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LETTER FROM THE EDITOR

Dear readers:

Our final 2013 edition of ReFlections is special in that, as RGA associates around the world continue to celebrate RGA's 40th Anniversary, this edition features an article celebrating the 15th Anniversary of the Longer Life Foundation, a unique collaboration between RGA and Washington University. In the article, Dr. Phil Smalley describes the mission of the foundation as well as its notable accomplishments over the past 15 years.

Our second contributor is Dr. Dhiraj Goud, who will provide you with valuable information on an emerging new medical technology, Magnetic Resonance Spectroscopy, as well as discuss its potential applications in both clinical and insurance medicine.

The next article, authored by Dr. Oscar Cartaya, is the second part of the article on Cancer Development that he contributed in our Summer 2013 edition.

The final article has been provided by Jeffrey Heaton, who is a member of the team of RGA associates that helps all of us keep track of developments in Electronic Health Records. In his article, Jeffrey outlines the structure of ICD-10 codes and illustrates their value to insurers.

I trust that you will enjoy this edition!

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

THE LONGER LIFE FOUNDATION – 15 YEARS OF INDEPENDENT RESEARCH

By Philip Smalley M.D., F.R.C.P.C.

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New Insights for Better and Longer Lives

The Longer Life Foundation is a not-for-profit partnership between the Washington University in St. Louis School of Medicine and RGA. Since its creation in 1998, the foundation has supported and funded independent research into longevity and enhancing quality of wellness.

This innovative partnership was the brainchild of A. Greig Woodring, President and Chief Executive Officer of RGA, and RGA board member Dr. William A. Peck, then Dean of Washington University School of Medicine and Executive Vice Chancellor for Medical Affairs. The idea of creating and funding a foundation that would partner an academic institution with the insurance industry appealed to the two executives, as the resulting medical research could benefit both public health and the insurance industry, and help people live longer, improved lives.

Increased lifespans and the consequential rising incidence of critical illness conditions are leading to decreasing mortality and rising morbidity, which makes access to cutting-edge medical research and information a necessity for actuaries, underwriters and claims professionals.

Benefits to the Insurance Industry and to Public Health

The Longer Life Foundation (LLF) provides the insurance industry with access to the most current scientific research about medical conditions and public health issues that affect mortality and morbidity. Actuaries are able to use the information to design insurance products for more segments of the public, and at better rates. Discovering new methods to predict disease prognosis and progression more accurately gives underwriters and claims adjudicators additional information when assessing insurance applicants and claims, and allows insurers to offer coverage to the public more cost-effectively.

Funding early-stage medical research also lays the groundwork for next-step research proposals that may increase practical knowledge about longevity, older-age cognition, genomics, obesity, heart disease and cancer. There are also potential public health benefits, as clinical doctors gain knowledge that can help them assess, diagnose, treat and possibly even prevent many common diseases and conditions.

15 Years of Success

Every year, dozens of Washington University School of Medicine's faculty members apply for the LLF's one-year research grants of \$25,000 to \$50,000. All applications are reviewed by the LLF's Board of Advisors, composed of Washington University School of Medicine research academics and insurance company medical officers and underwriting experts.

At this time, 79 research projects have received funding, and the foundation has disbursed \$4 million in research grants to fund medical and public health research. The grants have generated research that has advanced human understanding of impairment states, as well as led to funding for further investigation from large, high-profile research facilities. LLF-funded researchers have secured funding from external sources to continue their research in amounts of at least 10 times LLF's initial outlay.

More than 65 articles on research projects and results have been published in peer-reviewed scientific journals, and LLF-funded researchers have also been quoted in the consumer press. The partnership also sponsors lectures, seminars, forums and symposia on a wide cross-section of medical, insurance and public health topics, and information on these projects, results and events can be found at www.longerlife.org.



Dr. Samuel Klein, Director of the Longer Life Center, giving an address in October at the Washington University Obesity Symposium

Research Generating Industry-Changing Discoveries

With older-age individuals now the fastest-growing life and health insurance market, the LLF is conducting successful research into ways to assess neurologic fitness and distinguish normal signs of brain aging from dementia.

Among results in this area, Dr. Reina C. Villareal has found a particular gene mutation that, when present, can be an early marker indicating an increased possibility of developing Alzheimer's disease. Dr. Catherine Roe studied brain biomarkers that improve pre-symptomatic detection of Alzheimer's and can predict longevity and disability. These biomarkers became part of the new definition for Alzheimer's disease published in April 2011 by the National Institute on Aging and the Alzheimer's Association.

Other biomarkers discovered through LLF-funded research include a protein in urine that could serve as a marker for renal cell carcinoma, discovered by Drs. Jeremiah Morrissey and Evan D. Kharasch, and a particular cardiac abnormality present in diabetic patients, detectable by echocardiogram, which can

predict whether that individual will develop coronary artery disease, discovered by Dr. Ravi Rasalingam. Comorbidity, or the interaction of various impairments within the human body, is of vital interest to insurers. Often, an applicant may have multiple impairments (obesity, diabetes, heart problems), and research that can clarify how impairments interact in a human can improve both clinical prognostication and underwriting.

Obesity, for example, compounds aging's physical and mental degeneration, and the LLF is funding research into ways to limit and treat its effects. The Longevity Research Program (LRP), a joint venture of the Washington University School of Medicine and the LLF led by Dr. John Holloszy, Director, and Dr. Luigi Fontana, Associate Director, focuses on identifying biomarkers that can predict mortality and improve understanding of ways to promote disease-free longevity.

The primary focus of the LRP is the impact of Caloric Restriction (CR) on longevity, mortality and morbidity. CR has been shown to increase life expectancy in animals, and the LLF has funded several LRP-sponsored human CR studies. Dr. Fontana's first study, in 2006, evaluated adults who followed a Calorie Restriction with Optimum Nutrition (CRON) eating plan over a long time period. This plan, which restricted calories to 1,800-1,900 per day and provided more than 100% RDA of all essential nutrients, led to decreases in biomarkers such as insulin resistance, growth factors, arterial stiffness and inflammation, and showed improved heart function.

Dr. Jay Piccirillo, whose research analyzed National Cancer Institute data in concert with cancer survival statistics from St. Louis's Barnes-Jewish Hospital, assessed and quantified the impact of certain comorbid impairments on survival rates for adult cancer patients. He found that the survival rate, especially for those with slower-growing cancers, can be strongly influenced by the presence or absence of other comorbid conditions. His research lets underwriters see how cancer's mortality risk can vary by age, stage and time since diagnosis, and has practical utility in underwriting applicants with a history of cancer and in adjudicating terminal illness benefit claims.

On the public health side, Dr. Shelby Sullivan is investigating the impact of high-fructose corn syrup (HFCS) on non-alcoholic fatty liver disease (NAFLD). 33% of the U.S. adult population has NAFLD, which

has several comorbidity complications such as diabetes, high blood pressure, high triglycerides and heart attacks. Recent studies have shown that HFCS, if eaten in large amounts by people with normal livers, could cause those livers to use it to make fat. Dr. Sullivan is seeking to determine if reducing dietary HFCS can reduce the risk of NAFLD as well as decrease insulin resistance.

