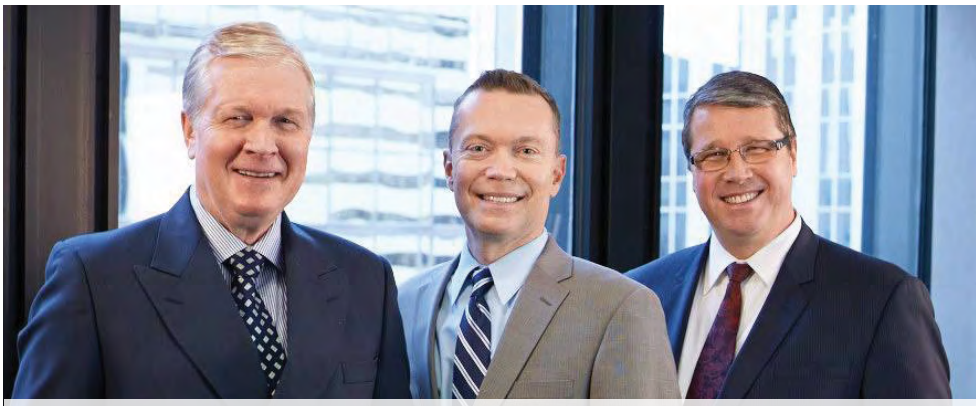
ReFlections

RGA's Global Medical Newsletter

Volume 41, May 2017



Neil Wilkinson
Vice President, Medical Services
nwilkinson@rgare.com

Daniel Zimmerman
Vice President, Medical Director
dzimmerman@rgare.com

Philip Smalley
Senior Vice President
Global Chief Medical Officer
psmalley@rgare.com

IN THIS ISSUE

FROM THE EDITORS

Welcome to the May 2017 edition of ReFlections, RGA's global medical newsletter. This edition includes an update by Dr. Elyssa Del Valle on the current role of genomics in breast cancer management and its implications for insurance medicine. Dr. Dave Rengachary's article, which focuses on arteriovenous malformations, simplifies the nomenclature of cerebral vascular lesions and provides a risk stratification framework, and Rebecca Abayakoon and Dr. Sheetal Salgaonkar provide a comprehensive update on the role of human papillomavirus testing in cervical cancer screening.

Rounding out this issue, The Longer Life Foundation report focuses on research results of recent grant recipients and their relevance to insurance medicine, and ReCite again presents articles from recent medical literature that are essential reading for underwriters, product developers, claims assessors, and medical directors.

It is with mixed emotions that we announce that this is the last issue of ReFlections for two members of our three-editor team, as Neil Wilkinson, Vice President, Medical Services, and Dr. Philip Smalley, Senior Vice President and Global Chief Medical Officer, are both retiring in May 2017.

Neil and Phil's three decades in this industry (Neil as an underwriter and Phil as a medical director) have seen tremendous changes worldwide, both in the basic work of underwriting and in the products insurers now sell to protect customers. Technology and the philosophy of underwriting are evolving with increasing speed, yielding exciting and challenging times ahead.

Stewardship of ReFlections will stay in the hands of Dr. Dan Zimmerman, whose dedication and enthusiasm over the past two years has brought new authors and a greater global focus to ReFlections. Peter Barrett, who leads RGA's Global Claims, Underwriting Quality & Risk Assurance, and Global Medical Services, will join our editorial team with the next issue, and we look forward to his contributions and expertise.

For the three of us, it has been our privilege to bring ReFlections to you for the past two years. We retiring editors are looking forward to new challenges and new opportunities ahead, and we all wish each of our readers much success in the future and our sincere gratitude for your continued support.

Thank you,

Phil, Dan, and Neil

RISK ASSESSMENT OF NON-METASTATIC BREAST CANCER IN THE GENOMIC ERA

Abstract

Underwriting breast cancer in 2017 will require an understanding of the current and growing role of genomics in the assessment of its mortality risk. This is not to lessen the importance of well-known prognosticators such as tumor/node/metastasis (TNM) staging, estrogen receptor/progesterone receptor (ER/PR) and human epidermal receptor growth factor 2 (HER2) receptor status, grade, or the mitotic activity index (MAI). Rather, it is to keep abreast of additional genomics-based prognostic tools that can be used to further stratify breast cancer and its risks.

The importance of genomics today is being seen in precision medicine: the increasing ability to predict the biological behavior of particular subclasses of diseases and then directly target treatments and hopefully influence favorable outcomes. Genomic-based treatments can also potentially reduce the use of ineffective therapies thereby avoiding the oft-used phrase "The treatment was a success, but the patient died."

This article will focus on current trends and advances in breast cancer genomics and prognostication and how they are enabling better assessments of individual mortality risk. Microarray studies, for example, that can distinguish breast cancer subtypes into luminal, basal and HER2-enriched, are enabling genetic profiling of breast cancers with validated recurrence scores using typing tests such as Oncotype DX and MammaPrint. The scores generated by these tests in combination with other prognosticators can be used to assess with greater precision the likelihood of long-term disease-free survival for these individuals.

Introduction

Breast cancer is the most common cancer in women worldwide. Nearly 1.7 million new cases were diagnosed in 2016 according to World Cancer Research Fund International, representing 12% of all new cancer cases and 25% of all cancers in women[1]. Breast cancer also ranks as the fifth most common cause of death from all cancers. While it is the most common cause of cancer death in women in less-developed regions, it is the second most common cause of cancer death in developed regions[1].

According to Globoscan, a project of the International Agency for Research on Cancer (IARC) that provides estimates by cancer site and sex for 184 countries, the highest breast cancer rates are found in Belgium, Denmark, France and the Netherlands, and the lowest in Asia and Africa.

With the emergence of genomics has come a surge of information that can help clinicians differentiate and predict the biological behavior of individual breast cancer types. Just as no two individuals have the exact combination of genes, no two breast cancer genomes are exactly alike. Making sense of these genetic variations to find usefulness in underwriting is the current goal.

ABOUT THE AUTHOR

Elyssa Del Valle M.D.
edelvalle@rgare.com

Elyssa Del Valle, M.D. is a Vice President and Medical Director for RGA Reinsurance Company. An emergency and internal medicine specialist, Dr. Del Valle's current responsibilities include client underwriting support as well as internal and external education. Her past experience encompasses both clinical and insurance medicine, teaching clinical reasoning to medical students and lecturing in physician assistant and athletic trainer programs. Dr. Del Valle frequently represents RGA to key industry professional organizations, and is a member of the Scientific Program Committee for the American Academy of Insurance Medicine's 2017 conference.

Microarray studies and genome sequencing have yielded advances which are substantially altering how breast cancer subtypes are risk-stratified. Insurers, in turn, would be well advised to adjust underwriting risk guidelines as information evolves, providing additional biomarkers to assess mortality risk including response to treatment and assessment of recurrence. Essentially, given the widening variety of prognostic tools, breast cancer might eventually be underwritten on a case-by-case basis, for what might appear to be the same assessment on the basis of TNM and grade could, in actuality, be far different in terms of biological behavior when comparing the DNA of one cancer tissue to another.

Traditional Prognosticators

In order to appreciate the progress in research, it is prudent to review prognosticators used since the 1980s. Many are still valid today and remain the primary basis for the current guidelines used by insurers to assess mortality. Valid, in this usage, means having analytical and clinical validity as well as clinical utility.[2]

These prognosticators fall into three distinct groups.

- **Age.** Older-age breast cancer patients have more estrogen/progesterone (ER/PR) positive hormone receptors than do younger patients. This correlates with better prognoses for postmenopausal women with early-stage breast cancer.[3]
- **Pathologic factors.** Valid factors include: tumor size, nodal involvement, metastasis, tumor morphology, histological grade, and degree of peritumoral lymphovascular invasion (PLVI). (Adverse pathologic factors associated with PLVI specifically for breast cancer include: large tumor size; high grade, positive nodal status; tubular, papillary, mucinous, medullary and adenoid cystic histology [as opposed to micropapillary and metaplastic carcinomas]; and estrogen-receptor negativity.)[4]
- **Tissue markers.** Receptor status, especially of hormone receptors such as estrogen and progesterone, as well as evidence of HER2 overexpression are important prognosticators.

> Genomics … can help clinicians differentiate and predict the biological behavior of individual breast cancer types.

Microarray studies of breast cancer subtypes show good correlation with these three groups, further supporting the validity of these prognosticators. These subtypes correlate most closely with hormone tissue markers and HER2 status.

Genomic Profiles

Microarray studies were first introduced in 1983 as a means to assess antibodies. It was not, however, until 1995 that microarrays were first used to assess DNA. Since then, the utility of microarray studies has grown significantly, paving the way for genomic profiling.

