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Pharmacogenomics: Biomarker directed therapy for bladder cancer

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Abstract

The clinical management of bladder cancer has seen little change over the last three decades and there is pressing need to identify more effective treatments for advanced disease. Low clinical utilization of neoadjuvant therapies stems from historical limitations in the ability to predict those patients most likely to respond to combination chemotherapies. Trials with targeted agents in bladder cancer have seen mixed results-possibly due to the lack of enrollment criterion that include molecular and genetic screening and limited knowledge of biomarkers that are predictive of response. Several recent genome-wide characterization studies have demonstrated bladder cancers are a highly heterogeneous set of diseases, comprised of a wide range of genomic and molecular alterations. Novel classification schemes have described new molecular subtypes by which bladder cancers may be grouped and might better predict patient response to various therapies. These findings have provided information about the molecular underpinnings of bladder carcinogenesis and progression and shed light possible reasons why some clinical trials with targeted therapies have failed to see improved patient outcomes. This review will focus on several recent molecular and genetic studies, highlighting promising clinical trials and retrospective studies and discuss emerging trials that utilize predictive biomarkers to match patients with the therapies to which they are most likely to respond. In the coming years, the implementation of predictive genomic and molecular biomarkers will revolutionize the field of urologic oncology and the clinical management bladder cancer.

Keywords

Bladder Cancer; Pharmacogenomics; Personalized Medicine; Immunotherapy; Clinical Trials; Molecular Subtype; Predictive Biomarker; Precision Medicine

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I. Introduction and Aims

It is estimated that 74,000 people in the United States and roughly 386,000 people globally will be newly diagnosed with bladder cancer in 2015 ([1,2]). Bladder cancer represents a significant global health problem, not only due to its high frequency of occurrence, but also due to high rates of recurrence and the need for routine monitoring via transurethral cystoscopy, which result in significant economic impact ([3]). By far the most common type of bladder cancer is urothelial (transitional) cell carcinoma (UCC), which accounts for greater than 90% of all bladder cancer cases ([4]). The advent of genomic technologies has led to major advances in molecular testing in cancer medicine for many cancer types with demonstrated clinical benefit in many cases. However, bladder cancer has yet to significantly benefit from these new technologies and its clinical management has changed minimally in the last 30 years.

The aim of this review is to discuss predictive UCC biomarker discovery efforts, and the problems that have impeded their application towards clinical use, while speculating regarding possible future directions that may allow for improved treatment. We will emphasize key original articles (and some reviews) and current views, rather than being all-inclusive and thus apologize to authors whose work was not cited. This review will discuss the following topics: 1.) The clinical need for predictive biomarkers 2.) Emerging opportunities for personalized bladder cancer therapy 3.) Individual biomarkers of response 4.) New approaches to the classification of bladder cancer, 5.) Immunotherapy and 6.) Clinical trials utilizing molecularly guided therapy selection.

II. The Clinical Need and Promise of Predictive Biomarkers

Standard clinical management for non-muscle invasive (NMI) bladder cancers consists of transurethral resection of the bladder, with bacillus Calmette-Guerin (BCG) immunotherapy being utilized in cases with a high risk of progression. For muscle-invasive (MI) disease, the current standard of care is radical cystectomy along with lymphadenectomy or radiotherapy. Platinum-based chemotherapy is often recommended, as gemcitabine and cisplatin combination therapy has shown response rates of approximately 38% and 50% in the neoadjuvant and metastatic settings respectively ([5,6]). These responses are not durable, however, as the overall 5-year survival benefit associated with this neoadjuvant cisplatin-based therapy is a very modest 5% ([7]). In the adjuvant setting, this survival benefit may in fact be as high as 25%, when compared to patients receiving surgery alone, though these values have been subject to debate([8]). These survival benefits are viewed by many as modest and have led to low utilization of neoadjuvant treatments clinically ([9]). The ability to reliably predict response to platinum-based therapies and other therapies, would be incredibly beneficial and would likely result in a change of this current paradigm – increasing the number of patients that are most likely to respond to a given treatment while sparing the majority unnecessary toxicity.

