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LETTER FROM THE EDITOR

Dear readers:

Welcome to the second edition of *ReFlections* for 2013. The first article in this issue illustrates important underwriting, actuarial, and epidemiological concepts regarding traumatic brain injuries. The authors of this article, Julianne Callaway and Michael Hill, discuss the risk factors related to head injuries as well as the possible sequelae associated with them.

The second article, contributed by Dr. Oscar Cartaya, is the first segment of a lengthy discussion regarding the roles of the genome and immunity in the development of cancer. I expect that it will stimulate your interest in this field. The second part of this article will be published in the next issue of *ReFlections*, later this year.

Finally, our regular contributor, Sue Wehrman, will continue with her mission of raising your awareness of Electronic Health Records and discussing their impact on how we underwrite in insurance medicine.

J. Carl Holowaty M.D., D.B.I.M.

THE INSURANCE IMPLICATIONS OF TRAUMATIC BRAIN INJURY

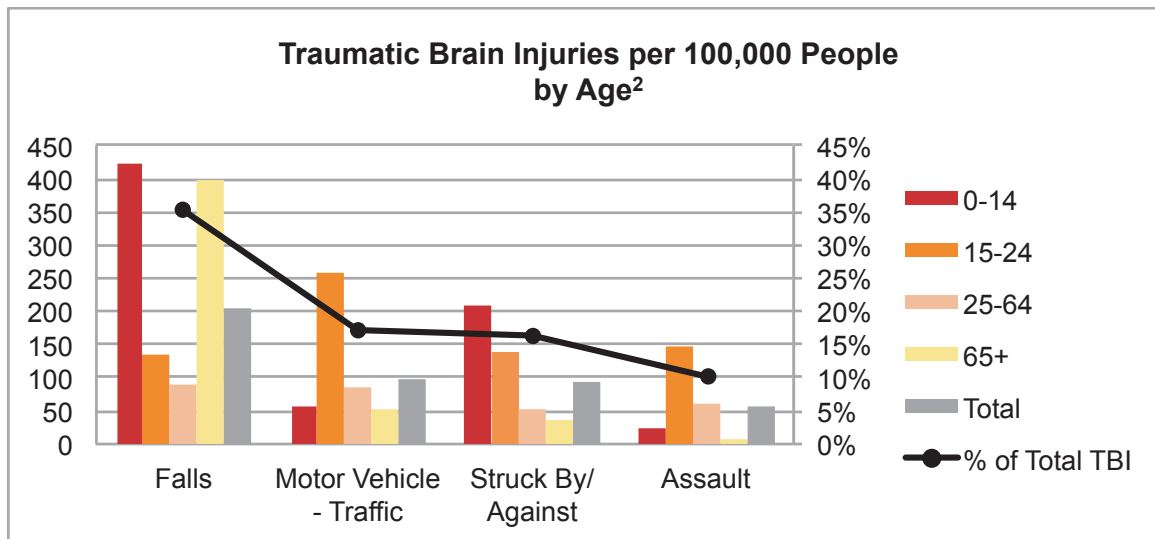
By Julianne Callaway, Assistant Actuary, Global Research and Development, RGA Reinsurance Company; and
Michael Hill, Senior Underwriting Consultant, U.S. Mortality Markets, RGA Reinsurance Company

Traumatic brain injuries (TBI) affect millions of American families each year. Injuries can range in severity from mild to severe to penetrating. Mild traumatic brain injuries are commonly referred to as concussions and account for approximately 75% of all traumatic brain injuries. These injuries can

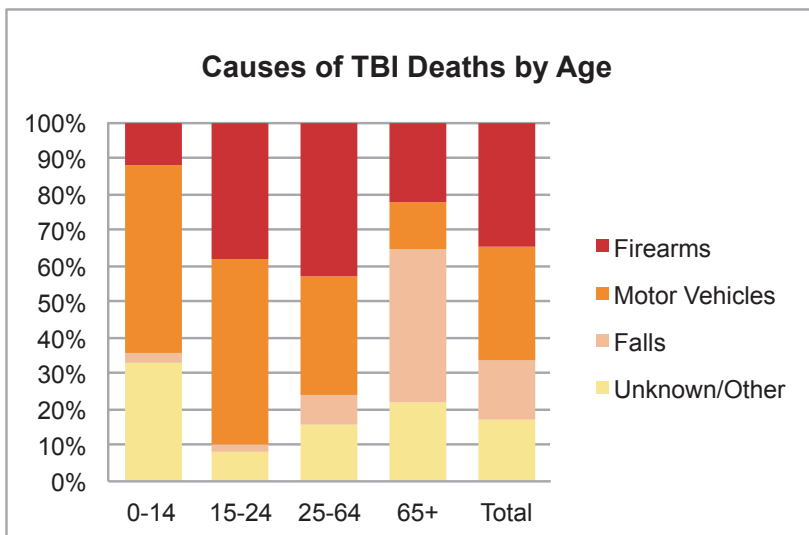
result in persistent neuropsychological problems and impede the injured person from returning to a pre-accident level of ability.¹ There are approximately 1.7 million traumatic brain injuries in the U.S. annually, many injuries result in a long-term disability and approximately 52,000 TBIs are fatal.² In fact, more people die each year in the United States from TBI than from HIV, prostate cancer and skin cancer combined.³ Everyone is exposed to the risk of injury, from children and older adults who are more likely to fall, to young adults who are disproportionately injured in motor vehicle accidents. People who experience a TBI have increased mortality and morbidity. Therefore, TBI may be a consideration for many insurance products including Life, Accidental Death, Disability, Critical Illness, and Long-Term Care.

