CANCER

Knowing what's growing: Why ductal and intraductal prostate cancer matter

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Prostate cancer is a common malignancy, but only some tumors are lethal. Accurately identifying these tumors will improve clinical practice and instruct research. Aggressive cancers often have distinctive pathologies, including intraductal carcinoma of the prostate (IDC-P) and ductal adenocarcinoma. Here, we review the importance of these pathologies because they are often overlooked, especially in genomics and preclinical testing. Pathology, genomics, and patient-derived models show that IDC-P and ductal adenocarcinoma accompany multiple markers of poor prognosis. Consequently, "knowing what is growing" will help translate preclinical research to pinpoint and treat high-risk prostate cancer in the clinic.

INTRODUCTION

In oncology, pattern recognition is crucial to diagnosis, treatment, and research. Whereas pathologists diagnose tumors by scrutinizing the patterns that cancer cells form in patient tissues, scientists help identify new treatments by searching for patterns in the molecular aberrations of tumors or the features of patient-derived models. Bringing these approaches together has renewed interest in the need to know what pathologies are growing in patient samples and how to replicate them in patient-derived models. Accurate tumor pathology influences the interpretations of molecular sequencing and preclinical drug testing, and here, we illustrate how the convergence of pathology, genomics, and biology provides a more comprehensive understanding of prostate cancer pathogenesis.

The most common type of prostate cancer is acinar adenocarcinoma, where cancer cells form glands and cribriform structures that lack basal epithelial cells and are classified using Gleason grading (*1*). Low-grade tumors are typically low risk, so patients may choose active surveillance to delay or avoid surgery or radiotherapy. In contrast, high-grade tumors pose a higher risk of progressing to advanced disease, so they often require more urgent treatment. Yet, poorly differentiated acinar adenocarcinoma is not the only tumor type that signifies high-risk prostate cancer. Intraductal carcinoma of the prostate (IDC-P) and ductal adenocarcinoma are also associated with poor patient outcomes; however, they are often under-recognized and even sometimes confused with one another, in both the laboratory and the clinic (*2*, *3*).

IDC-P and ductal adenocarcinoma (originally classified as endometrioid carcinoma) were first reported several decades ago (*4*, *5*). Since then, the definitions of these pathologies and the understanding of their clinical relevance have evolved. The increasing number of studies of IDC-P and ductal adenocarcinoma reflects the major clinical challenge of accurately identifying patients with high-risk prostate cancer. The scope of these studies is also expanding beyond histological analyses. New technologies, such as whole-genome sequencing, have produced detailed molecular profiles of IDC-P and ductal adenocarcinoma (*6*–*8*). More recently, patient-derived models have also been used to study these tumor types across time and in response to treatment (*9*, *10*). Although IDC-P and ductal adenocarcinoma are distinct pathologies, they share some common clinical and molecular features. Therefore, this review examines the current understanding of these tumor types. In particular, this review focuses on the convergence of pathology, genomics, and cell biology, where cross-disciplinary studies demonstrate the importance of IDC-P and ductal adenocarcinoma in clinical practice and preclinical research.

In focusing on IDC-P and ductal adenocarcinoma, our goal is to exemplify the broader importance of recognizing distinct tumor pathologies, even if they are considered to be rare. There are several other forms of prostate cancer that are under-researched. Given that prostate cancer is one of the most commonly diagnosed malignancies, with more than 1.2 million cases worldwide in 2018 (*11*), less common types of prostate cancer can still affect thousands of patients and should not be overlooked. There are also similar themes with other tumor types, where new pathologies are being recognized or redefined. Just as for IDC-P and ductal adenocarcinoma, greater recognition, reporting, and research will ultimately improve patient stratification based on these pathologies.

GLEASON GRADING AND THE IMPORTANCE OF PATTERN RECOGNITION IN PROSTATE CANCER

IDC-P and ductal adenocarcinoma rarely occur on their own within tumors. Rather, they usually coexist with acinar adenocarcinoma. This means that the features of IDC-P and ductal adenocarcinoma are typically studied and reported in the context of the accompanying acinar adenocarcinoma. Because acinar adenocarcinoma is the most common form of prostate cancer, there has been a longstanding effort to describe and categorize its different growth patterns to determine the likelihood that tumors will progress to advanced prostate cancer.

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The current approach for grading acinar adenocarcinoma originated from studies by D. Gleason and the Veterans Administration Cooperative Urological Research Group in the 1960s and 1970s (*12*, *13*). They devised a histological grading system based on the overall pattern of tumor growth observed at relatively low magnifications rather than cytological details at higher magnifications. These patterns were numbered from 1 to 5, from most to least differentiated in appearance. Crucially, Gleason and colleagues acknowledged that individual tumors often have heterogeneous growth patterns, so they reported the primary and secondary grades as a combined Gleason score (for example, Gleason score 3 + 4 = 7). Higher scores were associated with greater prostate cancer–specific mortality, affirming the concept that histological growth patterns reflect the aggressiveness of prostate cancer (*12*).

Since the Gleason grading system was first proposed, it has evolved in stages, prompted by changes in patient care, increased availability of markers for immunohistochemistry, and deeper understanding of the importance of specific growth patterns (*14*). Major changes to Gleason grading were adopted through pathology consensus panels in 2005 and 2014 (*15*, *16*) and, most recently, the conversion of Gleason scores into grade groups (*17*). These changes were then promulgated by the World Health Organization classification of tumors, tumor-node-metastasis classification on cancer staging, and clinical guidelines (*18*–*21*). These modifications include the ways that particular growth patterns are classified. For example, pattern 3 has been restricted to individual well-formed glands, with reclassification of cribriform and poorly formed glands as pattern 4 to recognize their association with poor outcome (*15*, *16*). As a result, some 3 + 3 = 6 (grade group 1) tumors based on current guidelines may be less aggressive than those reported using the original classifications.

The changing definitions of Gleason patterns have been accompanied by updates in how they are reported. For example, patterns 1 and 2 are now seldom assigned, making Gleason scores 2 to 5 very uncommon (*22*, *23*). Pattern 1 often represents adenosis, a benign process mimicking adenocarcinoma, whereas pattern 2 lesions are difficult to reproducibly report in biopsies (*15*). Another change in reporting is that biopsy scores now combine the most common pattern with the highest grade pattern, rather than the secondary pattern (*15*). This acknowledges that small amounts of high-grade cancer in biopsies can still be important.

The most recent change in reporting is that Gleason scores are converted into grade groups (Gleason score $\leq$ 6 is grade group 1; Gleason score 3 + 4 = 7 is grade group 2; Gleason score 4 + 3 = 7 is grade group 3; Gleason score 8 is grade group 4; Gleason score $\geq$ 9 is grade group 5) (Fig. 1) (*17*, *24*). This modification separates 3 + 4 = 7 (grade group 2) tumors from 4 + 3 = 7 (grade group 3) tumors, which have worse prognosis (*17*). It is also intended to reduce confusion among patients with low-grade prostate cancer, who might wrongly assume that a Gleason score of 3 + 3 = 6 denotes moderately aggressive prostate cancer, rather than the least aggressive diagnosis.

The original intention for Gleason grading was to address the wide variation in the natural history of prostate cancer with a system for stratifying patients and predicting their likely course of disease (*12*, *13*). The goals of subsequent changes were to increase the accuracy of stratification, enhance the ability of Gleason grades to predict clinical outcomes, improve the correlation between pathology reporting of biopsy and radical prostatectomy specimens, and, most recently, clarify the meaning of Gleason scores for clinicians and patients (*14*–*17*). This iterative process demonstrates the importance of recognizing growth patterns, refining their definitions, and reporting them consistently. The same thinking applies beyond acinar adenocarcinoma to IDC-P and ductal adenocarcinoma. Increasing the awareness and acceptance of these pathologies, alongside acinar adenocarcinoma, has the same goal as the Gleason grading: improving the accuracy of patient stratification to guide decisions about patient treatment.

DIAGNOSIS AND CLINICAL IMPORTANCE OF IDC-P

IDC-P was recognized as a pathologic entity in the 2016 World Health Organization classification of tumors (Fig. 1) (*18*). It is defined by the expansive proliferation of malignant cells within preexisting prostatic ducts and acini with a full or partially conserved basal cell layer (Table 1 and Fig. 2A). Different diagnostic criteria have been proposed for IDC-P (*25*–*27*), but Guo and Epstein's criteria are the most widely used and were cited by the 2014 International Society of Urological Pathology consensus conference (*16*, *25*). They require that IDC-P displays solid or dense cribriform architecture (typically with tumor cells occupying >50% of the ducts) or loose cribriform or micropapillary architecture with either marked nuclear atypia or central comedonecrosis (patches of dying or necrotic cells) (*25*).

