ReFlections

RGA's Global Medical Newsletter

Volume 42, September 2017

Peter Barrett
Vice President and Head of Global Underwriting, Claims and Medical Support Team
pbarrett@rgare.com

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

IN THIS ISSUE

FROM THE EDITORS

We wish to welcome all of our global readers to the September edition of ReFlections. With this edition, our 42nd, we are pleased to introduce Peter Barrett, Vice President and Head of Global Underwriting, Claims and Medical Support Team, to our editorial leadership team. He has more than 30 years of experience in life re/insurance, holds a Bachelor of Laws (LLB) degree, and is a Fellow of the Assurance Medical Society (FAMS) and of the Chartered Insurance Institute (FCII). We are delighted and honored to have him on board and look forward to his expertise and contributions.

Additionally, with this edition, we welcome two new authors to ReFlections. Dr. Valerie Kaufman, Vice President and Medical Director, RGA Reinsurance Company, updates us on what's new with hypertrophic cardiomyopathy and Dr. Radi Counsell, Consulting Medical officer, RGA UK Services Limited, gives insight into the rapidly evolving world of lung cancer and the impact of newer treatments on morbidity and mortality. Sue Wehrman, Vice President, Electronic Health Record Initiatives, RGA Reinsurance Company, continues her technology-focused series of articles for ReFlections, this time turning her attention to potential applications of blockchain technology in insurance.

The Longer Life Foundation recently announced its 2017-18 grant awardees and we proudly present them here along with a short description of their proposed research. On a separate note, LLF will be celebrating its 20th anniversary in 2018 – so watch for special LLF features in ReFlections next year!

ReCite presents recent and relevant medical literature articles which we hope you will find useful. A new feature in this issue is a review of the book *Deadliest Enemy: Our War Against Killer Germs* by Dr. Michael Osterholm and Mark Olshaker. This insightful book will help anyone seeking to assess risks associated with infectious diseases.

Finally, we really want to hear from you, our readers! We would like to know what information in ReFlections you find useful and how best to present it. On page 23 of this issue, you will find a link to a survey that we hope will enable us to serve you better. Please take a few moments to respond – your opinion will truly make a difference.

Thank you,

Peter and Dan

AN UPDATE ON HYPERTROPHIC CARDIOMYOPATHY

Abstract

Hypertrophic cardiomyopathy (HCM) is a heterogeneous inherited cardiac condition which has been studied intensely ever since the publication of its first formal description in 1958. Research in this field has benefited greatly from the development of echocardiography and genetic testing. Estimates of long-term mortality have become more favorable over the past 25 years, as study cohorts broadened from those only receiving care at tertiary centers to include those being cared for in the community at large.

While much has been learned about this condition, it continues to pose many challenges for clinicians and insurance underwriters due to inconsistencies in diagnosis, controversies in risk stratification, and limited data regarding the long-term impact of treatments such as implantable cardioverter defibrillators and septal reduction therapy.

This article will provide a contemporary perspective of HCM, including potential treatment modalities and how its risk is currently stratified. Aspects of this condition that present particular challenges for the insurance underwriter will also be described.

Introduction

Since its first formal description in 1958, the medical understanding of and clinical approach toward hypertrophic cardiomyopathy (HCM) has evolved significantly. Not surprisingly, the terminology used to describe the condition has evolved as well. Once thought to be a rare, highly lethal and untreatable disease with an annual mortality rate as high as 6% per year, it is now known to be a common familial condition with only modest mortality (approximately 1%) in most cases.

In the January 1958 edition of the British Heart Journal, pathologist Donald Teare reported eight cases of sudden cardiac death in adolescents or young adults. Upon microscopic examination of the hearts at autopsy, all were found to have striking septal hypertrophy and a "bizarre arrangement of bundles of muscle fibres running in diverse directions and separated by connective tissue and clefts."[1] Teare postulated that the cause was a type of diffuse tumor that he called a "muscular hamartoma."

Extensive research over the last 50 years, helped considerably by the development of echocardiography in the early 1970s, has provided a much broader and deeper understanding of this condition while validating many of Teare's original observations. Rather than a tumor, this condition is now recognized as a genetically mediated primary disease of the myocardium – that is, a cardiomyopathy. Initially referred to by terms such as idiopathic hypertrophic subaortic stenosis (IHSS), hypertrophic obstructive cardiomyopathy (HOCM), muscular subaortic stenosis, and asymmetric septal hypertrophy (ASH), it has since been recognized that the condition can present in a variety of ways: not

ABOUT THE AUTHOR

Valerie R. Kaufman, MD, DBIM, FACC
vkaufman@rgare.com

Valerie R. Kaufman, MD, DBIM, FACC is a Vice President and Medical Director with RGA Reinsurance Company. She provides direct case consultation as well as teaching and training for life underwriters, and assists with underwriting guideline development for RGA's Global Underwriting Manual (GUM). She has more than 25 years of insurance industry experience and has board certifications in insurance medicine, cardiology, and internal medicine. Dr. Kaufman is a past president of the American Academy of Insurance Medicine (AAIM) and a past chair of the AAIM's Education Committee. She has spoken frequently on cardiology topics at local, regional and national industry meetings.

all cases affect the septum disproportionately, and about one-third of cases do not have obstruction to left ventricular outflow. Therefore the more general term “hypertrophic cardiomyopathy” (or HCM) is now preferred.

Definition, Epidemiology, and Cause

HCM is a disease found worldwide with a fairly consistent global prevalence of 0.2% (or 1 in 500). It is caused by pathogenic variations in at least one of the eight genes that encode for protein constituents of the sarcomere, which is the contractile unit of cardiac muscle. The disease is inherited in an autosomal dominant pattern; however, there is significant variation in expression even within families with the same mutation. At this point, more than 1,400 HCM-causing genetic mutations have been identified and novel mutations are common[6].

Since its first formal description in 1958, much has been learned about hypertrophic cardiomyopathy, however there are still many uncertainties.

The current generally accepted definition of HCM is a hypertrophied and nondilated left ventricle in the absence of other cardiac conditions (such as uncontrolled hypertension and aortic valve disease) that could also produce the findings. The hypertrophy may be quite focal or more generalized, and usually (but not always) has a wall thickness of ≥15 mm in adults (13-14 mm is considered borderline). In children, wall thickness of ≥2 standard deviations above the mean for age, sex, or body size meets the definition. MRI studies have shown that the left ventricular anterior free wall and contiguous basal anterior septum are the most frequently involved segments. A significant number of cases have involvement limited to areas of the left ventricle not well seen by echocardiography[4].

The increased availability of genetic testing is identifying a growing population of individuals known to carry a pathogenic mutation (genotype-positive) but without clear clinical manifestations of the disease. These manifestations are referred to either as phenotype-negative or hypertrophy-negative. Research is also indicating that there are certain structural changes aside from hypertrophy that may indicate a “subclinical” or “preclinical” state.

Clinical Manifestations

HCM is often asymptomatic, especially when there is no obstruction to left ventricular outflow. When present, symptoms may include palpitations, dyspnea, fatigue, and syncope, particularly following exertion. Sudden cardiac death due to ventricular arrhythmia may be the initial manifestation of the disease. Atrial fibrillation, heart failure, and thromboembolic events are also potential complications. The ECG is usually abnormal with findings suggestive of left ventricular hypertrophy, such as increased QRS voltage and ST-T wave changes, but it may also be completely normal in a small minority of cases.

Echocardiography is the mainstay for diagnosis and risk stratification, although there is an increasing role for MRI. In addition to a thickened, nondilated ventricle, the ejection fraction is often high despite evidence of diastolic dysfunction. There may be systolic anterior motion (SAM) of the mitral valve with eccentric mitral regurgitation and a dynamic left ventricular outflow tract gradient.

An MRI may enable a more accurate assessment of wall thickness in all areas of the ventricles and can also assess for fibrosis, which is an emerging marker for increased arrhythmia risk.