Microarray studies enabled the categorization of breast cancer tissue into four distinct subtypes.[5]

- **Luminal A.** This subtype comprises 40% of all breast cancers. It is associated with high expression of ER/PR positive receptors, low expression of HER2, and low proliferation clusters. It carries the best prognosis of all breast cancer subtypes. Luminal A expressed genes are associated with epithelial cells of normal breast tissue. They are characterized by the expression of luminal cytokeratins (8 and 18).

- **Luminal B.** This subtype is associated with low expression of ER/PR, variable expressions of HER2, and with high-proliferation gene clusters, comprising 25% to 35% of breast cancers. The prognosis for the B subtype is not as favorable as for the A subtype and those individuals will have higher Oncotype DX and MammaPrint recurrence scores.
- **HER2-enriched.** This subtype, 10% to 15% of breast cancers, is characterized by high expression of HER2, low expression of ER/PR, and low expression of luminal and basal clusters. Most are ER/PR negative and HER2 positive, but about 30% of HER2-enriched subtype are HER2 negative. This discordance likely represents HER2 mutations, producing a similar expression phenotype without the HER2 amplification or protein overexpression.
- **ER-negative.** These subtypes include multiple basal-like carcinoma subtypes. Basal-like types have similar gene expression to that of basal epithelial cells and make up 15% to 20% of breast cancers. These tumors are characterized by low expression of ER/PR and HER2 and are known as "triple-negative breast cancers" (TNBC). TNBC is associated with the poorest prognosis and highest recurrence rates. Most of these tumors are infiltrating ductal tumors and are characterized by high nuclear grade, presence of central necrosis, and high mitotic activity indices. These tend to have aggressive clinical behavior and high rates of metastasis to brain and lung[5].

Although an applicant may be ER/PR positive and HER2 negative, that does not confirm the best prognosis, nor does being TNBC automatically equate to a grim prognosis. Additional information on the subtype classifications can provide much more accurate prediction of mortality risk and if available should be used in the risk assessment.

Gene Expression Profiles

The emergence of DNA microarray studies enabled the simultaneous measuring of the expression of thousands of genes in order to identify biologically based prognostic profiles.

Breast cancer is a heterogeneous and phenotypically diverse disease with a range of genetic profiles and biological behaviors that respond uniquely to different forms of treatment. Since genetic profiles can predict breast cancer outcomes and responses to treatment, they can also be used to guide decision-making about adjuvant therapy[6].

Morbidity and mortality caused by adverse effects of adjuvant treatments are the primary reason all treatment arsenals cannot be implemented on each cancer type. With genetic profiling, adjuvant treatment can be spared for favorable breast cancer gene profiles and encouraged for those associated with aggressive behaviors and high recurrence rates. Thus, underwriting must take into account all information regarding prognostics, not just on TNM and hormone receptors, but on genomic and gene expression profiles as well.

> Genetic profiles can … also be used to guide decision-making about adjuvant therapy.

The most commonly used commercial providers of gene expression profiles are Oncotype DX, MammaPrint and PAM50.

- **Oncotype DX.** Oncotype DX's 21-gene recurrence score (RS) uses multianalyte reverse transcription-PCR genomic tests to predict the likelihood of breast cancer recurrence in early stage, node negative, ER-positive breast cancers. Measurement of gene expression from fixed formalin paraffin-embedded (FFPE) tissues yielded concordance in archival breast cancer specimens dating from 1985 to 2001 in all specimens when comparing ER/PR and HER 2 receptor status by Cronin et al.[7]

  Gene recurrence assay scores for breast cancer range from 1 to 100. The assay not only predicts the likelihood of tumor recurrence, but can predict the magnitude of chemotherapy benefit. High RS scores (≥31) predict benefit of chemotherapy (a decrease in 10-year distant recurrence risk) by 28%, whereas those with low RS scores (<31) derive minimal if any benefit from chemotherapy. In short, gene recurrence scores provide a benefit in adjuvant decision-making for node negative disease, but do not as yet have any role for hormone-negative cancer types and limited value for HER2 positive cancer types[9]. Underwriting may eventually incorporate the RS scores in these

scenarios as a prognostic tool, especially given their incorporation in adjuvant decision guidelines per the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), National Institute for Health and Care Excellence (NICE)[10], Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)[11] and the St Gallen International Expert Consensus[12].

- **MammaPrint.** The Amsterdam 70-gene prognostic profile MammaPrint classifies tumors as low- and high-risk for recurrence using frozen tissue specimens obtained within an hour of surgery and sent for DNA microarray analysis. Reliable results can also be obtained with FFPE tissue. Unlike gene recurrence assays, gene prognostic profiles can prognosticate breast cancer patients regardless of hormone status and those whose cancers are HER2-positive as well.

  Results from the Microarray in Node-Negative Disease May Avoid Chemotherapy Trial (MINDACT), an international randomized trial, suggest that certain genetic profiles may identify those whose cancers are at low risk of metastasis despite high-risk clinical features[13,14,15]. Observational studies are suggesting that the MammaPrint profiles may identify those with low chance of recurrence independent of nodal status, tumor grade, hormone receptor or HER2 status[16].

- **PAM50 (Prosigna).** A third prognostic genetic test for breast cancer is the Predictor Analysis of Microarray 50 (PAM50), a 50-gene test that characterizes an individual tumor by intrinsic subtype. Results can, with high degree of analytical validity, stratify patients who are ER-positive into high-, medium- and low-risk subsets.

  In two separate trials – an Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial and an Adjuvant Treatment in Patients with Hormone Receptor-Positive Breast Cancer with Good to Moderate Differentiation (ABCSG-8) trial – the risk of recurrence (ROR) score added prognostic information beyond what could be assessed by clinical factors in both node-negative and node-positive disease. The PAM50 ROR score also identified more patients with HER2 negative/node-negative tumors in the high-risk group and fewer in the intermediate group compared with the Oncotype DX RS gene recurrent test[17,18,19].

  Overall, the analysis of 1,478 postmenopausal patients who participated in the ABCSG-8 trial showed that the estimated 10-year distant relapse-free survival rates were 96.7%, 91.3% and 79.9% in the low-, intermediate- and high-risk groups respectively, based on the ROR score, regardless of whether pathological node involvement was present or not[20].

Other prognostic biomarkers

The protein Ki-67 has been shown in large meta-analyses to be an independent prognosticator associated with higher risk of relapse in node-positive and node-negative disease. There are, however, inconsistencies with retrospective studies and thus many medical societies such as ASCO and IMPAKT (Improving Care and Knowledge through Translational Research) do not recommend using proliferative markers such as Ki-67 for prognostic evaluation[21].

Cancers grow and metastasize through angiogenesis. NOTCH1 is a human gene found to be implicated in metastasis and maintenance of cancer cells. Recent studies indicate that NOTCH1 is closely associated with TNBC and high recurrence rates and is an independent predictor of disease-free survival.

Conclusion

The debilitating effects of chemotherapy, surgical complications, and/or radiation therapy are less likely to render morbidity and mortality concerns, given the added benefits genomics has provided in stratifying risk with a more direct, targeted approach.

Microarray studies that have molecularly divided breast cancers into subtypes such as luminal, basal, and HER2-enriched have advanced predictions of biological behavior of individual breast cancers that TNM staging, ER/PR, and HER2 status could not predict for long-term cancer-free survivals.

Genomics has provided precision medicine with a tool to enable more effective predicting of the behavior of cancers to the extent that genomic assessment may supersede traditional staging, allowing improved risk assessment of individual breast cancer patients.

Moving forward, insurance medicine needs to keep pace with advances in breast cancer genomics, thus allowing for more appropriate and equitable risk assessment. RF