Historically, IDC-P was considered rare; however, this may have been due to under-reporting and the previous lack of standardized reporting guidelines (*18*). Different diagnostic criteria also influence the identification of IDC-P (*28*), and it can be difficult to distinguish from other lesions, including high-grade prostatic intraepithelial neoplasia (HGPIN), cribriform adenocarcinoma, and ductal adenocarcinoma (*2*). Our recent systematic review found that IDC-P is more prevalent than commonly perceived and associated with greater risk of progression to advanced disease (*29*). IDC-P was rare in cohorts with low-risk disease (2.1% of patients) but increasingly prevalent in cohorts with moderate-risk (23.1%), high-risk (36.7%), and metastatic or recurrent (56.0%) disease (*29*). IDC-P was also reported in 59.7% of tumors after androgen deprivation or chemotherapy (*29*). Yet, there is still a wide range in the detection of IDC-P across different cohorts. For example, among nine studies of high-risk prostate cancer, the prevalence of IDC-P ranged from 0 to 60.9% of cases, probably due to differences in patient features and diagnostic criteria (*9*, *30*–*37*). Sample type is another source of variation because biopsies are less sensitive for detecting IDC-P and cribriform morphology than radical prostatectomy specimens (*38*–*40*). Notwithstanding this variability, the prevalence of IDC-P is strongly associated with higher-risk prostate cancers (*29*).

IDC-P is often associated with several adverse prognostic features and poor survival. Patients with IDC-P at biopsy or radical prostatectomy are more likely to have higher Gleason grade acinar adenocarcinoma, more advanced pathological stage, and worse clinical features, such as extraprostatic extension and regional lymph node involvement (*25*, *33*, *37*, *41*–*45*). Although IDC-P is typically associated with high-grade disease at biopsy, in some cases, it coexists with low Gleason score (3 + 3 = 6, grade group 1) acinar adenocarcinoma (*46*). In these cases, higher-grade cancer is often identified in the radical prostatectomy specimen (*46*). In rare cases, IDC-P exists in isolation without evidence of invasive disease (Fig. 2B) (*47*, *48*).

The existence of tumors where IDC-P does not accompany high-grade invasive acinar adenocarcinoma, albeit uncommon, has been a major consideration in the reporting of IDC-P (*16*). At the 2014 International Society of Urological Pathology Consensus Conference, 82% of members agreed that IDC-P without invasive cancer should

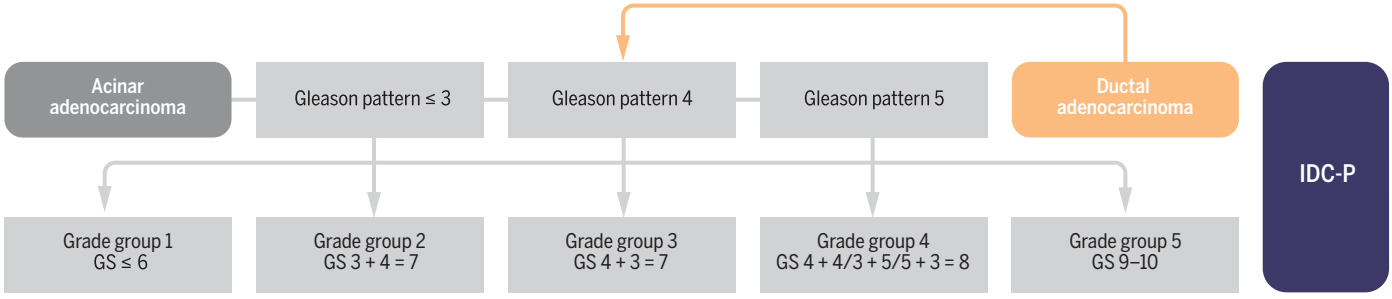

Fig. 1. The Gleason grading system for acinar adenocarcinoma. Different growth patterns of acinar adenocarcinoma are classified into Gleason scores (GS), which are then reported as grade groups. Ductal adenocarcinoma is assigned as Gleason pattern 4 by convention. IDC-P is included as part of the grade group of the whole tumor according to recent guidelines from the International Society of Urological Pathology. Previously, the 2014 International Society of Urological Pathology Consensus Conference determined that IDC-P should be reported separately.

not be assigned a Gleason grade (*16*). The concern was that grading IDC-P would overestimate the risk of poor prognosis in patients with isolated IDC-P. Instead, the approach was to report IDC-P separately, include a comment emphasizing its association with high-grade disease (*16*), and suggest a repeat biopsy for some patients (*18*). The International Collaboration on Cancer Reporting also recommended that IDC-P be included in pathological reports of radical prostatectomy specimens (*49*). Most recently, a modified grading scheme that incorporates IDC-P and cribriform glands was investigated (*50*), and members of the International Society of Urological Pathology recommended including IDC-P into the grade of the whole tumor (*51*). This new recommendation has yet to be endorsed by other groups, such as the World Health Organization.

The impetus for reporting IDC-P includes its association with poor outcome. When identified with intermediate- and high-risk disease at biopsy, IDC-P is independently associated with early biochemical and clinical reoccurrence after radiation therapy (*36*). Patients with IDC-P at surgery have decreased time to biochemical reoccurrence and progression-free survival (*32*, *37*, *41*, *52*–*54*), even after neoadjuvant hormonal therapy or chemotherapy (*30*, *32*, *35*). Across diverse cohorts, IDC-P is also associated with poorer cancer-specific and overall survival (hazard ratios from 1.95 to 4.48) (*32*, *55*–*58*). Furthermore, IDC-P is still associated with decreased survival in patients who have already progressed to metastatic disease, suggesting that it indicates worse clinical outcomes regardless of disease stage (*45*, *59*, *60*).

Surgery or radiotherapy have been recommended for patients diagnosed with IDC-P at biopsy, even with low-grade tumors (*18*, *25*, *47*), but the most appropriate clinical management remains to be determined. In retrospective analyses, patients with IDC-P who undergo radical prostatectomy have improved biochemical relapse–free survival when they receive adjuvant radiotherapy (*61*). Yet, a caveat to the intensification of local treatment is that patients with IDC-P often have distant metastases, especially bone metastases, at initial clinical recurrence after radical prostatectomy (*57*). Nevertheless, a retrospective study showed that adjuvant or salvage radiation therapy before recurrence still improves the cancer-specific survival of patients with IDC-P who later develop metastases (*57*). Another retrospective study found that patients with IDC-P had increased progression-free and overall survival when treated with abiraterone acetate, an androgen receptor (AR) pathway inhibitor, versus docetaxel, a taxane chemotherapy, as first-line therapy for metastatic castration-resistant prostate cancer (CRPC) (*60*). Further prospective studies are required to confirm the most appropriate clinical management for patients with IDC-P and determine whether it is a predictive marker for therapy response. Concurrent preclinical studies with patient-derived models could also determine whether the adenocarcinoma and IDC-P components of tumors respond to treatment the same way.

ORIGINS OF IDC-P

The recent convergence of pathology and genomics is beginning to clarify the origins of IDC-P and its relationship to other lesions. The overlapping features of IDC-P and HGPIN were once a source of confusion (*62*). However, compared to HGPIN and low-grade adenocarcinoma, IDC-P has more frequent and extensive allelic loss and higher rates of chromosomal rearrangements (*63*, *64*), including *ERG* (ETS transcription factor ERG) fusions (*65*, *66*) and loss of *PTEN* (phosphatase and tensin homolog), *TP53* (tumor protein p53), and *RB1* (RB transcriptional corepressor 1) (*64*, *65*, *67*–*69*). These genomic features distinguish IDC-P from HGPIN in prostate cancer progression.

IDC-P usually coexists with high-grade adenocarcinoma, so it was postulated to originate from adenocarcinoma spreading into native prostatic ducts (*70*). Multiple genomic studies now support this concept, showing that IDC-P and concomitant adenocarcinoma share common loss of heterozygosity, *PTEN* deletions, and fusions of *TMPRSS2* (transmembrane serine protease 2) and *ERG* (*63*, *65*–*67*). Whole-genome sequencing of sporadic and *BRCA2*-mutant (BRCA2 DNA repair associated) localized prostate cancer also showed that microdissected samples of IDC-P and adenocarcinoma share common clonal ancestry, before diverging during tumor evolution (*6*). Furthermore, a case study found concordant genomic breakpoints between IDC-P, adenocarcinoma, and lymph node metastases, suggesting that their shared cell of origin can acquire metastatic potential (*71*). Collectively, these studies show that, in most tumors, IDC-P arises when high-grade adenocarcinoma invades native prostatic ducts (Fig. 2C).