Clinical expression of HCM usually increases with age. Hypertrophy most often becomes apparent during adolescence, but a first appearance later in life is not uncommon. ECG changes, increased ejection fraction, and delayed myocardial relaxation may precede the onset of hypertrophy.

Mortality and Risk Stratification

The natural history of HCM is varied and unpredictable. Early studies from tertiary care centers reported adult HCM mortality as high as 6% per year. However, more recent research from community-based HCM populations has shown much more favorable outcomes, with mortality of less than 1% per year. The difference is thought to be due primarily to selection bias, with the tertiary care cohorts being more severely affected than the community-based cohorts. Mortality in children with HCM may be 2% per year or higher.

Despite this overall more optimistic view of HCM outcomes, there is a subset of those with HCM who are at significantly higher risk for complications such as sudden cardiac death and progression to heart failure. Although a number of risk markers have been identified, no universally accepted risk prediction model yet exists, and identifying those at increased risk remains imprecise.

The 2011 American College of Cardiology Foundation/ American Heart Association Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy lists the following factors as established or potential markers of increased arrhythmia risk[6]:

Figure 1: Risk Markers, Modifiers

ESTABLISHED RISK MARKERS	POTENTIAL RISK MARKERS
• Cardiac arrest or sustained ventricular tachycardia • Family history of HCM and sudden death • Unexplained syncope • Left ventricular hypertrophy of ≥30 mm • Nonsustained ventricular tachycardia on monitor • Failure to increase BP or a decrease in BP with exercise	• Resting left ventricular outflow gradient ≥30 mm Hg • Late gadolinium enhancements (LGE) involving ≥15% of LV mass (by MRI) • Left ventricular apical aneurysm

Other than previous cardiac arrest, established risk markers have fairly low positive predictive values (between 10% and 20%). Most HCM centers in the U.S., however, will consider placement of an implanted cardioverter/defibrillator (ICD) when one or two risk markers are present.

Because of their concern that the U.S. risk stratification approach overestimates risk, resulting in inappropriate ICD placements, a European group (the Hypertrophic Cardiomyopathy Outcomes Investigators) developed a risk prediction model that allows for weighting of factors and use of continuous (rather than binary) variables. The HCM Risk-SCD model is intended as a primary prevention risk stratifier – those with a personal history of cardiac arrest are excluded.

Risk stratification requires consideration of multiple factors and remains an imprecise process.

The model, which provides an estimate of the absolute risk of sudden death within the next five years, utilizes the following factors[7]:

- Age
- Maximal left ventricular wall thickness
- Left atrial diameter
- Left ventricular outflow gradient
- Family history of HCM and sudden death
- Nonsustained ventricular tachycardia
- Unexplained syncope

This approach, however, has been criticized for being unreliable for the classification of both high- and low-risk cases[8]. At this time, risk stratification requires consideration of multiple factors and remains an imprecise process.

Management

All cases of HCM should be assessed for arrhythmia risk, even those who are completely asymptomatic. Individuals should avoid strenuous physical exercise and other cardiovascular risk factors and comorbidities need to be treated aggressively. In addition, it is recommended that family members be screened by having echocardiograms and ECGs usually beginning around age 12 and continuing periodically throughout life.

Therapeutic options have become widely available over the last two decades for those at increased arrhythmia risk and for those with symptomatic obstruction. ICDs have been shown to successfully terminate ventricular arrhythmias; however there is a significant complication rate and long-term mortality data is not yet available. Likewise, septal reduction procedures such as myectomy and alcohol septal ablation can be effective in reducing obstructive symptoms but long-term mortality data is sparse.

Underwriting Challenges

Although there have been many advances in the field of HCM, many challenges remain both for the clinician and the insurance underwriter. Some important issues for an insurance underwriter to consider include the following:

- Since HCM is often asymptomatic, insurance applicants may be unaware of the condition, yet abnormalities may be recognized in medical records or in tests obtained in conjunction with the application.
- Mild or borderline hypertrophy may be attributed to other causes without full clinical investigation.
- Maximum wall thickness may occur in areas not well seen by echocardiography.
- A family history of HCM may be disclosed by a proposed insured; however, clinical evaluation may not have been completed.
- With more genetic testing and family screening, the population of those known to be genotype-positive hypertrophy-negative will increase, and the long-term outcome for these "preclinical" states requires more study.

Conclusion

The broad clinical spectrum of HCM was well-represented in Teare's original group of eight cases. With intense research and enhanced diagnostic tools, particularly echocardiography and more recently magnetic resonance imaging, much has been learned about it. However, there are still many uncertainties. Also, because of HCM's recognized high prevalence and potential for significantly increased mortality, insurance underwriters must be familiar with contemporary risk stratification approaches. The recommendation for family screening and the availability of genetic testing has added layers of complexity to this already difficult underwriting challenge. ReF

References

1. Teare D. Asymmetrical Hypertrophy of the Heart in Young Adults. British Heart Journal. 1958 Jan20(1):1-8. https://www.ncbi.nlm.nih.gov/pubmed/13499764
2. Maron BJ, Rowin EJ, Casey SA, et al. Hypertrophic Cardiomyopathy in Adulthood Associated with Low Cardiovascular Mortality with Contemporary Management Strategies. J Am Coll Cardiol. 2015 May 12;65(18):1915-28. https://www.ncbi.nlm.nih.gov/pubmed/25953744
3. Maron BJ, Rowin EJ, Casey SA, Maron MS. How Hypertrophic Cardiomyopathy Became a Contemporary Treatable Genetic Disease with Low Mortality – Shaped by 50 Years of Clinical Research and Practice. JAMA Cardiol. 2016;1(1):98-105. http://jamanetwork.com/journals/jamacardiology/fullarticle/2498963
4. Maron MS, Maron BJ, Harrigan C, et al.Hypertrophic Cardiomyopathy Phenotype Revisited After 50 Years with Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2009 Jul 14;54(3):220-8. https://www.ncbi.nlm.nih.gov/pubmed/19589434
5. Ho CY, Day SM, Colan SD, et al. The Burden of Early Phenotypes and the Influence of Wall Thickness in Hypertrophic Cardiomyopathy Mutation Carriers: Findings From the HCMNet Study. JAMA Cardiol. 2017 Apr 1; 2(4): 419-28. https://www.ncbi.nlm.nih.gov/pubmed/28241245
6. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011 Dec 13;58(25):e212-60. https://www.ncbi.nlm.nih.gov/pubmed/22075469
7. O'Mahony C, Jichi F, Pavlou M, et al. A Novel Clinical Risk Prediction Model for Sudden Cardiac Death in Hypertrophic Cardiomyopathy (HCM risk-SCD). Eur Heart Journal. 2014 Aug 7;35(30):2010-20. https://www.ncbi.nlm.nih.gov/pubmed/24126876
8. Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent Assessment of the European Society of Cardiology Sudden Death Risk Model for Hypertrophic Cardiomyopathy. Am J Cardiol. 2015 Sep 1;116(5):757-64. https://www.ncbi.nlm.nih.gov/pubmed/26183790

SCREENING AND NON–SMALL-CELL LUNG CANCER

Abstract

Lung cancer is the most frequently diagnosed cancer worldwide. It continues to be the leading cause of cancer mortality in both men and women, accounting for 1.69 million deaths worldwide in 2015[1].

This article reviews key advances in the management of non-small-cell lung cancer and the clinical gains in outcomes as well as the ability to deliver personalized cancer treatment.

Introduction

Non-small-cell lung cancer (NSCLC) is one of the two main types of lung cancer, accounting for about 85% of cases. NSCLC is a heterogeneous group of cancers that includes adenocarcinoma, squamous cell (epidermoid) carcinoma, and large cell (undifferentiated) carcinoma. Small cell lung cancers (SCLC), which represent the rest, have only two main subtypes – small cell carcinoma and combined small cell carcinoma.

