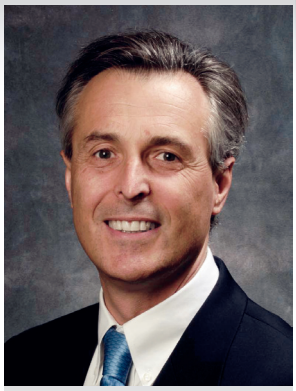
RGA®

ReFlections

RGA's Medical Underwriting Newsletter

Volume 28, Winter 2012



J. Carl Holowaty
cholowaty@rgare.com

LETTER FROM THE EDITOR

Dear readers:

It is always my great pleasure to introduce new writers from RGA's talented pool of medical associates in *ReFlections*. In this final edition for 2012 we are fortunate to have two new contributors from RGA's Global operations. Dr. Nontuthuzelo Thomas from South Africa has written our first article on the topic of Functional Impairments. From our India office, Dr. Sheetal Salgaonkar has provided an article that reminds us how important it is to consider the possibility of resurgence of infectious diseases such as tuberculosis.

In 2012 we have provided you with several articles regarding predictive modeling. This edition of *ReFlections* follows up on the prior two articles with an actuarial viewpoint on the subject, written by Richard Xu, Scott Rushing and Tim Rozar. If nothing else, this article will bring back memories of college math. I hope that is not too scary!

The final article in this edition is provided by Sue Wehrman, who continues to update us on Electronic Health Records. These updates provide valuable background information for a series of webcasts that RGA is preparing on this topic. Stay tuned for the announcement of the schedule for these webcasts.

I hope that you enjoy this edition!

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

FUNCTIONAL IMPAIRMENT: A LOOK AT FI PRODUCT BASICS IN SOUTH AFRICA

By Nontuthuzelo Thomas M.B.CH.B.
Chief Medical Research Officer
RGA Reinsurance Company of South Africa Limited

South Africa has a sophisticated insurance market that is innovative and continually developing new products or features. Insurers adopt several strategies to remain competitive and product innovation remains at the forefront of these strategies. One such innovative product is Functional Impairment (FI) which has become quite a common offering in risk products for the individual market. This is an innovative product that can be crudely described as a hybrid of lump sum disability and critical illness. It does have key differences to these two better-known products as summarized in the table below:

Table 1
Comparison of common product characteristics

Product Characteristics	Functional Impairment	Lump Sum Disability	Critical Illness
Fully underwritten	√	√	√
WOL cover	√		
Loss of Income		√	
Disease Permanence	√		
Intermediated	√	√	√
Lump sum payout	√	√	√
Treatment Compliance	√		

In the South Africa market, sale of these products is through intermediaries and advice is taken from a broker on the timing of a purchase and the extent of cover. The products themselves are quite complex and require a significant level of engagement and education to navigate with ease. The backbone of the products is a combination of sound product design and tangible living benefits in the eyes of the consumer.

There are many different views about the drivers of the purchase but certainly one of the attractive features of FI is that it is not subject to inability to earn an income. It is also seen as a form of 'disability cover' that is more suited to those in sedentary roles where there is less exposure to occupational hazards. FI is also seen as a useful alternative for those individuals who do not require own occupation type disability cover – i.e., less need for specialized job roles. FI is also viewed as a valuable alternative for pensioners who continue to work beyond the age of 65 years and who may not necessarily have steady income or be in formal employment.

This article will explore the basics of FI and highlight some of the unique features of this product as sold in this market. There have been enquiries about these products and a lot of interest from other markets on how FI differs from critical illness and disability products. This simple narrative will articulate what FI is and what it is not. For ease of reading the topic will be covered under four main headings as follows:

- Product overview
- Claim definitions
- Underwriting
- Distribution

Product overview

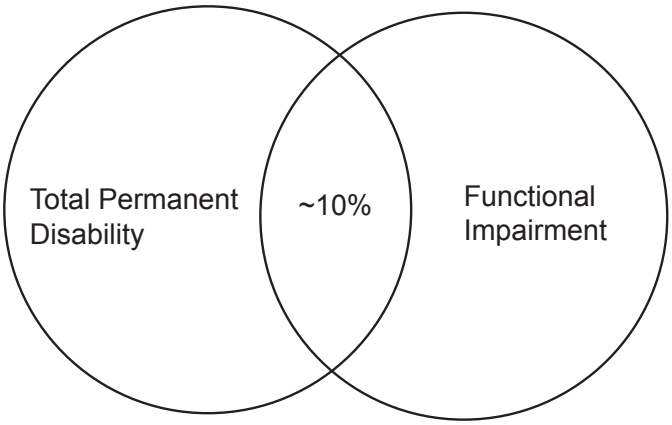
The Association of Savings and Investment South Africa (ASISA) describes Functional Impairment as follows:

