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THERAPY IN PRACTICE

Addressing Challenges and Controversies in the Management of Prostate Cancer with Multidisciplinary Teams

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Abstract
The diagnostic and treatment landscapes of prostate cancer are rapidly evolving. This has led to several challenges and controversies regarding optimal management of the disease that outpace guidelines and clinical data. Multidisciplinary teams (MDTs) can be used to engage the array of specialists that collaborate to treat complex malignancies such as prostate cancer. While the rationale for the use of MDTs in prostate cancer is well known, ways to optimally use MDTs to address the challenges and controversies associated with prostate cancer management are less well understood. One area of MDT care that remains undefined is how MDTs can most effectively provide guidance on clinical decision-making in situations in which information from novel diagnostic testing (genetic testing, molecular imaging) is substantially different from the established clinical risk factors. In this review, we provide a clinical perspective on ways that MDTs can be used to address this and other challenges and controversies across the prostate cancer disease continuum, from diagnosis to end-of-life considerations. Beyond clinical scenarios, we also review ways in which MDTs can mitigate disparities of care in prostate cancer. Overall, MDTs play a central role in helping to address the daily vexing issues faced by clinicians related to diagnosis, risk stratification, and treatment. Given the accelerating advances in precision medicine and targeted therapy, and the new questions and controversies these will bring, the value of MDTs for prostate cancer management will only increase in the future.

1 Introduction

Prostate cancer (PC) is the most common cancer among men in the USA, with 268,490 new cases estimated for 2022 [1]. Despite advances in disease detection and treatment, PC is the second leading cause of cancer deaths in men, and the last decade has witnessed an increase in the number of advanced-stage diagnoses [1]. The diagnosis, risk stratification, and treatment of PC are characterized by controversies and uncertainty, posing significant challenges to individual clinicians attempting to navigate complex pathways of care.

The inherent biologic heterogeneity of PC drives many of the challenges associated with managing the disease.

Key Points

There are numerous challenges and controversies associated with the management of prostate cancer.

Multidisciplinary teams are valuable in helping clinicians address these challenges and controversies, especially in the gray areas of care where questions produced by information from novel diagnostic technologies outpace the answers that clinical guidelines and trials provide.

As prostate cancer management continues to rapidly evolve, multidisciplinary teams will become even more important, and future studies should focus on studies of optimal processes, functions, and success metrics of modern multidisciplinary teams.

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Prostate cancer has been described as a model example of cancer heterogeneity, and it is characterized by widely varying clinical presentation (indolent tumors to aggressive metastatic disease) and outcomes, multifocality, and genetic/phenotypic heterogeneity (interpatient, intertumoral, and intratumoral) [2, 3]. Because of clinical heterogeneity, clinicians must be sensitive to the risks of both undertreatment and overtreatment in any individual patient. Essentially, treatment decision-making is not "one size fits all." This has resulted in numerous controversies for managing the PC patient journey. For example, debate continues over whether the benefits of early detection with routine PC screening outweigh the risks of over-detection and overtreatment [1, 4]. In another example, concerns regarding overtreatment have led to shifting guidelines with regard to active surveillance.

In addition to heterogeneity, PC often has a chronic and persistent disease course necessitating a series of personalized treatment and sequencing decisions that balance disease control, safety, quality of life, and patient values/preferences. A variety of approaches (e.g., observation, active surveillance, definitive treatment, treatment escalation and de-escalation) and multimodal treatment options are available at each stage of the disease. Judicious and evidence-based changes in management strategy, guided by imaging and molecular testing, may be required over the course of the disease.

Other challenges are created by the rapid evolution in the diagnostic and treatment landscapes. Although advances in imaging and genetic testing have increased the potential for precision medicine in PC, clinicians face educational and accessibility challenges regarding the clinical utilization of this information, especially when it conflicts with risk assessments from more established methods of risk stratification (e.g., histopathology/prostate-specific antigen [PSA] metrics). Additionally, the treatment landscape continues to rapidly evolve, with the resultant complexity of physician-patient shared decision-making, driven by the numerous unique therapeutics with life-prolonging benefit. Unfortunately, patients with metastatic castration-resistant prostate cancer (mCRPC) in the USA typically succumb to the disease in less than two years from starting first-line therapy [5]. Given the rapid approval of life-prolonging therapies in the last decade, there is a paucity of head-to-head data. Also contributing to the lack of data is the long follow-up time required to robustly assess survival, quality of life, and toxicity of novel therapies in clinical trials (especially in early lines of therapy).

Overall, these considerations increase uncertainty about which patients with PC to treat and when and how to treat them. The increasing number of challenges has outpaced the ability of clinical trials and consensus guidelines to provide definitive recommendations, often requiring clinicians to use their subjective judgment and benefit-risk assessments or institutional pathway management guidelines when refining management strategies for individual patients with PC. Consequently, there is global variability in the way in which clinicians approach the management of PC, with one survey study showing less than 50% agreement in management issues related to advanced PC [6]. These and other similar results have underscored the need for consensus initiatives, such as multidisciplinary teams (MDTs) and consensus conferences, to optimize the management of PC [6–9].

Multidisciplinary teams have been used to address the management of complex and chronic diseases such as PC that require an array of specialized clinicians to diagnose disease, stratify risk, and deliver multimodal treatments [10]. Ostensibly, MDTs are intended to ensure that patients receive coordinated, evidence-based care, and when multiple medically reasonable treatment options are available (as in PC), promote shared decision-making to help tailor treatment to a patient's unique values and preferences. In PC, the use of MDTs has been shown to result in changes in management, reduce bias and increase adherence to evidence-based guidelines, potentially improve clinical outcomes, and increase efficiency/accuracy of diagnosis and tissue testing as summarized in Table 1 [11–26]. In this review, we offer a clinical perspective on how modern MDTs can be used in a variety of settings to address the clinical challenges and controversies associated with contemporary PC diagnosis, risk-stratification, and treatment selection.

2 Considerations for MDTs in Modern PC Management

The complexity of PC management has increased in recent years with novel drug therapies and diagnostic technologies. Modern MDTs will need to evolve along with these advances to ensure that patients with PC receive timely and evidence-based care. In this section, we review key aspects of ways in which PC management has changed and the resulting considerations for the structure and function of modern PC MDTs.

