BLADDER CANCER

A GIVING SMARTER GUIDE

PHILANTHROPY ADVISORY SERVICE
MILKEN INSTITUTE

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We graciously thank the members of and liaisons to the Bladder Cancer Scientific Advisory Board for their participation and contribution to the Bladder Cancer Project and Giving Smarter Guide. The informative discussions before, during, and after the Bladder Cancer Retreat were critical to identifying the key unmet needs and ideal philanthropic opportunities to benefit patients and advance bladder cancer research.

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CONTENTS

EXECUTIVE SUMMARY

More than 500,000 people in the United States (U.S.) suffer from bladder cancer, and nearly 70,000 new cases are diagnosed each year. Bladder cancer is the fifth most common cancer in the U.S. and the most expensive cancer to treat. The standard of care for bladder cancer has remained unchanged for more than two decades, and therefore treatment options are very limited. In addition, nearly 80 percent of bladder cancers recur after standard first-line treatment, which underscores the limited efficacy of these therapies. Moreover, these treatments often require drastic lifestyle changes that diminish quality of life while falling far short of achieving cure.

The dearth of federal funding for bladder cancer is arguably the field's biggest limitation. Federal funding for bladder cancer is less than 1 percent of care costs and is woefully disproportionate to disease prevalence. The reduction in funding affects nearly every aspect of research, from the ability to attract and retain new talent to the ability to run innovative clinical trials—all of which the bladder cancer field so desperately needs.

The bladder cancer field also faces other challenges that hamper progress, including:

- Lack of collaboration to effect systemic change
- Poor clinical trial infrastructure to support innovative studies
- Poor understanding of disease genomics

Despite the underinvestment in the field, recent progress has resulted from large-scale genomic profiling efforts. The Cancer Genome Atlas (TCGA) study, a major federal initiative to genomically profile patient tumor samples, has revealed new insights about bladder cancer biology that may affect future drug discovery efforts. In addition, newly identified genetic targets may be therapeutically relevant—thereby opening up new treatment possibilities for patients.

Overall, this is an exciting time for cancer research, as national attention on the disease has intensified. With the launch of the Cancer Moonshot and the Parker Institute for Cancer Immunotherapy, it is clear that both the public and private sectors are devoted to large-scale efforts to find more effective treatments for cancer. The bladder cancer field will benefit from these efforts; however, strategic investment in collaborative research models, infrastructure, and discovery science is essential.

Philanthropy is poised to tackle the field's challenges because it is nimble enough to capitalize on the dynamic changes occurring in cancer research. Channeling private investment to incentivize multidisciplinary inter-institutional collaboration can effectively address unanswered research questions. Private giving can also transform the ineffective clinical trial infrastructure that plagues the bladder cancer field. An infusion of funds to support creation of a coordinated clinical trial network would allow for innovative, adaptive trials. Finally, leveraging the success of TCGA, philanthropic giving can expand that large-scale genomic profiling effort to account for the full spectrum of genetic changes driving various bladder cancer subtypes. Although the Bladder Cancer Advocacy Network is leading the charge on genomic profiling of patient bladder cancer samples, much more can be done to bolster its efforts and eventually bring routine genomic sequencing to the bedside and thereby transform care. Harnessing the power of philanthropy to narrow the gap between funding and disease prevalence is what the bladder cancer field needs.

The Milken Institute Philanthropy Advisory Service has developed this Giving Smarter Guide for Bladder Cancer with the express purpose of empowering patients, supporters, and stakeholders to make informed, strategic decisions when directing their philanthropic investments and energy into research and development efforts.

IMPERATIVE TO ADVANCE BLADDER CANCER RESEARCH

Of all cancers, bladder cancer is the fifth most common and has the highest lifetime treatment costs per patient in the United States (U.S.). Furthermore, treatment options for bladder cancer, particularly **metastatic** bladder cancer, have not changed from the standard of care from more than 20 years ago. This represents a significant unmet need for patients suffering with this disease. Additionally, the bladder cancer field lacks an understanding of the key molecular changes that drive the disease. ***The primary aim of this report is to highlight these unmet needs and potential solutions to address them.***

EPIDEMIOLOGY

More than 500,000 individuals in the U.S. currently live with bladder cancer. In 2015, there were approximately 74,000 new diagnoses and 16,000 deaths from the disease. The 5-year survival rate for bladder cancer, which is currently 77.4 percent, has not increased in the past three decades, despite significant improvements in survival rates for related cancers such as prostate and kidney.

Bladder cancer is most common in elderly men. Approximately 75 percent of patients are male, and the average age at diagnosis is 73 years. Although the disease is more prevalent in men, women are more likely to have advanced tumors and a less favorable prognosis.

ECONOMIC IMPACT

Bladder cancer is the most expensive cancer to treat on a per patient basis. The lifetime treatment cost per patient typically ranges from $129,000 to $251,000. In aggregate, direct medical costs are estimated to exceed $4 billion per year in the U.S. alone. High patient costs are primarily driven by the recurrent nature of the disease. Nearly 80 percent of bladder cancers return after initial treatment, thereby requiring life-long surveillance and management of the disease. Intensive monitoring strategies, treatment of recurrent tumors, and treatment complications are all key drivers of the enormous financial burden caused by the disease. Furthermore, because these estimates exclude indirect costs, including those associated with poor quality of life and lost productivity, the total economic burden of bladder cancer is considerably higher.

INSUFFICIENT RESEARCH INVESTMENT

Although bladder cancer costs the U.S. economy more than all other cancers on a per patient basis, government investment in the disease is not proportional to the economic burden. The National Cancer Institute (NCI)'s investment in bladder cancer research was only about $20 million in fiscal year 2013, ranging from 11 to 27 times less than the other four more prevalent cancers (see Figure 1).

Bladder cancer also lacks public awareness and charitable support, with only three nongovernmental organizations worldwide providing more than $500,000 in research grants per year (page 27). Considering the

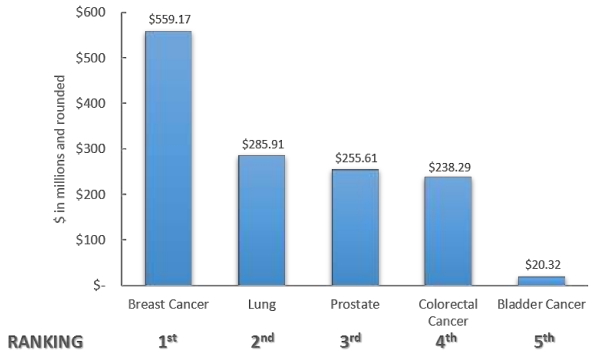


Figure 1. NCI Funding for Top Five Most Common Cancers (FY 2013)
Federal funding for bladder cancer is disproportionate to its prevalence and cost of care.

immense burden of the disease on patients, caregivers, and society, bladder cancer research is grossly underfunded.

Bladder cancer is the “invisible cancer.” Despite the prevalence, high economic cost, and lack of improvement in clinical outcomes, research activity and investment in the disease is disproportionally low. ***To address the growing burden of bladder cancer, it is imperative to commit focused resources to raise awareness, support research, and encourage patient participation in clinical research studies.***

OVERVIEW OF BLADDER CANCER

Cancer arises after several cellular processes that control cell division, growth, and death go awry. Cancer cells multiply more rapidly than normal cells and can ignore growth-suppressing signals. These cells can also evade detection and destruction by the immune system and resist other cell death processes. These abnormal abilities are acquired through **mutations** in genes that control the cellular functions listed above. Cancer can arise in almost any organ of the body, and cancers that arise in the bladder are the fifth most common in the United States.