Computed tomography (CT) scans, which provide three-dimensional images, can detect non-small-cell lung cancers at earlier stages than other scanning methods, allowing it to be treated with surgery. Radiation therapy improvements over the past two decades have made it a viable treatment alternative as well.

Unfortunately, the majority of those with lung cancer continue to be undiagnosed until the cancer is at an advanced stage. The American Cancer Society reports that only 16% of lung cancers are diagnosed at a localized stage – that is, while the tumor is still confined to the lung[2].

Prevention of smoking and cessation of smoking offer the most important route to decreasing morbidity and mortality, as approximately 90% of cases are due to smoking. With the introduction of molecular tumor testing (or biomarker testing), which looks at tumor DNA mutations and levels of specific proteins, it is now possible to individualize systemic treatment for NSCLC. Expanded drug therapies (including targeted agents) and immunotherapy advances means that systemic treatment can now be optimized for each individual. As a result, life expectancies as well as quality of life have been improving for lung cancer patients: survival rates, according to the National Cancer Institute's SEER database, are 18.1% for patients treated between 2007 and 2013 versus 15.7% between 1995 and 2000.

Screening for Lung Cancer

Although screenings have been proven effective in detecting earlier stage lung cancers, adoption is not yet worldwide. Screening has long been well-accepted in the U.S.: The National Lung Screening Trial[3], conducted in the U.S. from 2002 to 2009, demonstrated that annual low-dose single CT (LDCT) scans reduce lung cancer mortality in high-risk individuals based on age and smoking history. Compared with chest

ABOUT THE AUTHOR

Radhika (Radi) Counsell MBBS, MD
Consulting Medical Officer,
RGA UK Services Limited
counsellr@rgare.com

Radhika (Radi) Counsell, MBBS, MD, is a Consulting Medical Officer with RGA UK Services Limited. A specialist in gynecological and breast cancers, she provides direct case consultation for annuities, critical illness, terminal illness, and medical insurance claims, and review and input for RGA Global Underwriting Manual's oncology guidelines and for new products under development in Asia. Dr. Counsell's managerial role in the National Health Service (from which she recently retired) included the launching of the NHS Trust's Acute Oncology Outreach Service, which provides opinions on cancer patients presenting with acute problems, and leadership of the regional gynecological brachytherapy service. She has also taught and trained medical students, acute medicine doctors, oncology specialty trainees, and therapy radiographers. She continues to work as an appraiser for NHS Trust medical consultants.

Dr. Counsell is a member of the Royal College of Physicians (MRCP) of the United Kingdom and a Fellow of the Faculty of the Royal College of Radiologists (FRCR). Her Bachelor of Medicine & Bachelor of Surgery (MBBS) degree, and her medical doctorate (M.D.) for research on magnetic resonance spectroscopy in breast cancer, are from University of London medical school. She has lectured on oncology at both medical and insurance events.

x-rays – an older, traditional mode of screening – the relative reduction in deaths was 20% and the absolute reduction 62 per 100,000 person-years. The trial also found that the number of individuals that needed to be screened in order to prevent one lung cancer death was 320.

In the U.S., lung cancer screening was expanded in February 2015 by Medicare, which covers people age 65 and older. Smokers of at least 30 pack-years, or who are between the ages of 55 and 74 and quit less than 15 years ago, are considered good screening candidates under American Cancer Society guidelines for annual CT scans.

A key question: are lung cancer screenings cost-effective? At this point, that's not an easy question to answer. LDCT, in both trials and practice, has been found to be associated with a false positive rate of greater than 90%. The need for repeat scans and invasive procedures for these individuals could cause physical and psychological harm.

Are lung cancer screenings cost-effective? At this point, that's not an easy question to answer.

A recent study of Veterans Health Administration[4] (U.S.) efforts to set up a comprehensive lung cancer screening service highlighted both the logistical difficulties in performing screenings and the immense resources required to do so effectively. In contrast to the National Lung Screening trial, the veterans population not only had significant comorbidity, but also incidental findings such as emphysema, other pulmonary abnormalities, and coronary artery calcification in 40.7% of the patients screened. This can complicate or confound lung cancer screening results.

Screening trials are also currently underway in Europe, but in Asia, which has 51% of lung cancer deaths worldwide, only Japan and Korea have well-established lung cancer screening programs. Other countries – most notably China – are investigating emplacing screening programs. In Japan, where lung cancer is a leading cause of mortality for both men and women, nationwide screening started in 1987. The screens consisted of chest x-rays and sputum cytology (another way of testing who might be at risk for developing lung cancer), and annual LDCT screening was added in 1993. In Hitachi City Prefecture, where low-dose CT screening among employees and communities began in 2001, lung cancer mortality among employees and in the community of those aged 50-69, in the period from 2005 to 2009, fell by 24% compared with national statistics[5].

NSCLC Diagnosis and Staging

The most common signs of lung cancer are cough, hemoptysis (blood in sputum) and dyspnea (difficulty breathing). These symptoms often represent advanced-stage lung cancer. In cases where distant metastases have occurred, common sites are liver, adrenal glands, bones, and brain.

Tumor biopsy and histology are essential for confirming a lung cancer diagnosis and for determining if it is a metastasis from a different primary cancer. Testing for molecular or genetic markers now guides systemic therapy for advanced and recurrent cancers.

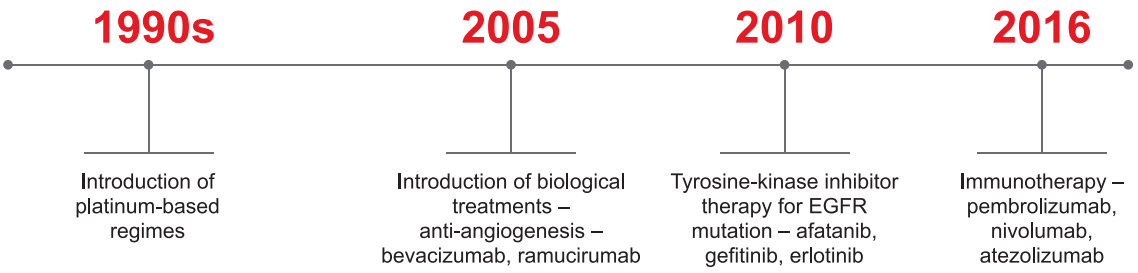
Positron emission tomography-computed tomography (PET-CT) scans are more accurate for evaluating the mediastinal lymph nodes with positive predictive value of approximately 75%[6]. False positive results are seen with infection, inflammation and granulomatous disease. Biopsy may be required for clarification before proceeding with surgery.

Treatment of Early-Stage NSCLC

Only 30% of those diagnosed with NSCLC have Stage I or II disease. Its cure rate has improved with aggressive multi-modality treatment. Currently, the definitive treatment is lobectomy. Video-assisted thoracoscopic surgery reduces incidence of complications and duration of hospital stay without compromising outcomes. Post-operative radiotherapy is considered for tumor at resection margin or positive lymph nodes to improve locoregional control[7].

Chemotherapy for Stage II tumors is associated with a 5% survival advantage[8]. Certain Stage I tumors greater than 4 cm and other adverse features such as poor grade, lymphovascular invasion and high uptake on PET-CT scan, may also receive chemotherapy. For Stage II and IIIA, the addition of chemotherapy to surgery achieves 33% survival at five years[9].

Figure 1: Evolution of Non-Small-Cell Lung Cancer Treatments



Radical radiotherapy (also known as external beam radiation therapy, or EBRT) is done on patients who are not medically fit for surgery. For Stage I peripheral tumors, stereotactic ablative radiotherapy (SABR) where available is considered best practice.

