (34)	Clinical utility study (survey)	611	-Reduction in biopsy number -likelihood of biopsy	-Reduction in biopsy= 64% reduction -The higher the score the greater the likelihood to do biopsy(p=0.001)	1/3	64
	Gupta, et al. 2010 (61)	Cohort using data from trial	925	Decrease in unnecessary biospy	-Reduction in biopsy= 817 per 1000 (82%) men using of threshold= > 20% -Treatment reduction = 135 surgeries (14%) per 1000 -Missed: 67 cancers	3	78.5
Prostate Health Index (PHI)	Filella , et al. 2014 (67)	Prospective and Retrospective study	354	Reduction in biopsy number	-Reduction in biopsy= 19% using of cut-off 31.94 -Miss= 17 of 175 PCa (5 gleason> = 7)	1	64
	Lazzeri, et al. 2013 (70)	Clinical performance study	158	Reduction in biopsy number	-Reduction in biopsy= 16.5% using of cut-off 25.5 -Miss= 6of 71 cancers would have been missed: four with GS 6 (3+3) and two with a GS of 7 (3+4).	1	73
	Ng, et al. 2014(72)	Retrospective study	230	Decrease in unnecessary biospy	-Reduction in biopsy= 104/209 (45.2%)using of cut-off 27.6 -Missed: 9.5%	1	89
	Lazzeri, et al. 2013(71)	Observational, prospective cohort study	646	Reduction in biopsy number	-Reduction in biopsy= 15.5% biopsies avoided using of cut-off 27.6/52 % avoided and 37,1 % missed with cutoff 41.5 -Miss= 9.8%	3	83

	Foley, et al. 2015 (68)	Cohort mainly performance study	250	Stratification	-PHI model showed best correlation between predicted probabilities and actual outcome (scatter plot)	1/3	60
	Gnanapragasam, et al. 2016 (69)	Prospective clinical trial	279	Decrease repeat biopsy	-PHI not useful in deciding if mpMRI will be positive -94 MRI negative images that include 21 gleason >= 7→ if PHI done after only miss 1 out 21 -Reduction in biopsy=31/73	3	71
	Hirama, et al. 2013 (35)	Retrospective clinical utility study	67	Likelihood of reclassification	-PHI significantly higher in the reclassification group in patients who were on AS (p=0.010)	3	59
MRI Magnetic resonance imaging	Pokorny, et al. 2014 (22)	Prospective blinded diagnostic study	223	-Reduction of Biopsy	-Reduction in biopsy= 51.1% if restricting MRGB to PIRADS 4/5 -Missed = 15 patients intermediate/high on biopsy	1	65
	Vilanova, et al. 2016 (85)	Prospective trial	81	Reduction in biopsy number	-Reduction in biopsy= 63% -Miss= 30% missed (7 out of 23)	1	38
	Grenabo Bergdahl, et al. 2016 (83)	Pilot study	124	Biopsy reduction	-70% decrease in biopsy indication when using MRI imaging prior to repeat biopsy - After compare to repeat biopsy→ 23% of those with PIRADS 3, 75% of those with PIRADS 4, 100% of those with PIRADS 5→ significant cancer	1/3	78.5
	(Chamie, 2013) (82)	Retrospective, observational study	104	Reduction of Under-staging Over-staging	-Epstein's criteria→ understaged 12 men as insignificant Pca -MRI→understagesd 4 vs 12 (when matched with pathologic findings) (diagnosed +on AS)	2	78.5
	(Porpiglia, 2016) (84)	Retrospective, observational study performance	120	Reclassification	-Reclassification: 47% of cases eligible for AS to significant disease - PHI with MRI better accuracy but not PCA3	2	89
Progensa PCA3 Assay	Malavaud et al. 2013(77)	Economic study	698	Reduced Repeat biopsy	-Reduce repeat biopsy by : 37% = estimate if PCA3 used prior to repeat biopsy	3	80
	Tombal et al. 2013 (78)	Prospective study	1024	Reduced Repeat biopsy	-Reduce repeat biopsy by : 63% at cut-off 25/ 48% at cut-off 20	3	66
	Crawford, et al. 2012 (51)	Prospective clinical trial	1913	Reduced Repeat biopsy	-Reduce repeat biopsy by : 77.1% at cut-off 35 -But 21.6% missed	3	68