Bladder cancer typically starts in the innermost layer of the bladder called the **transitional epithelium**. Figure 2 illustrates the urinary system (also called the urinary tract), which consists of:

- Kidneys—these organs filter blood and produce urine.
- Ureters—these tubes carry urine from the kidneys to the bladder.
- Bladder—this hollow organ stores urine prior to excretion.
- Urethra—this tube expels urine.

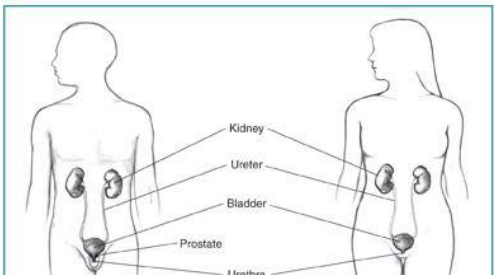


Figure 2. The Urinary System
Illustration of the male (left) and female (right) urinary system. Image courtesy of the National Institute for Diabetes and Digestive and Kidney Diseases (Source).

TYPES

The five types of bladder cancer are distinguished by which wall layer the cancer starts in, which wall layer the cancer grows into, and what the cancer cells look like under the microscope (Figure 3).

Transitional cell carcinoma (TCC), which starts in the transitional epithelium, accounts for more than 90 percent of bladder cancers in Western countries. Two distinct subtypes of TCCs are characterized by how they grow:

- **Papillary carcinoma** typically grows from the transitional epithelium toward the center of the bladder in finger-like projections.
- **Flat carcinoma** typically grows in flat sheets and do not grow toward the center of the bladder.

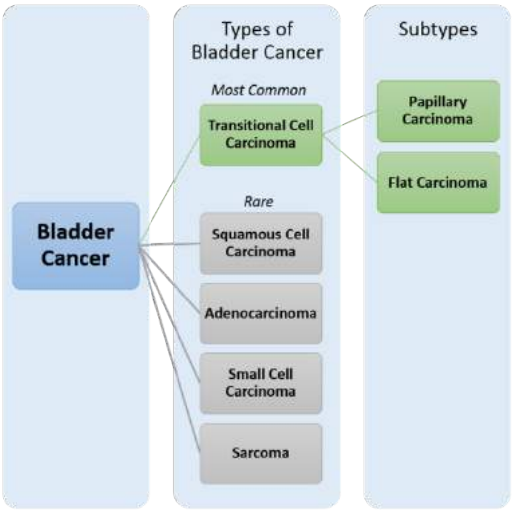


Figure 3. Types of Bladder Cancer
This diagram illustrates the most common types of bladder cancer and its subtypes, as well as the four rare types of bladder cancer.

Because other organs in the urinary system are also lined with transitional epithelium, TCCs can arise throughout the urinary tract.

Depending on which wall layer the bladder cancer grows into, it is described as **noninvasive** or **invasive**. Cancers that are confined to the innermost transitional epithelium are noninvasive, and cancers that grow beyond the transitional epithelium into the connective tissue layer and beyond are called invasive. The patient's prognostic outcome worsens as the degree of invasiveness increases.

The four less common types of bladder cancer are as follows:

- **Squamous cell carcinoma** accounts for about 1-2 percent of all bladder cancers. These cells are characterized as invasive and resemble flat skin cells under the microscope.
- **Adenocarcinoma** accounts for about 1 percent of all bladder cancers. These cells are similar to gland-forming colon cancer cells. Adenocarcinomas are also characterized as invasive.
- **Small cell carcinoma** accounts for less than 1 percent of all bladder cancers. These cells are similar to small cell lung cancers (SCLCs), in that they can receive signals from neurons and release hormones into the blood (neuroendocrine characteristics) and are particularly aggressive. This bladder cancer type is often treated similarly to SCLC.
- **Sarcoma** is the rarest type of bladder cancer and arises in the muscle layer of the bladder wall.

STAGES

The staging of cancer is used to describe the characteristics of the cancer in terms of the size of the primary tumor and the extent to which the cancer has spread to other organs. The TURBT procedure and various imaging scans (described in the Diagnosis section on page 14) are important for accurately staging bladder cancer. Treatment options, disease prognosis, and eligibility for clinical trials are largely determined by cancer stage.

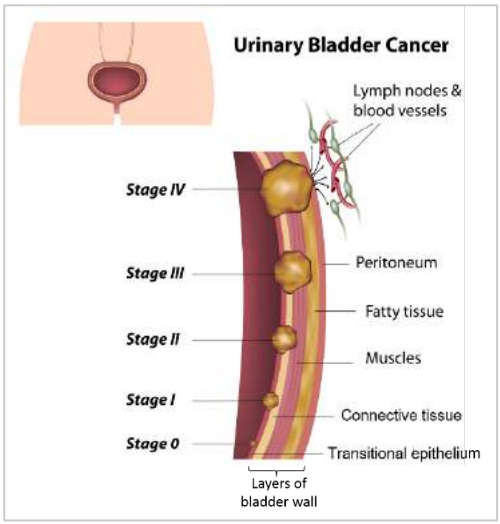


Figure 4. Stages of Bladder Cancer

As depicted in Figure 4, there are five stages of bladder cancer that are generally discussed based on their degree of muscle invasiveness. They are as follows:

NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC):

- *Stage 0 (noninvasive)*—Tumor is confined to the innermost layer of the bladder. This stage is further subdivided depending on the tumor cell type:
  - *Stage 0a*—TCC papillary carcinoma
  - *Stage 0is*—TCC flat carcinoma of the bladder; also known as carcinoma in situ (CIS).
- *Stage I (minimally invasive)*—Cancer has spread into the connective tissue layer.

MUSCLE INVASIVE BLADDER CANCER (MIBC):

- *Stage II (muscle-invasive)* — Cancer has spread into the muscle layer.
- *Stage III (invasive)*—Cancer has spread beyond the muscle layer and into the fatty layer. Cancer at this stage may have also spread to the surrounding reproductive organs, for example, prostate and uterus.
- *Stage IV (metastatic)*—Cancer has spread beyond the bladder and into one or more of the following areas:
  - Pelvis or abdomen

- Surrounding lymph nodes. Lymph nodes play an important role in maintaining proper function of the immune system by filtering out foreign particles from the lymph fluid.
- Distant parts of the body, such as the lungs, bone, or liver.

RISK FACTORS

Several risk factors are associated with an increased likelihood of developing bladder cancer (see Table 1).

Table 1. Common Risk Factors for Bladder Cancer

Lifestyle	• Current or past history of smoking tobacco products (e.g., cigarettes, cigars, or pipes). • Exposure to industrial chemicals used in dye, metal, paint, or petroleum processing. • Consumption of arsenic-contaminated water. • Low fluid consumption leading to chronic dehydration.
General	• Age—About 90 percent of bladder cancer patients are older than 55. • Gender—Men are four times more likely to develop bladder cancer than women. • Race—Whites are more likely to develop bladder cancer compared to other racial groups.
Genetics	• Family history of bladder cancer. • Other inherited genetic disorders such as Cowden's syndrome, Lynch syndrome, or retinoblastoma gene (*RB1*) mutations.
Other Medical Conditions and Treatments	• History of cancer in other organs of the urinary system. • Bladder defects at birth. • Chronic bladder infection or irritation. • Chemotherapy and radiation therapy.

Having one or several risk factors does not guarantee that one will develop bladder cancer; risk factors simply denote probability measures of likelihood.

PREVENTION

Currently the best known preventative measures against bladder cancer are to abstain from smoking, avoid exposure to industrial chemicals, avoid consuming arsenic-tainted water, and avoid chronic dehydration. Living a healthy lifestyle, including a balanced diet and physical activity, is also recommended to decrease the risk of bladder cancer.

