Molecular Biomarkers in the Context of Focal Therapy for Prostate Cancer: Recommendations of a Delphi Consensus from the Focal Therapy Society

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Abstract

Background: Focal Therapy (FT) for Prostate Cancer (PCa) is promising. However, long-term oncological results are awaited and there is no consensus on follow-up strategies. Molecular biomarkers (MB) may be useful in selecting, treating and following up men undergoing FT, though there is limited evidence in this field to guide practice. We aimed to conduct a consensus meeting, endorsed by the Focal Therapy Society, amongst a large group of experts, to understand the potential utility of MB in FT for localised PCa. **Materials and Methods:** A 38-item questionnaire was built following a literature search. The authors then performed three rounds of a Delphi Consensus using DelphiManager, using the GRADE grid scoring system, followed by a face-to-face expert meeting. Three areas of interest were identified and covered concerning MB for FT, i) the current/present role; ii) the potential/future role; iii) the recommended features for future studies. Consensus was defined using a 70% agreement threshold. **Results**: Of 95 invited experts, 42 (44.2%) completed the three Delphi rounds. Twenty-four items reached a consensus and they were then approved at the meeting involving (n=15) experts. Fourteen items reached a consensus on uncertainty, or they did not reach a consensus. They were re-discussed, resulting in a consensus (n=3), a consensus on a partial agreement (n=1), and a consensus on uncertainty (n=10). A final list of statements were derived from the approved and discussed items, with the addition of three generated statements, to provide guidance regarding MB in the context of FT for localised PCa. Research efforts in this field should be considered a priority. **Conclusion**: The present study detailed an initial consensus on the use of MB in FT for PCa. This is until evidence becomes available on the subject.

Keywords: prostate cancer, localised, focal therapy, molecular biomarker, Delphi

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1. Introduction

Focal therapy (FT) for prostate cancer (PCa) is an emerging treatment option, introduced to reduce the side effects of radical treatments, whilst maintaining a similar oncological control[1,2].

Currently, guidelines suggest FT to be restricted to clinical trials and prospective registries [3].
Absence of long-term results and of randomized controlled trials (RCT) against radical treatments remain amongst the major arguments hampering its introduction in clinical practice [2,4].

On the one hand, complications are low and short-to-medium term results are favourable[2,5].
On the other hand, up to one in five men has a disease recurrence or persistence if prostate biopsies are performed at 12 months after treatment[3], and approximately 50% may need at least one re-treatment within five years [6]. Re-do treatments may have low morbidity and salvage radical prostatectomy following FT, if performed in expert hands, may be comparable to a first-line setting except for the poor post-operative erectile function[7]. A critical assessment of FT outcomes clearly shows that it is still far from achieving optimal oncological control, and the urological community should strive to identify and implement the weak points seeking for improvement[8,9].

Amongst the possible reasons for disease recurrence/persistence after FT are: i) an inappropriate ablation leaving PCa untreated due to technical and/or operator-dependent issues; ii) incorrect targeting either due to limitations of the imaging modality to identify the precise boundaries of each tumor or the inability of the chosen imaging modality to identify the tumor itself (eg MRI-invisible tumor); iii) the PCa microenvironment being modified in a pro-tumorigenic fashion by treatment-induced inflammation and possibly favouring the development of resistant clinically significant PCa clones; and iv) inappropriate patient selection due to the limitations of the current risk stratification tools[8].

The latter, in particular, may lead to undertreatment of high-risk disease, significantly increasing the risk of recurrence/progression after FT when compared to intermediate-risk PCa[6,10], to underestimation of the disease volume, and to underdetection of clinically significant disease in the non-ablated prostate.

Molecular Biomarkers (MB) have been introduced in clinical practice, in order to provide a more precise, patient-based risk stratification. Several validated kits are commercially available for PCa diagnostic, prognostic, and in adjuvant treatment settings. These include blood, urine, and prostate tissue based-markers, which evaluate a wide variety of cellular pathways involved in the prostate cancer pathway, from baseline gene mutations to RNA, methylation patterns, and protein expression levels[11–13]. MB have been mainly studied in the context of active surveillance, with the aim of identifying patients who would benefit the most from treatment. They have also been studied in a first-line diagnostic or post-prostatectomy context, to identify those at high risk of developing PCa metastases, and eventually, to identify those who might benefit from adjuvant treatment[11–13].

Nonetheless, little if no evidence exists on the use of MB in the context of FT, whether to improve risk stratification, to reduce an inappropriate treatment delivery, or to improve outcomes. Furthermore, the lack of criteria/biomarkers to reliably follow-up patients receiving FT and even patients simply on active surveillance is well acknowledged.

With this in mind, a Delphi Consensus was devised and conducted by the Focal Therapy Society (FTS) aiming to frame the current and future potential role of MB in the context of FT for PCa and to ascertain needs of clinicians regarding MB application in the FT context going forward. We hereby aim to describe the results and recommendations of this Consensus.

2. Material and Methods

In 2019, a Delphi consensus on the role of Biomarkers in FT of PCa was endorsed by the FTS. The 'a priori' study methodology comprised of three phases.