	de la taille, et al. 2015 (75)	Prospective multicenter rea life study	516	Reduced biopsy	-Reduce biopsy by : 60% at cut-off 35/ 40% at cut-off 20 -But 11% missed of gleason = > 7 at 35 cut-off / 2 % missed at cutoff 20	3	56
	Haese, et al. 2008 (76)	Prospective multicenter study	463	Reduced biopsy	-Reduce biopsy by : 67% at cut-off 35/ 44% at cut-off 20 -But 9% missed of gleason = > 7 at 20 cut off/ 21 % missed at cutoff 35	3	68
	Gittelman,et al. (52)	prospective multicenter clinical study	466	Reduced biopsy	-Reduce biopsy by 49.51% (231 out of 466) -Missed: 22.5% (23 out of 102)	3	82
Confirm MDx	Wojno, et al. 2016 (53)	Clinical utility observational study	138	Quantify number of repeat biopsies	-Repeat biopsies had been performed in 6 of the 138 (4.3%) men with a negative assay result -10-fold reduction in the rate of repeat biopsy as compared to the reported standard of care	3	60
Prolaris	(Crawford, et al. 2014) (45)	Observational prospective study	305	-% Change in treatment after CCP test results	-Change in treatment: 64.9% -Interventional treatment : a 37.2% reduction /23.4% increase -Surgeries and radiation: decreased by 49.5% and 29.6%	2	62
	(Shore, et al. 2016) (47)	Report on prospective observational	1206	Change in txt recommendations pre and post CCP	-Change in treatment: 47.8% -Interventional treatment : a 72.1% of change is reduction /26.9% intensification	2	67
	(Shore, et al. 2014) (46)	Observational retrospective survey	294	-Possible Change in treatment after CCP test results	-Possible Change in treatment: 32% -Likelihood of change is tested and not actual	2	59
	(Cuzick, et al. 2015) (73)	Observational retrospective validation study	585	Reclassification	-Reclassified: 14% of <3 CAPRA→ higher risk /44% of intermediate CAPRA=3 to be lower risk	2	70