Causes of Traumatic Brain Injury

Falls are the most common cause of traumatic brain injury in the United States. According to the Centers for Disease Control and Prevention (CDC), over 35% of all TBIs are the result of falls, and the rate of fall-related TBIs is highest among young children and older adults. Approximately 50% of all TBIs among children under age 15 are due to falls, while falls account for more than 60% of all TBIs experienced by adults over age 65. Motor vehicle accidents are the second leading cause of TBI, with the highest rate experienced by 15-24 year-olds. Additionally, motor vehicles accidents are a leading cause of death resulting from traumatic brain injury. Accidents classified as resulting from a strike to the head ("Struck by/Against") tend to receive the most attention, but account for about 16.5% of all TBIs. This category would include sports-related injuries as well as many occupational injuries. Assaults account for roughly 10% of all TBIs, with the highest rate of injury among 15-24 year-olds.²



While over 80% of people who experience a traumatic brain injury are treated and released from an emergency room, an estimated 52,000 deaths occur annually as a direct result from traumatic brain injury.²



Fatal TBIs are a consideration for both Accidental Death and Life Insurance policies. Motor vehicle accidents are the leading cause of TBI-related death in young adults and children, under age 24. Roughly 50% of these fatalities occur from being an occupant of the motor vehicle, while approximately 10% are accidents involving bicycles and pedestrians.⁴

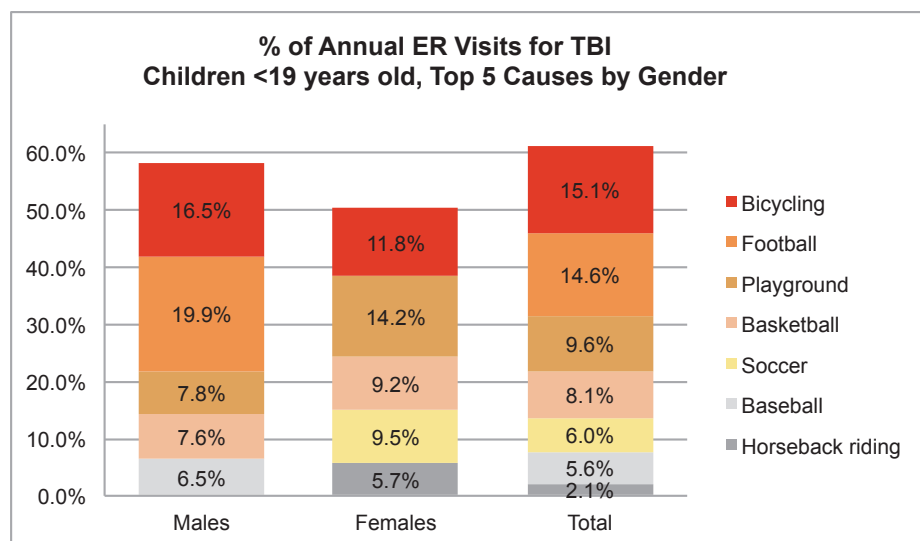
Source: ⁴

Injuries from firearms are the leading cause of death from TBI. This includes both suicides and homicides, where suicides comprise roughly 75% of all firearm fatalities. Causes of traumatic brain injury resulting in death vary by age group. People age 15-24 are more likely to die in a motor vehicle accident and older adults are more likely to die as the result of a fall.⁴

At-Risk Activity and Ways to Prevent Injury

Falls are the leading cause of TBI in the elderly and children. People can decrease the risk of falling by considering prior falls and making modifications to mitigate the factors that contributed to the fall. Older adults can reduce the risk of falling by considering health conditions, and improving mobility through exercise and use of assistive devices.⁵ Parents can reduce the risk of injury to children by appropriately child-proofing the home as well as carefully supervising play.⁶ While falls are the primary source of TBIs among younger children, the overwhelming majority of TBIs for youth aged 15-19 years are transportation-related. The rate of TBI from transportation incidents for youth aged 15-19 is 2.5 times as high as the overall transportation average.² Appropriate use of seatbelts can greatly reduce injury in automobile accidents.

Participation in sports and recreation activities exposes people to risk of TBI. For children under age 19, the most common activity associated with a TBI treated in an emergency room (ER) is a bicycling accident. Children should wear an appropriate helmet any time they are on a motorcycle, bicycle, skateboard, snowmobile, scooter, skates, or an all-terrain vehicle.⁴ The rate of injury from sports and recreation activity varies by age and gender. The most common activity resulting in a traumatic brain injury in 10-19 year-old U.S. boys is football, while playground accidents are the cause of the most TBIs in all children under age four. The chart below shows the five most common activities for boys and girls under age 19 resulting in a TBI-related ER visit. These activities in total account for over 60% of all TBI-related ER visits for children.⁷



Source: ⁷

The remaining 39% of annual emergency room TBI visits for children are due to a wide range of various other causes, each accounting for 0.1%-4% of ER visits.

Each year, more than 300,000 people experience a sports-related TBI.⁸ Use of protective equipment and adopting safety measures can minimize the number and severity of sports-related injuries. When a head injury has occurred it is imperative that the symptoms are recognized and the player is removed from a game. Evaluation should consider concussion history because it can affect the severity and duration

of symptoms. A player should only return to play after all symptoms have resolved and an evaluation with an experienced healthcare provider has determined it is safe for the player to return to the game. By increasing awareness of TBI risks from sports and recreation, employing proper technique and protective equipment, and quickly responding to injuries, the incidence, severity, and long-term negative health effects of TBIs among athletes can be reduced.⁷

Occupational injuries also pose a risk for traumatic brain injury. It is estimated that 20% of workplace traumatic brain injuries are caused by slips and falls.⁹ Additionally, workers over the age of 65 are the most at risk to experience a fatal TBI. The occupations with the highest risk of brain injury include construction, transportation, agriculture, forestry and fishing. These industries also pose the greatest risk of death from TBI, accounting for roughly half of all workplace TBI fatalities.¹⁰

The causes of traumatic brain injury are diverse, yet all people who experience a TBI are exposed to an increased likelihood of long-term sequelae resulting from the injury.

Consequences Resulting from Traumatic Brain Injury

The majority of people who experience a TBI expect a full recovery with no long-term consequences; however, approximately 15% of traumatic brain injuries result in long-term disability or impairment.¹¹ The residual cognitive impairment, emotional disturbances, and behavioral changes after head injury can continue long after the physical disabilities have resolved.

