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Precision Molecular Pathology of Prostate Cancer

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Part I
General Principles

Chapter 1
Precision Medicine in Prostate Cancer: Approach to the Patient

Beerinder S. Karir, Bishoy M. Faltas, and Scott T. Tagawa

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Introduction

The advent of genomic discoveries and decreasing cost of next-generation sequencing (NGS) technologies has ushered in a new era of precision medicine [1]. The early effects of this paradigm shift in oncology are beginning to impact patient care and thus increase the relevance of a discussion on the approach to patients with

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Table 1.1 Summary: approach to patient

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May be a deterrent for some patients to get genomic sequencing done
Future directions
Annotating genomic with clinical data
PC biomarkers
Realistic expectations

prostate cancer (PC). Bringing the application of precision medicine to the clinic raises new challenges related to informed consent prior to testing, effectively communicating the results of cancer genomic testing to the patient, understanding and managing the patient's expectations, and working with the patient to select the best treatment options based on genomic tests (or not) [2, 3]. This introductory chapter will cover the approach to men with PC undergoing genomic testing of their tumors (see Table 1.1 for summary).

Precision Medicine in Prostate Cancer

Prostate cancer (PC) is the most common non-skin cancer and the second leading cause of cancer death in men in the United States [4]. This disease is on the forefront of precision medicine with multiple opportunities for benefiting from translational genomics [5]. While any given man might benefit from individualized tumor testing, two very important clinical subsets within PC that might benefit most from additional molecular analysis are patients with clinically localized "indolent" disease that are probably best served without treatment and those with more aggressive, particularly advanced disease with no curative therapy.

Newly Diagnosed Prostate Cancer

Every year more than 1,000,000 men in the United States undergo prostatic biopsies based on elevated levels of prostate-specific antigen (PSA). Among the newly diagnosed PC patients, many patients have clinically diagnosed (presumed) low-volume and low- to intermediate-risk Gleason scores (3 + 3 or 3 + 4 in a small percent of cores). This subset of PC patients presents a clinical dilemma for patients and their treating physicians. Various non-genomic biomarkers like Prostate Health Index (PHI) have been shown to better identify patients with aggressive disease, but there is still an unmet need for better biomarkers [6]. Genomic biomarkers including gene panels like the Decipher genomic classifier and Oncotype DX have demonstrated the ability to better stratify PC patients [7]. After various positive validating studies, Oncotype DX has recently been included under Medicare coverage thereby making such PC genomic-based diagnostics reimbursable [8]. In addition to gene panels, various other genomic biomarkers like urine TMPRSS2-ERG fusion transcripts and long noncoding RNAs(lncRNAs) may show promise in identifying PC patients who may need aggressive treatments [9, 10].

Advanced Prostate Cancer

On the opposite end of the spectrum, advanced PC represents another disease state that could benefit from precision medicine approaches. Prostate tumors may remain responsive to androgen deprivation therapy for years (variable among patients) until it evolves into the castration-resistant state (CRPC), which generally is still driven by the AR pathway. The median overall survival after diagnosis of CRPC is 18–32 months. Although newer-generation hormonal, cytotoxic, immunotherapeutic, and bone-targeted drugs have increased survival in CRPC patients leading to their FDA approval, the development of resistant PC disease remains inevitable. Using a combination of improved biopsy techniques and NGS technologies, molecular characterization of such advanced prostate tumors is increasingly being done. Recently, one such multi-institutional study found that 90% of advanced PC tumor harbor molecular alteration with potential targeting agent/drugs [11]. Another study that included mostly prostate cancer patients also demonstrated targetable alterations with an in-depth analysis of an “exceptional responder” based upon this mutation [12]. This highlights the importance of precision medicine for subclassification of prostate disease into molecularly defined subgroups with each subtype amenable to different targeted therapies [13].

Initial Clinical Encounter

The initial patient visit to a physician’s office generally includes comprehensive elicitation of disease history including diagnosis and initial treatments. Successful integration of precision medicine into oncology clinic will further emphasize

clinical data recording and sharing. Without accurate linkage of genomic data to clinical data, even the latest genomic technologies will have a limited impact on patient outcomes [14].

Family History in Prostate Disease

Within PC patients' histories, ethnicity is relevant as PC may sometimes harbor genetic determinants. Various single nucleotide polymorphism (SNPs) and copy number variants (CNVs) have been shown to be determinants of familial risk of prostate cancer [15]. Additionally, it is being increasingly realized that germline alterations like BRCA2, ATM, and BRCA1 mutations also play an important role in PC pathogenesis [11, 16]. So, any family history of such gene abnormalities can warrant increased level of diagnostic and therapeutic interventions.