> "The purpose of this benefit is to provide a lump sum or income benefit in the event of the life assured becoming permanently impaired in accordance with pre-defined criteria. With traditional disability living benefits, a person's ability to carry on with a current or similar job is a determining factor for the payment of living benefits. This is not the case with functional impairment as you are insured against the loss or impairment of a particular function and not against the inability to continue generating an income.
>
> "This benefit is payable in the event of the insured becoming permanently impaired, due to accident or illness, which results in a loss of ability to function. Either a lump sum or monthly income amount is paid to provide for the costs associated with living with impairment, such as specialised care, equipment or a home nurse. Living benefits are 100% of the sum insured for severe impairments and tiered for less severe impairments. It is possible to claim more than once against this cover, although overall claims cannot exceed 100% of the sum insured. As the claim events are not linked to your ability to perform your current job, the benefit provided is not income dependent and is not intended to replace lost income.
>
> "The sum insured (total cover) may be increased by means of voluntary premium increases. For example, the policyholder may elect a cover (sum insured) increase of 5%. The premium will then increase annually in order to pay for the annual sum insured increase. Functional impairment policies can be taken out for a maximum term of 20 years, with an upper age limit of for example 65."

This is a succinct description and captures the most salient product features. There are, however, important differentiators between the various product designs – for example, whole of life vs. term life cover with the necessary adjustments in product features, price and positioning. There are also products that offer cover beyond the age of 65 years.

FI is named different things by the various insurance companies, so an FI product may not necessary bear the name FI but still be FI cover. One would have to closely interrogate the product particularly because there are also combinations of FI, lump sum disability and sickness benefits that are sold together. FI can be sold as a standalone policy or as an accelerator to another type of cover, such as death. A popular combination seems to be Total Permanent Disability in combination with FI sold as an accelerator. This approach from a pricing point of view takes advantage of the synergistic nature of these two types of insurance products.

Diagram 1
FI and TPD overlap illustration



Claim definitions

It is important to note that FI demands a very different philosophical approach in that at face value FI definitions can look very similar to critical illness definitions; however, close inspection will reveal that the FI definitions are quite severe and demand more than just diagnosis of a medical illness.

With FI the severity and permanence of a particular medical illness is a very important aspect of the definitions. FI also tends to demand compliance with appropriate medical care and maximum medical improvement (usually following the WHO concept of MMI). The claim will usually be assessed for admissibility some time after the medical event has occurred (at least 3-6 months).

The other key difference with FI is the reliance on life quality measures like Activities of Daily Living (ADLs) to assess impact on lifestyle especially for neurological illness and psychiatric disorders. Evidence of existence of disease is not sufficient as there needs to be a quantifiable impact on the day-to-day existence of the affected individual.

To illustrate the point two definitions for the same medical illness are juxtaposed below, one for critical illness and one for functional impairment. We have chosen arrhythmia - an irregular heartbeat associated with significant cardiac impairment. The claim definitions for the same illness are quite different as they demand very different criteria for payout.

Table 2
An example of a Functional Impairment definition for Arrhythmia

Arrhythmia	
Impairment Definition and Severity Criteria	Percentage of Sum Assured Payable
The insured must be diagnosed by a registered cardiologist with recurrent uncontrollable ventricular arrhythmias as proven on ECG or Holter monitoring. These arrhythmias must cause recurrent syncope and persistent Class IV symptoms according to the New York Heart Association (NYHA) as defined below. **These symptoms must be present for more than 6 months despite optimal therapy** with anti-arrhythmic medications, artificial pacemaker, implantable cardioverter-defibrillator or ablation therapy. The arrhythmia must require permanent defibrillator insertion.	100

Note that the section highlighted with underlining and bold font refers very specifically to persistency of symptoms for a stipulated time frame and compliance with the various forms of medical interventions to manage the medical illness.

