Prostate cancer

Richard J. Rebello[1,9], Christoph Oing[1,2,9], Karen E. Knudsen[3], Stacy Loeb[4], David C. Johnson[5], Robert E. Reiter[6], Silke Gillessen[7], Theodorus Van der Kwast[8] and Robert G. Bristow[1] ✉

Abstract | Prostate cancer is a complex disease that affects millions of men globally, predominantly in high human development index regions. Patients with localized disease at a low to intermediate risk of recurrence generally have a favourable outcome of 99% overall survival for 10 years if the disease is detected and treated at an early stage. Key genetic alterations include fusions of *TMPRSS2* with ETS family genes, amplification of the *MYC* oncogene, deletion and/or mutation of *PTEN* and *TP53* and, in advanced disease, amplification and/or mutation of the androgen receptor (AR). Prostate cancer is usually diagnosed by prostate biopsy prompted by a blood test to measure prostate-specific antigen levels and/or digital rectal examination. Treatment for localized disease includes active surveillance, radical prostatectomy or ablative radiotherapy as curative approaches. Men whose disease relapses after prostatectomy are treated with salvage radiotherapy and/or androgen deprivation therapy (ADT) for local relapse, or with ADT combined with chemotherapy or novel androgen signalling-targeted agents for systemic relapse. Advanced prostate cancer often progresses despite androgen ablation and is then considered castration-resistant and incurable. Current treatment options include AR-targeted agents, chemotherapy, radionuclides and the poly(ADP-ribose) inhibitor olaparib. Current research aims to improve prostate cancer detection, management and outcomes, including understanding the fundamental biology at all stages of the disease.

Acini
A cluster of cells which form the rounded termination of an exocrine gland where secretions are produced.

The prostate gland is a male reproductive accessory organ located beneath the bladder and surrounding the urethra. The main function of the prostate is to contribute essential secretions to semen which formulate ejaculate and maintain sperm viability[1] (FIG. 1). The cells within the prostate gland frequently give rise to tumours, most often in the mid-to-late stage of life[2]. The adult human prostate can be divided into central, transition and peripheral zones, and also contains fibromuscular and periurethral regions[3–5]. In young adult men, the peripheral zone makes up >70% of the prostate glandular tissue and makes the largest contribution to normal prostate function. It is also the most common site of origin of neoplasms in the aged prostate, as almost 80% of prostate tumours arise in this area[3,4,6] (FIG. 1a). The normal gland consists of ducts and acini embedded in stroma. The ducts and acini comprise a single layer of simple, columnar epithelium surrounded by a layer of basal epithelium, which produces the basement membrane. This layer of extracellular matrix is anchored to stromal cells, which are predominantly smooth muscle myocytes that promote spontaneous contractility and prevent fluid stagnation[7,8] (FIG. 1b). The stroma also contains fibroblasts, which mostly support the ducts in the adult prostate, but fibroblast paracrine signalling is believed to be integral in the patterning of the duct during prostate development[4,9,10]. Laboratory evidence suggests that these stromal fibroblasts have protumorigenic capacity in the tumour microenvironment (termed tumour stroma) by inducing epithelial transformation and stimulating survival signalling, and they are believed to contribute to persistent cancer cell growth following therapeutic intervention[11–13].

Importantly, these epithelial cells in the normal and cancerous organ express high levels of *AR* which encodes the androgen receptor (AR), and this is believed to drive hormone dependency in prostate cancer. In addition, these cells secrete prostate-specific antigen (PSA), a serine protease that is transcriptionally activated by the AR and frequently elevated in men with prostate cancer, and is used in disease detection and diagnosis[14].

Millions of men are affected by prostate cancer each year. In high-income regions, the disease is among the most common solid malignancies and prognosis varies widely with age, ethnicity, genetic background and stage of progression[15,16]. An individual's disease trajectory may be anticipated based on a histopathological, anatomical and molecular profile of the tumour and the health condition of the patient.

For many men with prostate cancer, living with the disease involves managing a tailored treatment plan for a slow-growing and often indolent tumour, but for many

✉*e-mail: robert.bristow@manchester.ac.uk*

https://doi.org/10.1038/s41572-020-00243-0

Western diet
A diet that is generally characterized by high-fat, high-sugar foods and processed or pre-packaged meat, eggs and grains along with low consumption of fruits, vegetables, unprocessed meat and whole grains.

Germline mutations
Any detectable mutation in germ cells (carried in oocyte or sperm) that are heritable and become expressed in every somatic and germline cell within an organism.

others disease relapse is expected following a definitive treatment, which may be rapid, aggressive and, in rare cases, unresponsive to standard care. Currently, there is no infallible method of distinguishing aggressive from indolent tumours. However, breakthrough discoveries during the past century have profoundly altered the outlook for patients with prostate cancer, including the seminal discovery of the hormone-dependent nature of prostate cancer[17,18] and the high therapeutic efficacy in targeting this key feature with selective inhibitors, now known to be the high expression and frequent genetic amplification of *AR*[19]. In particular, the past decade has seen unparalleled advances in whole-genome DNA sequencing, mRNA sequencing and proteome profiling, which have provided unique insights into the genetic basis that is believed to underpin distinct prostate cancer subtypes and subpathologies[20–27]. In addition, major improvements in PSA screening guidelines and the use of imaging modalities have led to their increased adoption in prostate cancer diagnostics.

Prostate cancer research is a highly active area of multidisciplinary investigation which now involves computational biology as well as laboratory and clinical science. These investigations include exploring new preclinical hypotheses, experimental validation of scientific findings and translating these findings into clinic practice. These steps are essential before performing clinical studies to try to improve disease management. The increased understanding of the molecular basis of the disease has also advanced the design and specificity of treatment strategies and new therapeutics, such as those that better target key features of AR biochemistry. Progress continues in multiple areas from early detection and treatment of disease to enhanced biological understanding of each disease stage, which informs clinical care.

In this Primer, we review prostate cancer epidemiology, pathogenesis and genetic determinants, and provide an overview of disease diagnosis. We detail prostate cancer management and patient quality of life for each disease stage, and summarize current and potential future innovations in detection, management and treatment.

Epidemiology

Incidence and mortality

Prostate cancer affects millions of men worldwide[15,16]. The disease is the second most common cancer in men after lung cancer and accounts for 7% of newly diagnosed cancers in men globally (15% in developed regions)[16]. In addition, more than 1.2 million new cases are diagnosed and global prostate cancer-related deaths exceed 350,000 annually, making it one of the leading causes of cancer-associated death in men[16,28,29] (FIG. 2a).

Prostate cancer risk increases strongly with age and >85% of newly diagnosed individuals are >60 years of age[15,16,30]. Consequently, prostate cancer incidence is particularly high in regions with high life expectancy, such as the USA and the UK[16]. The worldwide incidence of prostate cancer correlates positively with the human development index (HDI) and gross domestic product, so that developed nations generally have a higher incidence than developing nations[29]. Interestingly, in Asia, some countries with a high HDI, such as Japan and South Korea, have a comparatively lower incidence than Western countries with a similarly high HDI; however, the incidence in these regions is increasing[16,31]. The regions with the highest incidence are Australia and New Zealand in Oceania, North America and Europe, as well as regions in South America, such as Brazil. Regions that encompass many of the world's low-income nations, such as South Asia, Central Asia and sub-Saharan Africa, currently have the lowest incidence of prostate cancer but some of the highest rates of annual increase in incidence[29,32]. The rise in incidence may reflect increasing awareness of prostate cancer through access to diagnostic screening in many of these regions, as increased screening frequency is related to increased incidence through overdiagnosis[33]. In addition, these regions have the highest age-standardized rates of prostate cancer death, although access to early detection is expected to reduce this[29,32] (FIG. 2b). Studies in Europe with long-term follow-up data have shown that repeated screening increases detection of all prostate cancers (including those that are indolent)[34,35] and reduces prostate cancer-specific mortality[34,35] (see Diagnosis, screening and prevention). The causes for the rising age-adjusted mortality in developing nations may also relate to an increase in prostate cancer risk factors associated with economic development that outpaces the benefits gained through progress in public health and treatment. Non-heritable factors that are generally thought to increase prostate cancer-related mortality include exposure to cigarette smoke, obesity and a predominantly Western diet; however, evidence for an effect on disease incidence is lacking[36,37].

Racial disparities

Some ethnic groups living in the USA, such as those of African or Caribbean descent, are at a twofold higher relative risk of early, more aggressive prostate cancer than white populations[38,39]. By contrast, men of Asian descent living in Asia are at lower risk of prostate cancer than white men living in the USA, but the risk within Asian men reaches levels similar to those of white men when living in the USA[31]. For some ethnic groups, such as Ashkenazi Jews and those of Icelandic descent, the risk of early, more aggressive prostate cancer is linked to germline mutations in genes such as *BRCA2* (REFS[40,41]). However, for many other ethnic groups, reasons for a disparity in prostate cancer incidence and/or mortality are not known.

Author addresses

[1]Cancer Research UK Manchester Institute, University of Manchester, Manchester Cancer Research Centre, Manchester, UK.
[2]Department of Oncology, Haematology and Bone Marrow Transplantation with Division of Pneumology, University Medical Centre Eppendorf, Hamburg, Germany.
[3]Sidney Kimmel Cancer Center at Jefferson Health and Thomas Jefferson University, Philadelphia, PA, USA.
[4]Department of Urology and Population Health, New York University and Manhattan Veterans Affairs, Manhattan, NY, USA.
[5]Department of Urology, University of North Carolina, Chapel Hill, NC, USA.
[6]Department of Urology, Jonssen Comprehensive Cancer Center UCLA, Los Angeles, CA, USA.
[7]Faculty of Biomedical Sciences, USI, Lugano, Switzerland.
[8]Laboratory Medicine Program, Princess Margaret Cancer Center, University Health Network, Toronto, Canada.
[9]These authors contributed equally: Richard J. Rebello, Christoph Oing.

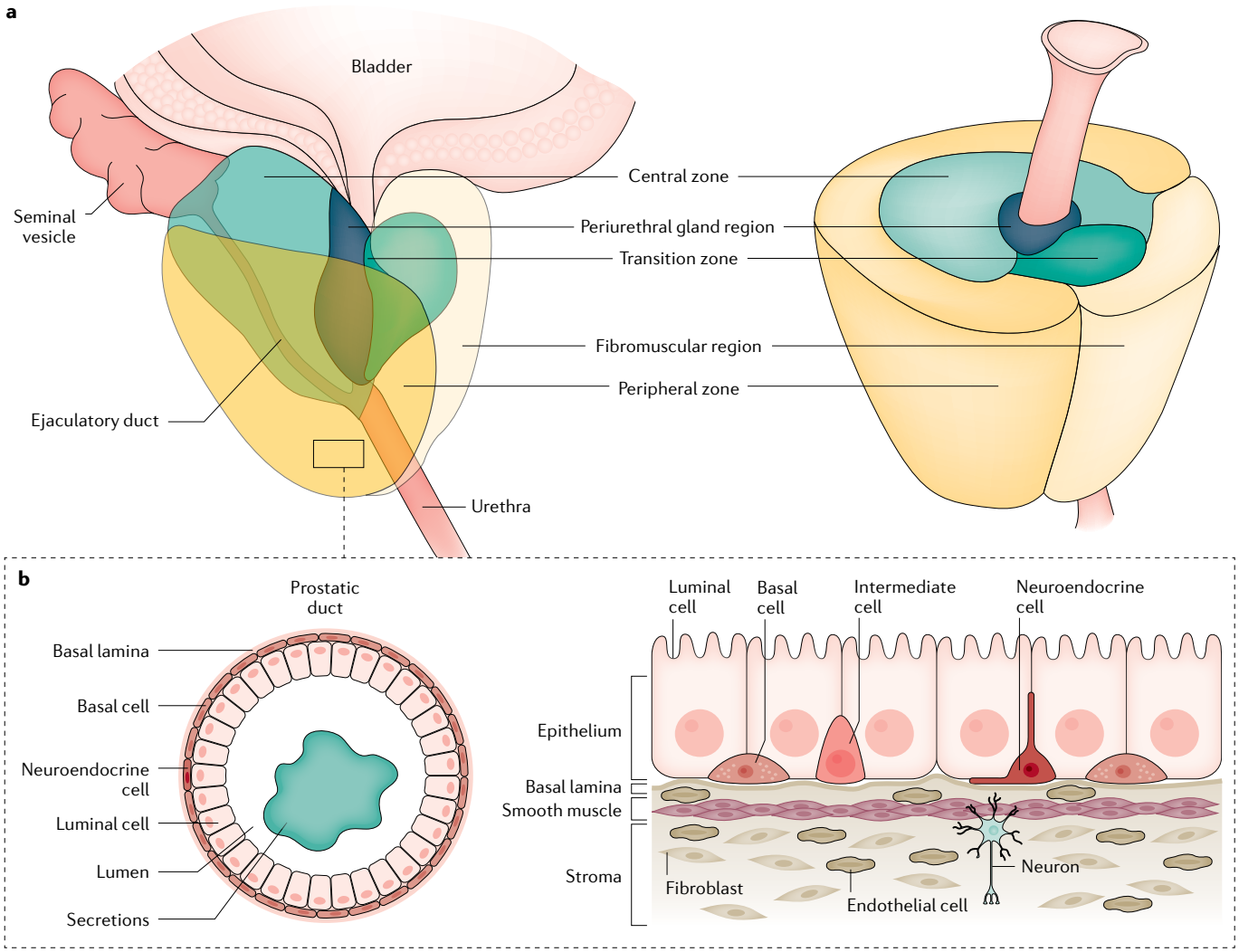


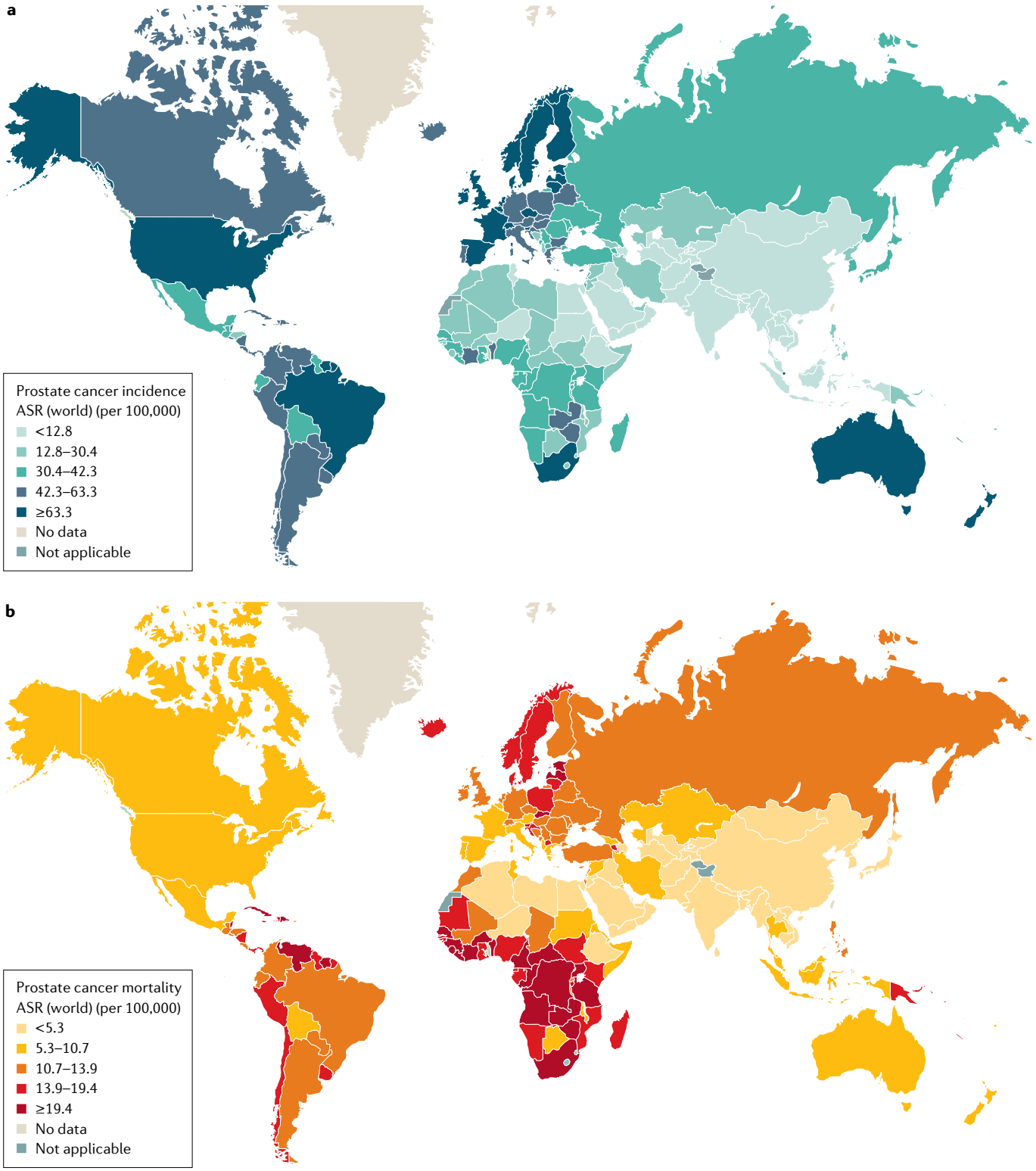
Fig. 1 | **Anatomy and histological structure of the human prostate gland. a** | The prostate can be divided into five anatomical regions: the central zone, the periurethral region, the transition zone, the peripheral zone and the fibromuscular region (or stroma). Most tumours originate in the peripheral zone. **b** | Each region comprises ducts and acini embedded in the stroma, which contains various cell types, predominantly smooth muscle cells but also fibroblasts, which have important roles in prostate development. The ducts and acini comprise a single layer of columnar epithelium (AR^+, $CK8^+$, $CK18^+$, PSA^+), surrounded by a layer of basal epithelial cells ($CK5^+$, $CK14^+$, $p63^+$), which produce the basement membrane, a layer of extracellular matrix that is anchored to the stromal cells (α-SMA^+, $vimentin^+$). Neuroendocrine cells (Syn^+, CGA^+, NSE^+) are also present within the duct. Parts **a** and **b** adapted from Verze et al. (2016), Springer Nature Limited[1].

Genetic predisposition

Prostate cancer risk is strongly associated with a family history of any cancer, and incidence of prostate cancer within these families is considered to be among the highest of any malignancy (~9% of individuals diagnosed with prostate cancer have a family history of cancer)[42,43]. In determining familial risk, the number of affected individuals, the degree of relation and age at disease onset are considered. Prostate cancer is considered familial when a patient has three or more affected relatives, with at least two of these relatives developing prostate cancer early (onset at <55 years of age)[44]. Men who have first-degree relatives with prostate cancer have a twofold increased risk of developing the disease[45].

Germline mutations in DNA damage repair (DDR) genes may confer increased risk of early onset prostate cancer (onset at <60 years of age), and include *BRCA1*, *BRCA2*, *ATM*, *ATR*, *NBS1*, mismatch repair (MMR)-related genes (*MSH2*, *MSH6* and *PMS2*), *CHEK2*, *RAD51D* and *PALB2* (REF.[1]). Interestingly, men with these mutations also constitute a large proportion of those with metastatic prostate cancer[46]. The mutations that confer the highest risk are those in *BRCA2* (REFS[46,47]) and *HOXB13* (REFS[48–50]), which confer a sevenfold to eightfold and threefold increased relative risk, respectively[49,51]. These findings have prompted further studies in large cohorts; for example, the IMPACT trial (NCT00261456), which aimed to identify men with pathogenic *BRCA1* or *BRCA2* mutations to assess the benefit of a targeted genetic screening approach in individuals at higher risk of prostate cancer[52].

Complementing these findings, genome-wide association studies have identified >170 single nucleotide polymorphisms (SNPs) associated with prostate cancer



incidence, including in the genomic region 8q24 where the *MYC* oncogene is located[53]. Strong and reproducible risk-associated SNPs may become useful for detecting early onset and familial prostate cancers (such as rs72725854 in African American men)[54–56]. Generally, SNPs might also be used in the calculation of genetic risk scores or prostate cancer risk scores for early detection in large populations[57,58]. Of note, these scores have not demonstrated the ability to preferentially detect clinically aggressive disease over indolent disease, but they have shown utility in increased detection of low-risk cancers and in identifying men for targeted screening[59,60]. This is an ongoing investigation in the BARCODE 1 pilot study (NCT03158922), which aims to associate the result of a prostate biopsy with the genetic risk score in men undergoing targeted screening based on SNP risk profiling[61].

Oncogene
A gene that controls normal cell growth for which mutation results in gain of function and promotes malignant transformation.

◀ Fig. 2 | **Global geographical incidence and mortality of prostate cancer. a** | Global incidence of prostate cancer in 2018. **b** | Global mortality from prostate cancer in 2018. Data are expressed as age-standardized rates (ASR; adjusted to World Standard Population) to account for differing age profiles among regions. In general, regions with a high human development index (HDI) with ageing populations have higher incidence of prostate cancer and lower mortality than regions with a low HDI. Data are from the Global Cancer Observatory[16,315].

For most prostate cancer risk SNPs, the functional link between the SNP and causation of prostate tumorigenesis remains unknown.

Prognosis and survival

The prognosis for an individual with prostate cancer is highly variable and dependent on tumour grade and stage at primary diagnosis. In Western regions and regions with a high HDI, such as the USA and UK, current early detection methods, such as PSA testing and digital rectal examination (DRE), enable diagnosis in most men at an early disease stage. Approximately 80% of men are diagnosed with organ-confined disease, 15% with locoregional metastases and 5% with distant metastases[15] (FIG. 3). Life expectancy for men with localized prostate cancer can be as high as 99% over 10 years if diagnosed at an early stage[15]. This long survival can largely be attributed to improvements in lead time to diagnosis through PSA screening which can be up to 12 years compared with 7 years without screening[62,63]. PSA screening results in the high diagnosis rate of clinically indolent tumours, which progress slowly and can be treated effectively. Men who are diagnosed with late-stage disease (distant metastases) have a poor overall survival of only 30% at 5 years[15]. Early detection of localized disease may also have a pivotal role in efforts to increase life expectancy of patients with prostate cancer by also preventing the onset of metastatic disease[64]. In addition, tailoring therapy to men who are likely to benefit from immediate definitive treatment and those who are not remains a key clinical challenge.

Mechanisms/pathophysiology

Genetics

Prostate cancer is believed to be strongly associated with the accumulation of somatic mutations in the prostate epithelial cell genome over a patient's lifetime. These aberrations can occur in oncogenes or tumour suppressor genes[53,54] and result in changes in gene transcription and/or translation and functional defects, which lead to deregulated cell homeostasis. Mutations predominantly involve genes that regulate cell growth, DDR, cell proliferation and cell death[24,25]. Prostate cancer is considered a C-class tumour that has a limited mutational burden (3–6% of the primary cancer genome), as most prostate cancer-associated genetic changes are copy number alterations (CNAs) or gene structural rearrangements[23,65,66].