Informed Consent

Precision medicine informed consents are important part of this new paradigm. Informed consents must delineate all the details including risks and also elaborate upon likelihood of finding somatic molecular alterations of unknown significance as well as incidental germline mutations. Pretest counseling should focus on addressing the key components of informed consent.

Patient Preferences and Data Privacy

One of the most important parts of the consent is the preferences of patients and families regarding level of detail and the scope of genetic information resulting from molecular testing, especially regarding incidental findings. This issue is discussed in detail in a separate section. Risks due to testing procedures (i.e., biopsy procedures) as well as data privacy should also be clearly detailed. Patients should also be made aware of existing legal protection against discrimination and the provisions of the Genetic Information Nondiscrimination Act (GINA). GINA protects US citizens from discrimination and restricts insurers from limiting coverage/altering premiums based on such genetic information. It prevents insurers from requiring policyholders to undergo genetic testing but could make testing a requirement for treatment [17].

Actionability of Precision Medicine Results

Due to enormous media attention generated by the precision medicine initiative started by President Obama [18], patients have high expectations from genomic profiling and its implications especially in terms of cancer cure [19]. These

expectations, especially as they relate to the "actionability" of results, should be addressed up front within the framework of the consent process. The possibilities of nonactionable genomic results, biopsy failure (poor tissue quality/tumor content), analytical validity issues, and turnaround time should be discussed with the patient during this process [20]. Realistic expectations set through early patient education lead to better patient compliance and satisfaction. When managed appropriately, the potential for personal benefit from targeted therapy raises hopes and drives enhanced participation of patients in clinical trials [3].

It is important to understand that the definition of "actionable" molecular alterations is dependent on several molecular, patient-specific, and practical factors. A recent survey of practicing oncologists who had just received their patients' cancer genome sequencing reports showed that 78% did not expect to implement any changes to the current treatment plan [21]. In this study, barriers to "actionability" included lack of local clinical trials (41%), absence of actionable mutation (33%), and good response to ongoing treatment (16%). In light of these findings, physicians need to explain to patients all the factors that could limit actionability of precision medicine test results.

Turnaround Time

Patient's expectations about the turnaround time for genomic profile results also need to be recalibrated. Presently, waiting time ranging from weeks to months is needed starting with acquisition of tumor sample plus germline sample to generation of a precision medicine report. This is acceptable to stable patients and their treating physicians, but for patients with progressive advanced cancer, such long waiting time may not be clinically useful. Though the latest NGS methodologies have significantly shortened turnaround times, bottlenecks in the process still remain. These include sample acquisition and logistics and data analysis and interpretation [20].

Tissue for Genomic Profiling and Need for Serial Biopsies

Successful application of precision medicine requires availability of tissue of origin and/or metastatic site [22]. In many cases with a distant history of prostatectomy, tissue acquisition is not feasible thus leaving only the option of metastatic site biopsy. As most common site for PC metastasis is the bone which is a difficult organ to biopsy, metastatic site biopsies in PC have been very daunting process until lately. However, advancements in biopsy technology have increased the chances of successful tissue procurement from a PC patient [11, 23].

Over time, the true success of precision medicine may hinge on our ability to get serial biopsies to see real-time genomic evolution of the prostate disease. Liquid biopsy technologies such as circulating tumor cells (CTCs) or cell-free DNA (cfDNA) are a good surrogate for tissue biopsies [24]. Though true utility of liquid

biopsies needs further validation [25], application of liquid biopsies seems immense extending to CTC-derived xenografts [26]. Another useful application of CTCs for prostate cancer patients may be in generation of patient-derived organoid cultures. Such cultures have shown to recapitulate the entire molecular diversity of prostate disease and hold promise for use in genetic and pharmacologic studies [27].

Understanding "Precision Medicine Reports"

All procedures for precision medicine outside of a research setting should be performed in CLIA-certified labs. After running the tissue sample through sequencing pipelines, genomic data is streamed through analytical/bioinformatic pipeline. The entire process needs to be standardized throughout for validity. Eventually a precision medicine report on patient's tumor-specific somatic alterations is generated and usually contains the following elements:

- Somatic alterations in clinically relevant genes—these alterations occur in genes that are potentially actionable as drug targets or confer resistance or susceptibility to treatment.
- Somatic alterations of unknown significance in known cancer genes—these alterations occur in genes that are cancer associated, but their impact on the disease is not fully understood.
- Somatic alterations of unknown significance—these alterations are not known to have any effect on the disease but are profiled in the event that, in future, progress in scientific knowledge could determine their role.