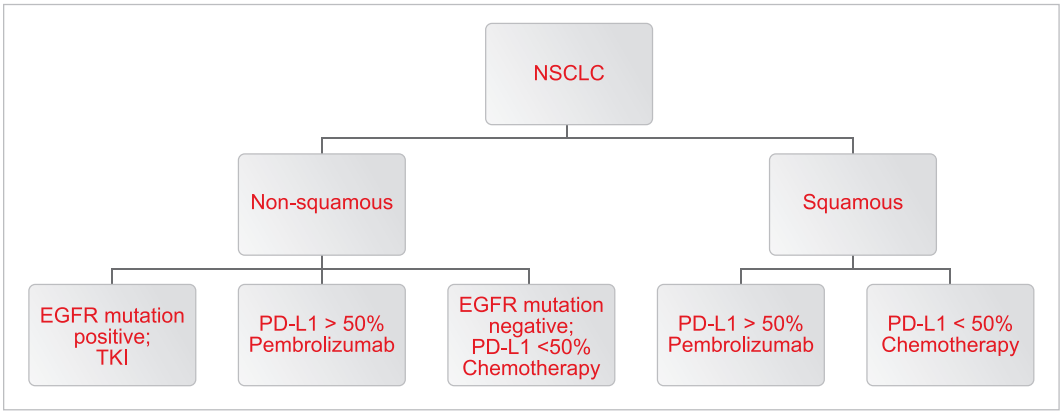
The thorax is a difficult site to treat with radiotherapy due to the low density of the lung, breathing movements during treatments, and the proximity of critical structures in the mediastinum. Recent innovations in treatment planning and delivery have led to more precise and accurate targeting of treatment.

3D conformal radiation treatment techniques utilize CT scans to shape treatment volumes and optimize dosimetry. Sharper dose gradients can be achieved with intensity-modulated radiation therapy (IMRT), giving the option of treating larger tumors. These techniques have also reduced the rate of radiation-induced esophagitis. Whether adjusting treatment volumes during a course of radiotherapy as the tumor shrinks can be beneficial is under study.

Respiratory gating 4D techniques can reduce the risk of geographical miss, which occurs due to the up-and-down movement from breathing during treatments. To further refine the gating, MRI visualization during treatment is being explored so that radiation delivery can be switched off when the target treatment volume is outside a pre-specified safety margin[10].

Stereotactic ablative radiotherapy (SABR) is able to deliver high doses of radiation to a defined target volume using multiple convergent beams, with rapid dose fall-off at the edge of the volume, which reduces dosage to adjacent normal tissue. Usually three to eight daily treatments are given, whereas conventional radiotherapy treatments are over four to seven weeks.

Figure 2: First-Line Systemic Therapy for NSCLC Based on Molecular Profiling or Predictive Biomarkers



SABR may also be a viable alternative to surgery for operable tumors as Phase II trials indicate similar outcomes[11]. The failure rate for regional lymph nodes is 15% and at distant sites 20% for both SABR and surgery[12]. However, due to risk of severe damage, it is not safe to employ SABR for central tumors within two centimeters of any critical structure in the mediastinum such as bronchial tubes, esophagus, heart, major blood vessels, nerves and spinal cord. The role of SABR in surgical patients is under study in four trials.

Treatment of Unresectable NSCLC

Stage III NSCLC remains a challenging disease to treat. Chemoradiotherapy – that is, having both chemotherapy and radiotherapy treatments together – is the international standard of care, but can only be tolerated by those with excellent performance status[13]. The median survival rate for those who have undergone chemoradiotherapy is 17 to 28 months, and after five years, only 20% to 30% are still alive. Rates of treatment failure (disease recurrence) are 30% to 40% in the chest and 40% to 50% at distant sites[14].

If using radical radiotherapy alone for these tumors, continuous hyperfractionated accelerated radiotherapy (CHART) and shortening treatment duration to 12 days with three equally spaced fractions (or treatments) daily has been shown to improve outcomes. Overall survival rates at two, three and five years are 29%, 20%, and 11%, respectively[15].

Treatment of Stage IV NSCLC

The majority of people with NSCLC present with advanced disease, and treatment goals are controlling disease, relieving symptoms, improving life expectancy, and optimizing quality of life.

The recognition that patients with small volume disease (i.e., a tumor or lesion that can be removed surgically or treated with a moderate to high dose of radiotherapy) in a single site or multiple distant sites can achieve long-term survival has led to more aggressive treatment management, with selective use of ablative surgery and radiotherapy in addition to systemic therapy. Small studies have reported two-year survival rates of 23% to 38%, and five-year survival rates of 14%, even for those where the cancer metastasized to the brain[16].

In recent years, major advances in our understanding of the molecular biology of NSCLC has led to an explosion of choices for systemic therapy. Figure 1 shows the time scale for

the evolution of treatments over the past 25 to 30 years. Today, treatment is guided by histology and molecular markers. Figure 2 shows the decision-making process for first-line NSCLC therapy, based on molecular profiling or predictive biomarkers for biological treatments and immunotherapy.

For adenocarcinoma, tyrosine-kinase inhibitors (TKIs) such as erlotinib and gefitinib are used in the presence of tumors that show epidermal growth factor receptor mutation(s). For NSCLC where high levels of the protein PD-L1 are present, immunotherapy has now supplanted chemotherapy as first line treatment. Comparing such biological treatments with chemotherapy, the side-effect profile is different and often less frequent and less severe.

The top challenge currently is that of improving treatment of advanced stage (lung) cancers.

Immunotherapy with Checkpoint Inhibitors

NSCLC has the ability to evade attack by the immune system. About 30% of cases have high levels of PD-L1. When this ligand binds to the PD-1 checkpoint protein on T cells, the immune system is switched off. Blocking this pathway with the checkpoint inhibitor pembrolizumab allows T-cell activation.

The pivotal KEYNOTE-024 trial[17] with 305 patients shows that pembrolizumab is superior to cisplatin doublet chemotherapy regimens as first-line therapy. The objective response rate was 44.8% vs 27.8%. Median progression free survival with pembrolizumab was 10.3 months, compared with six months for chemotherapy. The one-year survival was 70% vs. 54%, and the risk of death reduced by 40%.

As a result, pembrolizumab has been heralded as a new era in the treatment of NSCLC and is now recommended as front-line therapy for advanced stage disease where the level of PD-L1 is 50% or greater. This treatment is active in both squamous and non-squamous histology. Pembrolizumab was approved by the FDA in October 2016 and by the European Commission in January 2017.

Conclusion

NSCLC survival is gradually improving, but the majority of patients will die from their cancers as they usually have advanced disease at diagnosis. In the last two decades, considerable progress has been made in staging and selecting treatments based on tumor biology and patient characteristics and preferences.

Technical improvements in planning and delivery of radiotherapy with SABR, 3D conformal techniques, IMRT and respiratory gating mean that higher doses can be delivered to the tumors while minimizing significant damage to adjacent tissue. This in turn can improve the likelihood of long-term control and cure for early-stage tumors.

The major gains in lung cancer survival have come from improved treatment of early-stage or localized (in the chest) lung cancer. The big challenge currently is that of improving treatment of advanced stage cancers. Very few patients survive beyond two years. With the advent of biological therapy in addition to chemotherapy, there are now more options for both first-line and subsequent courses of treatment. The latest practice-changing development has been the introduction of immunotherapy as first-line therapy for advanced disease.