The number of treatment options for PC has burgeoned since 2010 and continues to progressively evolve (Fig. 1). Several distinct classes of agents are available for the treatment of advanced PC including androgen-targeted therapy (abiraterone, enzalutamide, apalutamide, and darolutamide), immunotherapy (sipuleucel-T, pembrolizumab, dostarlimab), poly-ADP ribose polymerase (PARP) inhibitors (rucaparib, olaparib), chemotherapy (docetaxel, cabazitaxel), bone-directed radiopharmaceuticals (radium-223 dichloride), and prostate-specific membrane antigen (PSMA)–targeted radioligand therapy (lutetium-177 [^{177}Lu]

Table 1 Evidence for the impact of MDTs on PC management and outcomes

References	Study design	Key findings	Impact of the MDT
Clinical decision-making			
Creemers et al. [11]	Analysis of Netherlands Cancer Registry ($N = 904$) examining role of MDTs on receipt of chemo-hormonal therapy vs ADT monotherapy in mPC	Presence of an MDT was independently associated with receipt of chemo-hormonal therapy (OR= 2.77, 95% CI 1.68–4.59)	An MDT may facilitate adoption of innovative therapy
De Luca et al. [12]	Single-center prospective analysis of cases ($N = 201$) discussed at uro-oncology MDT to assess impact of MDT discussion on PC clinical decision-making	Following MDT review, patients with local, advanced, and metastatic disease had a change of diagnostic or therapeutic management in 23.2, 46.9 and 33.4%, respectively ($p < 0.001$)	MDT discussions impact PC clinical decision-making
Guy et al. [13]	Retrospective analysis of patients with newly-diagnosed PC from a single-center diagnostic assessment program ($N = 1277$)	MDT consultation was associated with significantly different management decisions compared with consultation with a urologist only ($p < 0.0001$)	MDT discussions impact PC clinical decision-making
Kurpad et al. [14]	Re-evaluation of outside diagnostic and treatment plans by a single-center MDT ($N = 269$, including 92 with PC)	Among patients with PC evaluated by an MDT: 50% had no change in diagnosis or treatment 18.5% had a change in treatment with no change in diagnosis 6.5% had a change in diagnosis with no change in treatment 3.3% had a change in both treatment and diagnosis	MDT discussions impact PC clinical decision-making
Rao et al. [15]	Single-center prospective analysis comparing provisional management plans by presenting clinicians with the subsequent MDT consensus decision (120 discussions about 107 patients [PC, kidney, and testis cancer])	The MDT made high-impact changes to original treatment plans in 26.7% of cases High-impact changes were more common in patients with metastatic disease vs those without (38 vs 23%; $p < 0.05$)	MDT discussions impact PC clinical decision-making
Scarberry et al. [16]	Prospective single-center analysis comparing management plans from treating physicians and an MDT ($N = 321$ patients, including 125 with PC)	Among patients with PC, 22/125 (17.6%) received a change in treatment plan following MTD meetings	MDT discussions impact PC clinical decision-making
Bias and treatment guideline adherence			
Korman et al. [17]	Single-center analysis of treatment decisions before and after establishment of a dedicated prostate and genitourinary MDT in the community oncology setting ($N = 182$)	MDT establishment led to statistically significant increased use of NCCN first-line treatment for intermediate-risk patients (89.8 vs 75.9%; $p = 0.01$), and nonsignificant increases for low-risk (100 vs 98.9%; $p = 0.43$) and high-risk patients (100 vs 94.2%; $p = 0.26$).	Establishment of MDTs improves quality of patient care and adherence to NCCN guidelines
Tang et al. [18]	Analysis of treatment choices for PC made at a single-center MDT ($n = 4451$) clinic vs national trends ($n = 392{,}710$; SEER database)	From 2004 to 2015, use of nondefinitive therapy in low-risk patients increased from 13 to 74% in the MDT cohort compared with 18–54% for SEER database patients A high proportion of nondefinitive therapy was used for high-risk patients in the SEER group compared with almost none in the MDT cohort In the MDT cohort, African American patients had higher rates of definitive therapy compared with white patients while the opposite was true for the SEER group	MDTs may promote greater adherence to evidence-based national guidelines and reduce the influence of race on treatment decisions

Table 1 (continued)

References	Study design	Key findings	Impact of the MDT
Clinical outcomes and patient satisfaction			
Gomella et al. [19]	Retrospective analysis of outcomes for newly diagnosed localized PC from a single-center MDT (≈ 384 PC patients per year over 10 years) compared with the SEER database	Stage III disease: OS was significantly longer for MDT patients vs SEER ($p = 0.0007$) Stage IV disease: trend for longer OS for MDT patients vs SEER ($p = 0.0847$) > 90% of patients reported the MDT clinic experience as good or very good	MDT management of PC may lead to improved outcomes
Knipper et al. [20]	Retrospective analysis of the impact of adherence to MDT aRT recommendations on clinical outcomes for RP patients at high risk of recurrence ($N = 1140$)	At 8 years (adherent vs nonadherent patients; $p < 0.001$ for all comparisons): BCR-free survival: 57.7 vs 20.1% Metastasis-free survival: 76.5 vs 75.4% Cancer-specific survival: 91.7 vs 87.4% OS: 80.4 vs 75.8%	Adherence to MDT recommendations may improve outcomes
Zhu et al. [21]	Single-center retrospective analysis of the impact of the MDT model on OS in patients with mCRPC ($N = 422$)	MDT management was associated with a longer median OS vs no MDT management (39.7 vs 27.0 months; HR = 0.549; $p = 0.001$)	MDT management may contribute to improved outcomes for patients with mCRPC
Litton et al. [22]	Description of the experience of implementing a community-based MDT cancer clinic (including PC)	98% of patients rated their experience with the MDT clinic as "excellent"	In the community setting, MDTs may offer an avenue of care that is highly valued by patients
Diagnosis and testing			
Cai et al. [23]	Pilot study evaluating pathologic concordance of bio-banked tissue and RP specimens with a standard vs a next-generation, multidisciplinary protocol The next-generation protocol included MDT discussion to coordinate tissue sampling and biobanking priorities	Utilization of the next-generation protocol resulted in a significantly higher rate of pathologic concordance between the bio-banked and RP specimens (61.8 vs 37.9%; $p = 0.0231$)	MDTs can play a role in optimal tissue selection for subsequent testing
Kotamarti et al. [24]	Description of a multidisciplinary review protocol for cases in which targeted biopsies of suspicious MRI lesions does not return clinically significant PC	Authors presented several case studies highlighting the importance of multidisciplinary consensus recommendations in resolving discordance and determining next steps	MDTs can help resolve discordant imaging and biopsy and inform next steps
Li et al. [25]	Single-center retrospective analysis assessing the impact of second-opinion MDT review of prostate MRI for cancer detection compared with initial community radiologist interpretation ($N = 303$)	There was only fair agreement ($\kappa = 0.353$) between community radiologists and MDT review boards for prostate MRI interpretation	Variability in prostate MRI interpretation suggests added value of MDT review
Sethukavalan et al. [26]	Semi-structured patient interview and chart abstraction to assess wait-time intervals for patients diagnosed and referred through an MDT RDU compared with usual community processes ($N = 87$)	Median wait-time intervals were shorter for the MDT RDU vs community patients including: Suspicion of PC to RT (138 vs 183 days; $p = 0.046$) Suspicion to DTT (85 vs 148 days; $p = 0.012$) Urologist's visit to diagnosis (20 vs 39 days; $p = 0.0094$) Diagnosis to DTT (34 vs 64 days; $p = 0.018$) Diagnosis to RT (79 vs 112 days; $p = 0.016$)	MDTs can reduce wait time intervals from suspicion to treatment for patients with PC