Predictive biomarkers are molecular or other tumor characteristics that can predict the likelihood of an individual’s response to a given therapy. Several large-scale studies published within the last few years, have revealed that bladder cancer is a significantly

heterogeneous disease in terms of its genetic drivers, RNA expression profiles, and chemoresponsiveness ([10–12]). The utilization of genetic profiling has historically been limited to small gene panels and costly molecular diagnostics, however, with the increasing incorporation of next-generation sequencing and other high-throughput technologies in molecular diagnostic laboratories, physicians increasingly have the ability to obtain a more comprehensive understanding of the molecular alterations driving an individual patient's disease ([13,14]). These molecular characterization techniques have long been utilized in other cancers such as breast, lung, melanoma and others to guide therapeutic selection, however, when targeted agents have been trialed in bladder cancer the results have been mixed.

This has resulted in few FDA approved targeted agents for bladder cancer treatment ([15]). Part of the issue with the utilization of targeted or personalized approaches to bladder cancer treatment is due to the fact that few clinical trials have enrolled patients based on genomic or RNA expression based biomarkers. A recent review found that of 96 drugbased clinical trials for urothelial carcinoma from January 2012 to January 2015 only 37 (39%) included targeted agents, and of these only 11 (12%), sought to enroll patients based on the appropriate matched molecular or genomic biomarkers ([16]). These results highlight the need for increased utilization of predictive biomarkers in the design of future clinical trials in bladder cancer.

In the following sections we will discuss recent studies that have revealed that the majority of bladder cancers harbor potentially actionable mutations that are likely to respond to existing targeted therapies and molecular profiles that can not only predict untreated patient outcome (prognostic), but also an individual's responsiveness to specific therapy.

III. Emerging opportunities for personalized therapeutic regimens

In recent years, several large-scale studies have dramatically expanded on our understanding of the molecular and biochemical underpinnings of bladder cancer. The Cancer Genome Atlas (TCGA) project performed integrative analyses on 131 bladder cancer specimens including whole-exome and whole-genome sequencing, mRNA-and miRNA sequencing, as well as total and phosphorylated protein expression studies[10]. This study, in combination with several others ([11,12]) has provided a more comprehensive picture of the complex molecular landscape underlying bladder cancer development and progression. Perhaps the most important and exciting clinical implication of the TCGA data, is that it is rapidly being used to redefine how we classify bladder cancers.([17–20]) These new classifications hold tremendous promise to revolutionize the way bladder cancers are treated and how to better predict which patients will respond to various therapeutic options. Newly identified biomarkers will be integral in providing clinicians with the information needed to significantly expand their therapeutic armamentarium for the first time in over 30 years. TCGA identified potentially actionable alterations in 69% of tumors analyzed. Of these, alterations in the PI3K-Akt-mTOR pathway were seen in 42% of cases and 45% of cases had an alteration in RTK-MAPK pathways[10].

The complex and heterogeneous array of alterations underlying bladder cancer makes it all the more critical that we utilize molecular screening techniques in bladder cancer

diagnostics. There are already a number of promising examples of the clinical utility of genomic biomarkers in the treatment of bladder cancer patients. A discussion of genomic biomarker-based clinical trials and promising retrospective studies are discussed below.

IV. Individual biomarkers of response

DNA Repair Pathway Alterations – ERCC1 and ERCC2

As described above, platinum-based therapies are the current mainstay of bladder cancer care, with a subset of patients having remarkable responses. Platinum-based chemotherapies function by forming adducts to DNA and introducing crosslinks. These alterations result in inhibition of DNA replication, leading to cell cycle arrest and the induction of apoptosis ([21]). ERCC1 and ERCC2 are members of the nucleotide excision repair (NER) family of proteins, which function to repair DNA damage in the cell. It is therefore not surprising that cancers with high levels of expression of NER genes have been shown to be more resistant to these platinum-based therapies. ([22,23]). Conversely, low expression of ERCC1 and ERCC2 has been correlated with responsiveness to cisplatin in bladder cancer ([24]). Recently another study performed whole-exome sequencing on 50 patients prior to receiving neoadjuvant cisplatin and identified a strong association between responders and ERCC2 mutations. The authors further show that these mutations could result in increased cisplatin sensitivity *in vitro*, while overexpression of wild-type ERCC2 resulted in increased therapeutic resistance ([25]).

