LETTER FROM THE EDITOR

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Dear readers:

This edition of Reflections features articles on two major causes of excess mortality. The first article, which is entitled "Advances in Cancer", is written by Dr. Oscar Cartaya, who discusses in great detail the newest concepts of the understanding and detection of cancer. This 'forward-thinking' approach will hopefully lead to breakthroughs in the early detection and treatment of malignancies. It is very thought provoking.

Our second article has been contributed by Dr. Paul Davis, who is RGA's Chief Regional Medical Director in Asia-Pacific. This article, entitled "Insights on Heart Failure" is his first contribution to *ReFlections*. He shares his extensive clinical and insurance knowledge with us regarding this increasingly diagnosed heart condition, as it applies to life and disability applications and claims.

Please enjoy these articles, and as always feel free to contact us with your feedback or questions.

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

ADVANCES IN CANCER

By Dr. Oscar A. Cartaya M.D., M.P.H., M.S., D.B.I.M.
Vice President and Medical Director
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Despite a "war on cancer" waged since the 1970s and untold amounts of money spent in research, the mortality caused by cancer has remained very high over the years. Part of this is probably due to a narrow conceptual framework, based upon dated morphological and pathological findings, originating at the end of the 19th century, regarding the nature of cancer and how to treat it. In essence, cancer has traditionally been thought of as masses of tissue within an organ capable of uncontrolled growth and metastasis, but basically remaining in variable degrees the same type of tissue it originally was. As such, breast cancer remains breast tissue which behaves abnormally.

Our new abilities to analyze the molecular biology of cells and tissues and the function of the genome have lead to a new and broader conceptual framework of cancer – one that offers great promise for advances in this field. Under this broader conceptual framework, cancer tissue of whatever origin is perceived as something different than the tissue of origin. This new conceptual framework has led to developments in treatment, diagnosis, and imaging that should see widespread application, some of them in the not very distant future.

The new conceptual framework looks upon cancer as a separate organ – one that 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 which 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.

This article is based upon a state-of-the-art conference I attended last September entitled: "Critical Issues in Tumor Microenvironment, Angiogenesis, and Metastasis, from Bench to Bedside to Biomarkers", presented by Harvard Medical School. This conference provided a comprehensive review of the new conceptual framework about cancer and indicated some of the directions which we may expect treatment to take. The purpose of this article is to present some of these developments, emphasizing new diagnostic and treatment techniques, and briefly discuss their potential impact upon insurance and underwriting.

The process of transformation of an abnormal tissue cell into a fully invasive cancer has a well-defined progression of morphological stages. In ascending order of severity, the stages are: hyperplasia, metaplasia, dysplasia, carcinoma in situ, and invasive carcinoma.

Please note that under the traditional morphological/pathological framework, some of these stages are not considered to be malignant or to require therapy. Under the new conceptual framework of cancer, the early non-malignant stages may well become targets for early therapy aimed at preventing the development of invasive cancer. The broadening of the conceptual framework defining what cancer is and how it develops has numerous ramifications that show great promise for improved treatment of cancer.

Activity of the Supporting Tissues

Under the new conceptual framework of cancer, the growth and development of the tumor depends upon the degree of activity of the supporting tissues. A rapidly growing cancer requires high activity of its supporting tissues, with rapid growth of the cancer stroma and vasculature, and changes in the supporting tissues' metabolic activities in response to the tumor's needs. Slow or stable tumors, on the other hand, require comparatively less supporting tissue activity. This is illustrated in Figure 1, which shows experimental metastasis produced by injecting a test animal with suspensions of cancer cells and tissues. The tumor on the left has taken to the supporting tissue, but without an adequate vascular supply it lies dormant and has little activity. The tumor on the right, however, has produced stimulating factors, causing new blood vessels to be formed. These new vessels will form the vasculature of the tumor, allowing it to grow rapidly.

Figure 1
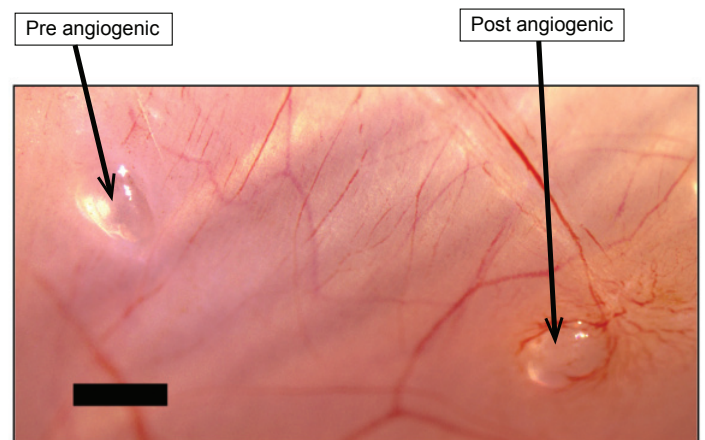
Scale: Bar = 1mm.

▪ *Moses MA, Harper J. The Regulation of Tumor Angiogenesis: From the Angiogenic SwitchThrough Tumor Progression. In: L. P. Bignold, Volume Editor. Cancer: Cell Structures, Carcinogens and Tumor Pathogenesis; EXS 96: 2005. p.223--268*

The high level of activity of the tissue stroma and vascular supply required by an actively growing cancer can be detected by a variety of techniques, without need for a biopsy of the tissue. The primary factor stimulating new growth of vascular tissue (angioneogenesis) is the Vascular Endothelial Growth Factor (VEGF); please note that, as is the case in many other important molecular pathways, there are many other factors involved in angioneogenesis. High metabolic activity and rapid growth of tissue stroma can be related to high activity of any number of proteases like Matrix Metalloproteinases (MMP), which are found ubiquitously in body tissues but are generally in a stable or inactive state unless there is a great deal of tissue growth and stromal remodeling, in which case they become quite active and their levels increase rapidly. These and many other compounds associated with high metabolic activity of the cancer stroma and rapid vascular growth can be detected in body fluids by standard assay methods.

Of particular significance is work done using body fluids of cancer patients to detect compounds related to high levels of metabolic activity and growth of the stromal tissues, and using them to diagnose the presence of active cancer. Much work has been done using MMPs (numerous types of MMPs have been identified and labeled with numbers, as in MMP9 or MMP2), and Neutrophil Gelatinase-Associated Lipocalin (N-Gal).

These enzymes are found in the urine of patients with active cancer of different kinds. Figure 2 shows chromatographic identification of high molecular weight proteases in the urine samples of patients with various types of active cancer. Normal patients without active cancers or rapidly growing tissues of any kind do not excrete these high molecular weight proteases in their urine. This has led to the development of diagnostic tests for active cancer, now in the process of seeking FDA approval.

Figure 2

### Identification of HMW MMPs in the Urine of Cancer Patients
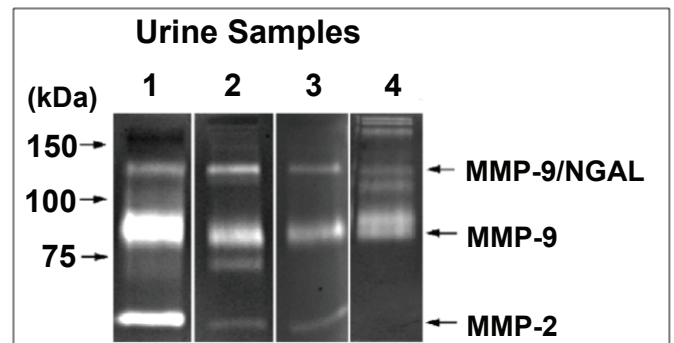
Yan, L, Borregaard, N, Kjeldsen, L, Moses, MA. J. Biol. Chem. 276: 37258-37265 (2001)

To emphasize the significance of these diagnostic tests for the insurance industry, let us review some of the results obtained with cancers that are difficult to diagnose or to follow using current diagnostic techniques. We can start with prostate carcinoma, a common cause of death in males. As we all know it is difficult to determine if PSA elevations are due to benign prostatic hypertrophy (BPH) or to prostate cancer. The development of free PSA assays has helped to some degree, but the free PSA test is still unable to make the distinction with any degree of certainty.