ADT androgen deprivation therapy, *aRT* adjuvant radiotherapy, *BCR* biochemical recurrence, *CI* confidence interval, *DTT* decision to treat, *HR* hazard ratio, *mCRPC* metastatic castration-resistant prostate cancer, *MDT* multidisciplinary team, *mPC* metastatic prostate cancer, *MRI* magnetic resonance imaging, *NCCN* National Comprehensive Cancer Network, *OR* odds ratio, *OS* overall survival, *PC* prostate cancer, *RDU* rapid diagnostic unit, *RP* radical prostatectomy, *RT* radiotherapy, *SEER* Surveillance, Epidemiology, and End Results

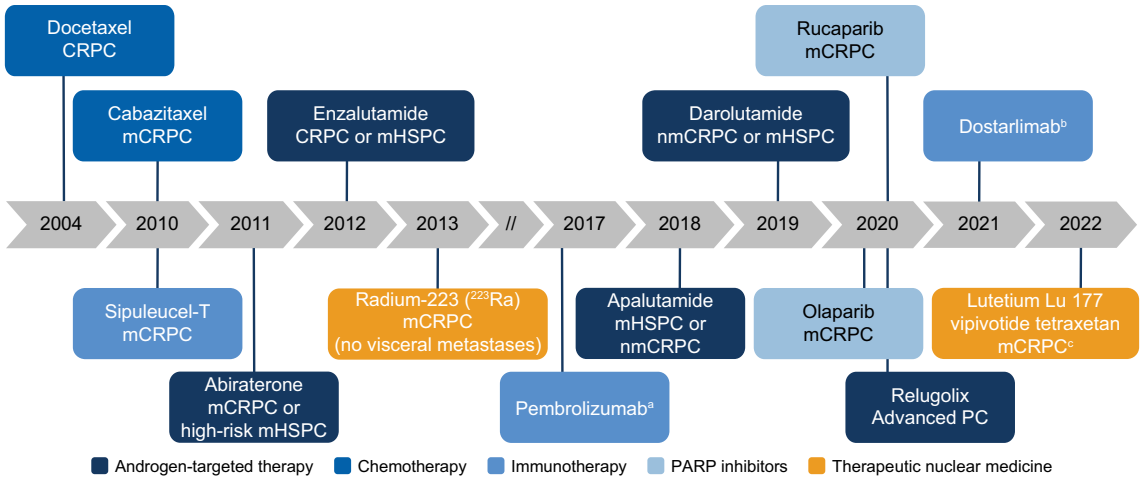

Fig. 1 FDA-approved therapies for advanced PC. Initial years of approval in the USA are shown. [a]Approved for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high, or deficient mismatch repair solid tumors (including PC) that have progressed following prior treatment and for whom no satisfactory alternative treatment options exist. [b]Approved for the treatment of adult patients with mismatch repair–deficient recurrent or advanced solid tumors (including PC), as determined by an FDA-approved test, that have progressed on or following prior treatment and for whom no satisfactory alternative treatment options exist. [c]Approved for the treatment of adult patients with prostate-specific membrane antigen–positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. *CRPC* castrate-resistant prostate cancer, *FDA* Food and Drug Administration, *^{177}Lu* lutetium-177, *mCRPC* metastatic castrate-resistant prostate cancer, *mHSPC* metastatic hormone-sensitive prostate cancer, *nmCRPC* nonmetastatic castrate-resistant prostate cancer, *PARP* poly (ADP-ribose) polymerase, *PC* prostate cancer

vipivotide tetraxetan). Novel combinations of effective therapies are changing practice by extending survival and maintaining quality of life [27–29]. The availability of numerous, medically reasonable treatment options, each with their own benefit-risk profiles, gives clinicians the flexibility to align the management strategy with a patient's values and preferences. Thus, MDTs should be increasingly fortified and amended to optimize shared decision-making in accordance with the evolution of treatment strategies in PC.

In addition to novel treatments, new diagnostic technologies (next-generation imaging, genetic testing, and artificial intelligence [AI]) for PC have emerged in recent years, supporting opportunities for precision oncology in PC. Next-generation nuclear medicine imaging techniques, including PSMA positron emission tomography (PET), are expected to reshape the diagnosis, staging, guidance of treatment, and response monitoring for PC [30–34]. This transformation in the landscape will spur greater needs for timely critical assessments of next-generation imaging to aid MDT clinical decision-making. Collaboration among nuclear medicine specialists, radiation oncologists, urologists, medical oncologists, and pathologists is essential in assessing the clinical utility of next-generation imaging against the disadvantages (costs, radiation exposure, adverse events, false positives, over-detection) and thus mitigate these risks. Multidisciplinary team collaboration will be especially important for challenging cases as recognized by clinical guidelines [35].

Germline and somatic genetic testing are currently recommended in several specific patient subgroups [35]. These tests may inform prognosis/risk stratification and targeted treatment decisions (PARP inhibitors, pembrolizumab) [35–37]. Ongoing data analyses and gene alteration targeted therapeutics may further democratize these guidelines [38]. As novel targeted therapies enter the treatment landscape, the impact of genomic profiling on treatment decisions will increase. Given the importance of genetic testing in clinical decision-making, MDTs will need to ensure timely assessment of genomic profiling platforms with appropriate validity and efficient turnaround times, thereby establishing their clinical relevance. Molecular tumor boards have been described as a multidisciplinary method to help combine medical oncology with genetic testing expertise and integrate genomic data into clinical decision-making for precision oncology [39–41]. Although experience with molecular tumor boards is accumulating in PC [39, 41], they are currently underutilized [41]. Of course, there will be a continued debate and required education on how genomic profiling information is best conveyed to patients and their families.

Artificial intelligence-based tools for the diagnosis, prognosis, and treatment selection in PC are emerging and are likely to play an increasingly prominent role in the management of the disease [42–48]. For example, a novel, AI-derived digital pathology biomarker of androgen-deprivation therapy (ADT) benefit was recently validated in patients with localized PC [47]. Although such tools will likely

improve patient care, enhance MDT discussions, and potentially streamline the workload of radiologists/pathologists [48], they will also add to the already considerable amount of information MDTs need to consider. Multidisciplinary teams will need to be prepared to integrate information from AI-based tools into their discussions, understanding the limitations and benefits of these tools.