LLF-funded research into genomics is improving diagnostic biomarkers as well as the ability to customize treatment via patient gene profiles. Dr. Anthony J. Muslin, for example, recently found that patients with a specific genetic mutation will respond better to a particular drug for coronary disease.

Summary

Over its 15 years, the LLF has added substantially to the body of research that has and will continue to improve lifespans and quality of life. The LLF has received excellent feedback from the insurance industry, and has added value by leading the industry to new products and giving insurance companies the ability to offer more insurance to more people. Public health also benefits, ultimately helping people to live longer, better lives. ■



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Dr. Phillip Smalley is an internal medicine specialist, with more than 20 years of insurance medicine experience. He is Vice President and Medical Director of RGA International Corporation, and a recognized lecturer, traveling extensively and giving many presentations to the insurance industry on a wide range of mortality and morbidity topics. Dr. Smalley is also the Managing Director of the Longer Life Foundation.

By Dhiraj P. Goud M.D.

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Introduction

Magnetic Resonance Spectroscopy (MRS), especially brain MRS, is among the new emerging MRI techniques, and is proving to be of great interest, mainly because it is readily available and has important clinical applications.

In this article, we will discuss this imaging technique in simple terms and provide a basic understanding for our Insurance colleagues. We will also follow an easy-to-understand and recall clinical approach rather than starting with the complex physics involved. We discuss the different MRS techniques, the normal spectra in adults and children, applications in clinical and possible insurance medicine and the significance of brain metabolites both under normal and abnormal conditions particularly in the evaluation of brain tumors.

What is Magnetic Resonance Spectroscopy?

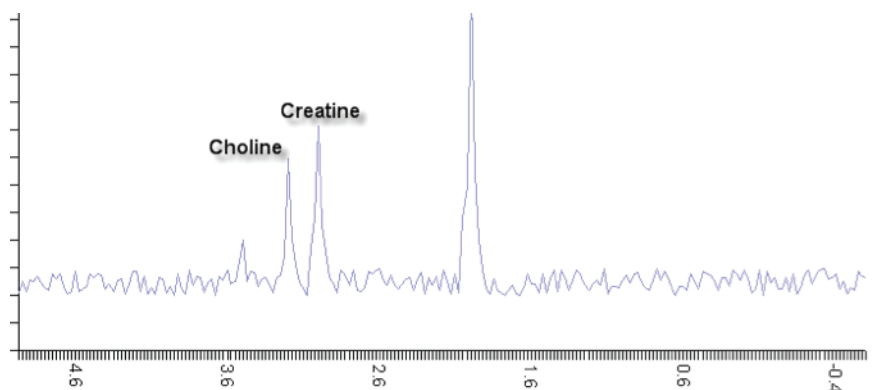
Magnetic Resonance Spectroscopy is an analytical method that, by the use of magnetic resonance, enables the identification and quantification of metabolites in different tissues of the body. The main difference between MRS and conventional Magnetic Resonance Imaging (MRI) is that MRS provides the physiological and chemical information as a spectrum, whereas MRI provides the anatomical information on a gray scale as an image depending on its relative signal strength. The resonance frequency of each metabolite is represented on a graph and is expressed as parts per million (ppm). This is because the resonance frequency is in MHz or 106 Hz.¹

MR spectra may be obtained from different nuclei. Protons (^1H) are the most-used nuclei for clinical applications in the human brain mainly because of their high sensitivity and abundance.³ The proton MR (H-MRS) spectrum could be altered in almost all neurological disorders.³ In this discussion, unless otherwise specified, MRS refers to proton MRS.

Normal MRS

MRS allows for the detection of brain metabolites. The changes in metabolite can often precede any changes in the structure, i.e., the structural abnormalities, and MRS can demonstrate these abnormalities significantly before conventional MRI does.² To detect these spectral alterations, it is important to understand the normal brain spectra and their variations according to the each technique, patient age and brain region.

The spectra of metabolites are shown on x and y axes. The x, horizontal, axis displays the chemical shift of the metabolites in units of parts per million (ppm), which increases from right to left. The y, vertical, axis demonstrates arbitrary signal amplitude of the metabolites. The height of metabolic peak refers to a relative concentration and the area under the curve to metabolite concentration.²



Normal MRS

(Source: MR spectroscopy, Dr. Frank Gaillard, Radiopaedia.org)

Brain Metabolites:

There are several metabolites included in the spectrum of MRS but the important ones are **N-acetylaspartate, Choline, Lactate** and **Lipids**

N-acetylaspartate (NAA)

Peak of NAA is the highest peak in normal brain. This peak is assigned at 2.02 ppm. NAA is considered to be a marker of neuronal and axonal* viability and density.

Absence or decreased concentration of NAA is a sign of neuronal loss or degradation. Decreased concentration of NAA could be as result of neuronal destruction from malignant neoplasms and many white matter diseases, whereas increased NAA is nearly specific for Canavan disease.† NAA is not demonstrated in extra-axial lesions such as meningiomas or intra-axial ones originating from outside the brain such as metastases.

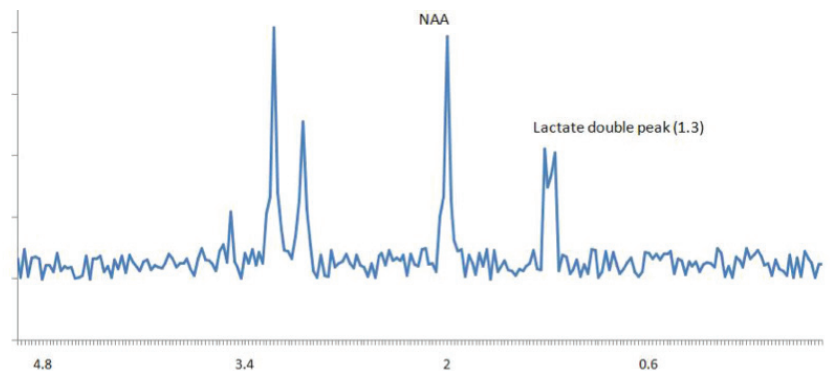
Choline (Cho)

Its peak is assigned at 3.22 ppm and represents the sum of choline and choline-containing compounds (e.g. phosphocholine). It is present in the cell walls of the normal brain tissue. Cho is a marker of cellular membrane turnover (phospholipids synthesis and degradation) reflecting cellular proliferation. In tumors, Cho levels correlate with degree of malignancy reflecting of cellularity. Cho levels may also be increased in infarction (from gliosis or ischemic damage to myelin) or inflammation (glial proliferation) but these can be a transient effect. Elevated Cho at a specific period could be non-specific but if it is persistently elevated, it could be an indication of tumor growth.

Lactate (Lac)

Peak of Lac is not seen or is hardly visualized in the normal brain. The peak of Lac is a doublet (two peaks close to one another) at 1.33 ppm.

Observable Proton Metabolites ³		
ppm	Metabolite	Properties
2.02	NAA	Neuronal marker
3.22	Choline	Cell membrane marker
1.33	Lactate	Product of anaerobic glycolysis
0.9-1.3	Lipid	Products of brain destruction
3.02	Creatinine	Energy metabolism
3.56	Myo-inositol	Glial cell marker, osmolyte hormone receptor mechanism
1.48	Alanine	Present in Meningiomas
2.05-2.50	Glutamate-Glutamine	Neurotransmitters



Lactate Double peak at long echo time

(Source: MR spectroscopy, Dr. Frank Gaillard, Radiopaedia.org)

* Neurone – a nerve cell

Axon - the process of a nerve cell along which impulses travel away from the cell body.