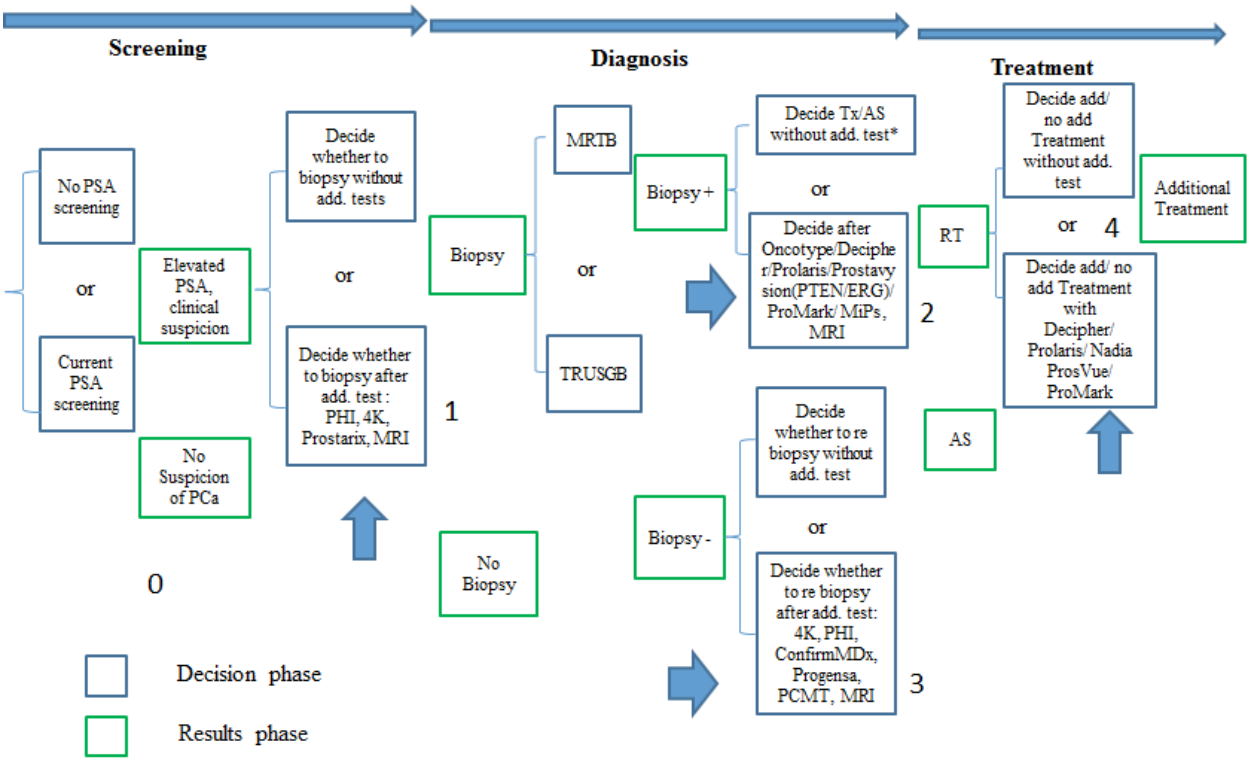
	(Oderda, et al. 2016) (48)	Observational retrospective cohort clinical utiltiy	585	Reclassification	-Reclassified: discordance in risk categorization based on pathological findings, 7 high risk and 13 intermediate risk were misclassified -CCP had better accuracy vs EAU	2	37
	(Cooperberg, et al. 2013) (42)	Prospective specimen collection, retrospective design	413	Reclassification	-Reclassified: 56% of low risk CAPRA(0-2) were reclassified by CCP -All patients classified as low risk of recurrence by CCP <-1→ didn't have recurrence	4	72
ProMark	(Blume-Jensen, et al. 2014) (74)	Assay development and validation study	381 and 256	Outcome of interest : reclassification measured as NRI	-Net reclassification Improvement (NRI): 0.34 for NCCN (P < 0.00001; 95% CI, 0.20–0.48) and 0.24 for D'Amico (P < 0.0001; 95% CI, 0.12–0.35).	2	80.76
Oncotype DX	(Albala et al. 2016) (49)	Prospective clinical utility study	180	Change in management patterns + costs	-Interventional treatment : a 21% reduction in low and very low NCCN -Radiation and RP: decreased by 14% and 10% -Reclassification: 4.3% of very low NCCN and 35.7% of low NCCN→ into intermediate risk	2	59
	(Dall'era et al. 2015) (50)	Retrospective chart review	211	Change in txt recommendations	-Interventional treatment : 24% reduction to AS	2	36
Decipher	(Badani, 2013) (36)	Prospective study	24	change in adjuvant and salvage treatment recommendatio-ns	-Change in treatment: 43% of adjuvant, 53% of salvage -Interventional treatment : a 27% (adjuvant) /16% (salvage) reduction / 37% (adjuvant) and 61% (salvage) Intensification	4	61
	(Badani, 2015) (54)	Multicenter prospective,decision-impact study	122	-change in adjuvant treatment recommendations	-Reclassified : 51% of patients as having low risk -Change in treatment: 31% -Interventional treatment : 40% reduction to observation /20% increase	4	89
	(Michalopoulos,	Prospective study	146	-change in clinical	-Reclassified : 60% of high risk patients as low risk	4	68