DISEASE BIOLOGY

Bladder cells are controlled by tightly regulated processes that dictate when they grow, divide into new cells, and die. The genes that control these cellular processes fall under one of the following categories:

- **Tumor suppressor genes** suppress cell division to prevent rapid and uncontrolled cell division. If a cell begins to divide out of control, these genes can initiate a signal that will prompt the cell to die. ***These genes suppress tumor growth.***
- **Oncogenes** override a cell death signal and allow a cell to grow uncontrollably and evade death from tumor suppressor gene signals. ***These genes promote tumor growth*.**

Gene sequence changes (mutations), deletions, and other alterations that affect the normal function of these genes lead to the development and progression of bladder cancer. When a cell is in a cancerous state, tumor suppressor genes are usually inactivated (turned off) and oncogenes are usually activated (turned on). However, the specific gene changes are not the same in all cases, and alterations of certain genes are associated with distinct tumor features and clinical outcomes. This section describes some of the most frequent genetic changes in bladder cancer.

FGFR3 ONCOGENE IS ACTIVATED IN NONINVASIVE PAPILLARY TUMORS

The fibroblast growth factor receptor 3 gene (*FGFR3*) is the most frequently mutated oncogene in bladder cancer, occurring in up to 80 percent of TCCs. Normal *FGFR3* plays a role in several important cellular processes, including blood vessel formation, embryonic development, and cell growth and division. Activating *FGFR3* mutations are strongly associated with noninvasive papillary tumors that have a low risk of progression and a high tendency for recurrence, representing a favorable clinical outcome for bladder cancer. *FGFR3* mutations may also be found in 15-20 percent of more advanced bladder cancers and represent a target of drugs currently in clinical development.

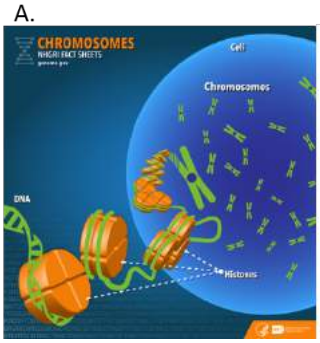
TP53 TUMOR SUPPRESSOR GENES ARE INACTIVATED IN INVASIVE TUMORS

Alterations in the tumor protein 53 (*TP53)* gene are implicated in most cancers, including bladder cancers. *TP53* prevents tumor formation by halting cell division if damaged DNA is detected. Inactivating mutations in *TP53* are strongly associated with high-grade, invasive tumors with adverse clinical outcome. *TP53* and *FGFR3* mutations are generally mutually exclusive.

CHROMOSOME 9 ALTERATIONS OCCUR IN BOTH NONINVASIVE AND INVASIVE BLADDER CANCER

Chromosomes are small thread-like structures, made of histone proteins and DNA, found inside the cell nucleus (see Figure 5). Of the 23 pairs of chromosomes found in the human cell, portions of chromosome 9 are often deleted in noninvasive and invasive bladder cancers. The lost regions include one or more tumor suppressor genes. These chromosome 9 alterations begin before the

A.



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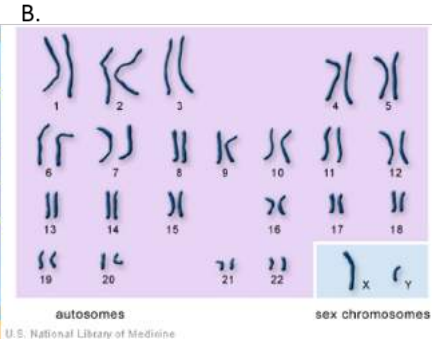

Figure 5. Chromosome Basics

A. Depiction of chromosome structure in the cell. Image courtesy of National Human Genome Research Institute (Source).

B. The 23 pairs of chromosomes found in humans, numbered by size. Image courtesy of the U.S. National Library of Medicine (Source).

formation of papillary tumors or CIS and are considered a primary event in bladder cancer development.

DIAGNOSIS AND TREATMENT

DETECTION

Bladder cancer is usually first detected using imaging methods, which help to identify the presence of lesions in the bladder, or laboratory tests, which help to identify precancerous or cancerous cells in bodily fluids. The most commonly used imaging methods and lab tests for this purpose are described below:

- ***Intravenous pyelogram (IVP)/urogram (IVU)***—This procedure is an x-ray exam of the urinary system, often performed after the intravenous administration of a specialized dye that accumulates in the patient's urinary system and allows for detection of any unusual masses. If any masses are detected, then further imaging and diagnostic tests will be performed.
- ***Cystoscopy***—During this procedure, the physician will feed a lighted, flexible fiber-optic tube (cystoscope) up through the urethra and into the bladder to visualize the inner lining of the bladder. If an unusual mass is detected, then a biopsy may be taken for further study under the microscope.
- ***Computer Tomography (CT) scan***—This scan provides information about the size, shape, and position of any urinary tract masses. A CT scan of the urinary tract is also known as a CT urogram. CT urograms can also detect enlarged lymph nodes that may contain cancer cells that have spread, or metastasized, from the bladder. This scan uses computer processing to create cross-sectional images from a series of x-ray images taken from several different angles.
- ***Positron Emission Tomography (PET)***—This imaging test requires intravenous administration of a radioactive tracer, which accumulates in the patient's organs and allows for 3D imaging of the radioactively traced organs, including the bladder. The PET scan is often used in combination with other imaging tests (e.g., PET/CT). For bladder cancer cases, PET scans are often used for detection, tracking metastasis, and monitoring response to treatment.
- ***Urine cytological exam***—During this laboratory test, the patient's urine sample is microscopically examined for the presence of precancerous or cancerous cells.

DIAGNOSIS

Although detection methods provide visual evidence of potentially cancerous lesions, a formal diagnosis of bladder cancer can only be made after bladder tissue and/or cells are microscopically examined by a pathologist. To accurately diagnose bladder cancer, physicians will obtain bladder specimens by one of the following ways:

- ***Transurethral resection of bladder tumor (TURBT)***—This surgical exam is used to provide the formal diagnosis of bladder cancer. During this exam, any visible tumor tissue is removed from the bladder and examined under a microscope. The tumor is visualized by cystoscopy (described above). The removed tumor tissue is used to diagnose and stage bladder cancer.
- ***Brush biopsy***—Following a cystoscopy (described above), if an unusual mass is detected, then a nylon or steel brush is passed through the cystoscope and rubbed over the mass. The tissue and cells that are collected in the brush are examined under a microscope.

CURRENT TREATMENTS

The current treatment options for bladder cancer can be divided into four categories:

- Surgery
- Immunotherapy
- Chemotherapy
- Radiation Therapy

SURGERY

Surgical removal of bladder cancer is performed to either remove the cancerous lesion(s) or portions of the bladder depending on the degree of invasion into the bladder wall.

- ***TURBT***—This surgical procedure is described in the Diagnosis section above (also known as transurethral resection (TUR)) and is performed on non-muscle invasive bladder cancer. Because most patients present with noninvasive, superficial bladder cancer upon diagnosis, this is usually the first treatment received.
- ***Cystectomy***—This surgical procedure is performed on invasive bladder cancer and involves the partial (partial cystectomy) or whole removal (radical cystectomy) of the bladder. In cases where the whole bladder is removed, the patient typically undergoes reconstructive surgery to provide a new method to store and pass urine.
- ***Bladder reconstruction surgery***—Following whole removal of the bladder, there are several surgical options to reroute urine (called urinary diversion):
    - *Neobladder*—This surgical procedure uses part of the small intestine to construct a bladder substitute (also called a neobladder) that connects to the ureters at one end and the urethra at the other end, thereby allowing for "normal" urination.
    - *Ileal conduit*—A surgical procedure, called a urostomy, is performed to create an artificial opening, called the stoma (usually located near the navel), for the urinary system. A portion of the small intestine is then used to connect the ureters to the stoma to create a new route, or conduit, for urine to pass through. The urine is collected in a urostomy bag that is worn on the outside of the body.
    - *Continent cutaneous reservoir*—With this surgical procedure, a portion of the intestine is used to create an internal pouch, or reservoir, that connects to the stoma. The patient has to insert a catheter to drain urine from the internal pouch several times per day.