Localized disease. The most commonly observed alterations linked to pathogenesis of localized prostate cancer are fusions of AR-regulated promoter regions with regions encoding members of the erythroblast transformation specific (ETS) family of transcription factors[67] (FIG. 4). Of these, the predominant fusion is of transmembrane protease serine 2 (*TMPRSS2*) with ETS-related gene (*ERG*), which is detected in almost 50% of prostate cancer biopsy specimens from white men, but less frequently in Black and Asian men (27–31%)[68–71], which may underlie a racial disparity in cancer survival outcomes. Whole-genome sequencing of localized, low-risk to high-risk prostate tumours has also revealed fairly infrequent gene alterations in *TMPRSS2–ERG*-negative tumours, including loss-of-function mutations in *SPOP*, fusion of *TMPRSS2* with *ETV1*, and gain-of-function mutations in *FOXA1*, which occur in 11%, 8% and 3% of primary prostate cancers, respectively[21,24]. Functional validation of the transforming potential and therapeutic implications of these genetic events is ongoing. For example, preclinical studies have revealed that mutations in *SPOP* promote genetic instability in mouse models[72–74].

Notable genetic disparities exist between Chinese and Western cohorts of patients with prostate cancer: 41%, 18% and 18% of Chinese patients show recurrent hotspot mutations in *FOXA1*, *ZNF292* and *CHD1*, respectively, and Chinese patients show a far lower rate of ETS fusions[75,76]. These data may indicate a very important biological difference in the pathogenesis of prostate cancer between racially disparate populations[75,76]. Of note, FOXA1 is essential for organogenesis of the prostate and, in prostate cancer, functions as an oncoprotein that increases transcription of *AR*, particularly in advanced prostate cancer, to drive metastatic progression[77,78]. These findings demonstrate the need for systematic and comprehensive prostate cancer mutation analyses in other ethnic groups to produce a global genomic atlas of the disease.

In addition, in an aggressive, rare variant of prostate cancer that typically lacks AR expression, termed poorly differentiated neuroendocrine prostate cancer (NEPC; also known as small cell carcinoma), the most frequent alterations thought to be disease drivers are gene amplifications of *AURKA* and *MYCN*, which are present in up to 40% of patients with localized NEPC[79]. This disease variant is more frequently seen as treatment-emergent NEPC in men who have undergone androgen deprivation therapy (ADT). Preclinical models of these single-gene alterations recapitulate the clinical features and neuroendocrine phenotypes seen in patients[79–81]. Additionally, *ONECUT2* expression is enriched in treatment-emergent NEPC, and has been found to regulate tumour hypoxia signalling and cell differentiation state away from hormone dependence[82,83]. By contrast, these alterations in *ONECUT2* are rarely seen in localized prostate adenocarcinoma that remains hormone-dependent[24].

In patients with localized disease, specific gene alterations that distinguish aggressive from indolent prostate cancer have been difficult to establish, probably owing to a range of driver mutations giving rise to the disease (genetic heterogeneity), and current management is not generally determined by molecular profiling of the tumour. Instead, genetic signatures comprising multiple features, including CNA, gene methylation and complex mutational phenomena, such as kataegis, chromothripsis

Tumour suppressor genes
Genes that control normal cell growth for which mutation results in loss of function and promotes malignant transformation.

Genetic instability
High frequency of mutations within the genome of a cell that can result in chromosomal rearrangements or aneuploidy.

Hotspot mutations
A phenomenon in which the same amino acid position is mutated in many tumours, often occurring as activating mutations in oncogenes.

Kataegis
Regions of localized gene hypermutations within a small region of DNA.

Chromothripsis
Regions of chromosome shattering and reinsertions of minute DNA fragments within a single event and often confined to one or two chromosomes.

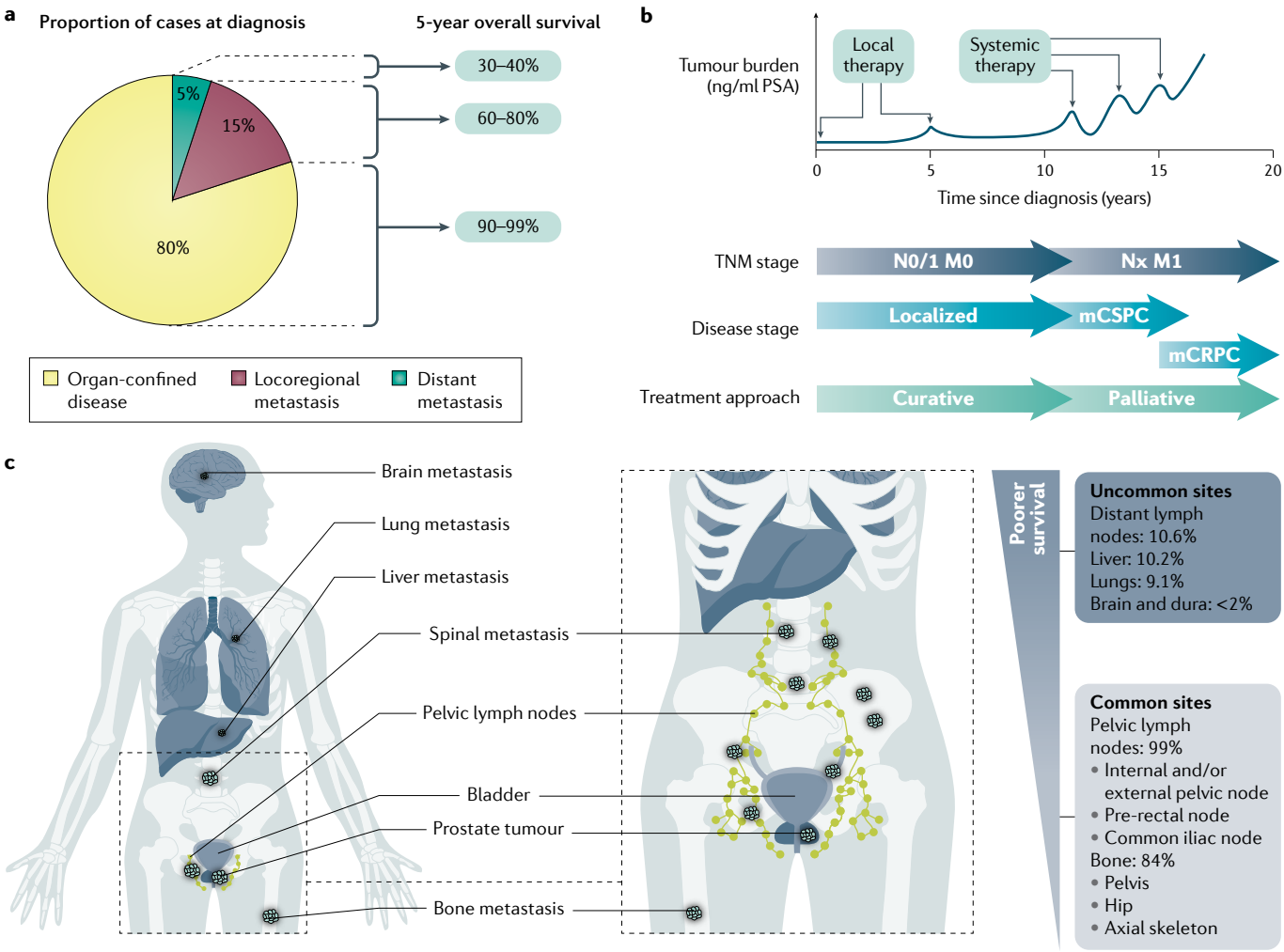


Fig. 3 | **Prostate cancer stages and progression. a** | Relative prostate cancer stage distribution at the time of diagnosis. Most cancers at diagnosis are localized and fully contained within the prostate gland (organ-confined disease, 80%). A minority of patients have local positive lymph nodes (locoregional metastasis,15%) or distant metastasis (5%) at diagnosis[15]. The 5-year overall survival of patients with localized disease is 60–99%[316], whereas that of patients with distant metastases is 30–40%[15,235]. **b** | Tumour burden, estimated by prostate-specific antigen (PSA) level over time since diagnosis, increases in patients whose cancer fails to respond to local and systemic therapies as the disease progresses to metastatic disease. These aggressive prostate cancers are associated with high tumour–node–metastasis (TNM) staging, progression from localized to metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC) and a change from curative to palliative care. **c** | Common sites of metastatic spread in advanced prostate cancer include locoregional spread to lymph nodes (99%) and bone (84%). Uncommon sites of metastasis include distant lymph nodes (10.6%), viscera (~10%) and the brain and dura (<2%). Spread to these soft tissue sites is associated with even poorer survival[317–319]. Estimates are for index regions with a high human development index and best practice early detection or PSA screening protocols in place.

and chromoplexy, may be more indicative of disease aggressiveness, as increasing genetic instability is considered to be associated with biochemical failure and clinical progression including metastasis development[26,84,85]. In localized disease, few genes are broadly clinically targetable and none of these is common in patients with prostate cancer; for example, *ATM* is the most commonly altered gene in non-indolent localized disease, occurring in 7–10% of patients[26], and druggable targets within its signalling pathway exist. Certainly, this heterogeneity of potential disease driver genes adds to the challenge of understanding the clinical profile of a prostate tumour at diagnosis and how to treat it with possible future targeted agents.

Metastatic disease. Metastatic prostate cancer encompasses a range of advanced disease states that are no longer organ-confined and often involve lymph node and/or bone sites. Importantly, this group includes de novo metastatic castration-sensitive prostate cancer (mCSPC), as well as cancers that progress during or after ADT, termed castration-resistant prostate cancer (mCRPC). mCSPC and mCRPC tumours (often in multiple sites per patient) have a distinctly higher mutational burden and frequency of CNAs than localized prostate cancer[24,25,27,86]. Of note, most biopsy samples used for whole-genome sequencing analysis to date were obtained from mCRPC tumours that had been treated locally and systemically with active therapies (see Management); thus, some of the

Chromoplexy
Highly complex and high-frequency genome-wide, gene structural rearrangements which create gene fusions and/or disrupt several genes.

Biochemical failure
An increase in blood PSA levels despite sufficient treatment.

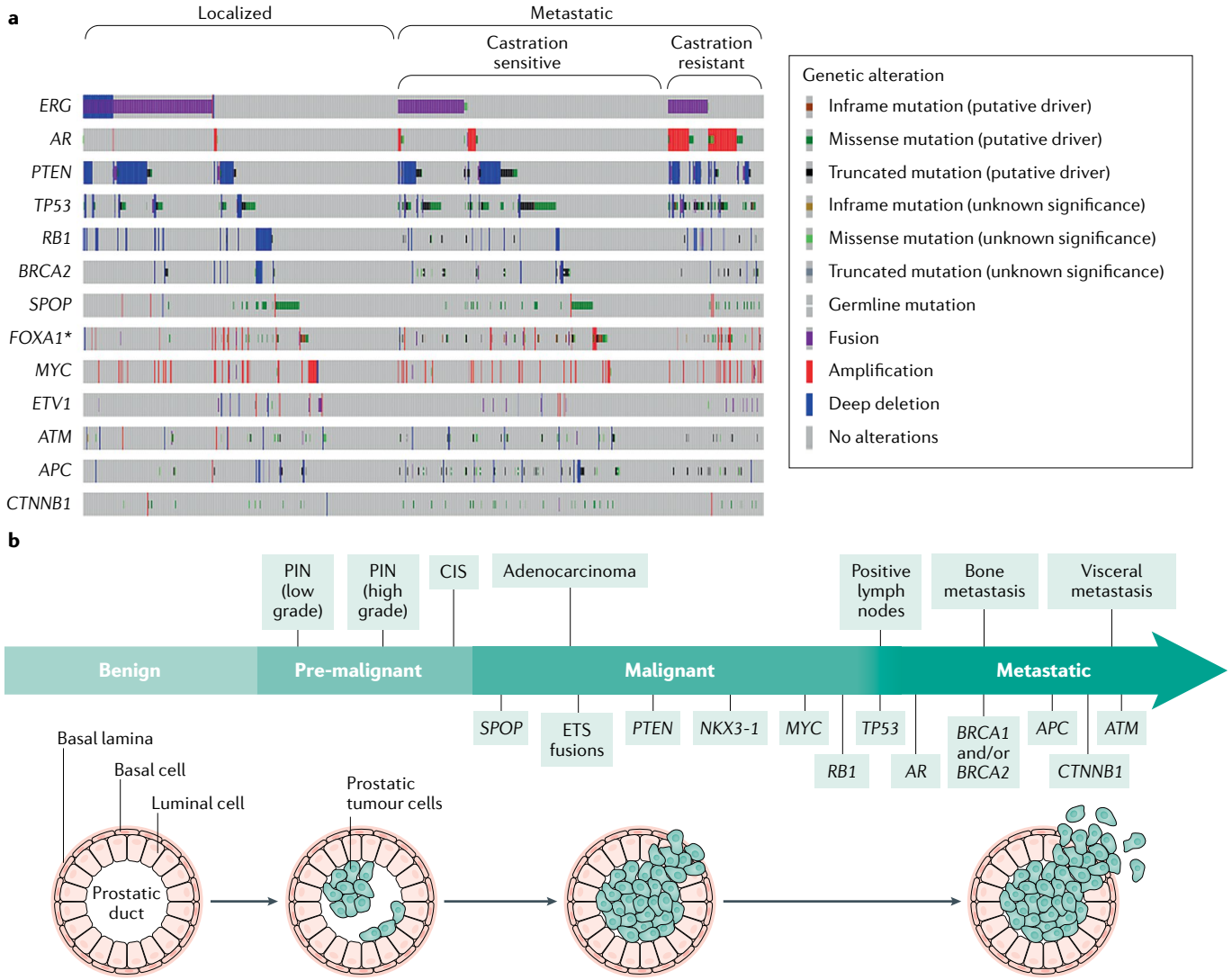


Fig. 4 | **Genetic alterations in prostate cancer. a** | Genetic alterations in localized, metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC). An oncoPrint of individual patient tumours which are positive for genetic alterations in oncogenes or tumour suppressor genes, in different patient cohorts (localized, 494 samples; mCSPC, 424 samples; mCRPC, 150 samples). Prostate cancer is highly heterogeneous and patients may have a combination of one or more of these genetic changes. For example, *TMPRSS2–ERG* fusion, *PTEN* and *RB1* deletion, *TP53* mutation and amplification of *MYC* are very common genetic changes in all stages of prostate cancer. This contrasts with *SPOP* mutations which are enriched in localized and mCSPC and *AR* amplification which is enriched in mCRPC. Data are from cBioPortal[320,321] using the PanCancer Atlas TCGA-PRAD (localized disease)[24], MSK (mCSPC)[27] and SU2C-PCF[25] (mCRPC) cohorts. **b** | Common mutations in prostate cancer are shown according to their enrichment at different disease stages. CIS, carcinoma in situ; PCF, Prostate Cancer Foundation; PIN, prostatic intraepithelial neoplasia; TCGA, The Cancer Genome Atlas. **FOXA1* mutations are enriched in prostate cancers of Chinese men, whereas ETS fusions are less prevalent, similar to prostate cancers of Black men. Part **b** adapted from Mills et al. (2014)[89].

mutational changes in these tumours are likely to also reflect treatment-associated genetic perturbations[20,22,25].

In mCRPC, the most common mutations are amplification of, and gain-of-function mutations in, *AR* or amplification of regulators of *AR* transcription (such as *FOXA1*), as well as inactivating mutations or deletions of genes that repress AR pro-tumorigenic signalling (such as the tumour suppressors *ZBTB16* and *NCOR1*), which collectively are present in >70% of patients[25,87,88] (FIG. 4a). By contrast, for mCSPC, follow-up targeted genetic studies in matched samples before treatment of patients who later relapsed with mCRPC have shown that AR is altered in only 2–6%, which suggests an acquired role for AR amplifications and mutations in mCRPC[27,86].

AR is one of the most studied and therapeutically targeted oncogenes in prostate cancer. In the luminal epithelium of the normal prostate, the binding of androgens, such as dihydrotestosterone (DHT), initiates a cytoplasmic to nuclear translocation of the AR where it binds target genes (those with an androgen response element (ARE)) to elicit a transcriptional response[19]. The luminal cells of the prostate normally express high levels of AR, which can act to increase cell proliferation in neoplasia[89]. Accordingly, growth control in the

normal prostate must be tightly regulated but is lost in neoplasia[19,90]. AR predominantly functions as a transcription factor that regulates the expression of genes that maintain cellular homeostasis and genes encoding proteases that are important for normal prostate function (such as *KLK3*, encoding PSA)[19]. In the diseased state, AR primarily promotes a growth-related transcription programme to drive tumorigenesis[90]. Importantly, ADT frequently leads to alterations of *AR*, AR expression or post-translational modifications that result in resistance to therapy over time via multiple mechanisms. First, overexpression of *AR* can occur by amplification of the gene or by alteration of factors that control *AR* expression[91]. Second, somatic gain-of-function mutations, which predominantly occur in the ligand-binding domain and result in constitutively active AR mutants, as well as mutations that reduce AR specificity, enabling activation by other agonists, including other steroid hormones (for example, oestrogen and glucocorticoids), occur at high frequency[92]. Third, post-translational modifications of AR can sensitize the receptor to activation even at the low levels of testosterone that remain after castration[93]. Fourth, alternative splicing in some tumours leads to increased production of short splice isoforms of *AR*, termed AR splice variants (SVs)[94,95]. The protein products of AR SVs typically lack the ligand-binding domain and are weak but constitutively active transcription factors. Preclinical evidence suggests that AR SVs can promote the transition from CSPC to CRPC; hence, the clinical utility of AR SVs for predicting outcomes is an active area of investigation. Last, *AR* overexpression is almost exclusively observed in CRPC, and laboratory studies confirm that increased AR levels alone are sufficient to induce therapeutic resistance[96]. This dependence on AR for disease progression makes prostate cancer an almost uniquely targetable disease by blockade of AR signalling.

Progression from localized to metastatic disease and from CSPC to CRPC is also thought to involve deregulation of key genes in growth control (FIG. 4b). Homozygous deletions in chromosome 10q, which contains *PTEN*, and loss-of-function mutations are present in >12–17% of localized and mCSPC tumours but are enriched in mCRPC (>40% of tumours)[24,25], suggesting that these are significant transforming genetic events in carcinogenesis and progression. Furthermore, phospho-inositol 3 kinase (PI3K) pathway alterations are also fairly common, including gain-of-function mutations in the pathway intermediates *PIK3CA* and *PIK3CB* in 6% and in *AKT1* in 2% of advanced tumours[25]. PI3K pathway intermediates have been shown to facilitate progression to CRPC in mouse models, which is an ongoing area of interest, especially because a range of small-molecule inhibitors of key intermediates are now available[97,98]. Activation of the WNT signalling pathway is not a prominent feature of localized disease but alterations in pathway intermediates occur in 18% of mCRPC tumours, such as loss-of-function mutations in *APC* in 9% and gain-of-function mutations in *CTNNB1* in 4% of tumours[22,25]. Of note, instability of chromosome 8, including CNAs of genes on 8q, which contains the *MYC* oncogene, as well as loss of 8p, which contains the *NKX3-1* tumour suppressor, are both frequent, occurring in 20–30% of patients with advanced disease[22,25]. *MYC* is also suspected to have a wider role in prostate carcinogenesis, as MYC is almost ubiquitously expressed at every stage of tumour development, even in the absence of CNA, and can be upregulated through direct transcriptional targeting by many other genes to drive proliferation and therapy resistance[99,100].

Control of genetic stability is also frequently lost in prostate cancer progression and may be one of the most important events in tumorigenesis. Genes regulating cell cycle arrest, such as *TP53* and *RB1*, are frequently altered in mCRPC (FIG. 4). In localized disease, *TP53* and *RB1* are only altered at a frequency of 8% and 1% but are enriched in metastatic disease, occurring in 27% and 5% of mCSPC and 50% and 21% of mCRPC, respectively[24,25,27,86], which suggests a role for their dysfunction in metastatic progression. Furthermore, in mouse models, *Rb1* loss is sufficient to drive the transition from CSPC to CRPC, and is strongly associated with poor outcomes[101–103]. Cell and mouse models have revealed that the combination of *Rb1* loss and *Tp53* loss promotes lineage plasticity and transition to adenocarcinoma with neuroendocrine features under continuous ADT, as well as metastasis[104–107].

Somatic defects in DDR genes are also highly prevalent in mCRPC. Cells with defects in double strand break repair genes may have homologous repair pathway deficiency, which results in high CNA burden and increased sensitivity to DNA strand intercalators, ionizing radiation and PARP inhibitors, potentially defining a subset of patients who may respond to a non-standard therapy[108,109] (see Management). Two key genes involved in homologous repair that are frequently altered in advanced disease are *BRCA2*, which is altered in 7% of mCSPC and 12.5% of mCRPC, and *ATM*, which is altered in 5% of mCSPC and 7% of mCRPC; by contrast, mutations in these genes are rarely seen in localized disease[25,27,86]. Genetic instability is an active area of research, and agents that specifically target its drivers have shown promise in delaying cancer-specific death, both in preclinical studies using ex vivo cancer models and in clinical trials in patients with mCRPC[110,111].

Disease initiation

The tumour-initiating cells or the cells of origin of a prostatic adenocarcinoma are thought to originate from the basal[112] or luminal[113,114] prostate epithelial cells, and genetic mutation is thought to be a primary driver of disease. Experimental genetic mutation of basal or luminal cells can give rise to high-grade tumours that histologically resemble distinct forms of adenocarcinoma but not basal cell carcinoma[115]. Interestingly, luminal cell specification of the tumour has been linked to a high frequency of *TMPRSS2–ERG* fusion in these models[115,116], a feature which is commonly seen in patient specimens[24]. The identity of a true cell of origin of all human prostatic adenocarcinomas remains contentious[112,116], but it is generally accepted that the transformed epithelium must have undergone a series of phenotypic changes during tumorigenesis, including cell signalling changes, perhaps as a consequence of genetic mutation, which aided the transformation from benign to malignant

disease[113,116–118]. By its definition, the transformed epithelium must possess the capacity to invade the basement membrane to be classed as cancerous (FIG. 4b). This aetiology contrasts with that of benign prostatic hyperplasia (BPH), another disease of the prostate, in which abnormal, non-cancerous cell growth and proliferation occurs in the transition zone of the prostate. Similar to prostate cancer, BPH is also a condition associated with ageing but is not thought to be linked to prostate cancer predisposition[119], even though prostate cancer can also arise in the transition zone of the prostate.