†Canavan disease is one of a group of genetic disorders known as the leukodystrophies. These diseases cause imperfect growth or development of the myelin sheath, the fatty covering that acts as an insulator around nerve fibers in the brain. Myelin, which lends its color to the "white matter" of the brain, is a complex substance made up of at least 10 different chemicals. Each of the leukodystrophies affects one (and only one) of these substances. Canavan disease is caused by mutations in the gene for an enzyme called aspartoacylase.

A small peak of Lac can be visible in some physiological states such as newborn brains during the first hours of life.⁵ Lac is a product of anaerobic glycolysis, so its concentration increases under anaerobic metabolism such as cerebral hypoxia, ischemia, seizures and metabolic disorders (especially mitochondrial ones). Increased Lac signals also occur with macrophage accumulation (e.g., acute inflammation). Lac also accumulates in tissues with poor washout such as cysts, normal pressure hydrocephalus, and necrotic and cystic tumors.⁶ In short, lactate is normally not detectable on human brain MRS – it is mostly detected in necrotic tumors, in strokes due to destruction of cells and in cystic disorders.

Lipids (Lip)

Lipids are components of cell membranes. There are two peaks of lipids: methylene protons at 1.3 ppm and methyl protons at 0.9 ppm.⁷ These peaks are absent in the normal brain.

Lipid peak can be seen when there is cellular membrane breakdown or necrosis such as in metastases or primary malignant tumors.

Other metabolites that are seen in the spectrum are discussed below:

Creatine (Cr)

The peak of Cr spectrum is assigned at 3.02 ppm. It receives contribution from other molecules containing creatine and phosphocreatine. Cr is a marker of energetic systems and intracellular metabolism. Concentration of Cr is relatively constant and it is considered a most stable cerebral metabolite. Therefore it is used as an internal reference for calculating metabolite ratios.

In brain tumors, there is a reduced Cr signal. On the other hand, gliosis may cause minimally increased Cr due to increased density of glial cells (glial proliferation).

Myoinositol (Myo)

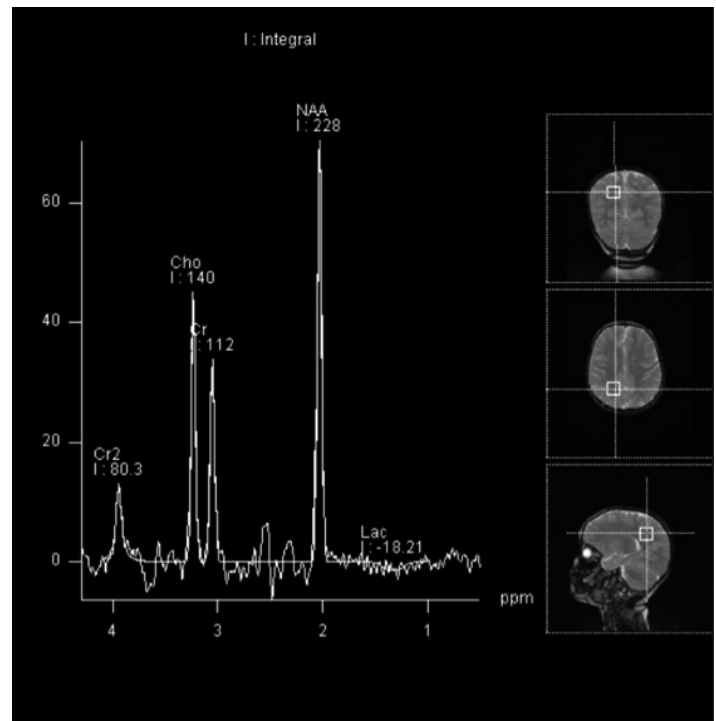
Myo is a simple sugar assigned at 3.56 ppm, considered a glial marker as it is primarily synthesized in glial cells, almost only in astrocytes and may represent a product of myelin degradation.³ Myo is elevated in gliosis, astrocytosis and in Alzheimer's disease.^{5,6}

Alanine (Ala)

Ala is an amino acid that has a doublet centered at 1.48 ppm. The function of Ala is currently uncertain. Increased concentration of Ala may occur in oxidative metabolism defects.⁶ In tumors, elevated level of Ala is specific for meningiomas.³

Glutamate-Glutamine (Glx)

Glx is a complex peak formed by glutamate (Glu), Glutamine (Gln) and gamma-aminobutyric acid (GABA) assigned at 2.05-2.50 ppm. These metabolite peaks are difficult to separate at 1.5 T. Glu is an important excitatory neurotransmitter and also plays a role in the redox[†] cycle.^{5,6} Elevated concentration of Gln can be found in hepatic encephalopathy.^{2,6}



Normal MRS of a two-year-old

(Source: MR spectroscopy, Dr. Frank Gaillard, Radiopaedia.org)

Techniques of MRS

Going into details regarding the techniques of MRS is beyond the scope of this article, but a brief discussion may be worthwhile for better understanding of this modality. The H-MRS acquisitions usually start with anatomical images, which are used to select a volume of interest (VOI), where the spectrum will be acquired.

[†]Redox – Oxidation – reduction reaction - the chemical reaction whereby electrons are removed (oxidation) from atoms of the substance being oxidized and transferred to those being reduced (reduction).

For the spectrum acquisition, different techniques may be used including **single- and multi-voxel[§] imaging using both long and short echo times (TE)**. Each technique has its own advantages and disadvantages and is chosen for a specific purpose to improve the quality of the results.

As in MR imaging, the echo time affects the information obtained with MRS. With a short Echo Times (TE) of 30 msec, metabolites with both short and long T2 relaxation times are observed. With a long TE of 270 msec, only metabolites with a long T2 are seen, producing a spectrum with primarily NAA, creatine, and choline.

Clinical Applications

Brain Tumors

Brain tumors are currently the main application of MRS. This technique is usually used as a complement to conventional MRI, along with other advanced techniques, such as perfusion. Combined with conventional MRI, proton MR spectra may improve diagnosis and treatment of brain tumors. H-MRS may help with differential diagnosis, histologic grading, degree of infiltration, tumor recurrence, and response to treatment mainly when radionecrosis develops and is indistinguishable from tumor by conventional MRI.

Elevation of Cho is seen in all neoplastic lesions. Cho peak may help with treatment response, diagnosis and progression of tumor. Its increase has been attributed to cellular membrane turnover, which reflects cellular proliferation, whereas a signal of Cho is consistently low in necrotic areas.

Another MRS feature seen in brain tumors is decreased NAA. This metabolite is a neuronal marker and its reduction denotes destruction and displacement of normal tissue. Absence of NAA in an intra-axial tumor generally implies an origin outside the central nervous system (metastasis) or a highly malignant tumor that has destroyed all neurons in that location. Cr signal, on the other hand, is slightly variable in brain tumors – it changes according to tumor type and grade. The typical MRS spectrum for a brain tumor is one of high level of Cho, low NAA and minor changes in Cr.