Figure 3 shows a chromatographic analysis of the urine of patients diagnosed with prostate cancer, both metastatic and organ-confined, BPH, and Neuroepithelial Differentiation (NED), which is associated with the development of Prostate Intraepithelial Neoplasia (PIN) and cancer. It is clear that the urine of patients with active cancer contains high molecular weight MMP proteases, and the urine of patients with NED and BPH does not.

Figure 3

Urinary MMPs Predict Disease Status in Cancer Patients
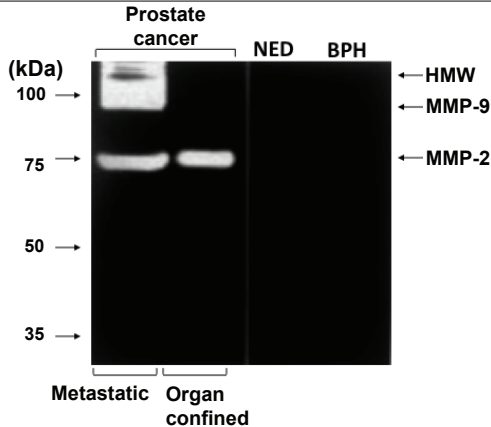
n = 150 patients, but has now been validated in > 8,500 patients

Moses, MA, Wiederschain, D, Loughlin, KR, Zurakowski, D, Lamb, CC, Freeman, MR. Cancer Res. 58: 1395, 1998

Let us consider breast cancer, a common cause of death among women. We are all aware how difficult it is to screen for breast cancer in women with dense fibrocystic and fibronodular disease of the breast. These women require serial mammograms and, frequently, serial biopsies, and there is always a good chance of missing a small focus of breast cancer with the biopsies. Underwriting these cases is sometimes challenging.

Figure 4 shows a chromatographic analysis of the urine of women with breast cancer and matched controls without breast cancer. None of the controls showed high molecular weight proteases (MMPs and N-Gal) in their urine, but 19 out of 22 women with breast cancer did. This is a preliminary study, but it is clear that the number of false negatives among women with cancer is exceedingly low and that there are no false positives among the matched normal controls tested.

Figure 4

MMP-9/NGAL is Detected with High Frequency in the Urine of Women with Metastatic Breast Cancer
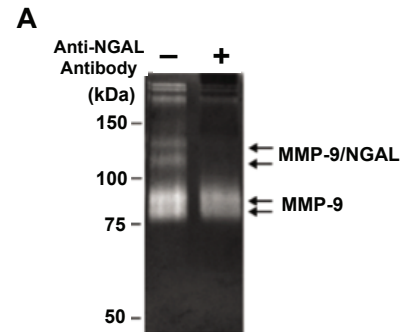
Urine Samples	Number of Patients	MMP-9/ NGAL Positive	MMP-9/ NGAL Negative
Breast cancer	22	19*	3
Health age-matched control	27	0*	27

n = 150 patients, but has now been validated in > 8,500 patients

Fernandez CA, Yan L, Louis G, Yang J, Kutok JL, Moses, MA Clin. Cancer Res. 11:5390, 2005

Let us consider brain cancer. By nature of its location within the brain, it is difficult to follow up brain cancer after treatment, particularly if there are any small residual areas of enhancement in the post-treatment MRI.

Figure 5 shows the result of urine chromatography for high molecular weight proteases in a patient with brain cancer before and after surgical excision of the tumor, and in a matched normal control. Matched MRIs of the cancer patient's brain before and after excision of the tumor are also shown. It is clear that MMPs are present in the urine of the patient with cancer before the excision of the tumor, but not in the urine of the matched normal control or in the post-excision urine sample from the cancer patient.

Figure 5

Urinary MMP Detection Correlates With Brain Tumor Status
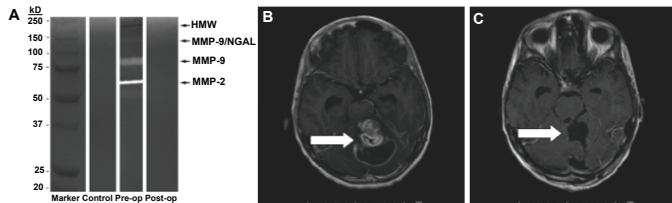
Smith, E, Manfredi, M, Scott, RM, Black, PM, Moses, MA, Neurosurgery, 60: E1148-9, 2007
Smith ER, Zurakowski D, Saad A, Scott RM, Moses MA, Clin Cancer Res, 14(8): 2378-86, 2008

From an underwriting point of view, availability of these urine biomarker tests might make favorable decisions possible at a much earlier date, without the postponements required to see if there are MRI changes. The availability of these tests should also facilitate making adverse decisions in specific cases where the urine biomarkers indicate the presence of an actively growing tumor. Considering these are relatively simple tests done in the urine of applicants, their use in the industry might produce favorable results.

I must restate that these tests are not yet approved by the FDA, and that they are not designed for diagnosing specific cancers. What they do show is abnormally increased supporting tissue activity associated with active cancer. The specific cancer diagnosis must be made separately. It is possible that disorders or normal processes causing high metabolic activity of supporting tissues (such as recovering from extensive trauma or surgery, or rapid growth during childhood) may produce false positives with these tests. I cannot say if these conditions have been tested for the presence of high molecular weight proteases in the urine.

Imaging

Imaging of cancer presents unique difficulties. It must be understood that imaging by MRI is based upon density and contrast differences between tissues. Active cancers are known to have abnormal, although abundant and actively developed, vasculature. Blood vessels in cancer are leaky, or leakier than normal blood vessels, and this causes leakage of the contrast materials used in imaging techniques. So, what we see in an MRI as a tumor mass may represent a smaller tumor mass together with extravasated contrast material. As chemotherapy progresses, the leakiness of the tumor's vasculature will change, making it difficult to determine the actual size of the tumor and follow up the effects of the therapy by imaging. A standard T1 weighted image of a brain with an occipital tumor is shown below.