References

1. Antoni S, Soerjomataram I, Møller B, Bray F, Ferlay J. An assessment of GLOBOCAN methods for deriving national estimates of cancer incidence. Section of Cancer Surveillance, International Agency for Research on Cancer. 2016 Jan 28; 94:174-84. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4773935/
2. Febbo PG, Ladanyi M, Aldape KD, et al. NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw. 2011 Nov; 9 Suppl 5:S1. https://www.ncbi.nlm.nih.gov/pubmed/22138009
3. Partridge AH, Hughes ME, Warner ET, et al. Subtype-Dependent Relationship Between Young Age at Diagnosis and Breast Cancer Survival. J Clin Oncol 2016 Sep 20; 34(27):3308-14. https://www.ncbi.nlm.nih.gov/pubmed/27480155
4. Viale G, Giobbie-Hurder A, Gusterson BA, et al. Adverse prognostic value of peritumoral vascular invasion: is it abrogated by adequate endocrine adjuvant therapy? Results from two International Breast Cancer Study Group randomized trials of chemoendocrine adjuvant therapy for early breast cancer. Annals of Oncology. 2010 Feb; 21(2):245-54. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2813305/
5. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. World Journal of Clinical Oncology. 2014 Aug 10; 5(3): 412-24. https://www.ncbi.nlm.nih.gov/pubmed/25114856
6. Carey, LA. Prognostic molecular profiles of breast cancer. Up To Date 19.3. http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?18/2/18479?source=HISTORY
7. Cronin M, Pho M, Dutta D, Stephens JC, Shak S, Keifer MC, Esteban JM, Baker JB. Measurement of Gene Expression in Archival Paraffin-Embedded Tissues: Development and Performance of a 92-gene Reverse Transcriptase-Polymerase Chain Reaction Assay. American Journal of Pathology. 2004 Jan; 164(1):35-42. https://www.ncbi.nlm.nih.gov/pubmed/14695316
8. Cronin M, Sangli C, Liu ML, Pho M, Dutta D, Nguyen A, Jeong J, Wu J, Langone KC, Watson D. Analytical Validation of the Oncotype DX Genomic Diagnostic Test for Recurrence Prognosis and Therapeutic Response Prediction in Node-Negative, Estrogen Receptor-Positive Breast Cancer. Clinical Chemistry. 2007; 53(6):1084-91. https://www.ncbi.nlm.nih.gov/pubmed/14695316
9. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006 Aug 10; 24(23): 3726-34. https://www.ncbi.nlm.nih.gov/pubmed/16720680
10. National Institute for Health and Care Excellence. NICE Guidance on Breast Cancer. Available from http://www.nice.org.uk/guidance/conditions-and-diseases/cancer/breast-cancer
11. Guidelines of the AGO Breast Committee. Available from http://www.ago-online.de/en/guidelines-mamma/march-2016
12. Primary Therapy of Patients with Early Breast Cancer: Evidence, Controversies, Consensus: Opinion of German Specialists to the 14th St. Gallen International Breast Cancer Conference 2015 (Vienna 2015). Geburtshilfe Frauenheilkd. 2015 Jun; 75(6):556-65. https://www.ncbi.nlm.nih.gov/pubmed/26166836
13. Cardoso F, Van't Veer L, Rutgers E, et al. Clinical application of the 70-gene profile: the MINDACT trial. J Clin Oncol. 2008 Feb 10; 26(5):729-35. https://www.ncbi.nlm.nih.gov/pubmed/18258980
14. Piccart M, Rutgers E, van't Veer L, Slaets L. Primary analysis of the EORTC 10041/ BIG 3-04 MINDACT study: A prospective, randomized study evaluating the clinical utility of the 70-gene signature (MammaPrint) combined with common clinical-pathological criteria for selection of patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes. AACR 2016. https://s3.amazonaws.com/v3-app_crowdc/assets/a/a9/a9f949981f16e94f/S1-05.original.1448391522.pdf

References

15. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. New England Journal of Medicine. 2016 Aug 25; 375:717-29. http://www.nejm.org/doi/full/10.1056/NEJMoa1602253#t=article

16. Mook S, Knauer M, Bueno-de-Mesquita JM, et al. Metastatic potential of T1 breast cancer can be predicted by the 70-gene MammaPrint signature. Ann Surg Oncol. 2010 May; 17(5):1406-13. https://www.ncbi.nlm.nih.gov/pubmed/20094918

17. Nielsen TO, Parker JS, Leung S, et al. A Comparison of PAM50 Intrinsic Subtyping with Immunohistochemistry and Clinical Prognostic Factors in Tamoxifen-Treated Estrogen Receptor-Positive Breast Cancer. Clin Cancer Res. 2010 Nov 1; 16(21): 5222-32. https://www.ncbi.nlm.nih.gov/pubmed/20837693

18. Chia SK, Bramwell VH, Tu D, et al. A 50-gene Intrinsic Subtype Classifier for Prognosis and Prediction of Benefit from Adjuvant Tamoxifen. Clin Cancer Res 2012 Aug 15; 18(18):4465-72. https://www.ncbi.nlm.nih.gov/pubmed/22711706

19. Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. J Clin Oncol 2013 Aug 1; 31(22):2783-90. https://www.ncbi.nlm.nih.gov/pubmed/23816962

20. Filipits M, Nielsen TO, Rudas M, et al. The PAM50 risk-of-recurrence score predicts risk for late distal recurrence after endocrine therapy in postmenopausal women with endocrine-responsive breast cancer. Clin Cancer Res. 2014 Mar 1;20(5): 1298-305. https://www.ncbi.nlm.nih.gov/pubmed/24520097

21. Cuzick J, Dowsett M, Pineda S, et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. J Clin Oncol 2011 Nov 10; 29(32):4273-8. https://www.ncbi.nlm.nih.gov/pubmed/21990413

22. Zhong Y, Shen S, Zhou Y, Mao F, et al. NOTCH1 is a poor prognostic factor for breast cancer and is associated with breast cancer stem cells. Onco Targets Ther. 2016 Nov 7; 9: 6865-71. https://www.ncbi.nlm.nih.gov/pubmed/27853380

RGA MEDICAL TEAM UPDATE

RGA welcomes Dr. Tsukasa Nagaoka to our global network of medical officers. Dr. Nagaoka is a Chief Medical Director, and is based in our Japan office.

CEREBRAL VASCULAR LESIONS: FOCUS ON ARTERIOVENOUS MALFORMATIONS

Abstract

The complex anatomic structure of cerebral arteriovenous malformations (AVMs) can present both physicians and underwriters with many challenges, including correct diagnosis and classification, appropriate risk prognostication, and most important, selection of appropriate treatment. This article clarifies the often confusing nomenclature of cerebral vascular lesions, discusses epidemiology and clinical presentation, and reviews some studies that have significantly altered their treatment paradigms. It also clarifies assessment criteria underwriters can use for risk prognostication and mortality prediction.

Nomenclature of Cerebral Vascular Lesions

Characterizing and risk-classifying cerebral vascular lesions can be quite confusing for underwriters, as radiologists and treating physicians will often use the existing variety of descriptive terms interchangeably and incorrectly. A simplified classification system is presented here in Table 1.

Table 1: Simplified Classification of Cerebral Vascular Lesions

High-Flow Lesions

- Cerebral AVM (CAVM)
- Dural Arteriovenous Fistula (DAVF) (Can also be low-flow)
- Carotid Cavernous Fistula (CCF) (Can also be low-flow)

Low-Flow Lesions

- Venous
  - Developmental Venous Anomalies (DVA)/Venous Angiomas
  - Vein of Galen Malformation (Can also be high-flow)
- Capillary Telangiectasia
- Cavernous Hemangioma
- Mixed Vascular Lesion

Modified from Radiopaedia.org (https://radiopaedia.org/articles/cerebral-vascular-malformations)

The first step in both risk assessment and classification is to separate high-flow from low-flow lesions. The classic high-flow lesion is an arteriovenous malformation (AVM), a three-part vascular lesion consisting of: a feeding artery (or arteries); a draining vein (or veins); and a nidus, the actual tangle of vessels between the feeding artery and the draining vein. The capillary system normally functions to gradually reduce the pressure gradient from artery to vein, but an AVM causes blood to bypass the capillary system and brain tissue, generating elevated cerebrovascular pressures.

ABOUT THE AUTHOR

Dave Rengachary M.D.
drengachary@rgare.com

Dave Rengachary, M.D., is Senior Vice President and Chief Medical Director for U.S. Mortality Markets for RGA Reinsurance Company. He is also Vice President of the Midwestern Medical Directors Association and a member of the Educational Committee of the American Academy of Insurance Medicine.

He serves on the board of directors of the St. Louis-based organizations Memory Home Care Solutions and ABC Brigade, which are dedicated to Alzheimer family and stroke survivor support respectively. He also serves as Deputy Managing Director of the Longer Life Foundation, a partnership with Washington University. Dr. Rengachary is the primary author and editor of the Washington University Neurology Survival Guide.

Cerebral AVMs can be graded using the Spetzler-Martin AVM Grading System[1] (Table 2). This system takes into account a lesion's size, the eloquence of adjacent brain tissue (eloquent brain tissue refers to the degree to which that area is responsible for multiple functions), and the amount and type of venous drainage (superficial or deep). Each of these factors have point values, and the sum of the values of these factors results in a grade based upon the sum of the point values, which will be between 1 and 5. A Grade 1 AVM is small and superficial, is located in non-eloquent brain tissue and is considered low-risk for surgery. A Grade 4 or 5 AVM, on the other hand, is large and deep, and adjacent to eloquent brain tissue. (The system uses the term "Grade 6" to refer to an inoperable lesion.)

Although several academic centers have developed treatment protocols corresponding to each Spetzler-Martin grade, it would be inadvisable for an underwriter to draw any conclusions as to mortality outcomes based on these grades alone, as studies to date have been small, retrospective and, most notably, non-randomized to multiple classes of treatment.