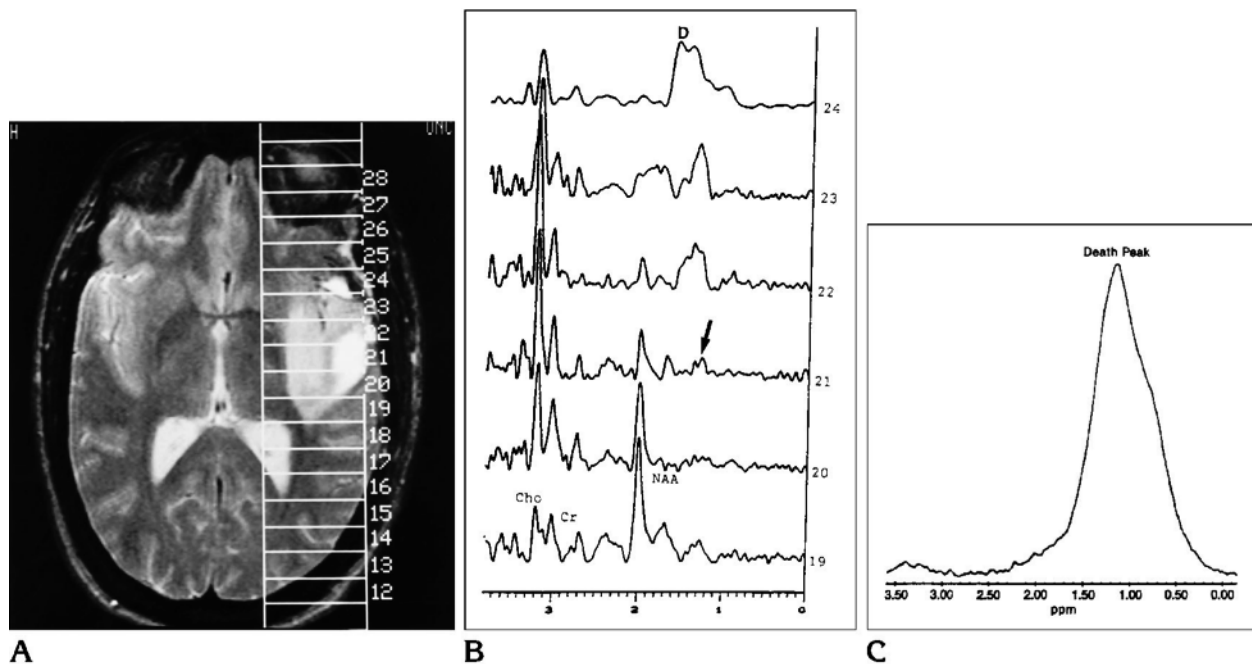
With respect to intracranial expansive lesions, conventional MRI with or without perfusion does provide a reliable diagnosis. In doubtful cases, MRS could play a significant role in pre-operative differential diagnoses. Few such illustrations are mentioned below:

- Choline (Cho), N-acetylaspartate (NAA) and Myoinositol (Myo) may be increased in low grade tumors
- Cho, Lactate (Lac), Lipids (Lip) may be elevated in high grade tumors. In these tumors, NAA may be decreased
- In metastasis – Cho, Lac and Lip may be elevated. NAA maybe absent in the core of the tumor, but may be present where it infiltrates brain parenchyma
- In demyelinating disease - Cho, Lac, Lip, Myo, Glutamine (Glu) tend to rise in this disease. But Lac and Glu could be increased only in the early stage of the disease

Similarly, levels of various metabolites can help differentiate between an abscess and a neoplasm.³ Also in some cases where biopsy is inevitable in spite of using various imaging sequences in conventional MRI, MRS may help to establish a diagnosis.³ MRS can also help in the differentiation of high-grade gliomas from solitary metastasis.³ A number of studies in one systematic review have reported that MRS can accurately differentiate between low- and high-grade gliomas, but the results of glioma grading by using MRS alone may vary widely. By combining MRS with conventional and other advanced MR imaging techniques such as perfusion MRI, grading becomes more precise.

In post-radiation therapy patients with brain tumors, differentiation between recurrent brain tumor and radiation injury/change may sometimes become difficult because of the characteristics and position of the lesions seen on the image. In such cases, MRS may help differentiate tumor from radiation injury.^{10,11,12,13}

[§]Voxel - abbreviation for volume element, the three-dimensional version of a pixel.



Recurrent tumor versus radiation necrosis.

A, Axial MR T2-weighted image (2300/90/1) in a patient after resection of a left temporal anaplastic astrocytoma and treatment with Intra-arterial chemotherapy and radiation. There is an abnormal area of increased signal intensity encompassed in volumes 19 to 24. No enhancement was present after gadolinium administration.

B, Proton MR spectroscopy in volumes 19 to 24. The concentrations of Cho, Cr, and NAA are normal in volume 19. Volume 21 shows low NAA, high Cho, and lactate (arrow) compatible with a recurrent tumor (later confirmed by surgery). Volume 24 shows no NAA, low Cho, and a "death peak" (D) (combination of lactate and cellular breakdown products). At surgery, this region was necrotic brain probably as a sequela of irradiation.

C, Single-voxel proton MR spectroscopy in a surgically proved region of radiation-induced necrosis shows large death peak.

(Source: *Clinical Applications of Proton MR Spectroscopy, A Special Report*. Mauricio Castillo, Lester Kwock, and Suresh K. Mukherji, *AJNR* 17:1–15, Jan 1996)

Human Immunodeficiency Virus (HIV) Infection

In more than 60% of people with acquired immunodeficiency syndrome (AIDS), a dementia complex will develop.¹⁴ But these complexes are evident by conventional MRI only in advanced cases of AIDS. It would be advantageous if such complexes could be detected much earlier. H-MRS can demonstrate marked metabolite alterations in patients with only mild AIDS-related dementia.¹⁵

H-MRS can prove to be very useful in the detection of HIV in newborn children of HIV-infected mothers. Determining positive seroconversion in the first six months of life may be difficult. Despite normal MR brain images, HIV-positive newborns may show abnormal proton MR spectra as early as 10 days after birth.¹⁶

Degenerative Disorders of the Elderly

Alzheimer's and Parkinson's Diseases

Patients with Alzheimer's disease have shown very specific changes in brain metabolites, which may not be seen with other forms of dementia.^{17,18,19} The same is the case with Parkinson's – the metabolite variations are specific to this condition.²⁰ In Parkinson's patients with superimposed dementia the spectrum looks different than in patients with isolated Parkinson's disease because of significant elevation of lactate.¹⁴

Metabolism Errors

The diagnosis of an inborn error of metabolism is always challenging and mainly based on clinical and laboratorial findings, evolution, and genetic tests. Brain MRI may help in narrowing the differential diagnosis, avoiding expensive genetic tests, or even establishing a final diagnosis. Since these disorders are caused by inherited enzymatic defects, concentrations of some metabolites may be abnormally low or high. Metabolites with a very small concentration in brain tissue are not depicted on MRS. In these cases, the spectrum changes usually correspond to a general pathology, such as demyelination or ischemia. On some diseases, however, MRS may identify a specific biomarker that helps in the diagnosis.²¹

Disorders that have specific proton MRS patterns may manifest as an increase or absence of particular metabolites. Specific biomarkers can be seen in phenylketonuria (phenylalanine), Canavan disease (NAA), non-ketotic hyperglycinemia (glycine), creatine deficiency (Cr), and maple syrup urine disease (branched-chain amino acids and keto acids).²²

