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## INVITED PERSPECTIVE

Prostate Cancer

# Personalized prostate cancer care: from screening to treatment

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Unprecedented progress has been made in genomic personalized medicine in the last several years, allowing for more individualized healthcare assessments and recommendations than ever before. However, most of this progress in prostate cancer (PCa) care has focused on developing and selecting therapies for late-stage disease. To address this issue of limited focus, we propose a model for incorporating genomic-based personalized medicine into all levels of PCa care, from prevention and screening to diagnosis, and ultimately to the treatment of both early-stage and late-stage cancers. We have termed this strategy the “Pyramid Model” of personalized cancer care. In this perspective paper, our objective is to demonstrate the potential application of the Pyramid Model to PCa care. This proactive and comprehensive personalized cancer care approach has the potential to achieve three important medical goals: reducing mortality, improving quality of life and decreasing both individual and societal healthcare costs.

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### INTRODUCTION

The fundamental principle of personalized medicine is to offer healthcare tailored to an individual’s specific genetic composition and environment, rather than providing recommendations based on one-size-fits-all standards and population averages. Great progress has been made in genomic medicine in the last several years; although, most genomic-based personalized medicine efforts have focused on late-stage disease and genetic analysis of tumor tissue (somatic DNA).<sup>1</sup> While profiling of tumor DNA mutations is helpful in identifying the best-matched targeted therapy and in prolonging the lives of cancer patients, it is often too little, too late, and too costly. To address this issue of limited focus in personalized medicine, we propose a model for incorporating genomic-based personalized medicine into all levels of cancer care, from prevention and screening to diagnosis and ultimately to the treatment of early-stage and late-stage cancers. We have termed this strategy the “Pyramid Model” of personalized cancer care.

### PYRAMID MODEL OF PERSONALIZED CANCER CARE

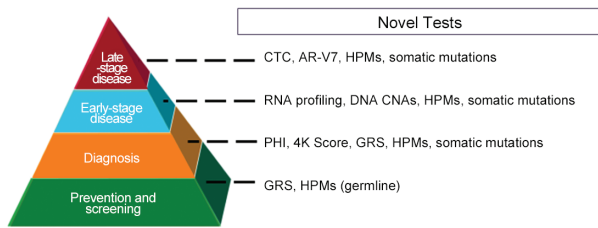
The Pyramid Model of cancer care describes a proactive approach that broadens the focus from personalized treatment to include screening, prevention, and diagnosis. As shown in **Figure 1**, the pyramidal organization follows the chronologic progress of disease development. The major principle on which the Pyramid Model is based is that personalized medicine should not be limited to treatment, and is likely to be far more effective if implemented earlier (e.g., for personalized prevention and screening).<sup>2</sup> With personalized screening plans, patients who develop cancer are more likely to be diagnosed at an earlier, more treatable stage.

The DNA profiling aspects of the Pyramid Model involve two main strategies: (1) the analysis of germline (inherited) DNA early in

adulthood targeting disease-specific, risk-associated single nucleotide polymorphisms (SNPs) and high penetrance mutations (HPMs) to guide targeted screening, prevention, and diagnostic strategies, and (2) the analysis of both germline and somatic (tumor) DNA in patients diagnosed with cancer to individualize and optimize therapy. In addition to DNA analyses, novel tests assessing RNA and tumor-specific biomarkers should also be incorporated into the Pyramid Model.

### APPLICATION OF THE PYRAMID MODEL TO PROSTATE CANCER (PCA)

The need for and feasibility of engaging this Pyramid Model of personalized cancer care can be best illustrated in prostate cancer (PCa) due to current clinical challenges and availability of genomic findings at each stage of PCa. Prostate-specific antigen (PSA) is an excellent serum-based biomarker for PCa and is used for screening for early-stage PCa. Since widespread PSA screening was introduced several decades ago, it has led to a significant decline in PCa mortality.<sup>3</sup> However, because risks of developing PCa are different among men in the general population, the one-size-fits-all screening approach currently used has led to “over-screening” among men at average or low risk.<sup>4</sup> In addition, because PSA is prostate-specific, but not PCa-specific, its use has also lead to “over-biopsy,” as most men who undergo biopsy due to elevated PSA levels are not diagnosed with PCa.<sup>5,6</sup> Furthermore, because moderately-elevated PSA levels do not accurately differentiate aggressive from indolent PCa, PSA screening also leads to “over-treatment,” in which cases the benefit of radical treatment among indolent PCa patients is offset by potentially adverse urinary, bowel, and sexual side effects.<sup>7,8</sup> The two largest randomized PCa



**Figure 1:** The pyramid model for prostate cancer care.

screening trials have demonstrated either no or only a moderate reduction in PCa mortality.<sup>9,10</sup> Concluding that the benefits of PSA screening in reducing mortality are outweighed by potential harms, the United States Preventive Services Task Force recommended against PSA screening for all men in 2011.<sup>11</sup> This drastic, nonpersonal approach has resulted in a decreased incidence of PCa in the US, a migration to a higher PCa stage at the time of diagnosis, and a delay in detection and treatment of potentially aggressive PCa that may ultimately result in increased PCa mortality.<sup>12,13</sup>

