Transforming The Face of Medicine: Advances in Biomedical Science
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Tammy has 14 years of experience in the healthcare industry as a Psychiatric Nurse Clinician and Healthcare Administrator. Before joining Muhlenkamp & Company, she served as Director of Operations for the University of Pittsburgh, Department of Psychiatry Faculty Practice Plan.

Tammy received a dual Bachelor of Science in Nursing and Psychology from Carlow College in 1989. She completed a Master’s in Business Administration from the University of Pittsburgh in 1994. She holds a Chartered Financial Analyst (CFA) designation and maintains Series 6, 63, and 65 securities registrations.
Transforming the Face of Medicine: Advances in Biomedical Science

Advances in biomedical science are transforming the way healthcare is being provided. This booklet examines some breakthrough innovations, along with a look at some of the companies making these advancements. Areas of interest include:

- Personalized medicine;
- Cancer and targeted cancer therapies;
- Immune system;
- Viruses; and
- 3-D bioprinting.

Personalized Medicine

Personalized medicine is the application of information learned from studying the human proteome. Scientific discoveries in the lab continue to make their way into clinical practice, ushering in a new era of medicine. Arriving at this point requires some background.
In the early 1900s, healthcare was provided in the comfort of one’s home. Doctors made house calls to deliver babies and care for the sick. People routinely died at home, often attributed to “old age” or “natural causes.” Doctors didn’t always know why.


By the 1920s, doctors used insulin to treat diabetes and penicillin to ward off bacterial infections. Advances in the 1930-40s led to blood typing and the establishment of the first blood bank, along with a vaccine for the flu. In the 1950s, Jonas Salk developed a vaccine for polio, and Watson and Crick described the structure of DNA as a double helix. Biomedical advances in the 1960s led to the first human heart transplant in South Africa. The 1970s brought us MRI technology (magnetic resonance imaging), which is more accurate than X-rays, along with the first “test-tube baby.” In the ’80s, advances in cardiology enabled a patient to live 112 days with an artificial heart. “Dolly,” a sheep and the first cloned mammal, was “born” in a laboratory in 1996. In 2005, a team of surgeons successfully performed a partial facial-transplant. This is a mere sampling of the numerous biomedical innovations that have taken place over the past century.
Fast forward to today…

There are specialists, high-tech diagnostic equipment, and treatments for just about everything that ails us: orthopedic surgeons who perform hip and knee replacements, surgeons who use robots to assist with procedures, and oncologists who prescribe medicines that target cancer cells, while sparing healthy ones.

Source: Wesley Medical Centre; surgeons using da Vinci® Surgical System.

Using robotics allows doctors to perform complex surgeries with minimally invasive procedures, improving patient outcomes.
We are living in an era of near optimal diagnosis and treatment to manage most diseases. Lifespans have increased significantly:

![Life expectancy graph](image)

Source: 1900-1960 Andrew Noymer, University of California Berkeley; 1961–2012 World Bank. The average life expectancy for men and women in the U.S. has increased from age 47 to 77 since 1900. The exception was in 1918-19 during a flu pandemic that infected an estimated 500 million people worldwide (about one-third of the world’s population at the time) and claimed an estimated 20 million to 50 million victims.

But we still don’t have all of the cures…

Today, in response to ailments, doctors prescribe a course of action to diagnose and treat what is wrong. While the predominant model of healthcare remains curative, advances in biomedical science are shifting this model of care towards one of prevention and personalized medicine.

How so?
With the mapping of the human genome that was completed in 2003, scientists have an inventory of our genetic makeup. This was a monumental achievement as it provides scientists with a catalogue containing the code of life.

Source: http://novaonline.nvcc.edu

DNA is the genetic blueprint found in cells, responsible for the transmission of inherited traits. The structure of DNA was discovered in 1953 by James Watson and Francis Crick.
Think of the human genome as a globe of the earth. It is a useful model, providing a complete, albeit broad picture.

Source: Wake Up World; July 2012
Funded by the US government, the Human Genome Project began in 1984 and was completed in 2003. This international scientific collaboration sequenced human DNA, resulting in a map of the human genome.

But, how many of us would use a globe for driving directions?
About 99.90% of the genetic material in human beings is the same for any two people. It is the remaining 0.10% that is critical, as the risk for disease and the response to medication are contained in these functional variants. This is why we need a more dynamic and precise navigation system—like Global Positioning Satellite or GPS. Scientists are now developing this more specific map, known as the human proteome, to better understand how our genes are related to life, disease, and death.

Source: Journal of Proteome Research; January 2013.