Image 1
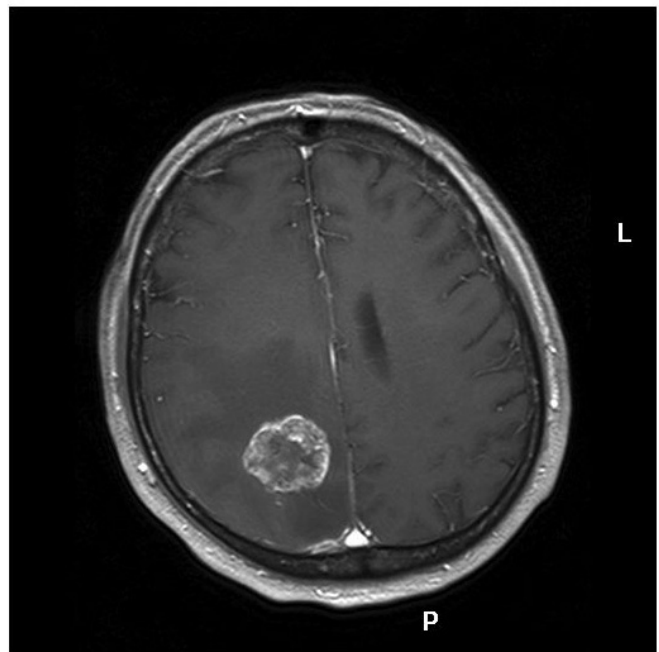
Occipital lobe tumor, T1 weighted image

benutzer:marvin_101   *Wikipedia*

To solve this problem, various newer imaging techniques, many of them directed to the identification of extravasated fluids and edema, have been developed and will be increasingly used in the future, making it necessary for the industry to keep pace with what these newer techniques are actually measuring. Some of these newer techniques use special contrast materials to examine permeability and water mobility (edema) to allow a better determination of the real size of a tumor. Many of these newer techniques are being used in academic medical centers to determine levels of response of the tumor to chemotherapy.

Some of the more advanced, experimental imaging techniques attempt to detect heightened levels of metabolic activity associated with suspicious areas of the brain. Some of these techniques are very interesting in concept. BOLD (blood oxygen level dependence) MRIs indicate elevated levels of oxygen use in specific sections of the brain. These have been used to indicate high levels of neural activity. Since normal brain tissue is quiescent unless activated, the BOLD technique may be used to determine functional brain tissue. Brain tumors do not exhibit the characteristic pattern of activation following a stimulus. Therefore, using the BOLD technique, it is theoretically possible to detect where the normal brain tissue ends and where the tumor begins. This use of BOLD MRIs is still experimental but promises to be of great importance in planning the extent of resections during neurosurgery, and avoiding critical brain areas that are free of tumor.

Image 2
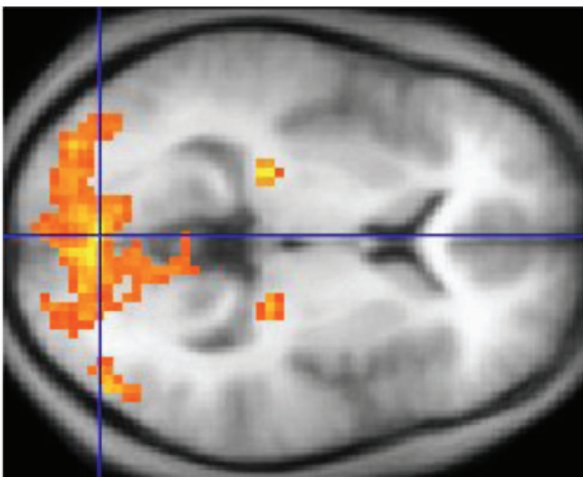
Blood Oxygen Level Dependence (BOLD) MRI showing increased blood flow to specific areas of the brain which occur with neural activation.

Washington Irving   *Wikipedia*

Methods are being developed in which sequential PET scans, showing metabolic activity of the tissues and MRI scans, may be combined or superimposed, showing abnormalities in the MRI and how they correlated to the metabolic activity of the underlying tissue. The idea is to use these superimposed imaging techniques to determine high metabolic activity in correlation to MRI lesions, thereby showing a higher probability of active cancer.

A totally new development is tractography, which is a technique to study the path of movement of liquids within the white matter of the brain. The white matter has well-defined tracts through which liquids flow in specific directions. The appearance of a tumor disturbs these tracts and creates an area devoid of these tracts. These areas devoid of tracts are identifiable and comparable to standard MRI lesions. As therapy takes effect, and the tumor shrinks in size, the normal-looking tracts return to the area previously occupied by the tumor. Tractography images can be manipulated in 3D.

Image 3
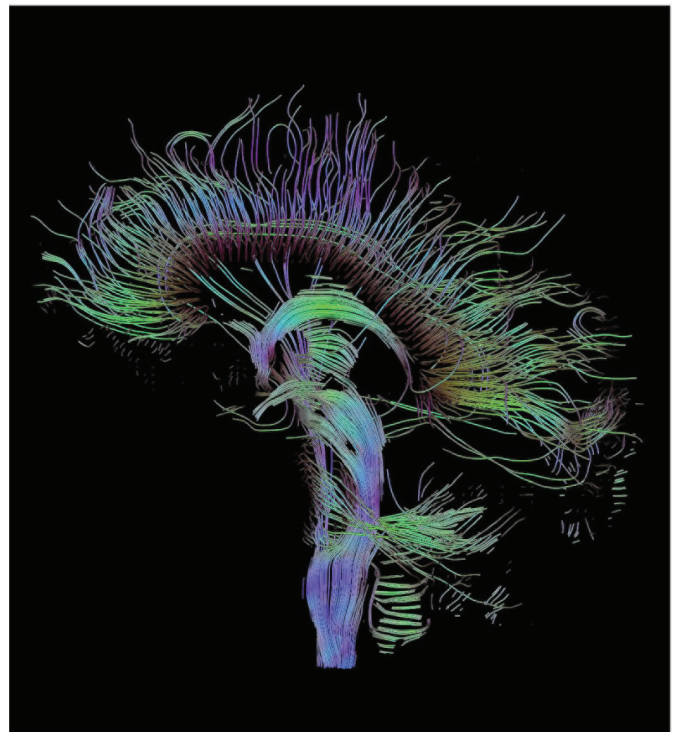
Tractography using diffusion tensor imaging (DTI) to demonstrate the flow of water within the brain.

Thomas Schultz   *Wikipedia*

Genome Subtypes

As Dr. George Sledge stated in his 2007 work on breast cancer, the behavior of cells within a cancer can be compared to the Darwinian behavior of the members of a species. Each cell is subject to evolutionary pressures from its environment and reacts accordingly to achieve survival and reproduction. Targeted therapies for cancer must be considered in such classical evolutionary terms. The individual cancer cells are locked in by their genome with major genome categories identifiable for each type of cancer. Each of these genomic categories are complex systems with individual molecular and pathway variations which must be addressed or targeted by the therapies used. Not all cells within a cancer tumor will respond the same way to therapy depending upon environmental and genomic issues.

Although it is difficult to conceive of the individual cells in a malignant tumor being subject to evolutionary forces as happens with species in nature, a significant body of evidence exists supporting this view. This means that the individual cells in a malignant tumor, while subject to limitations imposed by their common genome, may react individually to adapt and survive external stimuli pressures, such as chemotherapy.

At this point, I would like to show the effect of major genomic tumor categories or subtypes upon survival after therapy. These major genomic tumor subtypes are present in all tumors. The example shown in Figure 6 is from pancreatic cancer – a particularly deadly tumor that does not respond to treatment and which may cause death rapidly.

In the example below, cancer tumor patients, all of whom received the same therapy with Bevacizumab, were divided into three different genomic subtype groups. It is not difficult to see major differences in survival between these groups. Medial survival for the three genomic groups in Figure 6 was: AA genome, 309 days, AC genome, 171 days, and CC genome, 144 days. The median survival of genomic group AA was more than twice as long as the median survival of group CC.