IMMUNOTHERAPY

Immunotherapy refers to therapeutic strategies that stimulate a patient's immune response to attack and destroy tumor cells. Traditionally, in the treatment of bladder cancer, immunotherapy is administered locally (meaning confined to one organ), known as intravesical immunotherapy.

- ***Bacillus Calmette-Guérin (BCG) treatment***—BCG is a weakened version of a tuberculosis bacterium that is administered directly into the bladder through a catheter. BCG stimulates an immune response causing the patient's immune cells to attack the bladder cancer cells. BCG was the first immunotherapy approved by the Food and Drug Administration (FDA) and is highly effective at treating noninvasive bladder cancer.

BCG is a standard of care with a success rate of approximately 70 percent for non-muscle invasive bladder cancer.

- ***Interferon alpha treatment***—Interferons are proteins that are naturally made by several types of immune cells. Synthetic interferon alpha is made in the lab to mimic natural interferon alpha and is administered to the bladder directly.

Recently, as of May 2016, a new class of immunotherapeutic agent was approved for the treatment of bladder cancer. See the Immune Checkpoint Inhibitors section on page 19 for more details.

CHEMOTHERAPY

Chemotherapy agents actively target dividing cells. One of the hallmarks of cancer is that tumor cells divide very rapidly and are thus key targets for chemotherapy agents. These drugs limit the ability of tumor cells to divide and spread. In the treatment of bladder cancer, chemotherapeutic agents can be administered directly into the bladder (intravesical) or into the bloodstream (systemically). The FDA has approved seven chemotherapeutic agents for the treatment of bladder cancer (see Table 2). The timing of chemotherapy can also vary depending on the stage of bladder cancer and at the physician's discretion. Chemotherapy can be given before (neoadjuvant) or after (adjuvant) surgery.

- ***Intravesical Chemotherapy***—Chemotherapeutic agents that are administered directly into the bladder have the advantage of only affecting the bladder rather than other parts of the body. Intravesical chemotherapy is typically used for noninvasive or minimally invasive bladder cancer.
- ***Systemic Chemotherapy***—This refers to chemotherapeutic drugs that are injected into a vein and thus travel throughout the patient's body. Unfortunately, normal cells throughout the body also divide (albeit at a slower rate) and thus are impacted by chemotherapy as well. The effect on normal cells causes unwanted side effects (e.g., nausea, vomiting, hair loss). Systemic chemotherapy is typically used for invasive or metastatic bladder cancer.

Table 2. FDA-Approved Chemotherapeutic Agents for Bladder Cancer

Generic Name	Brand Name; Manufacturer	Method of Action	Stage of Disease Treated
Cisplatin	Platinol® or Platinol-AQ®; Bristol-Myers Squibb	Binds to and crosslinks DNA, leading to the inhibition of DNA synthesis and repair.	Stages 0-IV
Doxorubicin	Adriamycin®; Pfizer, Inc.	Inserts itself in between DNA base pairs, thus preventing DNA replication and protein synthesis.	Stages 0-IV
Gemcitabine	Gemzar®; Eli Lilly and Company	Prevents cellular division when the cell attempts to metabolize this agent—an *antimetabolite*.	Stages 0-IV
Mitomycin C	Mutamycin®; Bristol-Myers Squibb	Generates oxygen radicals in the cell and crosslinks DNA, leading to the inhibition of DNA synthesis.	Stages 0, I
Methotrexate	Trexall™; Teva Pharmaceutical Industries Ltd.	Prevents cellular division when the cell attempts to metabolize this agent—an *antimetabolite*.	Stages 0-IV
Thiotepa	Thioplex®; Bedford Laboratories	Damages DNA by adding an alkyl group to the guanine base pair, thereby preventing DNA replication.	Stages 0, I
Vinblastine	Velban®; Eli Lilly and Company	Prevents cellular division by inhibiting spindle fiber formation during mitosis.	Stages 0-IV

RADIATION THERAPY

This localized treatment uses focused, high-energy rays (such as x-rays) to kill cancer cells. External beam radiation therapy (EBRT) is used most often to treat bladder cancer.

A treatment plan for bladder cancer may include one or more of these treatment options and is highly dependent on the stage of disease progression, previous treatments, patient health, and treatment tolerance. As bladder cancer becomes more invasive and eventually metastatic, the treatment options and disease prognosis decreases considerably.

TREATMENT BY STAGE

Treatment options vary by stage of bladder cancer and the physician's discretion. Below is a list a common treatments by stage:

NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC):

- **Stage 0 (noninvasive) and Stage I (minimally invasive):** TURBT surgery followed by intravesical chemotherapy and/or BCG.

MUSCLE INVASIVE BLADDER CANCER (MIBC):

- **Stage II (muscle-invasive):** TURBT surgery is performed to determine the extent of cancer invasion, after which point there are several treatment options:
    - Chemotherapy: Because of muscle invasion, systemic chemotherapy is preferred to intravesical chemotherapy. The physician will also decide whether to administer chemotherapy before (neoadjuvant) or after (adjuvant) cystectomy. The advantage to neoadjuvant chemotherapy is that it allows for tumor reduction before surgery.
    - Radiation: Following TURBT surgery, some patients may undergo a combination treatment of radiation and chemotherapy in lieu of cystectomy. If cancer growth progresses after a follow-up scan, then partial or radical cystectomy will likely be the course of action.
    - Partial cystectomy: This option is viable for patients whose cancer is confined to one side of the bladder; however, it is not common at this stage.
    - Radical cystectomy: This option is dependent on extent of muscle invasion and how many tumors are found in the bladder. Nearby lymph nodes may also be removed at the physician's discretion.
- **Stage III (invasive):** TURBT surgery is performed to determine the extent of cancer invasion. Because the cancer has progressed past the muscle and into nearby tissues at this stage, radical cystectomy with lymph node removal is the standard treatment. In some cases, nearby organs are also removed—prostate and seminal vesicles in men; uterus, fallopian tubes, ovaries, and possibly some portion of the vaginal wall in women. To increase the likelihood of cure, chemotherapy is often administered before cystectomy (referred to as neoadjuvant chemotherapy). In some cases, chemotherapy may be administered after cystectomy (referred to as adjuvant chemotherapy).
- **Stage IV (metastatic):** Surgery is not the first treatment option because the cancer has spread to the pelvic and/or abdominal wall. Systemic combination chemotherapy with or without radiation is the primary option at this stage. MVAC (methotrexate, vinblastine, Adriamycin, cisplatin) is the most widely used combination chemotherapy for treating advanced-stage bladder cancer patients.

THERAPEUTIC DEVELOPMENT

CLINICAL TRIALS—OVERVIEW

Clinical trials are research studies with human subjects that evaluate the safety and efficacy of potential interventions, including drugs, vaccines, and medical devices. To obtain FDA approval for use in human patients, a new treatment must undergo a series of clinical trials from a small-scale Phase I study testing safety and dosage to a large-scale Phase III study testing efficacy and adverse effects (Figure 6).