Table 3
An example of a Critical Illness definition for Arrhythmia

Arrhythmia	
Claim Definition and Criteria	Percentage of Sum Assured Payable
Arrhythmias are defined as conditions in which the electrical activity of the heart is irregular, or is faster or slower than normal. For this definition arrhythmias are deemed to be those of a pathological variety, and which lead to, or may potentially have, life-threatening consequences. **The diagnosis, as well as the need for any procedures, is to be verified by a certified cardiologist, and there must be clear ECG evidence indicating the arrhythmia.** A permanent defibrillator insertion must have been performed.	100

Note that the section highlighted with underlining and bold font refers to the diagnosis or confirmation of medical illness by the appropriate medical specialist and through special investigations.

Underwriting

FI relies very heavily on rigorous underwriting as it is a benefit that covers the end state of medical illness as opposed to onset of illness. These are fully underwritten products and require detailed information about the proposer's past and present overall state of health. It is important for the underwriter to follow up and investigate not only known illnesses but any symptoms or signs that can potentially be a problem further down the life cycle of the FI policy. It is of utmost importance to weed out any early signs and symptoms of medical illness as well as load all necessary exclusion clauses where illness predates policy inception. There are no black and white rules for medical underwriting of FI but in general the approach to benefits is more prudent than with life cover.

When underwriting living benefits like FI it is important to guard against anti-selection and to place the right customer profile in the books. A life that would be perfectly suitable for life cover might not be placed for FI because of concerns that surface in the medical examination or past medical history. A checklist with 10 of some of the important factors in risk assessment is outlined below for ease of reference:

1. Age
2. Gender
3. Family History
4. Co-morbidities
5. Habits: Alcohol, Drug and Tobacco use
6. Past medical history and investigations
7. Occupation
8. Lifestyle (sedentary or active)
9. Previous insurance assessments and loadings
10. Type of cover vs. expected needs

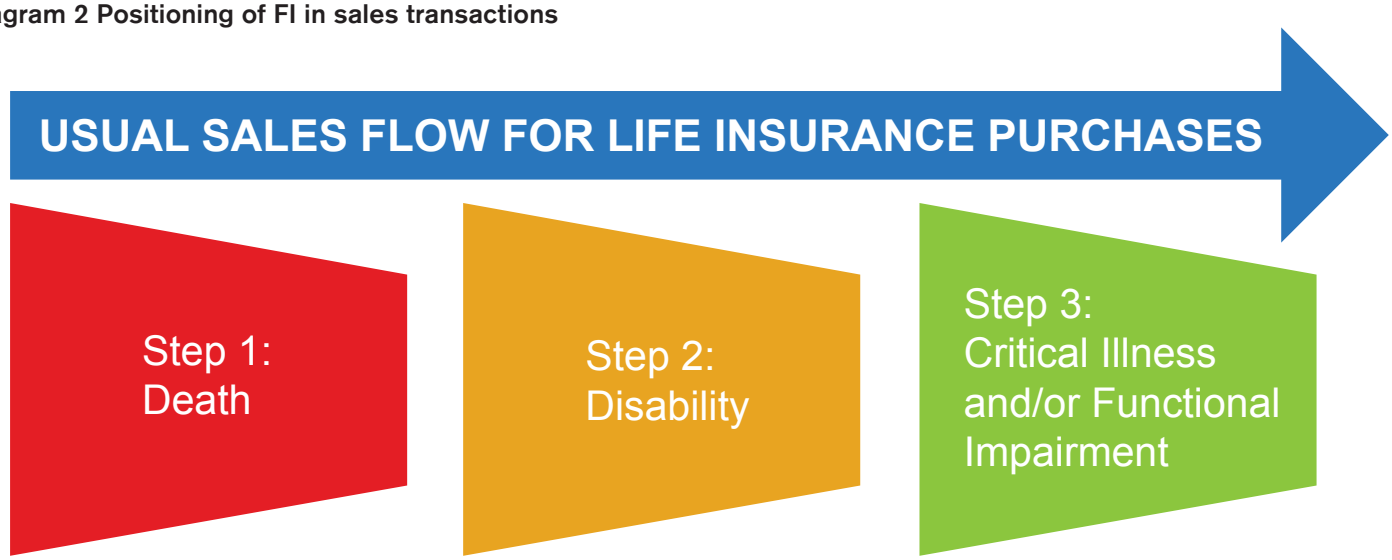
As suggested earlier, there is no 'cookie cutter' formula, so underwriting of living benefits like FI is usually allocated to the most experienced members of the team due to the level of skill required to evaluate associated extra mortality and impairment. FI products by design already feature quite prominent exclusions. The commonly cited categories are major back pathology and psychiatric illnesses. The underwriter would therefore have to load all other additional exclusions that are applicable to that case.