2.1 Phase I: Literature Review and Questionnaire Design

A non-systematic review of the English language literature was conducted by two authors (G.M. and R.S.S.) on the 5th January 2020 using the PubMed portal, using the terms ''focal therapy'' AND ''prostate cancer'' AND 'biomarkers'', to summarise the current evidence on MB and their current and potential use in FT. No papers investigating MB in the context of FT for PCa were identified.

Two authors designed a 38-item questionnaire that covered three main areas concerning the current and future use of MB in FT for PCa:

1) Current evidence and the role of MB;
2) Future/Potential role of MB;
3) Important tests to be included in future studies for assessing the role of MB.

The literature review summary, the preliminary survey design, and the Delphi methodology were evaluated by an advisory panel composed of 2 opinion leaders in FT (M.P.L., T.P.) and by a team of dedicated methodologists (Department of Trials Methodology, Liverpool Clinical Trials Centre, Liverpool University, Liverpool, UK). The panel was asked to review the questionnaire, integrating any other points if necessary, and to implement/comment on the methodology, before starting the consensus rounds. The questions/items in their final form are shown in **Supplementary Material 1**. The definitions used in the consensus are displayed in **Table 1**.

2.2 Phase II: Delphi Consensus

All of the included statements were entered into DelphiManager, a bespoke online tool, in order to perform the Delphi Consensus[14].

The survey was sent to Urologists, Radiologists and Pathologists who are experts in the field of FT. An expert was defined as having performed at least 100 FT cases with one or multiple energies and/or having published at least 10 PCa papers one of whom in the field of FT. As FT is currently focused on localised PCa treatments, no Oncologists were included. Since FT is not recognized as a standard of care, patient representatives were not included.

The levels of agreement were based on a nine-point scale, according to the GRADE grid[14,15]: 1–3 disagree; 4–6 uncertain; and 7–9 agree. An ''Unable to Score'' option was also added in the case of insufficient knowledge/expertise. Consensus was defined when at least 70% of the participants were agreeing (score 1-3), being uncertain (score 4-6), or disagreeing (score 7-9) as previously described [14,15] . However, as the field of biomarkers in FT is currently unexplored, no concomitant ≤15% disagreement threshold was used.

Repeated anonymous voting was performed in three rounds (1st round: 16th-27th January 2020; 2nd round: 28 January-2nd February 2020; 3rd round 3rd-7th February 2020). After the first round, the questions reaching consensus were removed from the subsequent round and the participants were provided with the results from the previous round, in the form of histograms plus percentages – **See example in Supplementary Material 2**. Those items that reached a consensus of agreeing or disagreeing with a statement were presented for approval but not re-discussed in Phase III. Conversely, the items reaching a consensus on uncertainty towards a statement and the items not reaching a consensus were re-discussed in Phase III.

2.3 Phase III: Face-to-face expert meeting

The last phase included a face-to-face consensus meeting during the Focal Therapy Society Congress, 9th February, 2020, in Washington D.C., USA. The discussion was chaired by two Urologists (R.S.S., G.M.) and included 15 experts.

The voting panel consisted of the 15 participants (Urologists). The statements reaching consensus by the 3rd survey round (agreement or disagreement), were presented for approval and all of the statements not reaching consensus or uncertainty after the three Delphi rounds were formally re-discussed (**Figure 1**). The anonymous voting was performed live during the meeting through Poll Everywhere Voting Software (https://www.polleverywhere.com/, last accessed, 11th February 2020) by using individual smartphone devices. Each participant was asked to provide a score to approve, disapprove, or express uncertainty, towards a statement/item.

For inclusion in the final recommendations, each survey item was required to have reached group consensus by the end of the three survey rounds (Phase II), plus approval at the face-to-face meeting (Phase III), or consensus at the face-to-face meeting (Phase III). All of the meeting discussions and the statements were recorded.

The resulting document was distributed for approval to all survey participants that completed the 3 Delphi rounds and to face-to-face meeting attendees.

3. Results

The Study Flow Chart and an overview of the Delphi results are provided in **Figure 1**. From the 95 invited experts, 54 (56.8%), 46 (48.4%) and 42 (44.2%) completed the first, second and third round respectively (third round n=40 Urologists; n=2 Radiologists). Overall, consensus was reached in 29 of 38 items (76.3%) across the three rounds (**Table 2, 3 and 4**). The distribution of the items reaching consensus was: agreement in 19 items, disagreement in 5 and uncertainty in 5 items.

Consensus was reached in 14/38, 9/24 and 6/15 items in the first, second and third round respectively. Overall, the 24 items were scored in agreement or disagreement with consensus at the Delphi-were presented and approved during the face to face meeting and approved. From the 14 items that did not reach consensus or were scored with uncertainty and consensus, 3 were scored in agreement but without consensus and in 1 partial agreement but without consensus (**See statement 3.3 – Table 5**) was reached. For the remaining 10, there was agreement regarding uncertainty and thus no specific statements could be made. During the face-to-face meeting, 3 new statements were generated and added to the final list of statements. The final list of statements is displayed in **Table 5**.