We are now in the era of being able to provide personalized cancer care for the full range of NSCLC, providing real hope for the future. ReF

References

1. World Health Organization Cancer Fact Sheet. February 2017. http://www.who.int/mediacentre/factsheets/fs297/en/
2. American Cancer Society: Cancer Facts and Figures 2017. Atlanta, Ga: American Cancer Society, 2017. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf
3. The National Lung Cancer Screening Trial Research Team, Reduced Lung Cancer Mortality With Low-Dose Computed Tomographic Screening. N Engl J Med 2011; 365:395-409. http://www.nejm.org/doi/full/10.1056/NEJMoa1102873#t=article
4. Kinsinger LS, Anderson C, Kim J et al. Implementation of Lung Cancer Screening in the Veterans Health Administration. JAMA Intern Med. 2017 Mar 1;177(3):399-406. https://www.ncbi.nlm.nih.gov/pubmed/28135352
5. Nawa T, Nakagawa T, Mizoue T, Endo K. Low-dose Computed Tomography Screening in Japan. J. Thoracic Imaging. 2015 Mar;30(2):108-14. https://www.ncbi.nlm.nih.gov/pubmed/25658475
6. Fischer B, Lassen U, Mortensen J, et al. Preoperative Staging of Lung Cancer with Combined PET-CT. New England Journal of Medicine. 2009 Jul 2; 361:32-9. http://www.nejm.org/doi/full/10.1056/NEJMoa0900043#t=article
7. Bezjak A, Temin S, Franklin G, et al. Definitive and adjuvant radiotherapy in locally advanced non-small cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence -Based Clinical Practice Guideline. J Clin Oncol 2015 Jun 20; 33(18):2100-5. https://www.ncbi.nlm.nih.gov/pubmed/25944914
8. Bradbury P, Sivajohanathan D, Chan A et al. Postoperative Adjuvant Systemic Therapy in Completely Resected Non-Small-Cell Lung Cancer: A Systematic Review. Clin Lung Cancer. 2017 May; 18(3):259-73. https://www.ncbi.nlm.nih.gov/pubmed/28162945
9. Burdett S, Pignon JP, Tierney J et al. Adjuvant chemotherapy for resected early stage non-small cell lung cancer. Cochrane Database Syst Review. 2015 Mar; 2(3):CD011430. https://www.ncbi.nlm.nih.gov/pubmed/25730344
10. Hardy K. MRI-Guided Radiation Therapy. Radiology Today. 2014 September; 15(9):20. http://www.radiologytoday.net/archive/rt0914p20.shtml
11. Timmerman R, Paulus R, Pass H et al. RTOG 0618: Stereotactic Body Radiation Therapy (SBRT) to treat Operable Early-Stage Lung Cancer Patients. Journal of Clinical Oncology. 2013 May; 31: suppl 15:7523. http://ascopubs.org/doi/abs/10.1200/jco.2013.31.15_suppl.7523
12. Nagata Y, Hiraoka M, Shibata T et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys. 2015 Dec 1; 93(5):989–96. https://www.ncbi.nlm.nih.gov/pubmed/26581137
13. Eberhardt WE, De Ruysscher D, Weder W et al. 2nd ESMO Consensus Conference in Lung Cancer: Locally Advanced Stage III Non-Small-Cell Lung Cancer. Ann Oncol 2015 Aug; 26(8):1573–88. https://www.ncbi.nlm.nih.gov/pubmed/25897013

14. Baker S, Dahele M, Lagerwaard FJ, Senan S. A Critical Review of Recent Developments in Radiotherapy for Non-Small-Cell Lung Cancer. Radiation Oncology 2016 Sep 6; 11:115. https://ro-journal.biomedcentral.com/articles/10.1186/s13014-016-0693-8

15. Saunders M, Dische S, Barrett A et al. Continuous, Hyperfractionated, Accelerated Radiotherapy (CHART) Versus Conventional Radiotherapy in Non-Small-Cell Lung Cancer: Mature Data from the Randomised Multicentre Trial. CHART Steering Committee. Radiother Oncol. 1999 Aug; 52(2):137-48. https://www.ncbi.nlm.nih.gov/pubmed/10577699

16. Ashworth AB, Senan S, Palma DA et al. An Individual Patient Data Meta-analysis of Outcomes and Prognostic Factors after Treatment of Oligometastatic Non-Small-Cell Lung Cancer. Clin Lung Cancer. 2014 Sep; 15(5):346-55. https://www.ncbi.nlm.nih.gov/pubmed/24894943

17. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New England Journal of Medicine. 2016 Nov 10; 375(10):1823-33. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1606774

ELECTRONIC HEALTH RECORDS: IS BLOCKCHAIN A GOOD FIT?

Abstract

Even though paper records for most medical practices have evolved to digital, all of that data currently resides in silos, where consumers attempt to reconcile data among their providers and health payors. This can be challenging, as there is no single source that identifies where all of an individual's health data resides, let alone the order in which it was entered.

From the proliferation of digital health data comes a second challenge: that of keeping the data secure. The past few years have seen an explosion of data breaches and medical identity theft. Consequently, health care providers are looking for the most effective ways to secure the personal health information they hold.

Could blockchain technology provide an answer? Blockchain is one of the hottest topics related to data security today, but beyond the inherently sensitive nature of health data are the persistent challenges of interoperability, patient record-matching, and health information exchange.

Up to this point, providers have exchanged health data via one (or more) of these three models:

- ***Push:*** medical information is sent from one healthcare provider to another
- ***Pull:*** Providers request information from other providers
- ***View:*** Providers can view data inside another provider's record

Blockchain offers a fourth model – one which has the potential to enable secure lifetime medical record-sharing across providers. Several InsurTech startups and incubators are already investigating how to use blockchain technology to secure, store, and access medical data, both for underwriters and healthcare providers.

What is Blockchain?

Blockchain technology is far more than a buzzword: in simple language, it is a generic tool that enables data to be recorded and stored in an authoritative, distributed, encrypted and secure ledger. The technology enables control of who can have access to that ledger.

Blockchain is also a write-once and append-only system, which means the records comprising the database, once uploaded and accepted, cannot be changed: records can only be added to the ledger. Multiple parties with access can share data and the structure ensures these participants that past records have not been altered[15].

The term "distributed database" refers to the fact that the data as well as the devices in the chain are not in one central location or controlled by one gatekeeper. Rather, the system is decentralized: a constant and growing list of ordered records, or "blocks," are stored in secure sequences, or "chains," on all participating systems. Each block in a chain is time-stamped when it is created and contains a link to a previous block in the chain, so it is clear when a record was uploaded and in what order.

ABOUT THE AUTHOR

Susan L. Wehrman FLMI, ACS
swehrman@rgare.com

Susan L. Wehrman, Vice President, Electronic Health Record Initiatives, founded and heads RGA's now five-year-old electronic health record (EHR) initiatives unit, one of the first such units in the insurance industry. EHRI conducts in-depth research and analyses of this fast-evolving segment, monitors all pertinent activity in the U.S. and around the world, and assists clients with EHR-related issues. Sue has an Master of Science (M.S.) degree in Health Information Management, and has published frequently on EHR-related topics.

There are three types of blockchains: public (bitcoin is the best-known example), private, and consortium. For bitcoin, the data is organized so that transactions can be verified and then recorded into the system through the consensus of every party in the network (essentially, a peer-to-peer network). This distributed infrastructure translates to the highest degree of security – even if one device is compromised, it does not affect the rest of the computers in the chain.

In a private or consortium network, an individual entity controls the blockchain and determines which entities can participate as nodes.

Since records in a blockchain are decentralized, each individual participant in the chain holds a copy of the record and each copy constitutes a block in the chain. Each member of a blockchain network (known as "nodes," or "miners" for public networks) contributes to the collective process of validating and certifying digital transactions for the network. Potential revisions to a record must be compared against each and every participant's copy before being approved, which strengthens security and reduces the likelihood of unauthorized changes. Once a change has been approved by all participants, the revised block/record (copy) is redistributed to each participant (or node)[13]. Since all members of a network have a complete copy of all updates, no single member has the power to tamper or alter the data as no single entity exclusively owns the data.

Cryptography ensures that participants can only edit the parts of the blockchain for which they have privileges. This is accomplished through the use of private keys which are needed to confirm that the information sent comes from a particular user, prevents the information from being altered once the information has been sent, and allows only authorized individuals to alter data. It also ensures that everyone's copy of the distributed records are synchronized. For example, in the case of an electronic health record, each entry to a chain is time-stamped at creation and becomes a permanent part of the record – it cannot be changed retroactively or removed. Therefore, original records of test results, diagnoses, and treatments, once uploaded, are preserved and will remain unmodified. Each transaction is digitally signed by authorized users to ensure its authenticity.