In addition, localized prostate cancer is often morphologically heterogeneous within a patient. Heterogeneity occurs intertumourally, whereby multiple tumour foci can appear within a cancerous prostate, and these foci can even show genetic differences[120,121]. Additionally, intratumoural heterogeneity also occurs, whereby cells within a focus may arise from distinct cellular ancestors that became transformed independently[122,123] or from a single transformed ancestor clone that then diverged into multiple distinct clones within a focus[124,125]. Even metastases, which are thought to be clonally derived and, therefore, mostly homogeneous, can harbour multiple genetically distinct subclones with distinct molecular features[126–128]. Tumour heterogeneity is an area of continued research interest owing to its suspected role in disease progression during or after standard systemic ADT[129]. As large datasets detailing the biology of tumour heterogeneity continue to be compiled, we may identify patients who should be given an active therapy based on multifocal tumour genetics, which is not currently standard practice[128].

Disease progression

Prostate cancer progresses in a substantial proportion of patients, and this remains a therapeutic challenge[2]. Progression is accompanied by rising PSA levels, which suggests AR activity, owing to proliferation of luminal epithelial cells. Disease progression after a definitive therapy, either local or systemic, is multifactorial and tumours may arise from cells that are resistant de novo by possessing intrinsic features (thought to be cell subpopulations within a tumour) or may acquire resistance induced by ADT or AR antagonists. Mechanisms of disease progression during and after ADT combined with an AR signalling inhibitor (ARSI), such as enzalutamide, are under ongoing investigation. Using genetic and gene expression data, efforts have been made to assign risk and subclassify tumours into groups in combination with the Gleason score and risk of PSA recurrence, which are currently the strongest conventional risk variables for non-indolent prostate cancer (see Diagnosis, screening and prevention). To further classify tumours into high and low risk of disease progression under ADT, additional characteristics, such as high polyclonality, might dictate disease severity and insensitivity to conventional therapy[130]. The results of these efforts may affect future patient treatment based on genetic and cellular profiling combined with standard measures in risk and/or treatment stratification.

The mechanisms that promote recurrent AR activity are not mutually exclusive and may restrict efficacy of second-line therapies, such as treatment with an ARSI (FIG. 5). For example, somatic mutations in *AR* have been identified that turn enzalutamide into an AR agonist[131]. Alternatively, *AR* mutants have been identified that are

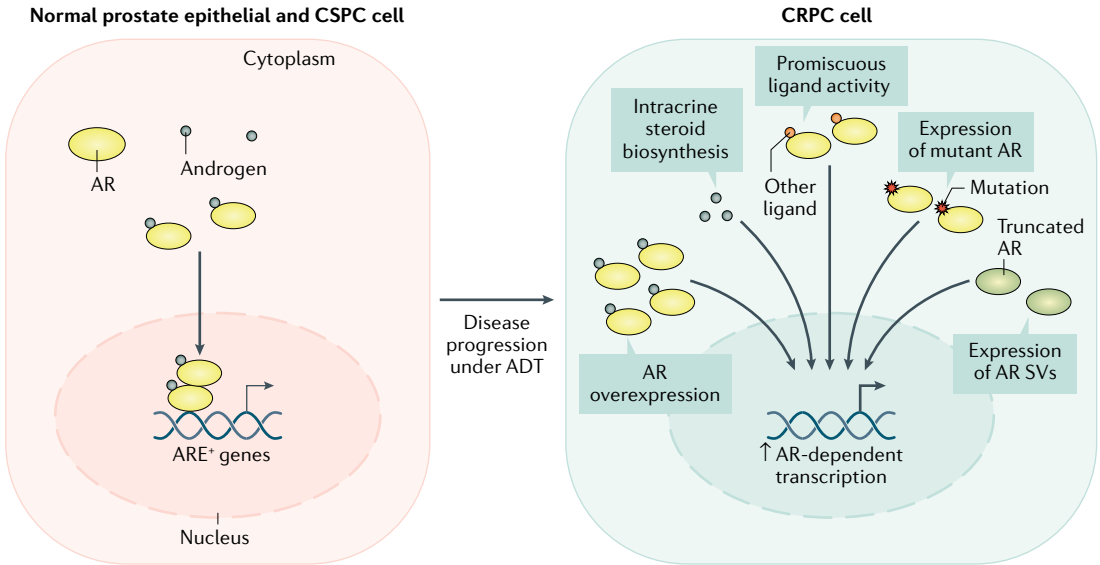


Fig. 5 | **Androgen and/or AR dependence and prostate cancer progression.** Prostate cancer cell progression from castration-sensitive epithelium to castration-resistant prostate cancer (CRPC) is often associated with treatment (for example, androgen deprivation therapy (ADT)) and is strongly associated with the alteration and/or mutation of the androgen receptor (AR) signalling axis. Following androgen ligand binding, in non-malignant and castration-sensitive prostate cancer (CSPC), activated AR forms dimers in the nucleus, which bind to androgen-response elements (AREs) in AR-regulated genes and upregulate their transcription. The abnormal cellular AR signalling changes seen during cancer progression in CRPC result from *AR* gene amplification and/or AR overexpression, point mutations that result in expression of AR splice variants (SVs) or mutant (truncated) AR with constitutive activity, or sustained AR signalling by binding of non-specific ligands (promiscuous activity). Furthermore, prostate cancer cells can also synthesize androgen from precursor steroids intracellularly (intracrine production), leading to activation of AR.

activated by glucocorticoids, and preliminary studies suggest that, in some instances, the glucocorticoid receptor may act instead of AR to drive tumour growth[132]. Of note, in some patients in whom therapy fails and PSA levels are rising, biopsy of metastatic disease reveals clinical features that suggest a loss of AR dependence. This subclass of tumour cells shows low AR expression and concomitant reduced PSA expression, which frequently occurs in combination with loss of both *RB1* and *TP53* expression[105,106], which may be associated with treatment-emergent, poorly differentiated NEPC[133]. Understanding the contribution of a putatively AR-indifferent prostate cancer cell to disease progression and identifying novel targeted strategies is an active area of investigation. On balance, AR activity is not only essential for tumour development but is the major driver of disease progression to the castration-resistant phase during ADT and/or ARSI therapy.

Further understanding of resistance mechanisms driving subsequent transitions will be essential for development of durable treatments for castration-resistant disease. Further pathways to resistance include restoration of AR signalling independent of AR alterations, including AR cofactor alterations and intracrine androgen biosynthesis. For example, loss of transcriptional co-repressors that attenuate AR activity (such as *NCOR1* and *NCOR2*) or enhance expression of co-activators (such as *NCOA1*) that promote activity and/or sensitize AR to low levels of agonist can occur[20,91]; however, whether these alterations are causative for therapeutic resistance requires confirmation. Comparison of CSPC and CRPC revealed that a subset of CRPCs can still produce enzymes that convert weak adrenal androgens into testosterone. CYP17A1, an enzyme essential for androgen biosynthesis from pregnenolone and progesterone, is expressed in both CSPC and CRPC[134–136]. CYP17A1 induction can result in intratumour androgen levels that are sufficient to reactivate AR signalling in CRPC and promote resurgent tumour growth. In addition, gain-of-function alterations in the androgen synthesis pathway also contribute to this process[137]. Importantly, these findings have resulted in the implementation of the CYP17A1 inhibitor abiraterone acetate as a second-line hormonal therapy after disease progression under ADT.

Metastasis of prostate cancer is mostly associated with lymphatic spread to locoregional lymph nodes and/or hematogenous spread and homing to bone marrow stroma predominantly in the axial skeleton and, in rarer cases, to distant visceral sites (FIG. 3c). This feature is the principal cause of prostate cancer morbidity and mortality[138,139]. In this process, local invasion is a necessary early step and cells must undergo extensive proliferation, neovascularization and extravasation at the primary site of high-risk localized disease. Malignant epithelial cells must downregulate expression of proteins involved in cell–cell and cell–matrix attachment and become motile, a process known as epithelial to mesenchymal transition. These cells are thought to degrade the extracellular matrix with secreted factors, such as matrix metalloproteinases, and intravasate the systemic circulation[139]. Disseminated tumour cells must then evade immune surveillance and resist destruction and intrinsic cell death mechanisms as they travel to locoregional lymph nodes, from where clones subsequently travel through the bloodstream to a secondary site[138]. At a secondary site, cells are thought to arrest first by epithelial–endothelial binding and then transmigrate through the endothelial wall[138,139]. The cells can then remain dormant, interacting with native cells in the niche, before proliferating to form a new tumour, which in turn has the capacity to become metastatic[138,139]. The new tumour may perturb normal physiological function at the metastatic site (for example, activating bone remodelling) and, with increasing tumour burden, will eventually lead to physiological and anatomical dysfunction.

Prostate cancer cells have a propensity for homing to red bone marrow in the axial skeleton and >80% of patients with metastatic disease have bone metastasis[139]. Both local chemokine signalling (CXCR4 expressed on prostate cancer cells interacts with CXCL12 expressed in bone) and red bone marrow adipocytes, which contain energy-rich lipid sources, are a key attractant in the metastatic niche[138,139]. Modelling prostate tumours using transgenic mice has provided important insights into primary disease biology but has not been able to recapitulate the same aetiology of metastatic spread as in humans, as mouse models predominantly have high visceral metastatic burden, whereas human prostate cancer spreads almost exclusively to bone[139]. Targeting stromal–epithelial interactions and understanding vulnerabilities in disseminated tumour cells homing to bone are under ongoing preclinical investigation.

Diagnosis, screening and prevention

Screening and early detection

Screening for prostate cancer is the primary way to detect localized prostate cancer in asymptomatic individuals, the stage at which the disease is potentially curable. The aim of screening methods (all-comer, targeted population-based or individual-based) is to improve prognostic discrimination of tumours that require upfront, definitive therapy with curative intent from those that remain indolent and can be managed with active surveillance[140]. Screening methods primarily involve measurements of the blood serum biomarker PSA. A Cochrane review and meta-analysis of five randomized studies assessing the effect of PSA screening in 341,342 men failed to detect a statistically significant reduction in prostate cancer-specific mortality through a screening intervention[140]. The largest single study (European Randomized Study of Screening for Prostate Cancer, ERSPC), which included 182,160 men from eight European countries, showed a 20% reduction in prostate cancer-specific mortality, and that 570 men need to be screened by PSA testing to prevent one prostate cancer-related death. Thus, screening comes with a substantial risk of overdiagnosis and overtreatment of clinically indolent prostate cancer[35,141]. In addition, the psychological implications for individuals identified via population screening who have increased PSA levels but do not have prostate cancer need to be considered. Psychological effects to men with low-risk prostate cancer identified by overdiagnosis include increased anxiety

Overdiagnosis and overtreatment
Detection and treatment of cancer in men whose disease would not have become symptomatic during their lifetime; treatment results in harm rather than benefit.

and depression in addition to symptoms associated with a biopsy and overtreatment[142]. Despite these reported adverse effects of screening, no evidence of reduced quality of life years at a population level has been found between screened and non-screened men[140]. However, these considerations have led to strong advice against the implementation of population-based screening and this approach has not been adopted in any region[44]. Subsequently decreased screening prompted a sustained fall in prostate cancer diagnoses, while the incidence of metastatic disease at primary diagnosis may now be increasing[143]. New approaches have been developed that enable individuals to elect to have their baseline PSA level determined at the age of 40 years as a historical comparison to aid in accurate individual prostate cancer screening[44].

Consequently, current guidelines recommend informed decision-making for individual prostate cancer screening or testing, explaining the potential benefits and harms to the individual, and the use of a multivariable approach that also takes into account factors such as age and family history in addition to PSA[44] (BOX 1). Men who are at high risk of prostate cancer occurence (either age >50 years or >45 years with a positive family history of prostate cancer or people of African descent, or PSA >1 ng/ml at age ≥40 years or >2 ng/ml at age ≥60 years) are considered for screening based on thorough counselling about risks and benefits of early prostate cancer detection, if the Eastern Cooperative Oncology Group (ECOG) performance status is good and a life expectancy of at least 10–15 years is estimated[44]. In this setting, pretreatment risk calculators[144,145] (TABLE 1) may be useful to reduce the number of unnecessary biopsies and aid in decision-making[126,127].

In addition, a strong family history of prostate cancer or known germline mutations in homologous repair (HR) pathway genes are risk factors for early-onset and progression to metastatic prostate cancer and are important considerations for decision-making and targeted population screening. This targeted screening is especially recommended for *BRCA2* carriers, with consideration for carriers of *HOXB13*, *BRCA1*, *ATM* and MMR pathway genes, such as *MLH1*, *MSH2*, *MSH6* and *PMS2* for Lynch syndrome[52,146–148]. At the 2019 Philadelphia Prostate Cancer Consensus Conference, recommendations were made to commence screening at the age of 40 years or 10 years before the youngest prostate cancer diagnosis in a family. Active surveillance was recommended for men with germline *BRCA2* mutations[147]. In addition, in patients with metastatic prostate cancer, priority genes, including *BRCA1*, *BRCA2* and MMR genes, were recommended and *ATM* was to be considered in gene panel testing for treatment selection and clinical trial eligibility[147]. The US National Comprehensive Cancer Network (NCCN) also includes guidance on somatic tumour testing in metastatic disease, including screening for mutations in DDR genes, such as *BRCA2* and *ATM*, and for microsatellite instability[148,149]. If any alterations are found, the patient is recommended for genetic counselling for possible cancer syndromes, which may also promote secondary cancers in an individual[148,149].

Diagnosis

Standard diagnostic tools for detecting prostate cancer include a DRE to assign clinical stage and a blood-based analysis of PSA levels as well as MRI[44]. DRE is a physical palpation of the prostate to assess gland enlargement, texture and stiffness, which has a positive predictive value in detecting prostate cancer of 5–30% in men with PSA ≤2 ng/ml[44,150]. A prostate biopsy is indicated for an abnormal DRE result, which is associated with a worse differentiation grade, but a definitive diagnosis depends on histopathological verification[44] (FIG. 6). Measuring serum PSA levels complements prostate cancer detection efforts and is a better independent predictor of prostate cancer than DRE[44,151]. However, both DRE and PSA testing can be abnormal without prostate cancer being present (false-positive) and can be normal despite the presence of prostate cancer (false-negative). Serum PSA level is a continuous parameter that can be elevated owing not only to prostate cancer but also to BPH and infection; thus, an elevated PSA value (from 3 to 10 ng/ml) must be considered relative to the patient's baseline level and confirmed with repeated assessment after a few weeks under standardized conditions for the individual to avoid unnecessary biopsies[152,153]. The optimal interval for PSA testing and DRE follow-up are unknown but life expectancy should be considered, as those with a life expectancy of <15 years are unlikely to benefit[44]. Follow-up PSA measurements may be indicated every 2 years for men at risk, or after up to 8 years for those not at risk[154].

A prostate biopsy is used to assess for the presence of prostate cancer if DRE and/or imaging results are suspicious or if the PSA value is confirmed to be elevated or rising without any other explanation[152,153]. Transrectal ultrasound-guided (TRUS) biopsies are employed for systematic sampling of 10–12 cores for histopathological diagnosis. Samples are taken from the peripheral zone bilaterally from apex to base of the organ and especially from suspicious areas; however, TRUS biopsies tend to miss anteriorly located tumours[44]. Transperineal mapping biopsies (TPMB) are becoming preferred to TRUS biopsies. TPMB obtains samples by needle through the perineum rather than through the rectum leading to a reduced risk of urinary tract infections but higher risk of urinary retention[155]. In addition, multiparametric MRI (mpMRI)-guided biopsies have been shown to greatly increase the diagnostic yield of prostate biopsy for clinically significant prostate cancer and enhance its early detection, enabling selection of a smaller group of men for biopsy compared with systematic sampling of all men[156]. This method also has better sensitivity for locating and detecting clinically significant tumours and is used to specifically target biopsies to these suspicious areas[157–159]. mpMRI-guided transperineal biopsy is superior to mpMRI-guided transrectal biopsy regarding detection of clinically significant prostate cancer in MRI-visible index lesions[160]. mpMRI may also enable visualization of anterior tumours, increasing their detection rate[44]. mpMRI increases the accuracy of tumour localization and detection of clinically relevant disease and is now recommended to guide biopsy procedures world-wide. By contrast, systematic

Eastern Cooperative Oncology Group (ECOG) performance status
A measure ranging from 0 (no effect on daily functioning) to 4 (100% bed-bound) to estimate a patient's ability to perform certain activities of daily living.

Microsatellite instability
The condition of genetic hypermutability caused by a predisposition to mutation, resulting from DNA mismatch repair deficiency.

Multiparametric MRI
A detailed high-resolution technique to image the physiology of an organ using strong magnetic fields, field gradients and radio waves combined with a contrast agent.

Box 1 | **Screening for prostate cancer in different regions**

Prostate cancer screening (on a population or individual level) is a matter of ongoing controversy, and national and international guidelines have not reached a consensus. Thus, it is recommended that defined populations are screened by different modalities, including prostate-specific antigen (PSA) serum levels, digital rectal examination, modern imaging techniques (for example, multiparametric MRI), prostate biopsy and liquid biopsy, and the approach varies between regions. It is generally accepted that population-based screening with PSA measurement may reduce prostate cancer mortality at the expense of overdiagnosis and overtreatment[35]. Two aspects of early detection are important when PSA is used as a biomarker for prostate cancer screening: overdiagnosis and overtreatment must be avoided, and shared decision-making is of the utmost importance, as most national guidelines endorse screening only for informed men insisting on testing for an early diagnosis.

Most randomized controlled screening studies were conducted in predominantly white populations in Oceania, North America and Europe, which have the highest incidence of prostate cancer. These were the PLCO (USA) study, which found no benefit, and the ERSPC (Europe) and Göteborg (Sweden) studies, which found 21% and 42% relative risk reduction, respectively, in favour of screening. Of note, the PLCO study included men who had received at least one PSA test (>80% in the control arm), which could have biased the study to no difference observed[324]. Guidelines for PSA screening have generally been adopted in North American and European regions, as summarized in the table. The US Preventive Services Task Force (UPSTF) and American Urological Association (AUA) recommend that men 55–69 years of age are informed about the risk and benefit of PSA screening before offering PSA testing, but do not recommend population-based screening or screening of men ≥70 years of age[325]. Similarly, the Canadian Urological Association (CUA) suggests offering screening to men who have >10 years life expectancy, with screening to start at 50 years of age in most men and 45 years of age in men with a familial risk[326]. Despite this, the Canadian Task Force on Preventive Health Care (CTFPHC) recommends against screening at any age[326]. All North American guidelines agree that one suspicious PSA value should not prompt immediate biopsy, and confirmation in repeated PSA measurements is sought first before any consideration of biopsy. Screening is to cease at 60 years of age in men with PSA <1 ng/ml and stop completely at 70 years of age. The same applies to the European Society for Medical Oncology (ESMO) clinical practice guidelines[327]. The European Association of Urology (EAU), European Society for Radiotherapy and Oncology (ESTRO) and the International Society of Geriatric Oncology (SIOG) jointly recommend PSA testing only for well-informed men with increased prostate cancer risk >50 years of age (>45 years of age in those with a family history or of African descent and >40 years of age in *BRCA2* mutation carriers) with a life expectancy of 10–15 years[44]. Follow-up testing after 2 years is recommended in men with initial PSA levels >1 ng/ml at the age of 40 years or >2 ng/ml at the age of 60 years; all other patients are recommended to have repeated tests after 8 years[44].

A factor affecting screening studies in Asia is that screening compliance rate is quite low (20% of men >50 years of age in Japan are routinely screened compared with >80% in the USA and Western Europe)[328,329]. The studies on population-based screening have been largely based on populations of European ancestry, but their results have influenced detection of prostate cancer in Asian regions as well. For example, the Japanese Urological Association (JUA) currently recommends PSA-based population screening in Japan without an upper age limit. This recommendation applies to men ≥50 years of age (or men ≥40 years of age with a family history). For individual-based screening, the JUA recommends baseline PSA levels to be recorded at 40 years of age to decrease the chance of missing clinically important prostate cancer in men in their 50s[330,331]. For many regions with a low human development index, including India and many in Africa, prostate cancer is detected at a late and often symptomatic stage and PSA screening is rarely used to identify prostate cancer[332]. Increased adoption of PSA-based strategies as well as advanced imaging modalities, such as multiparametric MRI, to detect suspicious lesions for biopsy is expected to increase the rate of incidence of early-stage prostate cancer and decrease mortality from late-stage prostate cancer.

Country/region	Recommendation			
	Without additional risk factors	Family history of any cancer	*BRCA2* germline mutation carrier	African American ancestry
USA (USPSTF, AUA)	From age 55 to 69 years and if >10 years LE; stop at age 70 years	Individual decision-making before age 55 years	N/A	Individual decision-making before age 55 years
Canada (CUA)	From age 50 to 70 years and if >10 years LE	From age 45 years if >10 years LE	N/A	N/A
Europe (EAU, ESTRO, SIOG)	From age 50 years and only if >10 years LE	From age 45 years if >10 years LE	From age 40 years	From age 45 years if >10 years LE
Japan (JUA)	From age 50 years	From age 40 years	N/A	N/A

Based on shared decision-making with their clinician, patients can take a PSA test to screen for prostate cancer. LE, life expectancy, N/A, not assessed.

biopsies mostly diagnose clinically indolent or low-risk lesions that may not require active therapy[44]. Lymph node metastasis detection in men with high-risk disease can be aided by PET using a traceable molecule marking prostate-specific membrane antigen (PSMA) localization[161]. PSMA PET has shown superiority over conventional CT in accurately staging men with high-risk prostate cancer[162].

For diagnosis, each biopsy site, including for mpMRI-targeted biopsy, is reported individually, including information about location, differentiation grade (that is, Gleason grade or International Society of Urological

Table 1 | **Prostate cancer risk classification at diagnosis and after treatment**

Assessment tool (type of risk)	Measured variables	Low risk	Intermediate risk	High risk
Before treatment (at diagnosis)				
Partin table (organ confinement, percent likelihood)	PSA, GS, T-Cat	OC 88%, EPE 11%, SV^+ 1%, LN^+ 0%	OC 38–58%, EPE 36–48%, SV^+ 4–7%, LN^+ 2–6%	OC 5–12%, EPE 23–33%, SV^+ 22–23%, LN^+ 32–48%
D'Amico risk group (risk of BCR)	PSA, GS, T-Cat	PSA <10 ng/ml and GS ≤6 and T-Cat T1–T2a	PSA 10–20 ng/ml or GS 7 or T-Cat T2b	GS 8–10 or PSA >20 ng/ml or T-Cat T2c–T3
ISUP grade group (risk of BCR)	GS	Grade 1: GS 3+3=6	Grade 2 (low intermediate risk): GS 3+4=7 (predominantly well-formed/fused/cribriform glands) Grade 3 (high intermediate risk): GS 4+3=7 (predominantly poorly formed/fused/cribriform glands)	Grade 4: GS 4+4=8; (only poorly formed/fused/cribriform glands OR predominantly well-formed glands with lesser component lacking OR predominantly lacking glands with lesser component of well-formed glands) Grade 5: GS 9 or 10 (lacking gland formation with or without poorly-formed/fused/cribriform glands; necrosis)
CAPRA score (risk of MFS, CSS, OS)	Age, PSA, GS, T-Cat, percent positive biopsies	0–2	3–5	6–10
Before treatment and after treatment				
Kattan nomogram (pre-surgery OR; post-surgery BCR)	Age, PSA, GS, T-Cat, percent positive biopsies, prostatectomy report details (OC, EPE, SV^+, LN^+)	Pre-radical prostatectomy nomogram (no prior treatment)	Pre-radical prostatectomy nomogram (no prior treatment) Post-radical prostatectomy nomogram (PSA <0.1 ng/ml after surgery)	Pre-radical prostatectomy nomogram (no prior treatment) Post-radical prostatectomy nomogram (PSA <0.1 ng/ml after surgery) Salvage radiation therapy nomogram (PSA <0.05 ng/ml after surgery)

Partin tables[312] and CAPRA score[313] are tools for prospective pretreatment outcome prediction based on a retrospectively studied cohort with known disease outcome data. The Kattan nomograms[314] aid pre-prostatectomy and post-prostatectomy estimation of likely treatment outcomes and even risk of prostate cancer-related death in the case of post-surgery biochemical relapse (BCR). The use of these tools can aid clinical decision-making for choosing an active therapy by a clinician and are often used in conjunction with D'Amico risk group[171] and International Society of Urological Pathology (ISUP) grade group[168]. BCR, biochemical relapse; CSS, cancer-specific survival; EPE, extraprostatic extension; GS, Gleason score; LN^+, pelvic lymph node positivity; MFS, metastasis-free survival; OC, organ confinement; OR, overall recurrence; OS, overall survival; PSA, prostate-specific antigen; SV^+, seminal vesicle positivity; T-Cat, tumour category (tumour–node–metastasis classification).