Although the composition of MDTs varies across institutions regionally and globally, the advancements in PC management highlight the important roles that nuclear medicine specialists, pathologists, genetic counselors, and molecular testing experts are likely to play in current and future practice. Multidisciplinary teams will be critical for situations in which imaging/genomic data and treatment options are incorporated into treatment guidelines as well as become part of randomized controlled trials. Nuclear medicine and genetic testing experts will have crucial roles in situations in which the "novel" information is substantially different from the established clinical risk factors and there is uncertainty on the optimal therapeutic approach. Additionally, imaging, genomic, and biomarker expertise will be needed to interpret and compare results from contemporary/future clinical trials using advanced diagnostic technologies with historical trials based on conventional diagnostics, especially as a confounding effect of stage migration (e.g., patients previously classified as low risk now classified as high risk because of improved detection of metastatic disease) [49]. In the next section, we highlight how modern MDTs can be used to address such situations and other contemporary challenges in the management of PC to ensure patients receive evidence-based care and the opportunity for improved outcomes.

3 Addressing Contemporary Challenges and Controversies in PC with Modern MDTs

Multidisciplinary teams have the specialized expertise to help address many of the challenges surrounding clinical decision-making amid complexity and uncertainty (Table 2). They also have an important role in assessing patients for clinical trials. In this section, we present examples showcasing how MDTs can be implemented to address the challenges of PC management across the disease continuum and patient journey (Fig. 2).

3.1 Diagnosis of PC

The two most applied metrics for the early detection of PC are PSA testing and digital rectal examination (DRE). After diagnosis, treatment decisions are based on risk stratification and consideration of the options for management based on disease risk, patient clinical factors, and patient preferences. A portion of risk stratification is based on imaging and biopsy results.

A variety of tools are available to prescreen patients for biopsy, including risk calculators based on clinical parameters (e.g., age, family history, PSA levels, DRE findings), magnetic resonance imaging (MRI), and biomarkers beyond serum total PSA (tPSA) [50]. There is uncertainty about how best to apply these tools because of a lack of clinical data and guidelines, particularly with regard to the order of testing (e.g., biomarker followed by MRI, or vice versa), which specific biomarkers to use and when, and the correct course of action when multiple tests deliver contradictory results [50]. Given the absence of specific recommendations from national guidelines and because prebiopsy procedures require specialized knowledge across different specialties (e.g., radiology for MRI), MDTs play an important role in setting institutional guidelines for prebiopsy screening strategies that can be used in the shared decision-making process. For example, in our experience, MDTs have helped set institutional guidelines for which set of tests an institution will conduct, the order of testing, and what thresholds will be used for risk stratification.

The multifocality and multiclonality of PC can contribute to complexity of treatment decisions if there are concerns related to sampling error and uncertainty about whether the limited tissue collected in a biopsy sample represents the presence/absence or nature of PC in the entire prostate [3]. Many men have multifocal disease [51, 52], and the genetic profile determined from the biopsy may not reflect the entirety of genetic aberrations in the prostate or metastatic lesions [53]. To help mitigate these issues, pathologists, imaging specialists, and genetic experts on an MDT can advise and collaborate on the careful selection of tissue samples for genetic testing as well as the potential use of image-guided biopsy. Correlating imaging data with tumor molecular features, a technique incorporating radiology and pathology, is emerging as a multidisciplinary method to improve tissue sampling and diagnostic accuracy [3]. Multidisciplinary teamsthat include pathologists, imaging specialists, and genetic experts are uniquely positioned to provide access to and accurate interpretation of these evolving diagnostic techniques and to provide PC patients with cutting-edge care. Multidisciplinary team workflow pathways for tissue sampling and molecular diagnostic testing have recently been proposed. Gonzalez et al. described the importance of MDT in maintaining a patient-centric approach to testing [54]. They proposed a workflow emphasizing the diagnostic pathologist as an MDT champion to ensure that best practices are followed for tissue collection (e.g., adequate cellularity and neoplastic content), assessment (e.g., need for re-biopsy or liquid biopsy), processing (e.g., fixation and decalcification procedures), and storage (e.g., formalin-fixed paraffin-embedded block archiving), and laboratory

Table 2 The value of MDTs in addressing challenges/controversies across the PC disease continuum

Disease stage	Challenges/controversies	Value provided by the MDT
Diagnosis	Shared decision-making regarding PSA screening; incorporation of blood/urine testing, family history, race, etc., in this process Determining the need for biopsy Assessing whether the tissue sample from the biopsy accurately represents the presence or absence of cancer For negative biopsies, determining the need for repeat biopsies For positive biopsies, determining whether the tissue sample reflects the nature of the multifocal cancer (e.g., genetics)	MDTs can provide support/guidance for additional testing MDTs help ensure that testing procedures are conducted in a timely and coordinated manner
Localized	Incorporation of advanced genetic and imaging information into patient risk stratification Establishing a personalized medical plan (e.g., observation, active surveillance, medical intervention [surgery vs treatment]) based on patient risk profiles, especially when combining information from genetic testing or imaging with established risk factors Identification of patients for treatment intensification or deintensification based on genetic testing or imaging	Genetic and imaging expertise within the MDT can support interpretation of genetic testing and imaging results Molecular tumor boards can integrate medical oncology and genomics to inform personalized medical plans
Biochemical recurrence	Immediate vs deferred imaging and salvaging therapy Determining optimal management in individuals with no metastases detected by conventional imaging Identifying suspicious foci of recurrence for biopsy or treatment	MDT radiology review and possibly pathology review are critical components of MDTs at this point MDTs can perform longitudinal review of imaging and provide recommendations for additional imaging (e.g. advanced imaging) Inform on the use of novel techniques when they emerge (e.g., liquid biopsies)
Metastatic hormone-sensitive PC	Choosing an imaging strategy (e.g., next-generation vs bone scans, timing) Determining the need for rebiopsy for new genetic testing Defining oligometastatic vs extensive metastatic disease and determining optimal treatment for each case (e.g., metastasis-directed therapy) Determining candidates for combination therapy including triplets Evaluation of adding local radiotherapy to systemic treatment	The MDT can provide radiology review to define oligometastatic vs extensive metastatic disease The MDT can advise on the need for rebiopsy MDTs can help interpret current and historical trials in light of increased sensitivity of advanced imaging (stage migration) and advise on treatment approaches
Nonmetastatic castration-resistant PC	When to switch systemic therapy given new options or consider additional treatment Risk stratification by genetic testing and imaging	Genetic and imaging expertise within the MDT can support interpretation of genetic testing and imaging results (with potential upstage to oligometastatic disease)
Metastatic castration-resistant PC	Choosing an imaging strategy Determining the best treatment regimen for each patient with consideration of prior therapies (e.g., monotherapy vs combination therapy) Managing adverse events (e.g., dose interruptions/reductions) of novel therapies Incorporation of precision medicine and choosing treatment sequencing with novel therapies, considering that there is an absence of head-to-head clinical trial data	MDTs can help manage the unknowns of novel treatments, including adverse events Genetic, imaging, and medical oncology expertise within the MDT can help guide patient selection and appropriate use of precision medicine approaches (e.g., molecular tumor boards) MDTs are important for creating prospective treatment sequencing plans