Blockchain offers a fourth model – one which has the potential to enable secure lifetime medical record-sharing across providers.

How Blockchain Technology Could Benefit Healthcare

"EHRs were never designed to manage multi-institutional life time medical records. Patients leave data scattered across various organizations as life events take them away from one provider's data silo and into another." Dr. John Halamka, CIO, Beth Israel Deaconess, Boston, Massachusetts.[2]

The average individual in the U.S. has approximately 19 distinct medical records from seeing 18.7 different doctors during their lives[18]. This is problematic for a number of reasons, but most importantly, because the U.S. has no unique patient identifier. Therefore, it is nearly impossible to aggregate every individual's encounters into a single, longitudinal health record.

Blockchain could benefit the health care space in a number of ways:

- **Identity Management:** Could be resolved since every transaction must be validated by all members of a chain before it is approved.
- **Managed Consent:** Patients could authorize all data-sharing, allowing them to specifically manage who is accessing their information.
- **Data Preservation:** Multiple health care providers could view, edit, and share data while safeguarding records of diagnoses, medications, and services rendered.
- **Privacy:** Unauthorized individuals could be prevented from accessing patient records.
- **Health Information Exchanges (HIEs):** Rather than relying on intermediaries for data exchange such as public exchanges or private provider networks, participants could join a network without building specific interfaces between entities.
- **Health Care Claims Processing/Validation:** Current processes could be simplified to eliminate a series of

validations and multiple third parties acting on behalf of other entities.

- **Public Health:** By creating shared streams of de-identified patient information, authorities could more readily identify epidemiologic trends or threats, e.g. pandemics.
- **Patient-Generated Data:** Could easily be uploaded and stored securely with all other medical data.

Challenges / Remaining Questions

"It's psychology that's a challenge. We still have the culture where every health care provider thinks of themselves as the single steward of the data that is deposited in that organization." Dr. John Halamka, CIO, Beth Israel Deaconess, Boston, Massachusetts. [17]

Before a health care blockchain system could be adopted nationwide, several technical, organizational, and environmental challenges must be addressed. These include: uncertainty, scalability, data standardization and scope, operational costs, and regulatory considerations.

- **Uncertainty:** One of the biggest challenges in implementing blockchain in health care is that there are few successful models of blockchain-based initiatives to follow.
- **Scalability:** A distributed blockchain that contains health records, documents, and images would have significant data storage implications and transaction limitations. Conceptually, every member in the blockchain would have a copy of every health record for every individual in the U.S. This volume far exceeds the storage capabilities of current blockchain technology.
- **Standardization:** There are no established standards for the use of blockchain in healthcare – especially in terms of protocol which dictates how the technology can be implemented.
- **Costs:** The costs of developing and operating a blockchain-powered healthcare network are currently unknown.
- **Regulatory:** There are no regulations that address the unique properties of blockchain data exchange and there is uncertainty around how it might conform to current privacy regulations like the Health Insurance Portability and Accountability Act (HIPAA).

Finally, two critical issues facing health care today that present significant barriers to blockchain adoption are:

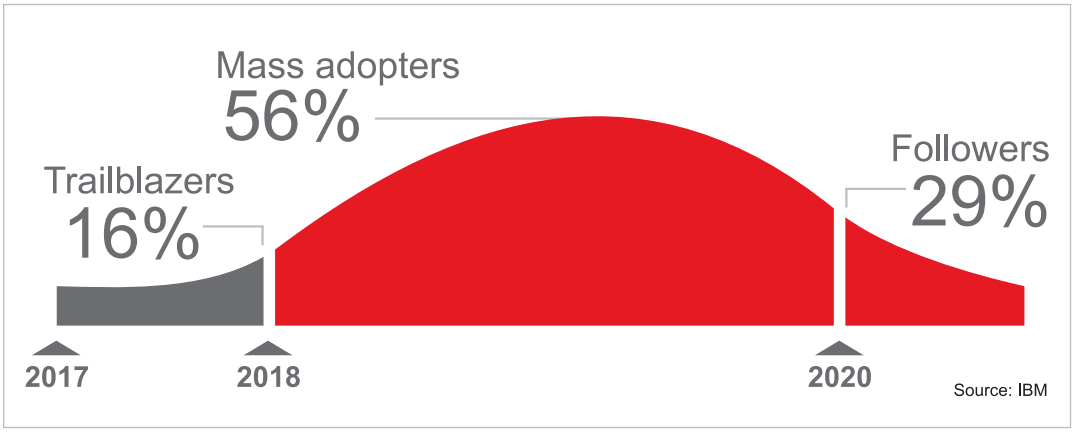
- Data ownership – who owns health data, and who can grant permission to share it?
- Since each blockchain relies on a unique identifier to link events together, one of the fundamental requirements for blockchain adoption will be the use of a unique patient identifier.

Adoption and Real-World Examples

Despite these hefty challenges, InsurTech players are forging ahead. Major corporations currently operating in the health care blockchain market are Philips AG, IBM Corporation, and Deloitte. Others are also emerging, including Microsoft Corporation, Blockchain Tech Ltd., and Digital CC Ltd.

Health care and life sciences have the most aggressive deployment plans of any industry: According to a survey by IBM, 35% of health care and life science respondents plan to have blockchains in production within the next calendar year[5].

Figure 1: When healthcare companies expect to have blockchains in production.



Following are some notable examples of current efforts:

- In the U.S., the Office of the National Coordinator for Health Information Technology (ONC) recently released a paper on the applicability of blockchain technology in securing and recording medical record components. In the near future, the ONC plans

to introduce a blockchain-based infrastructure which healthcare companies can leverage to build their own proprietary systems.

- The information technology department of Beth Israel Deaconess Medical Center in Boston, along with researchers at MIT, conducted a six-month test of blockchain in the real world. They entered patient's medication data, prescriptions, and vaccination history, on separate sites and then used blockchain technology to see if specific doctors could easily access those records. The project was a success and they are planning additional pilots with larger networks of hospitals.
- IBM has supported blockchain implementations for more than a year. It recently announced a beta version 1.0 of a new service, Hyperledger, which has the potential to process up to 1,000 transactions per second.
- Patientory, a new provider of blockchain solutions for healthcare, has launched a blockchain-based electronic medical storage service. Users create an individual profile using the company's mobile app, and their medical information is stored in a secure, HIPAA-compliant blockchain platform. The platform allows users with similar health issues or concerns to connect with one another, their physicians, and their care teams. Users can then actively learn more about their overall health and wellbeing. In addition, users and clinicians can utilize the platform to better manage patient care across multiple teams. The technology is compatible with a number of EHR systems, including Epic, Cerner, Allscripts, and Meditech.
- IBM Watson Health has partnered with the U.S. Food and Drug Administration (FDA) to define a secure, efficient, and scalable exchange of health data using blockchain technology. This initiative will explore the exchange of data from several sources, such as electronic medical records, clinical trials, genomic data, as well as health data from mobile devices, wearables, and the Internet of Things. The initial focus will be on oncology-related data.

International Initiatives

Estonia has partnered with the data security startup Guardtime for a new blockchain initiative aimed at electronic patient records. It has issued one million personal identity smart cards. The blockchain files and signs the data (new signatures are generated whenever the information is altered). The actual records aren't stored on the blockchain; only the hash values (tags/identifiers) indicate when files have been updated, thereby creating an audit trail of all transactions.

The United Arab Emirates-based telecom company, du, has partnered with NMC Healthcare to introduce blockchain technology to store patient information. Additionally, the government of Dubai aims to have all of its documents on a blockchain platform by the year 2020.