3.1 Current Evidence/Role of MB in the context of FT for localised PCa

Six of the eight formulated items found agreement in the three Delphi rounds, leading to six statements on the current role/evidence of MB (**Table 2**). An overall agreement was found on the lack of evidence supporting the present role of MB, their routine use and their impact on clinical decision making. Multi-parametric magnetic resonance imaging (mpMRI) was recognised as more accessible and useful than MB in the current FT scenario (**Table 5 – 1.1 to 1.3.2**).

3.2 Future/Potential Role of MB in the context of FT for localised PCa

3.2.1 Single MBs

Overall, items 9 to 21 included a list of single MB (**Table 3**). Only three items found consensus; PSA and PSAd were recognised as having a current role (**Table 5 - 2.2.1, 2.2.2 -**) whilst there was a consensus on the lack of interest towards the application of PCA3 in the context of FT (**Table 5 - 2.3.1**). On the contrary, consensus on uncertainty (n=5) or no consensus (n=5) **(Table 3**) was present on the majority of items, as no other available MB have a proven impact in the field of FT. *During the meeting, the panel agreed on uncertainty for all of these items; consequently, no statements were made on the single MBs*.

3.2.2 MBs overall

Three statements were generated and added by the panel (**Table 5 - 2.1; 2.4.1; 2.4.2**). The panel recognised that research in the field is a priority. Whilst no preferred source (tissue or biological fluids) for MB was identified in a diagnostic setting, there was an agreement in ideally preferring non-tissue based MB in the follow-up setting after FT treatment.

3.2.3 Ideal Features and Endpoints for MB

Full agreement was reached during the Delphi rounds and this was confirmed by the panel on the six items that concerned ideal features for MB in the context of FT for localised PCa (**Table 4 and Table 5 – 2.5.1 to 2.5.6**). The ideal features/endpoints included: i) an accuracy improvement over currently available diagnostic tools; ii) the ability to rule out high risk disease; iii) the ability to identify men with intermediate risk disease; iv) the ability to rule out intermediate risk disease outside of the treated/target area; the ability to predict a high risk of PCa recurrence/persistence v) overall, and vi) requiring a radical treatment; vii) the ability to decrease PCa recurrence/persistence when incorporated in clinical decision-making.

3.3 Tests/Exams in Future Studies to assess the role of MB in the context of FT for localised PCa

Five of 10 items concerning the ideal tests/exams that should be included in future studies for assessing the role of MB in the context of FT reached agreement during the Delphi survey rounds (**Table 5 – 3.1.1 to 3.2.5**). The panel agreed that digital rectal examinations (**Table 5 - 3.1.6**) should also be included as a relevant test. On the contrary there was consensus that 3 items, Choline C-11 PET scan, CT scan, and bone scan (**Table 5 – 3.2.1 to 3.2.3**) should not be used as standard for comparison when assessing the usefulness of a MB in a FT context.

The use of PSMA-PET in the context of MB for PCa FT (**Table 5 – 3.3**) was found to be of interest by the panel (**Table 5 – 3.3**).

4. Discussion

The present study reports on the first Delphi Consensus evaluating the role of MB in the context of FT for localised PCa. Currently, no evidence concerning in this field is present. Our work pioneered this area aiming to: i) clarify the current role of MB in routine clinical practice when involving urologists using FT; ii) define the main ideal features for future studies aiming to deal with this subject when involving researchers, funders, and industry.

4.1 Current role of MB in the context of FT for PCa

The first key point was the unanimous acknowledgement that there was no evidence surrounding the use of MB in the context of FT for PCa.

This derived both from the absence of any relevant articles being found during the literature search process and from the personal experience of panel and Delphi members. Despite FT has good oncological results for low- to intermediate risk PCa on the medium term[6,10,16,17], a room for improvement exists. Optimization of FT patient selection and timely detection of treatment failures/relapses through tools other than those currently avaible is indeed key.

However, MB have been evaluated in different contexts than FT (e.g. active surveillance, radical prostatectomy and following chemotherapy) and have frequently not been adjusted for the current risk stratification/diagnostic pathway. Namely, mpMRI and mpMRI-targeted biopsies were not performed in the majority of the cohorts investigating and/or validating MB[11–13,18]. Pre-biopsy mpMRI and mpMRI-targeted biopsies in the case of a suspicious imaging result[19] are now recommended by the major guidelines and they constitute *“de facto”* the basis -of FT feasibility for PCa. Hence, for all of these reasons, until supporting evidence becomes available, a patient should not be offered, or precluded, from gland preserving strategies that are based on MB.

4.2 Future/potential role of MB in the context of FT for PCa

The second important finding was that tools to correctly allocate (diagnostic setting – before FT) and safely monitor (follow-up setting – after FT) FT patients are urgently awaited beyond mpMRI. Consequently research in the field of MB FT related should be considered a priority. The outcomes of the consensus underscore the need for collaboration among the different stakeholders involved in the field, and the implementation of 'smart" research protocols while partnering with the industry. FT has been proven safe, with improved functional outcomes compared. Nonetheless, oncological outcomes are suboptimal, and improving patient selection is perfunctory to decrease the recurrence rates [6,10,16]. In addition, especially when in-field, the disease relapse/persistence may harbour aggressive cancer. Thus, early recognition may translate into therapeutic benefit[7,20–22]

The third point was the uncertainty on which biomarkers will likely have a role in the context of FT. Neither agreement nor disagreement was reached for the majority of the currently commercially available MB, either during the Delphi rounds or in the face-to face meeting. In spite of a lively discussion on each single available test, we could not formulate any statement on which test/s may be worth investigating in future studies. However, overall, the panel agreed there was uncertainty and this remains to be addressed.