The Human Proteome Project, by characterizing all 20,300 genes of the known genome, will generate the specific map of the protein-based molecular architecture of the human body. The human proteome will become a resource to help illustrate biological and molecular function, and advance diagnosis and treatment of diseases. As of May 2014, two independent teams have assembled draft maps of the human proteome. The future is very promising, but this global collaboration will take time to translate insights from the lab into clinical care.

The word proteome comes from the phrase “PROTEins expressed by a genOME.” This is important because the proteins expressed by our genes and how they work—their sizes, shapes, functions, interactions, and signaling pathways—are the dynamic and precise part of our genetic code. The human proteome is the critical link to understanding the relationships among genes, proteins, and disease.
Biomedical insights gained from studying the human proteome provide the foundation for personalized medicine. There are two broad implications:

- Information can show up in our genetic material long before we have any symptoms of illness. Knowing what to look for, we can take steps to potentially prevent or delay disease from occurring.
- When disease does occur, we have a better understanding of the underlying cause based on the genetic material, and personalized, targeted medical treatments can be developed and delivered.

An individual’s genetic code becomes an “Owner’s Operations Manual.” It is a tool that allows you and your doctor to establish a personalized plan of health and treatment. It is important to remember this “manual” does not predict the future. When an individual carries a genetic mutation associated with a specific disease, it does not necessarily mean it will develop; several factors enter the equation.

**Source:** [www.lifetechnologies.com](http://www.lifetechnologies.com)

Ion Torrent® is an example of a desktop printer-sized personal genome machine that can sequence your entire genome, or relevant parts of your exome, in a few hours. Sequencing provides doctors with the “Owner’s Operations Manual” to determine your personalized plan of health and treatment. (Exome sequencing targets the region of the genome responsible for complete coding. The exome is often where the functional variants responsible for disease occur in proteins.)
Examples of Personalized Medicine in Clinical Care

Today, there are genetic tests for a variety of diseases. For example, the BRACAnalysis® is a genetic test that confirms the presence of a BRCA1 or BRCA2 gene mutation associated with future development of a specific type of breast and ovarian cancer. (You may recall Angelina Jolie brought this issue front and center in May 2013, when she announced her decision to have elective surgery to reduce her risk of developing cancer based on her positive test and family history.)

Source: http://www.cdc.gov/Features/HereditaryCancer
Between 5%-10% of breast cancers are inherited and up to 90% of these are related to mutations in BRCA1 and BRCA2. When healthy, these genes repair damaged DNA and protect against certain cancers. Women who inherit a mutated BRCA gene have a higher risk of developing breast and/or ovarian cancer.

Genetic testing is also available for other types of cancer, including prostate and thyroid. The Prolaris® test measures the level of genes involved in prostate tumor proliferation. This test helps doctors determine disease aggressiveness, as well as prescribe personalized treatments. The Afirma Thyroid FNA Analysis®, a 142-gene expression test, allows doctors to determine if the thyroid nodules in question are benign or cancerous. This test can prevent unnecessary invasive surgery, along with life-long thyroid replacement medication.

Providing doctors and patients with more effective treatment options and improved outcomes is the goal of personalized medicine.
Cancer and Targeted Cancer Therapies
What “causes” cancer? Biomedical research has concluded that cancer is a genetic disease.

Cells are the basic unit of life that contain our genetic code. The average human being has more than 100 trillion cells. Each cell has a specific purpose; some cells have short lives, others long. It is estimated that about 1 million cells die every second, amounting to our body weight annually. Normally, to replace one of the dead cells, an existing cell must divide. For each division to be successful, the entire genetic code of the mother cell must be copied to the daughter cell.

Compare cell replication to photocopying every page of an encyclopedia a trillion times a day. You can begin to imagine the number of errors that may occur, resulting in genetic mutations.

Just like attempting to photocopy massive volumes of paper, errors can occur in cell replication. Fortunately, our cells are equipped with enzymes that help copy, proofread, edit, and correct errors. As with most things in life, this system is not foolproof. Sometimes, errors get passed along. Errors in our genetic material are called mutations.
Over time, mutations can accumulate and cause cancer and other diseases. Mutations may occur on their own, as part of the normal process of life. Other times, they are inherited. Mutations can also be activated by repeated exposure to environmental hazards like high doses of radiation. When mutations accumulate, they often form solid masses known as tumors.

Source: Foundation Medicine; www.foundationmedicine.com

Imagine if tumors could talk! This illustration depicts a tumor (purple mass) expressing its unique genetic makeup, a combination of the three billion subunits (Bases A,C,T, and G).

Through biopsy or surgery, solid tumor tissue can be analyzed using next-generation genomic sequencing technology. The FoundationOne® test decodes a tumor’s DNA, compares it with all genes known to be relevant in human cancers, and matches any mutations with targeted therapies.