Table 2: Spetzler-Martin AVM Grading System

HISTOLOGY	POINTS
SIZE	
<3 cm	1
3 - 6 cm	2
>6 cm	3
LOCATION	
Non-Eloquent	0
Eloquent	1
VENOUS DRAINAGE	
Superficial	0
Deep	1

Grade = Total Points

An AVF – arteriovenous fistula – although considered a higher-flow lesion, differs from an AVM in that it presents with a direct connection between a feeding artery and a draining vein and lacks an intervening nidus. The most common location for an AVF occurs between the carotid artery and cavernous sinus, and these lesions are specifically termed carotid-cavernous fistulas (CCF). Another common AVF consists of a direct connection between a meningeal artery and meningeal vein that traverses the dura, and is known as a dural arteriovenous fistula (DAVF).

The most common low-flow lesion is a developmental venous anomaly (DVA). In most classifications schemes, the term DVA has supplanted the older term "venous angioma," although the latter terminology is still frequently encountered in radiology and physician reports. As the name implies, DVAs are considered congenital lesions. They have larger-than-normal collections of veins, but are for the most part small and histologically normal, and thus represent a low overall bleed risk. They can, however, be frequently associated with the cavernous malformation types described below.

For ease of classification, Table 1 lists the vein of Galen malformation as a low-flow lesion, but these can also exist in high-flow, AVM, AVF, aneurysmal, and other forms as well. Vein of Galen malformations are abnormal connections between the cerebral arteries and the vein of Galen (the main draining deep vein of the brain). Although these lesions are rare, they can be significant: large pediatric vein of Galen malformations, for example, can be the cause of high-output cardiac failure in infants or children, as their hearts struggle to maintain the vascular demands of these lesions.

Cavernous hemangiomas, which are also classified as low-flow AVMs, may have the most names. Nomenclature encountered in physician reports includes cavernomas, cavernous angiomas, and cerebral cavernous malformations (CCMs). This particular lesion type refers specifically to compact collections of abnormally dilated blood vessels without intervening normal brain tissue which are prone to small hemorrhages. Note that these and other vascular lesions are classified histologically by the International Society for the Study of Vascular Anomalies (ISSVA) as "benign tumors," so for critical illness underwriting purposes it would be beneficial to either specifically include or exclude coverage of these lesions and price accordingly.

Capillary telangiectasias are low-flow lesions that present with a small collection of dilated capillaries. They are distinguished from cavernous hemangiomas by the presence of normally interspersed brain tissue. These are most commonly found in the brain's pontine region and are usually clinically asymptomatic, and therefore considered lower in risk from an insurance standpoint. These lesions are unrelated to hereditary hemorrhagic telangiectasias.

Mixed vascular lesions have varying combinations of components from the other vascular lesions. These can take several forms, and the insurance risk can vary, depending on the composition of the lesion.

> …it is increasingly clear that consistently viewing untreated AVMs less favorably than treated AVMs from underwriting risk perspective may not be warranted.

Epidemiology and Clinical Presentation

According to recent studies, the estimated incidence and prevalence of cerebral AVMs is 1 per 100,000 and 18 per 100,000, respectively[2]. The studies, however, vary greatly in terms of how they define AVMs and in indicating whether the AVMs were symptomatic at diagnosis. When pricing for these lesions, it can be reasonably predicted that overall incidence figures are likely to increase over time due to both increasing utilization of radiographic studies and greater sensitivity of imaging techniques.

Surprisingly, few risk factors for AVMs have been established, but they do exist. AVMs are slightly more common in males. They occur in varying frequencies as part of neurocutaneous disorders such as hereditary hemorrhagic telangiectasia (HHT), Sturge-Weber syndrome (encephelotrigeminal angiomatosis), Wyburn-Mason syndrome, and blue rubber bleb nevus syndrome (BRBNS).

While there is significant variation, AVMs also tend to be a disorder of younger adults. In a large retrospective study, the average age of symptomatic presentation was 36 years. Symptoms can include hemorrhage (46%), seizures (24%), headache (14%), and focal deficit (8%), either singly or in combination. Only 4% of cases were asymptomatic or incidental findings[3].

Treatment

The primary clinical consideration upon discovery of an AVM is whether to pursue medical or surgical treatment. Medical treatments commonly include medications to ensure adequate blood pressure control and antiepileptic medications for seizure prophylaxis, although there is little evidence to support either of these interventions. Conservative medical therapy also indicates that patients' AVMs will be followed with serial imaging studies.

Surgically, an increasing array of options are available. The traditional surgical therapy consisted of resecting the lesion with craniotomy (ligating the feeder arteries and resecting the nidus)[4]. The decision to pursue an open procedure depended largely on the accessibility of the lesion.

Currently, less invasive surgical options are available. One, embolization of an AVM, involves injection of a thrombosing, embolic, or coiling agent, usually in multiple stages. Embolization can be pursued as definitive therapy, palliative therapy (e.g. to reduce symptoms only), or to reduce the size of the lesion prior to subsequent surgical extirpation or radiosurgery. Radiosurgery (also termed radiotherapy) is another, and involves directing focused radiation to the AVM to elicit a thrombotic effect. Radiosurgery can be pursued in multiple stages, in conjunction with embolization and/or surgical resection.

Today, surgery is performed less often as treatment for these lesions. The 2014 ARUBA trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)[5] significantly dampened enthusiasm for surgical intervention of these lesions. This trial, the first large-scale randomized prospective study to compare serious outcomes (death or symptomatic hemorrhage) in adults with a history of unruptured AVMs who were treated with medical therapies versus intervention (some combination of surgery, embolization or radiotherapy), found that at a mean of 33 months, the group receiving medical therapy had significantly better outcomes (RR of 0.27 for the combination of death and stroke) than those in the surgical group. Extending analysis of the study group to five years only further supported non-surgical treatments. Additionally, a 12-year prospective study from Scotland[7] published near the same time also supported conservative management of these lesions.

Several criticisms have been directed at these studies, including limited follow-up time, selection bias, and failure to standardize the treatment arm. While these studies have had their detractors, it is increasingly clear that consistently viewing untreated AVMs less favorably than treated AVMs from an underwriting risk perspective may not be warranted, especially in the absence of presenting hemorrhage.

Mortality and Risk Prognostication

Unfortunately, large-scale prospective population-based mortality data for cerebral AVMs is not currently available. Survival data varies significantly, based upon populations studied (e.g., admitted to the hospital versus outpatient) and means of presentation (hemorrhage versus other symptoms). One must therefore be careful when applying the data to insured populations. The best available data according to a systematic review of available research[2] suggests a case fatality rate of between 1% and 1.5% per year. The same research also offered a first-ever hemorrhage rate of approximately 2% per year. Gross et al.[8] reported a recurrent hemorrhage rate of 8% (and of 16% if it occurs within the first year), indicating that the risk of recurrent hemorrhage is higher than of first hemorrhage.

The Spetzler-Martin grading system, meanwhile, implies several factors that have been associated with higher risk of adverse outcome. A deep location, for example, implies both more eloquent brain at risk and greater access challenges. As hemorrhage represents by far the greatest cause-specific mortality risk, prognostic factors from studies[9,10] examining both hemorrhage and death can be reasonably combined and summarized (Table 3).

Table 3: Factors to Consider When Underwriting Cerebral AVM

Favorable

- Asymptomatic/no history of hemorrhage
- Small (<3 cm)
- Female gender
- Superficial location
- Well-defined nidus and >1 draining vein

Conclusion

Perhaps the most challenging aspect of evaluating cerebral AVMs for underwriters as well as clinicians is their heterogeneity. These lesions occur in many diverse patient populations, innumerable anatomic variations, and with no single stereotypical presentation.

The first step for underwriters and clinicians both is to make sure the nomenclature being applied to the lesion is appropriate. The next consideration is whether the lesion has presented with hemorrhage, with another symptom complex, or was found incidentally. Finally, anatomic and individual patient characteristics can be used to refine risk prognostication. Emerging data suggests that conservative treatments may be the preferred approach in many individuals. Developing this stepwise framework to assess cerebral AVMs offers the most effective approach to demystifying this tangled web.