MDT multidisciplinary team, *PC* prostate cancer, *PSA* prostate-specific antigen

technicians and scientists to guide the assessment and extraction of DNA from tissue samples [54]. Whereas Gonzalez et al. focused on the role of the pathologist after tissue sample collection, other members of the MDT are instrumental in targeting tissue selection for subsequent collection and testing. For example, radiologists and other clinicians can help determine which lesions (e.g., primary vs metastatic) to target for biopsy. Similarly, Cai et al. evaluated pathologic concordance between radical prostatectomy (RP) specimens and bio-banked primary PC tissue collected from the RP specimen using either a multidisciplinary, next-generation biobanking protocol, or a standard protocol [23]. Notably, the multidisciplinary protocol used an MDT consisting of pathologists, urologists, and research investigators to target tissue sampling and determine bio-banking priorities based on discussion of several patient/disease features including age, biopsy results, MRI, and genomic testing. Use of the multidisciplinary biobanking protocol led to increased pathologic concordance compared with the standard protocol (61.8 vs 37.9%; $p = 0.0231$) [23].

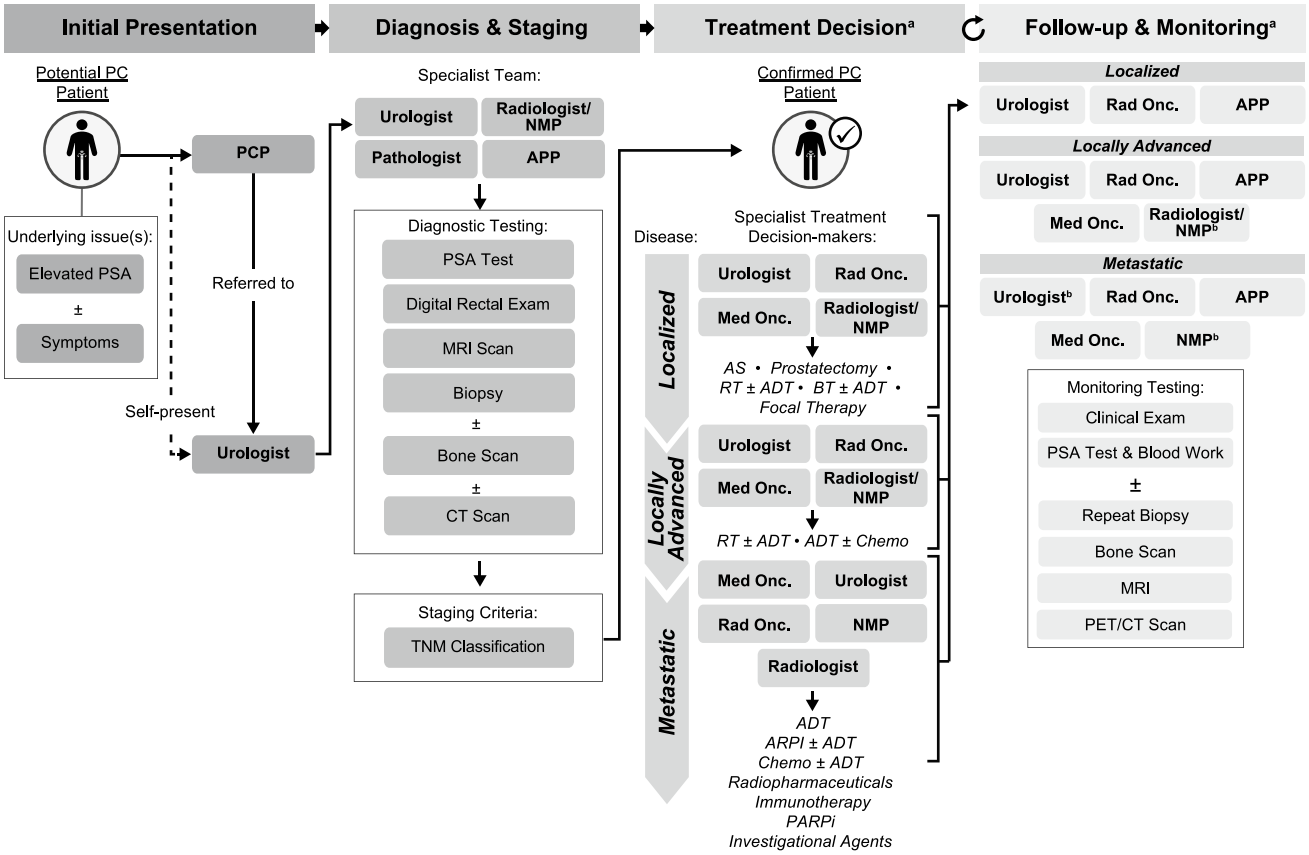

Fig. 2 Involvement of the PC MDT along the patient journey. The patient journey in PC consists of 4 core steps (initial presentation, diagnosis and staging, treatment decision, and follow-up and monitoring). With rapidly evolving diagnostic and treatment landscapes, MDTs play central roles in addressing challenges and controversies related to the diagnosis, treatment, and monitoring of the disease. These challenges include deciding on which diagnostic tests to complete, interpreting the results of novel genetic testing and imaging, choosing an appropriate course of action when results from novel tests conflict with conventional risk factors, and selecting among multiple medically reasonable treatment options. Typical members of a PC MDT include urologists, med oncs, rad oncs, nurses, and radiologists/NMPs; however, composition of the MDT can vary be center and the extent of disease. Additionally, nuclear medicine specialists, pathologists, genetic counselors, and molecular testing experts will play increasingly prominent roles in current and future practice. [a]The treatment decision and follow-up and monitoring steps can be part of a repetitive cycle if a patient's disease is progressing and/or failing to respond to multiple therapies. [b]Varying involvement. *ADT* androgen deprivation therapy, *APP* advanced practice provider, *ARPI* androgen receptor pathway inhibitor, *AS* active surveillance, *BT* brachytherapy, *chemo* chemotherapy, *CT* computed tomography, *MDT* multidisciplinary team, *med onc* medical oncologist, *MRI* magnetic resonance imaging, *NMP* nuclear medicine physician, *PARPi* poly (adenosine diphosphate [ADP]) ribose polymerase inhibitors, *PC* prostate cancer, *PCP* primary care physician, *PET* positron emission tomography, *PSA* prostate-specific antigen, *PSMA* prostate-specific membrane antigen, *rad onc* radiation oncologist, *RT* radiation therapy, *TNM* tumor-node-metastasis

3.2 Risk Stratification and Management of Localized Disease

A diagnosis of PC via positive biopsy triggers additional assessments to properly stratify the risk of the disease. Although risk is a continuous variable (e.g., probability of disease progression), patients are placed into predefined risk categories. This creates two sources of prognostic uncertainty: first, there is heterogeneity within individual risk categories, and second, there is uncertainty for patients who exist on the borders between risk strata. Clinical guidelines for PC detection recognize this uncertainty. Although they state that conventional assessments (life expectancy estimation, nomograms, and other clinical parameters) should be the foundation of risk-based treatment decision-making, they acknowledge the role of genetic testing and advanced imaging [35]. However, guidelines do not offer concrete guidance on how the results from these tests should be used in specific clinical scenarios because of a lack of robust, head-to-head data that are readily translatable to real-world practice. Thus, a key question in contemporary PC management is how to incorporate information from advanced diagnostic technologies into the foundational risk-stratification parameters to make tailored decisions about whether to intensify or de-intensify treatment for individual patients.