TP53

The transcription factor p53 has long been known to play an important role in DNA repair, as well as other cellular processes including the promotion of apoptosis and cell cycle regulation ([26,27]). TCGA described the inactivation of functional TP53 in 76% of samples through a constellation of mutations in TP53 itself, combined with amplifications and overexpression of MDM2 ([10]). TP53 currently remains an elusive drug target ([28]), but there are ongoing clinical trials examining the use of Wee-1 inhibitors, which are thought to sensitize chemo-resistant tumors to platinum based therapies (NCT01827384)([16,29]). That being said, there have been a number of studies suggesting that p53 expression and mutational status may be predictive of therapeutic response. These studies have produced somewhat confounding results, however, with different studies showing that p53 mutations can confer chemosensitivity or chemoresistance depending on the specific alteration ([30,31]). In the context of bladder cancer, there has been some difficulty defining p53's role in therapeutic sensitivity. One retrospective analysis, utilizing immunohistochemistry (IHC), showed that patients who had elevated p53 expression and received adjuvant cisplatin saw a survival benefit. ([32]). Conversely, in a phase III trial that sought to explore the use of p53 expression as a predictive biomarker (again determined by IHC) showed no significant association between p53 expression and methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) sensitivity([33]). While TP53 appears to be a major contributor to the development of bladder cancer, more investigation is needed to determine its clinical utility as a predictive marker.

PI3-Kinase pathway—PI3-Kinase pathway alterations were observed in 42% of samples analyzed by TCGA. The alterations seen in this pathway include PIK3CA mutations (17%), TSC1 or TSC2 alterations (9%) and overexpression of AKT1 (9%)[10]. Other studies have described cases where TSC1 mutations may confer exceptional sensitivity to targeted therapy – describing the first bladder cancer case of complete response to treatment with everolimus, an MTOR inhibitor ([34]). Another recent study described exceptional response in a patient with advanced metastatic bladder cancer to treatment with everolimus and the multi-target receptor tyrosine kinase inhibitor pazopanib ([35]). These papers suggest that perhaps activating mutations within the PI3K pathway could serve as biomarkers of response to targeted agents already in use in other cancers.

Receptor Tyrosine Kinases – FGFR3 and ERBB2

Mutations of FGFR3, a receptor tyrosine kinase, have been well characterized in both non-invasive and invasive bladder cancers, with approximately 12% of advanced bladder cancers harboring a mutation in this gene ([10]). This provides an opportunity to select bladder cancer patients based on FGFR3 mutation status for potential use of one of the many of the agents designed to target this gene. One such trial wherein patients were screened for FGFR3 mutation status, found that treatment with the pan-FGFR inhibitor BGJ398, saw an exceptional response in a subset of bladder cancer patients, with 4 out of 5 responding to treatment. Tumors in these patients were reduced anywhere from 27%–48% ([36]). Another phase I trial recently found a patient with metastatic bladder cancer harboring an FGFR3-TACC3 translocation showed partial response to treatment with JNJ-42756493, another pan-FGFR targeted agent that has shown promising results in patient-derived explant models harboring various FGFR alterations ([37]). It is worth noting that these fusions have been identified as actionable targets across other cancers ([38]) and in bladder cancer ([39]), with TCGA identifying recurrent FGFR3-TACC3 translocations in 3 out of 114 tumors analyzed. While these studies are currently being expanded, the prospect of utilizing FGFR3 as a biomarker of therapeutic response is very promsing[10].

HER2 is another receptor tyrosine kinase that has been utilized as a predictive biomarker of response to targeted agents and conventional chemotherapies in urothelial cancers and other cancer types. The role of HER2 in the promotion of bladder cancer has also been explored in a number of studies and has been associated with increased sensitivity to chemotherapy. Recently, it has been shown that *ErbB2* mutations are associated with pathologic complete response (P0) following treatment with platinum-based therapies[40]. This study suggests that *ErbB2* could serve as a good genomic biomarker and could provide a basis for selecting patients. Preclinical studies and Phase I trials have shown high response rates to HER2-targeted therapies and there are currently phase II trials underway for trastuzumab (NCT01828736) and lapatinib (NCT00949455) in the treatment of bladder cancer.