References

1. Spetzler RF, Martin NA. A Proposed Grading System for Arteriovenous Malformations. Journal of Neurosurgery. 1986 Oct 1;65(4):476-83. https://www.ncbi.nlm.nih.gov/pubmed/3760956
2. Al-Shahi R, Warlow C. A Systematic Review of the Frequency and Prognosis of Arteriovenous Malformations of the Brain in Adults. Brain. 2001 Oct 1;124(10):1900-26. https://www.ncbi.nlm.nih.gov/pubmed/11571210
3. Lunsford LD, Niranjan A, Kondziolka D, Sirin S, Flickinger JC. Arteriovenous Malformation Radiosurgery: A Twenty-Year Perspective. Clin Neurosurg. 2008;55:108-19. https://www.ncbi.nlm.nih.gov/pubmed/19248675
4. Souvik S. Arteriovenous Malformations Treatment & Management. 2016 Dec 5 [cited 2017 Jan 4]. http://emedicine.medscape.com/article/1160167-treatment#d7
5. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al. Medical Management With or Without Interventional Therapy for Unruptured Brain Arteriovenous Malformations (ARUBA): a Multicentre, Non-blinded, Randomised Trial. Lancet. 2014 Feb 15;383(9917):614-21. https://www.ncbi.nlm.nih.gov/pubmed/24268105
6. Jeffrey S. Less Is More: ARUBA Confirms Intervention Unwise in AVM [Internet]. Medscape. [cited 2017 Jan 4]. http://www.medscape.com/viewarticle/859120
7. Salman RA-S, White PM, Counsell CE, du Plessis J, van Beijnum J, Josephson CB, et al. Outcome After Conservative Management or Intervention for Unruptured Brain Arteriovenous Malformations. JAMA. 2014 Apr 23-30;311(16):1661-9. https://www.ncbi.nlm.nih.gov/pubmed/24756516
8. Gross BA, Du R. Rate of Re-bleeding of Arteriovenous Malformations in the First Year After Rupture. J Clin Neurosci. 2012 Aug;19(8):1087-8. https://www.ncbi.nlm.nih.gov/pubmed/22705133
9. Pollock BE, Flickinger JC, Lunsford LD, Bissonette DJ, Kondziolka D. Factors that Predict the Bleeding Risk of Cerebral Arteriovenous Malformations. Stroke. 1996 Jan 1;27(1):1-6. http://stroke.ahajournals.org/content/27/1/1
10. Du X, Li X, Wang S, Li S, et al. Risk factors for hemorrhage in patients with cerebral arteriovenous malformations. Int J Clin Exp Med. 2016;9(3):6649-55. http://www.ijcem.com/files/ijcem0019824.pdf

CERVICAL SCREENING AND HPV TESTING

Abstract

Understanding the association between persistent cervical infection with high-risk human papillomavirus (HPV) and the development of cervical cancer and its immediate precursor lesion, cervical intraepithelial neoplasia grade 3 (CIN3), is fundamental when underwriting cases where HPV is present. The addition of HPV testing to cytology-based cervical screening has significantly increased the detection of prevalent CIN3, with a concurrent decrease in CIN3+ or cancer detected in subsequent/follow-up screening. Across studies, a positive HPV test is the strongest independent predictor of recurrent disease or progression to invasive cancer. As such, underwriting guidelines that consider HPV test findings are critical for prudent underwriting decision-making when assessing cervical screening results. Current clinical cervical screening guidelines, however, should not be changed on the basis of HPV vaccination status due to a lack of empirical data concerning the age when screening is to be initiated or the screening interval for women who have been vaccinated.

Introduction

Cervical cancer is the fourth most common cancer among women and second most common female-specific cancer, with human papillomavirus virus (HPV) genotypes 16 and 18 accounting for more than 70% of the world's cervical cancer cases.[1,2] Over the past 50 years, cytology-based screening (Papanicolaou or Pap test or smear) has been used routinely to screen women for precancerous or cancer cells in the cervix. Pap tests can detect cervical cancer and precancerous cells in the early stages, and the screening process has proven to be highly effective in reducing the number of deaths from squamous cell cervical cancer, which makes up 80% to 90% of cervical cancers[3-5].

While the Pap test can detect abnormal cell changes, testing for HPV detects the viral infection that can cause the abnormal cell changes prior to the development of cancer. Importantly, numerous studies have shown that screening for HPV leads to earlier detection of cervical intraepithelial neoplasia (CIN) than cytology. Accordingly, the U.K., Australia and several countries in Europe have introduced HPV primary screening into their national screening programs[6]. This article discusses the important role HPV testing plays in cervical cancer screening, changes to the screening guidelines with HPV as a primary screening tool, and its direct impact on the way Pap smear results are currently underwritten in an insurance setting.

ABOUT THE AUTHORS

Rebecca Abayakoon ANZIIF
rabayakoon@rgare.com

Rebecca Abayakoon is a Senior Consultant, Underwriting Research and Manual Development for RGA UK Services Limited. She is involved in the research and development of underwriting guidelines for RGA's Global Underwriting Manual (GUM). She provides training to regional offices on GUM-related matters and is a member of RGA's Global Support Team. She is also a senior associate of the Australian and New Zealand Institute of Insurance and Finance (ANZIIF).

Sheetal Salgaonkar M.D.
ssalgaonkar@rgare.com

Sheetal Salgaonkar, M.D., is a Medical Director with RGA Life Reinsurance Company of Canada – India Branch. An internal medicine specialist and a member of RGA's Global Support Team, she provides consultative medical underwriting, claims and product development services for clients and conducts medical underwriting training seminars. She has been a member of the Federation of Indian Chambers of Commerce and Industry's (FICCI) Task Force for Critical Illness as well as its subcommittee on Policy Formation on Financial Inclusion of Persons with Disabilities. She is also treasurer of the Indian Insurance Medical Officer's Association (IMOK), and is a member of the national committee for the International Committee of Insurance Medicine's (ICLAM) 2019 conference, to be held in Mumbai. Additionally, Dr. Salgaonkar has contributed significantly to the course curriculum of the Underwriting Diploma and Advanced Underwriting Diploma, a joint initiative of the Association of Insurance Underwriters (AIU) and the Insurance Institute of India.

Human Papillomavirus

Studies have confirmed that persistent cervical infection with high-risk human papillomavirus (HPV) is necessary for the development of cervical cancers (both squamous and adenocarcinoma) and its immediate precursor lesion, cervical intraepithelial neoplasia grade 3 (CIN3)[7,8].

Currently, more than 100 HPV genotypes have been identified[9]. The two high-risk HPV genotypes responsible for about 70% of all cases of cervical carcinomas are HPV 16 and HPV 18[10,11,12,13], with one study observing 74% of squamous cell carcinomas and 78% of adenocarcinomas testing positive for either type[14]. HPV 16 accounts for approximately 55% to 60% of all cervical cancers while HPV 18 accounts for approximately 10% to 15%. Approximately 10 other HPV genotypes cause the remaining 25% to 35% of cervical cancers[7,8,15].

The majority (~90%) of HPV infections are transient and become undetectable within one or two years[16,17]. Infections which are persistent have a high risk of developing into precancerous lesions. For example, a persistent two-year infection of HPV 16 strongly predicts CIN3 or a more severe diagnosis (CIN3+) in the following years (i.e., 20% to 30% risk of CIN3+ over five years for one-year or two-year persistent HPV 16). If left untreated, CIN3 has a 30% probability of becoming invasive cancer over a 30-year period. However, if treated, only approximately 1% will become invasive[18].

Numerous studies have shown that screening for HPV leads to earlier detection of cervical intraepithelial neoplasia (CIN) than cytology.

Updated Terminology

There are multiple nomenclatures for reporting HPV-associated lesions. Starting in the mid-1960s, premalignant squamous changes of the cervix were classified as mild, moderate, or severe cervical dysplasia. Dysplasia is a lesion in which part of the thickness of the epithelium is replaced by cells showing varying degrees of atypia (i.e., structural abnormalities).

In 1988 the Bethesda system was introduced. In this system, which underwent revisions in 1991 and 2001, different terminology was used for cytologic (Pap test) and histologic (biopsy) findings. Cytologic findings were described with the term "squamous intraepithelial lesion (SIL)" whereas histologic findings were described with the term "cervical intraepithelial neoplasia (CIN)"[19]. The term "cervical intraepithelial neoplasia" (CIN) was originally introduced by Richart to present the concept of cervical neoplasia as a disease continuum[20].

In 2012, the Lower Anogenital Squamous Terminology (LAST) consensus project was convened to reassess and harmonize the biopsy and cytology terminology used to report HPV-associated squamous lesions of the lower anogenital tract. The LAST nomenclature, which is now the global standard, relies on HPV 16 staining (though not routinely recommended) to triage CIN2. CIN2 with HPV 16-positive is classified as CIN3, representing a high-grade squamous intraepithelial lesion (HSIL), the immediate precursor to cervical cancer. In contrast, CIN2 with HPV 16-negative is classified as CIN1, representing a low-grade squamous intraepithelial lesion (LSIL), the histologic sign of HPV infection[21,22].

Table 1: Histology and Cytology Terminology

HISTOLOGY			CYTOLOGY	
Dysplasia Nomenclature	CIN Classification System (Richart)	LAST Nomenclature	Papanicolaou Classification	Bethesda System
Negative	Negative		I	Negative for intraepithelial malignancy NILM
Squamous atypia	Squamous atypia		II	ASCUS
Mild dysplasia	CIN 1	LSIL	III	LSIL
Moderate dysplasia	CIN 2	HSIL*	IV	HSIL
Severe dysplasia/ carcinoma in situ	CIN 3	HSIL	IV	HSIL

* Per LAST nomenclature, CIN2 with HPV 16-negative test is considered as LSIL.