	2014) (55)			treatment decision post RP -effect on physicians' uncertainty	-Change in treatment: 30.8% -Interventional treatment : 42.5% reduction to observation /17.6% increase -number of patients on treatment before and after stayed same, but allocation differed		
	(Nguyen, 2015) (56)	Multicenter, prospective study	11	-Changes in adjuvant treatment recommend atio-n	-Change in treatment: 35% and 45 %of treatment by radiation oncologists and urologists -high GC risk → urologists and oncologists recommended adjuvant treatment 91% or 89% of the time, respectively, vs 62% and 79% for those same cases before the GC results	4	43
	(Cooperb erg 2014) (79)	Retrospective cohort	185	reclassificati on	-Reclassification: In 82 patients stratified to high risk based on CAPRA-S score > or =6, GC scores were likewise high risk for 33 patients, among whom 17 had CSM events. GC reclassified the remaining 49 men as low to intermediate risk; among these men, three CSM events were observed	4	85
	(Den, et al. 2016) (80)	Prospective observational study	2342	reclassificati on	-Reclassification: Decipher reclassified 52%, 76% and 40% of patients in CAPRA-S low-, intermediate- and high-risk groups, respectively	4	89
	(Ross, 2015) (81)	Retrospective case-cohort	260	reclassificati on	--Reclassification: Decipher reclassified 71%, 52% and 19% of patients in CAPRA-S low-, intermediate- and high-risk groups, respectively	4	76.6
NaDIA ProsVue	(Moul, et al. 2013) (57)	Prospective multicenter clinical trial	225	Reduction in intervention al treatment	-Interventional treatment: 63.4% reduction of secondary treatment recommendation (adjuvant RT =/- ADT)	4	70.5

Group (Gr.) 1: Screening (before initial biopsy): Decide who to Biopsy
Group (Gr.) 2: After a positive biopsy: Indolent vs. Aggressive: Who to treat
Group (Gr.) 3: Tests after negative (or indeterminate) biopsy: To decide when to re-biopsy
Group (Gr.) 4: After an intervention: To decide who needs additional treatment
Score interpretation: excellent quality, studies scoring >75%; good quality, studies scoring between 50% and 75%; and poor quality, studies scoring <50%
*two studies are done to study the utility of 4Kscore after a prostate cancer diagnosis, but this is not yet approved for clinical use.

Table 4: Quality of publications for each intervention

Intervention	**Excellent Quality (above 75%) number (articles)**	**Good Quality (50-75%) number (articles)**	**Poor Quality (below 50%) number (articles)**
4Kscore	4 (61,63, 64, 65)	6 (34,58,59,60,62,66)	
PHI	2 (72,71)	5 (35,67,68,69,70)	
MRI	3 (82,83,84)	1 (22)	1 (85)
PCA3	2 (52,77)	4 (51,75,76,78)	
ConfirmMDx		1 (53)	
Prolaris		5 (42,45,46,47,73)	1 (48)
Oncotype		1 (49)	1 (50)
Decipher	4 (54,79,80,81)	2 (36,55)	1 (56)
Nadia ProsVue		1 (57)	
ProMark	1 (74)		



Prostate specific antigen(PSA), prostate cancer (PCa), prostate health index (PHI), 4Kscore (4K), magnetic resonance imaging (MRI), phosphatase and tensin homolog/ERG gene (PTEN/ERG), mi-prostate score (MiPs), radical treatment (RT), active surveillance (AS), prostate core mitomic test (PCMT), magnetic resonance imaging-

targeted biopsy (MRTB), transrectal ultrasound-guided biopsy (TRUSGB) ;1) Tests before 1st biopsy; 2) Tests after a positive biopsy; 3) Tests after a negative biopsy; 4) Tests after Radical treatment (RT)