V. New approaches to the classification of bladder cancer

Molecular analysis has clearly shown that cancers of specific histological types are rarely genomically monolithic – very infrequently are they defined by a single characteristic mutation nor universally predictable in terms of therapeutic sensitivity based on a single genotypic change ([41]). While individual biomarkers may predict response in a single patient

or small subset of patients, no single biomarker has the ability to predict every individual's responsiveness to a given therapy. Patients typically have many co-occurring alterations that can modify their sensitivity to given compound and may benefit from personalized combination therapies[41]. In order to better predict the effects these co-occurring events might have on therapeutic sensitivity, several recent studies have aimed to classify tumors across cancer types – describing novel "pan-cancer" subtypes based on shared genetic, molecular, and biochemical features. One of these studies has uncovered remarkable similarities across many cancer types, with bladder cancer standing out as a uniquely heterogeneous and divergently clustered disease type[17]. In this study they evaluated 3,527 samples across 12 cancer types, performing integrative analyses across five genome-wide platforms including: whole-exome sequencing, DNA copy number analysis, methylation profiling, mRNA sequencing, and microRNA sequencing. Furthermore, data from Reverse Phase Protein Array (RPPA) provided proteomic characterization of 131 proteins. Interestingly, bladder cancer primarily clustered into three distinct "pan-cancer" subtypes – the most divergent classification of any of the cancer types analyzed. Of the 12 cancer types analyzed, five clustered into groups corresponding to their tissues of origin, whereas seven had features that could be clustered into "pan-cancer" subtypes based on shared molecular characteristics with other cancer types. One of these pan-cancer groups, included a subset of bladder tumors, along with samples from the squamous lung and head and neck cancer cohorts. The authors noted that this "squamous-like" subtype was characterized by p53 mutations, along with amplifications of p63 and enrichment of immune and proliferation pathway features. Aside from the squamous-like subtype, most other bladder tumors clustered into either a group comprised of mostly lung adenocarcinomas, or another bladder cancer-specific subtype, which was comprised primarily of tumors originating in the bladder([17]). These results, suggest that bladder cancer might be looked at through the lens of other cancer types, such as lung, where there is a wealth of data focused on predicting therapeutic response. These sorts of analyses promise to inspire a new wave of clinical trials in which therapeutic decisions are made based on molecular classification rather than traditional pathologic/histologic classification.

Another series of papers has recently been published describing intrinsic subtypes of bladder cancer based on unsupervised clustering derived from genome-wide RNA expression profiling data ([10,12,18,42,43]). These independent analyses of the bladder cancer genome and transcriptome have resulted in the identification of several subtypes which share common expression profiles. The concept of intrinsic subtypes based on unsupervised clustering, has been previously established in breast cancer ([44]). This concept of classifying breast tumors based on their molecular taxonomy has been reproduced by many groups independently and is commonly utilized clinically to inform prognosis and predict response to therapy. ([45–47]). Other groups have recently described molecular classification schemes in breast cancer based on normal cell types, and found these may better predict response to therapy than the existing classifications based on tumor derived profiles ([48]). This perhaps suggests that a similar taxonomic approach might be clinically informative in the context of bladder cancer as well. The classification of these intrinsic subtypes in bladder cancer may have remarkable implications on how bladder cancer patients are treated and may improve the ability to predict responsiveness to various therapies. A very comprehensive description of these

subtypes and their role in predicting response in bladder cancer has recently been published ([20]).

VI. Immunotherapy: Promising New Horizons

A promising approach that has for years been associated with sometimes remarkable and durable response, is cancer immunotherapy.[4950] It is hypothesized that the immune system plays a natural role in the prevention of cancer. In addition to being a primary means for combatting foreign pathogens, the immune system exists as a means of surveillance for aberrant processes within one's own cells.[51] In an actively functioning immune system, when a cell becomes malignant, it displays a variety of metabolic and paracrine cell surface abnormalities, which are recognized as abnormal by both the innate and adaptive immune systems, causing the cell to be eliminated.[52] Cancer represents a fundamental failure of the immune system to fully execute on its duties as the sentinel to protect against malignant cellular processes, and can derive from either cancer-mediated depression of the natural immune response, or an inherent failure to recognize the cancer cells as needing to be eliminated, since fundamentally they do derive from self, and bear many similar characteristics to one's own somatic cells.[53] The concept behind cancer immunotherapy is to unleash the powerful cell-regulating potential of this system to effectively target abnormal cells within the body. The concept of immunotherapy has been attempted for many years, but with a few exceptions, until recently, there had been very few breakthroughs.