Recurrence, Follow-up, and HPV Co-Testing

A long-term multi-cohort study observed that the five-year risk of post-treatment CIN2 or higher in women with three consecutive negative cytology or negative co-testing (Pap smear and HPV test) results at six and 24 months was similar to that of women with normal cytology results in population-based screening. This justifies returning post-treatment women to regular screening schedules[23]. HPV co-testing also has the benefit of diagnosing cervical adenocarcinoma and adenocarcinoma in situ, which traditional cytology often fails to detect[24].

The Katki et al. study of five-year risk of CIN2+ for three follow-up testing strategies after treatment (Pap test alone, HPV alone, and co-testing) indicated that women with prior diagnoses of atypical glandular cells of undetermined significance (AGC), atypical squamous cells – high-grade lesion (ASC-H), or high-grade intraepithelial lesion (HSIL+) Pap test results treated for CIN2 or CIN3/adenocarcinoma in situ (AIS), had a substantial risk of developing CIN2+ post-treatment. However, post-treatment risk was dependent on the severity of the treated histology (CIN2 = 10% versus CIN3/AIS = 16%). The authors concluded that after negative test results post-treatment, no women had achieved risk sufficiently low to permit them to return to five-year routine screenings. Furthermore, negative co-tests after treatment were associated with a lower (five-year) risk of recurrent CIN2+ (one test = 2.4%; two tests = 1.5%) than either a negative HPV test (one test = 3.7%; two tests = 2.7%) or Pap test(s) alone (one test = 4.2%; two tests = 2.7%), although the differences were not significant due to considerable uncertainty around estimates because of the relatively small numbers of recurrences observed[25].

A retrospective analysis of long-term clinical outcomes after treatment for high-grade cervical lesions found that progressive disease was detected only in the first year after treatment. The main predictors of long-term outcomes depended upon the type of transformation zone, the lesion grade, the status of the margins and the result of HPV testing at six to 12 months follow-up[26]. The study by Costa et al. of the performance of HPV DNA testing in the follow-up after treatment of high-grade cervical lesions, adenocarcinoma in situ and micro-invasive carcinoma observed that HPV testing was significantly more sensitive (95%) compared to follow-up cytology (70%) in detecting post-treatment squamous intraepithelial high-grade lesions. Furthermore, for individuals who had been treated conservatively for cervical adenocarcinoma in situ, HPV testing was the strongest independent predictor of recurrent disease or progression to invasive cancer, and co-testing achieved 90% sensitivity in detecting persistent lesions at the first follow-up visit and 100% at the second follow-up visit[27].

A study of long-term risk of invasive cervical cancer after treatment of squamous cell intraepithelial neoplasia found that after the first year following treatment for CIN, the rate of invasive disease remained about 56 per 100,000 woman-years until at least 20 years after treatment. In contrast, the risk of post-treatment CIN declined steadily with time to about 190 per 100,000 women in year 10. Although the post-treatment rate of CIN falls with time, the rate of invasive disease remains static. Therefore, annual Pap smears are recommended for at least 10 years post-treatment[28]. Guidelines for the U.K.'s National Health Service (NHS) Cervical Screening Program, for example, recommend women have annual follow-up tests for at

least 10 years after the treatment of CIN2 or worse before returning to the routine screening interval. Women treated for CIN1 can be returned to routine recall (i.e., screening) after two years of negative post-treatment cytology tests[29].

Medical Guidelines for Screening

In cervical cancer screening, the addition of HPV testing to cytology testing has increased the detection of prevalent CIN3 and a simultaneous decrease in the detection of CIN3+ or cancer in subsequent and follow-up screenings[30,31,32], yielding a decrease in the development of invasive cancers such as SCC (squamous cell cancers) and invasive adenocarcinoma of the cervix. Cytology testing alone, however, has been relatively ineffective in reducing the incidence of invasive adenocarcinoma of the cervix[33] [34]. A systematic review of randomized studies of HPV testing conducted for the U.S. Preventive Services Task Force showed that HPV screening was consistently more sensitive than Pap tests for the detection of ≥CIN2 and ≥CIN3[35].

In addition, a number of studies have reported that co-testing detected a greater proportion of CIN3+ in the first round of screening compared to cytology alone[30,31,32]. Research completed by the International Collaboration of Epidemiological Studies of Cervical Cancer Group pooled screening data from 12 epidemiological studies involving 1,374 women with adenocarcinoma and concluded that the reduction of risk due to a preceding cytology test was greater for squamous cell carcinoma than for adenocarcinoma[11]. Testing positive for HPV is strongly associated with a diagnosis of cervical adenocarcinoma[36].

The latest cervical cancer testing guidelines, published in the *Journal of Global Oncology*, recommend that asymptomatic women in all settings (i.e., medical circumstances) undergo HPV DNA testing. Table 2, below, outlines the recommendations[37].

Table 2: Testing Recommendation by Setting

SETTING	AGE	FREQUENCY OF SCREENING
Maximal source setting: May use high-resource setting guidelines; high level/state-of the art resources or services that may be used in some high-resource countries and/or may be recommended by high-resource setting guidelines that do not adapt to resource constraints. This should be considered lower priority than in the other settings on the basis of cost impracticality for limited-resource environment.	25-65	Screen every five years.
Enhanced setting: Third-tier resources or services that are optional but important. Enhanced-level resources may produce further improvements in outcome but increase the number and quality of screening/treatment options and individual choice (perhaps ability to track patients and links to registries).	30-65	Women in this age range who have had two consecutive negative HPV tests five years apart can extend their screening intervals to every 10 years.
Source limited setting: Second-tier resources or services that produce major improvements in outcomes, such as incidence and cost effectiveness, but that are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple interactions; universal public health interventions are feasible for a greater percentage of the population than primary target group.	30-49	Women in this age range can be screened every 10 years.
Basic setting: Core resources or fundamental services absolutely necessary for any public health/primary health care system to function; basic-level services typically are applied in a single clinical interaction; screening is feasible for highest need populations.	30-49	Women in this age bracket may be screened one to three times in their lifetimes.

In Europe, cervical cancer screening guidelines recommend the use of HPV testing (high-risk HPV 16 and 18) to triage women and as a standalone primary screening test without cytology. Guidelines from the American Cancer Society (ACS), the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Colposcopy and Cervical Pathology (ASCCP) suggest that cervical cancer screening should only begin at age 21, as evidence shows that cervical cancer is rare among adolescents and young women[38]. Australia's National Cervical Screening Program recently announced that its current screening program will be renewed in May 2017 and will invite women aged 25 to 74 years, both HPV vaccinated and unvaccinated, to undertake an HPV test every five years.

In July 2016, it was announced that primary testing for HPV of cervical screening samples would be rolled out across all of England. Cervical screening guidelines for the country are recommending that routine HPV and Pap screenings be offered to women as follows:

- Ages 25 to 49 – every three years
- Ages 50 to 64 – every five years
- Age 65 and older – only to women who have not been screened since age 50 or who have recently had abnormal tests

All of the aforementioned guidelines include women who have had the HPV vaccination, as the vaccine doesn't guarantee complete protection against cervical cancer[39].

HPV Vaccination and Screening

Two HPV vaccines have been licensed globally since 2006. The first was Cervarix®, a bivalent vaccine that targets HPV 16 and 18. The second was Gardasil®, which additionally targets HPV 6 and 11 (which are responsible for about 90% of anogenital warts)[40]. In the U.S., one systematic review and meta-analysis of research found that HPV vaccine (HPVV) uptake varied by ethnicity and healthcare coverage[41]. In addition, although the HPVV is provided free of charge in most European countries, a recent systematic review also found that ethnocultural and educational factors play an important role in HPVV uptake in Europe[42].

The introduction of HPV as a primary screening tool is becoming standard practice in many parts of the developed world, with developing countries most likely to follow in kind.

Both the European guidelines for quality assurance in cervical cancer screening and the ASCCP have recommended that current cervical screening practices should not be changed on the basis of HPV vaccination status at present[5,43]. This is due to a host of factors, including: a lack of empirical data concerning the age when screening is to be initiated or in the screening interval for women who have been vaccinated; that vaccinated women are unprotected from 30% of cervical cancer cases (due to other HPV genotypes not included in the vaccine); that many women who have been vaccinated did so subsequent to HPV exposure (decreasing efficacy); poor vaccination compliance rates; and geographic and socioeconomic disparities in vaccination coverage both within and across countries[5,37,43,44]. Similar screening recommendation guidelines are given by the WHO (World Health Organization) and FIGO (International Federation of Gynecology and Obstetrics)[45,46].