In addition to these, details on quality control metrics like depth and coverage of sequencing are often provided [12].

Communicating Genomic Information to Clinicians and Patients

A recent study done at Duke Medical Centre has found a number of challenges faced by institution when implementing genomic testing into patient care [28]. This necessitates a policy and education program to improve clinician support, enabling them to effectively deliver precision medicine care. One such problem is that precision medicine reports may or may not yield actionable somatic alterations in cancer-related genes. If such molecular alterations are found, these can either be targeted by FDA-approved drug for PC or other cancer types (i.e., "off-label" use), or there may be approved or investigational drug available as a clinical trial. Such drugs/trials are often enlisted in precision medicine reports made available to treating physician. But procuring the drugs targeting actionable genomic alteration can be a big hurdle. This can be especially problematic if PC is an off-label use of the drug [29].

For effectively communicating genomic results to patients, the treating physician needs to ensure proper patient education (starting with pretest counseling) and decision support systems are in place. This may require strong collaboration among genetic counselors, physicians, and nurses. Realistic expectations set during informed consent education can be especially helpful if sequencing results yield no obvious actionable alterations. In the case of incidental germline finding, the role of genetic counselors is very important to facilitate family communication [30] (see next section). To conclude, the proper utilization of cancer genomic medicine needs to be accompanied by careful thought about how the genetic test results will be communicated to patients in order to maximize their benefit.

Unique Issues Related to Incidental Discovery of Germline Mutations

Genome sequencing provides unprecedented opportunities to study the genomic landscapes and identify the actionable driver mutations for targeted therapy in precision medicine clinics. Because some NGS approaches rely on comparison between germline and somatic variants, germline alterations may be incidentally discovered. These alterations may be associated with inherited health risk or familial susceptibility to cancer. In the setting of cancer, some patients may find it burdensome to bear the knowledge of such inherited health risk in family [31]. This may have psychological consequences associated with the guilt of passing the inherited risk or increased cost of health care. This knowledge is perceived as an obligation to family and is difficult to refuse. Providing patients with simple summaries to share with their families and making local genetic counseling resources available at point of contact for the family can be helpful during the process [32]. Implications of reporting such incidental discoveries of germline mutations are very complex. Discussing these issues during the informed consent for sequencing highly penetrant disease genes and genetic counseling is essential to address the challenges faced in this situation [33]. Overall, the likelihood of finding incidental genetic variants does not appear to significantly discourage patients from adopting genomic profiling though the extent of incidental findings patients wish to be disclosed varies significantly [34].

Future Direction

Successful application of precision medicine approaches in the routine clinical care of patients requires not only a wider availability of next-generation sequencing technologies but also resourceful databases possessing consolidated clinical information [14]. As we proceed ahead, the missing metrics of clinical data will need to be “filled in” and clinical information annotated with genomic data. Another issue

will be to improve our ability to complete the entire process of genomic sequencing, generating reports, and matching/administering drugs targeting driver alterations within a rapid turnaround time. This may further require sophisticated rapid machine learning methods [35]. In addition to therapeutic benefits, the promise of precision medicine in prostate cancer will also lie in discovering and validating molecular biomarkers that distinguish aggressive from indolent disease and those that predict treatment resistance [36, 37]. Finally regarding our heightened expectations, we will need to be cautious in terms of seeking quick results through this new paradigm of precision medicine. As Amara's law correctly states "We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run." We may have outclassed Moore's law for NGS method cost efficacy, but regarding patient outcomes, it may take few years before we realize the full potential of precision medicine for prostate cancer patients.

Resources for Patients and Clinicians

- My Cancer Genome—http://www.mycancergenome.org/: This is a personalized cancer medicine knowledge resource for physicians, patients, caregivers, and researchers. It provides latest information on what mutations make cancers grow and related therapeutic implications, including available clinical trials.
- cBioPortal—http://www.cbioportal.org/: This portal maintained by Memorial Sloan Kettering Cancer Center stores genomic data from large-scale, integrated cancer genomic data sets. It allows explorative genomic data analysis
- COSMIC database—http://cancer.sanger.ac.uk/cosmic: COSMIC is a freely available online database of somatically acquired mutations found in human cancer. It is maintained by Sanger Institute, UK.
- National Cancer Institute Cancer Genetics Services Directory—http://www.cancer.gov/about-cancer/causes-prevention/genetics/directory: This NCI directory lists professionals who provide services related to cancer genetics (cancer risk assessment, genetic counseling, genetic susceptibility testing, and others).
- National Society of Genetic Counselors (NSGC)—http://nsgc.org/p/cm/ld/fid=164: For finding genetic counselors in a local area, United States.

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