Pathology (ISUP) grade group) and extent. If present, adverse pathologies such as intraductal carcinoma of the prostate (IDCP), lymphovascular invasion and extra-prostatic invasion are noted, as these features affect definitive treatment decisions[44].

Prostate cancer aggressiveness has historically been graded using the Gleason system in which features of tumour architecture discerned through microscopic assessment of histological features are used to classify the tumour tissue as well-differentiated (the lowest grade) to poorly-differentiated (the highest grade)[163] (FIG. 6; TABLE 1). The Gleason score is the summation of the most prominent and second most prominent Gleason pattern numbers, which results in a low (≤6), intermediate (7) or high (8–10) Gleason grade[164–166]. In 2014, these grades were reorganized into the ISUP grade groups 1–5, so that the scale starts at 1 and to account for the differential prognosis of Gleason grade 7 tumours (3+4 and 4+3 tumours; the predominant pattern is stated first)[167,168]. This grade group system was adopted by the WHO as a recommended classification system in conjunction with risk groups incorporating PSA levels and clinical T category (cT), owing to a growing consensus as to its superiority in predicting the risk of potentially lethal prostate cancer[168–170]. Patients are classified as low risk (cT1–cT2a, PSA <10 ng/ml and ISUP grade 1), intermediate risk (cT2b or PSA >10–20 ng/ml or ISUP grade 2 or 3) or high risk (>cT2b or PSA >20 ng/ml or ISUP grade >3), which is used to guide the staging evaluation and to inform management decisions[44,171] (TABLE 1). Patients with low-risk disease are highly unlikely to have metastatic disease and, therefore, no further staging is necessary. By contrast, some patients with intermediate-risk and all who have high-risk disease should undergo further imaging, such as a contrast-enhanced CT and bone scintigraphy, to identify metastatic disease.

Non-malignant lesions termed high-grade prostatic intraepithelial neoplasia (PIN) are commonly considered to be carcinoma precursors and are frequently detected in association with carcinoma (often adjacent) (FIG. 6a,b). PIN are characterized as an intraglandular proliferation of luminal epithelial cells with reduction or loss of the basal epithelium[121,172]. Luminal cells in high-grade PIN have enlarged nuclei with prominent nucleoli and cytoplasmic basophilia[121,172]. High-grade PIN also have increased cell cycle marker expression[173,174]. Further pathological discrimination between PIN and adenocarcinoma can be achieved by immunostaining; for example, absence of the basal cell markers p63 and cytokeratin 5 and/or cytokeratin 14 (REF.[118]), and the presence of luminal cell markers cytokeratin 8 and/or

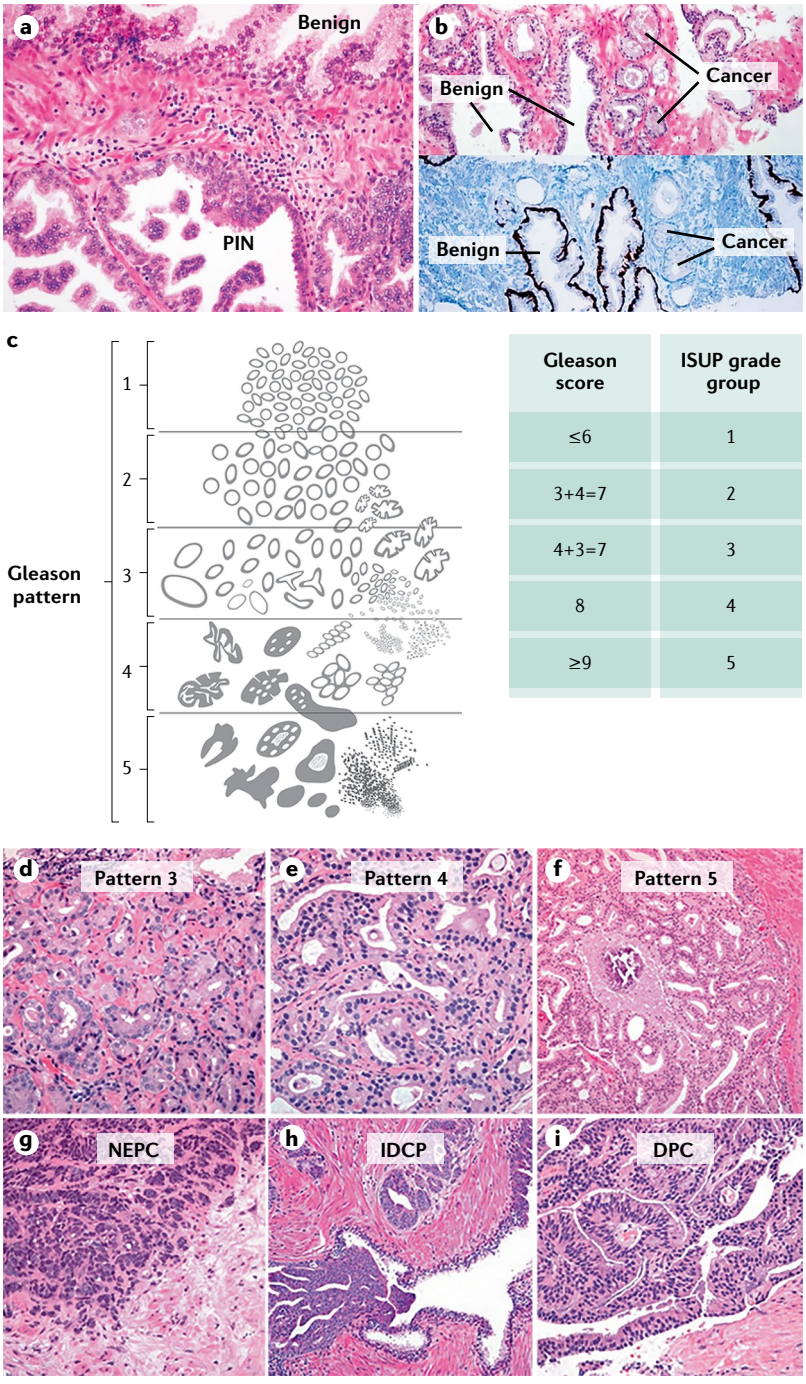


Fig. 6 | **Histological features of prostate cancer.** Histology of prostate cancer, ranging from benign, low-grade lesions to high-grade neoplastic glandular lesions. **a** | Benign glands display the same architecture as high-grade prostatic intraepithelial neoplasia (PIN) but PIN is discriminated by cytonuclear atypia, including prominent nucleoli. Haematoxylin and eosin (H&E) stain, ×200. **b** | Upper panel: adenocarcinoma is characterized by small, round acini lacking basal epithelium interspersed between benign glands. H&E stain. Lower panel: Lack of basal epithelium is highlighted by absence of immunostaining for high molecular weight cytokeratin in contrast to strong staining in benign glands. Haematoxylin counterstain, ×100. **c** | Schematic depicting Gleason patterns to score prostate cancer severity, in which increasing numbers equate to increased severity. Gleason scores, calculated as the sum of the most prominent and second most prominent Gleason pattern numbers, can be converted to International Society of Urological Pathology (ISUP) grade groups 1–5, which better accounts for the differential prognosis of Gleason grade 7 tumours. **d** | Gleason pattern 3 adenocarcinoma, characterized by small, closely packed individual acini with a single lumen. H&E stain, ×200. **e** | Gleason pattern 4 adenocarcinoma forming a retiform (fused) pattern. H&E stain, ×200. **f** | Gleason pattern 5 adenocarcinoma showing a central plug of comedo necrosis in the context of a large cribriform (sieve-like) architecture. H&E stain, ×100. **g** | Poorly differentiated (small-cell) neuroendocrine prostate carcinoma (NEPC) consisting of strands of tumour cells with high nuclear to cytoplasmic ratio and hyperchromatic nuclei often indenting each other. H&E stain, ×200. **h** | Intraductal carcinoma of the prostate (IDCP) evident from proliferation of carcinoma cells within an antecedent prostatic duct, filling up the lumen. H&E stain, ×50. **i** | Ductal prostate cancer (DPC) with typical papillary architecture and lining by tall columnar carcinoma cells. H&E stain, ×200. Part **c** © The Trustees of Indiana University.

cytokeratin 18 and overexpression of α-methylacyl-CoA racemase[118,175,176] in regions of adenocarcinoma (FIG. 6b).

Most prostate cancers have conventional acinar morphology, but variant prostate cancer pathology, such as mucinous carcinoma and ductal adenocarcinoma, may also occur[163]. Rarely, tumours may consist of neuroendocrine cells[177] or myofibroblasts[178,179]. NEPC and sarcomatoid prostate cancer occur in <2% and <1% of all patients, respectively, and they are associated with poor survival[180,181]. De novo NEPC may present as a pure, poorly differentiated small-cell carcinoma or mixed with conventional acinar adenocarcinoma, and is insensitive to ADT[133], owing to reduced or absent AR activity in most cases. Treatment-emergent poorly differentiated NEPC (tNEPC) is more commonly seen (~20% of CRPCs) and is associated with continuous ADT and ARSI therapy[133,182,183] (FIG. 6g). In mixed tumours, the NEPC component is genetically related to adjacent adenocarcinoma, which suggests a common cellular ancestor and potential clonal differentiation and expansion[184]. This transdifferentiation may be a mechanism for the emergence and therapeutic resistance of NEPC[184]. Poorly differentiated NEPC may be diagnosed histologically, but often expresses the neuroendocrine markers synaptophysin and chromogranin A enabling confirmation[177].

IDCP and ductal prostate cancer (DPC; also known as ductal adenocarcinoma of the prostate) are distinct prostate cancer pathologies that commonly occur in association with conventional acinar adenocarcinoma[185]. IDCP is characterized by the distension of antecedent ducts and acini by carcinoma cells (FIG. 6h). Variable amounts of basal cells surrounding the carcinoma remain and can be detected by immunostaining[185]. IDCP often appears as a loose or dense cribriform (sieve-like) pattern or solid accumulation of tumours occasionally with central necrosis. DPC is an invasive carcinoma characterized by papillary formations with fibrovascular cores, cribriform and solid patterning and often with a visible stromal reaction[185] (FIG. 6i). Patients who present with these additional features have a higher

Transdifferentiation
A process in which a mature somatic cell is transformed into another without first undergoing dedifferentiation into a pluripotent or multipotent cell type.

risk of biochemical failure and poorer overall survival than those with stage-matched classic adenocarcinoma only[183,185–188]. Furthermore, these subpathologies are associated with high genetic instability and mutations in DDR genes and have been shown to be clonally derived from a cellular ancestor common with adjacent adenocarcinoma[186,189]. The presence of these features has become an important consideration for clinical management.

Prevention

Early stages of prostate cancer do not cause symptoms and no interventions for primary disease prevention have been established, although many methods have been proposed to decrease risk. Whilst a link of incidence of more aggressive prostate cancer with smoking and obesity has been observed[190,191], the effect of lifestyle modifications, such as cessation of smoking, increased exercise and weight control, to decrease the risk of prostate cancer is not currently known. Instead, pharmacological agents, such as 5α-reductase inhibitors (5-ARI), including dutasteride and finasteride, have been proposed as chemopreventative agents[192]. These agents function by preventing testosterone conversion to DHT thereby reducing activity of the AR; therefore, they might have the potential to prevent the development of prostate cancer, but clinical trials of their use had complex outcomes[193]. The PCPT[192] and REDUCE[194] studies evaluated 5-ARI as chemoprevention in men with low PSA levels and no evidence of disease, finding that low-grade tumours were less frequent but the incidence of higher-grade tumours was not affected[194]. Thus, owing to concerns over a lack of effect on high-grade tumour incidence, 5-ARIs have not been approved for use in prostate cancer prevention. However, results of the REDEEM study[195] showed a benefit of 5-ARI use as an adjunct to active surveillance, raising interest for their use in low-risk disease management, but neither indication is suggested in any clinical guidelines[193].

Management

Clinical management of patients with prostate cancer needs to account for various factors for appropriate risk-adapted and patient-oriented treatment, including varying clinical characteristics at different stages (localized, locally advanced and metastatic stage; castration-sensitive and castration-resistant status), histopathological and molecular features (neuroendocrine, cribriform or intraductal patterns and/or DNA repair alterations) and patient characteristics (life expectancy, health status, family history and personal preferences).

Generally, for localized non-metastatic disease (cT1–2 cN0 M0), options include active surveillance and local ablation through surgical or radiotherapeutic intervention with or without antihormonal treatment. Treatment decisions depend on the risk of biochemical relapse (BCR), which is estimated based on baseline PSA level, Gleason score or, more accurately, ISUP grade, and clinical T stage. Patients are stratified into a low-risk, intermediate-risk or high-risk category with respective 5-year BCR rates of >25%, 25–50% and >50%[171]. The intermediate-risk group is highly heterogeneous and differentiation into a low intermediate (ISUP grade 2) and high intermediate (ISUP grade 3) risk group enables more precise risk stratification[167,168]. In locally advanced disease with non-organ confined prostate cancer growth (cT3–4) and/or pelvic lymph node metastases (N1), multimodal concepts of the above-mentioned options are recommended.

The treatment landscape of metastatic prostate cancer has undergone remarkable changes in the past decade. For metastatic (M1) disease, ADT with luteinizing hormone-releasing hormone (LHRH) analogues for mCSPC until disease progression followed by docetaxel plus prednisolone with continued ADT for mCRPC has been the gold standard since 2004 (REF.[196]). Since then, various new classes of agents have emerged, including next-generation ARSIs (abiraterone acetate, enzalutamide, apalutamide and darolutamide), bone-targeting radionuclides (radium-223 chloride), novel taxanes (cabazitaxel) and poly(ADP-ribose) polymerase inhibitors (PARPi)[197]. These options keep changing the treatment landscape and their use evolves from single-agent to combination treatments and from late-stage CRPC to early CSPC treatment settings.

Suppression of gonadal androgen production to castration levels induces prostate cancer cell death and transient clinical remission, indicated by a decrease in PSA level and/or radiographic shrinkage of the tumour in most patients with mCSPC[198]. Conventional ADT comprises LHRH analogues, including LHRH agonists (goserelin, leuprorelin and buserelin) and LHRH antagonists (degarelix), or first-generation ARSIs (bicalutamide and flutamide). LHRH agonists bind the LHRH receptor of the pituitary gland, which leads to its overstimulation with a brief surge of luteinizing hormone (LH) release before the pituitary gland stops LH production. LHRH antagonists instead block LHRH to bind to its pituitary receptor, preventing secretion of LH directly. The drop in LH results in the cessation of testicular testosterone production and in medical castration[199]. In patients with metastasis, the initiation of LHRH agonist treatment can cause tumour flare with transient worsening of cancer-related symptoms[200].

The pivotal role of sustained AR signalling in driving CRPC progression despite castration-level serum testosterone levels, through acquired ability to convert precursor steroids to DHT, prompted the introduction of novel agents, such as C17,20-lyase (CYP17A1) inhibitors, that target androgenic steroid synthesis[201]. CYP17A1 is found in testicular, adrenal and prostatic tissue and catalyses DHT production from glucocorticoids and cholesterol[202]. Abiraterone acetate targets the androgen signalling axis by both suppressing CPY17A1-mediated androgen synthesis and direct AR-inhibitory properties[202]. Abiraterone is used in combination with low-dose prednisolone, which itself has some limited antiproliferative activity on prostate cancer cells, to limit abiraterone-induced mineralocorticoid excess[203]. By contrast, the next-generation ARSIs enzalutamide, darolutamide and apalutamide directly block AR activation in a similar manner to first-generation AR blockers, such as bicalutamide, but also inhibit nuclear translocation and AR transcription factor activity[204].

Tumour flare
Acutely accelerated tumour growth and exacerbation of symptoms due to a transient surge in luteinizing hormone and testosterone after luteinizing hormone-releasing hormone agonist introduction.

Abiraterone-induced mineralocorticoid excess
An adverse effect of abiraterone use defined by hypertension, fluid retention and low serum levels of potassium.

Occult metastasis
The presence of metastases that are not detected with routine imaging or clinical examination.

Localized disease

Patients with localized low-risk disease are unlikely to have metastasis and, therefore, no further staging is necessary. By contrast, patients with high intermediate-risk (ISUP grade 3) and high-risk disease should undergo further imaging with at least cross-sectional abdominopelvic CT and bone scintigraphy to identify possible metastases[44]. This is crucial to inform treatment decision-making before curative local ablation, as incorrect diagnosis of localized disease that misses already present metastatic spread to the pelvic lymph nodes or distant metastasis inevitably leads to relapse after local treatment. Conventional CT imaging and routine bone scintigraphy have only low sensitivity (38%) to accurately stage high-risk prostate cancer[162]. Reliable detection of pelvic lymph node metastasis or occult distant metastasis can be improved by PSMA PET imaging[161]. Gallium-68 PSMA PET–CT has a 27% greater accuracy, and higher sensitivity and specificity, than conventional imaging with CT and bone scans to reveal otherwise occult metastasis in men with high-risk disease[162].

Various options can be considered for the treatment of organ-confined prostate cancer (pT1–T2, N0, M0) (FIG. 7). These include active interventions, such as active surveillance, radical prostatectomy (open retropubic or perineal, laparoscopic or robotic) with or without pelvic lymph node dissection, as well as radiotherapy with external beam radiotherapy (EBRT; either intensity-modulated (IMRT) or volumetric arc (VMAT)) and/or interstitial brachytherapy, either as low dose-rate permanent radioactive seed implantation (for low-risk to intermediate-risk disease) or an interventional boost to EBRT with short-term introduction of a high dose-rate radioactive source into the prostatic area

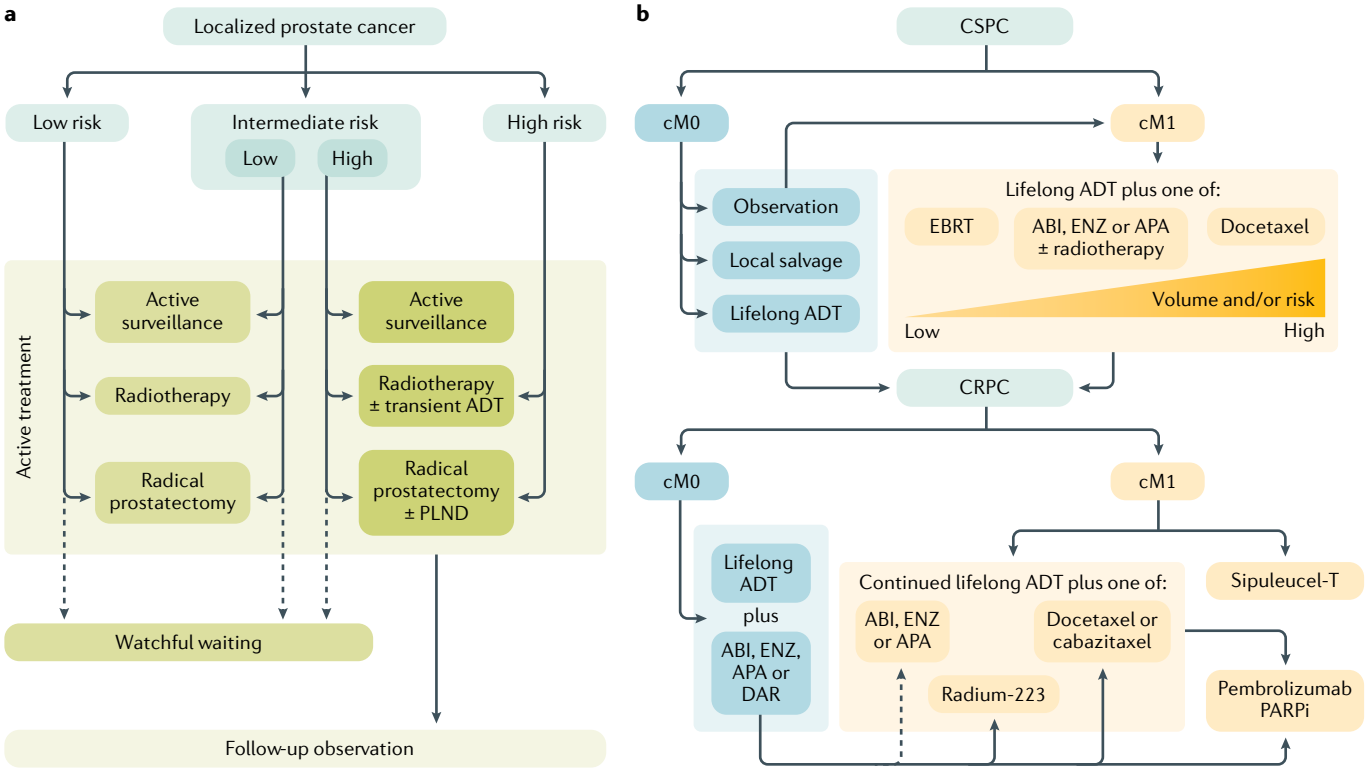


Fig. 7 | **Overview of prostate cancer management. a** | In general and in regions with high human development index, men with localized prostate cancer are predominantly actively managed with either active surveillance or radical local treatment. Patients with low-risk or low intermediate-risk disease undergo active surveillance, radiotherapy (external beam radiotherapy (EBRT) or low-dose brachytherapy) with or without transient androgen deprivation therapy (ADT), or radical prostatectomy. Those with high intermediate-risk or high-risk disease are recommended to undergo either active surveillance, radiotherapy plus transient ADT or radical prostatectomy with or without pelvic lymph node dissection (PLND) at their physician's discretion based on patient characteristics. Selected patients with a limited life expectancy of <10 years should be offered watchful waiting and receive treatment at the time of progression. Ongoing serum prostate-specific antigen (PSA) tests and digital rectal examinations can indicate whether a management change is required. Patients who have received definitive local treatment are subsequently observed for disease recurrence and may not require any further management. **b** | Biochemical relapse indicates disease relapse, classified as castration-sensitive prostate cancer (CSPC), which is subdivided into clinically non-metastatic (cM0) understood to have micrometastatic disease or overtly metastatic (cM1) disease. Patients with cM0 CSPC undergo local salvage treatment based on the primary treatment approach, lifelong ADT or observation until metastasis is detected. Those with cM1 CSPC are treated with continuous lifelong ADT plus either docetaxel or an androgen receptor signalling inhibitor (ARSI; abiraterone (ABI), enzalutamide (ENZ) or apalutamide (APA)) with or without radiotherapy or EBRT to the prostate, depending on the extent of metastatic spread. Disease progression beyond this point is termed castration-resistant prostate cancer (CRPC) and is treated with continued lifelong ADT and other agents based on the absence or presence of metastases on routine imaging. For cM0 CRPC, an ARSI (ABI, ENZ, APA or darolutamide (DAR)) can be added. For cM1 CRPC, an ARSI (ABI, ENZ or APA), radium-223 (if bone metastases only), or chemotherapy (docetaxel before cabazitaxel) can be added to continued lifelong ADT. Selected patients may benefit from novel agents including pembrolizumab (if microsatellite-instable) or PARPi (olaparib or rucaparib, if homologous recombination deficient).

of interest (for high-risk localized disease). Importantly, no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall and prostate cancer-specific survival for clinically localized disease[44].