It is worth noting that two statements on the ideal MB source were added to the initial Consensus items. As PCa diagnosis relies on histology, with Gleason score being fundamental in risk stratification, there was no preference for tissue, blood, urine, or other marker sources in the diagnostic setting. On the contrary, in the follow-up setting, a non-invasive MB (biological fluids easy to obtain) that allows for reducing or avoiding monitoring biopsies, would be preferred over a tissue-based molecular test. When considering that PSA changes can be challenging to interpret when evaluating for recurrence of PCa after FT, and that mpMRI warrants further investigation in the follow-up setting, the search for an adequate biomarker capable to monitor progession after FT becomes an important issue.

A fourth relevant point of discussion was the definition of the endpoints that will need to be addressed by future research on MB in the context of FT. Intermediate risk disease remains the current ideal FT candidate but it has a relatively slow evolving course, even when left untreated[23]. Thus, intermediate surrogate endpoints would likely allow for short-to-medium term answers on a potential role for biomarkers. In particular, a key achievement will be to impact on clinical decision-making, allowing for a reduction in the number of in- and out-of field persistence/recurrence, while providing timely information on persistences/recurrences post-treatment, reducing or virtually avoiding, the control biopsies.

Lastly, a MB will need to demonstrate its independent ability to improve the current pathway. A fairly strict list on what will be the standards for comparison to determine the prognostic or predictive ability of the chosen MB regarding risk-groups categorization and response to treatment has been devised for oncoming studies. Interestingly, while PSMA-PET was not considered amongst the recommended tests for comparison as still subject to accessibility issues and pendent of validation [24–28], it is increasingly used in a treatment-naïve context and was felt of interest.

Multicenter trials are ongoing or about to start in the field of FT or MB [29–31]. Our consensus provides scientific and practical information, obtained from an international expert panel through a validated methodology, to implement MB in these studies, possibly providing and/or

planning to obtain timely evidence to further improve our current outcomes.

Some limitations in this study have to be acknowledged. First, the work produced statements based on an expert consensus, which represents the lowest level of evidence. However, with exclusion of the present report, the field remains unexplored. Second, a literature review summary concerning current evidence on MB in the context of FT for PCa did not provide any published studies on this topic. Third, no panelists other than urologists were present at the face-to-face meeting. The three Delphi rounds were completed mainly by urologists and by some radiologists. This limits the generazability of the findings in a multi-stakeholder context. However, it may be partly related to chance (the non-attending/non-replying invited non-urological experts) and because the target audience of the first FTS meeting being mainly urological. Similarly, no patient representatives were included, mainly due to the developmental nature of FT. Finally, we could not find clear positions and/or agreement on some items. This uncertainty, which is linked to the absence of evidence, will hopefully be addressed by future research on MB in the context of FT.

5. Conclusions

At present, there is limited evidence regarding the use of MB in the context of FT for PCa. A Delphi Consensus, including a group of experts in the field, was therefore performed in order to produce consensus recommendations on this subject. Currently, no evidence supports the use of MB in the field of FT. Thus, MB should not be routinely offered in this field. Nonetheless, tools to correctly allocate (before FT) and safely monitor (after FT) FT patients are urgently awaited. MB should play an important role in future research in FT and should be considered a priority. Meaningful endpoints should be chosen to identify a molecular biomarker that will objectively improve the current FT pathway in a clinically significant manner compared to to existing options.

Ethics: the present study did not involve patients. No ethical committee approval was needed.

Conflict of Interests: none to declare.

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Authors contributions: All authors significantly contributed to the manuscript. Giancarlo Marra and Rafael Sanchez-Salas were involved in study design, data acquisition, statistical analysis and in drafting the manuscript. Giancarlo Marra, Maria Pilar Laguna, Jochen Walz, Christian P. Pavlovich, Fernando Bianco, Justin Gregg, Amir H. Lebastchi, Herbert Lepor, Petr Macek, Soroush Rais-Bahrami, Cary Robertson, Daniel Rukstalis, Georg Salomon, Osamu Ukimura and Rafael Sanchez-Salas participated to the face-to-face consensus meeting during the Focal Therapy Society Congress in Washington DC, US. All authors successfully completed all the three rounds of the Delphi consensus and read and approved the last version of the manuscript.

Figure and Tables Legend

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Figure 1. Study Flow Chart.

Table 1. Definitions used in the Delphi rounds and in the face-to-face consensus meeting.

Table 2. Delphi Items to reach consensus statements on the current role of Molecular Biomarkers in the context of Focal Therapy for Prostate Cancer. Scores in the three Delphi rounds and final outcomes. MB=Molecular Biomarkers; FT=Focal Therapy; PCa=Prostate Cancer; UTS=Unable to Score; NC=not completed; Green= consensus on agreement; Red=consensus on disagreement; Yellow=consensus on uncertaninty.