Occasionally, IDC-P may arise independently of high-grade adenocarcinoma. A subset of tumors has "isolated" or "precursor-like" IDC-P, where the corresponding adenocarcinoma is absent, distant from the site of IDC-P, or only low grade (*26*, *43*, *46*–*48*). Patients with isolated IDC-P have fewer high-risk clinicopathological features and longer biochemical relapse–free survival compared to patients where IDC-P coexists with high-grade disease (relative risk of relapse

Table 1. Comparison of the histopathological, clinical, and molecular features of IDC-P and ductal adenocarcinoma.

Feature	IDC-P	Ductal adenocarcinoma
Diagnosis	Based on morphological features	Based on cytological features
Morphological and cytological features	•Malignant cells within preexisting prostatic ducts and acini	•Large, atypical glands with fibrovascular cores
	•Solid, dense, or loose cribriform architecture	•Papillary, cribriform, or solid architecture
	•Full or partially conserved basal cell layer	•Absent or patchy basal cell layer
	•Rounded nuclei with less columnar epithelium	•Stratified nuclei with tall columnar epithelium
Reporting	•Reporting of IDC-P is controversial	Reported as Gleason 4 + 4 (or 4 + 5 if necrosis is present)
	•The 2014 International Society of Urological Pathology consensus conference endorsed reporting IDC-P separately from grade group. New recommendations include it in the grade group of the whole tumor	
	•The extent of IDC-P is not measured	
Coexists with acinar adenocarcinoma	Usually (except isolated IDC-P)	Usually, may be pure
Origin	Usually shares cell of origin with acinar adenocarcinoma	Usually shares cell of origin with acinar adenocarcinoma
Clinical significance	Associated with poor prognosis	Associated with poor prognosis
Responds to androgen deprivation therapy	Yes but contains castrate-tolerant cells	Yes, presence of castrate-tolerant cells unknown
Genomic and transcriptomic features	Tumors enriched for:	Tumors enriched for:
	•High genomic instability	•High genomic instability
	•Frequent loss of *PTEN*, *RB1*, and *TP53*	•*PTEN* loss
	•Aberrations in DNA damage repair pathways, including *BRCA2* mutations	•Aberrations in DNA damage repair pathways, including *BRCA2* mutations
	•Transcriptional markers of poor prognosis, including *SChLAP1* expression and hypoxia	•Alterations in the WNT pathway, including *APC* and *CTNNB1* mutations

for regular versus isolated or precursor IDC-P is 7.96) (*48*). Yet, tumors with isolated IDC-P at biopsy are often upstaged by surgery (*47*). Isolated IDC-P has a distinctive genomic profile enriched for driver mutations in the MAPK (mitogen-activated protein kinase) and PI3K (phosphatidylinositol 3-kinase) pathways (*72*). Furthermore, at least in some tumors, isolated IDC-P has discordant staining of ERG and PTEN compared to nearby low-grade adenocarcinoma (*72*). Thus, in some cases, isolated IDC-P may be an in situ lesion genomically distinct from acinar adenocarcinoma.

The existence of isolated IDC-P raises alternative possibilities about the origins of IDC-P other than acinar adenocarcinoma. One theory is that IDC-P occasionally arises de novo, perhaps as a precursor to invasive cancer (*46*, *72*). Another putative source of IDC-P is HGPIN, which is also a potential precursor of acinar adenocarcinoma. HGPIN often coexists with the regular and isolated forms of IDC-P (*47*, *48*, *73*). As first described by McNeal and colleagues (*73*), this can include individual ducts where the epithelium transitions from normal morphology to HGPIN and then intermediate morphologies toward cribriform lesions or IDC-P (*48*, *73*, *74*). This continuum from premalignant to malignant cells suggests a possible clonal relationship where HGPIN evolves into IDC-P (*26*, *73*, *74*). Together, this means that there are three potential origins for IDC-P: de novo pathogenesis, progression from HGPIN, and invasion of acinar adenocarcinoma into ducts. However, isolated IDC-P is comparatively rare, and the genomic features of IDC-P more closely resemble high-grade acinar adenocarcinoma than HGPIN. Therefore, among the possible origins of IDC-P, the spread of acinar adenocarcinoma into existing ducts is the most common.

MOLECULAR FEATURES OF TUMORS WITH IDC-P

The adverse clinical features of tumors with IDC-P may be due to their underlying molecular features (Table 1). Early reports identified extensive allelic loss in IDC-P (*63*, *64*). Subsequent studies combined IDC-P and cribriform pathology because basal cell staining was not available. They showed that these pathologies are associated with higher genomic instability, measured by the percentage of genome alterations (PGA) (*7*, *75*, *76*). Moreover, the combination of IDC-P or cribriform pathology and high PGA was associated with poorer biochemical relapse–free and metastasis-free survival (hazard ratio, 3.3 and 5.5, respectively) (*7*). The increase in PGA is predominantly due to somatic copy number alterations, including frequent chromosomal deletions of 8p, 6q, and 10q. These regions contain several tumor suppressor genes, such as *PTEN*, *NKX3-1* (NK3 homeobox 1), and *MAP3K7* (MAPK kinase kinase 7) (*75*, *77*). Indeed, *PTEN* loss is frequently observed in tumors with IDC-P (*69*, *76*, *78*). Deletions of *RB1* and *TP53* and mutations in *SPOP* (speckle type BTB/POZ protein), *ATM* (ATM serine/threonine kinase), *TP53*, and *FOXA1* (forkhead box A1) are also more frequent in tumors with IDC-P and/or cribriform architecture (*75*, *77*). This concurs with earlier studies showing more frequent loss of heterozygosity of *RB1* and *TP53* in IDC-P compared to adenocarcinoma (*64*).

Tumors with IDC-P may also be enriched in aberrations in DNA damage repair pathways. The association between IDC-P and germline *BRCA2* mutations was first observed in primary patient-derived xenografts (PDXs) of localized prostate cancer (*9*). A subsequent retrospective pathology review identified IDC-P in 42% of localized tumors from germline *BRCA2* mutation carriers versus only 9% of