Post-Concussion Syndrome occurs when concussion symptoms persist for weeks, months, or rarely, years following a brain injury. Approximately 60% of those with a concussion will continue to experience symptoms one month after injury. For 15%, concussion symptoms continue for a year or more.¹¹ The most common persistent symptom is a headache. A study of children and adolescents who were seen in an emergency room for TBI, found that those patients who had a headache and required hospitalization were most likely to experience post-concussion syndrome.¹²

One of the consequences of severe traumatic brain injury may be a shortened expected life. One study estimated the remaining life expectancy for a severely brain damaged 30-year-old man is 18.6 years shorter than an average 30-year-old man. Further, a severely brain damaged 30-year-old man is 10 times more likely to die in the next 12 months than an average man of the same age.¹³

People who experience repeated traumatic brain injury may have increased likelihood for neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS), later in life. A study of former professional football players found that their neurodegenerative mortality was four times higher than the general population for Alzheimer's disease and ALS and three times higher for Parkinson's disease.¹⁴

There is increasing research around the long-term consequences of repetitive TBI. Athletes who participate in contact sports and have experienced several traumatic brain injuries may be at risk for developing chronic traumatic encephalopathy (CTE). Many of the same symptoms of neurodegenerative diseases, as well as depression, aggressive and suicidal behavior, are present in people who are later determined to have had CTE.^{15,16}

Because traumatic brain injuries can result in persistent neuropsychological problems, a comprehensive neuropsychological evaluation may be appropriate. A neuropsychologist can measure cognitive and behavioral functions using a set of standardized tests and procedures to confirm or clarify a diagnosis, track progress in rehabilitation, guide effective treatment methods, and localize organic abnormalities in the central nervous system.¹⁷ An additional value of neuropsychological testing is to document persistent cognitive changes which, even while subtle, may have an impact on expected mortality. A neuropsychological evaluation may be used to identify neuropathological impairments in specific cognitive domains, as well as relate the test results to an individual's ability to perform everyday tasks. This evaluation is beneficial in rehabilitation to assess the functional abilities of the injured person and develop an individualized treatment plan.¹⁸

Factors that Influence Recovery

There is evidence that age is a factor contributing to recovery from a TBI. A study comparing length of recovery following a concussion of collegiate and high school athletes found that high school students had a significantly longer recovery period than college age athletes.¹⁹ The younger brain may be more vulnerable to injury because it is not fully developed, is protected by thinner cranial bones and youths have a higher 'head-to-body' ratio.⁸ However, while children take longer to recover, the elderly are more likely to die or require hospitalization for an injury.²

Traumatic brain injuries that result in long-term impairment may be a consideration for Disability Insurance. Likewise, shortened life expectancy resulting from TBI impacts Life Insurance experience. Additionally, people with impairment or subsequent neurodegenerative diseases may have increased Long-Term Care benefits.

Males account for the majority of traumatic brain injuries in the U.S.² However, in sports in which both genders participate, women have a higher rate of injury.²⁰ Additionally, women have a longer recovery time than men. Studies have shown that women take longer for symptoms to resolve and are more likely to experience long-term cognitive difficulties.¹¹

Concussion history also affects recovery. People with prior concussions take longer to recover and experience more-severe symptoms compared with those without prior concussions. Additionally, a study that compared athletes without a history of concussion with those that had three or more previous concussions found that those with a history of concussion were 7.7 times more likely to have a drop in memory abilities a few days after a concussion.²¹ Athletes with a history of concussions are more likely to experience a prolonged length of recovery as well as an increased likelihood of experiencing a subsequent concussion.²²

Trends

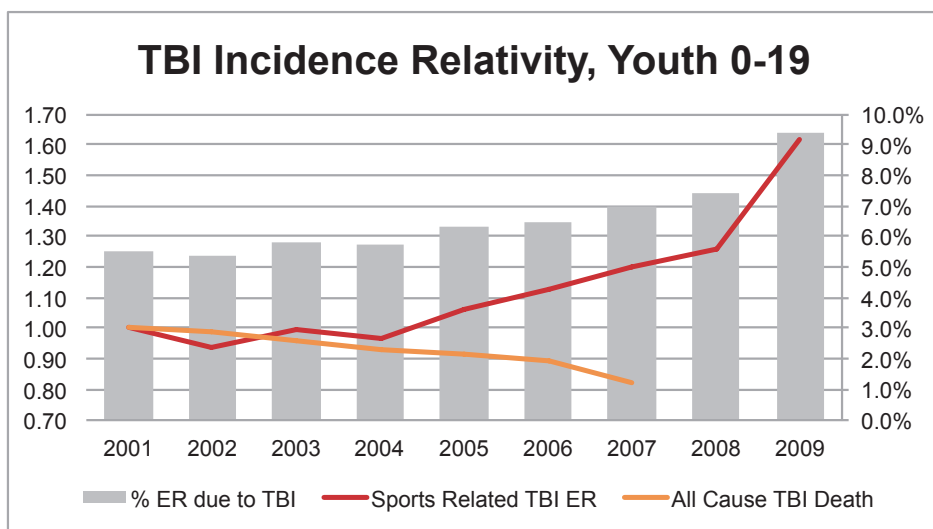
Over the period from 1997 to 2007, the average annual death rate associated with TBIs declined by 8.2%, from 19.2 to 18.1 per 100,000 population. The TBI death rate decreased over this period for all causes of injury except falls. However, the overall decline was not consistent by age group. While TBI-related death rates decreased over 25% for people under age 25, they increased by 14% for older adults over age 65. This increase was especially high for those over age 85.⁴

While TBI-related deaths declined in recent years, especially for youth, the number of TBI-related ER visits for children related to sports and recreation accidents increased. From 2001 to 2007 the annual number of non-fatal sports and recreation TBI ER visits for children under age 20 increased 20%; the annual number of visits increased by more than 60% when comparing 2001 to 2009.