One of the immunotherapy breakthroughs prior to activated T cell therapy and immune checkpoint inhibitors was the use of Bacillus Calmette-Guerin (BCG), a bovine derived vaccine for tuberculosis, which is injected intravesically into the bladder.[54] The notion of stimulating immune response via the introduction of potent antigens to introduce collateral damage of tumor cells, while conceptually primitive, has a long history first stating in the late 1800's when Coley's toxin (derived from S. pyogenes) was injected intratumoral.[55] Because the body mounts a significant innate immune response to the presence of BCG, the idea behind introducing this into the bladder, was to essentially target UCC cells through a sort of bystander effect, by triggering inflammatory processes due to the presence of BCG (the precise mechanism is not exactly understood, but BCG administration has been shown to activate both the innate and adaptive immune systems, and equally targets healthy somatic bladder in addition to cancer cells).[56] Nevertheless, this approach has had significant success in treating UCC, and has been shown to be superior or equivalent to any single chemotherapeutic agent tested to date in terms of reducing progression and recurrence.[49] Associated toxicities are often manageable, since the response is mainly confined to the bladder, given the method of delivery.[57]

However, in our present age of targeted therapy, it should be possible to elicit an immune response in a more focused and specific manner, with minimal collateral damage. The most appealing aspect of targeted immunotherapy is the potential promise for a durable immune response via adaptive immune conditioning, which should prevent recurrence of malignant cells expressing the same antigenic profile. Within the last several years, there have been several breakthroughs in this area, the most successful of which utilize an armed cytotoxic T lymphocyte response. The characteristics of an effective antitumor immune response involve

1.) a mechanism for cancer antigen release, uptake, and presentation by dendritic and other antigen presenting cells, 2.) the recognition of the antigens presented on these cells by appropriate T cell clones, to prime them for clonal expansion, and 3.) the creation of durable immune reserves, in the form of circulating cytotoxic T lymphocytes (CTLs), which will recognize and destroy cells expressing markers of nonself.

One of the most exciting advances in this area has been the development of immune checkpoint inhibitors for PD-1/PDL-1, and CTLA-4. Programmed Death 1 (PD1) is a receptor found on CTLs and some other immune cells that interacts with two ligands: PDL-1 and PDL-2, which when triggered, turns off the activated T cell response and halts the production and release of cytokines.[58] In a healthy immune system, these signaling mechanisms exist to reestablish tissue homeostasis following successful defeat of a foreign pathogenic infection, however with cancer, tumor cells have evolved to also engage this receptor via synthetic creation of their own PDL-1, which effectively allows them to avoid the wrath of the CTL response.[5960] Several drugs have entered clinical trials to target PDL1. One of these, MPDL3280A, an anti-PD-L1 antibody, recently received breakthrough therapy status by the FDA, due to a 43% objective response rate in patients with PDL1+ tumors in Phase I trials for metastatic UCC.[6162] Though under half of patients saw this clinical benefit, the most exciting aspect of this trial was the fact that even following cessation of treatment after the allotted period, the response seen in patients appeared to be sustained, and through at least the end of the data collection period, a median duration of response was not reached. Phase II trials for this drug have recently finished enrollment. Other exciting antibody-based trials to target the PD-1/PD-L1 axis are ongoing with drugs pembrolizumab, nivolumab (already approved for metastatic melanoma and squamous non-small cell lung cancer), MSB0010718C, and MEDI-4736, amongst others.[49] Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) is a biomarker-based target that functions much in the same vein as PD1/PDL-1, inhibiting activated T cell response, via an alternative mechanism through regulation of the T-helper cell signaling that allows for the priming and expansion that ordinarily occurs to build up an army of antigen-specific reactive CTL clones.[63] Preliminary results of ipilimumab, a monoclonal antibody against CTLA-4, in bladder cancer cohorts have been promising,[64] and shown to upregulate immune response small cohort of UCC patients when administered preoperatively.[6566]