Fig. 1: Diagram of interventions grouped according to different stages of PCa

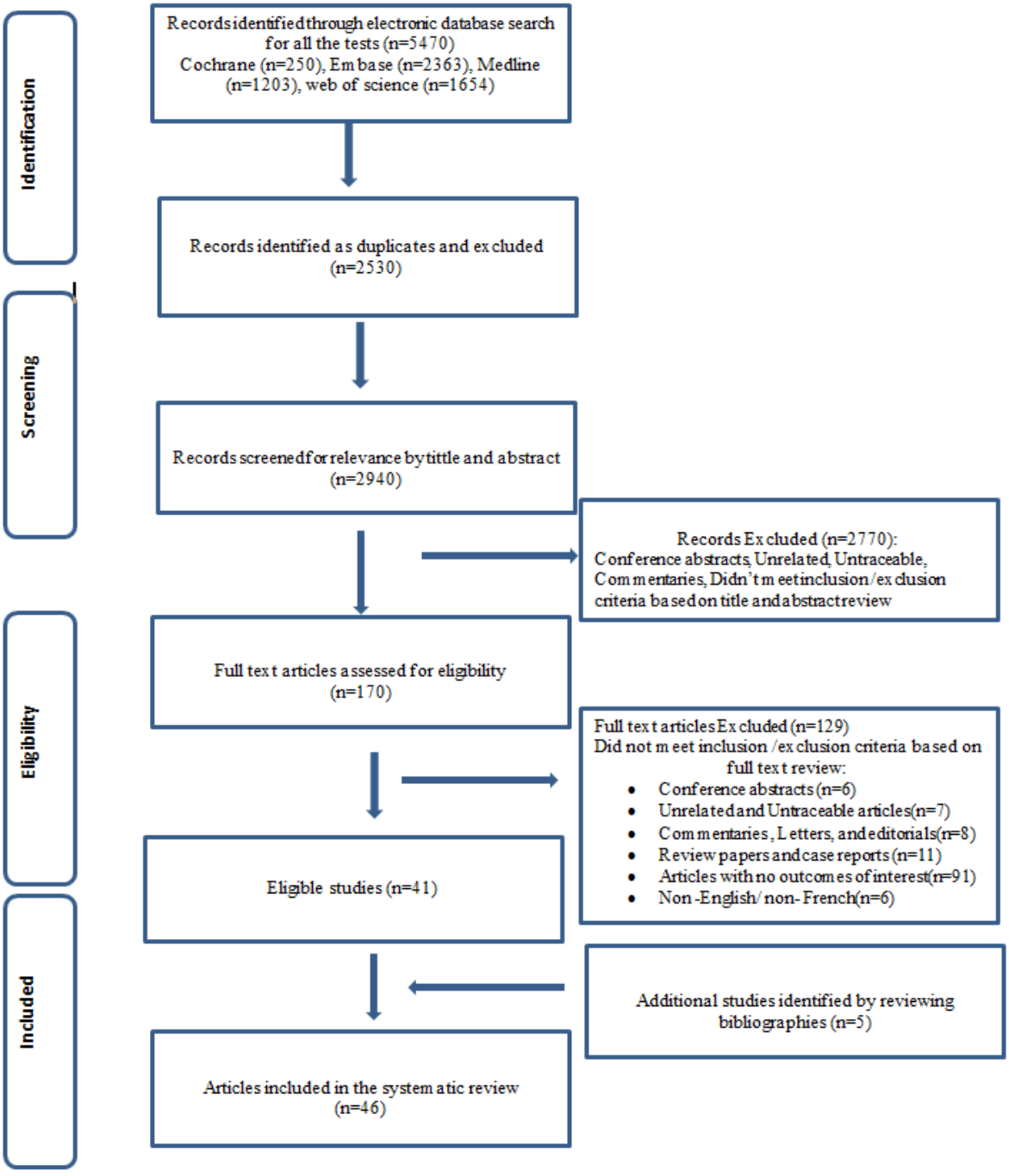


Fig. 2: Study flowchart

MRI	PHI	4K	Prostarix	Oncotype	Decipher	Prolaris
5	7	10	0	2	4	5

ProstaVysion	Promark	MiPS	ConfirmDX	Progensa	PCMT	Nadia
0	0	0	1	6	0	1

TOTAL
46

Articles added after bibliography search

Promark	Decipher	Prolaris
1	3	1

Prostate health index (PHI), 4Kscore (4K), magnetic resonance imaging (MRI), mi-prostate score (MiPs), prostate core mitomic test (PCMT).

Fig. 3: Retrieved articles after full text assessment

6. DISCUSSION

6.1 Overview

Although tools used in current practice lack precision to guide treatment decisions, Gleason score, T staging, PSA, and DRE continue to be important in risk stratification, diagnosis, and management of PCa patients. Finding and developing new prognostic tests and interventions won't be enough to directly improve treatment decisions. After validating these interventions, they should be integrated into clinical practice to provide insight on their benefits and applicability. This depends on the ability to access the interventions, which mainly depends on their ability to understand intervention's results and scores, to link all these to patient's outcomes, and their costs. After effective access to an intervention and adoption in real life clinical utility can be evaluated, which demonstrates the usefulness of this test, and what value does this intervention add to clinical management (204).