Interestingly, the overall number of sports-related ER visits for children under age 20 from all types of injury declined from 2001 to 2009. In 2001, just over 5% of children seen in the ER for sports-related injuries had experienced a TBI; by 2009 that number had increased to almost 10%.⁷ Also, over the same period, the annual number of deaths from TBI for children under age 20 declined by 18%.⁴

Additionally, from 2005 to 2009, the overall annual number of adolescents, age 10-19, hospitalized due to TBI decreased by more than 20%. The rates of hospitalization from TBI declined for all severities, from mild to severe.²³ Therefore, while there has been a significant increase in sports-related TBI ER visits by children in recent years, it should be noted that it is unclear whether the rise is due to an increase in incidence or heightened awareness of TBI and concussions.

According to the CDC, fall-related TBI rates for adults over age 65 increased from 2002 to 2006. Emergency department visits increased 46% and the rate of hospitalization increased 34%.² These costs have an impact on the benefits insurers provide, such as Long-Term Care.



The trends in traumatic brain injury incidence vary by age and activity. While the overall rate of TBI fatalities has declined in recent years, several groups of people have experienced an increase in injuries. The elderly, who are a growing segment of our population, have seen a rise in TBI fatalities. Children participating in sports and recreation have experienced an increase in the number of TBI-related emergency room visits. Therefore, it is clear that the effects of TBI will be present for many Americans in the years to come.

Source: ^{4, 7}

Future

There is currently no consensus regarding a safe level of head trauma. No standard exists to assess the number or severity of hits that will lead to impairment or cognitive problems. Researchers have used sensors in helmets to assess the level of impact a player experiences in a game. There is evidence that concussions can result from the cumulative total of smaller events, rather than a single impact.²⁴

Researchers are investigating the relationship between repeated head trauma and neurodegenerative diseases. Many people who experience multiple concussions develop diseases such as Alzheimer's, Parkinson's and ALS later in life. In a recent study, autopsies were conducted on brains of 85 people who had experienced repeated mild TBI. The study found that 80% of these people showed signs of chronic traumatic encephalopathy, CTE.²⁵ Therefore, there is some evidence that suggests repeated minor impacts may have long-term neurological consequences.

On April 2, 2013, U.S. President Barack Obama announced plans for an initiative, Brain Research through Advancing Innovative Neurotechnologies (BRAIN). The ultimate goal of the initiative is to identify ways to better understand neurological and psychiatric disorders in order to treat, cure, and perhaps prevent brain disorders such as Alzheimer's Disease, Parkinson's disease and traumatic brain injury.²⁶

Insurance Implications

Millions of Americans experience traumatic brain injuries each year. While most expect a full recovery, many will experience long-term sequelae from their injury. Because the causes of TBI are diverse and affect people of all ages, the insurance implications of traumatic brain injury are far-reaching. While the numbers of deaths and hospitalizations have decreased in recent years, traumatic brain injuries continue to have significant implications for multiple product lines within the insurance industry. Life insurance and Accidental Death products are exposed to the 52,000 Americans who die annually as a direct result of a TBI. Further, some people who survive a traumatic brain injury may have a shortened life expectancy, thus resulting in an increase in mortality experience. Similarly, people who experience a TBI may have increased morbidity, impacting products such as Long-Term Care, Disability, and Critical Illness.

Various occupations and avocations may be worth considering in the underwriting process, given the increased exposure risk involving specific activities. When underwriting a risk with a history of traumatic brain injury, the most-important prognostic factors include "age, mechanism of injury, post-resuscitation GCS (Glasgow Coma Scale) score, post-resuscitation pupillary reactivity, post-resuscitation blood pressures, intracranial pressures, duration of posttraumatic amnesia or confusion, sitting balance, and intracranial pathology identified on neuroimaging."²⁷

Although TBI currently represents a considerable risk to the insurance industry, increased public awareness, combined with the advancement of technology and research, will play a vital role in mitigating the risk of traumatic brain injuries in the future. ■



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CANCER DEVELOPMENT DEVELOPMENTAL ROLES OF THE GENOME AND IMMUNITY - PART I

By Oscar A. Cartaya M.D., M.P.H., M.S., D.B.I.M.

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This article is part of a two-piece follow-up to Dr. Cartaya's article, "Advances in Cancer", published in the Fall 2011 edition of ReFlections.

In the previous article I had described the new conceptual framework that looks at cancer as a separate organ, rather than looking at cancer as a collection of morphologically and functionally different cells within an organ. To briefly review this concept, cancer shares some of the characteristics of the originating organ, but has its own characteristics and specific functions which are not the same as those of the original organ. Looked upon as a separate organ, cancer has its own supporting stromal tissue matrix and its own vascular supply, both of which are controlled and influenced by the cancer cells, and both of which are necessary for the growth and survival of the cancer. To obtain supporting tissues and vasculature of their own, malignant cells must co-opt or recruit normal stromal tissue and vasculature from the surrounding organ to support their growth, otherwise the budding malignant tumor cannot grow or develop. The process during which a fully developed invasive cancer forms is therefore not dependent upon the appearance of a single mutated malignant cell that inexorably develops into an invasive cancer. Instead, it depends upon the ability of the malignant cells to co-opt and organize surrounding tissue elements, both vascular and stromal, of the original organ to support the functions and growth of the malignant cells. It is the combination of these elements – malignant cells, stromal and vascular support tissues – that forms the new invasive cancer organ. However there is new evidence that shows the process of cancer development requires interaction between normal organ cells that contain altered genetic material. In other words, a normal organ cell cannot transform itself into a malignant cell.

In the previous article I had touched upon our new ability to analyze the molecular biology of the tissues forming an invasive malignant tumor, as well as our ability to analyze the role of the genome as the blueprint for this tumor. Taken together, these new developments in molecular biology and genome sequencing and function form the basis for the creation of this new conceptual framework treating cancer as a separate organ. What I intend to do in this article is to go deeper into the roles the cancer cell genome and immune reactions from the surrounding/supporting tissues play in the development of cancer. I will show current evidence pointing to a shared role between tissue cells containing gene abnormalities and the stromal cells surrounding them in the development of cancer. This area of study is a very recent development which gives a glimpse of possible major advances in treatment, response to treatment, and intrinsic survival patterns for different types of cancer. The present article will be published in two parts, with this being the first part.