The other highly promising area of bladder cancer immunotherapy comes in the form of adoptive T cell transfer (ACT), a proven approach in many tumor types. ACT relies on the extraction and genetic engineering of a patient's own CTLs to become reactive to tumor based antigens, through ex vivo priming, clonal expansion, and reinfusion. These enriched CTLs can take the form of traditional α/β T cell receptors, or be further modified to contain an extracellular domain designed as a mimetic of a tumor-specific antibody, linked to the intracellular domain of the T cell receptor and costimulatory receptors, to generate enhanced response. This latter approach is known as chimeric antigen receptor (CAR) therapy.[67] ACT is still in the fairly early stages of testing in bladder cancer, with several ongoing trials, and a new study out of Sweden has just reported a couple highly promising results from a small cohort of individuals with metastatic UCC, including one patient who demonstrated a complete response.[68] More research into optimizing and expanding this technology is needed to assess its potential in UCC patients, and though it is a relatively high cost

technology, due to the highly personalized nature of taking each individual patient's own T-cells for the ex vivo modifications, that is also a large part of what makes it so appealing, at least in concept, in our current world of modern precision medicine.

VII. Clinical trials utilizing molecularly guided therapy selection

While the aforementioned predictive biomarkers hold great promise for improving the management of bladder cancers and the likelihood of therapeutic responsiveness on an individual patient level, more prospective clinical trials are needed to demonstrate clinical benefit of these tools (Figure 1). Few trials to date have used genetic or expression-based biomarkers for patient enrollment, and as such, may have been underpowered to detect the small subset of patients most likely to respond to treatment based they individual molecular profiles. Of note, the Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis trial (iSPY) has shown that utilization these types of molecular analyses can improve one's ability to predict chemo-sensitivity and chemo-resistance[47]. Moreover, the Southwest Oncology Group (SWOG) has another large trial intended test if CoXEN-based classification of patients, can improve rates of chemoresponsiveness. There have also been a limited number of trials in bladder cancer which have enrolled patients based on specific mutations or biomarkers, but of those which have several have seen significantly improved patient responses when compared to previous trials, most of which have failed to stratify patients based on appropriate predictive biomarkers[16].

Recently, there has been an increasing number of prospective clinical trials wherein individuals will be matched to targeted therapies based on genomic and other molecular alterations([69]). These include several trials originated by the National Cancer Institute (NCI) such as the NCI-Molecular Profiling-based Assignment of Cancer Therapeutics (M-PAC) (NCT01827384) as well as the NCI- Molecular Analysis for Therapy Choice (MATCH) (NCT02465060). Others include institutional trials such as the IMPACT2 (NCT02152254) study being conducted at the University of Texas MD Anderson Cancer Center, which aims to expand on the early promise demonstrated by the earlier IMPACT (NCT00851032) study ([70]). Another exciting study that is expected to begin in late-2015, launched by the American Society for Clinical Oncology is the Targeted Agent and Profiling Utilization Registry (TAPUR) study, which aims to facilitate the matching of patients for which other therapeutic options are unavailable and whom harbor potentially actionable genomic alterations([71,72]). In this study patients alterations will be evaluated by a molecular tumor board, which will contain experts in genomically-guided medicine and the study will facilitate access to various targeted agents through collaborations with the pharmaceutical industry. The hope of these studies and many others not mentioned here, are our first opportunities to see the practical utility of precision cancer medicine. The results of these studies promise to revolutionize not only the way bladder cancer is treated, but how all cancers are managed clinically. While the management of bladder cancer has seen little change over the last several decades, the near future promises a paradigm shift based on integration of genomics and other molecular biomarkers to guide therapeutic decisions.

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Key Points

- Predictive biomarkers that can identify patients most likely to respond to a given therapy will be of critical importance in advancing bladder cancer management.
- Genome-wide DNA and RNA sequencing efforts have revealed bladder cancer to be a heterogeneous disease that harbors alterations conferring sensitivity of targeted agents in other cancer types.
- Bladder cancers have recently been described as having shared properties with several other tumor types such as lung and breast and be composed of molecularly distinct subtypes that might predict therapeutic sensitivity.
- Immunotherapies targeted the PD1/PDL1 axis along with CTLA-4, have shown promising results in recent early phase clinical trials.
- Emerging clinical trials which utilize molecularly-guided therapy selection will determine the clinical efficacy of using predictive biomarkers to guide therapeutic decision-making.