Historically, cancers were categorized and treated based on where they occurred in the body: lung, breast, colon, pancreas, skin, blood, etc. With advances in biomedical science, cancers are now being categorized and treated based on their underlying genetic mutations.
Traditional cancer treatments include surgery, radiation, and chemotherapy. Newer treatments include targeted cancer therapies: drugs or other substances that interfere with specific proteins involved in cancer cell growth and survival. Traditional chemotherapy acts against all actively dividing cells and, typically, has more harmful side effects. Targeted cancer therapies use information about a person’s genes and proteins to prevent and treat disease.

Several types of targeted cancer therapies have been approved for use:

<table>
<thead>
<tr>
<th>TYPE OF TARGETED THERAPY</th>
<th>HOW THEY WORK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone Therapies</td>
<td>Slow or stop growth of hormone-sensitive tumors; prevent body from producing the hormone, or interfere with how hormone works.</td>
</tr>
<tr>
<td>Signal Transduction Inhibitors</td>
<td>Block harmful communication between molecules within cancer cells; stop cancer from growing.</td>
</tr>
<tr>
<td>Gene Expression Modulators</td>
<td>Modify the function of proteins that control how genes are expressed in cancer cells.</td>
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<tr>
<td>Apoptosis Inducers</td>
<td>Apoptosis is one way the body rids itself of abnormal cells. Cancer cells block apoptosis; these therapies restart the apoptosis process.</td>
</tr>
<tr>
<td>Angiogenesis Inhibitors</td>
<td>Block the formation of new blood vessels necessary for tumor growth.</td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>Deliver toxic molecules or radioactive substances, killing targeted cancer cells, without affecting surrounding cells.</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Preventive vaccines inoculate healthy people against cancer. Treatment vaccines strengthen a cancer patient’s immune system.</td>
</tr>
</tbody>
</table>

Source: Muhlenkamp & Company, Inc.

Despite their promise, targeted cancer therapies have limitations. Cancer cells can continue to mutate and develop resistance to these medications. Further, the complexity in structure and function of some proteins makes it challenging to develop new therapies. As an example, scientists are working with the ras gene family, which is elusive and difficult to regulate. Continued research is important because ras genes—signaling proteins involved in tumor formation and growth—occur in as many as one-quarter of all cancers and in the majority of pancreatic cancers.
The Immune System

In an effort to find a cure for cancer, researchers continue to broaden their scope. Immune oncology marks an entirely new way of approaching cancer. Scientists are developing treatments that target the immune system—not cancer cells—making it applicable to a broad range of cancers.

Our immune system helps to protect us from disease. We have a front line of defense like our skin and the body’s general response that prevents infection with every little cut. We also have more specific defenses deep within our cells. Every day, we encounter countless external threats, such as bacteria, viruses, parasites—any foreign invader—and our immune system selects the appropriate response. There are also internal threats, including the mutations and cancer cells previously discussed. Known as immunosurveillance, the immune system recognizes and attacks these cancer cells.

How does immunosurveillance work?

Simply stated, the body can tell the difference between cancer cells and non-cancer cells based on specific proteins that are released. Remember, cancer cells are very clever. They have the capacity to cloak themselves and evade detection. Further, they can deregulate, disarm, and shut down the immune system. When the immune system shuts down, cancer cells accumulate and overrun the body.

Many of the immune system’s anti-cancer responses are being studied in clinical trials. As referenced in the table on page 13, monoclonal antibodies are “delivery vehicles,” historically used to target and destroy cancer cells. In immune oncology, scientists engineer these vehicles to specifically target and reregulate components of the immune system. Think of this new class of medications as akin to driving a car. In order to initiate a successful tumor-killing immune response, you need to “fill the tank.” Once started, you need to “take your foot off the brake” and, then, “press the gas.” Though simply stated, this analogy explains how a new class of medications is being designed to reregulate different parts of the immune system that had been shut down. Because the relationship between cancer and the immune system is so complex, scientists think the greatest potential in the field of immune oncology is to target two or more of these immune drivers at the same time: “1+1=3.” Additionally, scientists are evaluating the benefits of prescribing both immune oncology and targeted cancer therapies, referred to as “combination therapy.”

Scientists think that restoring appropriate function of the immune system will greatly improve outcomes and, possibly, provide a cure.
Viruses

Viruses are tiny organisms that cannot exist on their own. A virus requires a host—be it plant, animal, or human. Once it invades the host, a virus hijacks a cell’s replicating hardware and inserts its own DNA. Then the virus begins to reproduce, forever altering the host’s genetic material.

Broadly speaking, viruses vary in their potency; some are benign like strains of the flu, while others are more life-threatening, such as HIV and hepatitis.