Active surveillance involves scheduled, predefined follow-up examinations using DRE, PSA measurement and repeat biopsy (mpMRI-guided), and is employed to reduce overtreatment in men with very low-risk prostate cancer[44]. In contrast to active surveillance, which is a management strategy, radical prostatectomy and radiotherapy pursue curative intent in this disease setting. Treatment decisions are predominantly based on disease characteristics, such as local tumour growth (clinical T stage), tumour characteristics on imaging and pathology, including grade group and PSA levels. They also strongly consider patient characteristics, such as age, health status, comorbidities, germline mutational background, patient preferences and health-care system attributes related to treatment availability and accessibility[44].

For localized disease, a life expectancy of ≥10 years is considered essential for any benefit from local treatment owing to very slow progression rates and low metastatic potential. Such patients have a favourable prognosis and the risk of death is only 1% at 10 years after diagnosis, irrespective of primary management pathway[205,206]. Comorbidities are more important than age in predicting life expectancy (for example, by the Charlson Comorbidity Index or ASA Physical Status Classification), as increasing comorbidities and poor health status increase the risk of dying from causes other than prostate cancer[44]. Watchful waiting is a reasonable palliative approach in patients with low-risk disease and a limited life expectancy, in whom deferred symptom-guided treatment is initiated at symptomatic progression[207]. Patients with low-risk disease are often managed with active surveillance in the first instance, enabling deferral of curative treatment, avoiding overtreatment and unnecessary adverse effects, but this varies between regions[208]. Choosing active surveillance requires a thorough clinical assessment, which may include mpMRI, and confirmatory systematic and targeted MRI-guided biopsies of Prostate Imaging–Reporting and Data System (PI-RADS) lesions with a score of ≥3 to minimize the risk of underestimating tumour aggressiveness[44]. Owing to an increased risk of progression, patients with low-risk disease and histopathological signs of cribriform or intraductal patterns should be advised against active surveillance[44].

Patients with intermediate-risk disease and a life expectancy of >10 years should be offered active intervention with prostatectomy or primary ablative radiotherapy, delivered either by EBRT with transient ADT, over a 4–6-month period, or by low-dose brachytherapy, which have similar efficacy but different adverse effects[209,210]. In fact, radiotherapy is curative in 60% of men with localized prostate cancer[211]. Active surveillance is also an option for highly selected patients with favourable intermediate-risk disease (<10% Gleason pattern 4) after accounting for patient-related factors, such as age, comorbidities and patient preferences[205,212–214].

Patients with high-risk localized disease (PSA >20 ng/ml, ISUP grade >3) have a high risk of rapid progression and subsequent development of metastatic, incurable disease with substantial cancer-specific mortality. Local treatment is recommended in these patients. Options include radical prostatectomy with extended pelvic lymph node dissection or EBRT alone or with a brachytherapy boost plus long-term ADT[205]. Of note, the risk of occult metastasis is non-negligible in high-risk disease, which may lead to relapse regardless of the type of invasive local treatment. Thus, additional imaging studies are recommended before local interventions. Patients undergoing surgery and achieving undetectable PSA levels (<0.1 ng/ml) should generally not be offered adjuvant radiotherapy owing to associated adverse effects and lack of benefit compared with salvage radiotherapy (SRT) upon BCR[215,216]. Urinary incontinence and erectile dysfunction are more frequent after adjuvant radiotherapy than after post-surgical SRT at BCR[217]. Patients with locally advanced disease (cT3–4 cN0 or T_{any} cN1 or positive resection margins) are at exceptionally high risk of relapse. Radical local treatment (surgery or EBRT) combined with ADT provides best outcomes, but high-level evidence is lacking and standard approaches remain to be defined[44,218].

Biochemical recurrence and residual disease. After radical prostatectomy, PSA levels upon ultra-sensitive PSA-testing should be undetectable (<0.1 ng/ml), whereas a PSA >0.1 ng/ml is a surrogate marker of prostate cancer residues. After radiotherapy, PSA levels do not return to undetectable levels as the prostate remains[44]. Rising PSA levels are seen in ~27–53% of patients after prostatectomy or radiotherapy[219].

BCR precedes metastatic progression, which may be postponed or even avoided by local SRT. Importantly, not all patients with BCR have similar outcomes: predictors of worse overall survival are a short PSA doubling time, and a high Gleason score or ISUP grade of the primary tumour after radical prostatectomy and a short interval to BCR after primary radiotherapy[219]. To date, optimal management for patients with rising PSA levels but no signs of metastasis remains controversial with only limited evidence[197].

Patients with either BCR after normalization of PSA or persistently elevated PSA levels after radical prostatectomy can be offered SRT (≥66 Gy) to the former prostatic tumour bed. SRT achieves a 75% risk reduction for systemic progression[220] and an 88% chance of being progression-free after 5 years[216,221]. Patients with a short PSA doubling time (<6 months and a PSA of ≤0.2 ng/ml before SRT) seem to benefit most from SRT, emphasizing the need for repeated PSA assessment and early initiation of SRT at BCR after primary treatment to increase the chance of cure[220,222,223]. Metastasis-free survival is a strong surrogate for improved overall survival in these patients. Adding ADT with LHRH analogues for 6 months[224] or blocking the AR with bicalutamide for 2 years to SRT may further improve survival and should be considered individually based on PSA levels before SRT, positive surgical margin status and high ISUP grade[225]. In patients with persistently elevated

Prostate Imaging–Reporting and Data System (PI-RADS). A reporting tool that defines standards for the image creation and reporting of multiparametric MRI data.

PSA doubling time
The number of months it would take for the PSA to increase by twofold.

PSA values of ≥0.2 ng/ml after prostatectomy, PET/CT (choline-based or PSMA-based) may help identify occult metastases that are not detected with routine imaging (contrast-enhanced CT and bone scintigraphy) and may lead to a change in management in up to 62% of patients in whom salvage local treatment is highly unlikely to be curative[226].

For patients with BCR after primary radiotherapy, evidence to guide treatment decisions is limited, but local interventions such as salvage radical prostatectomy may be offered for selected patients[44].

Metastatic disease

Metastatic disease is the most lethal form of prostate cancer and can be subdivided into different treatment categories based on stage at presentation and treatment response (FIG. 7). Trials of new treatment agents and new treatment regimens are conducted with patients who have late-stage disease to achieve further improvements in cancer-specific survival.

Metastatic hormone-sensitive prostate cancer. Patients with metastatic prostate cancer are either diagnosed with de novo metastatic disease (M1), owing to disease progression of a previously unobserved primary tumour, or develop metastasis from their previously localized prostate cancer with or without primary local treatment, the latter owing to occult metastasis at the time of locally ablative treatment or spread of radioresistant disease (FIG. 7). For decades, the standard of care for these patients has been surgical orchiectomy or systemic ADT. ADT with LHRH agonists is considered the gold standard and is commonly given continuously until biochemical and/or radiographic disease progression occurs[198,227].

In patients with de novo mCSPC, several clinical studies have assessed whether early treatment intensification by adding docetaxel or an ARSI to conventional ADT improves outcomes[228–231]. All following studies confirmed a beneficial effect of intensified first-line treatment on key clinical outcomes, including progression-free survival (PFS) and/or overall survival and/or skeletal-related events (SREs) in selected patient populations[232]. Decision-making for one or another option needs to account for distinct clinical characteristics, such as number and site of metastases. Two studies introduced slightly different definitions for high or low burden of metastatic spread. The CHAARTED study defined high-volume disease as the presence of visceral metastases or four or more bone metastases with at least one outside the vertebral column and pelvis[233]. The LATITUDE study defined a slightly different high-risk status as the presence of at least two characteristics from a Gleason score of ≥8, the presence of three or more bone metastases or the presence of visceral metastasis[234]. In patients with high-volume mCSPC, the addition of six cycles of docetaxel to ADT in the CHAARTED trial[235], and the addition of six cycles of docetaxel plus prednisolone to ADT in the STAMPEDE trial prolonged overall survival by 10–18 months irrespective of disease burden according to CHAARTED criteria[236]. In the GETUG-AFU 15 trial, the addition of up to nine cycles of docetaxel to ADT prolonged PFS[237]. Overall survival, PFS and SREs were also improved by the addition of abiraterone plus prednisolone to ADT in patients with high-risk disease in the LATITUDE trial[234] and in unselected patients in the STAMPEDE trial[238]. Of note, the efficacy of either docetaxel or abiraterone combined with long-term ADT in the STAMPEDE trial did not differ regarding survival end points (overall survival, PFS and prostate cancer-specific survival) and SREs[239]. The addition of enzalutamide (ENZAMET study[233]) or apalutamide (TITAN study[231]) to ADT also improved PFS and overall survival. Interestingly, the ENZAMET study did not show a beneficial effect but increased toxicity from the addition of docetaxel to ADT and enzalutamide, raising a question as to the value of further treatment intensification using triplet combinations[233]. Another emerging treatment option is the addition of EBRT of the primary prostate tumour in patients with newly diagnosed mCSPC and low metastatic burden, which was shown to improve failure-free survival and overall survival in this subgroup of patients in the STAMPEDE study[240].

Consequently, combination treatment approaches are now considered standard of care in patients with mCSPC deemed sufficiently fit for these treatment approaches. Decision-making should consider disease characteristics, patient performance status, comorbidities and preferences, as well as increased toxic effects of combination approaches and treatment availability. An important lesson learned so far is that combining AR-targeting drugs or docetaxel with ADT early in the treatment sequence is safe and has life-prolonging effects. Results of ongoing studies, such as PEACE1 (NCT01957436), in which ADT and docetaxel are combined with local radiotherapy and/or abiraterone, or ARASENS, in which ADT and docetaxel are combined with darolutamide (NCT02799602), will elucidate whether triple combination approaches further improve important clinical outcomes. Other key questions are how to safely identify and how best to treat patients with oligometastatic disease, who have a limited number of metastases, and whether metastasis-directed therapy has additional beneficial effects in this subset of patients.

Metastatic castration-resistant prostate cancer. Despite good initial responses to systemic treatment, standard ADT or primary combination treatments for mCSPC eventually fail in nearly all patients, as indicated by radiographic disease progression and/or rising PSA levels, despite sustained suppression of serum testosterone to castration levels[241]. ADT is commonly continued on a lifelong basis, as AR function remains a driving force of prostate cancer cell survival and proliferation even in the castration-resistant stage[242] (FIG. 7). In mCRPC, several additional treatment options have shown overall survival benefit, including taxane-based chemotherapy, ARSIs, radium-223 chloride and a therapeutic vaccination treatment (sipuleucel-T)[197] that is available only in the USA. All the studies showing a benefit of these agents have been performed in an era when ADT alone was used as a treatment for mCSPC; thus, their benefits specifically in patients who have received these agents for mCSPC are not known.

Skeletal-related events (SRE). Complications associated with metastasis that usually manifest as fractures, spinal cord compression, bone pain and high blood calcium levels.

The traditional standard of care for mCRPC was treatment with docetaxel plus prednisolone based on superior overall survival compared with mitoxantrone plus prednisolone in the TAX-327 trial[196]. For almost a decade, docetaxel remained the first-line standard of care, and studies focused on identifying second-line options after docetaxel failure. Cabazitaxel, a derivative of docetaxel, plus prednisolone has been approved for the treatment of docetaxel-pretreated mCRPC after showing superior activity over mitoxantrone plus prednisolone in docetaxel-insensitive mCRPC in the TROPIC trial[243]; however, cabazitaxel did not outperform docetaxel as first-line treatment in the FIRSTANA trial[244].

Beyond chemotherapy, abiraterone and enzalutamide led to substantially prolonged survival and increased response rates in placebo-controlled randomized phase III trials in patients with docetaxel-pretreated mCRPC (COU-AA-301 and AFFIRM trials[245,246]) and in patients with chemotherapy-naive mCRPC (COU-AA-302 and PREVAIL trials[247,248]), and these drugs have since become standard of care before or after docetaxel.

Optimal sequencing of the various treatment options for mCRPC, especially when certain agents have been used previously in mCSPC, is a matter of ongoing debate. Docetaxel seems to be less efficacious in mCRPC when it had previously been used in mCSPC[249] but abiraterone and enzalutamide remain active. Cabazitaxel maintains activity after pretreatment with docetaxel and enzalutamide[250]. Unfortunately, biomarkers to aid in personalizing the choice and sequence of first-line and subsequent treatments remain largely elusive, as even the utility of one of the most promising potential biomarkers, ARSV 7 (AR-V7), is limited to indicating an improved efficacy of a taxane agent over another ARSI, and has not been shown to encompass full guidance in treatment decision-making[251].

Other therapeutic approaches include treatment with immunogenic stimulants, such as sipuleucel-T, an autologous dendritic cell vaccine that is designed to immunize against the distinct prostate epitope prostatic acid phosphatase (PAP) and stimulate tumour cell clearing through T cell recognition[252]. In mCRPC, this treatment improves overall survival by 4 months but no advantage of time to disease progression was seen the IMPACT trial[253]. Sipuleucel-T was the first FDA-approved immunotherapy for cancer in general and has driven interest in improving immune recognition of prostate cancer. Subsequent trials have not had as much success. PROSTVAC, an immunotherapy that directs lymphocytes to recognize PSA-expressing cells, showed initial efficacy in phase II trials, but failed to show survival advantages in phase III trials[254–256]. The monoclonal antibody pembrolizumab antagonizes the immune evasion capacity of a tumour by binding the T cell antigen PD1 on tumour-infiltrating lymphocytes, preventing binding to PDL1 expressed on tumour cells. Pembrolizumab has shown low efficacy as monotherapy in men with both PDL1-negative and PDL1-postive mCRPC in an early phase clinical trial (KEYNOTE-199)[257]. Interestingly, pembrolizumab showed promising efficacy in men with bone-predominant metastasis irrespective of PDL1 expression status[257]. The efficacy of PD1 and PDL1-targeted agents, such as pembrolizumab or durvalumab, respectively, may be improved in combination with enzalutamide or in patients with frequent DNA repair mutations in combination with PARPi[258,259]. The FDA has approved pembrolizumab for all cancers with high microsatellite instability and/or MMR deficiency and those with a high tumour mutational burden; hence, assessing these markers in patients with mCRPC in whom several lines of established therapies have failed may provide a further individual treatment option despite a lack of strong evidence in patients with prostate cancer.

Radium-223 is a bone-seeking, α-particle-emitting radionuclide that was tested in the phase III ALSYMPCA trial in symptomatic men with mCRPC regardless of previous docetaxel treatment[260,261]. This trial showed an overall survival benefit for radium-223 treatment compared with the standard of care at that time[262,263]. Men with metastatic disease experience bone-related effects and are prone to spontaneous fractures resulting in spinal cord compression. Bone-targeted agents, such as bisphosphonates, zoledronic acid and denosumab (a bone-strengthening monoclonal antibody therapy that inhibits RANKL activity of osteoclasts), are approved for the treatment of men with mCRPC that has spread to the bone to reduce the risk of SREs[264–266]. These therapies also counteract bone density loss caused by ADT[267].

An emerging approach to the treatment of mCRPC is targeting PSMA-positive cancers identified by ^{68}Ga-PSMA PET–CT with the novel radiopharmaceutical ^{177}Lu-labelled PSMA-617 (^{177}Lu-PSMA). The phase II LuPSMA study found a high PSA response rate and objective responses of bone, visceral and lymph node metastases in heavily pretreated patients with mCRPC along with low toxicity, improved quality of life and reduced pain[268]. Preliminary results of the first randomized phase II study TheraP showed superior activity of ^{177}Lu-PSMA over cabazitaxel in selected patients[269,270]. A large, prospective, randomized comparison of standard of care with or without ^{177}Lu-PSMA in patients with mCRPC progressing on docetaxel and enzalutamide or abiraterone is ongoing (VISION phase III trial; NCT03511664).

Beyond next-generation ARSIs and radionuclides, other classes of agents are emerging for specific at-risk patient groups informed by genomic sequencing approaches, particularly for men with mCRPC harbouring mutations in DNA repair genes, such as *BRCA1* and *BRCA2* (REF.[271]). In the setting of these aggressive tumours, PARPi, such as olaparib (TOPARP phase II trial[110,272] and PROfound phase III trial[111]), rucaparib (TRITON2 phase II trial[273]) and niraparib (GALAHAD phase II trial[274]) were evaluated in clinical trials, in an effort to exploit the synthetic lethal interactions in dysfunctional DDR.

The first small phase II study investigating olaparib in mCRPC, TOPARP-A, identified deleterious mutations in DNA repair genes in 33% of heavily pretreated patients, of whom 88% responded to olaparib. The phase II TOPARP-B study confirmed high responses to olaparib in patients with *BRCA1*, *BRCA2* and *PALB2* mutations, but found less activity in those with *ATM* mutations[111]. The PROfound trial evaluated olaparib versus abiraterone

or enzalutamide after failure of enzalutamide or abiraterone, respectively, in patients with mCRPC with HR gene mutations. Olaparib treatment resulted in prolonged radiographic PFS and overall survival in patients with somatic or germline mutations of *BRCA2*, *BRCA1* or *ATM*. Of note, this effect was strongest in those with *BRCA2* mutations, whereas little benefit was seen in those with *ATM* mutations[275,276]. In the TRITON2 phase II study, rucaparib showed similar promising activity. Highest objective responses were found in those with *BRCA1* or *BRCA2* mutations[111]. Responses in patients with *ATM*, *CHEK2* or *CDK12* mutations but without *BRCA1* or *BRCA2* mutations were less frequent[277]. A confirmatory randomized trial, TRITON3, is ongoing to directly compare rucaparib to docetaxel, abiraterone or enzalutamide in patients with mCRPC with *BRCA1*, *BRCA2* or *ATM* mutations after failure of at least one prior ARSI for mCRPC (NCT02975934).

PARPi are now considered a new standard of care for patients with pretreated mCRPC and distinct deleterious HR gene mutations (currently *BRCA1*, *BRCA2* and *ATM*). Both olaparib and rucaparib have received approval for use in selected patients, which requires targeted genomic HR deficiency testing to be integrated into routine care pathways. In light of various other DDR gene mutations that are also known to be present in these tumours, identification of reliable predictors of PARPi response beyond *BRCA1* and *BRCA2* mutations is a matter of ongoing research.

Non-metastatic castration-resistant prostate cancer. Patients without signs of metastasis (M0) on routine imaging (CT and bone scintigraphy) but with rising PSA levels with a PSA doubling time of <10 months despite standard ADT must be considered to have castration-resistant disease (M0 CRPC) with occult metastasis (FIG. 7). Functional imaging with PSMA PET can detect any active disease (pelvic disease including local prostate bed recurrence and/or M1) with high sensitivity in almost all patients (including 55% of those with M1 disease) who were considered M0 CRPC based on negative routine imaging[278]. These patients may benefit substantially from treatment intensification with a combination of continued ADT (despite quickly rising PSA levels) plus an ARSI (enzalutamide, apalutamide or darolutamide). The SPARTAN, PROSPER and ARAMIS trials found favourable outcomes of early treatment intensification compared with continued standard ADT alone until detection of metastasis, in particular a prolongation of ≥2 years in the time to metastasis detection and PSA progression along with an overall survival benefit in patients with M0 CRPC[279–282].

The range of new therapeutic agents and new indications has fundamentally changed the treatment landscape of both hormone-sensitive (localized and metastatic) prostate cancer and CRPC and has prolonged clinical control and life expectancy of patients with these tumours. However, early treatment intensification with a shift from single agents to treatment combinations raises further questions about optimal treatment sequencing for individual patients, the requirement of biomarkers to personalize management and the evaluation of cross-resistance mechanisms.

Quality of life

Patients must manage a range of symptoms and adverse effects associated with prostate cancer and with the treatment strategy recommended for them (TABLE 2). Symptom burden and adverse effects are closely related to the chosen clinical management approach. Prostatectomy immediately negatively affects erectile function, urinary continence and micturition, whereas radiotherapy mostly affects micturition and causes bowel irritability. Active surveillance and watchful waiting are advocated in those who are unlikely to die of their disease to minimize the adverse effects of definitive treatment. However, even these approaches

Table 2 | **Prostate cancer symptoms and treatment-related side effects**

Treatment	Short-term symptoms	Long-term symptoms
None or watchful waiting or active surveillance	Blood in urine (haematuria) or semen; difficulty urinating and/or full bladder (dysuria); unexplained weight loss; erectile dysfunction	Skeletal-related events (bone pain, pathological fractures, hypercalcaemia and spinal cord compression); weight loss; death
Surgery	Erectile dysfunction; urinary incontinence	Erectile dysfunction; urinary incontinence
Radiotherapy (external beam or brachytherapy)	Bowel irritability and/or mucus or blood in stools, diarrhoea, discomfort; urinary irritability and/or urgency, haematuria and urinary retention; secondary malignancy	Chronic bowel irritability; erectile dysfunction; chronic urinary irritability
Androgen deprivation therapy (LHRH analogues or surgical castration)	Cognitive dysfunction; bone pain (flair phenomenon); reduced libido and/or impotence; hot flushes; asthenia; fatigue; gynaecomastia	Loss of muscle mass and/or sarcopenia; osteopenia and/or osteoporosis; weight gain; reduced libido and/or impotence; hot flushes; asthenia; fatigue
Second-generation androgen receptor-targeting agents	Enzalutamide: cognitive dysfunction; seizures; falls; pathological fractures; pruritus Abiraterone acetate: fluid retention; hypokalaemia; oedema; arterial hypertension; cardiovascular events; elevated liver enzymes	Cognitive dysfunction; falls; pathological osteopenia
Chemotherapy (taxanes)	Myelosuppression (neutropenia, thrombocytopenia and/or anaemia); neutropenic fever; diarrhoea; sensory polyneuropathy; nausea and/or vomiting; oedema; alopecia; rash; fatigue; asthenia; allergic reactions	Sensory polyneuropathy; oedema; skin irritability (sun, irradiation); radiation recall phenomenon; chronic fatigue

LHRH, luteinizing hormone-releasing hormone.