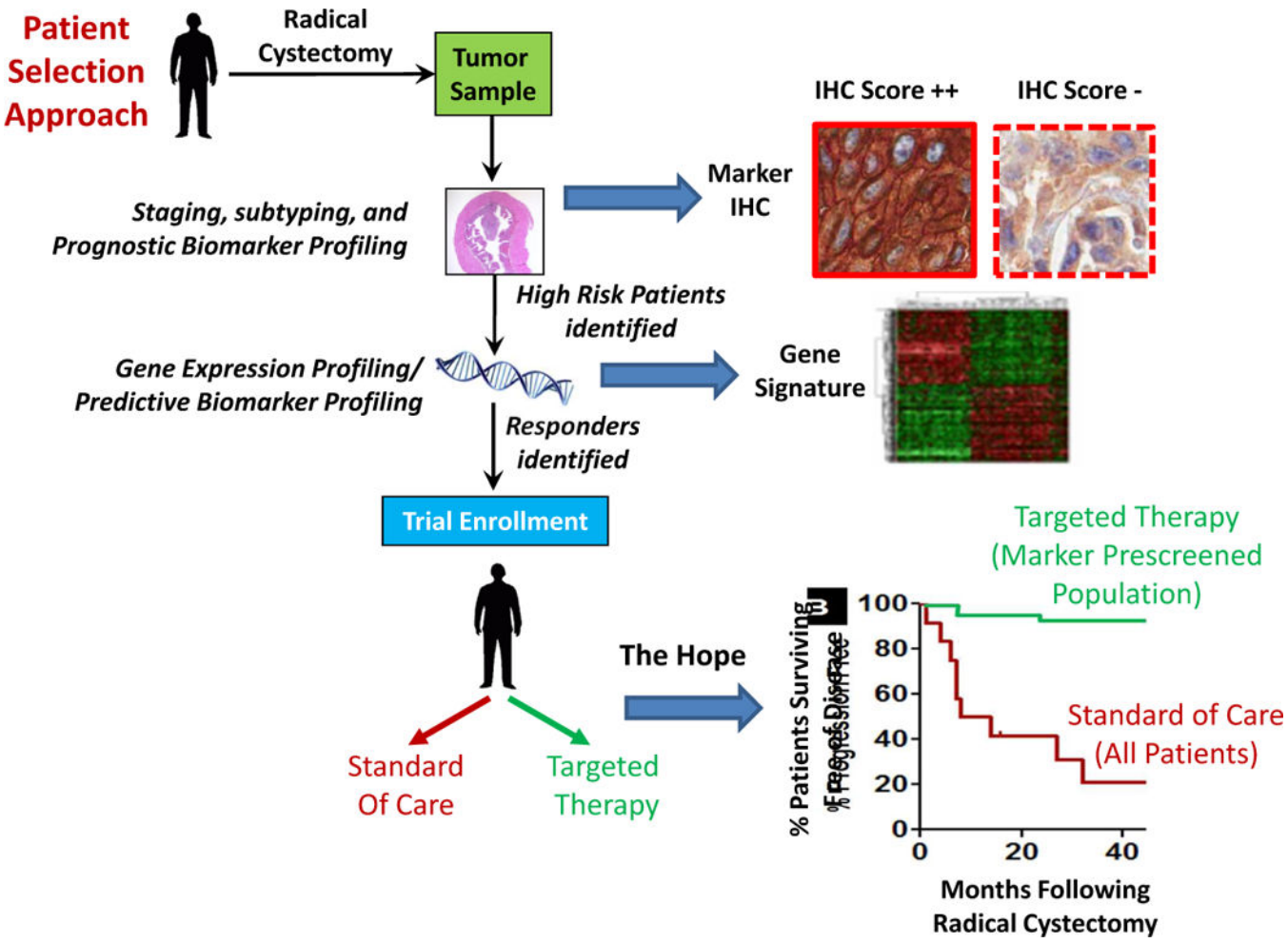

Figure 1.

Biomarker Directed Therapy For Bladder Cancer. The paradigm for the utilization of precision medicine in bladder cancer therapy will involve the prescreening of individuals bearing specific relevant molecular subtypes and stratifying them into groups with therapies likely to target molecules acting as drivers in the course of their disease. This more rational approach will hopefully lead to longer Kaplan-Meier curves and improved progression-free survival.