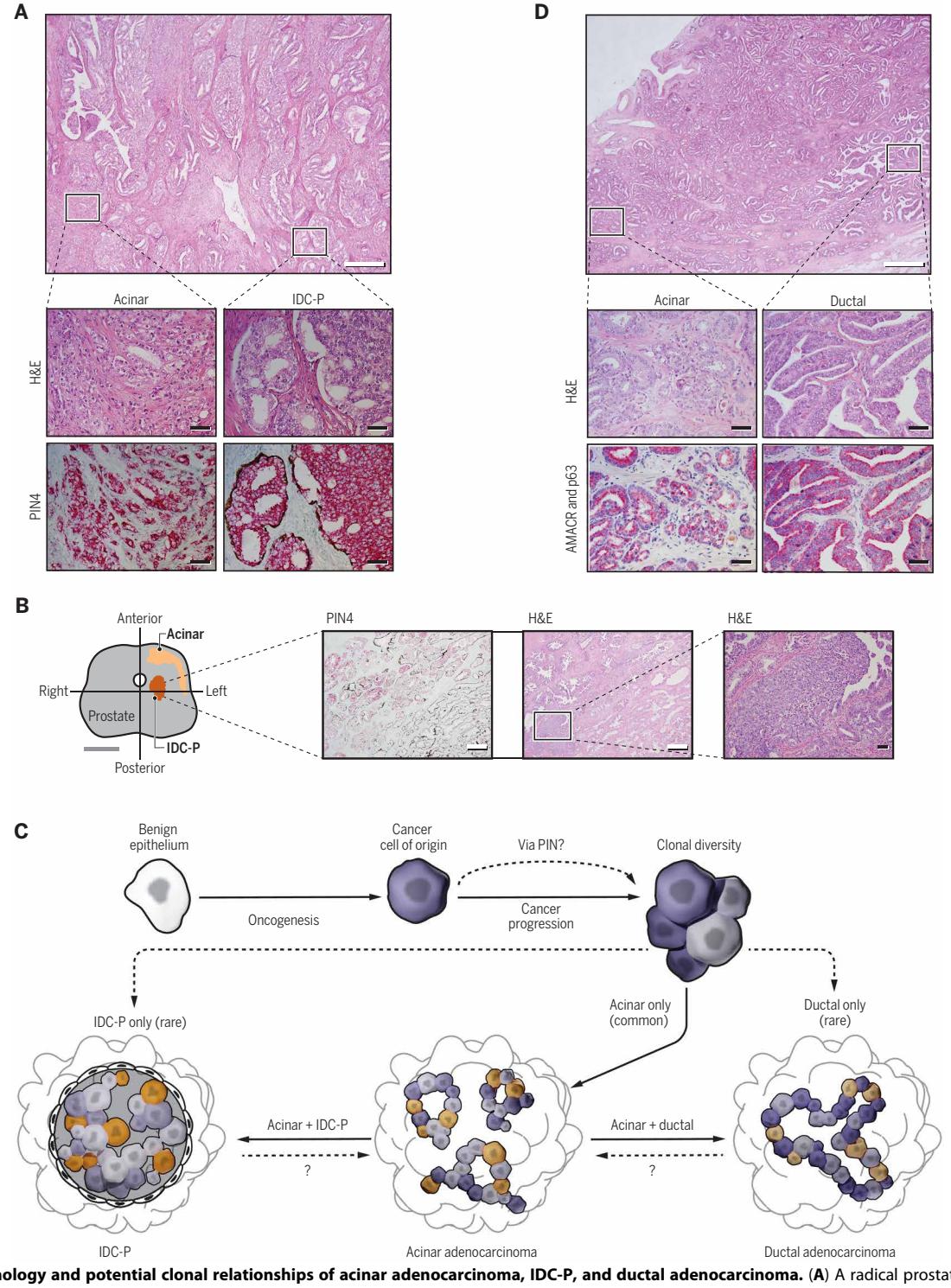

Fig. 2. The pathology and potential clonal relationships of acinar adenocarcinoma, IDC-P, and ductal adenocarcinoma. (**A**) A radical prostatectomy specimen containing acinar adenocarcinoma alongside IDC-P. The tumor was stained with hematoxylin and eosin (H&E) and PIN4 to show α-methylacyl-CoA racemase (AMACR) positive (pink) prostate cancer cells and p63 positive/high molecular weight cytokeratin positive (brown) basal cells. The foci of IDC-P have cribriform morphology and are surrounded by basal cells. (**B**) A radical prostatectomy specimen containing acinar adenocarcinoma and a separate region of isolated IDC-P. The schematic shows the locations of the different pathologies within the prostate. PIN4 and H&E staining show the region of isolated IDC-P. (**C**) Schematic of the likely clonal relationships between pathologies. IDC-P and ductal adenocarcinoma seldom arise in the absence of acinar adenocarcinoma. When IDC-P or ductal adenocarcinoma coexists with acinar adenocarcinoma within a tumor, they typically share genomic alterations from a common cancer cell of origin, represented by purple and gray cells. With tumor progression, IDC-P, ductal adenocarcinoma, and acinar adenocarcinoma may contain clones with further divergent alterations, represented by different shades of orange cells. (**D**) A tumor containing acinar and ductal adenocarcinoma with H&E, AMACR (pink), and p63 (brown) staining. The region of ductal adenocarcinoma has papillary morphology and lacks basal cells. Scale bars, 500 μm (white), 50 μm (black), and 1 cm (gray).

sporadic tumors (*9*). Further genomic analyses revealed that tumors with germline *BRCA2* mutations and IDC-P have a distinctive profile, including genomic and epigenomic dysregulation of *MED12* (mediator complex subunit 12L) and *MED12L* and copy number alterations that indicate poor prognosis, including gains of *BCL6* (BCL6 transcription repressor) and *CDK2* (cyclin-dependent kinase 2) and loss of *MTOR* (mechanistic target of rapamycin kinase) (*6*). These features may underlie worse overall and prostate cancer–specific survival of *BRCA2* mutation carriers with IDC-P compared to *BRCA2* mutation carriers without IDC-P (hazard ratio, 16.9) (*9*). Similar to *BRCA2* mutations, IDC-P is prevalent in tumors with germline mutations of *ATM*, *BRCA1* (BRCA1 DNA repair associated), *CHEK2* (checkpoint kinase 2), and canonical mismatch repair genes (*79*, *80*). The association between DNA repair defects and IDC-P is particularly notable, given that both features indicate poor prognosis. Therefore, National Comprehensive Cancer Network clinical practice guidelines recommend germline testing for variants in DNA repair genes for patients with IDC-P in biopsy samples (*21*).

The transcriptome profile of tumors with IDC-P/cribriform pathology also affirms their association with poor prognosis. The most highly up-regulated gene in tumors with IDC-P/cribriform pathology is *SChLAP1* (SWI/SNF complex antagonist associated with prostate cancer 1) (*7*). *SChLAP1* is a long noncoding RNA that promotes the invasion and metastasis of prostate cancer cell lines, although there is disagreement about the underlying mechanism (*81*, *82*). Nevertheless, high *SChLAP1* expression has previously been associated with higher Gleason score, pathological and clinical tumor stage, and shorter times to biochemical recurrence, development of metastases, and death from prostate cancer (*81*, *83*, *84*). Within tumors, *SChLAP1* is expressed in both IDC-P/cribriform lesions and adjacent acinar adenocarcinoma, showing that it is enriched in tumors with IDC-P but not restricted to foci of IDC-P (*7*). Notably, patients with both IDC-P/cribriform architecture and high *SChLAP1* expression have increased risk of biochemical relapse (hazard ratio of 2.6 versus low SChLAP1 and no IDC-P/cribriform) (*7*).

Tumor hypoxia is another marker of poor prognosis that is associated with IDC-P (*7*, *76*). Hypoxic subregions arise within tumors through decreased oxygen availability, due to poorly formed vasculature, or increased oxygen consumption, due to changes in metabolism (*85*). Tumor hypoxia has been associated with increased biochemical relapse of prostate cancer after radical prostatectomy or radiotherapy, although not in all studies (*86*–*88*). The association with poor outcome is strengthened when hypoxia is combined with other prognostic markers, including high PGA, *PTEN* loss, and polyclonal versus monoclonal genomic architecture (*76*, *88*). Based on intraprostatic measurements of oxygen pressures, a greater proportion of tumors with IDC-P or cribriform glands have hypoxic subregions than tumors without these pathologies (*7*). Furthermore, the presence of IDC-P or cribriform glands in localized prostate cancer has a stronger correlation with a transcriptional signature of tumor hypoxia than any other clinicopathologic or genomic feature, including Gleason score, tumor stage, prostate-specific antigen concentration, PGA, *PTEN* loss, and other genomic aberrations (*76*). Patients with both IDC-P/cribriform pathology and high hypoxia scores have increased risk of disease relapse within 2 years of primary therapy, independent of tumor stage and Gleason score (hazard ratio, 5.4) (*76*). Therefore, in tumors with a high risk of disease progression, IDC-P often coincides with other markers of poor prognosis, such as hypoxia.

Collectively, the genomic and transcriptomic features of IDC-P show that it is a pathological feature of high-risk tumors characterized by genomic instability, hypoxia, and pathogenic genomic aberrations, including *PTEN* loss and defects in DNA damage repair pathways. Sometimes, several of these features coexist in tumors with IDC-P, including the concurrent hypoxia and PTEN loss (*76*). These features are not exclusive to IDC-P but enriched in tumors with this growth pattern, with the caveat that some studies did not distinguish between IDC-P and cribriform architecture. Nevertheless, a consistent observation is that the co-occurrence of IDC-P with genomic or transcriptomic markers of poor prognosis indicates an increased risk of poor outcome. The corollary of this observation is that pathology is an important parameter in interpreting genomic and transcriptomic analyses of patient cohorts. Many sequencing studies do not record the presence of IDC-P, so pathology data are limited to the Gleason grade of acinar adenocarcinoma. More detailed pathology records would maximize the clinical relevance of these molecular datasets by comprehensively classifying the features of tumor pathologies with specific molecular signatures or aberrations.