Health-related quality of life (HRQOL). An individual's or group's perceived physical and mental health after considering factors that affect health status.

Obstructive voiding symptoms
Lower urinary tract symptoms that include hesitancy, poor or intermittent urinary stream, straining, incomplete bladder emptying, dribbling and or urine storage symptoms.

adversely affect health-related quality of life (HRQOL) over time[283]; for example, sexual and urinary function decline owing to local tumour progression[284]. Systemic treatment for metastatic prostate cancer causes general and treatment-specific adverse effects, such as flushes, decreased libido, loss of muscle mass and bone density (ADT), sensory polyneuropathy and oedema (docetaxel), arterial hypertension, oedema and hypopotassaemia (abiraterone), and arterial hypertension, cognitive dysfunction, nervousness and seizures (enzalutamide) (TABLE 2). In bone metastatic disease, metastases can cause bone pain, pathological fractures and spinal cord compression.

In the only randomized trial evaluating HRQOL after prostatectomy or watchful waiting, men in the watchful waiting group reported substantially better erectile function and libido, and less urinary incontinence but more frequent obstructive voiding symptoms[285]. Psychological well-being and overall HRQOL were similar in the two groups after 5 years but anxiety and depression intensified markedly in the watchful waiting group thereafter[286,287]. Regardless of whether they underwent surgery or watchful waiting, patients in this trial reported lower HRQOL, worse erectile function and more bothersome urinary incontinence than population-based cancer-free controls after a median follow-up period of 12 years[288]. Encouragingly, in a contemporary active surveillance cohort, urinary and erectile function and mental and physical well-being seemed to be stable in the short term and comparable to those in a similar cohort of men who underwent a prostate biopsy with benign findings[289,290].

Minimizing the sexual, urinary and bowel-related adverse effects of definitive treatment (radical prostatectomy or radiotherapy) is particularly relevant in men with localized prostate cancer given the high cure rate and extended survival after definitive treatment. As these relevant HRQOL domains were first defined in prostate cancer, enormous efforts have been made to develop, implement and assess instruments to reliably measure patient-reported outcomes[291–294]. Several large, non-randomized, prospective cohorts provide most of the knowledge comparing HRQOL before and after definitive prostate cancer treatment[295–297]. Patients who underwent surgery experienced a more pronounced deterioration in erectile function and a greater increase in urinary incontinence than those who received radiotherapy or active surveillance[284]. Conversely, bowel urgency was more common in patients who received radiotherapy. After either treatment, sexual and urinary HRQOL tended to recover modestly between 1 and 2 years and then slowly declined with age. At 15 years, sexual and urinary domains were similar for the two treatments, but more bothersome bowel urgency persisted in those who received radiotherapy[284].

In men with localized disease, ADT causes declines in general physical and psychological well-being, as well as sexual and bowel dysfunction[296,298]. Patients with advanced, recurrent and/or metastatic prostate cancer frequently experience similar declines in urinary, sexual and bowel functioning but often also contend with bone pain, increased fatigue and reduced stamina, body composition changes and body image issues, and poor physical and emotional well-being[299,300]. Metabolic, cardiovascular and cognitive complications are common with long-term ADT[301]. Poor tolerability is a key issue with non-targeted chemotherapeutic agents; hence, patients are given dosing regimens that consider their physical health and their expected benefit from therapy.

Psychological problems, such as depression and anxiety, are relatively common but under-appreciated contributors to poor HRQOL at all stages of disease but are more pronounced in advanced disease[302]. In particular, ADT in men with prostate cancer results in a substantial burden of de novo psychiatric illness (~30% of patients), most commonly depression (56%), dementia (14%) and anxiety (9%)[303]. Finally, partners of men with prostate cancer also frequently experience considerable psychological distress that needs to be better evaluated and addressed to support the entire patient–partner dyad[304].

Outlook

Prostate cancer remains a complex global health burden, but technological advances are considerably improving the biological understanding of this disease and should enable a future precision medicine approach to translating this knowledge into improved clinical outcomes (FIG. 8). Establishing disease risk based on clinical features and distinguishing indolent, localized tumours from those that are aggressive are key clinical challenges to further improving outcomes while adapting treatment to individual risk profiles and their related risk of prostate cancer-specific mortality[305]. Classification of disease subgroups based on computational histological pattern recognition and prediction of genomic features is now available for prostate cancer prognostication. Oncotype DX and Decipher are genomic classifiers that predict the probability of metastasis after surgery and are independent of clinical and pathological assessment of established tumour aggressiveness markers, such as PSA level and Gleason score[305–307]. Prolaris is a validated RNA test for expression levels of cell cycle progression genes that can be used to predict relative 10-year BCR-free or overall survival[308,309]. Prolaris has shown efficacy in the re-classification of patients who were predicted to have indolent tumours to a high risk status based on RNA biomarkers, and its clinical efficacy has been validated[225,310,311]. In addition, tumour classification of localized prostate cancer has yielded mutually exclusive genetic subtypes, such as ETS fusion-positive, SPINK1-overexpressing and CHD1 loss[109]. However, it is not yet clear whether knowing individual molecular subtypes is of prognostic or predictive benefit or whether any further improvements to molecular subtyping, such as mutational signatures, will inform risk-adapted management.

Another area of interest is the subgroup of patients with a limited number of metastases (oligometastatic disease). The following aspects remain to be elucidated: whether oligometastatic prostate cancer is a distinct disease entity with its own biological behaviour; how to set a cut-off to characterize patients as having oligometastatic disease; the optimal imaging approach (including functional imaging scans) to best identify this stage; whether targeting of metastatic lesions with

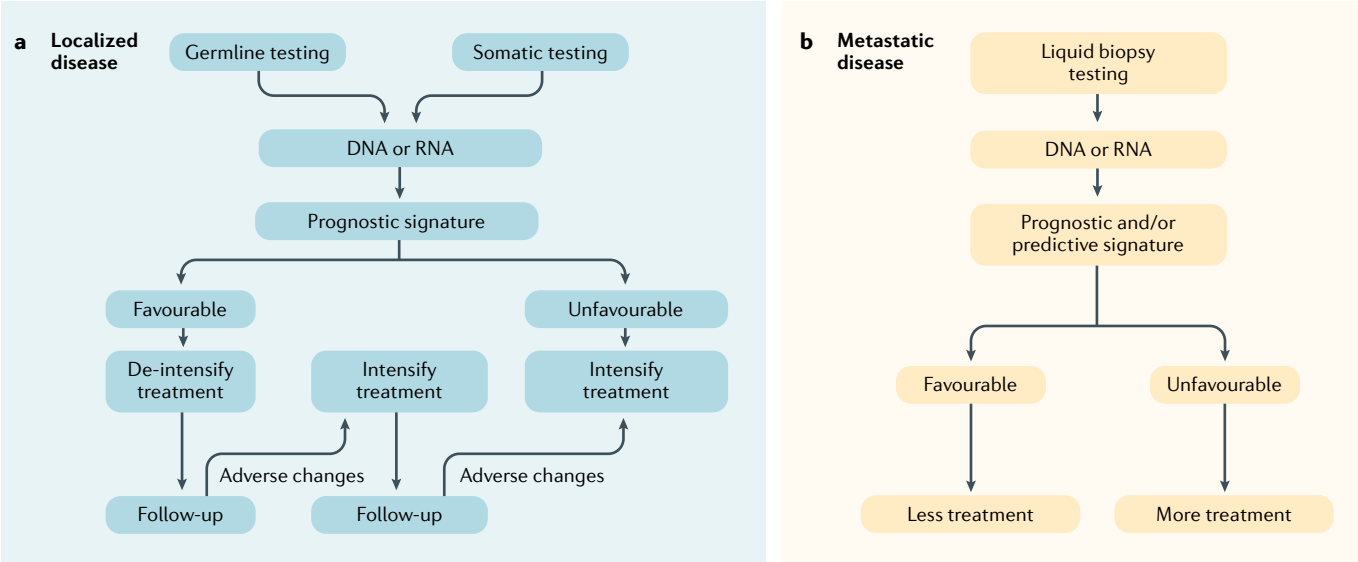


Fig. 8 | **Possible future precision medicine approach to prostate cancer management.** A hypothetical treatment approach based on clinical and laboratory evidence in prostate cancer research. **a** | For localized disease, men with prostate cancer could undergo germline testing at clinical presentation for mutations of genes that have strong prognostic value for risk of disease recurrence, in addition to standard diagnostic measures, such as clinical and pathological assessment: prostate-specific antigen (PSA) level, tumour–node–metastasis classification, multiparametric MRI findings and tumour attributes (grade group and presence of intraductal carcinoma of the prostate or ductal prostate cancer). Localized prostate signatures can be used to inform treatment choice, so that the most appropriate treatment is targeted to those patients who are likely to progress despite local therapy with intent to cure the patient. DNA-based or RNA-based prognostic tests, such as the Decipher[322] or Prolaris[323] gene signatures, can be used to assess risk of aggressive disease from a tumour biopsy or prostatectomy specimen. Treatment can be intensified or de-intensified as guided by these signatures or upon adverse changes to the patient's disease course. **b** | If metastatic disease is confirmed, through advanced imaging modalities (PSMA PET), DNA or RNA testing of circulating tumour DNA or tumour cells from a liquid biopsy can be used to assess adverse genomic or gene expression changes which predict risk of relapse for a specific systemic therapy. Unfavourable signatures may indicate that a patient should be given a novel agent or may be a candidate for a clinical trial instead of or in addition to standard treatment, whereas a favourable signature may indicate that less treatment is more suitable rather than further active treatment. Altogether, these approaches aim to precisely align adverse tumour characteristics with individualized treatment planning for a precision medicine approach to prostate cancer.

surgery or stereotactic ablative radiotherapy provides a survival benefit; and whether radical prostatectomy is as effective as prostate radiotherapy in patients with locally advanced, oligometastatic disease[240].

Currently, PARPi are being investigated in combined treatment approaches involving established ARSIs. PARPi are being combined with abiraterone plus prednisolone in placebo-controlled, randomized trials as first-line treatment for mCRPC regardless of DDR capacity (olaparib, PROPEL trial, NCT01972217; niraparib, MAGNITUDE trial, NCT03748641). Men with germline or somatic HR gene mutations, who often progress to mCRPC, may benefit from a similar management applying PARPi up-front before or during the use of a next-generation ARSI in mCSPC[46,187]. In this setting, niraparib plus abiraterone and prednisolone is currently being tested in patients with mCSPC with deleterious HR gene mutations in the phase III AMPLITUDE trial (NCT04497844). Which types of DDR alterations apart from *BRCA1* or *BRCA2* and *ATM* mutations may confer vulnerability to PARPi and patient benefit remain to be elucidated. Furthermore, whether the addition of PARPi to standard treatments in localized or locally advanced disease also improve efficacy is currently unclear.

Published online: 04 February 2021

1. Verze, P., Cai, T. & Lorenzetti, S. The role of the prostate in male fertility, health and disease. *Nat. Rev. Urol.* **13**, 379–386 (2016).
2. Attard, G. et al. Prostate cancer. *Lancet* **387**, 70–82 (2016).
3. McNeal, J. E. The zonal anatomy of the prostate. *Prostate* **2**, 35–49 (1981).
4. Timms, B. G. Prostate development: a historical perspective. *Differentiation* **76**, 565–577 (2008).
5. McNeal, J. E. Normal and pathologic anatomy of prostate. *Urology* **17**, 11–16 (1981).
6. Zlotta, A. R. et al. Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. *J. Natl Cancer Inst.* **105**, 1050–1058 (2013).
7. Abate-Shen, C. & Shen, M. M. Molecular genetics of prostate cancer. *Genes Dev.* **14**, 2410–2434 (2000).
8. Abate-Shen, C. & Shen, M. M. Mouse models of prostate carcinogenesis. *Trends Genet.* **18**, S1–S5 (2002).
9. Hayward, S. W. & Cunha, G. R. The prostate: development and physiology. *Radiol. Clin. North. Am.* **38**, 1–14 (2000).
10. Prins, G. S. & Putz, O. Molecular signaling pathways that regulate prostate gland development. *Differentiation* **76**, 641–659 (2008).
11. Olumi, A. F. et al. Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. *Cancer Res.* **59**, 5002–5011 (1999).
12. Cunha, G. R., Hayward, S. W. & Wang, Y. Z. Role of stroma in carcinogenesis of the prostate. *Differentiation* **70**, 473–485 (2002).
13. Corn, P. G. The tumor microenvironment in prostate cancer: elucidating molecular pathways for therapy development. *Cancer Manag. Res.* **4**, 183–193 (2012).
14. Toivanen, R. & Shen, M. M. Prostate organogenesis: tissue induction, hormonal regulation and cell type specification. *Development* **144**, 1382–1398 (2017).
15. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2018. *CA Cancer J. Clin.* **68**, 7–30 (2018).
16. Bray, F. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **68**, 394–424 (2018).
17. Huggins, C. Effect of orchiectomy and irradiation on cancer of the prostate. *Ann. Surg.* **115**, 1192–1200 (1942).

18. Huggins, C. & Hodges, C. V. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *CA Cancer J. Clin.* **22**, 232–240 (1972).
A reprint of the original article detailing the seminal findings of the hormone dependence of prostate cancer — a Nobel Prize winning discovery and a mainstay strategy for the treatment of prostate cancer.
19. Tan, M. H., Li, J., Xu, H. E., Melcher, K. & Yong, E. L. Androgen receptor: structure, role in prostate cancer and drug discovery. *Acta Pharmacol. Sin.* **36**, 3–23 (2015).
20. Taylor, B. S. et al. Integrative genomic profiling of human prostate cancer. *Cancer Cell* **18**, 11–22 (2010).
21. Barbieri, C. E. et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. *Nat. Genet.* **44**, 685–689 (2012).
22. Grasso, C. S. et al. The mutational landscape of lethal castration-resistant prostate cancer. *Nature* **487**, 239–243 (2012).
23. Baca, S. C. et al. Punctuated evolution of prostate cancer genomes. *Cell* **153**, 666–677 (2013).
24. Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. *Cell* **163**, 1011–1025 (2015).
A whole-genome analysis characterizing organ-confined and locoregional metastatic prostate cancer mutations.
25. Robinson, D. et al. Integrative clinical genomics of advanced prostate cancer. *Cell* **162**, 454 (2015).
A whole-genome analysis characterizing distant metastatic prostate cancer mutations.
26. Fraser, M. et al. Genomic hallmarks of localized, non-indolent prostate cancer. *Nature* **541**, 359–364 (2017).
27. Stopsack, K. H. et al. Oncogenic genomic alterations, clinical phenotypes, and outcomes in metastatic castration-sensitive prostate cancer. *Clin. Cancer Res.* **26**, 3230–3238 (2020).
28. Dy, G. W., Gore, J. L., Forouzanfar, M. H., Naghavi, M. & Fitzmaurice, C. Global burden of urologic cancers, 1990–2013. *Eur. Urol.* **71**, 437–446 (2017).
29. Wong, M. C. et al. Global incidence and mortality for prostate cancer: analysis of temporal patterns and trends in 36 countries. *Eur. Urol.* **70**, 862–874 (2016).
30. Crawford, E. D. Epidemiology of prostate cancer. *Urology* **62**, 3–12 (2003).
31. Kimura, T. & Egawa, S. Epidemiology of prostate cancer in Asian countries. *Int. J. Urol.* **25**, 524–531 (2018).
32. Chen, R. et al. Prostate cancer in Asia: a collaborative report. *Asian J. Urol.* **1**, 15–29 (2014).
33. Loeb, S. et al. Overdiagnosis and overtreatment of prostate cancer. *Eur. Urol.* **65**, 1046–1055 (2014).
34. Schroder, F. H. et al. Screening and prostate cancer mortality: results of the European randomised study of screening for prostate cancer (ERSPC) at 13 years of follow-up. *Lancet* **384**, 2027–2035 (2014).
35. Hugosson, J. et al. A 16-yr follow-up of the European randomized study of screening for prostate cancer. *Eur. Urol.* **76**, 43–51 (2019).
36. Huncharek, M., Haddock, K. S., Reid, R. & Kupelnick, B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am. J. Public Health* **100**, 693–701 (2010).
37. Salem, S. et al. Major dietary factors and prostate cancer risk: a prospective multicenter case-control study. *Nutr. Cancer* **63**, 21–27 (2011).
38. Shenoy, D., Packianathan, S., Chen, A. M. & Vijayakumar, S. Do African-American men need separate prostate cancer screening guidelines? *BMC Urol.* **16**, 19 (2016).
39. Zeigler-Johnson, C. M. et al. Genetic susceptibility to prostate cancer in men of African descent: implications for global disparities in incidence and outcomes. *Can. J. Urol.* **15**, 3872–3882 (2008).
40. Kirchhoff, T. et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. *Clin. Cancer Res.* **10**, 2918–2921 (2004).
41. Eldon, B. J., Jonsson, E., Tomasson, J., Tryggvadottir, L. & Tulinius, H. Familial risk of prostate cancer in Iceland. *BJU Int.* **92**, 915–919 (2003).
42. Hemminki, K. Familial risk and familial survival in prostate cancer. *World J. Urol.* **30**, 143–148 (2012).
43. Mucci, L. A. et al. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA* **315**, 68–76 (2016).
44. Mottet, N. et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur. Urol.* **71**, 618–629 (2017).
A comprehensive guide to localized disease management from screening to treatment.
45. Johns, L. E. & Houlston, R. S. A systematic review and meta-analysis of familial prostate cancer risk. *BJU Int.* **91**, 789–794 (2003).
46. Pritchard, C. C. et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N. Engl. J. Med.* **375**, 443–453 (2016).
47. Pritchard, C. C., Offit, K. & Nelson, P. S. DNA-repair gene mutations in metastatic prostate cancer reply. *N. Engl. J. Med.* **375**, 1804–1805 (2016).
48. Kote-Jarai, Z. et al. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. *Ann. Oncol.* **26**, 756–761 (2015).
49. Karlsson, R. et al. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. *Eur. Urol.* **65**, 169–176 (2014).
50. Ewing, C. M. et al. Germline mutations in HOXB13 and prostate-cancer risk. *N. Engl. J. Med.* **366**, 141–149 (2012).
51. Lynch, H. T. et al. Screening for familial and hereditary prostate cancer. *Int. J. Cancer* **138**, 2579–2591 (2016).
52. Bancroft, E. K. et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. *Eur. Urol.* **66**, 489–499 (2014).
53. Ahmadiyeh, N. et al. 8q24 prostate, breast, and colon cancer risk loci show tissue-specific long-range interaction with MYC. *Proc. Natl Acad. Sci. USA* **107**, 9742–9746 (2010).
54. Ahmed, M. & Eeles, R. Germline genetic profiling in prostate cancer: latest developments and potential clinical applications. *Future Sci. OA* **2**, FSO87 (2016).
55. Walavalkar, K. et al. A rare variant of African ancestry activates 8q24 lncRNA hub by modulating cancer associated enhancer. *Nat. Commun.* **11**, 3598 (2020).
56. Darst, B. F. et al. A germline variant at 8q24 contributes to familial clustering of prostate cancer in men of African ancestry. *Eur. Urol.* **78**, 316–320 (2020).
57. Li-Sheng Chen, S. et al. Risk prediction of prostate cancer with single nucleotide polymorphisms and prostate specific antigen. *J. Urol.* **201**, 486–495 (2019).
58. Huynh-Le, M. P. et al. A genetic risk score to personalize prostate cancer screening, applied to population data. *Cancer Epidemiol. Biomarkers Prev.* **29**, 1731–1738 (2020).
59. Nordstrom, T., Aly, M., Eklund, M., Egevad, L. & Gronberg, H. A genetic score can identify men at high risk for prostate cancer among men with prostate-specific antigen of 1-3 ng/ml. *Eur. Urol.* **65**, 1184–1190 (2014).
60. Goh, C. L. et al. Clinical implications of family history of prostate cancer and genetic risk single nucleotide polymorphism (SNP) profiles in an active surveillance cohort. *BJU Int.* **112**, 666–673 (2013).
61. Eeles, R. A., ni Raghallaigh, H. & BARCODE1 Study Group. BARCODE 1: a pilot study investigating the use of genetic profiling to identify men in the general population with the highest risk of prostate cancer to invite for targeted screening [abstract]. *J. Clin. Oncol.* **38** (Suppl. 15), 1505 (2020).
62. Draisma, G. et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European randomized study of screening for prostate cancer. *J. Natl Cancer Inst.* **95**, 868–878 (2003).
63. Draisma, G. et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J. Natl Cancer Inst.* **101**, 374–383 (2009).
64. Sammon, J. D. et al. Predicting life expectancy in men diagnosed with prostate cancer. *Eur. Urol.* **68**, 756–765 (2015).
65. Ciriello, G. et al. Emerging landscape of oncogenic signatures across human cancers. *Nat. Genet.* **45**, 1127–1133 (2013).
66. Hieronymus, H. et al. Copy number alteration burden predicts prostate cancer relapse. *Proc. Natl Acad. Sci. USA* **111**, 11139–11144 (2014).
67. Carver, B. S. et al. ETS rearrangements and prostate cancer initiation. *Nature* **457**, E1; discussion E2-3 (2009).
68. Tomlins, S. A. et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science* **310**, 644–648 (2005).
69. Tomlins, S. A. et al. Role of the TMPRSS2-ERG gene fusion in prostate cancer. *Neoplasia* **10**, 177–188 (2008).
70. Magi-Galluzzi, C. et al. TMPRSS2-ERG gene fusion prevalence and class are significantly different in prostate cancer of Caucasian, African-American and Japanese patients. *Prostate* **71**, 489–497 (2011).
71. Blackburn, J. et al. TMPRSS2-ERG fusions linked to prostate cancer racial health disparities: a focus on Africa. *Prostate* **79**, 1191–1196 (2019).
72. Blattner, M. et al. SPOP mutation drives prostate tumorigenesis in vivo through coordinate regulation of PI3K/mTOR and AR signaling. *Cancer Cell* **31**, 436–451 (2017).
73. Boysen, G. et al. SPOP mutation leads to genomic instability in prostate cancer. *eLife* **4**, e09207 (2015).
74. Dai, X. et al. Prostate cancer-associated SPOP mutations confer resistance to BET inhibitors through stabilization of BRD4. *Nat. Med.* **23**, 1063–1071 (2017).
75. Ren, S. et al. Whole-genome and transcriptome sequencing of prostate cancer identify new genetic alterations driving disease progression. *Eur. Urol.* **73**, 322–339 (2018).
76. Li, J. et al. A genomic and epigenomic atlas of prostate cancer in Asian populations. *Nature* **580**, 93–99 (2020).
77. Adams, E. J. et al. FOXA1 mutations alter pioneering activity, differentiation and prostate cancer phenotypes. *Nature* **571**, 408–412 (2019).
78. Parolia, A. et al. Distinct structural classes of activating FOXA1 alterations in advanced prostate cancer. *Nature* **571**, 413–418 (2019).
79. Beltran, H. et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. *Cancer Discov.* **1**, 487–495 (2011).
80. Dardenne, E. et al. N-Myc induces an EZH2-mediated transcriptional program driving neuroendocrine prostate cancer. *Cancer Cell* **30**, 563–577 (2016).
81. Lee, J. K. et al. N-Myc drives neuroendocrine prostate cancer initiated from human prostate epithelial cells. *Cancer Cell* **29**, 536–547 (2016).
82. Guo, H. et al. ONECUT2 is a driver of neuroendocrine prostate cancer. *Nat. Commun.* **10**, 278 (2019).
83. Rotinen, M. et al. ONECUT2 is a targetable master regulator of lethal prostate cancer that suppresses the androgen axis. *Nat. Med.* **24**, 1887–1898 (2018).
84. Lalonde, E. et al. Tumour genomic and microenvironmental heterogeneity for integrated prediction of 5-year biochemical recurrence of prostate cancer: a retrospective cohort study. *Lancet Oncol.* **15**, 1521–1532 (2014).
85. Lalonde, E. et al. Translating a prognostic DNA genomic classifier into the clinic: retrospective validation in 563 localized prostate tumors. *Eur. Urol.* **72**, 22–31 (2017).
86. Mateo, J. et al. Genomics of lethal prostate cancer at diagnosis and castration resistance. *J. Clin. Invest.* **130**, 1743–1751 (2020).
87. Hodgson, M. C. et al. The androgen receptor recruits nuclear receptor corepressor (N-CoR) in the presence of mifepristone via its N and C termini revealing a novel molecular mechanism for androgen receptor antagonists. *J. Biol. Chem.* **280**, 6511–6519 (2005).
88. Hsieh, C. L. et al. PLZF, a tumor suppressor genetically lost in metastatic castration-resistant prostate cancer, is a mediator of resistance to androgen deprivation therapy. *Cancer Res.* **75**, 1944–1948 (2015).
89. Mills, I. G. Maintaining and reprogramming genomic androgen receptor activity in prostate cancer. *Nat. Rev. Cancer* **14**, 187–198 (2014).
90. Lamb, A. D., Massie, C. E. & Neal, D. E. The transcriptional programme of the androgen receptor (AR) in prostate cancer. *BJU Int.* **113**, 358–366 (2014).
91. Chan, S. C. & Dehm, S. M. Constitutive activity of the androgen receptor. *Adv. Pharmacol.* **70**, 327–366 (2014).
92. Robins, D. M. Androgen receptor gene polymorphisms and alterations in prostate cancer: of humanized mice and men. *Mol. Cell. Endocrinol.* **352**, 26–33 (2012).
93. van der Steen, T., Tindall, D. J. & Huang, H. Posttranslational modification of the androgen receptor in prostate cancer. *Int. J. Mol. Sci.* **14**, 14833–14859 (2013).
94. Antonarakis, E. S., Armstrong, A. J., Dehm, S. M. & Luo, J. Androgen receptor variant-driven prostate cancer: clinical implications and therapeutic targeting. *Prostate Cancer Prostatic Dis.* **19**, 231–241 (2016).
95. Dehm, S. M., Schmidt, L. J., Heemers, H. V., Vessella, R. L. & Tindall, D. J. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. *Cancer Res.* **68**, 5469–5477 (2008).