Alternatively, genomic-based personalized PCa care is likely a better approach to address the PSA-related “over-screening,” “over-biopsy,” and “over-treatment” of PCa. This approach is feasible because of the extensive genomic discoveries of PCa in the past decade. Many PCa risk-associated SNPs and HPMs have been discovered.<sup>14,15</sup> Together with family history, germline genetic tests of SNPs and HPMs can be used to identify men who are at elevated risk for PCa and aggressive PCa and for whom to recommend targeted PCa screening.<sup>16,17</sup> Many novel biomarkers that are more specific to PCa and aggressive PCa than PSA are available and could be used to reduce the number of unnecessary biopsies.<sup>18–21</sup> In addition, RNA and DNA markers in prostate tumors have been shown to better predict disease progression, and could be used to determine which patients should receive curative treatment at the time of diagnosis.<sup>22–26</sup> Finally, both germline and somatic alterations in several key cancer-related genes have been found to be useful for selecting more effective hormonal and chemotherapy treatments.<sup>27–31</sup> In the following sections, we will further discuss the rationale and feasibility of genomic-based personalized PCa care at each stage of PCa.

## SCREENING AND PREVENTION

The bottom tier of the Pyramid Model of PCa care, earliest in disease chronology, utilizes analyses of germline DNA and family history (FH) to develop individualized screening and prevention strategies. There have been over 100 risk-associated SNPs identified for PCa.<sup>14</sup> When weighted by individual allele frequencies and impact (measured by odds ratio), a single, disease-specific Genetic Risk Score (GRS) can be calculated.<sup>32</sup> The presence of risk-associated SNPs can be assessed for PCa (as well as for other cancers using different sets of risk-associated SNPs) from genomic DNA obtained from a single blood or saliva sample. The GRS has been validated for PCa in nearly 100 000 cases and controls of various racial and ethnic groups, and all studies have shown that individuals with a higher GRS for PCa are more likely to develop PCa.<sup>14,16,17,32–45</sup> Thus, the GRS can be used in combination with FH and race information (e.g., African American descent) to develop targeted PCa screening and prevention strategies. Men with a low GRS and negative FH might be recommended to undergo PSA screening later in life and less often or even forgo PSA testing, while men with a high GRS and positive FH might be advised to undergo PSA screening earlier and more often, in addition to modifying

environmental factors (e.g., diet, exercise, smoking) to reduce their risk of developing PCa.

Recent studies suggest that HPMs in DNA repair genes such as *BRCA2* and *ATM* were common (8%–10%) in patients with metastatic castration-resistance prostate cancer (mCRPC).<sup>15,46</sup> This finding is important because the frequency of these HPMs in indolent PCa cases and in the general population were considerably lower in previously published studies.<sup>47</sup> If the difference of HPMs in DNA repair genes between aggressive and indolent PCa is confirmed in larger studies using the same sequencing method, HPMs can be included with GRS and FH to further refine and improve individualized PCa risk assessment, especially for aggressive PCa.

## DIAGNOSIS AND BIOPSY

Until recently, the recommendation to undergo prostatic biopsy for diagnosis of PCa was based primarily on the level of serum PSA. However, the specificity and positive predictive value (~30%) of PSA in diagnosing PCa are rather poor among patients with modestly elevated PSA levels (4–10 ng ml<sup>-1</sup>), which includes the vast majority of patients considered for biopsy in developed countries.<sup>5</sup> Furthermore, modestly-elevated PSA levels perform poorly in differentiating aggressive from indolent PCa, thus resulting in over-biopsy and overdiagnosis of indolent PCa. Conversely, PSA-based diagnosis may fail to detect poorly differentiated and potentially lethal PCa in some patients.

Several novel biomarkers that are more specific to PCa and aggressive PCa, including the Prostate Health Index (*phi*),<sup>18</sup> PCA3,<sup>19</sup> TMPRSS2-ERG,<sup>20</sup> and 4K Score,<sup>21</sup> are now available. Unfortunately, despite the fact that several of these novel biomarkers have been approved by the US Food and Drug Administration (FDA) and incorporated into the National Comprehensive Cancer Network (NCCN) guidelines, they are currently rarely used in routine clinical practice. In the second tier of the Pyramid Model of PCa care, we propose that these new tests be incorporated widely into clinical practice for personalized decision-making regarding prostate biopsies. Only patients who, based on these noninvasive tests, are predicted to be at increased risk of developing aggressive PCa should be recommended to undergo biopsy while other patients can be followed conservatively with serial testing. This personalized cancer care strategy will lead to earlier diagnosis of aggressive PCa and reduce the harms and cost caused by over-biopsy and over-treatment.