DIAGNOSIS AND CLINICAL IMPORTANCE OF DUCTAL CARCINOMA

Similar to IDC-P, ductal adenocarcinoma is an under-recognized form of prostate cancer associated with poor patient outcomes. Ductal adenocarcinoma is defined by its morphology—tall columnar epithelium with stratified nuclei, a papillary, cribriform, or solid architecture, and an absent or patchy basal cell layer (Table 1 and Fig. 2D) (*1*, *89*). Papillary architecture with characteristic fibrovascular cores is the most useful diagnostic feature for identifying ductal adenocarcinoma (*90*). Ductal adenocarcinoma and IDC-P share some morphological features: They both can have a cribriform architecture and can invade native ducts and glands (*89*). Adding further complexity, both pathologies coexist in some tumors (*89*). This may contribute to the interobserver variability in diagnosing both ductal adenocarcinoma and IDC-P, even among experienced uropathologists (*90*, *91*).

Accurate reporting of ductal adenocarcinoma is important because it is a sign of poor patient prognosis. Ductal adenocarcinoma usually coexists with acinar adenocarcinoma, with 0.8 to 12.7% of localized prostate cancers containing both pathologies but only 0.2 to 1.3% containing pure ductal adenocarcinoma, depending on the case series (*92*–*97*). The lower rates of ductal adenocarcinoma recorded in databases and registries suggest that it is often under-reported (*98*–*100*). Similar to IDC-P, an important caveat to the estimated prevalence of ductal adenocarcinoma is that it varies depending on the diagnostic criteria that are used (*90*, *92*).

The prevalence of ductal adenocarcinoma also increases among tumors with a higher risk of progressing to advanced disease. Tumors containing ductal adenocarcinoma have higher Gleason grade, tumor stage, volume, and incidences of extraprostatic extension, seminal vesicle invasion, positive surgical margins, and lymph node metastases (*92*, *94*, *98*, *101*–*105*). This culminates in high rates of metastasis, including uncommon visceral sites, and shorter biochemical recurrence–free and overall survival (*98*, *101*, *102*, *106*). A higher proportion of ductal adenocarcinoma is also associated with a greater risk of biochemical recurrence (*101*). The prostate cancer–specific mortality of patients with ductal adenocarcinoma is closest to Gleason 4 + 4 (grade group 4) disease when compared to patients with different grades of acinar adenocarcinoma (*98*). Therefore, not only does ductal

adenocarcinoma often coexist with high-grade acinar adenocarcinoma, but it also has a similar natural history.

Ductal adenocarcinoma is assigned a Gleason score (*15*) (Fig. 1). Reflecting its association with poor prognosis, pure ductal adenocarcinoma is designated as Gleason 4 + 4 = 8 (grade group 4) or 4 + 5 = 9 (grade group 5) if there is comedonecrosis (*15*). Despite being assigned a Gleason score, ductal adenocarcinoma is still reported as such to distinguish it as a distinct pathology. In tumors where ductal and acinar adenocarcinoma coexist, the ductal component is graded as pattern 4 (*15*). One rare exception is lesions of ductal adenocarcinoma that resemble HGPIN, with flat, tufted, or micropapillary architecture (*107*). This HGPIN-like ductal adenocarcinoma usually accompanies low-grade cancer, so it is recommended to be graded as Gleason 3 + 3 = 6 (*107*). Notwithstanding these PIN-like lesions, ductal adenocarcinoma is usually a marker of high-risk prostate cancer. Because it usually coexists with high-grade acinar adenocarcinoma, the contribution of ductal adenocarcinoma to tumor progression is uncertain; however, sequencing studies are beginning to unravel the relationships between these pathologies and potential mechanisms for poor patient outcomes.

ORIGIN AND GENOMIC FEATURES OF DUCTAL ADENOCARCINOMA

The origin of ductal adenocarcinoma has been the subject of much speculation. Initially, it was thought to arise from remnant Müllerian duct tissues (*5*); however, genomic analyses have clarified that ductal and acinar adenocarcinoma have a common origin when both pathologies are present (Table 1 and Fig. 2C). This includes concordant changes in driver genes, such as *TMPRSS2-ERG* fusions, a similar transcriptomic profile, and common genomic features, including losses in chromosome 8p and gains in 8q (*8*, *108*–*111*). Yet, there is also evidence of divergence in genomic alterations with tumor evolution (*8*). The ductal component of tumors often has more mutations and copy number alterations (*8*), with an average PGA similar to high-grade acinar adenocarcinoma, but has lower than metastases (*111*). Because high PGA indicates poor patient prognosis, genomic instability may be one mechanism underlying the aggressiveness of tumors with ductal adenocarcinoma.

The adverse clinical features of tumors with ductal adenocarcinoma may also be due to genomic alterations in specific pathways (Table 1). There is some disagreement about the prevalence of *TMPRSS2-ERG* fusions and *PTEN* loss in ductal adenocarcinoma, possibly due to differences in patient selection and methods (*8*, *108*, *109*, *112*–*115*). Nevertheless, *PTEN* loss in ductal adenocarcinoma is notable because it has been associated with earlier divergence between the ductal and acinar adenocarcinoma components within tumors (*8*). The PI3K-Akt (AKT serine/threonine kinase) pathway, which is activated by *PTEN* loss, is also enriched in the transcriptomic profile of some tumors with ductal adenocarcinoma (*8*). Because *PTEN* loss is a marker of poor prognosis, its potential association with ductal adenocarcinoma is intriguing (*116*). Therefore, using larger cohorts to clarify the prevalence of *PTEN* loss may help explain the aggressive clinical features of ductal adenocarcinoma.

The Wnt pathway has also been associated with ductal adenocarcinoma, with recurrent alterations in *APC* (APC regulator of WNT signaling pathway) and *CTNNB1* (catenin β1), which encodes β-catenin (*8*, *111*, *115*). The *CTNNB1* mutations were identified in the ductal component of tumors with late divergence from acinar adenocarcinoma. The activity of the Wnt pathway was also enriched in the transcriptional profile of ductal versus acinar adenocarcinoma samples (*8*). Alterations of the Wnt pathway are usually more common in metastatic CRPC than localized prostate cancer (*117*), and thus, their prevalence in ductal adenocarcinoma is consistent with the propensity of these tumors to progress to advanced disease.

There are also frequent genomic alterations of DNA repair genes in patients with ductal adenocarcinoma, although not in every cohort (*8*, *79*, *115*). The corollary is that ductal adenocarcinoma is more common in patients with known mutations in DNA repair genes compared to patients without these mutations (*79*). These genomic alterations affect genes involved in homologous recombination, such as *BRCA2*, and mismatch repair, such as *MSH2* (mutS homolog 2) (*8*, *79*, *115*). The defects in mismatch repair genes coincide with hypermutation and microsatellite instability in some patients with ductal adenocarcinoma, although not all (*79*, *115*). It is not yet known whether the combination of DNA repair defects and ductal adenocarcinoma further increases the risk of poor outcome, similar to the combination of germline *BRCA2* mutations and IDC-P (*9*). If the association is confirmed, then ductal adenocarcinoma might identify patients suitable for genetic testing of DNA repair defects, exemplifying how the integration of pathology and genomics could improve patient treatment.

PATIENT-DERIVED MODELS OF IDC-P AND DUCTAL ADENOCARCINOMA

Most studies of IDC-P and ductal adenocarcinoma have used fixed or frozen patient specimens. More recently, patient-derived models have emerged as a way to study the growth of these pathologies across time and in response to treatments. This makes them important preclinical tools in linking laboratory discoveries, such as the enrichment of actionable mutations in IDC-P and ductal adenocarcinoma, to future improvements in clinical practice. However, it is challenging to develop models of IDC-P and ductal adenocarcinoma because many laboratory models lack the elaborate architecture that characterizes these growth patterns in patient tissue.

There are three main types of patient-derived models of prostate cancer: primary PDXs, serially transplantable PDXs, and organoids, each with potential advantages and disadvantages for studying distinct pathologies (Table 2 and Fig. 3A). To date, only primary PDXs have been used to specifically study IDC-P or ductal adenocarcinoma. Primary PDXs are pieces of fresh patient tissue grown in immunodeficient mice for a limited number of generations (*118*). This makes them well suited to studying distinct pathologies because limited passaging helps maintain the complex architecture of the original tumor. Primary PDXs maintain the cribriform morphology and the surrounding basal cell layer of IDC-P (Fig. 3B) (*9*, *10*). Furthermore, in primary PDXs of high-risk prostate cancer, IDC-P occupies a similar volume to acinar adenocarcinoma, showing that it can comprise a substantial proportion of tumor burden (*10*). Similar to IDC-P, ductal adenocarcinoma can be grown in primary PDXs (Fig. 3C). Therefore, a major advantage of primary PDXs is that they maintain the growth patterns of patient tumors.