Other clinical applications

Several other applications of MRS in clinical medicine have also been mentioned in the literature such as:

- Possible non-invasive method that could provide an early diagnosis and follow-up for children with degenerative disorders
- Screening of subclinical hepatic Encephalopathy
- Differentiation of Neurofibromatosis type 1
- Differentiation of Head and Neck Tumors
- Innovative application of MRS – Measurement of Psychoactive Drugs

Impact on Insurance and Conclusion

MR Spectroscopy is a non-invasive technique that can be used to measure the concentrations of different chemical components in various tissues of the body. The studies currently available do not provide strong and consistent evidence regarding the diagnostic test characteristics of MRS. The studies do not clearly delineate how MRS information would be used to guide patient management, so it is not possible to determine whether MRS provides relevant clinical information that will safely influence diagnostic thinking and therapeutic choice. The scientific evidence at this time does not permit conclusions concerning the net effect of this technology on health outcomes. Therefore, for the

purpose of health insurance this imaging technique could still be considered investigational.

MRS has been demonstrated to be highly specific and sensitive to the diagnosis of Alzheimer's disease. The metabolite changes relating to Alzheimer's can be demonstrated even in cases of mild to moderate dementia. Could this lead to anti-selective behavior among insurance applicants? Some food for thought!

MRS is a technically demanding investigation and produces low Signal to Noise ratio (SNR). The possible causes of poor spectral quality on MR spectroscopy include hemorrhage, post-operative changes, fewer than 200 acquisitions, small voxel size, and automatic shimming. These causes either result in poor homogeneity of the magnetic field or poor SNR, making the interpretation of spectroscopy data unreliable. The presence of hemorrhage and post-operative changes within the volume of interest often leads to poor-quality measurements due to susceptibility effects caused by hemosiderin. The cortical brain lesions located close to the calvaria are often difficult to image on MR spectroscopy because of susceptibility artifacts and contamination from lipids located outside the dura. ■



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Dr. Dhiraj Goud has almost nine years of insurance experience, which includes six years in life and health reinsurance. Dr. Goud joined RGA as local lead for health underwriting and claims for RGA's India representative office, also providing medical and underwriting input on all products, including life, critical illness, health and disability. He is currently a member of RGA's international medical team.

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CANCER DEVELOPMENT DEVELOPMENTAL ROLES OF THE GENOME AND IMMUNITY, PART II

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In the previous segment of this article, published in the Summer 2013 edition of *ReFlections*, we explored how sequencing of the genome is altering our knowledge and views of cancer, and possibly other diseases as well. It appears that the concept of a single mutation causing a cell to become cancerous is incorrect. The work being done under the auspices of the National Cancer Institute documents that many alterations in the genome are associated with specific types of cancer. In some cases, the numbers of genetic alterations are very large and indicate that many, if not all, of these alterations must be inherited from our parents and be with us, in an inactive way, most of our lives. It appears that these genome alterations must be activated, in specific and likely very complex sequences, in order for cancer to develop. This second part of the article will describe some of the evidence that is being found which indicates that the immune capable cells in the tissues are a major contributor to the transformation of normal cells into cancer.

Development of Cancer

As we previously discussed, the development of cancer requires the sequential activation and deactivation of a large number of genes. Gene activation is a complex process with multiple steps:

- Uncoiling of the portion of the chromosome that is being activated.
- Transcription of the genetic code into mRNA.
- Use of the mRNA as a template to make specific proteins.
- Folding of the protein properly with active reaction sites.
- Transfer of the protein to the area where it is needed for biochemical reactions.

All of the steps described for gene activation are complex and may not work correctly, causing transcription errors and other problems. One area that is particularly complex and prone to errors is the area of protein folding. In order to be able to perform their function, proteins must be 'folded'.

Proteins work in biochemical reactions as enzymes by combining with other proteins or particles. These combinations are very specific, so that only a single kind of compound or peptide can be combined with a given protein. Specificity is achieved by lock and key coding. Proteins have active 'lock' sites located inside geometrically complex recesses, which are produced by folding the specific protein in very specific ways. Once a protein has been folded in a way that creates an active lock site, this site will be available only to compounds that have an active 'key' site in them. Specific keys fit only a single lock site. When a key enters a lock, the two compounds bind and trigger the desired biochemical reaction. The protein folding process required to produce locks and keys is complex and can go wrong, with defective, inactive proteins being formed. These defective proteins in turn have to trigger activation of 'garbage collection' processes that will destroy the abnormal protein and recycle its component parts.

The key point that needs to be emphasized is not the complexity of the process but the need for a trigger to cause the activation process to occur. Activation of these multiple steps required to turn genes on and off comes from triggers in two different locations:

1. Internal cellular mechanisms, in the target cell.
2. Substances secreted by other cells in the immediate micro-environment of the target cell.

It is thought that both of these activation pathways must act in concert to produce the type of complex sequential activation and deactivation of genes required to produce cancer. There is new and strong evidence showing that mediator signals in the surrounding micro-environment are a major contributor to the initiation of the developmental process that turns a target cell into a cancer tumor.

Evidence for External Pathways

Much research has been done documenting the interaction between secretions from totally normal

tissue cells and tumor cells. A research group headed by J. W. Pollard has investigated macrophage-secreted factors and their interaction with cancer cells. Colony stimulating factor 1 (CSF1) is one such factor normally secreted by tissue macrophages in female reproductive organs. This is a very commonly produced factor that regulates tissue immune cell development and tissue remodeling. CSF1 also has an important role in maternal / fetal interactions and is necessary for normal embryonic fetal development.

It has been demonstrated that endometrial carcinoma over-expresses CSF1 receptors (which are regulated by genes within the cancer cells) when compared to normal endometrial cells, and that levels of CSF1 (which are regulated by genes within surrounding tissue macrophages) are higher in women with endometrial carcinoma than in women without endometrial carcinoma. All the endometrial tumors tested, regardless of severity, are (+) for CSF1 receptor-specific mRNA showing specific activation of genes controlling the increase in CSF1 receptors. It has also been shown that, within the endometrial carcinoma group of tumors, a higher level of expression of CSF1 receptors, and a higher level of binding of circulating CSF1 are associated with larger tumor size, increased level of myometrial invasion by the tumor, and elevation of CA-125, all of which are indicative of more-severe disease. Breast carcinoma and ovarian carcinoma show a similar pattern of reaction to macrophage-secreted CSF1 factor. This shows that the severity of at least some forms of cancer may be regulated by secretions of normal substances or factors from non-malignant, normal cells that are commonly found in normal tissue.

External secretions or factors from normal cells control the development of cancer in many ways. A group headed by E.Y. Lin has done extensive studies using mice breast cancer. Normal mice injected in their breast pads with a polyoma virus develop rapidly growing breast cancer with wide metastatic spread. These mice also show an over-expression of the CSF1 receptors as described by Pollard. The contribution made by macrophages in the development of this type of experimental cancer is documented by using null mice.