In the absence of data, challenging cases benefit from discussion (emerging data, shared experience, best practices) and collaboration in an MDT setting. We present two clinical scenarios illustrating how MDTs can bring value to the key challenge of integrating advanced imaging and genetic testing into PC management by aiding clinical decision-making (treatment intensification vs deintensification).

The first scenario is the case of a patient considered at low risk by established risk factors (e.g., Gleason 3+3 [GG1]) but considered higher risk for disease progression according to genetic testing (e.g., *BRCA2* mutation). Until recently, active surveillance would normally be recommended for this patient on the basis of conventional risk factors. However, the high-risk genetic profile raises the question of whether treatment with definitive local therapy or additional testing (e.g., nuclear imaging) should be pursued. Multidisciplinary team discussions incorporating genetic testing and pathology expertise can help elucidate the tumor biology and the risk of disease progression with active surveillance versus definitive therapy (Fig. 3) [55, 56].

The second scenario describes the opposite situation. It involves the patient who is considered at high risk by established risk factors but is negative for high-risk disease via nuclear imaging and has a favorable genetic profile. Radiation therapy with ADT is a standard treatment approach for high-risk patients by established risk factors. Under this treatment paradigm, the duration of ADT treatment is a crucial consideration. Studies have shown that long-term ADT treatment results in better outcomes than does short-term treatment in high-risk patients on the basis of established risk factors [57, 58]. However, ADT is associated with a variety of side effects that become more common with prolonged treatment duration [59, 60]. An ongoing question is whether genomic data, imaging information, or AI-derived biomarkers can be used to identify patients for treatment deintensification and avoidance of long-term ADT effects. The ongoing Phase 3 NRG-GU009 study is addressing this question. It is assessing whether National Comprehensive Cancer Network (NCCN) high-risk patients with low genomic risk by the Decipher classifier can de-intensify treatment from 2 years to 1 year of ADT plus radiation therapy. Until data from this study can guide decision-making, most patients will likely continue with standard management approaches until data suggest that deintensification is justified. Guidance from nuclear medicine and genomic profiling experts on the MDT—as well as assessments of patient comorbidities, life expectancy, and personal preferences—can also contribute to personalized clinical decision-making.

3.3 Metastatic Disease

The treatment of metastatic PC is particularly difficult. Whereas a trend to decrease cost and patient burden of definitive therapy (e.g., hypo-fractionated radiation therapy) in low- and intermediate-risk patients has simplified clinical decision-making in certain contexts, the treatment of oligometastatic and extensive metastatic disease remains increasingly challenging and complex. This is exemplified by recent findings from the Advanced Prostate Cancer Consensus Conference 2021, during which an expert panel was not able to reach consensus (defined as $\geq 75\%$ agreement) on more than half of issues related to the management of advanced PC [61].

The challenges of managing oligometastatic PC were recently summarized by Fossati et al. [62]. An important controversy is the ideal management of patients with metastatic disease detected by PSMA PET/computed tomography (CT) but not conventional imaging. Although several studies have demonstrated improved accuracy of PSMA PET/CT over conventional imaging, the ultimate effect of higher sensitivity on patient outcomes has not yet been demonstrated. Fossati et al. further highlighted the point that all level 1 evidence guiding clinical decision-making for M1 patients comes from studies that used conventional imaging, and it is unclear whether this evidence can be extrapolated to PSMA PET/CT-defined M1 disease due to data interpretation issues such as stage migration [62]. Multidisciplinary team collaboration is critical in such scenarios. First, collaboration between pathology and nuclear medicine is needed to confirm PET/CT findings by histologic examination if feasible.

Second, collaboration between imaging and genetic testing experts can guide accurate and timely interpretation of imaging results and advise on the need for follow-up assessments. Finally, collaboration among all aforementioned MDT members as well as those from medical oncology, radiation oncology, and urology can help advise on the appropriate management plan in the absence of firm guidance from clinical guidelines or clinical trials.

As is typical in PC, new treatments are first evaluated in patients with the most advanced stage of disease. A key challenge in mCRPC is navigating the numerous treatment options, including targeted therapies, that have been approved, with more approvals expected in the next several years pending Phase 3 trial readouts. Given the lack of head-to-head trials of these novel agents, treatment selection and sequencing of therapy are difficult [63] and depend on disease characteristics (e.g., disease progression, tumor burden), adverse event profiles and patient comorbidities, physician education, patient preferences, and economic as well as accessibility considerations. Physician comprehension of the various therapies that are either approved or available through clinical trials is essential because this allows patients to receive evidence-based care that is not biased by an individual physician's perceptions or comfort level with new technologies (e.g., advanced imaging or genomic testing). With expertise in genomic profiling and nuclear medicine, MDTs can be well positioned to offer precision medicine and determine patient eligibility for novel targeted therapy, based on the presence of phenotypic or genetic biomarkers.

An illustrative scenario of where MDTs will be particularly valuable is the use of PSMA-targeted radioligand therapy (RLT) and imaging. Two PSMA-targeted PET tracers (gallium [^{68}Ga] gozetotide and piflufolastat [^{18}F]) and PSMA-targeted radioligand therapy with lutetium (^{177}Lu) vipivotide tetraxetan have recently been approved by the US Food and Drug Administration (FDA). As was demonstrated with other radiopharmaceuticals [64], multidisciplinary care