Figure 6
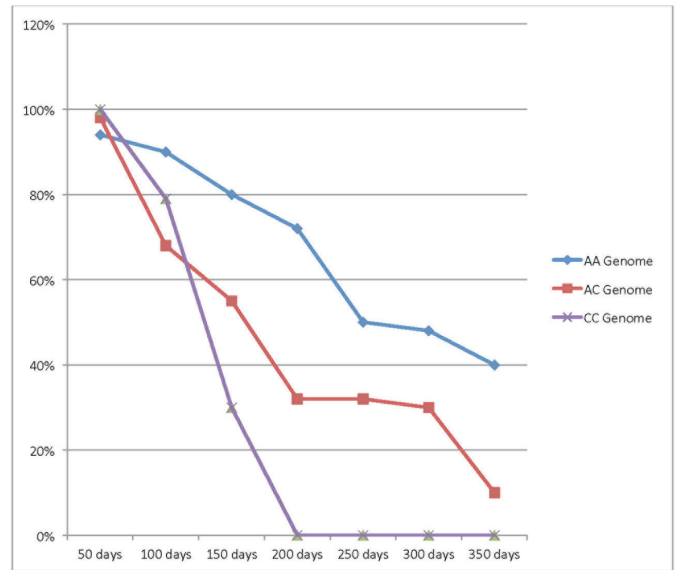
Lambrechts, Carmeliet, et. al.

It is clear from Figure 6 that cancer survival depends upon the tumor's major genome subtype group. This is logical, since a tumor's genomic subtype will determine how the cancer responds to its environment, including its responses to therapy. The prior example used pancreatic cancer, but it is clear that all types of cancers will exhibit genomic subtype variability and therefore will also exhibit genomic determined differences in survival after treatment.

From an underwriting point of view, it should be clear that survival of a patient with cancer will be determined by the tumor's genomic subtype. It should be understood that this type of genomic information is not currently part of standard pathology reports produced following biopsies or tumor excisions. However this genomic information may be incorporated in pathology reports in the near future, since the differences in survival to be expected may be significant. This is something to keep in mind when this information starts being incorporated in pathology reports.

Treating Cancer by Targeting its Supporting Tissues

Associated with the recognition of the important role of supporting tissues and vascular supply in the growth and development of cancer has been the idea of developing new ways of treating cancer targeting its supporting tissues. The obvious target for these therapies has been the tumor vascular supply, without which the tumor cannot develop.

Effective antineogenic agents have been developed, mostly based upon monoclonal antibodies to specific vascular growth factors, primarily VEGF.

The proper timing of such therapy has been discussed at length, with interest in starting therapy before the tumor becomes fully malignant and invasive. The aim of this early start of therapy is to prevent the formation of serious fully malignant invasive tumors. Initial attempts to use antineogenic agents to treat cancer was based on the concept of maximum cancer cell kill rates resulting from destruction of the cancer's vascular supply, an approach referred to as "pruning" in the literature.

Clear success for therapeutic programs using the vascular pruning approach has not been obtained so far at any stage of cancer development. The problem appears to be due to the complexity of the mechanism stimulating and regulating neovascular production. This complexity combines with the unique characteristics of cancer, as stated by Dr. Sledge, in which every single cancer cell acts and reacts as a separate entity to stresses produced by therapy, hypoxia, etc. … to cause failure of the vascular pruning therapies.

Some explanation is appropriate at this time. It is known that the vascular supply of a malignant tumor is different than the vascular supply of normal tissues. This is thought to occur because the tumor, seeking to stimulate vascular growth to provide support for its own growth, rapidly releases imbalanced amounts of the various vascular growth factors required for angiogenesis. These imbalanced vascular growth factor levels produce a tumor vasculature characterized by large vessels that are leaky, due to deficient endothelial junctions, with a relative paucity of smaller vessels and capillaries. As a result, portions of the rapidly growing tumor are relatively hypoxic, causing the malignant cells in these locations to become more stem cell-like (undifferentiated) than other tumor cells, and also more able to withstand relative hypoxia. These cells are also less reachable by therapeutic agents. The leakiness of the vessels in the tumor is also a factor favoring metastatic spread, by making it easier for malignant cells to enter the body's circulatory systems.

It is not difficult then to visualize what happens when the blood supply to the cancer is drastically reduced by a "vessel pruning" antineogenic type of therapy. Vast numbers of malignant cells perish, however those that survive are much more malignant (less differentiated), capable of surviving hypoxia, less reachable by chemotherapy, and loosened from other nearby tumor cells, which may be dead or dying. These are the cells that are more capable of causing metastasis, so this is not a favorable outcome. Therefore, antineogenic agents have been used not as mainline cancer killing therapy but as adjuncts to therapy with more conventional agents. This combined approach has had some degree of success.

A different approach is now being tested, based upon 'vessel normalization' of the vascular supply of the tumor. This is achieved by providing a balanced supply of stimulating factors and antagonistic factors as part of the therapy. This approach is expected to produce better blood irrigation of the tumor, therefore favoring less-undifferentiated malignant cells, which are less likely to cause metastasis, and better reach of the chemotherapeutic agents to the entire tumor. A massive cancer cell kill is not sought with this approach – the desired outcome is to lessen the potential for metastatic spread, and favor a steady kill rate of the more approachable cancer cells. This is a very promising approach. Please refer to the following table which compares these two approaches to the normal state of a cancer tumor.

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CONGRATULATIONS!

Dr. Robert Coates, Vice President and Medical Director, RGA-U.S. Division has been awarded this year's 'President's Award' at the American Academy of Insurance Medicine annual meeting for his contributions to the organization

Vessel Pruning	Cancer	Vessel Normalization
Anti neovascular therapy used as a form of chemotherapy	Normal tumor state	Balancing vascular growth agents combined with other chemotherapeutic drugs
Target: maximal kill of cancer cells through hypoxia		Target: restoring adequate circulation to the tumor
Causes extremely poor blood supply with few residual large blood vessels in the tumor	Poor blood supply with large caliber blood vessels, inadequate blood supply to the whole tumor	Restores a reasonable blood supply to all areas of the tumor, blood vessels are normal in appearance
Aims of the therapy: Maximal kill of tumor cells, the few residual malignant cells are very undifferentiated and very likely to form metastasis and be refractory to chemotherapy	Variable blood supply to the tumor cells, some are located in areas of hypoxia and become more undifferentiated. Some cells receive adequate oxygen supply and act more like normal tissue. These are susceptible to chemotherapy.	Aims of the therapy: The blood supply to the tumor is normalized causing increasing differentiation of the tumor cells making them less likely to form metastasis. These better-oxygenated tumor cells are more accessible and more susceptible to chemotherapy. A gradual steady kill of tumor cells with low risk of metastatic spread is the desired outcome
Chemotherapy: Very poor access to the few remaining tumor cells, increasing resistance to chemotherapy		Chemotherapy: Good access to the remaining tumor cells, maintained susceptibility to chemotherapy
The remaining malignant cells are not tightly connected to other tumor cells and become free to migrate via the vascular supply and form metastasis.		As long as the vascular supply is maintained in a normalized state the tumor cells will be less capable or likely to migrate and form metatasis
Pruning stresses a maximum rapid kill of malignant cells through hypoxia. This may increase the risk of metastatic spread and ultimately be a therapeutic failure		Vessel normalization stresses maintained access and susceptibility of the tumor cells to other chemotherapy agents. This is a gradual but steady malignant cell kill approach which minimizes metastasis risk and ultimately more successful than a pruning approach to therapy

A number of laboratories have confirmed that the traditional approach to cancer chemotherapy based upon the use of 'maximum kill' boluses of chemotherapeutic agents, as high as can be tolerated by the patient, produces worse results than more frequent, much smaller dosages of the same chemotherapeutic agents. This method of

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chemotherapy administration is called metronomic therapy. Metronomic therapy not only results in fewer side effects and better tolerance of the chemotherapy, but also produces better success in the treatment of the cancer itself. It is thought that this approach, which kills malignant cells at a lower but steadier rate than the traditional approach, also kills the supporting stroma of the cancer as well as the vascular supply, resulting in improved response to the therapy.