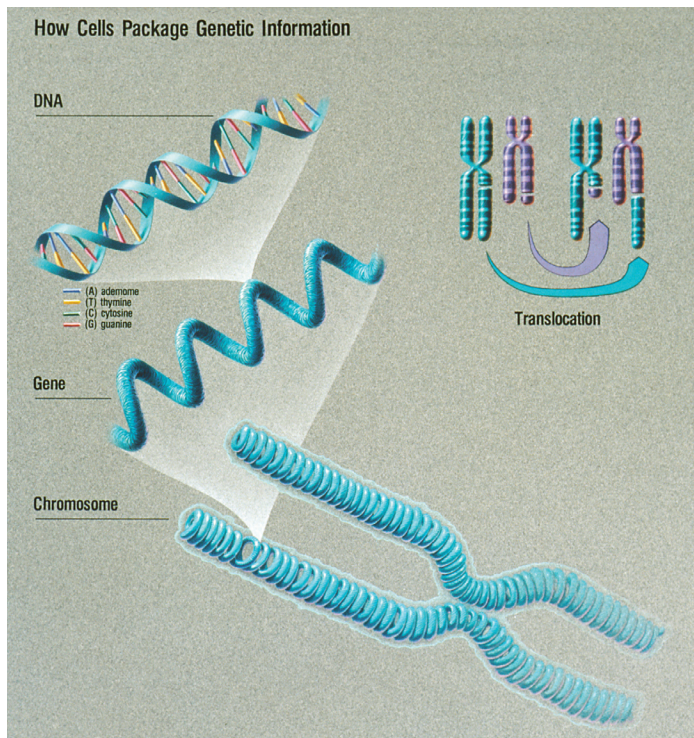
There is a very large amount of research currently being done many different portions of this field. This is research that is generally conducted piecemeal in very narrow areas generally involving specific molecular pathways. The results of these research programs are like pieces of a larger puzzle that are starting to fit together. To get a view of the overall developments in this field, vast amounts of research results must be combined and integrated into a broader framework. To present this type of result integration requires specialized multidisciplinary seminars covering many areas of research. As it was with the earlier article, this article is based upon a follow-up state-of-the-art conference which is presented yearly by the Harvard Medical School entitled "Critical Issues in Tumor Microenvironment, Angiogenesis and Metastasis." It attempts to provide a summary of the genomic and immune developments presented September 2012 at that conference.

This year I have chosen to talk about the genome of the cancer cell and its interaction with other cells in the surrounding tissues. The genome of the cancer cells is readily determinable with current technology and provides a wealth of information, including expected mortality and survival. The interaction with other cells in the surrounding tissues plays an important role in the development of cancer and in the way it will respond to therapy. The availability and application of this type of knowledge may have great impact in insurance.

The Genome

Let us start by talking about the genome. The genome is defined as the complete set of genes of a single person. It is a storehouse of micro-molecular information required for life and development. This information is stored in the DNA chains, which are organized in a manner similar to the binary codes used by computers. Genes are sequences of code that define a single protein or enzyme. As also occurs in computer binary code, the genes are separated from one another by special spacing sequences. The gene itself (the portion containing code) is called an exon; the separator (null) sequences of DNA are called introns. This allows each gene to be read separately from other genes.

Figure 1



Translocation: Source, National Cancer Institute

DNA is naturally inert; this is a quality of great value since it allows the passage of intact gene sets between generations of individuals. The genes are stored in a highly coiled manner in long strings (also coiled) that form individual chromosomes. There are 23 chromosome pairs in each nucleated cell of our bodies. In order to activate genes, the chromosome has to uncoil and allow the transcription of the gene sequences. This process of coiling and uncoiling is constantly taking place. At the time of cell reproduction the whole genetic content of the chromosomes is

replicated. Errors in the replication and transcription of the genetic material may occur, for example, translocations of pieces of a chromosome to other chromosome or deletion of a piece of a chromosome. There are genes controlling genome repair that minimize these errors. Mutations that do occur and persist generally have limited effect since they tend to occur in inactive or non-functional portions of the genome. These errors or mutations are not passed to the offspring unless they occur in the germ cells.

The total number of functional genes contained in the chromosomes is not yet known. Only a fraction of the protein coding genes have been identified so far, and the remainder of the DNA contains information that has no known function or that serves regulatory purposes. Research continues in the determination of what functions these portions of the DNA have.

There are trillions of nucleated cells in our bodies and they all share exactly the same genome. Within the body there are all kinds of different cell lines and organs, which are very different from one another. The differences between the cell lines are produced by the different sequences of genome activation, which vary from organ to organ.

Our ability to sequence the genome has provided researchers with a valuable tool to discover gene sequences and alterations. Each individual human being has innumerable minor sequencing alterations within his or her genome that makes it unique to that person. These alterations may not be functional or active and they may constitute a very minor portion of the total genome but they are present and under specific conditions may play a role in the development of cancer.

Genes and Disease

Some genes may cause disease by themselves, for example, the genes for Sickle Cell Anemia and Hemophilia, and manifest from very early in infancy. Certain combinations of genes are not compatible with life and result in stillbirths, fetal death, and miscarriages. However, there are any numbers of genes or combinations of genes that take years to cause disease. These genes or combinations of genes may or may not cause a specific disease to develop. For example, BRCA 1 and 2 cause various forms of cancer to develop in 85% of all the people that have them; however, 15% of all individuals with these genes may live their whole lives without developing cancer.