Thailand is headed for widespread adoption of blockchain technology within two years. In anticipation, the government amended its Electronic Transaction Act 2001 to support the use of smart contracts and is implementing new privacy laws that will take into account the sharing of personal data for public use via blockchain such as for patient records in hospitals.

Before a health care blockchain system could be adopted nationwide, several technical, organizational, and environmental challenges must be addressed.

The United Kingdom's chief scientific officer, Sir Mark Walport, recently issued a report calling for government investment in blockchain. He asserts the technology has potential application in the NHS where it could open up new ways to share patient records. Sir Walport's key recommendations are that the Government Digital Service and Digital Economy Unit at the Department of Business, Innovation and Skills should lead work on researching these technologies and their applications.

What Blockchain Can Mean for Insurance Underwriting

Insurance underwriters also have a vested interest in comprehensive, secure medical records and interoperability. Underwriters have long been concerned with "chain of custody" – that is, which entity or individual possesses underwriting (health) data and whether individuals can alter that data for purposes of anti-selection.

Insurance underwriters … have a vested interest in comprehensive, secure medical records and interoperability.

Even though blockchain appears to create a clear chain of custody and complete audit trail for medical data, questions remain related to access and data-sharing: First, who will assign access permissions and designate which parties can query and write data to their blockchain? At a minimum, a user should be able to view an audit log of who accessed their blockchain (including when and what data was accessed) and also be able to grant and revoke permissions for access. However, will owners be able to grant selective access to some records and not others, e.g., would users be able to decide what data is collected and how it can be shared? Finally, would an insurer be an actual participant in a blockchain or would it merely be a recipient of information?

When it comes to blockchain technology and its applications there are still many questions remaining for the insurance industry. However, the potential for opportunity is great and almost limitless.

References

1. Bresnick J. (nd). 16% of Healthcare Stakeholders Plan to Use Blockchain by 2017. HealthIT Analytics. Jan. 4, 2017. http://healthitanalytics.com/news/16-of-healthcare-stakeholders-plan-to-use-blockchain-by-2017
2. Bresnick J. (nd). Exploring the Use of Blockchain for EHRs, Healthcare Big Data. HealthIT Analytics. http://healthitanalytics.com/features/exploring-the-use-of-blockchain-for-ehrs-healthcare-big-data
3. Butler B. How IBM Wants to Bring Blockchain from Bitcoin to Your Data Center. Computerworld Hong Kong. March 22, 2017. http://cw.com.hk/news/how-ibm-wants-bring-blockchain-bitcoin-your-data-center
4. Das S. UAE Healthcare Provider to Store Patient Records on a Blockchain. Cryptocoins™ News. Jan. 4, 2017. https://www.cryptocoinsnews.com/uae-healthcare-provider-to-store-patient-records-on-a-blockchain/
5. Deloitte. Deloitte Survey: Blockchain Reaches Beyond Financial Services With Some Industries Moving Faster. Deloitte. Dec. 13, 2016. https://www2.deloitte.com/us/en/pages/about-deloitte/articles/press-releases/deloitte-survey-blockchain-reaches-beyond-financial-services-with-some-industries-moving-faster.html

6. Dietsche E. How Patientory Uses Blockchain to Keep Data Secure and Help Connect Patients. Becker's Health IT & CIO Review. January 18, 2017. http://www.beckershospitalreview.com/healthcare-information-technology/how-patientory-uses-blockchain-to-keep-data-secure-and-help-connect-patients.html
7. Halamka JD, Ekblaw A, Lippman A. (2017). The Potential for Blockchain to Transform Electronic Health Records. Harvard Business Review. March 3, 2017. https://hbr.org/2017/03/the-potential-for-blockchain-to-transform-electronic-health-records
8. Gordon W, Wright A, Landman A. Blockchain in Health Care: Decoding the Hype. NEJM Catalyst. Feb. 9, 2017. http://catalyst.nejm.org/decoding-blockchain-technology-health/
9. Bresnick J. Is Blockchain the Answer to Healthcare's Big Data Problems? HealthIT Analytics. April 27, 2016. Retrieved from http://healthitanalytics.com/news/is-blockchain-the-answer-to-healthcares-big-data-problems
10. IBM. IBM Watson Health Announces Collaboration to Study the Use of Blockchain Technology for Secure Exchange of Healthcare Data. Jan. 11, 2017. http://www-03.ibm.com/press/uk/en/pressrelease/51400.wss
11. Kern C. Blockchain's Value for Transforming Healthcare: Placing the Consumer at the Center. Health IT Outcomes. Sept. 2, 2016. https://www.healthitoutcomes.com/doc/blockchain-s-value-for-transforming-consumer-at-the-center-0001
12. Leesa-Nguansuk S. (2017). Thailand Prepares for Blockchain. http://www.bangkokpost.com/tech/local-news/1189341/thailand-prepares-for-blockchainLinn,
13. Linn LA, Koo MB. (nd). Blockchain for Health Data and Its Potential Use in Health IT and Health Care Related Research. HealthIT.gov. https://www.healthit.gov/sites/default/files/11-74-ablockchainforhealthcare.pdf
14. Marr B. A Complete Beginner's Guide to Blockchain. Forbes. Jan. 24, 2017. https://www.forbes.com/sites/bernardmarr/2017/01/24/a-complete-beginners-guide-to-blockchain/3/#48ac714125ce
15. Molteni M. Moving Patient Data is Messy, but Blockchain is Here to Help. Wired. Feb. 1, 2017. https://www.wired.com/2017/02/moving-patient-data-messy-blockchain-help/
16. Rosic A. (nd). Blockchain Technology in Healthcare: The Dream and the Reality. TNW. https://thenextweb.com/contributors/blockchain-technology-healthcare-dream-reality/#.tnw_emUO9yZ6
17. Silverman L. How Bitcoin Technology Could Securely Share Medical Records Among Your Doctors. Kera News. March 8, 2017. http://keranews.org/post/how-bitcoin-technology-could-securely-share-medical-records-among-your-doctors
18. Weare K. Building the Hyperconnected Future on Blockchains Paper Released at World Government Summit. InfoQ. March 4, 2017. https://www.infoq.com/news/2017/03/Blockchain-Future
19. Whitfield L. Bitcoin Tech has Role in NHS: Walport. Digital Health. Jan. 20, 2016. https://www.digitalhealth.net/2016/01/bitcoin-tech-has-role-in-nhs-walport/
20. Young J. U.S. Governs in Blockchain to Protect Healthcare Companies from Hackers. Exchange Union. April 16, 2017. https://cointelegraph.com/news/us-government-invests-in-blockchain-to-protect-healthcare-companies-from-hackers

Longer Life Foundation

An RGA/Washington University Partnership

LONGER LIFE FOUNDATION'S 2017-2018 RESEARCH GRANT RECIPIENTS

Every year, The Longer Life Foundation (LLF), the not-for-profit foundation launched in 1998 by Reinsurance Group of America, Incorporated in partnership with Washington University School of Medicine in St. Louis, awards grants to Washington University researchers undertaking important grass-roots investigations into topics of importance to both clinical and insurance medicine.

The recently announced grants for the 2017-2018 award year are for a diverse range of research areas ranging from Alzheimer's disease and urinary tract infections in the elderly to smoking cessation, longevity, and obesity.

In awarding these grants, LLF continues its nearly two decades of supporting groundbreaking medical research that helps people live longer, better lives while benefiting public health and the insurance industry.

For more information about LLF, grants funded by LLF, and peer-reviewed articles generated by our research, we invite you to visit www.longerlife.org.