Metastasis

Metastatic spread is the most common cause of death associated with cancer. Therefore, to maximize patient survival, metastatic spread has to be prevented. The metastatic process is continuous, but proceeds at different rates throughout the history of the disease, depending upon the status of the primary tumor and its response to therapy.

The metastatic process itself is markedly inefficient. It has been calculated that only one successful metastasis is created for every 10,000 malignant cells or clusters of cells reaching circulation.

In order to create a metastatic focus, the malignant cell or cluster of cells must go through a number of distinct steps, as follows:

1. Loss of adhesion to other tumor cells: The malignant cells gain mobility and become independent of the tumor.
2. Intravasation: Penetration of a vessel wall to gain access to the circulation or lymphatic stream. This is helped by the inherent leakiness of the tumor vasculature.
3. Fixation to the vascular wall at a distant site.
4. Extravasation: Penetration of the normal vascular wall (with tight endothelial junctions) into some surrounding tissue.
5. Proliferation into an active invasive tumor at the distant site: This requires co-opting the new organ's stromal tissue matrix and stimulating the development of new vasculature to support the tumor.

Each of these steps results in the death or inactivation of vast numbers of malignant cells reaching the particular step. Only a very limited number of cells, or clusters of cells, survive and successfully produce viable metastasis. Not every malignant cell is capable of producing metastasis – only the more undifferentiated (more stem-like) cells are capable of doing so.

Clusters of malignant cells, particularly those carrying supporting tissue stromal cells with them, are more likely to successfully produce successful metastasis than single cells. Additionally, regardless of the type, or, whether individual malignant cells or cluster of malignant cells and stromal cells are involved, in order to fix to a vascular wall, particularly to a normal vascular walls with tight endothelial junctions, the malignant cells or clusters of cells must be surrounded by platelets. Without the platelet clusters, the malignant cell or malignant cell cluster cannot fix or penetrate distant vascular walls or form metastasis. Once the process is completed, and a new active, invasive tumor focus is formed, the cycle of growth and spread starts anew.

New Goals for Cancer Therapy

New knowledge gained about cancer biology allows the creation of new treatment paradigms. It is known, for example, that some types of cancers will react to chemotherapy by rapidly becoming resistant to it. This is dependent upon genomic activation and the production of factors that cause this resistance, not dependent upon mutation as it occurs with bacteria. As a cancer becomes resistant to one chemotherapeutic agent, it may become more sensitive to others. Treatments that facilitate access of the chemotherapy to the tumor are to be favored, as well as therapies that maintain the malignant potential of the tumor low, and prevent metastasis.

Biomarkers derived from blood and body fluids, as well as tumor cells obtained from the blood stream in limited quantities, may be used to guide any required therapeutic changes. Essentially, we are reaching a stage where the greatest promise for successful cancer therapy lies not in developing extremely lethal chemotherapeutic agents, but upon individually tailored therapies.

Individually tailored therapies will depend upon the ability to test cancer sensitivity to chemotherapeutic agents or combinations of chemotherapeutic agents, which will need to be administered in optimal form, quite likely in frequent small dosages. These tailored therapies will have to be changed frequently in response to changes in malignant cell reactions to the therapy, so the patients will need constant follow-up and testing, and every effort will have to be made to maintain the metastatic potential of the cancer at a minimum. This type of therapy will be very costly, and likely will only be available to the wealthiest individuals. It is likely that some of the drugs required to meet

the objectives listed will remain experimental. Actual approval for these kinds of therapies may not be obtainable from the regulatory agencies, since the treatment protocols will have to be varied in an almost infinite manner in response to the way the cancer reacts to the therapeutic intervention. Therefore, centers providing this type of care may be considered experimental, not mainstream. However, the potential for success in treating cancer is likely to be maximized using this approach, and many companies are busy at work developing cancer sensitivity testing techniques and devices.

Conclusion and Insurance Impact

Much of the work described in this article, particularly the urine biomarkers, is fairly far along in the process of obtaining regulatory approval. The industry impact of the urine biomarker technology alone may be important in life underwriting. We may have a new tool to clear up the difficulties associated with underwriting rising PSAs, clear those pesky cases with residual areas of enhancement in post-cancer excision MRIs, and act more quickly in cases involving the large numbers of women with dense fibrocystic and fibronodular disease who require serial mammography. The preceding discussion about the use of urine biomarkers for active cancer detection is not to be interpreted as an endorsement by RGA

The discussion about metastatic spread, and the new avenues of therapy, may become important, particularly with very high amount life insurance applicants who may, and probably will at some time in the future, seek treatment with tailored cancer therapies. These applicants may have very bad cancer histories with surprisingly good outcomes, and may have received successful offshore experimental therapies. These cases will be difficult to evaluate, but we may all see them in the future and should be ready for them when they come.

Finally we are likely to start receiving and reviewing new types of MRI imaging used in specific circumstances, in addition to the standard MRIs we have been accustomed to interpreting. As an industry, we need to be aware of these developments and of their potential impact upon us. ■

References:

1. The primary source for this presentation was a conference by Jain, R.K., Director, *Critical Issues in Tumor Microenvironment, Angiogenesis, and Metastasis. From Bench to Bedside.* Harvard Medical School, Department of Continuing Medical Education and Massachusetts General Hospital, Boston, MA, September 27 to 30, 2010. The following presenters were quoted in this presentation:

   Carmeliet, P., vascular growth, genomics
   Fidler, I.J., metastasis
   Jain, R.K., tumor microenvironment
   Moses, M.A., urinary biomarkers
   Sledge, G.W., "evolutionary" forces in cancer
   Sorensen, A.G., imaging
   Weinberg, R.A., metronomic therapy

2. Specific references used in this presentation or in the illustrations provided follow:

   Batchelor, T.T., et. al., <u>Cancer Research</u>. 11:83-95, 2007.
   Fernandez, C.A., et. al., <u>Clinical Cancer Research</u>. 11:5390, 2005.
   Jain, R.K. <u>Scientific American</u>. January, 2008.
   Moses, M.A. et. al., "The regulation of tumor angiogenesis." *From the Angiogenic Switch to Tumor Progression.* Bignold, L.P. Volume Editor. <u>Cancer Cell Structures, Carcinogenesis, and Tumor Pathogenesis,</u> EXS 96:223-268, 2005.
   Moses, M.A., et. al., <u>Cancer Research</u>. 58:1396, 1998.
   Sledge, G.W. "The evolution of targeted biological therapies." <u>The Breast</u>. :S1-S3, 2007.
   Smith, E., et. al., <u>Neurosurgery</u>. 60:E1148-49, 2007.
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   Yan, L., et. al., <u>J. Biol. Chemistry</u>. 276:37258-65, 2001.

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INSIGHTS ON HEART FAILURE

By Dr. Paul Davis FRACP

Chief Regional Medical Director, Asia Pacific

RGA International Corporation

Insights on Heart Failure
- What is heart failure?
- How is it diagnosed and assessed?
- What are the mortality considerations?

Chronic congestive cardiac failure is a major cause of death and disability. It remains one of our major public health problems despite considerable advances in the understanding and treatment of ventricular dysfunction.

Mortality from heart failure is higher than the mortality associated with most cancers and is as high as 20% per annum.[1] Severe symptomatic heart failure unresponsive to therapy carries an annual mortality of 40%. Overall, 50% of patients are dead at four years.[2] The population prevalence of heart failure is 2-3% and incidence rates are continuing to rise.