Null mice are mice born with a homozygous mutation that limits macrophage growth and prevents them from secreting CSF1 factor. These mice are effectively depleted of functional macrophages. When a null

mouse receives an injection of polyoma virus in its breast pads the result is very different than what is seen when injecting normal mice. Without functional macrophages, the null mice develop slowly growing breast cancers with essentially no metastatic spread. This work shows a direct relationship between normal macrophage function and breast cancer progression and metastatic spread. Similar results have been found by using xenografts of human breast cancer in both normal and null mice.

Macrophages are not the only normal external cells that activate cancer cell genomes by secreting normal factors. There is evidence that other cells of hematological origin work the same way. For example, a group led R.O. Hynes has shown that platelets are necessary for metastatic spread of cancer. It is known that the vast majority of cancer cells are epithelioid in nature, that is, fixed in place and unable to migrate. In order to produce metastasis, the cancer cells have to migrate via the blood stream to other locations within the body. There is generally no great problem for the epithelioid cancer cells to gain access to the blood stream. Cancer tumors have large and leaky blood vessels with weak cell-to-cell connections and, under a variety of circumstances, cancer cells can become loosened from attachment to other cancer cells and gain access to the blood stream. However, exiting the blood stream through the tight cell connections of the intact blood vessels requires the cancer cells to transition into migratory or mesenchymal cells. Mesenchymal cells are not tightly bound to one another and are not fixed. They possess slender cytoplasmic projections called filipodia which allow them to break open the tight connections between the cells lining blood vessels and escape into the surrounding tissue. This epithelial-to-mesenchymal transition is facilitated by factors secreted by platelets that coat the cancer cells, or cancer cell clumps, when they enter the blood stream. The platelets surrounding the malignant cell or clumps do not enter the surrounding tissue when the malignant cells penetrate the blood vessel walls. Once penetration of the tight blood vessel wall occurs, and without contact with platelet secreted factors, the cancer cell transitions back to epithelioid morphology and becomes fixed in place again. Hynes showed that metastatic spread of cancer decreases markedly when the platelets are blocked or depleted.

Finally, there is work showing that metastasis are significantly different from the primary tumor:

- The metastasis acquires some characteristics of the tissue surrounding it at the new location which makes them different from the primary.
- The metastasis does not respond to therapy in the same manner the primary does. This makes treatment of the metastatic foci difficult, if at all possible. The problem of treating metastasis is not trivial. Approximately 5% of all newly diagnosed malignant tumors do not have identifiable primaries.

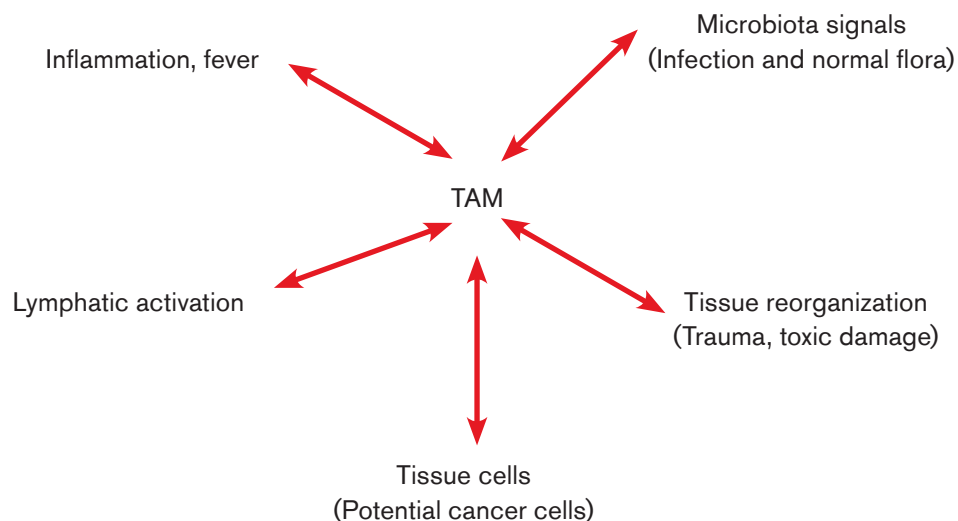
The new characteristics exhibited by a metastasis when compared to the primary tumor are most likely due to interactions between the metastatic tumor focus and the new surrounding tissue causing activation and deactivation of tumor genes. This is an interaction that involves abnormal and normal cells and which depends, to a large degree, upon normal surrounding tissue cells acting in normal ways and secreting normally found substances.

Chronic Inflammation and Cancer

It has been recognized for many years that chronic inflammation is associated with the development of cancer. The cause of the chronic inflammation may be quite varied. Infections are associated in some way with approximately 15% of all cancers, particularly infections with *H. pylori* which is associated with cancer of the stomach, and *Schistosoma hematobium* which is associated with cancer of the bladder. Chronic exposure to agents causing irritation, like smoking and asbestos, is associated with cancer of the lungs and pleura. Chronic inflammatory disease like Crohn's has been associated with cancer. The relationship between chronic inflammation and cancer is an area that has been extensively investigated by a group led by L. Coussens, who also has found that the use of non-steroidal anti-inflammatory agents (NSAIDs) causes a reduction in the incidence of cancer.

The key connection between chronic inflammation and cancer is provided primarily by immune-capable cells in the tumor's surrounding environment, primarily macrophages, but also other cells of hematologic origin. Macrophages, designated as Tissue Associated Macrophages (TAMs), and other immune-capable cells are an integral part of all tissues and organs. These TAMs and other immune-capable cells are specific to the tissue they are found in and different from organ to organ. They have normal functions that are tissue-specific and are found in the tissues in numbers that are tissue-specific. For example, 20% of brain cells are TAMs. The TAM numbers can increase rapidly with inflammation or tumor development.

TAMs play a central role in embryonic development by sending signals (secreting substances that act as signals) that modify the activity or responses, presumably through gene activation and suppression, of target cells. Deficiencies in TAM function result in developmental delays or malformations. These functions of TAMs are entirely normal. Similar TAM functions are triggered in response to infection, trauma, or chronic inflammation. In other words, TAMs act like tissue integrators processing a variety of signals or substances of different origin and producing their own response signals which in turn affect the response of other cells, as follows:



It is clear that the substances produced by TAMs when stimulated by events like trauma or infection are normal signals produced by normal immune-capable cells. It is also clear that these substances activate and deactivate genes in tissue cells that may lead to the development of cancer. It is postulated that, if the tissue target cells contain the necessary altered genes, the target cells will at some point in time produce their own signal substances to create a reinforcing loop with the TAMs and continue TAM activation of their (the target cells') genome. Eventually the whole complex sequence of gene activation and deactivation is achieved and cancer develops from the target cells with the now activated altered genes.

It is not clear where some of the activation signals required for cancer development originate – in the TAMs, the cell lines, or other stromal cells. What is clear is that an ongoing interaction between normal stromal cells, TAMs, and target tissue cells with inactive genome alterations is required to develop cancer tumors. The development process for cancer is not instantaneous, a significant amount of time is required to activate and deactivate the required genes to form a new cancer tumor. The amount of time required is variable.

It should also be evident that, in order to change a normal tissue cell containing dormant cancer associated genes into a fully invasive cancer, the developing tumor has to go through a number of intermediary stages:

Normal cell to **Hyperplasia** to **Metaplasia** to **Dysplasia** to **Cancer**

Please note that most of these intermediary stages that precede the development of invasive cancer are labeled as “benign” in standard histology-based pathology reports. There has been much discussion on the topic of early start of cancer therapy when one of these benign stages is identified.