Our systematic review was performed to assess clinical utility evidence on available interventions, hoping this will influence their utilization to achieve a better personalized treatment in prostate cancer management. Choosing the appropriate intervention where it is applicable, throughout the states of the disease from screening to treatment, is important to reduce the uncertainty related to diagnosis and treatment. Hence we divided all the interventions into groups where each intervention could be employed, Table 2. Our findings showed that some interventions might have as many as 10 publications that have clinical utility evidence such as 4Kscore, whereas others might have none. The quality of the articles also

differed between interventions, table 4. The interventions with highest clinical utility evidence were 4Kscore, PHI, MRI, PCA3, Prolaris, and Decipher.

4Kscore and PHI are two tests that could be used for screening and after a negative biopsy. These tests proved their ability in decreasing unnecessary biopsies ranging between 15% and 64 % at varying thresholds and cut-offs, while missing some cancers (35, 157, 186, 187). This agrees with many publications that correlate PHI to GS (205, 206) and ability of avoiding unnecessary biopsies. MRI is an intervention that can accurately identify significant cancer, even tumors missed in anterior region (177). Retrieved articles showed clinical utility evidence on MRI at different disease stages (207, 208).

PCA3 is able to identify men with higher risk of cancer. This test demonstrated a reduction of repeat biopsy up to 77% at cut-off 35 (144). Although we had these findings on PCA3, we found difficulty choosing the most appropriate PCA3 cut-off that is useful in predicting PCa aggressiveness. The literature search yielded articles talking about PCA3 ability to reduce biopsies, however, at different cut-offs. And this agrees with Roobol et al. that concludes that PCA3 cannot replace PSA, underlining that it could be used along with other assessment tools(209).

Decipher, for instance, is one test that has potential ability to identify who have higher risk of metastasis and death post RP, thus resolving uncertainties on who will benefit from adjuvant therapy. Clinical utility evidence showed that 31 to 53% of post RP treatment recommendations

were changed, with 16% to 43% of recommendations changing from any to no treatment (37, 199, 210). In addition, GC reclassified up to 60% of high risk patients to low risk. Similarly, Prolaris was associated with post-operative adverse outcome prediction (43). In addition to that, Prolaris showed a change in treatment ranging between 48% and 65%, while reclassifying up to 56% of low risk CAPRA patients (43, 171, 172).

6.2 Study Limitations

Our study has some limitations related to the studies selected in the final step of the systematic review. First in our study some studies were not blinded and others had potential biases. However, all of these issues were taken into consideration in the quality appraisal score. Secondly, we didn't assess grey literature; however, this won't affect significantly our results especially that these tests were recently developed.

On the other hand, our study has important strengths. Many articles in the systematic review were clinical utility studies designed primarily to evaluate the new interventions of prostate cancer. And after organizing a protocol, we were able to assess the articles by two interpreters at each step, thus assuring our results. Most articles included in our review were of good and excellent quality, thus yielding important evidence on the new interventions that could be employed in PCa management.

6.3 Implications of Our Findings and Future Directions

As previously mentioned, deciding when and how to treat prostate cancer could be suboptimal. Current screening and diagnostic tools limit appropriate risk stratification and treatment. Overdiagnosis and overtreatment are concerning clinicians nowadays. To solve these obstacles, using additional tools and interventions in PCa screening, diagnosis, and treatment might help clinical decision process. Literature proved that new interventions and tests could make a significant difference in achieving personalized treatment. The benefits of these new tests and interventions could be summarized in this manner.

Our study identified groups of interventions that could be used in men with suspicion of prostate cancer or who performed screening for prostate cancer or at different moments of prostate cancer management, in addition to current assessment tools. Using these will enable clinicians to decide which type of additional testing might be used in particular groups of patients. Employing these tests might save many patients from unnecessary 1st time biopsy or subsequent biopsy. After prostate cancer diagnosis, there is a group of interventions that might differentiate between aggressive and indolent disease, thus decreasing overtreatment. Furthermore, if suspicion persists after a negative biopsy, a group of interventions might help decide if a repeat biopsy is warranted. Finally, a group of tests might be used to decide what treatment to give based on predicting the risk of recurrence and mortality. These interventions might allow clinicians to decrease uncertainty faced during PCa diagnosis and management. Literature demonstrated the clinical validity and analytical validity for some of these interventions, and now in our systematic review we gathered information on clinical usefulness

in having an impact on disease management and treatment decision, and hopefully on patients' outcomes.