In this market we have not yet seen a limited underwriting product or a product without any underwriting for FI. To a large extent because of the combination of policies we also do not see a lot of standalone FI policies so underwriting is usually for a suite of products bought simultaneously.

Distribution

Looking at the South Africa office's in-force book and some limited informal research that was performed locally, it is clear that the biggest perceived individual insurance need is death and disability cover. Living benefits like critical illness and FI are an overlay on top of death and disability. FI therefore tends to be sold at the tail end of the transaction or as part of ongoing portfolio review management as opposed to the initial sale.

Diagram 2 Positioning of FI in sales transactions



FI is also not commonly seen as part of group products as these tend to focus predominantly on death, disability and very little, if any, critical illness.

All in all, FI is a product still in its infancy but all indications at this stage are that it meets a need in the market and has created opportunities to offer a form of 'disability cover' that appeals to administrative type roles as well as older lives who may no longer be in full-time employment.

Nontuthuzelo Thomas M.B.CH.B.
nthomas@rgare.com

Dr. Nontuthuzelo Thomas is Chief Medical Research Officer, RGA Reinsurance Company of South Africa Limited. She works in the Strategic Marketing division on both internal and external Research and Development projects. She is a general practitioner with clinical research and managed care experience.

PREDICTIVE MODELING – YES, THERE IS SOME MATH

By Richard Xu, Senior Data Scientist and Actuary, Global Research and Development; **Scott Rushing**, Vice President and Actuary, Global Research and Development; and **Tim Rozar**, Vice President and Head of Global Research and Development, RGA Reinsurance Company

While parodying a bewildered President Ford during the 1976 presidential debates, comedian Chevy Chase famously deadpanned, "It was my understanding that there would be no math." The past two issues of *ReFlections* have included high-level discussions of predictive modeling by RGA underwriters Dave Wheeler and Mark Dion. They introduced the readers to many of the exciting applications for data-driven analytics. This article will build upon that foundation by providing a deeper dive into the nuts and bolts of predictive models. We will provide an overview of the statistical frameworks commonly used by predictive modeling practitioners in order to help the reader become better acquainted with the terms and process involved. And with all due apologies to President Ford, yes, there will be some math.

Model Basics

As discussed in prior *ReFlections* articles, there are countless applications for predictive modeling in insurance. Among these are target marketing, underwriting triage, predictive underwriting, fraud detection, experience analysis, pricing optimization and many others. The key unifying feature of these applications is the availability of robust, quality data that can be mined to develop algorithms that can be used to predict the likelihood of the event being modeled. There are many statistical techniques that can be utilized as predictive modeling tools in these insurance applications.

Generally speaking, any statistical model that relies on variables to explain the variance of a target variable can potentially be used for the purpose of predicting future outcomes. In the language of mathematics, we like to build a model as

$$y_i = f(x_{ij}, \beta_j) + \varepsilon_i \qquad \text{(i)}$$

where y_i is called the *response variable, dependent variable,* or *target variable*. This is the variable that has been observed in experience and is to be predicted by model. x_{ij} are called the *explanatory variables covariates, input variables,* or *independent variables*. These are variables that have been observed in historical data, and will be observable in the future for the purpose of forecast. β_j are coefficients to be estimated in the model-building process. ε_i is the error term, which is very important for modeling, but usually not so for prediction, because in most cases we are interested in expected mean values.