The majority of heart failure patients are elderly, with prevalence rates rising sharply in older age to around 10-20% in those over 70-80 years.[2]

Age-adjusted incidence rates are 3.8:1000 for males and 2.9:1000 for females, with incidence rates approaching 10:1000 at age >65 years.[4, 5]

The lifetime risk for the development of heart failure is between 10% and 20%.[12]

At younger ages, heart failure is more common in males than females, reflecting the higher prevalence of ischaemic heart disease in males in that age bracket. At older ages the prevalence is equal between the sexes.[2]

Age-adjusted mortality rates after the diagnosis of heart failure are higher among men than women (RR mortality M vs. F 1.33).[5]

The prevalence of heart failure and the incidence of heart failure admissions to hospital is increasing as a consequence of our aging population, increased survival rates from precipitating events such as myocardial infarction, an increased population prevalence of heart failure risk factors such as obesity and diabetes, improved diagnostic techniques, and the advent of improved heart failure therapies.

Heart failure is the most frequent cause of hospital admission in those aged over 65 years and is said to be present in 10% of patients occupying hospital beds.[5]

Heart failure admissions have increased by 160% over the last decade in the U.S. The mortality following any admission to hospital with heart failure is 30-40% at two years, rising to 70-80% at 10 years.

Mortality remains high despite an increase in survival after diagnosis of heart failure over the last 15 years in many countries. [3, 4, 5]

Heart failure accounted for approximately 284,000 deaths in the U.S. in 2009 whereas lung cancer, breast cancer and prostate cancer accounted for approximately 160,000, 41,000 and 30,000 deaths respectively.

Many definitions of heart failure have been proposed over the last few decades, with the emphasis being on the presence of diminished effort capacity and breathlessness in the context of fluid retention and pulmonary congestion.

Heart failure is best considered as a clinical syndrome defined by three parameters:
- symptoms of heart failure (such as breathlessness and leg swelling) plus
- clinical signs of heart failure (such as lung congestion and venous distension) plus
- objective evidence of a structural or functional cardiac abnormality on examination or on imaging

Clinical heart failure is the end of a continuum which begins with the presence of risk factors for the development of heart failure. Over time, these various risk factors lead to the development of structural cardiac disease and the eventual precipitation of cardiac dysfunction with a failure of cardiac output and the associated symptoms and signs.

The major risk factors for the development of heart failure include:

- age
- hypertension
- ischemic heart disease
- diabetes
- obesity
- sleep apnea
- alcohol, viral and chemotherapy-induced cardiotoxicity
- renal failure
- valvular heart disease
- cigarette smoking
- genetic predispositions – genetic cardiomyopathies

The anatomical and structural causes of functional deterioration include:

- LVH
- atrial fibrillation and other tachyarrhythmias
- conduction system disease
- functional loss from extensive ischemia
- muscle loss from myocardial infarction or cardiotoxic agents
- progressive valvular heart disease
- worsening chronic pressure loads and volume loads

Heart failure has been staged on the basis of heart structure and function:

Stage A
- risk factors for heart failure
- no structural heart disease
- no signs or symptoms of heart failure

Stage B
- structural heart disease resulting from risk factors
- no signs or symptoms of heart failure

Stage C
- structural heart disease resulting from risk factors
- signs and symptoms of heart failure

Stage D
- advanced structural heart disease
- severe signs and symptoms of heart failure despite maximal medical therapy

Heart failure by these criteria is under-reported with data on community-based populations being limited. Population data are crucial to insurance medicine and accurate underwriting.

The population-based Rochester Epidemiology Project conducted in Olmsted County, Minnesota, U.S. in 2004 reported on the temporal trends, risk factor prevalence and mortality estimates in heart failure.[5] Over the survey period 1979 to 2000 the incidence of heart failure increased in both males and females.

Heart failure incidence correlated strongly with age and with the prevalence of coronary heart disease, myocardial infarction, valvular heart disease and the traditional cardiovascular risk factors. Despite increases in heart failure incidence, the mortality from heart failure declined.

An analysis of mortality by heart failure stage in that cohort was undertaken in 2007.[6]

- Stage A HR 1.6
- Stage B HR 1.8
- Stage C HR 8.7 (7.3-15.0 depending on severity)
- Stage D HR 31.5

This mortality data is in keeping with the usual underwriting guidelines for extra mortality in those with risk factors for heart failure (Stage A) and for those with structural heart disease (Stage B).

The extra mortality in those with symptomatic heart failure (Stages C and D) requires that these cases be declined.

This analysis also reported on the prevalence of each stage of heart failure by age. From an underwriting standpoint this community-based study has important implications.

There were high age-related prevalence rates of risk factors for failure in those with no cardiac disease or failure[6]:

- 27.9% age 45-54
- 25.1% age 55-64
- 18.3% age 65-74
- 12.3% age ≥75

The rates of isolated risk factors diminished with age as they were replaced by overt structural heart disease.

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There were high age-related prevalence rates of structural heart disease in those with no clinical heart failure[6]:

- 23.0% age 45-54
- 32.3% age 55-64
- 46.2% age 65-74
- 39.0% age ≥ 75

The prevalence rates of overt symptomatic heart failure rose dramatically in older ages[6]:

- 2.2% age 45-54
- 6.6% age 55-64
- 14.6% age 65-74
- 39.4% age ≥75

Age, ischemic heart disease, ischemic heart disease with myocardial infarction, hypertension, diabetes, obesity and alcohol are the main drivers of heart failure in most communities, although the etiology of heart failure is not always identified.

The survival curves by stage support our usual underwriting stance.
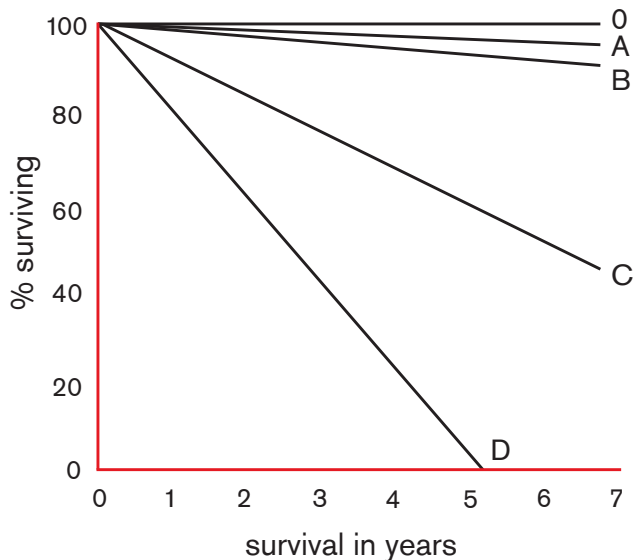
Various studies have attempted to estimate the magnitude of risk for heart failure by individual risk factors:
- Diabetes increases heart failure risk by 200-500%.
- In diabetics there is a 12% increase in heart failure death or hospitalization for each 1% rise in HbA1c.

- In obesity there is an increase in heart failure incidence of around 7% for each unit of BMI.
- Following myocardial infarction age 40-70, the 5-year risk of symptomatic heart failure is 10%.
- Following myocardial infarction age >70, the 5-year risk of symptomatic heart failure is 25%.
- Hypertension increases heart failure risk by 200-300%.
- Obstructive sleep apnea increases heart failure risk by 240%.
- Smoking increases heart failure risk by 150%.

Heart Failure assessment:

In addition to the defined stages of heart failure, a severity classification of heart failure based on symptoms has been developed by the New York Heart Association (NYHA). This-severity based classification has formed the basis for most of the insurance definitions for living benefits.