The issue in these cases, of course is what to do with a (+) test for a 'bad' gene known to cause disease. We have to be aware that, with the development of gene sequencing, we have a new and extremely sensitive test that will be able to detect all manner of gene alterations. In some cases, a number of bad genes may be required for the development of a particular disease. The ability to sequence the genome will make it possible to identify these bad genes more frequently and the increased numbers will make the association between any specific altered gene and its role in the development of disease harder to determine. Let me present a brief general description of the relationship between newly discovered diseases and the sensitivity of the diagnostic tests used to detect it:

- When a new disease is recognized, only the very worst and most highly likely to cause death cases of the new disease are identified. Diagnostic tests are not available; the disease is diagnosed by its clinical manifestations only
- This results in significant efforts to develop better methods of diagnosis, particularly early diagnosis, and treatment for the new disease
- As new methods of diagnosis are developed and new cases are found, less-severe cases are found. These have a better survival rate than what was found initially
- Finally, as very sensitive diagnostic tools are developed, cases at risk for the disease but without clinical disease are found

As an example of this progression, pulmonary coccidioidomycosis was first described early in the 20th century as a new and devastating but very rare disorder. People with this disease were acutely ill and died within a short time span after the diagnosis. There was no cure for the disease at the time. In time, diagnostic methods were developed based upon X-ray findings and cultures. More and more cases were identified, most of which were not acutely ill and recovered spontaneously without treatment. As the knowledge of the nature of this disease increased, two forms of the disease were recognized, Valley Fever and disseminated pulmonary coccidioidomycosis. The vast majority of the patients with this infection had Valley Fever, which resolves spontaneously, and only a few patients develop the severe form of the disease. This is a demonstration that merely by using increasingly sensitive methods of diagnosis, a very rare and deadly disorder was transformed into a fairly common disease with a rather benign prognosis in the majority of cases.

We have to realize that genome sequencing is such an extremely sensitive diagnostic tool that it can identify large numbers of people at risk for specific diseases. The people found to be at risk may or may not develop the disease within their lifetime. The development of such a genetic-based disease is likely to follow a complex pattern of activation and deactivation of genes. Finding a single abnormal gene or group of genes associated with a particular disease does not mean that this disease will develop.

Genes and Cancer

The issue of how many genetic alterations are found in different types of cancer is the subject of active investigation. There is a large body of data being developed by the National Cancer Institute (NCI) documenting that most forms of cancer have large numbers of genetic alterations. An even more important discovery is that all human beings have some, although not all, of these gene alterations in their own genomes, passed on to them by their parents and preceding generations. Since most people do not develop cancer in their lifetimes it must be concluded that these gene alterations are present in their genomes either in an inactive state or have normal duties to perform. These altered or 'bad' genes are not present in the genome just to cause the development of cancer. The concept of bad genes is largely incorrect. For example, the BRCA1 and 2 mutations may increase the survival time for certain kinds of breast and ovarian tumors.

The NCI is engaged in preparing an Atlas of the Cancer Genome. It is collecting samples of specific cancer tumors and analyzing their genomes. The tissue samples are obtained, analyzed, and sequenced by a number of independent institutions and medical centers. The results are not reported in a standard format, and may not follow identical analysis; however, the data is available free to all interested investigators. The idea behind this research initiative is to obtain large amounts of data on the genetics of specific kinds of tumors. This data can then be used for multiple purposes such as the development of new therapies or the classification of specific tumors into subtypes with common characteristics.

The first thing that must be said about the results obtained so far is that cancer tumors have very large numbers of genetic alterations. Tumors of different kinds, for example breast tumors vs. colorectal tumors, are very different in the types of genetic alterations they

show. All breast tumors present similarities in the genetic alterations they show, although individually they are never identical. The same applies to colorectal tumors, etc. It is important to keep in mind that the genetic alterations found in a specific tumor originate from both the cancer cells and the supporting tissue cells within the tumor. With this in mind let us review some of the NCI's Atlas of Cancer Genome's findings.

	Number of Genomic Alterations	Number of Genomic Subtypes
Breast CA	36,626 somatic mutations found	4 Subtypes The Basal Subtype is very similar to Ovarian CA
Colorectal CA	24 genes with mutations, 16% of the tumors are hyper-mutated.	1 Subtype
Lung CA	360 exonic mutations, 323 copy alterations, 165 rearrangements average per tumor tested	? Subtypes
Glioblastoma Multiforme	?	4 Genomic Subtypes
Ovarian CA	? 96% express the TP53 gene	4 Genomic Subtypes Better chance of survival with a Suppressed BRCA1 or 2 gene

Now let us deal with the concept of cancer Subtypes. I will use the breast CA as an example to show the uses of genetic subtyping of cancer. Breast CA has in excess of 30,000 genomic alterations associated with it. These 30,000+ genomic alterations were initially divided into 73 determinant groupings of alterations which were found in any number of combinations among the tumors tested. After much analysis of the tumors using multiple techniques, it was found that breast CA could be classified into four separate subtypes, two of which are very similar, as follows:

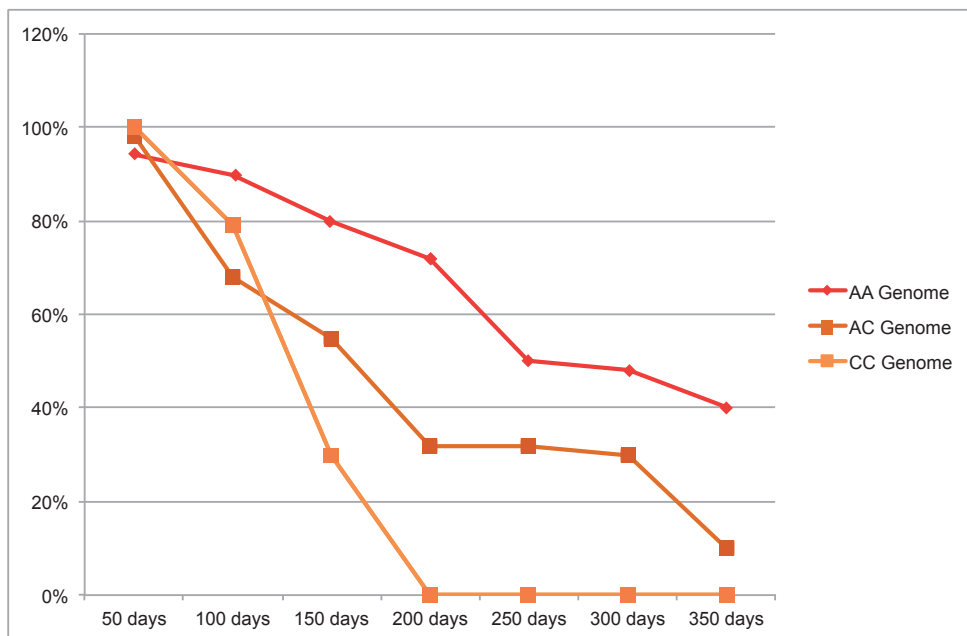
Luminal A	Luminal B	Basal	HER2E
Best survival	Best survival	Worst survival	Intermediate survival
Most treatable	Most treatable	Least treatable	New therapies found
Most heterogeneous	Most heterogeneous	Triple negative Similar to Ovarian CA	Two HER2E subtypes