Conclusion

The introduction of HPV as a primary screening tool is becoming standard practice in many parts of the developed world, with developing countries most likely to follow in kind. Understanding HPV and its role in cervical carcinogenesis is crucial when assessing HPV test and cytology results. Having appropriate underwriting guidelines which cater to HPV test findings is essential if cervical screening results are to be used accurately and consistently when making underwriting decisions. RGF

References

1. Ferlay J et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr/Pages/references.aspx
2. Smith JS et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. International Journal of Cancer. 2007 Aug 1;121(3), 621-32. https://www.ncbi.nlm.nih.gov/pubmed/17405118
3. Gustafsson L, Pontén J, Zack M, Adami HO. International incidence rates of invasive cervical cancer after introduction of cytological screening. Cancer Causes Control. 1997 Sep;8(5),755-63. https://www.ncbi.nlm.nih.gov/pubmed/9328198
4. Parkin DM, Bray F. The burden of HPV-related cancers. Vaccine. 2006 Aug 31;24 Suppl 3: S11-S25. https://www.ncbi.nlm.nih.gov/pubmed/16949997
5. Saslow D et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. CA Cancer J Clin. 2012 May-Jun; 62(3): 147-72. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3801360/
6. Wright TC et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. American Journal of Clinical Pathology. 2011 Oct; 136(4), 578-86. https://www.ncbi.nlm.nih.gov/pubmed/21917680
7. Walboomers JM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. The Journal of Pathology. 1999 Sep; 189(1), 12-9. https://www.ncbi.nlm.nih.gov/pubmed/10451482
8. de Sanjose S et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. The Lancet Oncology. 2010 Nov; 11(11), 1048-56. https://www.ncbi.nlm.nih.gov/pubmed/20952254
9. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. The Lancet. 2007 Sep 8;370(8590), 890-907. https://www.ncbi.nlm.nih.gov/pubmed/17826171
10. Lowy DR, Schiller JT. Reducing HPV-associated cancer globally. Cancer Prevention Research. 2012 Jan; 5(1): 18-23. https://www.ncbi.nlm.nih.gov/pubmed/22219162
11. The International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. International Journal of Cancer. 2007 Feb 15;120(4), 885-91 https://www.ncbi.nlm.nih.gov/pubmed/17131323
12. Jemal A et al. Annual report to the nation on the status of cancer, 1975-2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. Journal of the National Cancer Institute. 2013 Feb 5; 105(3):175-201. https://www.ncbi.nlm.nih.gov/pubmed/23297039
13. Division of STD Prevention. Prevention of Genital HPV Infection and Sequelae: Report of an External Consultants' Meeting. Department of Health and Human Services, Centers for Disease Control and Prevention. 1999 Dec. https://www.cdc.gov/std/hpv/hpvsupplement99.pdf
14. The International Collaboration of Epidemiological Studies of Cervical Cancer (2007). Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. International Journal of Cancer. 2007 Feb 15;120(4), 885-91 https://www.ncbi.nlm.nih.gov/pubmed/17131323
15. Muñoz N et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. New England Journal of Medicine. 2003 Feb 6; 348:518-27. http://www.nejm.org/doi/full/10.1056/NEJMoa021641#t=article
16. Rodríguez AC et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. Journal of the National Cancer Institute. 2008 Apr 2; 100(7):513-7. https://www.ncbi.nlm.nih.gov/pubmed/18364507

References

17. Maucort-Boulch D et al. Predictors of human papillomavirus persistence among women with equivocal or mildly abnormal cytology. International Journal of Cancer. 2009 July 16; 126(3): 684-91. http://onlinelibrary.wiley.com/doi/10.1002/ijc.24752/full

18. McCredie, MR et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. The Lancet Oncology. 2008 May; 9(5):425-34. https://www.ncbi.nlm.nih.gov/pubmed/18407790

19. Solomon D et al. The 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology. JAMA. 2002 Apr 24; 287(16): 2114-9. https://www.ncbi.nlm.nih.gov/pubmed/11966386

20. Richart RM. Natural history of cervical intraepithelial neoplasia. Clinical Obstetrics and Gynecology. 1967; 10: 748-84.

21. Darragh TM et al. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Archives of Pathology and Laboratory Medicine. 2012 Oct; 136: 1266-97. http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.LGT200570?code=coap-site

22. Schiffman M, Wentzensen N. Human papillomavirus (HPV) infection and the multi-stage carcinogenesis of cervical cancer. Cancer Epidemiology Biomarkers and Prevention. 2013 April; 22(4), 553-60. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3711590/

23. Kocken M et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. The Lancet Oncology. 2011 May; 12(5), 441-50. https://www.ncbi.nlm.nih.gov/pubmed/21530398

24. Ronco G et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. The Lancet. 2014 Feb 8; 383(9916), 524-32. https://www.ncbi.nlm.nih.gov/pubmed/24192252

25. Katki HA et al. Five-year risk of recurrence following treatment of CIN2, CIN3, or AIS: performance of HPV and Pap cotesting in post-treatment management. Journal of Lower Genital Tract Disease. 2013 Apr; 17(5.0.1): S78-S84. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3616418/

26. Del Mistro A et al. Long-Term Clinical Outcome after Treatment for High-Grade Cervical Lesions: A Retrospective Monoinstitutional Cohort Study. BioMed Research International. 2015. https://www.hindawi.com/journals/bmri/2015/984528/

27. Costa S et al. Performance of HPV DNA testing in the follow-up after treatment of high-grade cervical lesions, adenocarcinoma in situ (AIS) and microinvasive carcinoma. Ecancermedicalscience. 2015; 9: 528. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431402/

28. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. International Journal of Cancer. 2006 Apr 15; 118(8), 2048-55. https://www.ncbi.nlm.nih.gov/pubmed/16284947

29. Public Health England. Colposcopy and programme management guidelines for NHS cervical screening programme. NHS. Updated 2016 March 14. http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.pdf

30. Naucler P et al. Human Papillomavirus and Papanicolaou Tests to Screen for Cervical Cancer. New England Journal of Medicine. 2007 Oct 18; 357, 1589-97. http://www.nejm.org/doi/full/10.1056/NEJMoa073204#t=article

31. Bulkmans NW et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. The Lancet. 2007 Nov 24; 370(9601); 1764-72. https://www.ncbi.nlm.nih.gov/pubmed/17919718

32. Ronco G et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. The Lancet Oncology. 2010 Mar; 11(3), 249-57. https://www.ncbi.nlm.nih.gov/pubmed/20089449

References

33. Cervical screening in Australia 2008-2009. The Australian Institute of Health and Welfare and the Australian Government Department of Health and Ageing for the National Cervical Screening Program. 2011 Oct. http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737420248

34. Bray F et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiology Biomarkers and Prevention. 2005 Sep; 14(9): 2191-9. https://www.ncbi.nlm.nih.gov/pubmed/16172231

35. Whitlock EP et al. Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a systematic review for the U.S. Preventive Services Task Force. Annals of Internal Medicine. 2011 Nov 15; 155(10): 687-97. https://www.ncbi.nlm.nih.gov/pubmed/22006930

36. Castellsagué X et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. Journal of the National Cancer Institute. 2006 Mar 1; 98(5): 303-15. https://www.ncbi.nlm.nih.gov/pubmed/16507827

37. Jeronimo J et al. Secondary Prevention of Cervical Cancer: ASCO Resource-Stratified Clinical Practice Guideline. Journal of Global Oncology. 2016 Oct 28; DOI: 10.1200/JGO.2016.006577. http://ascopubs.org/doi/abs/10.1200/JGO.2016.006577

38. Castle PE et al. The age-specific relationships of abnormal cytology and human papillomavirus DNA results to the risk of cervical precancer and cancer. Obstetrics and Gynecology. 2010 Jul; 116(1): 76-84. https://www.ncbi.nlm.nih.gov/pubmed/20567171

39. NHS (U.K.). Cervical screening – When it's offered. 2015 Sep 7. http://www.nhs.uk/Conditions/Cervical-screening-test/Pages/When-should-it-be-done.aspx

40. Kessels SJ et al. Factors associated with HPV vaccine uptake in teenage girls: a systematic review. Vaccine. 2012 May 21; 30(24), 3546-56. https://www.ncbi.nlm.nih.gov/pubmed/22480928

41. Fisher H, Trotter CL, Audrey S, MacDonald-Wallis K, Hickman M. Inequalities in the uptake of human papillomavirus vaccination: a systematic review and meta-analysis. International Journal of Epidemiology. 2013 Jun; 42(3): 896-908. https://www.ncbi.nlm.nih.gov/pubmed/23620381

42. de Casadevante VF, Cuesta JG, Cantarero-Arévalo L. Determinants in the Uptake of the Human Papillomavirus Vaccine: A Systematic Review Based on European Studies. Frontiers in Oncology. 2015 Jun 24; 5:141. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4478848/

43. Herbert A et al. European guidelines for quality assurance in cervical cancer screening: recommendations for cervical cytology terminology. Cytopathology 2007 Aug; 18(4): 213-9. https://www.ncbi.nlm.nih.gov/pubmed/17635161

44. Roche Molecular Systems, Inc. Summary of cervical cancer screening recommendations based on ACS, ASCCP and ASCCP guidelines – issued 2012. https://www.hpv16and18.com/hcp/cervical-cancer-screening-guidelines/asccp-guidelines.html

45. World Health Organization. WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. 2013. http://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/

46. Global Guidance for Cervical Cancer Prevention and Control. International Federation of Gynecology and Obstetrics (FIGO). October 2009. http://screening.iarc.fr/doc/FIGO-Global-Guidance-for-Cervical-Cancer-Prevention-and-Control_1.pdf

Longer Life Foundation

An RGA/Washington University Partnership

Support of and by the Longer Life Foundation (LFF) is responsible for many fundamental research discoveries by academicians and scientists at Washington University in St. Louis' School of Medicine, who investigate longevity and health in ways that advance and benefit both clinical and insurance medicine.