NYHA class I
- no symptoms or limitations with usual activities

NYHA class II
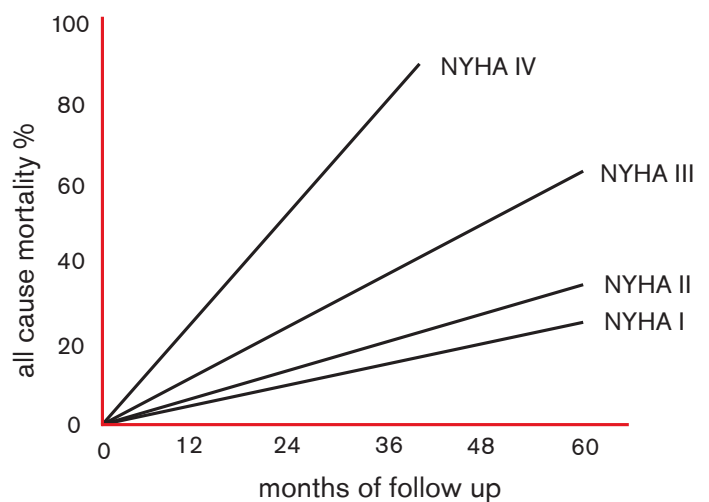- symptoms on modest or usual activity

NYHA class III
- symptoms on minimal activity and only comfortable at rest

**NYHA class IV**
- symptoms at rest

This classification has important prognostic implications and can be aligned with extra mortality but it is a largely subjective classification system.[7]

While this classification is well-validated, there is a clear advantage in being able to link NYHA severity to more objective measures of cardiac dysfunction.

In addition to imaging techniques (including echo, cardiac CT and cardiac MRI) there are now blood biological markers that provide information regarding heart failure severity and which provide useful end point measures for targeted heart failure therapies. These biological markers include the atrial and brain natriuretic peptides ANP, ProBNP and BNP. These natriuretic peptides are secreted by the myocardium and are elevated in heart failure to a degree that correlates with severity. This hormonal information is being increasingly provided to us as a consequence of an increased utility in clinical practice both for diagnostic and therapeutic purposes.

Natriuretic peptide levels equate to NYHA severity although the scatter and overlap is significant.[8,9]
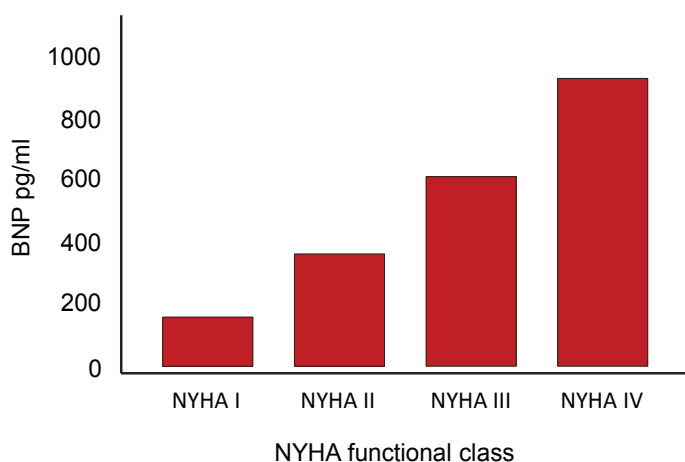
BNP levels vary with age and other factors but provide useful information about heart failure at all stages.

In insurance medicine the most valuable imaging tool remains the echocardiogram. The echo remains the most cost-effective and accessible imaging modality for assessing cardiac anatomy and function and provides validated mortality risk data. The ejection fraction in left ventricular dysfunction tracks with ANP, Pro BNP and BNP measurements.

An understanding of the use of the echocardiogram as a tool in heart failure evaluation requires the introduction of the concept of systolic and diastolic heart failure. It is now recognized that both heart contraction (systolic

function) and heart filling (diastolic function) are energy-dependent processes. The diastolic phase of cardiac function is not one of simple passive relaxation but an active process that can be impaired by heart muscle disease including hypertrophy, infiltrative processes and ischemia.

The heart has the capacity to fail in both systole and diastole. Systolic failure is associated with an impaired ejection fraction on the echocardiogram. Diastolic dysfunction is associated with a normal or 'preserved' ejection fraction but impaired left ventricular filling parameters.

Diastolic dysfunction is increasingly being recognized as an important cause of heart failure and is present in about 50% of cases. It is increasingly documented on echocardiogram reports. Systolic failure and diastolic failure often coexist.

Systolic heart failure tends to occur at younger ages than diastolic failure (typically age 50-70) and is most commonly precipitated by infarction of heart muscle or muscle damage from alcohol, viruses and cardiotoxic agents. These conditions are termed dilated cardiomyopathies and the heart is commonly enlarged on X-ray. There is a relationship between the severity of left ventricular dysfunction and mortality and with the potential for the development of clinical heart failure.

Diastolic heart failure tends to be a disease of older individuals. The heart is of normal size on chest X-ray and the ejection fraction is preserved. The condition is most prevalent in elderly females. Left ventricular hypertrophy and hypertension are common predisposing factors. The stiffness of thickened heart walls is responsible for impaired heart filling and the subsequent development of lung congestion. Left ventricular hypertrophy is an accompaniment of old age with left ventricular mass increasing by about 15% from age 20 to age 70.

Excess mortality is seen in systolic failure when the ejection fraction falls below 40-45%.[1] There is major excess mortality associated with ejection fractions of <30-35%. This group is often triaged to defibrillator therapy in an attempt to reduce the incidence of sudden cardiac death. These mortality risks for systolic failure are reflected in underwriting manuals for conditions such as myocardial infarction and cardiomyopathy.

In addition to the mortality risk associated with systolic dysfunction there is also a direct relationship between any reduction in ejection fraction and the development of clinical heart failure. This has been well-validated post myocardial infarction.[10]

There is a relationship between reduced ejection fraction and natriuretic peptide levels such that these two parameters can provide useful collaborative information when assessing applicants and claimants.[13]

Excess mortality is also seen in those with diastolic dysfunction. The mortality rates in heart failure with preserved ejection fraction (HFPEF) and heart failure with reduced ejection fraction (HFREF) are similar.

The 5-year mortality is around 70% after the onset of heart failure.[11] The extra mortality is higher in those with systolic heart failure than in those with diastolic disease. This probably reflects the higher prevalence of systolic disease in younger individuals and the higher prevalence of diastolic disease in the elderly.

Underwriting in Heart Failure:

The morbidity and mortality associated with overt symptomatic heart failure is such that these applicants are usual declines.

Applicants with histories of documented heart failure should be assessed conservatively and with regard to the precipitant.

While it may not be immediately obvious, the underwriting process has always involved an assessment of heart failure risk by way of the extra mortality we associate with those impairments that are known risks for heart failure development. Extra mortality is applied to risk factors such as diabetes, hypertension, ischemic heart disease, obesity and valvular heart disease. Extra mortality is also applied to the actual structural and functional cardiac abnormalities that might develop as a consequence of those rated pre-existing risks. This includes the mortality risk we associate with left ventricular hypertrophy, myocardial infarction, cardiac arrhythmias such as atrial fibrillation and conduction system disease such as LBBB.

Underwriting Systolic Heart Failure:
Symptomatic systolic heart failure and those with poor ejection fractions are clear declines.

Systolic dysfunction can only ever be considered at application when the ejection fraction is stable over a period of time and where there are no ongoing risks for deterioration.