So, given these facts, our study tried to answer the question: is there enough clinical evidence that these tests and interventions could be used in clinical practice? Genomic testing is advancing tremendously; however, still not used as a standard. Presented, there are many interventions that have the potential to optimize prostate cancer screening, diagnosis, and treatment, and thus personalizing treatment and improving clinical practice. These interventions demonstrated to be effective in patient stratification and treatment decision, but are they cost-effective? This enthusiasm for involving new interventions in clinical practice should be associated with studying their economic impact. Unfortunately, we lack real-world setting studies that could show the effectiveness of using these interventions and their associated costs. We need economic evaluations that assess and estimate the impact of these interventions on long term clinical outcomes and health care system. Our findings suggested tools that demonstrated efficacy and clinical usefulness, but are they applicable? Could clinicians adopt them in clinical practice?

At this point, the best suggestion is to develop and validate a predictive model of evolution and management of PCa. This model will help understand how the identified interventions would affect screening, diagnosis and treatment of prostate cancer, from screening to end-of-life. Thus simulates the impact of adopting such interventions on PCa evolution, outcomes, and costs. Outcomes such as overall survival, quality adjusted life-years gained, and associated costs

could be studied. If such study is done, we will understand if these PCa risk assessment tools have an impact on patients' outcomes and for what cost. If proved to be cost effective, decision makers and clinicians will be encouraged to use these interventions in practice, thus achieving individualized treatment.

7. Conclusion

This study is an overview of clinical utility evidence on many interventions that could have significant potential to impact personalized treatment decisions and to improve clinical outcomes if adopted in clinical practice. Yet, their cost-effectiveness should be proved before public access to these interventions. This review suggests that these tests in clinical practice could help achieve personalized treatment of PCa by adding meaningful new information for better risk assessment and disease prognostication. Further clinical utility and economic evaluation studies are warranted to provide further guidance.

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APPENDIX

APPENDIX I – MEDLINE search strategy [Ovid]

1. exp Prostatic Neoplasms/

2 .prostat*.hw. and exp Neoplasms/

3 .(prostat* adj5 (adenoma* or adenocarcin* or mass or masses or cyst* or cancer* or tumo?r* or neo?plas* or carcinom* or oncolog* or sarcom*)).tw,kf.

4 .1 or 2 or 3

5 .Animals/ not (Animals/ and Humans/)

6 .4 not 5

7. (PHI or prostat* health index*).tw,kf.

8. 6 and 7

9. (4Kscor* or 4K scor* or (("4" or four) adj3 (kallikrein* or Kallikurein*))).tw,kf.

10. 6 and 9

11. (Bostwick* or ProstaV?s* or Prosta V?s*).tw,kf.

12. ERG.tw,kf. and PTEN.tw,kf,hw.

13. 11 or 12

14. 6 and 13

15. Prostarix*.tw,kf.

16. (sarcosin* and alanin* and glycin* and glutamat*).tw,kf,hw.

17. 15 or 16

18. 6 and 17

19. prolar?s*.tw,kf. or ((ccp or cycle cell proliferat*) adj3 (test* or score* or assay*)).tw,kf,hw.

20. 6 and 19

21. (oncotyp* or (onco adj2 typ*)).tw,kf.

22. 6 and 21

23. (metamar* or meta-mar* or promar* or pro-mar*).tw,kf.

24. 6 and 23

25. Progensa*.tw,kf.

26. ((PCA3 or PCA 3 or gene 3) adj5 (test* or score* or assay*)).tw,kf.

27. 25 or 26

28. 6 and 27

29. (PCMT or mitom*).tw,kf.

30. 6 and 29

31. (Confirm MDx* or ConfirmMDx*).tw,kf.

32. 6 and 31

33. ((genomedx or deciphertest* or deciphertm or decipherdx or deciphergc or decipher*) and (tm or test* or score* or gc or rna or biomark* or bio-mark* or genom* or assay* or dx)).tw,kf.

34. 6 and 33

35. (ProsV* or prostat* specific antigen slope*).tw,kf.