Table 3. Delphi Items to reach consensus statements on the current role of Molecular Biomarkers in the context of Focal Therapy for Prostate Cancer. Scores in the three Delphi rounds and final outcomes. MB=Molecular Biomarkers; FT=Focal Therapy; PCa =Prostate Cancer; UTS=Unable to Score; NC=not completed; RT=radical treatment. Green= consensus on agreement; Red=consensus on disagreement; Yellow=consensus on uncertaninty.

Table 4. Delphi Items to reach consensus statements on important tests that have to be included in future studies evaluating the role of Molecular Biomarkers in the context of focal therapy for localised Prostate Cancer. *=studies assessing the role of Molecular Biomarkers in the context of focal therapy for localised prostate cancer should also include/allow comparison of the Molecular Biomarker'; MB=Molecular Biomarkers; FT=Focal Therapy; PCa =Prostate Cancer; UTS=Unable to Score; NC=not completed; DRE=Digital Rectal Examination; Green= consensus on agreement; Red=consensus on disagreement; Yellow=consensus on uncertaninty.

Table 5. Focal Therapy Society Statements on Molecular Biomarkers in the context of Focal Therapy for Prostate Cancer. MB=Molecular Biomarkers; FT=Focal Therapy; PCa=Prostate Cancer. For the definitions used, please see Table 1. *=statements generated and added by the consensus panel at the face-to-face meeting.

Supplementary Material 1. Delphi questionnaire.

Supplementary Material 2. Example of the graph being shown during the second and third Delphi round to summarise the results from the previous round.

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Table 1. Definitions used in the Delphi rounds and in the Face to face consensus meeting

- **Molecular Biomarker:** A biologic molecule found in human tissues and/or fluids able to provide information on the studied disease (diagnostic – presence or absence; prognostic – disease aggressiveness; likelihood of response to treatment).
- **Focal therapy for Prostate cancer:** An ablation/treatment not targeting the whole prostate gland but treating the area containing prostate cancer, plus a safety margin, whilst sparing the remaining benign prostatic tissue.
- **High risk prostate cancer:** Gleason Score ≥8 and/or cT3a disease and/or PSA>20ng/mL.
- **Localized prostate cancer:** Prostate cancer localized within the prostate gland and with no evidence of systemic spread.

Table 2- Current Evidence/Role of Molecular Biomarkers in the context of FT for Pca

		ROUND 1					ROUND 2					ROUND 3					OUTCOME	
		disagree	uncertain	agree	UTS	NC	disagree	uncertain	agree	UTS	NC	disagree	uncertain	agree	UTS	NC	Consensus	Round
1	Evidence on the role of MB in the setting of FT is absent (no evidence)	15.7 (8)	29.4 (15)	54.9 (28)	1	2	6.5 (3)	13.0 (6)	80.4 (37)	0	0	-	-	-	-	-	Yes	R2
2	Evidence on the role of MB in the setting of FT is low	2.0 (1)	17.6 (9)	80.4 (41)	1	2	-	-	-	-	-	-	-	-	-	-	Yes	R1
3	Evidence on the role of MB in the setting of FT is high	83.7 (41)	12.2 (6)	4.1 (2)	3	2	-	-	-	-	-	-	-	-	-	-	Yes	R1
4	MB should be used in the context of routine clinical decision making for FT for Pca	26.9 (14)	48.1 (25)	25.0 (13)	0	2	15.2 (7)	54.3 (25)	30.4 (14)	0	0	7.1 (3)	59.5 (25)	33.3 (14)	0	0	No	
5	MB should not be used in the context of routine clinical decision making for FT for Pca as their role in this setting is still unclear	30.0 (15)	22.0 (11)	48.0 (24)	2	2	19.6 (9)	10.9 (5)	69.6 (32)	0	0	16.7 (7)	11.9 (5)	71.6 (30)	0	0	Yes	R3
6	MB should not be used in the context of routine clinical decision making for FT for Pca as they have been tested in clinical scenarios different from FT	39.2 (20)	23.5 (12)	37.3 (19)	1	2	39.1 (18)	21.7 (10)	39.1 (18)	0	0	40.5 (17)	16.7 (7)	42.9 (18)	0	0	No	
7	At present, prostate mpMRI is more useful than MB in the context of FT for localized Pca	5.8 (3)	7.7 (4)	86.5 (45)	0	2	-	-	-	-	-	-	-	-	-	-	Yes	R1

8	At present, prostate mpMRI is more accessible than MB in the context of FT for Pca	15.7 (8)	17.6 (9)	66.7 (34)	1	2	4.3 (2)	8.7 (4)	87.0 (40)	0	0	-	-	-	-	-	Yes	R2
	TOTAL ITEMS FINDING AGREEMENT	3					2					1					6	