Types of Models

Linear regression and Generalized linear models

The most common and simplest model is a linear regression model. This is the bread-and butter model that is taught in almost all colleges, and most of the readers have probably had at least some exposure to it. The model essentially says the target variable is a linear combination of independent variable(s)

$$y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_n x_{in} + \varepsilon = \Sigma_j \beta_j x_{ij} + \varepsilon_i \qquad \text{(ii)}$$

To make a valid linear regression in this basic form, several assumptions are needed. A linear relationship between response and explanatory variables is obviously one, but usually this is not a problem. Either the relationship is inherently linear, or it can be well-approximated by a linear equation over short ranges. In addition, the error term ε_i must follow a normal distribution with mean value at zero and a constant variance, i.e. $\varepsilon_i \sim N(0, \sigma^2)$. Other requirements include: y_i is representative of the population, observations are independent from each other, and x_{ij} is error-free, etc.

A common method of estimating β_j is the least squares method, in which β_j is chosen such that $RSS = \sum_i (\hat{y}_i - y_i)^2 = \sum_i (\Sigma_j \beta_j x_{ij} - y_i)^2$ is at its minimum, where RSS stands for Residual Sum Square, and $\hat{y}_i$ is the fitted value. There are closed form solutions for β_j in matrix form. The other estimation method to find β_j is maximum likelihood in which the product of probability at all data points is at its maximum. Under the normal distribution, it can be proven in mathematics that both estimations will give the same result.

Unless given a very small data set, it is not possible to build a real model just with pen and paper. One has to rely on computing software to find β_j. The choice of statistical software is quite abundant; options include as R, SAS, SPSS, MatLab, MiniTab, etc. In fact, for a very small simple application, one can even use Microsoft Excel's built-in functionality by selecting "Data" -> "Data Analysis", although it has the limit of only 16 explanatory variables. For a large or complicated model, computing software is the only viable choice. Among the actuarial community, the two most commonly used are R and SAS. The R is free software under GNU license, while the latter one is a commercial product. R is unique, not only because it is free, but also because there is a large online community and a core statistics team to support it. One has a wide choice of educational and academic materials about R, and there will never be a shortage of statistic tools in R to build any particular model. As of now (October 2012), there are about 4,000 packages available on top of the already abundant basic tools that come with the R system, and the number is still growing.

A linear regression is very basic, yet very powerful and efficient. One can easily find a wide range of applications in almost all industry fields. However, one can hardly find any real application in the insurance industry. The main reason is not because of the ignorance of actuaries, but the unique business model and data structure of the insurance industry in which the assumptions of the linear regression model are no longer valid. For example, we know the number of claims in a certain group over a period of time is a Poisson distribution where the variance is not a constant but equal to the mean value. In this case, a linear model can not be used to describe the process of why a certain number of claims are observed. Other examples may include claim amount, which follows a Gamma distribution, or mortality rate on binomial distribution.

Luckily, the advance of statistics in the past few decades have prepared us with another model called generalized linear model (GLM). As the name indicates, this model is a natural extension of linear model. We can write the model as

$$g(E(y_i)) = g(\mu) = \eta = \Sigma_j \beta_j x_{ij} \quad or \quad E(y_i) = \mu = g^{-1}(\eta) = g^{-1}(\Sigma_j \beta_j x_{ij}) \qquad \text{(iii)}$$

where g(…) is called the link function which links the expected mean value of target variable and the linear combination of independent variable(s).

Compared to the linear model, the normal distribution assumption is no longer needed. Instead, y_i is required to belong to the exponential family of distributions, which is broader and includes most distributions we find in insurance application, such as Poisson, binomial, Gamma, etc. The expansion of distributions also accommodates the variance structure that comes naturally with the distribution. For example, in the Gamma distribution, the variance is proportional to the square of mean. The introduction of the link function makes it possible to drop the strict linear relation between y_i and x_{ij}, resulting in a very flexible model. It is worth pointing out that the logarithm

could be used as a link function for various distributions. The unique feature of the logarithmic function is that the inverse function is an exponential function such that the additive linear combination in its original form now becomes multiplicative factors. This makes GLM a very powerful tool in the insurance industry as many applications traditionally have multiplicative factors to account for various parameters, such as risk class, substandard rating, industry, location, etc. Of course, normal distribution is also a member of exponential family, and the basic linear regression model is a natural part of GLM.