Two LLF-funded researchers recently presented their achievements to the Longer Life Foundation Scientific Advisory Committee:

Early Adulthood Predictors of Mortality and Morbidity

Zachary Pincus, Ph.D. has long been researching various aspects of longevity in the nematode roundworm Caenorhabditis elegans (C. elegans) to gain a better understanding of the physiology of aging. In an LLF-funded study, he and his team used blood pressure, blood glucose, weight, and body mass index data tracked over a long time period in a subset of 1,349 participants from the Framingham Heart Study. The data was organized into age cohorts to determine if some of the elements of his worm research could translate to humans. He found that approximately 10% of the variability in lifespan between individuals can be predicted while those individuals are still in their thirties, based on simple clinical parameters (body mass index, blood pressure, and blood glucose). Moreover, he found that incorporating the later in life clinical history of these measures yields a better prediction of future lifespan or risk of death than does simply using their present value. In particular, summing the values over time to incorporate total past "exposure" to high blood glucose, high blood pressure, or obesity yields the strongest predictor.

The insurance medicine correlate of Dr. Pincus' work is that the wealth of data currently becoming available from electronic health records and being collected by wearable devices could feed into predictive models and dynamic underwriting frameworks.

For more information, please search here:
http://www.longerlife.org/research/early-aduthood-predictors-of-mortality-and-morbidity-226
Pubmed abstract - Framingham: https://www.ncbi.nlm.nih.gov/pubmed/26446764
Pubmed abstract – C. elegans: https://www.ncbi.nlm.nih.gov/pubmed/27720632

Discovery of Biomarkers to Predict Urinary Tract Infection (UTI) Severity in the Elderly

Jeffrey Henderson, M.D., Ph.D., who has been an LLF grantee since 2014, published a paper in 2016 that discussed his team's discoveries related to his research on UTIs in the elderly and their susceptibility to E. coli. His team's serendipitous finding was the presence or absence of urinary catechol metabolomes are a marker for risk. As urinary tract infections are very common in the elderly – especially among females – and are a major driver of antibiotic prescribing, understanding the mechanism underlying how UTIs progress could be a substantial step forward and could lead to a non-antibiotic approach to treating UTIs. Thus, this information may be very useful in preventing morbidity and mortality associated with UTIs.

For more information, please search here:
Final report: http://www.longerlife.org/research/discovery-of-urinary-tract-infection-biomarkers-to-predict-longevity-in-the-elderly-121
Pubmed abstract: https://www.ncbi.nlm.nih.gov/pubmed/27780864

ReCite

Interesting and relevant articles to the field of insurance medicine recently appearing in the literature...

Cell-free Circulating Tumor DNA in Cancer

Qin Z, et al. Chinese Journal of Cancer. 2016 Nov 2; 35:36.
https://cjcjournal.biomedcentral.com/articles/10.1186/s40880-016-0092-4

Despite the historical successes in treating cancers, the authors of this review article eloquently outlined the persistent clinical challenges of metastatic disease and drug resistance, primarily due to clonal evolution and tumor genomic heterogeneity. They propose that the use of circulating cell-free tumor DNA (ctDNA) may provide insight, and recount the more recent advances in the detection and analysis of ctDNA or so-called "liquid biopsies." While the technology is rapidly advancing and is considered to have the promise of providing highly specific and complementary information in the diagnosis, prognosis, and management of cancer, the authors note there has been slow uptake in routine clinical practice since several technical challenges remain.

Editor's Note: It will be useful for the insurance industry to monitor this line of research and clinical uptake as it may prove to have significant impact on both short- and long-term outcomes in individuals with cancer.

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A Summary

Louis DN, et al. Acta Neuropathol. 2016 Jun; 131(6):803-21.
https://www.ncbi.nlm.nih.gov/pubmed/27157931

This excellent review article presents and summarizes the new 2016 WHO classification of tumors of the central nervous system, which now incorporates additional genomic information when relevant. Per the report, "it is hoped that this additional objectivity will yield more biologically homogenous and narrowly defined diagnostic entities than in prior classifications, which in turn should lead to greater diagnostic accuracy as well as improved patient management and more accurate determinations of prognosis and treatment response." The documenting nomenclature should begin with the histological description followed by the genetic features. The paper indicates that in the event of discordant histological and genetic results, genotype trumps histological phenotype. The authors acknowledge that the classification system will be challenging for some medical centers with regard to testing and reporting.

Editor's Note: This paper is essential reading for insurance medical directors and product developers, as some of the new tumor definitions could impact existing products or new product research (e.g. scaled critical illness products which may be defined by WHO grade).

Return to Work after a Stroke in Working-Age Persons; A Six-Year Follow Up

Westerlind E, Persson HC, Sunnerhagen KS. PLoS One. 2017 Jan 6.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169759

The authors of this paper state that stroke in the working-age population is increasing in different parts of the world and that incomplete return-to-work after stroke has many negative consequences. In a working-age cohort of 211 people (age 18-63) with first-ever stroke analyzed for this paper, the median age was 53 years. Sixty-seven percent were male and

78% had experienced an ischemic stroke. In the six-year follow up period a total of 74.7% of participants did return to work. Predictors of non-return to work included being on sick leave prior to the stroke and more severe disability at discharge after the stroke. The authors point out that return-to-work continued for up to three years post-stroke, and this has not been shown on other studies with shorter follow-up periods. A significant limitation of the study; however, was the inability to determine to what level the participants returned to work, e.g. type of work, number of hours, etc.

Editor's Note: Stroke is an important claim trigger for many living benefits products. Knowledge that return-to-work potential in the working age population can take up to three years post-stroke should be considered when designing rehabilitation benefits and/or other inclusion/exclusion criteria.

Association of "Weekend Warrior" and Other Leisure Time Physical Activity Patterns With Risks for All-Cause, Cardiovascular Disease, and Cancer Mortality

O'Donovan G, Lee IM, Hamer M, Stamatakis E. JAMA Intern. Med. 2017 Mar 1; 177(3):335-42. Published online January 09, 2017.

https://www.ncbi.nlm.nih.gov/pubmed/28097313

This study represented a pooled analysis of 11 cohorts of respondents to the Health Survey for England and the Scottish Health Survey with prospective linkage to mortality records from 1994 to 2012. The analysis sought to determine the association with health for those who perform all their exercise in one to two sessions per week of either >150 minutes per week of moderate intensity exercise or >75 minutes per week of vigorous intensity exercise (i.e., weekend warriors). Four levels of self-reported leisure time physical activity were correlated with all-cause, cardiovascular, and cancer mortality. "Compared with the inactive participants, the hazard ratio (HR) for all-cause mortality was 0.66 (95% CI, 0.62-0.72) in insufficiently active participants who reported one to two sessions per week, 0.70 (95% CI, 0.60-0.82) in so-called 'weekend warrior' participants, and 0.65 (95% CI, 0.58-0.73) in regularly active participants." Similar trends were also demonstrated for cardiovascular and cancer mortality. The authors concluded that different levels of physical activity may be sufficient to reduce mortality, regardless of adherence to prevailing physical activity guidelines.

Editor's Note: This study adds to the growing insurance medicine understanding of the benefits of exercise and to the quantification of those benefits. This is especially important now as insurance trends are moving in the direction of providing wellness "credits" for many products based upon insureds' level of physical activity. RF

RECENT WEBCAST

Latest Developments in Polycythemia Vera

Presenter: **Stephen T. Oh, M.D. Ph.D.**
Assistant Professor, Medicine, Division of Hematology, Washington University School of Medicine in St. Louis

Polycythemia vera (PV) is a chronic stem cell disorder that can cause severe complications and premature death. Dr. Oh, whose research into phenotypes of PV is currently being funded by The Longer Life Foundation, discusses the current state of knowledge of PV.

To arrange to view this webcast and others, please contact jchurchill@rgare.com.

The security of experience. The power of innovation.