Developing an Immune Classification for Cancer

As we have reviewed, there is much information indicating that normal tissue immune-capable cells doing their normal functions may contribute to the development, severity, and metastatic spread of cancer. It has also been shown that depletion or inactivation of tissue immune cells slows cancer development and prevents metastatic spread. These effects can be expressed in terms of a tumor immune score. Such immune scores would summarize prognostic and treatment information for the specific tumor being scored. In other words, an immune score would be a functional score that could be used for treatment and prognostic purposes. Current tumor scores are based upon histopathological findings, not functional findings, and provide little prognostic and treatment information. An immune score classification for cancer is in the process of development. At this time, a consensus is developing regarding the parameters to be measured for such a scoring system. It is expected that such a scoring system will provide great advantages for treatment of cancer.

Conclusions

The information presented shows that cancer develops slowly from tissue cells that contain altered genes. These altered genes undergo a complex process of activation and deactivation through interactions with surrounding immune-capable cells in their surrounding environment that, with time, results in the development of cancer. Inflammation and normal events like trauma and infection play a role in the process of cancer development. The key determinant appears to be the tissue-associated macrophage, which triggers the process in the course of performing its normal function. It appears that the cancer cells by themselves do not coopt surrounding tissues to provide for their needs. The process of cancer development appears to be more of an interactive relationship between target cells which contain altered genomes and normal tissue cells reacting to outside influences and triggering the process.

This concept has vast implications:

- It affirms the concept that treatment of cancer should start as soon as possible, probably before a full invasive cancer is developed. This means that biopsy findings showing benign conditions like hyperplasia and metaplasia may trigger treatment at some time in the future.

- It provides new approaches to treatment focused on modification of TAM function, and opens a new field of investigation about the uses of anti-inflammatory agents in the treatment of cancer.

There is a definite possibility that this new knowledge about cancer development might result in effective preventative treatments for people known to have altered genes associated with specific kinds of cancer. In all there is every reason to believe that a combination of these approaches to the treatment and prevention of cancer may lower overall cancer mortality significantly. This has a definite impact upon the insurance business that will affect some lines positively and others negatively.

There is much detailed information presented in this and the preceding article about cancer classification and prognosis that is important from an insurance viewpoint.

1. The classification based upon genomic subtypes would be very useful to us since it would give a handle on the expected survival of patients with specifically subtyped tumors.
2. The immune classification or scoring of tumors is probably going to take more time to be developed since this work is just starting; however, once completed, it is expected that it will provide significant treatment and prognostic information.

With two new tumor classifications in the works there should be significant advantages for insurance use in the areas of underwriting and pricing. These are areas of which we must remain aware and ready to incorporate in our rating manuals and other materials. From the point of view of other kinds of insurance, it is likely that survival from cancer will improve. This will benefit mortality products and impact longevity products. Health insurance and other lines of insurance will have to adapt to the changes produced by these new classifications.

Finally, it must be recognized that the discovery that an applicant has one single altered gene that is associated with cancer, out of many gene abnormalities required, is likely to be unratable for the purposes of life insurance underwriting. As we have reviewed, the development of cancer requires the sequential activation and deactivation of many genes. A single gene abnormality is likely to be nothing cause to concern.

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THE STRUCTURE OF ICD-10 CODES

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Codes are a very important part of Information Technology. Codes standardize information and allow interoperability between computer systems. There are many different coding standards for medical information. Data items such as pharmaceuticals, medical procedures, medical conditions, medical treatments, lab results and more are all coded to standard formats. Unfortunately, there are many different, often overlapping standards.

One such standardized set of codes is ICD-10. The Centers for Disease Control (CDC) provide extensive electronic information for ICD-10 coding. This data comes in the form of Extensible Markup (XML) files. These files are typically imported into a database system to be used by computer programs. There is limited online information describing the exact format of these files. In this article I will describe the hierarchical structure of ICD-10 codes and how they are encoded into files.

ICD-10 is a set of code introduced by the World Health Organization (WHO) for medical classification. This standard set of codes is often used as a starting point for country-specific medical classification code sets. Country adaptations typically add additional detail to the WHO ICD-10 codes. The U.S. Centers for Disease Control (CDC) extended ICD-10 into two separate sets of codes.

- ICD-10-CM – Used to encode medical diagnoses.
- ICD-10-PCS – Used to encode medical procedures.

ICD-10 is of particular importance in the United States due to several government mandates. The deadline for the U.S. to begin using Clinical Modification ICD-10-CM for diagnosis coding and Procedure Coding System ICD-10-PCS for inpatient hospital procedure coding is currently October 1, 2014. The deadline was previously October 1, 2013.

CDC Provided Files

The CDC provides a number of files that can be imported into databases. These files are in XML format. The format is very different between PCS and CM, even for files accomplishing nearly the same function. The following two file types are provided for both PCS and CM.

- Index File
- Tabular file

The tabular file lists all of the codes in either CM or PCS. In both cases this file is organized by “chapter”. These chapters are very much like the chapters of a book. Groups of common codes are divided into various chapters. Codes in the tabular file attempt to use the most standard name for a medical term. This can make it difficult to quickly look up a term. One might not know to which chapter the code belongs. Further, one might know the term by a common name.

The index file solves this problem. The index file is arranged in a similar manner to a book’s index. It is alphabetical by the code name and description. Additionally, many codes are indexed under common names. This allows the user to quickly locate a term by either its common or more-scientific name. The only linkage between the index and tabular file is the ICD standard code. Software wishing to simultaneously use both files will need to bridge between the two files. This requires taking into account that the tabular file is ordered by code and the index file is ordered by multiple descriptions of the tabular file.

In addition to the above two files, the ICD-10-CM files also contain the following two files.

- Table of Drugs
- Table of Neoplasms

ICD-10-CM codes are medical diagnoses, so when we consider drugs in ICD-10-CM, we are not looking for routine prescriptions. Rather, we are looking at diagnoses that resulted from a patient’s interaction with a drug. The Table of Drugs file is essentially a

table, organized alphabetically. Its rows literally go from Abrine to Zyprexa. The columns specify the ICD-10-CM code that deals with the following seven ways an individual might be diagnosed due to a drug interaction.

- Substance
- Poisoning, Accidental (unintentional)
- Poisoning, Intentional self-harm
- Poisoning, Assault
- Poisoning, Undetermined
- Adverse effect
- Underdosing

The table of Neoplasms is also an index into the codes; however, now we are providing a similar grid for looking up codes related to neoplasms, or tumors. The rows of neoplasm table are an alphabetical listing of tumors. The columns list the ICD-10-CM code for the following diagnoses with the particular tumor.

- Malignant Primary
- Malignant Secondary
- Ca in situ
- Benign
- Uncertain Behavior
- Unspecified Behavior

Neoplasms span multiple areas in the ICD-10-CM master list. The index provides for a quick lookup when the user knows the name of the neoplasm and the result listed above.