The first thing that should be noticed in this data is the vast number of genome alterations that may be associated with any kind of cancer. As described in the breast cancer example, these alterations can be grouped as "determinants", which give the cancer cells certain specific attributes. In a broader scale, cancers of most types are classifiable into subtypes with general characteristics that hold true for all the cancers of the same subtype. However, each individual cancer tumor within a subtype may have many genomic differences from other individual tumors of the same subtype. It should be evident that genomic subtyping of cancer tumors allows a general determination of how well they respond to therapy and how long a survival may be expected if one has a tumor with this genomic subtype. Also it is shown that genomic analysis has been successful in pointing out new avenues for treatment of certain types of cancers. The implication of these findings is of great importance for insurance purposes.

The importance of these findings may be further documented by a brief study of the response to the identical therapy protocols by three different genomic subtypes of pancreatic CA. Pancreas CA was divided into three subtypes labeled AA, BB, and CC. All tumors were treated with the same Bevacizumab therapy protocol.

The median survival times were quite different for each tumor. The worst survival time was for subtype CC at 144 days. The best survival time was for subtype AA at 309 days. Subtype BB had an intermediate survival time at 171 days. This does illustrate that response to therapy and overall survival are genetically determined.

Figure 2



It is hoped that the current study of the genome of cancer tumors will allow classifying the main forms of cancer into subtypes. These results are likely to have enough clinical significance to be included in pathology reports and should be easy to adapt to our current underwriting rating systems and to cancer treatment protocols.

Survival of pancreatic cancer, by genome, treatment with Bevacizumab

There are a few points that should be obvious to everyone looking at these preliminary results from NCI:

1. Cancer development requires many, oftentimes hundreds of genetic alterations. Given the number of genomic alterations required, it is almost certain that we are born with and have these genomic alterations within our genomes from the time of birth.
2. In order to develop cancer the genomes of the cancer cells must go through a process of sequential activation and deactivation of genes. These sequences are likely to be timed in a complex fashion that is not yet understood.
3. Cancers of the same subtype have common characteristics.
4. There is tremendous genetic heterogeneity between cancers of the same subtype.
5. The currently held concept of "One Gene" diseases is likely to be incorrect, at least in a very large number of such diseases. As our sequencing of the genome helps build our knowledge of genetic alterations, many if not all of these diseases are likely to be shown to be associated with multiple genetic alterations that need to activate in specific sequences to produce the disease in question. In some diseases, the number of genetic alterations identified may be quite large and varied.

In the next issue of ReFlections, the second part of this article will attempt to describe how normal cells acting in a normal manner may trigger the activation sequences required to produce cancer.

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ELECTRONIC MEDICAL RECORDS – ARE WE READY?

By Susan L. Wehrman F.L.M.I., A.C.S.

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The evolution of medical records to digital (and interoperable) data is exciting and offers tremendous opportunity for transforming U.S. healthcare. Records will no longer be trapped in paper silos; access to this information will improve individual care and coordination of care, as well as the health of entire populations. However, access will be increased for everyone – including unintended audiences.

Ensuring the security of this data is critical to the success of health information exchange. Both providers and consumers must believe the data is secure.

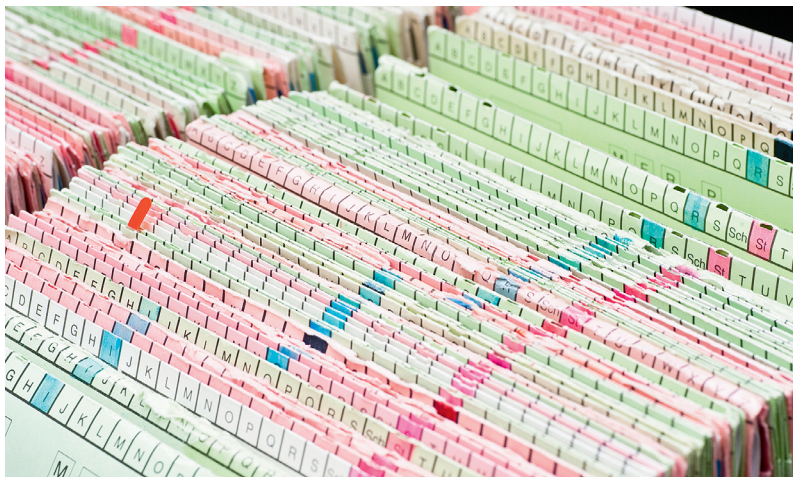
Data breaches in healthcare are on the rise. Nearly 20 million patient health records have been compromised in the past two years, according to the U.S. Department of Health and Human Services (HHS). While some believe external forces are the primary threat, it transpires that the biggest cause of Health Insurance

Portability and Accountability Act (HIPAA) data breaches is theft and loss of computers/laptops (39%) and other portable media (11%) – not hackers. This is why it is important for every organization to adopt appropriate access controls, which serve as gatekeepers managing admission to systems and network resources.