36. 6 and 35

37. (Mi-Prostat* or MiPS or (mi adj5 score*)).tw,kf.

38. 6 and 37

39. exp Magnetic Resonance Imaging/

40. (mri or (magnetic* adj3 resonanc*)).tw,kf.

41. 39 or 40

42. 6 and 41

43. exp Mass Screening/

44. (screen or screening).tw,kf.

45. 43 or 44

46. 42 and 45

APPENDIX II – Data Extraction Sheet

Name of reviewer:

Date:

Study ID (first author, year):

Notes:

Article's title
Type of study
1. Randomized, controlled clinical trial / survey / observational …? 2. Was the study designed to evaluate the clinical utility of new prognostic test, or was it a secondary analysis of data collected for other purposes? 3. Funding source: 4. To what phase does the study belong: Phase 1- screening /Phase 2- after positive biopsy/Phase 3- after negative biopsy/ Phase 4- add treatment

5. What was the testing scenario?

   (Is there in the study a comparison between cases and controls? Did the 2 groups have similar characteristics?)

Study population

6. Country and year where the study was conducted:

7. Number of subjects enrolled:

8. Number of subjects completed the study:

9. Duration of study:

10. Characteristics of subjects:

11. Inclusion /exclusion criteria:

12. Were the patients selected by the physician or randomly assigned?

13. Did the sample represent patients that would be tested in clinical practice?

14. Is there a concern for selection bias (systematic differences between baseline characteristics of the groups that are compared), explain:

Intervention

15. What is the used intervention?

16. Were investigators/physicians blinded to the test results?

(when they gave their first recommendation they didn't know about test results)
Outcome
17. What are the outcomes studied?
Outcome assessment
18. How were the outcomes assessed?
Results

APPENDIX III –Quality appraisal tool

Name of reviewer:

Date:

Study ID (first author, year):

Notes:

Scoring procedure: 0 if ‘‘not clear’’ or ‘‘not a relevant item’’ or “not good quality”, 1 for ‘‘good quality’’, 2 for ‘‘excellent quality’’.

Article’s title	**Score**
Type of study	
1. Was the study designed to evaluate the clinical utility of the new prognostic test, or was it a secondary analysis of data collected for other purposes? 2. Were there conflicts of interest? (0 if there is a conflict/ 2 if no conflict)	
Study population	
3. Was the clinical population clearly described including inclusion and exclusion criteria and subject participation? 4. How were the patients assigned to the chosen intervention? Were they selected by the physician or randomly assigned? 5. Is there a concern for selection bias (systematic differences between baseline characteristics of the groups that are compared)? 6. Did the sample represent patients that would be tested in clinical	

practice?	
Intervention	
7. Were the prognostic tests clearly described and conducted using a standardized, reliable, and valid method? 8. Was the test used and interpreted the same way by all sites/studies including any indeterminate test results? (Did they do and interpret as standards/ manufacturer says) 9. Were investigators blinded to the test results?	
Outcome	
10. Was the outcome being predicted clearly defined?	
Outcome assessment	
11. Was the outcome being predicted ascertained using a standardized, reliable, and valid method? (For example if there is a change in treatment, did a third party assess the change?) 12. Did everyone in the samples have a common starting point for follow up with respect to the outcome of interest including any treatments that could affect the outcome being predicted? (Did the patients receive any treatment /intervention that could affect the results/outcomes " DRE timing, 5-α-reductase inhibitors …/Were all the patients from same phase or were the patients who did the test from low risk group and who didn't from high risk group → overestimation since high risk groups are less	

likely to change treatment) 13. Is there a concern for performance bias (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest)? 14. Is there a concern for detection bias (systematic differences between groups in how outcomes are determined)?	
Follow-up	
15. How complete was the follow up of subjects, and were losses to follow up related to the test results or the outcome being predicted? Was the duration of follow up adequate? (If no follow up in a study where there is no need for follow up, then the answer is 0 not applicable) 16. Is there a concern for attrition bias (systematic differences between groups in withdrawals from a study, e.g. data not available or exclusions)?	
17. Is there a concern for reporting bias (systematic differences between reported and unreported findings, e.g. are both significant and non-significant differences reported)?	

Based on checklist published in Rector et al.