Another advantage of primary PDXs is the high take rate of patient samples that are grafted for a single generation (*118*, *119*), making them useful for growing rare pathological subtypes of cancer. However, primary PDXs are not renewable sources of tumor cells because they are not passaged indefinitely. Ideally, future studies

Table 2. Pros and cons of patient-derived models of prostate cancer.

Feature	Primary PDX	Serially transplantable PDX	Organoids
Take rate from patient tissue	High (~90%)	Low (<20%)	Low/unknown
Preserves IDC-P pathology	Yes	No	No
Preserves ductal adenocarcinoma pathology	Yes	Yes	Unknown
Enables paired comparisons to acinar adenocarcinoma	Yes	No	No
Contains different cell types	Yes	Yes	No
	•Human cancer epithelium, benign epithelium, and stroma	•Human cancer epithelium	•Only human cancer epithelial cells
	•Mouse stroma	•Mouse stroma	
Ongoing source of cancer cells	No	Yes	Yes/unknown
End points for preclinical testing		•Tumor size and weight	•Growth rate of organoid culture
	•Histopathology of tumor cells within grafts	•Histopathology	•Histopathology
	•Proliferation and apoptosis	•Proliferation and apoptosis	•Proliferation and apoptosis

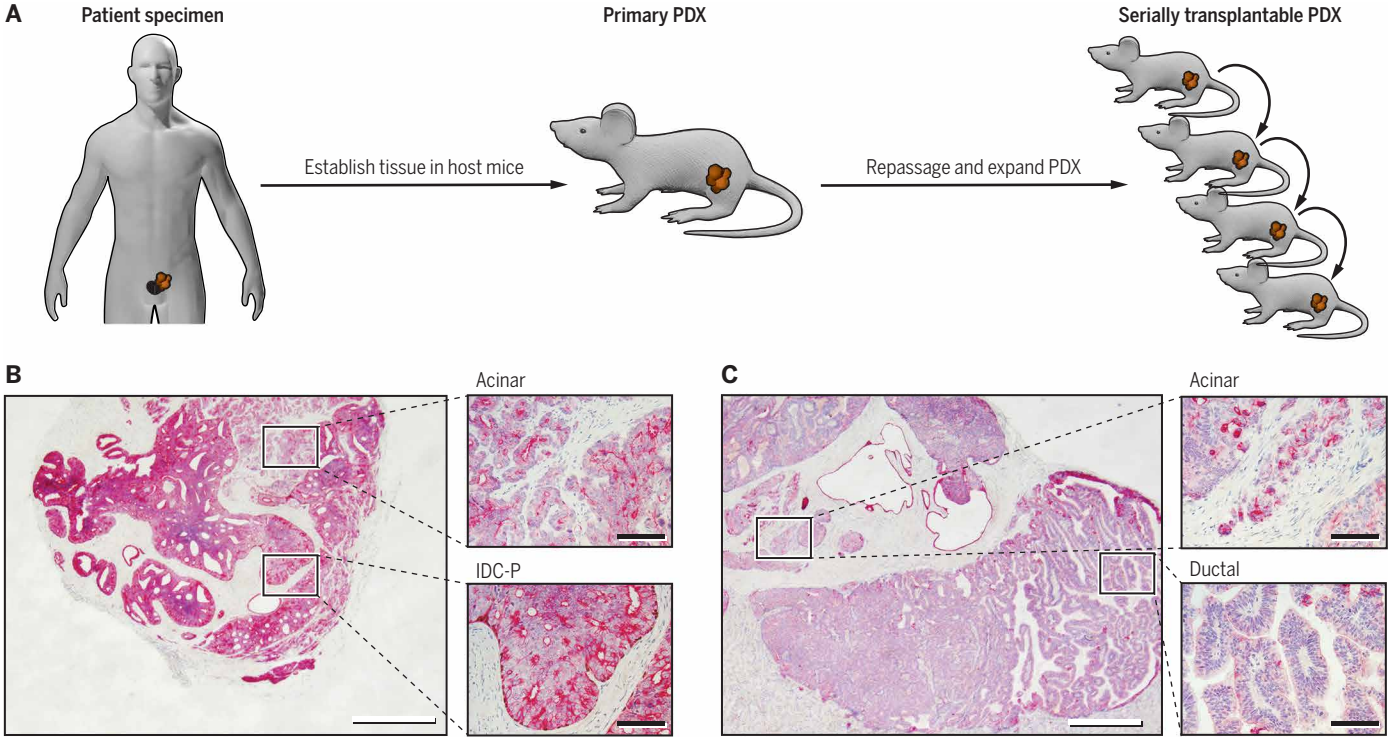

Fig. 3. Patient-derived models of IDC-P and ductal adenocarcinoma. (**A**) A summary of the process of establishing patient-derived xenografts (PDXs) of prostate cancer. Primary PDXs are grown for one generation before analysis, whereas serially transplantable PDXs are expanded by repassaging them into additional host mice. (**B**) Images of a representative primary PDX containing acinar adenocarcinoma (acinar) and IDC-P in the same section of tissue stained for the human-specific epithelial marker cytokeratin 8/18 (pink) and the basal cell marker p63 (brown). (**C**) Images of a representative primary PDX containing both acinar and ductal adenocarcinoma stained for cytokeratin 8/18 (pink). Scale bars, 500 μm (white) and 100 μm (black).

could use serially transplantable xenografts, which are continuously passaged between mice, or organoids, which are in vitro cultures of tumor cells grown in matrices such as Matrigel (Table 2). Both models produce ongoing sources of cells for multiple experiments and recapitulate some growth patterns due to their three-dimensional architecture. However, there are certain disadvantages to these models. Some architectural features, such as basal cells in IDC-P, will be lost with continual passaging, so it is not possible to directly compare IDC-P or ductal adenocarcinoma to acinar adenocarcinoma within each patient tumor. Nevertheless, PDXs and organoids retain underlying genomic features, which is important given the clonal origins of IDC-P and ductal adenocarcinoma with acinar adenocarcinoma

(*6*, *8*), and these models can be used to study tumors that originally contained these pathologies.

A further downside of organoids and serially transplantable PDXs is their low take rate because prostate cancer is more difficult to grow than many common tumor types. Although there is a high take rate for prostate cancer samples grown for a single generation as primary PDXs, fewer samples can be successfully grown beyond this. Typically, fewer than 20% of advanced prostate cancer specimens grow long term as xenografts or organoids (*120*–*123*). The take rate is probably lower for samples of localized prostate cancer. This makes it challenging to establish new models from rare specimens. Nevertheless, it is possible that selecting tumors with IDC-P or ductal adenocarcinoma would improve these low take rates. Both pathologies are associated with clinicopathologic and genomic features of poor prognosis, and in other cancers, aggressive tumors are often more likely to yield successful patient-derived models (*124*). Although these models are under development, it is important to accurately report the pathology of existing xenografts and organoids and the tumors from which they were derived. Furthermore, different patient-derived models, including primary PDXs, will continue to provide complementary approaches for studying IDC-P and ductal adenocarcinoma.

USING PATIENT-DERIVED MODELS TO INVESTIGATE RESPONSES TO TREATMENT

Patient-derived models can be used to test how tumors respond to treatments. This is relevant, given the speculation that IDC-P and ductal adenocarcinoma may be less sensitive to certain therapies, including androgen deprivation therapy (ADT). For IDC-P, this idea arose from retrospective pathology studies that showed it was more prevalent in localized tumors after ADT (*30*, *45*). The idea that ductal adenocarcinoma might also be resistant to ADT came from initial speculation that it had a female origin. This was based on its resemblance to endometrial carcinoma and purported development from the prostatic utricle, a small pouch in the urethra once thought to arise from Müllerian duct tissues (*5*, *125*).

To determine the sensitivity of IDC-P to ADT, we used primary PDXs of high-risk prostate cancer. Host mice were supplemented with testosterone to mimic androgen concentrations in men and then castrated to simulate ADT (*10*). Because IDC-P and acinar adenocarcinoma coexist in the primary PDXs, we could directly compare their responses to treatment. Contrary to speculation, IDC-P had the same sensitivity to ADT as adjacent acinar adenocarcinoma, with a substantial decrease in tumor burden after treatment (*10*). Furthermore, IDC-P and acinar adenocarcinoma both contained a rare subset of cells that withstood ADT and repopulated the tumor when androgen concentrations were restored. These so-called castrate-tolerant cells are notable because they may be a nidus for the development of CRPC (*126*). Primary PDXs were central to these observations because they enabled different pathologies within individual tumors to be studied across time and after treatment. This avoided sampling errors that might arise when patient tumors are rebiopsied in the clinic and demonstrates how preclinical experiments can complement clinical studies.