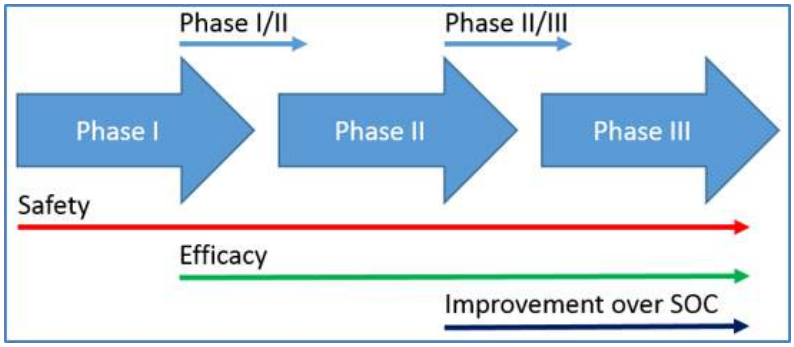

Figure 6. Phases of Clinical Trials

During Phase I, researchers test a new drug or treatment for the first time in a small group of people to evaluate its safety, determine a safe dose range, and identify potential side effects. **During Phase II**, proof-of-concept studies are performed as the drug or treatment is given to a larger group of people to determine effective and optimal dose. **During Phase III**, the drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, and assess its impact compared to the current standard of care (SOC). Some clinical trials involve multiple phases to facilitate seamless transition from one to another and are written as **Phase I/II** or **Phase II/III**. These designations are also used in adaptive trials, wherein study parameters are modified with respect to ongoing trial results.

As a crucial step in the therapeutic development process, clinical trials require substantial resources. On average, it takes $37 million and 5 to 7 years to complete the first three phases of clinical trials, according to Eastern Research Group in a report submitted to the U.S. Department of Health and Human Services (2014). Typical sponsors include pharmaceutical, biotechnology, and medical device companies as well as governmental organizations.

BLADDER CANCER CLINICAL TRIALS

As of April 2016, 203 active interventional clinical trials are evaluating experimental treatments for bladder cancer. Figure 7 illustrates the distribution of the studies by clinical trial phase. The potential interventions include immunotherapies, chemotherapies, gene therapies, cell therapies, small molecule drugs, medical devices, nutraceuticals, and combination therapies that combine any of the aforementioned therapies. Behavioral interventions, such as exercise, diet, and occupational therapy, are not included in the analysis. No new bladder cancer therapy has successfully completed the clinical trials process and received FDA approval in the past 30 years.

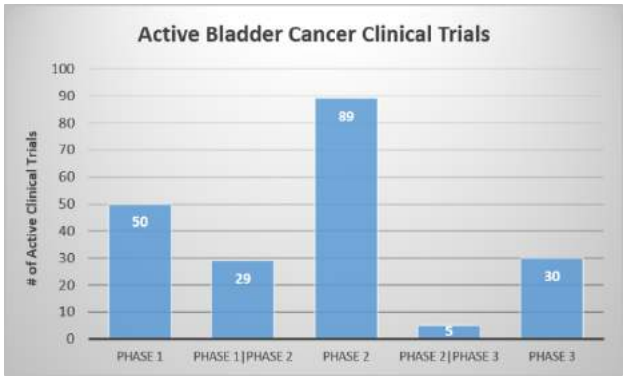

Figure 7. Bladder Cancer Clinical Trials (April 2016)

Eighty-five percent of active, interventional clinical trials have not yet reached Phase 3. Data obtained from www.clinicaltrials.gov.

INVESTIGATIONAL THERAPIES

As of April 2016, 42 distinct products were in in clinical development for the treatment of bladder cancer. This number differs from the number of trials documented in Figure 7 because it does not include combination therapies, nutraceuticals, medical devices, or drugs that may be repurposed from other indications. Figure 8 illustrates the distribution of the investigational therapies by latest phase of clinical development. These therapies aim to eliminate and/or prevent bladder tumors through various strategies, which are described below.

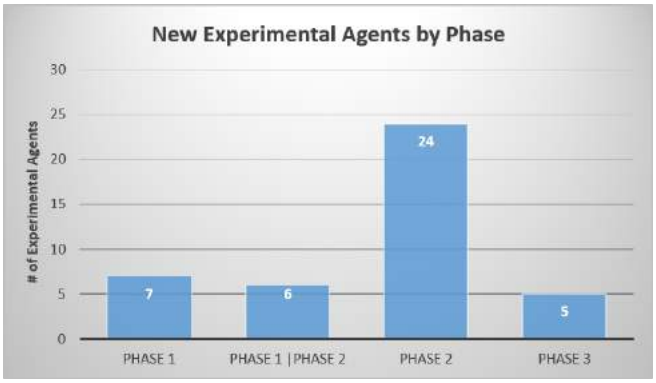

Figure 8. New Therapeutic Agents in Clinical Development for Bladder Cancer (April 2016)
Of the 42 new experimental agents, 5 (12%) have progressed to Phase 3. Data obtained from BioCentury Online Intelligence.

Given the unique unmet needs of bladder cancer treatment, improved therapies for the disease would be well tolerated, reduce recurrence rates or induce cancer regression, and significantly improve the survival of patients.

CANCER IMMUNOTHERAPY STRATEGIES

The immune system consists of several specialized cells that actively monitor the body to detect and destroy foreign agents (e.g., bacteria) and transformed cells. Transformed cells are distinguished from normal cells by their antigens, which are cellular proteins that cause the immune system to make antibodies against it. Although the immune system should be able to detect and destroy tumor cells, many tumors can develop evasion mechanisms to avoid destruction.

Cancer immunotherapy strategies stimulate the immune response to identify and destroy tumor cells, which are inherently masterful at disguising themselves as normal cells to evade the immune system. The relevant strategies discussed below are **immune checkpoint inhibition**, **immunomodulation**, and **vaccination**. In total, there are 17 new investigational immunotherapies for bladder cancer.

IMMUNE CHECKPOINT INHIBITORS

Cytotoxic T lymphocytes (CTLs), also known as killer T cells, are responsible for destroying foreign cells and tumor cells. To control the killing capacity of these cells, a "braking system" is in place to minimize killing of normal cells. This "braking system" is commonly referred to as immune checkpoints, which are molecules that deactivate the killing mechanism of killer T cells. Tumor cells can protect themselves by displaying molecules that can bind to immune checkpoints on T cells, which will activate the braking system and prevent T cells from killing them.

Immune checkpoint inhibitors are molecules that

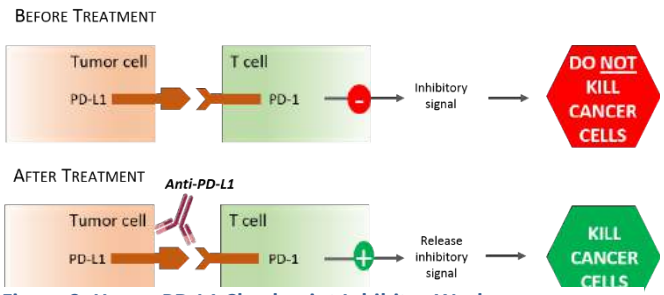

Figure 9. How a PD-L1 Checkpoint Inhibitor Works
A PD-L1 checkpoint inhibitor (called anti-PD-L1) works by binding PD-L1 on tumor cells, which blocks PD-1 on the killer T cell from binding; thus allowing killer T cells to attack and kill tumors. *In May 2016, Atezolizumab (anti-PD-L1, Genentech) became FDA-approved for the treatment of bladder cancer.*

can block the tumor cell from activating immune checkpoints, and thus allow the T cell to attack and kill the tumor (see Figure 9). The mostly actively studied immune checkpoint molecules are programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4).

Within the past 5 years, this therapeutic approach has fundamentally revolutionized the way that cancer is treated. *As of May 2016, Atezolizumab (anti-PD-L1, Genentech) became FDA-approved for the treatment of bladder cancer, representing the first immune checkpoint inhibitor to be approved for bladder cancer.* Two other immune checkpoint inhibitors are currently in clinical development for bladder cancer.

IMMUNOMODULATORS

Five new immunomodulators are currently in clinical development. The overall goal of this strategy is to boost the general immune response by delivering drugs that interact with receptors (a protein molecule that receives chemical signals) on immune cells. By doing so, these drugs activate immune cells to mount an immune response against surrounding tumor cells.