Current Evidece/Role of Molecular Biomarkers in the context of FT for Pca

Table 2		ROUND 1			OUTCOME	
		disagree	uncertain	agree	Consensus	Round
1	Evidence on the role of MB in the setting of FT is absent (no evidence)	6.5 (3)	13.0 (6)	80.4 (37)	Yes	R2
2	Evidence on the role of MB in the setting of FT is low	2.0 (1)	17.6 (9)	80.4 (41)	Yes	R1
3	Evidence on the role of MB in the setting of FT is high	83.7 (41)	12.2 (6)	4.1 (2)	Yes	R1
4	MB should be used in the context of routine clinical decision making for FT for Pca	7.1 (3)	59.5 (25)	33.3 (14)	No	
5	MB should not be used in the context of routine clinical decision making for FT for Pca as their role in this setting is still unclear	16.7 (7)	11.9 (5)	71.6 (30)	Yes	R3
6	MB should not be used in the context of routine clinical decision making for FT for Pca as they have been tested in clinical scenarios different from FT	40.5 (17)	16.7 (7)	42.9 (18)	No	
7	At present, prostate mpMRI is more useful than MB in the context of FT for localized Pca	5.8 (3)	7.7 (4)	86.5 (45)	Yes	R1
8	At present, prostate mpMRI is more accessible than MB in the context of FT for Pca	4.3 (2)	8.7 (4)	87.0 (40)	Yes	R2

Future/Potential Role of Molecular Biomarkers in the context of FT for Pca

Table 3		ROUND 1					ROUND 2					ROUND 3					OUTCOME	
		disagree	uncertain	agree	UTS	NC	disagree	uncertain	agree	UTS	NC	disagree	uncertain	agree	UTS	NC	Consensus	Round
The following MB may be used/have a role in the context of FT for Pca																		
9	PSA	5.9 (3)	17.6 (9)	76.5 (39)	0	3	-	-	-	-	-	-	-	-	-	-	Yes	R2
10	PSA density	3.9 (2)	23.5 (12)	72.5 (37)	0	3	-	-	-	-	-	-	-	-	-	-	Yes	R1
11	Prostate Cancer Antigen 3 (PCA3 or Progensa test)	54.9 (28)	35.3 (18)	9.8 (5)	0	3	71.7 (33)	26.1 (12)	2.2 (1)	0	0	-	-	-	-	-	Yes	R1
12	SelectMDx	30.0 (15)	50.0 (25)	20.0 (10)	1	3	21.7 (10)	67.4 (31)	10.9 (5)	0	0	19.0 (8)	76.2 (32)	4.8 (2)	0	0	Yes	R3
13	PHI (Prostate Health Index)	35.4 (17)	43.8 (21)	20.8 (10)	3	3	40.0 (18)	55.6 (25)	4.4 (2)	1	0	31.7 (13)	65.9 (27)	2.4 (1)	1	0	No	
14	4K Score	27.1 (13)	52.1 (25)	20.8 (10)	3	3	21.7 (10)	67.4 (31)	10.9 (5)	0	0	19.5 (8)	75.6 (31)	4.9 (2)	1	0	Yes	R3
15	ConfirmMDx	22.9 (11)	52.1 (25)	25.0 (12)	3	3	22.2 (10)	64.4 (29)	13.3 (6)	1	0	17.1 (7)	78.0 (32)	4.9 (2)	1	0	Yes	R3
16	Prolaris (Myriard Genetics)	19.6 (9)	47.8 (22)	32.6 (15)	5	3	15.6 (7)	60.0 (27)	24.4 (11)	1	0	9.8 (4)	65.9 (27)	24.4 (10)	1	0	No	
17	Oncotype Dx	21.7 (10)	45.7 (21)	32.6 (15)	5	3	17.8 (8)	53.3 (24)	28.9 (13)	1	0	14.6 (6)	56.1 (23)	29.3 (12)	1	0	No	
18	Decipher	14.9 (7)	48.9 (23)	36.2 (17)	4	3	13.3 (6)	55.6 (25)	31.1 (14)	1	0	12.2 (5)	68.3 (28)	19.5 (8)	1	0	No	
19	Promark	23.1 (9)	59.0 (23)	17.9 (7)	12	3	19.5 (8)	68.3 (28)	12.2 (5)	5	0	15.8 (6)	73.7 (28)	10.5 (4)	4	0	Yes	R3
20	Mi-Prostate Score	30.0 (12)	25.0 (19)	22.5 (9)	11	3	27.8 (10)	66.7 (24)	5.6 (2)	10	0	28.1 (9)	65.6 (21)	6.3 (2)	10	0	No	
21	ExoDx	27.5 (11)	57.5 (23)	15.0 (6)	11	3	22.2 (8)	72.2 (26)	5.6 (2)	10	0	-	-	-	-	-	Yes	R2