The response of ductal adenocarcinoma to ADT has not yet been studied in PDXs, but it is likely to be sensitive to treatment. The Müllerian origin of ductal adenocarcinoma has been disproved, and case reports show that patients with ductal adenocarcinoma respond to AR-directed therapies (*97*, *125*, *127*–*129*). However, responses may vary between patients because ductal adenocarcinoma was more common in a retrospective study of tumors with poor responses to neoadjuvant ADT (*130*). This might reflect the association between ductal adenocarcinoma and aggressive prostate cancer, rather than innate resistance to ADT. Indeed, there is no difference between ductal and acinar adenocarcinoma in AR staining or the enrichment of an AR-regulated signature (*8*, *114*). Indeed, Whether ductal adenocarcinoma also contains castrate-tolerant cells, as exist in IDC-P and acinar adenocarcinoma, is unknown but could be determined in future PDX studies.

Patient-derived models will also be useful for investigating potential treatments highlighted by recent genomic studies. For example, IDC-P and ductal adenocarcinoma have frequent alterations in actionable pathways, such as the PI3K pathway. In addition, the prevalence of genomic defects in the DNA repair pathway warrants preclinical testing of poly(adenosine diphosphate–ribose) polymerase inhibitors, platinum-based chemotherapies, and other agents with potential activity in such tumors (*131*). These therapies are currently used, or in trials, for advanced prostate cancer; however, PDX studies might show that they are effective as upfront treatments for some patients with IDC-P or ductal adenocarcinoma. Similarly, some cases of ductal adenocarcinoma have alterations in mismatch repair genes, indicating potential sensitivity to immune checkpoint inhibitors (*115*). It is difficult to test immunotherapies with PDXs because the host mice are immunocompromised, but organoid models that retain immune cells can be used instead (*132*). By providing a way to assess the dependence of tumors on these pathways, patient-derived models can confirm the insights from genomic analyses and identify potential therapeutic targets for further clinical validation.

EXAMINING PROSTATE PATHOLOGY IN GENETICALLY ENGINEERED MOUSE MODELS

Although patient-derived models are useful for comparing the pathology, genomics, and therapeutic responses of different tumors, they provide limited insight into cancer initiation because they are usually established from existing tumors. In contrast, genetically engineered mouse models (GEMMs) can reveal underlying mechanisms for tumorigenesis in a well-defined, autochthonous, and immunocompetent setting (*133*, *134*). GEMMs can be used to study the cell of origin, the functions of individual or multiple driver genes, and whether premalignant lesions further progress to invasive or metastatic disease (*134*). Moreover, some studies have noted that certain GEMMs develop lesions that are reminiscent of cribriform or IDC-P pathology in patients (*77*, *135*–*137*).

Investigating the development of specific tumor pathologies in GEMMs comes with the caveat that there are notable differences between the human and mouse prostates (*138*). In humans, the prostate is a single organ. Three zones with different histology and disease susceptibility (peripheral, central, and transition zones) and anterior fibromuscular stroma are surrounded by a stromal capsule that abuts adjacent tissues (*139*). In mice, the prostate comprises four pairs of separate lobes (anterior, dorsal, lateral, and ventral) that contain stroma but are not collectively embedded together within it (*140*). In addition to these anatomical differences, the human prostate is much more prone to prostate cancer, frequently developing tumors with age, whereas wild-type mice rarely develop spontaneous prostate tumors (*141*). Nevertheless, there are also similarities between the human and mouse prostates. Both species have a bilayered prostatic epithelium of basal and luminal cells (*138*). Gene expression signatures

and regulatory networks of transcription factors are also conserved across species (*142*, *143*), making GEMMs particularly useful for studying the cellular and molecular features of tumor development and progression.

The pathology of prostate malignancies is similar, but not identical, in humans and mice. Consensus committees have classified prostate pathologies in mice, echoing the consensus panels that propose guidelines for human prostate cancer (*138*, *144*). In GEMMs, premalignant lesions arise as proliferations of neoplastic cells within preexisting glands. These lesions are defined as mouse PIN, given their resemblance to human PIN (*138*, *144*). Mouse PIN includes a spectrum of lesions where foci of atypical cells progressively fill a greater proportion of glands in tufting, solid, cribriform, or papillary patterns (*145*, *146*). Eventually, mouse PIN can completely fill the lumen, expand or distort glands, and extend to adjacent ducts (*145*, *146*). Central necrosis may also be present. In some GEMMs, mouse PIN progresses to microinvasive lesions that breach the basement membrane and then to invasive carcinoma that disseminates into surrounding stroma (*134*, *138*, *144*).

Several studies have noted parallels between the lesions that arise in GEMMs and human cribriform or IDC-P pathology. For example, prostate-targeted *Pten* loss produces lesions likened to cribriform adenocarcinoma or IDC-P (*77*, *135*, *136*). Combining heterozygous *Pten* loss with an *Spop* mutation also produces foci with cribriform patterns (*77*). In Lo-MYC and Hi-MYC mice, which overexpress different amounts of human MYC (MYC proto-oncogene, bHLH transcription factor), cribriform pathology develops as an intermediate step between mouse PIN and microinvasive disease (*147*). Furthermore, in tissue recombination experiments, concurrent knockdown of *Chd1* (chromodomain helicase DNA binding protein 1) and *Map3k7* in mouse epithelium produces clusters of cells that grow within the lumen, akin to IDC-P (*137*). Prominent intraductal lesions also develop in GEMMs with *Apc* deletion, overexpression of human AR, or RB inactivation combined with *Pten* and *p53* deletion (*144*). Although mouse PIN can also have papillary morphology, its resemblance to ductal adenocarcinoma has not been explored.

The analogy between mouse and human prostate pathology has limitations. The solid cribriform foci in mice are usually preinvasive lesions, defined as mouse PIN, because they do not fully infiltrate surrounding stroma (*138*). In contrast, the solid cribriform pattern in humans represents either invasive cancer cells growing within the stroma, as Gleason pattern 4 acinar adenocarcinoma, or cancer cells spreading into preexisting ducts and acini, as IDC-P (*16*). Although human PIN can also form a cribriform pattern, it has loose morphology, and the cells lack prominent nuclear changes (*62*). Given this uncertainty about the link between mouse pathologies and human IDC-P, the consensus panel for mouse pathology recommends the term "intracystic carcinoma" rather than IDC-P for intraductal masses of atypical cells that expand existing structures without obvious invasive growth (*144*). It is possible that these dense, cribriform, gland-filling lesions in mice are more closely related to isolated or precursor IDC-P in humans. Similar to the cribriform foci in mice, isolated IDC-P may arise through neoplastic progression within ducts, rather than invasive cancer spreading back into ducts (*46*, *72*). Further studies into the parallels between these mouse and human pathologies may determine whether they undergo similar steps of tumorigenesis and have common trajectories of tumor progression.

Overall, the comparisons between mouse and human prostate pathology require careful interpretation. Human models of IDC-P and ductal adenocarcinoma are still emerging, and mouse models present further challenges because it is difficult to confirm a direct relationship between these pathologies across species. Nevertheless, GEMMs can provide important insights into the features of tumors with cribriform cancer, IDC-P, or ductal adenocarcinoma. GEMMs will be particularly useful for investigating the functions of specific driver genes that are frequently altered in these human pathologies. Modifying these driver genes, alone or in different combinations, will help resolve their roles in cancer initiation and in disease progression (*134*). Furthermore, GEMMs could be used to compare the effectiveness of new therapies across tumors with different genomic defects and in an immunocompetent setting. Therefore, as long as the pathology of GEMMs is interpreted judiciously, they can be used to complement and extend the studies of IDC-P and ductal adenocarcinoma with genomics and patient-derived models.