CANCER VACCINES

At present, nine new cancer vaccines are in clinical development. Cancer vaccines stimulate the immune system to recognize specific tumor antigens as a threat and destroy them. Tumor antigens are expected to be solely expressed by the tumor and not normal cells, or selectively overexpressed by tumor cells. *Prophylactic vaccines* are intended to prevent the development of cancer whereas *therapeutic vaccines* are intended to treat existing cancers. Vaccines can be delivered as oncolytic viruses, peptides (short amino acid sequences), or live cells.

- *Oncolytic virus vaccines*—With this approach, a virus that selectively infects tumor cells is injected into the patient. After infecting the tumor, the virus causes the tumor to break open and release tumor-specific antigens and other chemicals that will cause recruitment and activation of other anti-tumor immune cells.
- *Peptide vaccines*—With this approach, one or more peptides that mimic tumor antigens are used with an adjuvant (a substance that stimulates resting immune cells). This induces a potent immune response against the tumor antigens expressed on bladder cancer cells.
- *Live cell vaccines*—With this approach, an antigen is introduced to an immune cell (typically a dendritic cell), which will then activate T cells and cause them to attack tumor cells displaying the antigen that was introduced.

TARGETED THERAPY

At present, six new targeted therapies are in clinical development. Targeted therapies inhibit specific molecules in cell signaling pathways that promote tumor growth, survival, and spread. Cell signaling pathways are cascades of biochemical events that cells use to communicate and execute cellular functions. Abnormalities in signaling pathways that regulate cell growth and survival, such as the MAPK or PI3K/AKT/mTOR signaling pathways, are found in a majority of bladder cancers. As such, this therapeutic strategy involves inhibiting specific molecules within key signaling pathways, such as:

FGFR3-MAPK SIGNALING PATHWAY

FGFR3 is a protein involved in a MAPK signaling pathway. As discussed on page 12, *FGFR3* is either overexpressed or mutated in most bladder cancers and plays a key role in tumor cell proliferation. FGFR3 inhibition should combat the over-activation of the MAPK pathway and result in cell death. New evidence from The Cancer Genome Atlas (TCGA), discussed on page 24, suggests that *FGFR3* mutations are potentially actionable in bladder cancer. Researchers are actively investigating the safety and anti-tumor activity of FGFR3-targeting drugs that can inhibit both normal and mutated forms of *FGFR3*.

PI3K-AKT-MTOR SIGNALING PATHWAY

The mammalian target of rapamycin (mTOR) protein is involved in a PI3K-AKT signaling pathway. mTOR regulates cell growth, motility, and survival. In bladder cancer, mTOR expression increases with disease progression. mTOR inhibition should result in decreased tumor cell growth, motility, and survival. Researchers are currently investigating the safety and anti-tumor activity of mTOR-targeting drugs for NMIBC that is recurrent or refractory to standard BCG therapy.

GENE THERAPY

At present, three new gene therapeutic products are in clinical development. Gene therapy includes, but is not limited to, the administration of genetic materials as drugs. The investigational gene therapies for bladder cancer consist of genetic materials that either block the production of a specific protein, encode for a functional protein, or encode for a cellular toxin that will induce cell death.

CHROMATIN REMODELING THERAPY

At present, two chromatin remodeling agents are in clinical development. Chromatin (tightly packed chromosomes [see Figure 5]) structure contributes heavily to whether a gene is turned on or off. Chromatin structure can be chemically modified, resulting in a structure that is more open (allowing a gene to turn on) or condensed (preventing a gene from being turned on)—this is known as epigenetic modification. For example, histone deacetylases (HDACs) are proteins that chemically modify chromatin to become more condensed, thus promoting gene silencing (Figure 10). High expression of HDACs are found in many bladder cancers and correlates with poor prognosis. Researchers are investigating the anti-tumor activity of HDAC inhibitors and other epigenetic modifiers in bladder cancer.

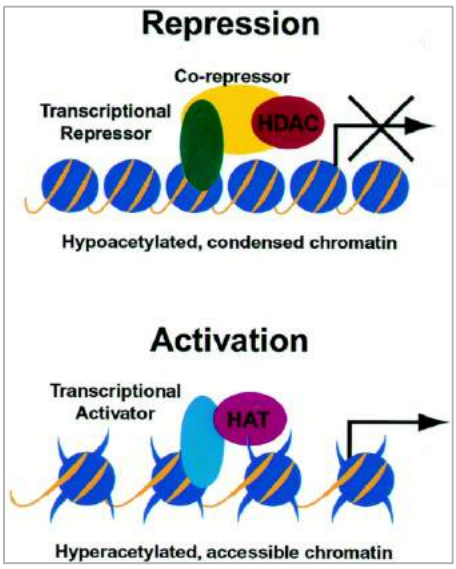

Figure 10. How HDACs Alter Chromatin Structure
HDACs encourage chromatin to condense, thus making genes less accessible and resulting in gene silencing (known as transcriptional repression). Proteins known as histone acetyltransferases (HATs) encourage chromatin to form an open structure, allowing proteins that promote gene expression to access the gene for transcription (the process of converting a DNA sequence to RNA). Wade PA. Human Molecular Genetics 2001; 10: 693-698, by permission of Oxford University Press.

CHALLENGES IMPEDING RESEARCH PROGRESS IN BLADDER CANCER

Though the standard of care has not changed in decades, recent advances in bladder cancer research are cause for optimism. The bladder cancer community stands poised to benefit from the increased understanding of cancer immunology and actionable mutations as both targeted therapy and immunotherapy continue to make a significant impact on other cancers. Yet, several unmet needs remain and must be addressed to effect field-wide change in bladder cancer research. The sections below discuss the following key challenges as identified by bladder cancer experts:

- Lack of collaboration
- Poor clinical trial infrastructure
- Poor understanding of disease genomics

LACK OF COLLABORATION

Science by collaboration—leveraging multiple areas of expertise to tackle multifaceted problems—is fast becoming the new standard. The bladder cancer field has been conducted in silos, because urologists, medical oncologists, and radiologists have not traditionally worked together, resulting in a lack of coordination in both research and clinical care. The lack of collaboration hampers progress and leads to duplicative efforts, which is even more detrimental to this cancer type because of the lack of funding to support duplication. On a systemic level, physicians in community hospitals and academic medical centers (AMCs) generally fail to collaborate. Although this issue is pervasive throughout oncology, the bladder cancer field is disproportionately affected because it is already starved for resources. This field would benefit from efforts to coordinate a research agenda to maximize available funding and move the field forward.

POTENTIAL SOLUTIONS:

- ***Encourage and foster collaborative efforts***—Exploring innovative mechanisms for funding multidisciplinary team science would incentivize researchers to work together. Lower barriers to support cross-institutional collaboration would also benefit the field.
- ***Organize an advisory board to set a coordinated research agenda***—Building on the collaborative funding model, the field would also benefit from a prioritized research agenda to guide philanthropic investment. Common scientific priorities identified by experts are as follows:
    - Understanding the interplay between genomics and immunology
    - Understanding how best to use immunotherapy in bladder cancer (mono- vs. combination therapy)
    - Identifying and validating predictive biomarkers
    - Understanding how to advance bladder-sparing treatments
- ***Incentivize community points of care***—The majority of patients are seen at a community hospital, which is therefore the prime place to coordinate biospecimen collection and clinical trial recruitment. A focused effort to ease biospecimen collection and processing as well as to facilitate coordination between physicians at community hospitals and AMCs would help to mitigate this issue.

POOR CLINICAL TRIAL INFRASTRUCTURE

Effective clinical trial infrastructure would accelerate and streamline translational and clinical research at a multi-institutional level. The bladder cancer field suffers from the lack of a coordinated clinical trial network to run innovative clinical trials. Networks such as the Prostate Cancer Clinical Trials Consortium and Children's Oncology Group have revolutionized the way that clinical trials are run in other disease areas by being nimble enough to react to new findings, streamlining administrative tasks, providing resources, and fostering collaboration.