Access controls can be technical or physical in nature. Examples include tokens, biometrics, firewalls, automatic logoffs, encryption/decryption of data, etc. Currently, user identification codes and passwords are the most-common access controls for healthcare information systems. A recent report by Verizon that examined cyber-attacks on healthcare organizations in 2011 and 2012 found that 72% of them were caused by hackers guessing (or using automated systems to guess) the passwords and other credentials that allowed them access to computer systems. SplashData produces an annual list of the top 25 most common hacked passwords. At the top of the list (compiled using files of stolen passwords posted online by hackers) were “password”, “123456”, and “12345678”.

Access controls are only part of the solution; organizations are also implementing Security Risk Analyses, which are mandated by HIPAA and now also included in the U.S. government's Meaningful Use criteria. Risk assessments conducted for Meaningful Use must more-specifically address encryption of data stored in electronic health records than do risk assessments for HIPAA. Providers also are now required to conduct a risk assessment every year under the Meaningful Use program.

In addition to creating financial incentives for providers to adopt electronic health records, The Health Information Technology for Economic and Clinical Health Act (HITECH) also expanded the reach of HIPAA and raised the bar for health data security with increased penalties, mandatory audits, and new security breach notification requirements. HITECH requires covered entities to report breaches of unsecured Personal Health Information (PHI) to patients, HHS, and the media (for cases affecting 500 or more individuals). At the same time, the government has significantly stepped up enforcement activities. Prior to 2009, the largest penalty listed on the HHS website was \$100,000. Since then, seven entities have been fined \$1,000,000 or more for HIPAA violations, which include both punitive and financial consequences. HITECH significantly increased the penalties for breaches of information (based on the conduct of the entity) ranging from \$100 to \$1,500,000 per violation.



All organizations – large and small – are affected by security breaches:

- A weak password was to blame for the hacking of a Utah Department of Technology Services server containing patients' Social Security numbers and data on children's health plans. 280,000 people had their Social Security numbers stolen and approximately 500,000 others had less-sensitive personal data, such as name, date of birth and address, compromised. Following the breach,

Utah Governor Gary R. Herbert requested an audit of all procedures for state security and data storage.

- Phoenix Cardiac Surgery, a five-physician practice in Arizona, became the first small practice to enter into a resolution agreement that included a civil money penalty over charges that it violated HIPAA's Privacy and Security Rule by posting surgery and appointment schedules on an Internet-based calendar that was publicly accessible. The practice agreed to pay \$100,000 and take corrective actions.

- Massachusetts Eye and Ear agreed to pay a \$1.5 million fine to the HHS after allegations were made they failed to comply with certain HIPAA requirements governing the security of individually identifiable health information. The actual breach

occurred due to the theft of a doctor's unencrypted laptop computer. Investigators concluded that the practice, "didn't perform a risk analysis on an ongoing basis ... portable devices were impacted... [T]hey didn't have good policies and procedures around their own home devices, but also

portable devices coming in and out that weren't owned by the entity..." The article points out that investing in encryption technology and other safeguards would have cost the organization one-tenth of the fine they ended up paying.

- The University of Texas MD Anderson Cancer Center reported two incidents in only three months. The first involved an unencrypted laptop and the second involved the loss of a USB thumb drive.
- Alaska's Medicaid program paid \$1.7 million as a result of HIPAA Security Rule violations. It was reported that the agency did not have adequate policies and procedures in place to safeguard PHI when a USB hard drive was stolen from an employee's vehicle.

Investigators also found that Alaska had not:

- Completed a risk analysis
 - Implemented sufficient risk management measures
 - Completed security training for its workforce members
 - Implemented device and media controls
 - Addressed device and media encryption as required by HIPAA
- Although not an actual case, Medicare has been criticized for using Social Security numbers on their beneficiary identification cards, which individuals must carry to obtain medical services. CMS contends it would cost at least \$803 million to remove SSNs from the cards. Much of this cost is attributed to upgrading computer systems not only at the federal level, but also at the state level, for coordination with Medicaid systems.

In addition to security breaches, another major concern is medical identity theft. Medical identity theft is the fastest-growing type of identity theft in the world. In 2011, approximately 1.5 million individuals in the U.S. were affected. Medical identities are used primarily to obtain prescription drugs, Medicare reimbursement or medical treatment. Sometimes it is simply a case of someone who needs access to healthcare, but can't afford it – nevertheless, it is also one of the fastest-growing areas of organized crime. There have even been cases where thieves have acquired data and held it for ransom. Irrespective of the means, medical identity theft typically results in erroneous entries being placed in existing medical records, and can involve the creation of fictitious medical records in the victim's name – which can lead to deadly consequences. For example, if a patient goes to the hospital with a ruptured appendix and the records state his or her appendix was removed a year ago, the doctor will rule out appendicitis as the cause.

The disparate nature of our healthcare system makes medical identity theft hard to detect – there are no credit bureaus or similar entities where individuals can find out whether their information or insurance has been used inappropriately. A recent survey reported that only 50% of individuals have reviewed their medical records, and only 24% have checked for fraud within their records. Medical identity thieves typically obtain treatment at five facilities or more. Further, most facilities do not have policies in place for responding to this crime or for correcting records – in fact, some providers will not allow the victim to access the records, as now they contain Protected Health

Information (PHI) on another individual and providers (incorrectly) believe they will be in violation of HIPAA rules if they provide the records to the patient.

While Electronic Health Records have many benefits, they also present unique challenges – even for our industry. It is much more difficult for a thief to walk away with 100 paper charts (also known as Attending Physician Statements) versus 10,000 electronic files on a thumb drive. Will we be ready for the change? ■



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Susan L. Wehrman, Vice President, Electronic Health Record Initiatives, heads RGA's newly created Electronic Health Record (EHR) Initiatives area. This function conducts in-depth research and analysis of this evolving segment and monitors all activity in the U.S. and around the world, with the objectives of positioning RGA as an industry thought leader and better assisting clients with EHR-related issues.

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September 12, 2013

Breast Cancer Prognosticators: Tumor Subtype and Future Potential of Cancer Genomics

A presentation for Medical Directors of Multinational Insurance Companies

Presenters

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