96. Chen, C. D. et al. Molecular determinants of resistance to antiandrogen therapy. *Nat. Med.* **10**, 33–39 (2004).
97. Carver, B. S. et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. *Cancer Cell* **19**, 575–586 (2011).
98. Pearson, H. B. et al. Identification of Pik3ca mutation as a genetic driver of prostate cancer that cooperates with Pten loss to accelerate progression and castration-resistant growth. *Cancer Discov.* **8**, 764–779 (2018).
99. Gurel, B. et al. Nuclear MYC protein overexpression is an early alteration in human prostate carcinogenesis. *Mod. Pathol.* **21**, 1156–1167 (2008).
100. Hubbard, G. K. et al. Combined MYC activation and Pten loss are sufficient to create genomic instability and lethal metastatic prostate cancer. *Cancer Res.* **76**, 283–292 (2016).
101. Sharma, A. et al. The retinoblastoma tumor suppressor controls androgen signaling and human prostate cancer progression. *J. Clin. Invest.* **120**, 4478–4492 (2010).
102. McNair, C. et al. Differential impact of RB status on E2F1 reprogramming in human cancer. *J. Clin. Invest.* **128**, 341–358 (2018).
103. Abida, W. et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc. Natl Acad. Sci. USA* **116**, 11428–11436 (2019).
104. Park, J. W. et al. Reprogramming normal human epithelial tissues to a common, lethal neuroendocrine cancer lineage. *Science* **362**, 91–95 (2018).
105. Ku, S. Y. et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. *Science* **355**, 78–83 (2017).
106. Mu, P. et al. SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. *Science* **355**, 84–88 (2017).
107. Zou, M. et al. Transdifferentiation as a mechanism of treatment resistance in a mouse model of castration-resistant prostate cancer. *Cancer Discov.* **7**, 736–749 (2017).
108. Scully, R., Panday, A., Elango, R. & Willis, N. A. DNA double-strand break repair-pathway choice in somatic mammalian cells. *Nat. Rev. Mol. Cell Biol.* **20**, 698–714 (2019).
109. Abida, W. et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. *JCO Precis. Oncol.* **1**, PO.17.00029 (2017).
110. Mateo, J. et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N. Engl. J. Med.* **373**, 1697–1708 (2015).
111. de Bono, J. et al. Olaparib for metastatic castration-resistant prostate cancer. *N. Engl. J. Med.* **382**, 2091–2102 (2020).
Practice-changing randomized phase III study (PROFound) confirming PARP inhibition as a highly active treatment in patients with metastatic castration-resistant prostate cancer with germline or somatic deleterious DNA repair gene mutations.
112. Goldstein, A. S., Huang, J., Guo, C., Garraway, I. P. & Witte, O. N. Identification of a cell of origin for human prostate cancer. *Science* **329**, 568–571 (2010).
113. Chua, C. W. et al. Single luminal epithelial progenitors can generate prostate organoids in culture. *Nat. Cell Biol.* **16**, 951–961 (2014).
114. Lee, S. H. & Shen, M. M. Cell types of origin for prostate cancer. *Curr. Opin. Cell Biol.* **37**, 35–41 (2015).
115. Park, J. W. et al. Prostate epithelial cell of origin determines cancer differentiation state in an organoid transformation assay. *Proc. Natl Acad. Sci. USA* **113**, 4482–4487 (2016).
116. Wang, X. et al. A luminal epithelial stem cell that is a cell of origin for prostate cancer. *Nature* **461**, 495–500 (2009).
117. Fine, S. W. & Reuter, V. E. Anatomy of the prostate revisited: implications for prostate biopsy and zonal origins of prostate cancer. *Histopathology* **60**, 142–152 (2012).
118. Shen, M. M. & Abate-Shen, C. Molecular genetics of prostate cancer: new prospects for old challenges. *Genes Dev.* **24**, 1967–2000 (2010).
119. Young, J. M., Muscatello, D. J. & Ward, J. E. Are men with lower urinary tract symptoms at increased risk of prostate cancer? A systematic review and critique of the available evidence. *BJU Int.* **85**, 1037–1048 (2000).
120. Boyd, L. K., Mao, X. & Lu, Y. J. The complexity of prostate cancer: genomic alterations and heterogeneity. *Nat. Rev. Urol.* **9**, 652–664 (2012).
121. Bostwick, D. G., Liu, L., Brawer, M. K. & Qian, J. High-grade prostatic intraepithelial neoplasia. *Rev. Urol.* **6**, 171–179 (2004).
122. Cheng, L. et al. Evidence of independent origin of multiple tumors from patients with prostate cancer. *J. Natl Cancer Inst.* **90**, 233–237 (1998).
123. Cooper, C. S. et al. Analysis of the genetic phylogeny of multifocal prostate cancer identifies multiple independent clonal expansions in neoplastic and morphologically normal prostate tissue. *Nat. Genet.* **47**, 367–372 (2015).
124. Liu, W. et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. *Nat. Med.* **15**, 559–565 (2009).
125. Boyd, L. K. et al. High-resolution genome-wide copy-number analysis suggests a monoclonal origin of multifocal prostate cancer. *Genes Chromosomes Cancer* **51**, 579–589 (2012).
126. Hong, M. K. et al. Tracking the origins and drivers of subclonal metastatic expansion in prostate cancer. *Nat. Commun.* **6**, 6605 (2015).
127. Gundem, G. et al. The evolutionary history of lethal metastatic prostate cancer. *Nature* **520**, 353–357 (2015).
128. Berglund, E. et al. Spatial maps of prostate cancer transcriptomes reveal an unexplored landscape of heterogeneity. *Nat. Commun.* **9**, 2419 (2018).
129. Shoag, J. & Barbieri, C. E. Clinical variability and molecular heterogeneity in prostate cancer. *Asian J. Androl.* **18**, 543–548 (2016).
130. Espiritu, S. M. G. et al. The evolutionary landscape of localized prostate cancers drives clinical aggression. *Cell* **173**, 1003–1013.e15 (2018).
131. Korpal, M. et al. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). *Cancer Discov.* **3**, 1030–1043 (2013).
132. Arora, V. K. et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. *Cell* **155**, 1309–1322 (2013).
133. Beltran, H. et al. Aggressive variants of castration-resistant prostate cancer. *Clin. Cancer Res.* **20**, 2846–2850 (2014).
134. Chang, K. H. et al. A gain-of-function mutation in DHT synthesis in castration-resistant prostate cancer. *Cell* **154**, 1074–1084 (2013).
135. Stanbrough, M. et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer Res.* **66**, 2815–2825 (2006).
136. Yin, L. & Hu, Q. CYP17 inhibitors–abiraterone, C17,20-lyase inhibitors and multi-targeting agents. *Nat. Rev. Urol.* **11**, 32–42 (2014).
137. Chang, K. H. & Sharifi, N. Prostate cancer-from steroid transformations to clinical translation. *Nat. Rev. Urol.* **9**, 721–724 (2012).
138. Clarke, N. W., Hart, C. A. & Brown, M. D. Molecular mechanisms of metastasis in prostate cancer. *Asian J. Androl.* **11**, 57–67 (2009).
139. Berish, R. B., Ali, A. N., Telmer, P. G., Ronald, J. A. & Leong, H. S. Translational models of prostate cancer bone metastasis. *Nat. Rev. Urol.* **15**, 403–421 (2018).
140. Ilic, D., Neuberger, M. M., Djulbegovic, M. & Dahm, P. Screening for prostate cancer. *Cochrane Database Syst. Rev.* **1**, CD004720 (2013).
141. Hayes, J. H. & Barry, M. J. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. *JAMA* **311**, 1143–1149 (2014).
142. Macefield, R. C. et al. Impact of prostate cancer testing: an evaluation of the emotional consequences of a negative biopsy result. *Br. J. Cancer* **102**, 1335–1340 (2010).
143. Shoag, J. E., Nyame, Y. A. & Hu, J. C. Reconsidering the trade-offs of prostate cancer screening. Reply. *N. Engl. J. Med.* **383**, 1290 (2020).
144. Louie, K. S., Seigneurin, A., Cathcart, P. & Sasieni, P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. *Ann. Oncol.* **26**, 848–864 (2015).
145. Zelic, R. et al. Predicting prostate cancer death with different pretreatment risk stratification tools: a head-to-head comparison in a nationwide cohort study. *Eur. Urol.* **77**, 180–188 (2020).
146. Page, E. C. et al. Interim results from the IMPACT study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. *Eur. Urol.* **76**, 831–842 (2019).
147. Giri, V. N. et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J. Clin. Oncol.* **38**, 2798–2811 (2020).
148. Mohler, J. L. & Antonarakis, E. S. NCCN guidelines updates: management of prostate cancer. *J. Natl Compr. Canc. Netw.* **17**, 583–586 (2019).
149. Mohler, J. L. et al. Prostate cancer, version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J. Natl Compr. Canc. Netw.* **17**, 479–505 (2019).
150. Hoogendam, A., Buntinx, F. & de Vet, H. C. The diagnostic value of digital rectal examination in primary care screening for prostate cancer: a meta-analysis. *Fam. Pract.* **16**, 621–626 (1999).
151. Nguyen-Nielsen, M. & Borre, M. Diagnostic and therapeutic strategies for prostate cancer. *Semin. Nucl. Med.* **46**, 484–490 (2016).
152. Lilja, H., Ulmert, D. & Vickers, A. J. Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. *Nat. Rev. Cancer* **8**, 268–278 (2008).
153. Ulmert, D. et al. Long-term prediction of prostate cancer: prostate-specific antigen (PSA) velocity is predictive but does not improve the predictive accuracy of a single PSA measurement 15 years or more before cancer diagnosis in a large, representative, unscreened population. *J. Clin. Oncol.* **26**, 835–841 (2008).
154. Gelfond, J. et al. Intermediate-term risk of prostate cancer is directly related to baseline prostate specific antigen: implications for reducing the burden of prostate specific antigen screening. *J. Urol.* **194**, 46–51 (2015).
155. Skouteris, V. M. et al. Transrectal ultrasound-guided versus transperineal mapping prostate biopsy: complication comparison. *Rev. Urol.* **20**, 19–25 (2018).
156. Ahmed, H. U. et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* **389**, 815–822 (2017).
157. Futterer, J. J. et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. *Eur. Urol.* **68**, 1045–1053 (2015).
158. Le, J. D. et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. *Eur. Urol.* **67**, 569–576 (2015).
159. Kasivisvanathan, V. et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N. Engl. J. Med.* **378**, 1767–1777 (2018).
160. Ber, Y. et al. A noninferiority within-person study comparing the accuracy of transperineal to transrectal MRI-US fusion biopsy for prostate-cancer detection. *Prostate Cancer Prostatic Dis.* **23**, 449–456 (2020).
161. Hoffmann, M. A. et al. The impact of 68Ga-PSMA PET/CT and PET/MRI on the management of prostate cancer. *Urology* **130**, 1–12 (2019).
162. Hofman, M. S. et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet* **395**, 1208–1216 (2020).
Strong evidence supporting the change of imaging standards with implementing PSMA PET for more precise staging procedures in routine care pathways.
163. Kweldam, C. F., van Leenders, G. J. & van der Kwast, T. Grading of prostate cancer: a work in progress. *Histopathology* **74**, 146–160 (2019).
164. Humphrey, P. A. Gleason grading and prognostic factors in carcinoma of the prostate. *Mod. Pathol.* **17**, 292–306 (2004).
165. Epstein, J. I. An update of the Gleason grading system. *J. Urol.* **183**, 433–440 (2010).
166. Lotan, T. L. & Epstein, J. I. Clinical implications of changing definitions within the Gleason grading system. *Nat. Rev. Urol.* **7**, 136–142 (2010).
167. Kane, C. J., Eggener, S. E., Shindel, A. W. & Andriole, G. L. Variability in outcomes for patients with intermediate-risk prostate cancer (Gleason score 7, International Society of Urological Pathology Gleason Group 2-3) and implications for risk stratification: a systematic review. *Eur. Urol. Focus.* **3**, 487–497 (2017).
168. Epstein, J. I. et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur. Urol.* **69**, 428–435 (2016).
169. Epstein, J. I. Prostate cancer: Urology journals recommend new prostate cancer grade groups. *Nat. Rev. Urol.* **13**, 374–375 (2016).
170. Ross, H. M. et al. Do adenocarcinomas of the prostate with Gleason score (GS) ≤6 have the potential to metastasize to lymph nodes? *Am. J. Surg. Pathol.* **36**, 1346–1352 (2012).
171. D'Amico, A. V. et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or

interstitial radiation therapy for clinically localized prostate cancer. *JAMA* **280**, 969–974 (1998).
172. Bostwick, D. G. & Qian, J. High-grade prostatic intraepithelial neoplasia. *Mod. Pathol.* **17**, 360–379 (2004).
173. Antonarakis, E. S. et al. An immunohistochemical signature comprising PTEN, MYC, and Ki67 predicts progression in prostate cancer patients receiving adjuvant docetaxel after prostatectomy. *Cancer* **118**, 6063–6071 (2012).
174. Nowak, M. et al. Prognostic significance of phospho-histone H3 in prostate carcinoma. *World J. Urol.* **32**, 703–707 (2014).
175. Hameed, O. & Humphrey, P. A. Immunohistochemistry in diagnostic surgical pathology of the prostate. *Semin. Diagn. Pathol.* **22**, 88–104 (2005).
176. Hameed, O. & Humphrey, P. A. p63/AMACR antibody cocktail restaining of prostate needle biopsy tissues after transfer to charged slides: a viable approach in the diagnosis of small atypical foci that are lost on block sectioning. *Am. J. Clin. Pathol.* **124**, 708–715 (2005).
177. Parimi, V., Goyal, R., Poropatich, K. & Yang, X. J. Neuroendocrine differentiation of prostate cancer: a review. *Am. J. Clin. Exp. Urol.* **2**, 273–285 (2014).
178. Sexton, W. J. et al. Adult prostate sarcoma: the M. D. Anderson Cancer Center experience. *J. Urol.* **166**, 521–525 (2001).
179. Janet, N. L., May, A. W. & Akins, R. S. Sarcoma of the prostate: a single institutional review. *Am. J. Clin. Oncol.* **32**, 27–29 (2009).
180. Sun, L. et al. High-grade neuroendocrine carcinoma of the lung: comparative clinicopathological study of large cell neuroendocrine carcinoma and small cell lung carcinoma. *Pathol. Int.* **59**, 522–529 (2009).
181. Markowski, M. C., Eisenberger, M. A., Zahurak, M., Epstein, J. I. & Paller, C. J. Sarcomatoid carcinoma of the prostate: retrospective review of a case series from the Johns Hopkins Hospital. *Urology* **86**, 539–543 (2015).
182. Epstein, J. I. et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. *Am. J. Surg. Pathol.* **38**, 756–767 (2014).
183. Aggarwal, R. et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. *J. Clin. Oncol.* **36**, 2492–2503 (2018).
184. Bellur, S., Van der Kwast, T. & Mete, O. Evolving concepts in prostatic neuroendocrine manifestations: from focal divergent differentiation to amphicrine carcinoma. *Hum. Pathol.* **85**, 313–327 (2019).
185. Zhou, M. High-grade prostatic intraepithelial neoplasia, PIN-like carcinoma, ductal carcinoma, and intraductal carcinoma of the prostate. *Mod. Pathol.* **31**, S71–S79 (2018).
186. Schweizer, M. T. et al. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. *JCO Precis. Oncol.* **3**, PO.18.00327 (2019).
187. Taylor, R. A. et al. Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. *Nat. Commun.* **8**, 13671 (2017).
188. Porter, L. H. et al. Systematic review links the prevalence of intraductal carcinoma of the prostate to prostate cancer risk categories. *Eur. Urol.* **72**, 492–495 (2017).
189. Chua, M. L. K. et al. A prostate cancer "nimbosus": genomic instability and SChLAP1 dysregulation underpin aggression of intraductal and cribriform subpathologies. *Eur. Urol.* **72**, 665–674 (2017).
190. Foerster, B. et al. Association of smoking status with recurrence, metastasis, and mortality among patients with localized prostate cancer undergoing prostatectomy or radiotherapy: a systematic review and meta-analysis. *JAMA Oncol.* **4**, 953–961 (2018).
191. Allott, E. H., Masko, E. M. & Freedland, S. J. Obesity and prostate cancer: weighing the evidence. *Eur. Urol.* **63**, 800–809 (2013).
192. Thompson, I. M. et al. The influence of finasteride on the development of prostate cancer. *N. Engl. J. Med.* **349**, 215–224 (2003).
193. Cuzick, J. et al. Prevention and early detection of prostate cancer. *Lancet Oncol.* **15**, e484–e492 (2014).
194. Andriole, G. L. et al. Effect of dutasteride on the risk of prostate cancer. *N. Engl. J. Med.* **362**, 1192–1202 (2010).
195. Fleshner, N. E. et al. Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. *Lancet* **379**, 1103–1111 (2012).
196. Tannock, I. F. et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* **351**, 1502–1512 (2004).
197. Gillessen, S. et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur. Urol.* **77**, 508–547 (2020).
Contemporary and comprehensive expert consensus guidance that fills gaps of evidence with useful interpretations and recommendations for advanced and metastatic prostate cancers.
198. Cornford, P. et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur. Urol.* **71**, 630–642 (2017).
199. Schally, A. V., Block, N. L. & Rick, F. G. Discovery of LHRH and development of LHRH analogs for prostate cancer treatment. *Prostate* **77**, 1036–1054 (2017).
200. Vis, A. N., van der Sluis, T. M., Al-Itejawi, H. H. M., van Moorselaar, R. J. A. & Meuleman, E. J. H. Risk of disease flare with LHRH agonist therapy in men with prostate cancer: myth or fact? *Urol. Oncol.* **33**, 7–15 (2015).
201. Attard, G., Belldegrun, A. S. & de Bono, J. S. Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer. *BJU Int.* **96**, 1241–1246 (2005).
202. Li, Z. et al. Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. *Nature* **523**, 347–351 (2015).
203. McKay, R. R. et al. A phase 2 trial of abiraterone acetate without glucocorticoids for men with metastatic castration-resistant prostate cancer. *Cancer* **125**, 524–532 (2019).
204. Schalken, J. & Fitzpatrick, J. M. Enzalutamide: targeting the androgen signalling pathway in metastatic castration-resistant prostate cancer. *BJU Int.* **117**, 215–225 (2016).
205. Klotz, L. & Emberton, M. Management of low risk prostate cancer-active surveillance and focal therapy. *Nat. Rev. Clin. Oncol.* **11**, 324–334 (2014).
206. Selvadurai, E. D. et al. Medium-term outcomes of active surveillance for localised prostate cancer. *Eur. Urol.* **64**, 981–987 (2013).
207. Albertsen, P. C., Hanley, J. A. & Fine, J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* **293**, 2095–2101 (2005).
208. Mahal, B. A. et al. Use of active surveillance or watchful waiting for low-risk prostate cancer and management trends across risk groups in the United States, 2010-2015. *JAMA* **321**, 704–706 (2019).
209. Trewartha, D. & Carter, K. Advances in prostate cancer treatment. *Nat. Rev. Drug Discov.* **12**, 823–824 (2013).
210. Vanneste, B. G., Van Limbergen, E. J., van Lin, E. N., van Roermund, J. G. & Lambin, P. Prostate cancer radiation therapy: what do clinicians have to know? *Biomed. Res. Int.* **2016**, 6829875 (2016).
211. Harmenberg, U., Hamdy, F. C., Widmark, A., Lennernas, B. & Nilsson, S. Curative radiation therapy in prostate cancer. *Acta Oncol.* **50**, 98–103 (2011).
212. Bangma, C. H. et al. Active surveillance for low-risk prostate cancer: developments to date. *Eur. Urol.* **67**, 646–648 (2015).
213. Wilt, T. J. The prostate cancer intervention versus observation trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy with watchful waiting for men with clinically localized prostate cancer. *J. Natl Cancer Inst. Monogr.* **2012**, 184–190 (2012).
214. Wilt, T. J. et al. Radical prostatectomy versus observation for localized prostate cancer. *N. Engl. J. Med.* **367**, 203–213 (2012).
215. Vale, C. L. et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet* **396**, 1422–1431 (2020).
Comprehensive review and meta-analysis collating data from three large, randomized studies (RADICALS, RAVES, GETUG-AFU 17) arguing against the use of adjuvant radiotherapy, which does not seem to offer benefit over early salvage radiotherapy at early biochemical recurrence following radical prostatectomy.
216. Parker, C. C. et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet* **396**, 1413–1421 (2020).
217. Zaffuto, E. et al. Early postoperative radiotherapy is associated with worse functional outcomes in patients with prostate cancer. *J. Urol.* **197**, 669–675 (2017).
218. Ventimiglia, E. et al. A systematic review of the role of definitive local treatment in patients with clinically lymph node-positive prostate cancer. *Eur. Urol. Oncol.* **2**, 294–301 (2019).
219. Van den Broeck, T. et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. *Eur. Urol.* **75**, 967–987 (2019).
220. Boorjian, S. A. et al. Radiation therapy after radical prostatectomy: impact on metastasis and survival. *J. Urol.* **182**, 2708–2714 (2009).
221. Kneebone, A. et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol.* **21**, 1331–1340 (2020).
222. Trock, B. J. et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA* **299**, 2760–2769 (2008).
223. Abugharib, A. et al. Very early salvage radiotherapy improves distant metastasis-free survival. *J. Urol.* **197**, 662–668 (2017).
224. Carrie, C. et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. *Lancet Oncol.* **20**, 1740–1749 (2019).
225. Spratt, D. E. et al. Performance of a prostate cancer genomic classifier in predicting metastasis in men with prostate-specific antigen persistence postprostatectomy. *Eur. Urol.* **74**, 107–114 (2018).
226. Roach, P. J. et al. The impact of (68)Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. *J. Nucl. Med.* **59**, 82–88 (2018).
227. Hussain, M. et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N. Engl. J. Med.* **368**, 1314–1325 (2013).
228. Rydzewska, L. H. M. et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. *Eur. J. Cancer* **84**, 88–101 (2017).
229. Vale, C. L. et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol.* **17**, 243–256 (2016).
230. Davis, I. D. et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N. Engl. J. Med.* **381**, 121–131 (2019).
231. Chi, K. N. et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N. Engl. J. Med.* **381**, 13–24 (2019).
232. Parker, C. et al. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **31**, 1119–1134 (2020).
233. Sweeney, C. J. et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N. Engl. J. Med.* **373**, 737–746 (2015).
234. Fizazi, K. et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N. Engl. J. Med.* **377**, 352–360 (2017).
235. Kyriakopoulos, C. E. et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J. Clin. Oncol.* **36**, 1080–1087 (2018).
236. Clarke, N. W. et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann. Oncol.* **30**, 1992–2003 (2019).
237. Gravis, G. et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. *Eur. Urol.* **70**, 256–262 (2016).
238. Hoyle, A. P. et al. Abiraterone in "high-" and "low-risk" metastatic hormone-sensitive prostate cancer. *Eur. Urol.* **76**, 719–728 (2019).
239. Sydes, M. R. et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. *Ann. Oncol.* **29**, 1235–1248 (2018).
Comparative analysis from the multi-arm trial STAMPEDE showing equal activity of docetaxel and