POTENTIAL SOLUTIONS:

- ***Establish a bladder cancer research consortium***—The field would benefit from an infrastructure that supports innovative clinical trials within an accelerated timeframe. Experts suggest that the field needs adaptive trial designs that incorporate the genetic profile of the patient's tumor.

POOR UNDERSTANDING OF DISEASE GENOMICS

The Cancer Genome Atlas (TCGA) bladder cancer project identified distinct molecular subtypes of disease, providing a fresh focus on the genomics of bladder cancer. This project was the first large-scale effort of its kind to sequence a large number of MIBC patient samples using next-generation sequencing platforms to analyze genetic alterations. A thorough understanding of the genetic landscape of a cancer plays an important role in treatment because several of the new therapeutics target actionable mutations. Additionally, new evidence suggests that the mutational frequency of a cancer can affect its response to immunotherapy. Several experts also echoed the need for integrating next-generation sequencing into clinical decision-making.

POTENTIAL SOLUTIONS:

- ***Encourage large-scale next-generation sequencing***—The TCGA project only utilized MIBC tissue samples from patients who had no prior chemotherapy, which does not capture the full spectrum of genetic alterations that may be important for other stages of bladder cancer. Although the TCGA project was a great start, experts suggested that the effort should be expanded. This would require an infrastructure that enables routine genomic analysis of patients before, during, and after treatment. The simultaneous collection of clinical data (e.g., tumor pathology, patient response to treatment) and genomic information will help researchers make important connections between molecular alterations and clinical outcomes.

COLLABORATIVE INITIATIVES

GOVERNMENT-SPONSORED PROGRAMS

SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPORE)

SPOREs are a part of the Translational Research Program at the National Cancer Institute (NCI) designed to speed the flow of promising knowledge from the laboratory to the clinic. SPOREs are required to reach a human endpoint within the 5-year grant period. The Bladder Cancer SPORE is located at MD Anderson Cancer Center and entails a 5-year, $13.9 million grant to the institution, which currently consists of a:

- ***Career development program*** that trains physician-scientists to formulate research plans with clinically testable hypotheses.
- ***Developmental research program*** designed to support pilot projects in bladder cancer research.
- ***Multidisciplinary research projects***:
    - Improving Diagnosis of Bladder Cancer
    - Role of MicroRNA in Bladder Cancer Risk and Outcome: A Genome-Wide Analysis
    - Targeting FGFR and EGFR in Bladder Cancer
    - Targeting Ral GTPases in Bladder Cancer

INTERNATIONAL CONSORTIUM OF BLADDER CANCER

The NCI International Consortium of Bladder Cancer program was formed in 2005 as an open scientific forum for epidemiologic research in bladder cancer. The main aims of the bladder cancer consortium are to:

- Create a forum for discussion of key challenges in understanding the molecular epidemiology of bladder cancer.
- Provide a mechanism to rapidly replicate previously reported associations.
- Facilitate the pooling of comparable data on environmental and genetic risk factors across studies in order to overcome the limited power of individual studies.
- Consider new ideas and initiate new large-scale efforts.

The consortium consists of a Coordinating Committee that manages its activities and creates working groups for specific projects.

THE CANCER GENOME ATLAS (TCGA)

The Cancer Genome Atlas (TCGA) is a large-scale effort to generate maps of key genomic changes in several types of cancer to thoroughly investigate the molecular basis of cancer. TCGA is a collaboration between NCI and the National Human Genome Research Institute (NHGRI), which began as a 3-year pilot project in 2006. The project was extended due to the success of the pilot, and overall tissue samples from 11,000 patients representing 33 different cancer types were characterized.

MIBC was one of the cancer types characterized in the TCGA. Recently released data analyzing 131 patient samples identified distinct bladder cancer subtypes, potentially actionable mutations, and epigenetic alterations that may

contribute to disease. These findings will help to spur research for many years as researchers investigate the impact of these findings on larger patient populations and drug development.

CONSORTIA AND INSTITUTES

BLADDER CANCER GENOMICS CONSORTIUM (BCGC)

The Bladder Cancer Genomics Consortium (BCGC) is a collaborative effort between the Bladder Cancer Advocacy Network (BCAN) and several medical centers recognized for their expertise in bladder cancer: Dana Farber Cancer Institute, Johns Hopkins, MD Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, The University of Chicago, University of Michigan, and University of North Carolina at Chapel Hill. The goal of the consortium is to develop an enriched understanding of the genomic profile of bladder cancer to facilitate the development of novel therapeutics.

Announced in September 2015, the first BCGC project will be a large-scale genomics study, in partnership with Paradigm, a nonprofit corporation bringing diagnostics and biomarker-driven clinical trials to cancer patients. The participating institutions will initially enroll 200 patients with metastatic bladder cancer. Paradigm will genomically profile the patients using next-generation sequencing (NGS). The patients' physicians will receive the results of the NGS profiles and information about potential clinical trials related to their patients' NGS findings. Hoosier Cancer Research Network (HCRN), an independent nonprofit clinical research organization, will house the data created in the study, which will be accessible to all partners of BCGC for collaborative translational research and development of novel clinical trials. BCAN is investing an initial $1.6 million to underwrite the study management, support services, and genomic sequencing.

BLADDER CANCER THINK TANK

The Bladder Cancer Think Tank, hosted since 2006 by BCAN, is an annual scientific meeting focused on identifying obstacles and creating solutions in bladder cancer research. This invitation-only meeting is attended by urologists, medical oncologists, basic scientists, radiation oncologists, pathologists, patient advocates, and industry representatives from across the U.S. and Canada. The Think Tank expert panels, group discussions, and networking opportunities help to generate ideas and strengthen collaborations between researchers and physicians across disciplines and between institutions, and to define priorities for advancing bladder cancer research.

JOHNS HOPKINS GREENBERG BLADDER CANCER INSTITUTE

The Johns Hopkins Greenberg Bladder Cancer Institute (JHGBCI) was established in 2014 from a $15 million gift from Erwin and Stephanie Greenberg and a $30 million investment from the Johns Hopkins University. Its mission is to develop new clinical strategies for combating bladder cancer through intensive, collaborative, and innovative research. Each year, the institute will award grants of $35,000 to $50,000 to encourage young investigators, support pilot and exploratory projects that help advance the state of science and clinical practice in bladder cancer, and leverage existing resources and expertise. JHGBCI accepts proposals from applicants within and outside of the Johns Hopkins School of Medicine. Grants will be awarded in the following research areas:

- Genetic and epigenetic approaches
- Immunotherapy
- Targeted therapies
- Patient care, prevention, and screening

- Pioneering studies (a flexible category that supports “out of the box” ideas)

LEO & ANNE ALBERT INSTITUTE FOR BLADDER CANCER CARE AND RESEARCH

The Albert Institute was founded in 2014 through a gift from the Leo & Anne Albert Charitable Trust. Its mission is to advance knowledge of, and care for people with, bladder cancer. The institute hosts an annual symposium that provides the platform for development of research agendas and multi-institution projects. In addition, the institute is vested in the development of the next generation of bladder cancer researchers and funds a summer fellowship program for medical students early in their careers.

KEY STAKEHOLDERS IN THE BLADDER CANCER COMMUNITY

This section provides a brief overview of nonprofit organizations that are currently funding bladder cancer research. Organizations that support one specific research center or that dedicate less than $500,000 toward bladder cancer research per year are excluded. The figures reported below are for FY 2014.