The best risks are those with stable ejection fractions over 40-45% and where the etiology is non-ischemic. The worst risks are in those with ejection fractions <40-45% and where there is a history of diabetes and myocardial infarction.

Applicants with systolic dysfunction should be assessed with regard to the following parameters:
- age
- etiology
- residual and associated risk factors
- functional capacity based on NYHA class
- severity based on imaging
- severity based on biological markers such as BNP and ProBNP

Underwriting Diastolic Heart Failure:
Overt symptomatic diastolic heart failure is a decline for insurance. Diastolic dysfunction reported on echocardiograms should be assessed in conjunction with the identified cause of the abnormal parameters. Diastolic dysfunction carries an extra mortality of approximately 4-8% per annum. That extra mortality should be considered when assessing conditions such as hypertension and left ventricular hypertrophy if diastolic dysfunction is identified on an echo at underwriting.

LVH on the ECG at underwriting is a clue to the likelihood of diastolic disease and should be underwritten accordingly.

Isolated diastolic dysfunction is increasingly being reported on echocardiograms in situations where there is no apparent cause for that abnormal parameter. Isolated diastolic dysfunction on echo, particularly in an older population, can usually be underwritten without applying any extra mortality, provided there is no history of heart failure and no risks for the development of heart failure.

Claims in Heart Failure:

Living benefits claims in heart failure can be the hardest of claims to assess. Critical illness and temporary and permanent disability are adjudicated according to various definitions in the market but often require assessments based on NYHA classes of disability.

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Claims are adjudicated with regard to the cause of heart failure and should only be admitted after some objective measure of severity is obtained. Liability is most easily admitted when the objective measures of severity are in accordance with the claimed degree of symptomatic severity. Occupation becomes an important consideration.

A major difficulty at claims time can be the well-recognized potential for a genuine disconnect between the estimated ejection fraction and the severity of symptoms in some heart failure patients. BNP can be a useful guide in that circumstance.

Treating specialist reports are required and independent specialist opinions are often sought. It is crucial that claims only be admitted when applicants remain disabled to the required degree despite best practice treatment regimens being applied by specialist practitioners.

Modern treatment strategies have the capacity to improve heart function, heart failure symptoms and mortality. Some causes of heart failure such as the viral cardiomyopathies and alcoholic cardiomyopathies may be reversible.

Unless there is clear evidence that heart failure "on diagnosis" is irrevocable, with no reasonable chance of improvement, it is recommended that living benefits only be admitted after a period of some months on treatment and when any capacity for improvement beyond a certain point is documented.

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WATCH THIS SPACE

The Longer Life Foundation is a not-for-profit partnership between RGA and the School of Medicine at Washington University in St. Louis, created to fund research that promotes health and assists in predicting longevity and wellness. The mission of the Foundation is to fund studies that may help the public live longer and better-quality lives and to find better ways to prognosticate disease, which is of benefit to both public health and the insurance industry.

Over the past decade, the foundation has funded 54 research grants that have led to more than 38 publications in peer-reviewed medical journals. Although all funded studies in some way benefit both public health and the insurance industry, a few of the studies have led to work that is of particular interest to the insurance world. A few studies of particular importance to actuaries, underwriters and insurance medical directors are described below.

- Longevity – study of the genetics and mechanisms that drive the aging process, with the goal of slowing the degenerative process and improving longevity.

- Caloric Restriction – studying a group of people who have volunteered to follow a strict diet called "calorie restriction with optimum nutrition", to determine the impact of calorie restriction on humans and longevity.

- Obesity – a multi-disciplinary team is investigating the efficacy of interventional therapy delivered via the Internet in relation to diet and obesity in children and adolescents; and the significance of waist circumference when assessing risk associated with build.

- Coronary Heart Disease – development of a new method to detect coronary artery disease in patients with diabetes, employing sound waves to determine blood vessel blockage and function by measuring the rate of blood flow in supplying blood vessels and the strength of heart muscle motion.

- Old-Age Cognitive Ability – development of a questionnaire to detect cognitive dysfunction and dementia; and studies of the relationship of physical activity to maintenance of cognitive ability.

- Genomics – studies of the genetic basis of disease and the use of genomics to better predict disease prognosis and tailor treatment.

- Cancer – studies related to cancer screening; development of a new test to reduce the reported 10% false negative rate on lymph node sampling in women with breast cancer; development of pictorial cancer survival curves illustrating the impact of other diseases or 'comorbidity' on cancer survival; development of a simple, non-invasive urine test using biomarkers to detect molecules in urine that signal the presence of kidney cancer; identification of genetic markers that predict treatment outcomes in cervical cancer patients.

You can read more about LLF at www.longerlife.org

Please feel free to contact Dr. Philip Smalley, Vice President and Medical Director, RGA International Corporation, if you have any questions or want more information.

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RGA Webcasts On Demand

RGA has been presenting webcasts on industry-related subjects to clients for several years. In April, 2007, Dr. Carl Holowaty, Senior Vice President and Chief Medical Director, presented RGA's first regional webcast, *Underwriting the Elderly*, a continuation of the series that Dr. Holowaty has been presenting to clients individually and at industry-wide meetings. Since then, RGA has hosted live, dial-in webcasts providing its clients with research data and timely updates on a wide variety of medical and underwriting subjects.

As of April, 2011, all new webcasts are provided on an 'on demand' basis, and are available to clients around the world 24-hours per day for those clients unable to attend the live presentation.

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Presenter: Paula Boswell-Beier, Senior Vice President, Chief Operations Officer, RGA
Target Audience: Pricing actuaries, underwriters, and marketing professionals
Topics Covered: ▪ Principles in managing reinsured policy data ▪ Policy data flow within reinsurers ▪ Challenges and best practices in managing 'per life' risk

Moral Hazard and Anti-Selection
Presenter: Tim Rozar, Vice President & Actuary, Client Services, RGA
Target Audience: Pricing actuaries, underwriters and risk management professionals
Topics Covered: ▪ The financial impact of policyholder choice and market ▪ Mitigants and opportunities ▪ Impact on specific areas of mortality experience including large face amount term insurance/simplified-issue business/post-level period term

Medical Advances Leading to Insurance Product Development Opportunities
Presenter: Dr. Philip Smalley, Vice President and Medical Director, RGA International Corporation
Target Audience: Medical directors, underwriters and actuaries especially product development actuaries
Topics Covered: ▪ Epidemiological trends ▪ Medical advances impacting Cancer ▪ Cardiovascular Disease and Infectious diseases ▪ Product initiatives

Upcoming live webcasts

Anticipating Global Infectious Disease Threats Mitigating their Health and Economic Impacts – October 27, 2011
Presenter: Dr. Kamran Khan, MD, MPH, FRCPC, Associate Professor, Department of Medicine, Division of Infectious Diseases, Department of Health Policy, Management & Evaluation, University of Toronto
Target Audience: Actuaries and medical underwriters
Topics Covered: ▪ Industry Risk ▪ Globalization of Travel ▪ Bio.Diaspora ▪ Economic Impact of Emerging Infectious Diseases

MIB Refresher for Experienced Underwriters – November 15
Presenter: Sue Corey, Director of Membership and Disclosure, MIB
Target Audience: Experienced underwriters
Topics Covered: ▪ Coding rules ▪ Current changes to MIB procedures ▪ Results of 2010 Protective Value Study ▪ Tools available at MIB ▪ Database trends ▪ What's coming at MIB

This webcast will provide a framework to understand better the impact of asymmetric information on life insurers, giving concrete examples of adverse selection and suggesting ways to bridge the applicant-insurer information gap.

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