Undetected and untreated, the hepatitis C virus can cause liver disease and cancer. Largely a mystery, hepatitis C viruses have no color and are smaller than the wavelength of visible light. Technically speaking, hepatitis C is an RNA virus, which means it mutates frequently. So, once an infection has begun, hepatitis C creates different genetic variations of itself within the host. These mutated forms are frequently different enough that the immune system cannot recognize them. Once thought of as a chronic life-long condition, a cure for hepatitis C is now available.

Despite their menacing features, viruses have attractive characteristics.
Given their ability to penetrate a host cell and alter the genetic material, scientists are reengineering viruses. They are creating therapeutic agents by inserting, deleting, and/or inactivating various genes within the virus to achieve a desired effect. A bioengineered virus can then be combined with a medication to target disease, including cancer.

Source: www.nature.com. Gene therapy.

When a bioengineered virus is combined with a cancer-fighting medication, it is known as oncolytic immunotherapy. This illustration shows the cancer-killing power of an oncolytic adenovirus (“oncolytic ad”). Oncolytic agents specifically target cancer cells, while sparing healthy cells. The viral “offspring” then spread throughout a tumor and surrounding area, ultimately resulting in improved antitumor effects.
3-D Bioprinting

Three dimensional (3-D) printing originated in the 1980s, providing a technology that is now used to manufacture everything from small houses for families in China, to prosthetic limbs for patients across the globe. Though an emerging field, the promise of 3-D bioprinting is even greater.

3-D bioprinting uses computerized additive manufacturing to build human tissues. Through this process, bio-ink (a “paste” of living cells) is deposited layer upon layer onto biological designs that have been programmed into a computer. This technology allows scientists to create human cells and tissues used for research, drug development, and personalized medicine.

Scientists are now experimenting with printing a wide variety of cells and tissues, including bits of lung, kidney, heart, liver, skin, muscle, and cartilage. The hope is that, someday, bioprinted organs can be created on demand using a patient’s own cells, lowering the risk of rejection by their immune system.
3-D bioprinting differs from traditional tissue engineering in which cells are cultured and then seeded onto individual biodegradable molds or scaffolds. 3-D bioprinting is more precise because the printers run under computer control. Organs and tissues vary in complexity. Flat structures like skin or cartilage are less complex than tubular ones like blood vessels or windpipes. Organs like the kidney, liver, and heart are even trickier.

Source: www.explainingthefuture.com

Scientists hope to bioprint replacement organs on demand according to patient-specific needs. 3-D bioprinting derived from today’s inkjet printers.
The NovoGen Bioprinting™ platform generates bioprinted liver tissue used in drug development, improving therapeutic drug discovery and development.

Biomedical research in the United States is a $100 billion industry, with approximately 65% supported by commercial enterprise. Advances that make their way into clinical practice are transforming the way healthcare is being provided. In addition to improving the human condition, we think there are ample investment opportunities.

Following are snapshots of some of the companies we find interesting:

**Gilead Sciences (GILD)**

Gilead has expertise in infectious diseases, especially viruses. For more than a decade, Gilead has been changing the face of HIV. Once considered a death sentence, HIV attacks the body’s immune system, making those infected susceptible to cancer and other life-threatening diseases. With Gilead’s medications, patients’ lives have improved, changing a death sentence into a condition that can be managed. Early treatments for HIV required taking handfuls of pills, several times a day and, if you failed to do so, you were at risk of developing AIDS and dying. Not only are Gilead’s medications more effective in treating HIV, they have combined several medications into one pill which makes managing the condition easier. But they haven’t stopped here. Gilead is working tirelessly to find a cure for HIV, much like they’ve found a cure for the hepatitis C virus.

Hepatitis C silently attacks the liver, causing increasing amounts of damage. Once diagnosed, it requires an extensive life-long medication regime. In December 2013, Gilead received FDA approval for its hepatitis C medication. The medication cures certain strains of hepatitis C in 8-12 weeks.

**Celgene (CELG)**

Celgene has expertise in understanding the relationship between cancer and the immune system. Their medications work by attacking cancer cells and boosting the immune system. With these characteristics, the medicines are helpful in treating a variety of cancers, ranging from blood and soft tissue to solid tumor. Additionally, Celgene has a broad and deep pipeline of cutting-edge compounds in clinical-research trials.

**Bristol-Meyers Squibb (BMY)**

Bristol-Meyers Squibb is a traditional pharmaceutical company in the midst of reinventing itself into a leading global biotech company. Bristol-Meyers Squibb was the first to obtain FDA approval for an immune oncology therapy.
Current and future portfolio holdings are subject to risk.

Company holdings and sector allocations are subject to change and should not be considered a recommendation to buy or sell any security.

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