AMERICAN CANCER SOCIETY

Founded: 1913
Location: Atlanta, GA
Bladder-cancer specific Grants: $1,562,000

The American Cancer Society (ACS) is a nationwide voluntary health organization dedicated to eliminating cancer as a major health problem through research, education, advocacy, and service. ACS supports research on various types of cancers and does not allocate a predetermined percentage of its funds to any particular type. In 2014, ACS provided approximately $1.5 million in research grants for bladder cancer, representing 1-2 percent of its total grant awards that year.

BLADDER CANCER ADVOCACY NETWORK

Founded: 2005
Location: Bethesda, MD
Bladder-cancer specific Grants: $600,000

The mission of Bladder Cancer Advocacy Network (BCAN) is to increase public awareness about bladder cancer, advance bladder cancer research, and provide educational and support services for the bladder cancer community. BCAN is the only organization whose research grants are exclusively focused on bladder cancer. In 2014, BCAN awarded $600,287 in research grants.

CANCER RESEARCH UK

Founded: 2002
Location: London, UK
Bladder-cancer specific Grants: $6,090,000

Cancer Research UK is a cancer research and awareness charity in the United Kingdom that aims to reduce the number of deaths from cancer. It funds research on the prevention, diagnosis, and treatment of various types of cancer. Research activities are carried out in institutes, universities, and hospitals across the UK, both by the charity's own employees and by its grant-funded researchers. In 2014, Cancer Research UK spent approximately $6.09 million on bladder cancer research, representing 1-2 percent of its total research expenditures that year.

GLOSSARY

Actionable mutations	Genetic mutations that can potentially be targeted by a drug.
Adenocarcinoma	Rare, invasive type of bladder cancer that begins in cells that make up mucus-secreting glands in the bladder.
Antigen	Substance that serves as a target for immune cells and causes an immune response.
Bacillus Calmette-Guérin (BCG)	BCG is a weakened version of a tuberculosis bacterium that is administered directly into the bladder through a catheter.
Biopsy	Medical procedure to remove a piece of tissue or a sample of cells from the body for laboratory analysis.
Carcinoma in situ (CIS)	Noninvasive Stage 0 is bladder cancer. These tumors typically grow in flat sheets and do not grow toward the center of the bladder. Also called flat carcinoma.
Chemotherapy	Type of cancer treatment that uses chemical substances to stop or slow the growth of cancer cells, which grow and divide quickly.
Chromatin	Tightly packed chromosomes.
Chromosomes	Small thread-like structures, made of histone proteins and DNA, found inside the cell nucleus.
Clinical trials	Research studies with human subjects that evaluate the safety and efficacy of potential interventions, including drugs, vaccines, and medical devices. In order to obtain FDA approval for use in human patients, a new treatment must undergo a series of clinical trials.
Computer Tomography (CT) scan	Imaging method that uses x-rays to create pictures of cross-sections of the body. This scan provides information about the size, shape, and position of tumors.
CT urogram	CT scan of the urinary tract.
Cystectomy	Surgical procedure that is performed on invasive bladder cancer and involves the partial (partial cystectomy) or whole removal (radical cystectomy) of the bladder.
Cystoscopy	Medical procedure that involves feeding a lighted, flexible fiber-optic tube (cystoscope) up through the urethra and into the bladder to visualize the interior of the urinary system.
Cytotoxic T-lymphocytes (CTLs)	Immune cells that bind tumor antigens and attack the tumor cells presenting them. Also called killer T cells.
Epigenetic modification	Chemical modification of chromatin to alter its structure and affect the accessibility of the DNA.
Flat carcinoma	Noninvasive Stage 0 is bladder cancer. These tumors typically grow in flat sheets and do not grow toward the center of the bladder. Also called **carcinoma in situ (CIS)**.
Immune checkpoints	Molecules that deactivate the killing mechanism of killer T cells. In essence, they act as the "brakes" for the immune system.
Immunomodulation	Any process that alters an immune response to a desired level. The alterations can either stimulate or suppress an immune response.
Immunotherapy	Cancer treatment that stimulates a patient's immune response to attack and destroy tumor cells. A type of immune modulation.
Interferons (alpha)	A class of proteins that are naturally made by several types of immune cells. A synthetic version of this protein is used to treat bladder cancer (interferon alpha specifically).
Interventional clinical trial	A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.
Intravenous pyelogram (IVP)/ urogram (IVU)	Imaging procedure that involves an x-ray exam of the urinary system, often after the intravenous administration of a specialized dye, which will accumulate in the patient's urinary system and allow for detection of any unusual masses.
Intravesical chemotherapy	Direct administration of chemotherapeutic agents into the bladder.
Invasive bladder cancer	Cancers that grow beyond the transitional epithelium into the connective tissue layer and beyond.
Investigational therapies	Treatments that are currently being evaluated in clinical trials and thus have not been approved for marketing by the FDA.
Metastatic	Spread of a cancer from the site of origin to another organ.
Mutation	A permanent alteration in the DNA sequence of a gene.

Noninvasive bladder cancer	Cancers that are confined to the innermost layer of the bladder, the transitional epithelium.
Oncogene	A gene that accelerates cell division and has the potential to cause cancer.
Papillary carcinoma	Noninvasive Stage 0a bladder cancer. These tumors typically grow from the transitional epithelium toward the center of the bladder in finger-like projections.
Phase I	A new drug or treatment paradigm is tested for the first time in a small group of people to evaluate its safety, determine a safe dose range, and identify potential side effects.
Phase II	A new drug or treatment paradigm is tested in a larger group of people to determine effective and optimal dosing.
Phase III	A new drug or treatment paradigm is tested in even larger groups of people to confirm its effectiveness, monitor side effects, and assess its impact compared to the current standard of care (SOC).
Phase I/II or II/III	Clinical trials that involve multiple phases (as indicated) to facilitate seamless transition from one phase to another.
Positron Emission Tomography (PET)	Imaging procedure that requires intravenous administration of a radioactive tracer, which will accumulate in the patient's organs and allow for 3D imaging of the radioactively traced organs, including the bladder.
Proto-oncogenes	A normal gene, which, when altered by mutation, becomes an **oncogene** that can contribute to cancer.
Radiation therapy	Localized cancer treatment that uses focused, high-energy rays such as x-rays to kill cancer cells.
Sarcoma	Rarest type of bladder cancer that arises in the muscle layer of the bladder wall.
Signaling pathway	Cascade of biochemical reactions inside the cell that eventually reach the target molecule or reaction.
Small cell carcinoma	Rare, highly aggressive type of bladder cancer, in which these cells receive signals from neurons and release hormones into the blood.
Squamous cell carcinoma	Type of bladder cancer that develops from infection and irritation of the bladder. Squamous cell carcinoma is rare in the United States and is more common in parts of the world where a certain parasitic infection (schistosomiasis) is a prevalent cause of bladder infections.
Stage of cancer	Classification of cancers that indicates the size of the tumor and the extent to which the cancer has spread to other organs.
Standard of care (SOC)	Treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals. Also called best practice, standard medical care, and standard therapy.
Systemic chemotherapy	Administration of chemotherapeutic agents into the bloodstream.
Targeted therapy	Form of therapy that uses agents that specifically engage certain biochemical molecules.
Transitional cell carcinoma (TCC)	Type of bladder cancer that starts in the innermost layer of the bladder wall, the transitional epithelium. TCCs account for more than 90 percent of bladder cancers in Western countries.
Transitional epithelium	The innermost layer of the bladder wall. See Figure 4 for illustration.
Transurethral resection of bladder tumor (TURBT)	Surgical exam that is used to provide the formal diagnosis of bladder cancer. During this exam, any visible tumor tissue is removed from the bladder and examined under a microscope. The removed tumor tissue is used to diagnose and stage bladder cancer.
Tumor suppressor genes	Genes that suppress cell growth and signal death when necessary. Normally, these genes inhibit tumor growth.
Urine cytological exam	Examination of a patient's urine under the microscope for the presence of precancerous or cancerous cells.

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