COMMON FEATURES OF IDC-P AND DUCTAL ADENOCARCINOMA

IDC-P and ductal adenocarcinoma are distinct pathologies but share some features (Table 1). Both pathologies usually coexist with acinar adenocarcinoma, and when they do, they typically arise from a common cell of origin. Both pathologies are also associated with genomic instability, *PTEN* loss, and defects in DNA damage repair pathways. Consistent with these genomic features, IDC-P and ductal adenocarcinoma often accompany other markers of poor prognosis. Most notably, both pathologies are associated with worse patient outcomes. Thus, IDC-P and ductal adenocarcinoma, as well as their accompanying molecular and clinical features, may help explain the heterogeneous outcomes of patients with prostate cancer, even within risk categories defined by current diagnostic parameters.

The combination of IDC-P or ductal adenocarcinoma with other markers of poor prognosis can also denote a greater risk of poor outcome. For example, IDC-P increases the risk of poor outcome when it coexists with high-grade acinar adenocarcinoma, germline *BRCA2* mutations, *SChLAP1* expression, or hypoxia (*7*, *9*, *76*). This led to the concept of prostate cancer "nimbosus," the Latin term for the gathering of storm clouds, where unfavorable pathologic and molecular features converge (*7*). Again, this demonstrates the importance of unifying different insights from pathology and genomics to improve risk stratification.

Despite their distinct pathology, no genomic, transcriptomic, or biological features have yet been identified that are unique to IDC-P or ductal adenocarcinoma. Instead, IDC-P and ductal adenocarcinoma often coincide with markers of poor prognosis that can also occur in tumors without these pathologies. For example, IDC-P is common in patients with pathogenic *BRCA2* mutations, but *BRCA2* mutations are not exclusive to tumors containing IDC-P. This enrichment of poor prognostic markers in tumors with IDC-P and ductal adenocarcinoma is consistent with their association with poor patient outcome and clonal relationship to acinar adenocarcinoma. It also suggests that tumors with aggressive phenotypes are more likely to acquire the ability to form IDC-P and ductal adenocarcinoma. Although future research may identify new features that are unique to IDC-P or ductal adenocarcinoma, current data suggest that these pathologies are manifestations of underlying tumor plasticity.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Despite the growing understanding of IDC-P and ductal adenocarcinoma, there are still limitations that provide opportunities for

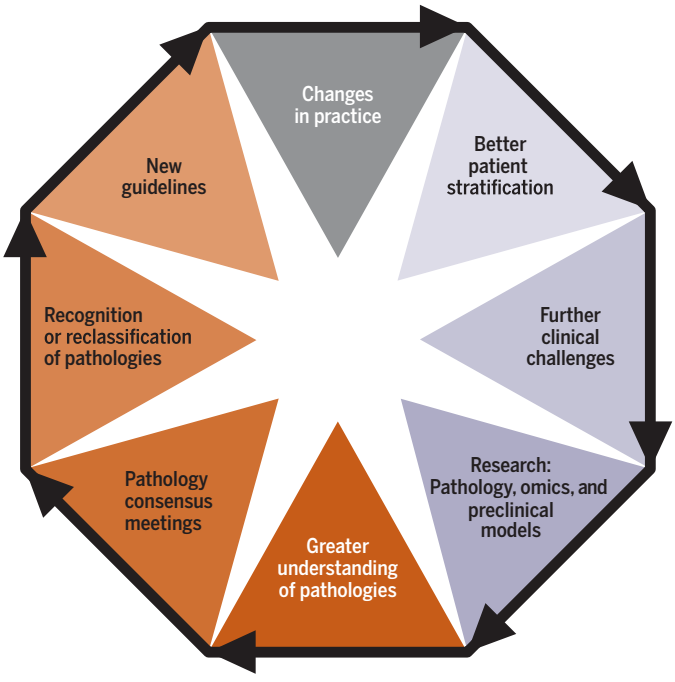

Fig. 4. The cycle of researching, recognizing, and reporting specific pathologies. In a continuous cycle, research leads to a greater understanding of tumor pathologies, new guidelines for reporting, and improved patient stratification. Remaining clinical challenges then foster further research.

further studies. Many genomic analyses and biological studies are from relatively small cohorts, explaining discrepancies in the frequency of some genomic alterations between studies. Furthermore, because of a lack of staining for basal cell markers, IDC-P is often incorporated with cribriform architecture in acinar adenocarcinoma. In some studies, IDC-P or ductal adenocarcinoma was separately microdissected from acinar adenocarcinoma, but this would be laborious to do for larger cohorts. Many of these challenges could be addressed by increased recognition and reporting of IDC-P and ductal adenocarcinoma. Retrospective pathology review of existing patient cohorts and patient-derived models would likely provide renewed interpretations of existing data. Similarly, the inclusion of IDC-P and ductal adenocarcinoma as standard data points in pathology reports and prospective prostate cancer registries would help track the clinical characteristics and outcomes of patients in real-world community settings (*49*, *148*). These datasets may guide treatment recommendations and refinements in future guidelines for reporting these pathologies. New cohorts of well-annotated patient samples should also provide greater power for genomic analyses and more specimens for preclinical models. These patient-derived models would also provide opportunities to study different combinations of pathologic and molecular features. In particular, they would help assess the sensitivity of tumors to treatments and determine whether the responses of IDC-P, ductal adenocarcinoma, and acinar adenocarcinoma are always the same.

IMPLICATIONS AND PERSPECTIVES

This review focused on IDC-P and ductal adenocarcinoma to highlight the importance of recognizing, reporting, and researching other pathologies beyond acinar adenocarcinoma. The same principles apply to other forms of prostate cancer that are less common and, therefore, often less well known and understood. For example, just as the World Health Organization classification of tumors recognized IDC-P as a new entity of prostate cancer in 2016, it also designated microcystic adenocarcinoma and pleomorphic giant cell adenocarcinoma as new variants of acinar adenocarcinoma (*18*). Furthermore, the International Society of Urological Pathology's consensus conferences that devised approaches for reporting IDC-P and ductal adenocarcinoma also recommended and revised procedures for scoring several other variants of adenocarcinoma. This included foamy gland and mucinous carcinoma, which are graded on the basis of their underlying growth patterns (*15*, *16*). In addition to epithelial tumors, the World Health Organization and International Society of Urological Pathology recognize neuroendocrine prostate carcinomas, which are not assigned Gleason patterns but are important to accurately diagnose, because they have very poor outcomes (*15*, *18*, *149*). Yet, with the exception of small cell neuroendocrine carcinoma, little is known about the transcriptomic or genomic features of these rarer forms of prostate cancer, and there is a paucity of human and mouse models to study them.

Beyond prostate cancer, specific pathologies of other types of cancer are also occasionally recognized or reclassified. For example, the 2016 World Health Organization classification of tumors also recognized new forms of renal cancer and urothelial lesions (*18*, *150*). It also instituted new classification systems for penile squamous cell carcinomas, based on human papillomavirus status, and testicular tumors, based on whether they are derived from germ cell neoplasia in situ (*150*).

Overall, there are common themes in the ways that particular pathologies of prostate cancer and other malignancies are recognized and classified. There is a continuous, iterative cycle of research and reporting aimed at progressively improving the precision of patient stratification (Fig. 4). As the most common form of prostate cancer, acinar adenocarcinoma is a prominent example of this cycle. The current guidelines for scoring acinar adenocarcinoma are based on multiple rounds of revision since the original studies by Gleason and co-workers (*12*, *13*, *15*, *16*). Gleason patterns have also become an obligatory aspect of prostate cancer research, from studies with next-generation sequencing to the characterization of preclinical models. In turn, this has informed the importance of specific growth patterns, such as cribriform glands (*7*, *75*, *77*). The cycle of research and reporting should be replicated for IDC-P, ductal adenocarcinoma, and other pathologies to maximize the accuracy of patient stratification. For this to occur, scientists and clinicians must be aware of these pathologies and incorporate them into research and practice. This will then improve the understanding of the biological and clinical features of less common pathologies and inform how pathology guidelines can be further refined.

CONCLUSION

In conclusion, it is essential to know what is growing in patient tumors. Pathologies such as IDC-P and ductal adenocarcinoma provide another layer of information about tumors, extending insights from clinicopathologic, genomic, transcriptional, and biological features. Because these features are interrelated, the whole profile provides greater distinction between tumors than any individual feature. This matters in clinical practice, where IDC-P and ductal adenocarcinoma are markers of poor prognosis that may improve patient risk

stratification and inform treatment decisions. It also matters in research, where recognizing IDC-P and ductal adenocarcinoma will help scientists unravel the multifactorial basis of high-risk prostate cancer.

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Knowing what's growing: Why ductal and intraductal prostate cancer matter

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