A MB in the context of FT for Pca should be able to:																	
22	Significantly improve accuracy of current diagnostic tools in ruling out high risk disease	2.0 (1)	10.2 (5)	87.8 (43)	0	5	-	-	-	-	-	-	-	-	-	Yes	R1
23	Rule in the presence of Intermediate risk with a X % and acceptable 95%CI	8.3 (4)	31.3 (15)	60.4 (29)	1	5	2.2 (1)	24.4 (11)	73.3 (33)	1	0	-	-	-	-	Yes	R2
24	Rule out clinically significant disease outside of the target/treated area (area to be treated based on imaging (mpMRI) and biopsy results)	2.0 (1)	28.6 (14)	69.4 (34)	0	5	0	8.7 (4)	91.3 (42)	0	0	-	-	-	-	Yes	R2
25	To predict those at a high-risk of recurrence after FT for localized Pca (in-field and/or out-of-field recurrence/persistence)	2.0 (1)	14.3 (7)	83.7 (41)	0	5	-	-	-	-	-	-	-	-	-	Yes	R1
26	To predict those at high risk of a recurrence requiring a RT after FT for localized Pca	4.1 (2)	8.2 (4)	87.8 (43)	0	5	-	-	-	-	-	-	-	-	-	Yes	R1
27	When incorporated in the clinical decision	4.1 (2)	18.4 (9)	77.6 (38)	0	5	-	-	-	-	-	-	-	-	-	Yes	R1

	making, to decrease overall recurrence after FT for localized Pca												
	TOTAL ITEMS FINDING AGREEMENT	6			4			4				14	

Future/Potential Role of Molecular Biomarkers in the context of FT for Pca						
		disagree	uncertain	agree	Consensus	Round
The following MB may be used/have a role in the context of FT for Pca						
9	PSA	5.9 (3)	17.6 (9)	76.5 (39)	Yes	R2
10	PSA density	3.9 (2)	23.5 (12)	72.5 (37)	Yes	R1
11	Prostate Cancer Antigen 3 (PCA3 or Progensa test)	71.7 (33)	26.1 (12)	2.2 (1)	Yes	R1
12	SelectMDx	19.0 (8)	76.2 (32)	4.8 (2)	Yes	R3
13	PHI (Prostate Health Index)	31.7 (13)	65.9 (27)	2.4 (1)	No	
14	4K Score	19.5 (8)	75.6 (31)	4.9 (2)	Yes	R3
15	ConfirmMDx	17.1 (7)	78.0 (32)	4.9 (2)	Yes	R3
16	Prolaris (Myriard Genetics)	9.8 (4)	65.9 (27)	24.4 (10)	No	
17	Oncotype Dx	14.6 (6)	56.1 (23)	29.3 (12)	No	
18	Decipher	12.2 (5)	68.3 (28)	19.5 (8)	No	
19	Promark	15.8 (6)	73.7 (28)	10.5 (4)	Yes	R3
20	Mi-Prostate Score	28.1 (9)	65.6 (21)	6.3 (2)	No	
21	ExoDx	22.2 (8)	72.2 (26)	5.6 (2)	Yes	R2

Future/Potential Role of Molecular Biomarkers in the context of FT for Pca

		disagree	uncertain	agree	Consensus	Round
	A MB in the context of FT for Pca should be able to:					
22	Significantly improve accuracy of current diagnostic tools in ruling out high risk disease	2.0 (1)	10.2 (5)	87.8 (43)	Yes	R1
23	Rule in the presence of Intermediate risk with a X % and acceptable 95%CI	2.2 (1)	24.4 (11)	73.3 (33)	Yes	R2
24	Rule out clinically significant disease outside of the target/treated area (area to be treated based on imaging (mpMRI) and biopsy results)	0	8.7 (4)	91.3 (42)	Yes	R2
25	To predict those at a high-risk of recurrence after FT for localized Pca (in-field and/or out-of-field recurrence/persistence)	2.0 (1)	14.3 (7)	83.7 (41)	Yes	R1
26	To predict those at high risk of a recurrence requiring a RT after FT for localized Pca	4.1 (2)	8.2 (4)	87.8 (43)	Yes	R1
27	When incorporated in the clinical decision making, to decrease overall recurrence after FT for localized Pca	4.1 (2)	18.4 (9)	77.6 (38)	Yes	R1

Important Tests/Exams to be included in future studies assessing the Role of Molecular Biomarkers*

Table 4.		ROUND 1					ROUND 2					ROUND 3					OUTCOME	
		disagree	uncertain	agree	UTS	NC	disagree	uncertain	agree	UTS	NC	disagree	uncertain	agree	UTS	NC	Consensus	Round
28	PSA	6.1 (3)	12.2 (6)	81.6 (40)	0	5	-	-	-	-	-	-	-	-	-	-	Yes	R1
29	PSAd	4.2 (2)	10.4 (5)	85.4 (41)	1	5	-	-	-	-	-	-	-	-	-	-	Yes	R1
30	DRE	36.7 (18)	32.7 (16)	30.6 (15)	0	5	43.5 (20)	23.9 (11)	32.6 (15)	0	0	47.6 (20)	19.0 (8)	33.3 (14)	0	0	No	
31	Target biopsy (if positive mpMRI)	0	6.1 (3)	93.9 (46)	0	5	-	-	-	-	-						Yes	R1
32	Targeted and systematic biopsy	0	6.1 (3)	93.9 (46)	0	5	-	-	-	-	-	-	-	-	-	-	Yes	R1
33	prostate mpMRI	0	0	100.0 (49)	0	5	-	-	-	-	-	-	-	-	-	-	Yes	R1
34	Prostate cancer risk calculators	6.1 (3)	46.9 (23)	46.9 (23)	0	5	4.3 (2)	30.4 (14)	65.2 (30)	0	0	0	11.9 (5)	88.1 (37)	0	0	Yes	R3
35	PSMA-PET	26.5 (13)	30.6 (15)	42.9 (21)	0	5	21.7 (10)	21.7 (10)	56.5 (26)	0	0	11.9 (5)	19.0 (8)	69.0 (29)	0	0	No	
36	Coline-PET	53.1 (26)	36.7 (18)	10.2 (5)	0	5	73.9 (34)	17.4 (8)	8.7 (4)	0	0	-	-	-	-	-	Yes	R2
37	CT-scan	67.3 (33)	26.5 (13)	6.1 (3)	0	5	87.0 (40)	8.7(4)	4.3 (2)	0	0	-	-	-	-	-	Yes	R2
38	Bone scan	61.2 (30)	30.6 (15)	8.2 (4)	0	5	82.6 (38)	13.0 (6)	4.3 (2)	0	0	-	-	-	-	-	Yes	R2
	TOTAL ITEMS FINDING AGREEMENT	5					3					1					9	