abiraterone in addition to androgen deprivation therapy in newly diagnosed metastatic castration-sensitive prostate cancer.
240. Parker, C. C. et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* **392**, 2353–2366 (2018). **Practice-changing results of STAMPEDE highlighting a survival benefit from local radiotherapy to the prostatic primary tumour in low-volume metastatic castration-sensitive disease, arguing for the primary tumour to be the driver of metastatic spread at least at early stages**.
241. Smith, M. R. et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J. Clin. Oncol.* **23**, 2918–2925 (2005).
242. Massard, C. & Fizazi, K. Targeting continued androgen receptor signaling in prostate cancer. *Clin. Cancer Res.* **17**, 3876–3883 (2011).
243. de Bono, J. S. et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* **376**, 1147–1154 (2010).
244. Oudard, S. et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized phase III trial-FIRSTANA. *J. Clin. Oncol.* **35**, 3189–3197 (2017).
245. Scher, H. I. et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* **367**, 1187–1197 (2012).
246. de Bono, J. S. et al. Abiraterone and increased survival in metastatic prostate cancer. *N. Engl. J. Med.* **364**, 1995–2005 (2011). **First large, practice-changing, randomized study showing high efficacy of targeting the androgen axis with abiraterone even in metastatic castration-resistant disease failing docetaxel, leading to dramatic changes of the prostate cancer treatment landscape**.
247. Ryan, C. J. et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N. Engl. J. Med.* **368**, 138–148 (2013).
248. Beer, T. M. et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N. Engl. J. Med.* **371**, 424–433 (2014). **Practice-changing, randomized study showing high activity of enzalutamide in chemotherapy-naive metastatic castration-resistant disease**.
249. Lavaud, P. et al. Anticancer activity and tolerance of treatments received beyond progression in men treated upfront with androgen deprivation therapy with or without docetaxel for metastatic castration-naive prostate cancer in the GETUG-AFU 15 phase 3 trial. *Eur. Urol.* **73**, 696–703 (2018).
250. Al Nakouzi, N. et al. Cabazitaxel remains active in patients progressing after docetaxel followed by novel androgen receptor pathway targeted therapies. *Eur. Urol.* **68**, 228–235 (2015).
251. Graf, R. P. et al. Clinical utility of the nuclear-localized AR-V7 biomarker in circulating tumor cells in improving physician treatment choice in castration-resistant prostate cancer. *Eur. Urol.* **77**, 170–177 (2020).
252. Kantoff, P. W. et al. Overall survival analysis of a phase II randomized controlled trial of a poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J. Clin. Oncol.* **28**, 1099–1105 (2010).
253. Kantoff, P. W. et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N. Engl. J. Med.* **363**, 411–422 (2010).
254. Shore, N. D. PROSTVAC(R) targeted immunotherapy candidate for prostate cancer. *Immunotherapy* **6**, 235–247 (2014).
255. Singh, P., Pal, S. K., Alex, A. & Agarwal, N. Development of PROSTVAC immunotherapy in prostate cancer. *Future Oncol.* **11**, 2137–2148 (2015).
256. Kantoff, P. W., Gulley, J. L. & Pico-Navarro, C. Revised overall survival analysis of a phase II, randomized, double-blind, controlled study of PROSTVAC in men with metastatic castration-resistant prostate cancer. *J. Clin. Oncol.* **35**, 124–125 (2017).
257. Antonarakis, E. S. et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. *J. Clin. Oncol.* **38**, 395–405 (2020).
258. Tucker, M. D. et al. Pembrolizumab in men with heavily treated metastatic castrate-resistant prostate cancer. *Cancer Med.* **8**, 4644–4655 (2019).
259. Karzai, F. et al. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. *J. Immunother. Cancer* **6**, 141 (2018).
260. Biersack, H. J., Ezziddin, S. & Knapp, F. F. Radium-223 in prostate cancer. *N. Engl. J. Med.* **369**, 1659 (2013).
261. Parker, C. & Sartor, O. Radium-223 in prostate cancer. *N. Engl. J. Med.* **369**, 1659–1660 (2013).
262. Parker, C. C. et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. *Eur. Urol.* **63**, 189–197 (2013).
263. Parker, C. et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N. Engl. J. Med.* **369**, 213–223 (2013). **First randomized study showing life-prolonging effect of a novel bone-targeted treatment with short-distance α-emitter radionuclide radium-223 in mildly symptomatic patients with bone metastatic mCRPC without visceral metastases**.
264. Saad, F. et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J. Natl Cancer Inst.* **94**, 1458–1468 (2002).
265. Fizazi, K. et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* **377**, 813–822 (2011).
266. Saad, F. et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J. Natl Cancer Inst.* **96**, 879–882 (2004).
267. Bienz, M. & Saad, F. Androgen-deprivation therapy and bone loss in prostate cancer patients: a clinical review. *Bonekey Rep.* **4**, 716 (2015).
268. Hofman, M. S. et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol.* **19**, 825–833 (2018).
269. Hofman, M. S. et al. TheraP: a randomized phase 2 trial of (177) Lu-PSMA-617 theranostic treatment vs cabazitaxel in progressive metastatic castration-resistant prostate cancer (Clinical Trial Protocol ANZUP 1603). *BJU Int.* **124**, 5–13 (2019).
270. Hofman, M. S. et al. TheraP: a randomised phase II trial of 177Lu-PSMA-617 (LuPSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: initial results (ANZUP protocol 1603) [abstract]. *J. Clin. Oncol.* **38** (Suppl. 15), 5500 (2020).
271. Antonarakis, E. S. et al. Germline DNA-repair gene mutations and outcomes in men with metastatic castration-resistant prostate cancer receiving first-line abiraterone and enzalutamide. *Eur. Urol.* **74**, 218–225 (2018).
272. Mateo, J. et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* **21**, 162–174 (2020).
273. Abida, W. et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J. Clin. Oncol.* **38**, 3763–3772 (2020).
274. Smith, M. R. et al. Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): preliminary results of GALAHAD [abstract]. *J. Clin. Oncol.* **37** (Suppl. 7), 202 (2019).
275. Hussain, M. et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N. Engl. J. Med.* **383**, 2345–2357 (2020).
276. de Bono, J. S. et al. Final overall survival (OS) analysis of PROfound: olaparib vs physician's choice of enzalutamide or abiraterone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations [abstract 610O]. *Ann. Oncol.* **31** (Suppl. 4), S508 (2020).
277. Abida, W. et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. *Clin. Cancer Res.* **26**, 2487–2496 (2020).
278. Fendler, W. P. et al. Prostate-specific membrane antigen ligand positron emission tomography in men with nonmetastatic castration-resistant prostate cancer. *Clin. Cancer Res.* **25**, 7448–7454 (2019).
279. Sternberg, C. N. et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N. Engl. J. Med.* **382**, 2197–2206 (2020).
280. Smith, M. R. et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N. Engl. J. Med.* **378**, 1408–1418 (2018).
281. Hussain, M. et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N. Engl. J. Med.* **378**, 2465–2474 (2018).
282. Fizazi, K. et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N. Engl. J. Med.* **380**, 1235–1246 (2019). **Practice-changing randomized phase III study (ARAMIS) adding darolutamide as a novel, well-tolerated next-generation androgen receptor inhibitor to the armamentarium in non-metastatic castration-resistant prostate cancer**.
283. Bergman, J. & Litwin, M. S. Quality of life in men undergoing active surveillance for localized prostate cancer. *J. Natl Cancer Inst. Monogr.* **2012**, 242–249 (2012).
284. Donovan, J. L. et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N. Engl. J. Med.* **375**, 1425–1437 (2016).
285. Bill-Axelson, A. et al. Long-term distress after radical prostatectomy versus watchful waiting in prostate cancer: a longitudinal study from the Scandinavian Prostate Cancer Group-4 randomized clinical trial. *Eur. Urol.* **64**, 920–928 (2013).
286. Steineck, G. et al. Cytotoxic treatment of aggressive prostate tumors with or without neuroendocrine elements. *Acta Oncol.* **41**, 668–674 (2002).
287. Johansson, E. et al. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the randomized Scandinavian Prostate Cancer Group Study number 4 (SPCG-4) clinical trial. *Eur. Urol.* **55**, 422–430 (2009).
288. Johansson, E. et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. *Lancet Oncol.* **12**, 891–899 (2011).
289. Vasarainen, H., Lokman, U., Ruutu, M., Taari, K. & Rannikko, A. Prostate cancer active surveillance and health-related quality of life: results of the Finnish arm of the prospective trial. *BJU Int.* **109**, 1614–1619 (2012).
290. Pham, K. N. et al. Prospective quality of life in men choosing active surveillance compared to those biopsied but not diagnosed with prostate cancer. *J. Urol.* **196**, 392–398 (2016).
291. Wei, J. T., Dunn, R. L., Litwin, M. S., Sandler, H. M. & Sanda, M. G. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* **56**, 899–905 (2000).
292. Clark, J. A. & Talcott, J. A. Symptom indexes to assess outcomes of treatment for early prostate cancer. *Med. Care* **39**, 1118–1130 (2001).
293. Litwin, M. S. et al. The UCLA prostate cancer index: development, reliability, and validity of a health-related quality of life measure. *Med. Care* **36**, 1002–1012 (1998).
294. Giesler, R. B., Miles, B. J., Cowen, M. E. & Kattan, M. W. Assessing quality of life in men with clinically localized prostate cancer: development of a new instrument for use in multiple settings. *Qual. Life Res.* **9**, 645–665 (2000).
295. Resnick, M. J. et al. Long-term functional outcomes after treatment for localized prostate cancer. *N. Engl. J. Med.* **368**, 436–445 (2013).
296. Punnen, S., Cowan, J. E., Chan, J. M., Carroll, P. R. & Cooperberg, M. R. Long-term health-related quality of life after primary treatment for localized prostate cancer: results from the CaPSURE registry. *Eur. Urol.* **68**, 600–608 (2015).
297. Barocas, D. A. et al. Using a population-based observational cohort study to address difficult comparative effectiveness research questions: the CEASAR study. *J. Comp. Eff. Res.* **2**, 445–460 (2013).
298. Potosky, A. L. et al. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. *J. Natl Cancer Inst.* **94**, 430–437 (2002).
299. Lubeck, D. P., Grossfeld, G. D. & Carroll, P. R. The effect of androgen deprivation therapy on health-related quality of life in men with prostate cancer. *Urology* **58**, 94–100 (2001).
300. Sartor, O. et al. Health-related quality of life in advanced prostate cancer and its treatments:

biochemical failure and metastatic disease populations. *Clin. Genitourin. Cancer* **13**, 101–112 (2015).
301. Nguyen, P. L. et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur. Urol.* **67**, 825–836 (2015).
302. Watts, S. et al. Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. *BMJ Open* **4**, e003901 (2014).
303. DiBlasio, C. J. et al. Prevalence and predictive factors for the development of de novo psychiatric illness in patients receiving androgen deprivation therapy for prostate cancer. *Can. J. Urol.* **15**, 4249–4256 (2008).
304. Wootten, A. C., Abbott, J. M., Farrell, A., Austin, D. W. & Klein, B. Psychosocial interventions to support partners of men with prostate cancer: a systematic and critical review of the literature. *J. Cancer Surviv.* **8**, 472–484 (2014).
305. Cucchiara, V. et al. Genomic markers in prostate cancer decision making. *Eur. Urol.* **73**, 572–582 (2018). **A review of prognostic signatures that can be used to assign risk of biochemical failure, metastasis or cancer-specific death**.
306. Teo, M. Y., O'Shaughnessy, M. J., McBride, S. M., Vargas, H. A. & Scher, H. I. Drug development for noncastrate prostate cancer in a changed therapeutic landscape. *Nat. Rev. Clin. Oncol.* **15**, 168–182 (2018).
307. Bostrom, P. J. et al. Genomic predictors of outcome in prostate cancer. *Eur. Urol.* **68**, 1033–1044 (2015).
308. Cuzick, J. et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br. J. Cancer* **106**, 1095–1099 (2012).
309. Cooperberg, M. R. et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J. Clin. Oncol.* **31**, 1428–1434 (2013).
310. Karnes, R. J. et al. Validation of a genomic risk classifier to predict prostate cancer-specific mortality in men with adverse pathologic features. *Eur. Urol.* **73**, 168–175 (2018).
311. Cullen, J. et al. A biopsy-based 17-gene genomic prostate score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racially diverse population of men with clinically low- and intermediate-risk prostate cancer. *Eur. Urol.* **68**, 123–131 (2015).
312. Tosoian, J. J. et al. Prediction of pathological stage based on clinical stage, serum prostate-specific antigen, and biopsy Gleason score: Partin tables in the contemporary era. *BJU Int.* **119**, 676–683 (2017).
313. Cooperberg, M. R. et al. The University of California, San Francisco cancer of the prostate risk assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *J. Urol.* **173**, 1938–1942 (2005).
314. Ondracek, R. P. et al. Validation of the Kattan nomogram for prostate cancer recurrence after radical prostatectomy. *J. Natl Compr. Canc Netw.* **14**, 1395–1401 (2016).
315. Ferlay, J. et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int. J. Cancer* **144**, 1941–1953 (2019).
316. Mazzone, E. et al. The effect of lymph node dissection in metastatic prostate cancer patients treated with radical prostatectomy: a contemporary analysis of survival and early postoperative outcomes. *Eur. Urol. Oncol.* **2**, 541–548 (2019).
317. Gandaglia, G. et al. Distribution of metastatic sites in patients with prostate cancer: a population-based analysis. *Prostate* **74**, 210–216 (2014).
318. Gandaglia, G. et al. The effect of age at diagnosis on prostate cancer mortality: a grade-for-grade and stage-for-stage analysis. *Eur. J. Surg. Oncol.* **40**, 1706–1715 (2014).
319. Hatzoglou, V. et al. Brain metastases from prostate cancer: an 11-year analysis in the MRI era with emphasis on imaging characteristics, incidence, and prognosis. *J. Neuroimaging* **24**, 161–166 (2014).
320. Cerami, E. et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* **2**, 401–404 (2012).
321. Gao, J. et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci. Signal.* **6**, pl1 (2013).
322. Nguyen, P. L. et al. Ability of a genomic classifier to predict metastasis and prostate cancer-specific mortality after radiation or surgery based on needle biopsy specimens. *Eur. Urol.* **72**, 845–852 (2017).
323. Cuzick, J. et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *Br. J. Cancer* **113**, 382–389 (2015).
324. Andriole, G. L. et al. Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: mortality results after 13 years of follow-up. *J. Natl Cancer Inst.* **104**, 125–132 (2012).
325. US Preventive Services Task Force. et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA* **319**, 1901–1913 (2018).
326. Rendon, R. A. et al. Recommandations de l'Association des urologues du Canada sur le depistage et le diagnostic precoce du cancer de la prostate. *Can. Urol. Assoc. J.* **11**, 298–309 (2017).
327. Parker, C., Gillessen, S., Heidenreich, A., Horwich, A. & ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **26** (suppl. 5), v69–v77 (2015).
328. Zhang, K., Bangma, C. H. & Roobol, M. J. Prostate cancer screening in Europe and Asia. *Asian J. Urol.* **4**, 86–95 (2017).
329. Baade, P. D., Youlden, D. R., Cramb, S. M., Dunn, J. & Gardiner, R. A. Epidemiology of prostate cancer in the Asia-Pacific region. *Prostate Int.* **1**, 47–58 (2013).
330. Kitagawa, Y. & Namiki, M. Prostate-specific antigen-based population screening for prostate cancer: current status in Japan and future perspective in Asia. *Asian J. Androl.* **17**, 475–480 (2015).
331. Kakehi, Y., Sugimoto, M., Taoka, R. & Committee for establishment of the evidenced-based clinical practice guideline for prostate cancer of the Japanese Urological Association. Evidenced-based clinical practice guideline for prostate cancer (summary: Japanese Urological Association, 2016 edition). *Int. J. Urol.* **24**, 648–666 (2017).
332. Jain, S., Saxena, S. & Kumar, A. Epidemiology of prostate cancer in India. *Meta Gene* **2**, 596–605 (2014).

Acknowledgements
R.J.R and R.G.B. are supported by core funding grants from Cancer Research UK (CRUK), Manchester Institute and CRUK Manchester Centre. R.G.B. is also supported by the CRUK Manchester RadNet and ACED grants, the NIHR Manchester Biomedical Research Council and Prostate Cancer UK through a Movember Centre of Excellence. C.O. is supported by the European Society of Medical Oncology (ESMO) with the aid of a grant from Roche. K.E.K. is supported by grants from Celgene, Sanofi, Novartis and CellCentric. S.L. is supported by the Prostate Cancer Foundation and the Edward Blank and Sharon Cosloy-Blank Family Foundation.

Author contributions
Introduction (R.J.R., C.O., R.G.B.); Epidemiology (R.J.R., C.O., T.V.d.K.); Mechanisms/pathophysiology (R.J.R., C.O., K.E.K., T.V.d.K.); Diagnosis, screening and prevention (R.J.R., C.O., S.L., R.E.R., T.V.d.K., R.G.B.); Management (R.J.R., C.O., S.G., T.V.d.K., R.G.B.); Quality of life (R.J.R., C.O., D.C.J., R.G.B.); Outlook (R.J.R., C.O., R.G.B.); Overview of the Primer (R.J.R., C.O., R.G.B.).

Competing interests
R.J.R.: No competing interests. C.O.: Travel reimbursement from Ipsen, PharmaMar and Medac; research funding from Roche and PharmaMar. Speakers honoraria from Ipsen, Roche and Medac. K.E.K.: Consultant/advisor to Cell Centric, Sanofi, Celgene, Atrin and Genentech. S.L.: Reimbursed travel to the Prostate Cancer Foundation Retreat from Sanofi; consulting fees from Lumenis and Bayer; equity in Gilead. D.C.J.: No competing interests. R.E.R.: Speakers bureau for Janssen and Genomic Health; consultant/advisor to Progenics, Pfizer, Janssen, Exact Biosciences and Bayer. S.G.: Consultant/advisor to Janssen, Astellas Pharma (Inst.), Curevac (Inst.), Novartis (Inst.), Active Biotech (Inst.), Bristol-Myers Squibb (Inst.), Ferring (Inst.), MaxiVax, Advanced Accelerator Applications, Roche, Janssen (Inst.), Innocrin Pharma (Inst.), Sanofi, Bayer (Inst.), Orion Pharma GmbH, Clovis Oncology (Inst.) and Menarini Silicon Biosystems (Inst.); patents, royalties or other intellectual property in Method for biomarker (WO 3752009138392 A1); other relationships with Nektar and ProteoMediX. T.V.d.K.: Consultant/advisor to Janssen. R.G.B.: Advisory board to AstraZeneca and Astellas; grant from GenomeDX.

Peer review information
Nature Reviews Disease Primers thanks S. Freedland, F. Saad, D. Murphy, W. Isaacs and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.