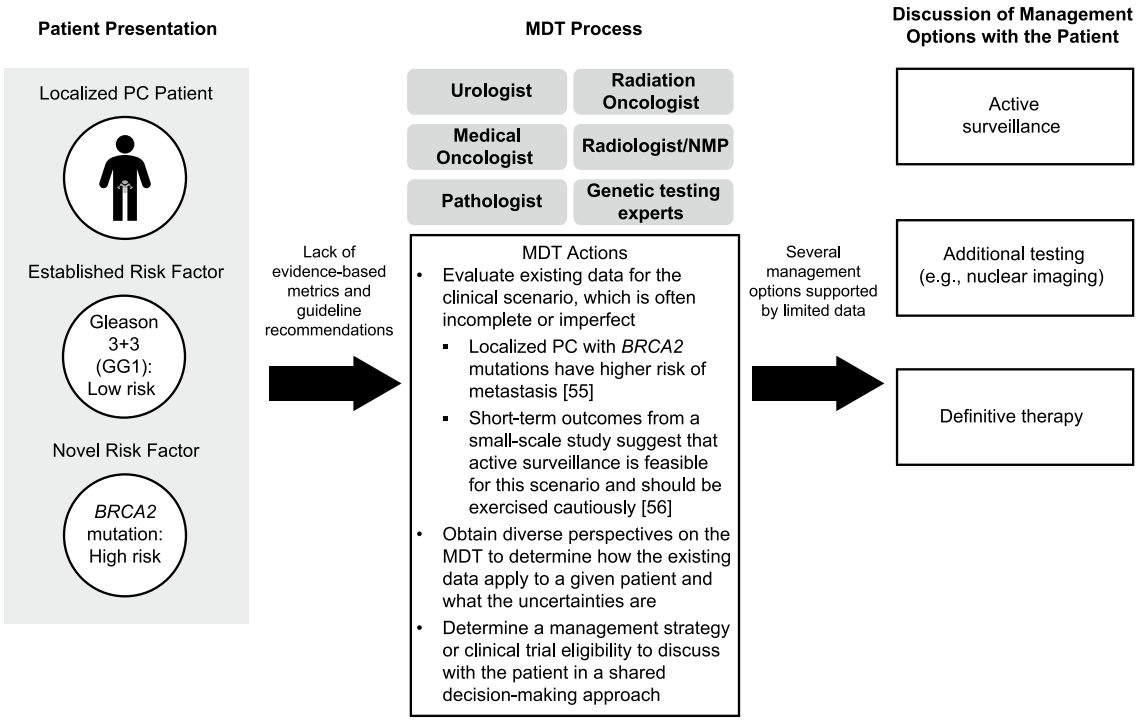

Fig. 3 MDT process for integrating information from established and novel risk factors to determine a management strategy. MDT process for integrating information from established and novel risk factors to determine a management strategy. There is often a lack of evidence-based metrics and guideline recommendations for patients who have different risk profiles based on established and novel risk factors, such as a patient with low-risk localized GG1 PC but with a high-risk *BRCA2* mutation. MDTs can help navigate situations in which the evidence base is incomplete by using the diverse perspectives and expertise of those members on the MDT to evaluate the existing data, assess the suitability of different management strategies, and determine the need for additional testing. Often, there will be several medically reasonable management options supported by limited data, necessitating a shared decision-making approach with patients, and making sure they understand the benefits, risks, and unknowns of each option. Key members of the MDT in this clinical scenario are the specialist treatment decision makers (urologists, radiation oncologist, medical oncologist), individuals who can advise on the nuances of the patients existing risk factors (pathologists, genetic testing experts), and other clinicians who can advise on additional testing such as nuclear imaging (nuclear medicine physicians). *GG1* Grade Group 1, *MDT* multidisciplinary team, *NMP* nuclear medicine physician, *PC* prostate cancer

and coordination will be crucial for appropriate patient selection based on PSMA imaging; safe delivery of PSMA-targeted radioligand therapy in accordance with label requirements, clinical guidelines, and regulations; and appropriate monitoring and follow-up. For example, nuclear medicine, radiology, and pathology expertise within an MDT is crucial for accurate assessment of patient eligibility for PSMA-targeted RLT given the complexity of PSMA PET imaging and risk of misinterpretation. Multidisciplinary consultation can help to adjudicate on borderline or unclear cases: discussions with pathologists may be needed for histopathological confirmation, and input from radiologists/nuclear medicine physicians may be required to compare/contrast PSMA PET imaging results with other modalities to decide the treatment plan. An MDT workflow for PSMA PET imaging and PSMA-targeted RLT in PC has been described by Murphy et al. [65]. They incorporated nuclear medicine professors, fellows, and trainees into their weekly PC MDT meetings; these experts were equipped with PET workstation software for display of advanced imaging to the rest of the MDT team with ensuing discussion determining patient eligibility for PSMA-targeted RLT [65]. Similar MDT workflows incorporating nuclear medicine consultation have been described for ^{177}Lu-based RLT in gastro-enteropancreatic neuroendocrine tumors (GEP-NETs), and these could also potentially be adapted for PC. At the Mayo Clinic, the GEP-NET MDT workflow begins with nuclear medicine consultation followed by an MDT team meeting (medical oncologists, nuclear medicine physicians and/or radiologists, and subspecialty clinical services) to confirm patient eligibility for RLT based on discussion of imaging, laboratory values, and patient/disease factors [66].

Metastatic castration-resistant prostate cancer is often a debilitating disease affecting the elderly and managing symptoms and side effects is a primary consideration in clinical decision-making. Multidisciplinary team communication and education are key to successfully managing the unknowns of a new treatment involving multiple specialties, especially in terms of adverse events. Finally, MDTs can provide support to providers when they feel the risk-benefit ratio has shifted away from treatment to symptom-based care.

4 Maximizing the Impact of MDTs in Contemporary PC Management

In the USA, men with PC may experience different patient journeys depending on the setting in which they receive care (academic research institutions, community hospitals, and

Table 3 Impact of setting (academic vs community, urban vs rural) on the MDT

Characteristic	Academic	Community	Impact on the MDT
Access to specialists and subspecialists	Greater	Lesser	Harder to have access to specialists who do MDT in rural areas and in community practices that are not all in same space
Emphasis on teaching and research	Greater	Lesser	MDT access to clinical trials or novel therapeutics is greater in the academic setting
Experience with "complex" cases	Greater	Lesser	Community MDTs may need consultation with academic MDTs for certain cases; academic-community partnerships may be beneficial
Approach to patient care	More team-oriented	More siloed	There may be more internal barriers to setting up and maintaining community MDTs

Characteristic	Urban	Rural	Impact on the MDT
Access to specialists and subspecialists	Greater	Lesser	Urban MDTs have potentially greater access to integrative care (exercise oncology/dieticians/emotional support), especially as part of an integrated team
Experience with "complex" cases	Greater	Lesser	Community MDTs may need consultation with academic/urban MDTs for certain cases; partnerships with academic/urban centers may be beneficial
Resource access	Greater	Lesser	Urban MDTs have freedom to use the best existing technologies, whereas rural MDTs may only be able to leverage the best available technology

MDT multidisciplinary team

urban versus rural centers), individual patient characteristics (e.g., race and ethnicity), and specific models of care and reimbursement. Multidisciplinary teams can mitigate potential disparities in care via shared knowledge and resources, minimization of individual treater bias, and creation of institutional standards/clinical protocols in which regional standards may be absent [18, 67, 68]. Across all settings, barriers to the success of MDTs include poor member attendance, lack of administrative support, and substantial distances between patients and centers of excellence. In this section, we review how MDTs can best support the patient journey for all men with PC.