Tests/Exams to be included in studies assessing the Role of MB*						
Table 4.					**OUTCOME**	
		disagree	uncertain	agree	Consensus	Round
28	PSA	6.1 (3)	12.2 (6)	81.6 (40)	Yes	R1
29	PSAd	4.2 (2)	10.4 (5)	85.4 (41)	Yes	R1
30	DRE	47.6 (20)	19.0 (8)	33.3 (14)	No	
31	Target biopsy (if positive mpMRI)	0	6.1 (3)	93.9 (46)	Yes	R1
32	Targeted and systematic biopsy	0	6.1 (3)	93.9 (46)	Yes	R1
33	prostate mpMRI	0	0	100.0 (49)	Yes	R1
34	Prostate cancer risk calculators	0	11.9 (5)	88.1 (37)	Yes	R3
35	PSMA-PET	26.5 (13)	30.6 (15)	42.9 (21)	No	
36	Coline-PET	73.9 (34)	17.4 (8)	8.7 (4)	Yes	R2
37	CT-scan	87.0 (40)	8.7(4)	4.3 (2)	Yes	R2
38	Bone scan	82.6 (38)	13.0 (6)	4.3 (2)	Yes	R2

Table 5. Focal Therapy Society Statements on Molecular Biomarkers in the Context of Focal Therapy for Prostate Cancer.

- **1. Current Evidence/Role of MBs in the context of FT for localised PCa**

1.1 Evidence on the role of MBs in the context of FT for PCa is absent *(i.e. no evidence).*

1.2 Currently/At Present, MBs should not be routinely [e.g. outside of research purposes] used in the context of FT for PCa as:
1.2.1 Their role in this setting is still unclear.
1.2.2 They have been tested in clinical scenarios different from FT.

1.3 At present, prostate mpMRI in the context of FT for PCa:
1.3.1 Is more useful than MBs.
1.3.2 Is more accessible than MBs.

- **2. Future/Potential Role of MBs in the context of FT for localised PCa:**

2.1 MBs in the context of FT for PCa are a research priority*

2.2 MBs currently having a role in the context of FT for PCa:
2. 2.1 PSA.
2. 2.2 PSAD.

2.3 MBs not potentially having a role/not worth investigating in the context of FT for localised PCa:
2.3.1 PCA3 (Prostate Cancer Antigen 3 or Progensa Test).

2.4 MBs source:
2. 4.1 In a diagnostic setting (treatment selection) - there is not a preferred MBs source (urine, blood, tissue, others)*
2.4.2 In a follow-up setting (after FT) - non-tissue based MBs (urine, blood, others) may ideally be preferred*

2.5 Ideal features for MBs in the context of FT for localised PCa. MBs in the context of FT for localised PCa should be able to:
2.5.1 Significantly improve the accuracy of current diagnostic tools in ruling out a high risk disease.
2.5.2 Rule in the presence of an intermediate risk disease.
2.5.3 Rule out a clinically significant disease outside of the target/treated area (area to be treated based on imaging (mpMRI) and biopsy results).
2.5.4 Predict those at a high-risk of recurrence after FT (in-field and/or out-of-field recurrence/persistence).
2.5.5 Predict those at a high-risk of a recurrence/persistence requiring a radical treatment after FT.
2.5.6 When incorporated in clinical decision-making, to decrease an overall recurrence after FT.

- **3. Tests/Exams of Future Studies assessing the role of MBs in the context of FT for localised PCa**

3.1 Future studies assessing the role of MBs in the context of FT for localised PCa should include the following tests/exams:
3.1.1 PSA.
3.1.2 PSAD.
3.1.3 mpMRI.
3.1.4 Target and Systematic Prostate Biopsies.
3.1.5 Prostate Cancer Risk Calculators.
3.1.6 DRE.

3.2 Future studies assessing the role of MBs in the context of FT for localised PCa should not include the following tests/exams:
3.2.1 Choline C-11 PET scan.
3.2.2 CT scan.
3.2.3 Bone scan.

3.3 There is interest for PSMA-PET in the context of FT for localised PCa and MBs.