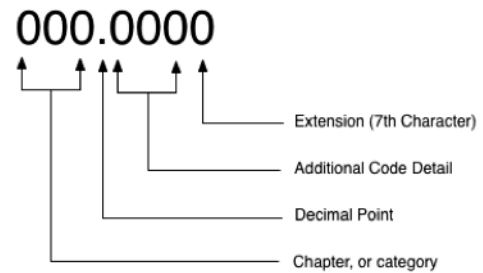
Inside ICD-10-CM Codes

ICD10-CM codes are hierarchical. Each position inside the code means something. By looking at two ICD10-CM codes, the user can tell how similar they are. An actual ICD10-CM code looks something like this.

A01.01

This is the code for typhoid meningitis. The code for typhoid arthritis is A01.04. The first five positions in the two codes are identical, which means that these two codes are very similar. There is a decimal place at the fourth position – this is a required part of the code. It really is just there to separate the chapter from the rest of the code. It is always in this position and is more of a placeholder than any meaningful part of the code. Nevertheless, for the code to be valid, the decimal place must be there.

The following diagram shows the parts of an ICD-10 code. Not counting the decimal place, an ICD-10 code can have up to seven positions.



The first three positions specify the chapter or category. Chapters are very high level. The ICD10-CM chapters are shown here.

- A00–B99: Certain infectious and parasitic diseases
- C00–D48: Neoplasms
- D50–D89: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
- E00–E90: Endocrine, nutritional and metabolic diseases
- F00–F99: Mental and behavioral disorders
- G00–G99: Diseases of the nervous system
- H00–H59: Diseases of the eye and adnexa
- H60–H95: Diseases of the ear and mastoid process
- I00–I99: Diseases of the circulatory system
- J00–J99: Diseases of the respiratory system
- K00–K93: Diseases of the digestive system
- L00–L99: Diseases of the skin and subcutaneous tissue
- M00–M99: Diseases of the musculoskeletal system and connective tissue
- N00–N99: Diseases of the genitourinary system
- O00–O99: Pregnancy, childbirth and the puerperium
- P00–P96: Certain conditions originating in the perinatal period
- Q00–Q99: Congenital malformations, deformations and chromosomal abnormalities
- R00–R99: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
- S00–T98: Injury, poisoning and certain other consequences of external causes
- V01–Y98: External causes of morbidity and mortality
- Z00–Z99: Factors influencing health status and contact with health services
- U00–U99: Codes for special purposes

The preceding list gives a good overview of the diagnoses covered by ICD-10-CM.

After the three chapter positions, there are three more positions that allow additional hierarchies under the chapters. These positions are immediately following the decimal point. Each of these three detail positions provides additional levels of detail for the code. The first of these three positions specifies the top level of the hierarchy; as one moves to the right, one goes further down the hierarchy.

For example A01 specifies typhoid and paratyphoid fevers. By itself, this is not a complete code. An ICD-10-CM code is only complete when it reaches a position that has no further possible positions to the right. Under A01 there is another level, A01.0 that specifies typhoid fever. Under A01.0 there is A01.01, which is typhoid meningitis. There are no additional levels under A01.01, so this code is considered complete. ICD-10-CM codes can have up to seven positions. The only way to know if there are additional levels is to look at the hierarchical XML files provided by the CDC. One cannot simply look at an ICD-10 code and determine if it is valid.

There is also a seventh character position. The seventh character is called the extension. It allows even further definition of what a code means. Usually this is very low-level detail. Often this specifies a stage or severity of the main code. For example, the partial code H40.14, which is “Capsular glaucoma with pseudoexfoliation of lens”, specifies a seventh character. The required seventh character codes for H40.14 are listed here.

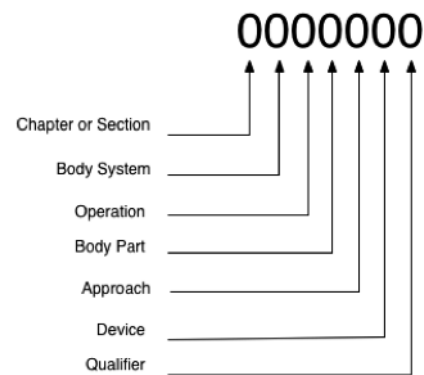
- 0: stage unspecified
- 1: mild stage
- 2: moderate stage
- 3: severe stage
- 4: indeterminate stage

When the seventh character is added to the partial code H40.14, the code now becomes H40.14X0, to specify “stage unspecified”. Notice the X? This is because the seventh character must be the seventh character. Of course, we do not count the decimal place as a position. If a code does not have any additional sub positions, then X’s must be filled in to get out to the seventh character.

It is also important to note that the above five definitions only apply to the H40.14 code parts. Different ranges of codes can specify different seventh character definitions. Most code ranges do not have a seventh character. The seventh character defined for various ranges of codes is defined in the CDC provided XML files.

Inside ICD-10-PCS Codes

Like ICD-10-CM codes, the ICD-10-PCS codes are also hierarchical. The structure is simpler than the ICD-10-CM. For ICD-10-PCS there are seven positions. There is no decimal place. The left-most position is the highest level. Just like CM, as more positions are added to the right the code is defined to greater detail. The structure of an ICD-10-PCS code is shown here.



The chapter, or section, is the first character. Unlike CM, there is only one character devoted to the chapter. The following high-level chapters are defined by the first position.

- 0: Medical and Surgical
- 1: Obstetrics
- 2: Placement
- 3: Administration
- 4: Measurement and Monitoring
- 5: Extracorporeal Assistance and Performance
- 6: Extracorporeal Therapies
- 7: Osteopathic
- 8: Other Procedures
- 9: Chiropractic
- B: Imaging
- C: Nuclear Medicine
- D: Radiation Therapy
- F: Physical Rehabilitation and Diagnostic Audiology
- G: Mental Health
- H: Substance Abuse Treatment

The above list gives a good overview of the procedures handled by ICD-10-PCS. As more positions are added

the code drills down to a more-specific definition of the medical procedure. Subsequent positions encode the body system, operation, body part, approach, device and qualifier for the procedure.

Unlike the ICD-10-CM codes, the ICD-10-PCS codes are not variable length. Every ICD-10-CM code is seven characters long.

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Jeff Heaton recently joined the Electronic Health Records (EHR) Initiatives team at RGA as an EHR Informatics Scientist. In one of his first tasks, he was asked to create a utility to allow an underwriter to enter information on a code-by-code basis. This required mapping the CDC-provided XML files to an Oracle database, while preserving the hierarchical nature of the codes.

ON DEMAND WEBCASTS

RGA and industry experts discuss the topics below in our 2013 webcasts.

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Presenters: Peter Banthorpe
Head of Actuarial Research
RGA UK Services Limited

Derek Kueker
Actuary
RGA Reinsurance Company

Moderator: Jonathan Porter
Senior Vice President and Chief Pricing Actuary
International Markets
RGA Reinsurance Company

Electronic Health Records

Presenters: Dr. Carl Holowaty
Senior Vice President and Chief Medical Director
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David Atkinson
Vice Chairman, Executive Vice President
RGA Reinsurance Company

Moderator: Dave Wheeler
Senior Vice President of RGA Underwriting
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Breast Cancer Prognosticators: Tumor Subtype and Future Potential of Cancer Genomics

A presentation for Medical Directors of Multinational Insurance Companies

Presenters: Ron Bose, M.D., Ph.D.
Assistant Professor of Medicine, Division of
Oncology, Section of Breast Oncology
Washington University School of Medicine

Moderator: Dr. Carl Holowaty
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