Non-academic centers constitute the majority of oncology practices in the USA [69], and approximately half of patients with cancer receive their first course of treatment in the community setting [70]. Additionally, one study found that about a quarter of men with PC resided in rural areas or large towns [71]. In comparison with academic or urban centers, community and rural institutions face several barriers to the delivery of evidence-based PC care, including access to specialists, access to clinical trials and novel therapeutics, and an inherently more siloed approach to patient care (Table 3). Indeed, several disparities in care have been found for patients with PC treated at community or rural centers, including lower likelihoods of receiving multidisciplinary consultation and guideline-recommended treatment in comparison with academic or urban centers [72–76]. There is evidence that the MDT approach can potentially mitigate these disparities and improve several facets of the patient journey in these challenging settings including accuracy of diagnosis [25], time to treatment [26], adherence to treatment guidelines [17], and overall patient satisfaction with care [22] (Table 1).

The experience of community centers that have implemented successful PC MDTs provides lessons for initiating and maximizing the impact of community MDTs. Various community institutions have highlighted the role of physician champions for the MDT, proper incentives for participating physicians, institutional support (scheduling meetings, setting up teleconferences/video conferences, secure transfer of medical records between institutions), support for patient follow-through, and effective communication with referring physicians [77, 78]. Indeed, community medical oncologists should be encouraged to be part of the MDT because this would support relevant referrals to other specialists (e.g., nuclear medicine for radiopharmaceuticals).

More recently, telehealth accessibility, use, and reimbursement have accelerated in the wake of the coronavirus disease 2019 (COVID-19) pandemic [79]. With the emergence of telehealth, virtual MDT meetings have the potential to facilitate academic-community/urban-rural partnerships, giving community or rural patients access to specialists and high-impact PC care. Furthermore, as health systems become more complex with clinicians spread out across secondary and tertiary sites, it becomes difficult to coordinate the time when everyone can be together in person. Virtual MDTs have the potential to overcome this barrier to coordinated care (as reviewed by Aghdam et al. [80]) and shifts to virtual MDTs have been described for various cancers, including PC [25, 40, 81]. Indeed, our institutions have transitioned to virtual MDT meetings facilitated by videoconferencing, the use of shared electronic medical record systems, and digital pathology. This is a virtual MDT workflow similar to others that have been previously described for other diseases, including cancer [80]. Our experience has been that virtual MDT meetings have increased participation in MDT discussions and the number of cases examined, not only at the central care center but also at satellite sites. Assessments of physician reimbursement for time spent in telehealth/virtual MDTs will be important to consider as this model of care continues to expand.

Racial and socioeconomic disparities in PC treatment and outcomes are prevalent in the USA. Black patients and patients without insurance are more likely to be undertreated than White patients and those with private insurance [18, 82]. Although population-based data indicate that Black patients have nearly twice the lifetime probability of dying from PC than do non-Hispanic White patients [83], this difference disappears when restricting analyses to health systems with uniform access or standardized treatment (universal healthcare models, Veterans Health Administration system, randomized clinical trials) or after controlling analyses of observational data for baseline socioeconomic factors. These findings suggest that most disparities in PC outcomes are driven by socioeconomic barriers to standardized treatment.

Multidisciplinary teams are a vehicle for delivery of evidence-based, standardized treatment for PC and thus may help mitigate disparities due to race and socioeconomic factors. For example, although Black men with high-risk PC are generally less likely to receive definitive therapy than White men [18, 82], Tang et al. showed that use of an MDT clinic obviated this difference in one of the first studies assessing the impact of MDTs on racial disparities in PC treatment [18]. Commenting on this study, Hoge and Sidana hypothesized that MDT PC clinics may foster increased involvement, trust, and knowledge of treatment options among Black patients [84].

More effective patient navigation has been suggested as a way to address racial disparities in PC management by helping underserved populations increase screening rates, maintain continuity of care, and increase awareness of and enrollment in clinical trials [85]. Patient care coordinators or patient navigators are often integral members of PC MDTs.

Leveraging their expertise is another way MDTs may help mitigate racial disparities in PC.

5 Summary and Future Perspectives

Previous studies and reviews have established the rationale for and benefits of MDTs for managing complex cancers that require diverse expertise and for promoting adherence to evidence-based guidelines. Less attention has been focused on the benefit of MDTs in addressing challenges and controversies that outpace guidelines and clinical trial data. In this review we have outlined scenarios illustrating the value of MDTs in addressing challenges related to both complex clinical scenarios and health disparities in PC. Currently, there are limited data related to the quantitative impact of using MDTs in these modern scenarios, most likely because there has not been enough time for these data to evolve and mature. However, MDTs play an essential role in creating standardized care pathways and data that will be amenable to future retrospective analyses.

This review emphasizes the rapidly evolving diagnostic and treatment landscapes as sources of complexity and uncertainty, which MDTs can help address. Such trends are likely to continue and become amplified, given the accelerating rate of development of new treatments in PC and advances in precision medicine, including potential incorporation of PSMA-targeted imaging and therapy in the near future. The value of MDTs for PC management will only increase in response to these innovations. Ongoing and future clinical trials will provide guidance to clinicians on certain management issues, but they will not be able to address all of the controversies. For example, head-to-head trials comparing different genomic classifiers and studies examining the effect of nuclear imaging on clinical outcomes are unlikely to occur [35, 50]. Thus, many PC treatment-related issues will remain complex and uncertain for the foreseeable future, and MDTs will have an integral and ongoing role in PC clinical decision-making.

With MDTs, issues are raised regarding the practicality of having numerous referrals, patient proximity to MDT centers and cost of travel, delivery of care in a timely manner, and accessibility of therapy, as well as health economic outcome efficiencies. Some of these issues may be mitigated by virtual/telehealth MDT strategies. From a payer perspective, it is important to consider how MDTs might be impacted by alternative payment models that shift from a volume-based to a value-based paradigm. Such a model may actually push PC care more toward MDTs because compensation is by diagnosis rather than by volume of care with questionable incentivization.

The integral role of MDTs necessitates frameworks for evaluating their benefits and costs and for determining success. Financial costs, time to next treatment, overall survival (cure), freedom from biochemical failure, and patient-reported outcome metrics are all important to consider. Adherence to evidence-based guidelines has also been described as a metric for the evaluation of PC MDTs [17]. In line with the alternative payment model described previously, payment adjustments based on these metrics may be relevant. Finally, mechanisms to account for clinician time spent in MDTs needs to be considered, given the value-based compensation models used by many employers.

In summary, this review highlights the increasingly central role that MDTs have in addressing contemporary challenges and controversies in the management of PC. The greatest value of MDTs is in the gray areas of care, where questions produced by information from novel diagnostic technologies outpace the answers that clinical guidelines and trials provide. The role of MDTs in PC clinical decision-making in these areas of high uncertainty will become more important in the future, and studies examining optimal processes, functions, and success metrics of contemporary MDTs are warranted.

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