## TREATMENT

### Early-stage PCa

Once diagnosed, it has been challenging to identify which men harbor potentially lethal PCa and should, therefore, undergo prompt radical treatment. Again, because PSA screening preferentially detects indolent PCa, most men with screen-detected PCa do not benefit from treatment and often undergo therapy that causes adverse side effects that negatively impacts the quality of life without increasing their longevity.<sup>11</sup> Although active surveillance (AS), close observation with delayed treatment when indicated, has gained popularity in recent years as an alternative to immediate therapy, because of understandable concern over silent disease progression and subsequent death from PCa, only a minority of men who are potential candidates for AS choose this treatment strategy.<sup>48</sup> There are now, however, several tests that can identify more aggressive and potentially lethal PCa, thereby guiding individual treatment decisions. These tests can be grouped into two categories: RNA-based tests (Oncotype DX Prostate Cancer, Prolaris, Decipher)<sup>21–23,25</sup> and DNA-based tests (for *PTEN* deletion and *MYC*

amplification).<sup>26,27</sup> Oncotype DX Prostate Cancer and Prolaris have been incorporated into NCCN guidelines. Nevertheless, the adoption of these novel genomic tests into clinical practice remains low at this stage.

Although additional clinical data are needed to further improve the predictive performance of these tests in identifying aggressive PCa, their clinical validity has been well established.<sup>25,26</sup> In the third tier of the Pyramid Model of PCa care, we propose that RNA and DNA-based tests be adopted clinically to supplement current standards of care to better predict prognosis of PCa based on tumor tissues from biopsy and surgery specimens. Patients with prostate tumors exhibiting RNA and DNA profiles that are associated with a poorer prognosis should be advised to receive aggressive treatment possibly including adjuvant therapy, while patients without these risk-associated alterations may consider AS.

#### Late-stage PCa

The top tier of the Pyramid Model of PCa care, last in disease chronology, utilizes analyses of genomic information in germline as well as tumors to develop individualized treatment strategies for the metastatic disease. Various genomic alterations in different biological pathways have been associated with the likelihood of progressing to metastatic disease. As a result, biologically rational treatment strategies that target these pathways have also been developed. For example, use of poly(ADP-ribose) polymerase (PARP) and DNA-protein kinase inhibitors directed at the DNA repair pathway,<sup>31</sup> and inhibition of the P13K-AKT-mTOR pathway in cancers associated with PTEN loss or inhibition represent some of these targeted strategies.<sup>49</sup> In addition, various genomic alterations that are associated with resistance to treatment have also been identified. For example, alterations of the androgen receptor (AR) gene in prostate tumors (AR-v7, AR amplification, and AR mutations) that result in resistance to AR-targeted treatment (abiraterone and enzalutamide) have been found.<sup>28,29,50–52</sup> While additional discovery research is needed to further understand the genetic basis of PCa development and resistance to treatment, available evidence justifies the exploration of its clinical implementation. Application of the Pyramid Model of PCa care at this last stage can improve the current practice of trial and error for selecting treatment strategies to better select more effective drugs more quickly.

#### IMPLEMENTATION CHALLENGES

Despite the feasibility and great promise that personalized PCa care offers, we face several potential barriers to the successful implementation of the Pyramid Model in clinical settings. These include physician education, uptake, and acceptance; patient education, acceptance, and willingness to act on genomic-based care recommendations; access to and education of genetic counselors; institutional support; funding; insurance reimbursement for genomic-based care; and CLIA-certified laboratory availability.

To address these barriers, we propose a four-step method for clinical implementation of the Pyramid Model. First, the clinical validity and potential utility of genomic findings must be established through evidence-based evaluation. In this step, it is important to focus on whether or not the test can improve the current standard of care; perfectly predicting each outcome should not be the primary concern. Second, robust, cost-effective genomic tests must be developed and made available in a CLIA-certified laboratory. Rapidly evolving genotyping and sequencing technology have made the efficient development of these DNA and RNA tests possible, and many more tests are expected to be developed and transferred to CLIA environments in the coming years. Third, the efficacy and feasibility of using these tests clinically must be demonstrated through pilot

clinical trials. Results from such trials will help to address current concerns and infrequent adoption of genomic tests among physicians and patients. Data from these trials will also provide critical data for cost-effectiveness analyses for uptake and support from insurance agencies. Finally, the National Human Genome Research Institute's Ethical, Legal and Social Implications (ELSI) program concerns and standards must be considered to ensure the ethical soundness of each test.

#### CONCLUSIONS

Although personalized medicine has usually focused on late-stage disease, its potential is far broader, encompassing the entire spectrum of cancer care. We refer to this approach as the Pyramid Model of personalized cancer care. PCa is well-suited for this approach; individualized risk assessment, prevention, and screening strategies can now be applied to all men, and personalized diagnostic and treatment strategies can be implemented when indicated. We believe that this proactive and comprehensive personalized cancer care approach will achieve three important medical goals: reducing mortality, improving quality of life and decreasing individual and societal healthcare costs.

#### AUTHOR CONTRIBUTIONS

CAC, CBB, and JX contributed equally to the drafting and revising of the manuscript. All authors have read and approved the final version of the manuscript and agree with the order and presentation of the authors.

#### COMPETING INTERESTS

None of the authors declare competing financial interests.

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