INVESTIGATOR/TITLE OF RESEARCH PROJECT	DESCRIPTION
A. Joseph Bloom, Ph.D. *Nicotine N-Oxidation, a Novel Target for Smoking Cessation*	Interventions to help people quit smoking are very limited. This study will investigate a new metabolic target which may lead to better pharmacologic therapies to help individuals quit smoking.
Brian Gordon, Ph.D. *Examining the Contribution of Diabetes and Obesity to Alzheimer's Disease*	Alzheimer's disease (AD) has great importance to both society and insurers. Dr. Gordon will examine the impact of obesity and diabetes on the risk of developing AD and its pathophysiology.
Jennie Kwon, D.O. *The Trajectory of the Fecal Microbiome in Patients with Multidrug-Resistant Urinary Tract Infections (UTIs)*	UTIs, especially those due to antibiotic-resistant organisms, cause significant morbidity and mortality. Dr. Kwon will attempt to identify characteristics of the fecal microbiome at the time of acute infection. Doing so will help further our clinical understanding of the risk of acquiring these infections and may help in the development of ways to prevent them.

INVESTIGATOR/TITLE OF RESEARCH PROJECT	DESCRIPTION
Dmitri Samovski, Ph.D. *Role of CD36 in the Obesity-Associated Fatty Liver Disease and Hepatic Insulin Resistance*	Non-alcoholic fatty liver disease is common and frequently encountered in insurance medicine. Dr. Samovski will investigate a novel metabolic pathway to further understand how abnormal levels of fat accumulate in liver cells which eventually may allow for the design of new therapeutic approaches.
Faye Womer, M.D. *The Structural and Functional Brain Network in Early- and Later-Onset Depressive Disorder*	Underlying mechanisms in the brain leading to depression are poorly understood. Dr. Womer will study structural and functional changes in the brain using new MRI technologies and graph theory. These results may lead to better ways to diagnose and treat depression.
Luis Batista, Ph.D. *The Impact of Progressive Telomere Shortening on Mitochondria Function and Energy Metabolism*	Progressive telomere shortening is associated with aging. Dr. Batista has mechanistically identified the impact this phenomenon has on mitochondrial (the cell's energy producer) function. This second year of funding will focus on the impact of telomere-associated mitochondrial changes on stem cells.
Kory Lavine, M.D., Ph.D. *Precision Therapeutics for Pediatric Dilated Cardiomyopathy (DCM)*	In his first year of LLF funding, Dr. Lavine has demonstrated that the pathophysiology of pediatric DCM is different from that of adults. He will now study unique pharmacologic compounds which could lead to novel therapies for pediatric DCM.
Luigi Fontana, M.D., Ph.D. Longevity Research Program *Metabolic and Molecular Effects of Prolonged Fasting*	Dr. Fontana will study the metabolic effects of prolonged fasting. This will provide valuable data which can be used as the benchmark to serve as the comparator for less restrictive dietary interventions. The goal is to understand and maximize dietary modifications to promote health, wellness, and longevity.

RGA MEDICAL TEAM UPDATE

RGA welcomes Dr. Jee Won Kim, MMS, ECFMG, Medical Doctor (Internist), RGA Reinsurance Company Korea Branch, to our global network of medical officers.

ReCite

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

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Rawshani A, et al. N Engl J Med 2017 April 13;376(15):1407-18. DOI: 10.1056/NEJMoa1608664.
https://www.scribd.com/document/345029558/Mortality-and-Cardiovascular-Disease-in-Type-1-and-Type-2-Diabetes

This original case-control study followed patients in the Swedish National Diabetes Register with both Type 1 and Type 2 diabetes from 1998 through 2014. Trends in deaths and cardiovascular events were estimated. Results demonstrated a significant reduction in mortality and cardiovascular events in both types of diabetics during the study period, yet a substantial excess overall rate of all outcomes analyzed persisted among those with either type of diabetes relative to the control population. The authors postulated that a combination of medical advances led to the improved outcomes for diabetics.

Editor's Note: The insurance risk assessment of diabetes is often considered to carry moderate to significant excess morbidity and mortality. This study indicates that a favorable trend is occurring and will help insurers gain a greater understanding of the long-term risks of both Type 1 and Type 2 diabetes.

Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017

MacMahon H, et al. Radiology. 2017 July; 284(1):228-43.
http://pubs.rsna.org/doi/abs/10.1148/radiol.2017161659

The Fleischner Society has updated its recommendations regarding the management of incidentally discovered pulmonary nodules. The guidelines only apply to those older than 35 year of age. They do not apply to people who are specifically undergoing lung cancer screening, who are immunosuppressed, or with known primary cancer. The Society now recommends that solid nodules 6 mm or less in diameter (which have a risk of cancer of <1%) in low-risk adults need no further evaluation. This change should significantly reduce the number of follow-up CT scans annually.

Editor's Note: Insurance underwriting frequently requires risk assessment of incidental lung nodules. This paper will help insurers to further refine and update their guidelines.

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Sabatine MS, et al. N Engl J Med. 2017 May 4;376:1713-22.
http://www.nejm.org/doi/full/10.1056/NEJMoa1615664

Evolocumab, a PCSK9 inhibitor, can reduce LDL cholesterol levels by 60%. This double-blind, randomized trial evaluated the clinical impact of that reduction. The primary efficacy endpoint was the composite of cardiovascular (CV) death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. After median duration follow up of 2.2 years, evolocumab significantly reduced the primary endpoint (9.8% in treatment group and 11.3% in the placebo group) by an HR of 0.85. However, there was no effect of additional lowering of LDL cholesterol on CV mortality.

Editor's Note: Insurance medicine is not typically focused on new clinical treatments. However, given the likelihood this new class of medication can further reduce CV events, it is worthy of insurance attention. Additionally, medical reimbursement insurers will need to assess the significant costs of new treatments such as evolocumab and the impact on product pricing.

Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers
Kuchenbaecker K, et al. JAMA. 2017 Jun 20;317(23):2402-16.
https://www.ncbi.nlm.nih.gov/pubmed/28632866
This large cohort prospective study estimated age-specific probability of BRCA1 and BRCA2 mutation carriers for developing breast, ovarian, and contralateral breast cancer. According to the authors, prior retrospective studies were prone to bias and have wide confidence intervals. Overall, for BRCA1 the cumulative risk of developing breast cancer by age 80 was 72% and for BRCA2 was 69%. With regard to ovarian cancer, BRCA1 risk by age 80 was 44% and 17% for BRCA2 carriers. Additionally, the study outcomes indicated that family history (number of affected relatives) and mutation location have an impact on clinical manifestations and risk.

Editor's Note: Results of genetic tests and specifically BRCA testing are frequently encountered in medical reports during underwriting. It is important for insurers to be aware of the most recent studies which document the potential predictive clinical outcomes of these tests and consider them, where allowed, for risk stratification.

BOOK REVIEW

Deadliest Enemy: Our War Against Killer Germs
Michael T. Osterholm, Ph.D., MPH, and Mark Olshaker. 2017. Little, Brown and Company

In this easy-to-read but comprehensive review of the risks associated with infectious diseases, Dr. Osterholm, director of the Center for Infectious Disease Research and Policy (CIDRAP), presents a historical and potential future perspective for the reader. He discusses everything from pandemic influenza, Ebola, MERS, and yellow fever, to antimicrobial resistance. In addition to the direct morbidity and mortality impact of infectious diseases, Dr. Osterholm makes the case for compounded risk in the form of social and economic disruption.

Editor's Note: This book is essential reading for insurers, especially for those individuals involved in stochastic modeling, estimating the risk of tail events, and compliance with key solvency regulations related to epidemic and pandemic planning. R&F

READERSHIP SURVEY

At RGA, we continually strive to share medical insights to advance the global industry. To help us serve you better, we are seeking feedback from you with regard to ReFlections, RGA's thrice-yearly global medical newsletter.

Please click on the link below, or type the URL into your browser, to connect to our short readership survey. All results will be completely anonymous.

https://www.surveymonkey.com/r/ReFlectionsReaderSurvey

Thank you for taking the time to give us your feedback!

The security of experience. The power of innovation.