Table 1 GLM: Link function, variance and application

Distribution	Link Function	Variance V(μ)	Sample Application
Normal	Identity	1	General Application
Poisson	Log	μ	Claim Frequency, Counts
Binomial	Logistic	$\mu(1-\mu)$	Retention, Cross-sell, UW
Gamma	Log	μ^2	Claim Severity
Poisson/Gamma Compound	Log	$\mu^p, p\in(1,2)$	Pure Claim Cost and Premium
Inverse-Gaussian	Log	μ^3	Claim Cost

As GLM covers most distributions that are found in insurance and includes various link functions, it is powerful and versatile, and is currently the main focus of PM in insurance. Its applications cover almost all aspects of the insurance business, such as underwriting, actuarial applications (pricing, reserves, experience study, etc.), claims administration, policy management, sales and marketing, etc. Please refer to Table 1 GLM: link function, variance and application.

Decision tree/CART

Besides GLM, another type of model that one may often hear of is an algorithm that is based on decision tree. In its simplest form, data are split into smaller sections, called leaves, such that data in each leaf will be homogeneous to a certain degree and the variance in the data can be explained by a chain of splits on a series of variables. Certain criteria are used to determine which variable to split and at which value so that the split will be optimal.

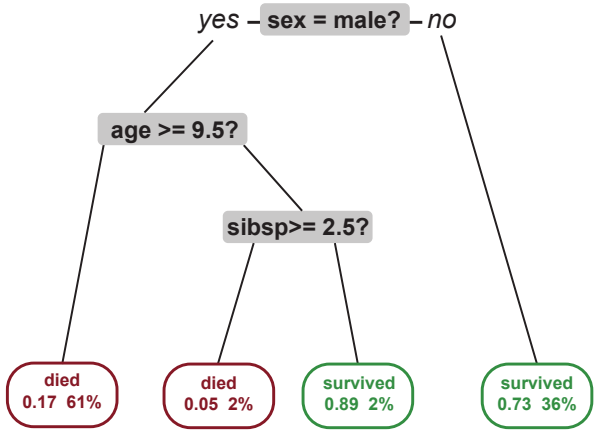
The most-popular decision-tree-based model is the Classification And Regression Tree, also referred as CART. As the name indicates, one can use this model for both regression and classification. For regression, the target variable is a continuous amount and the model is used to calculate the expected mean value. In this case, the sum of square error is used as a criterion to select split point. While for classification, the goal of the model is to separate data into two or more groups. There are several options to accomplish this, such as Gini measure, entropy, etc.

The main advantage of the CART model is its intuitiveness and simplicity. When one lays out the tree diagram and presents it to audience, it is very easy to understand and discuss. For example, the Figure 1 A CART model shows a CART model to explain the difference of mortality rates for Titanic passengers. The decimals at the bottom of each leaf are the probabilities of survival, and the percentages are a fraction of the observations. Considering how split variables are chosen and at what value to split, the model itself is quite sophisticated, yet it is intuitively simple for audience to grasp the essence of the model without complicated math involved. Other advantages include the non-parametric nature in which one does not have to specify a distribution as assumption, and the automatic handling of possible missing variables. As no model is perfect, the main issue with using the CART model is its low efficiency in dealing with linear relationships and its sensitivity to random noise.

Actually, we have already seen this type of model in the insurance business. Think of the process in underwriting, where the information about the applicant will go through an array of decision-making points and finally reach its final underwriting results. This is exactly the same idea of the CART model, although the underwriting processes are built based on experience and business expertise, not on statistic algorithms. We believe the current underwriting can be further improved with the help of a decision tree algorithm.

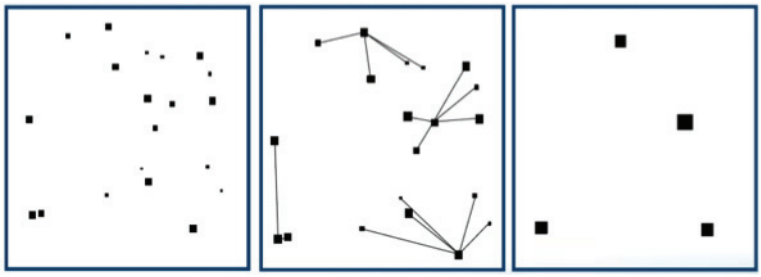
Besides the CART model, there are some other algorithms that are based on the decision tree, but instead of only one decision tree, a group of decision trees are built to extract more information from data. These algorithms are usually much more advanced and sophisticated, but also hard to interpret and gain business insights from. Examples include random forests and Ada-boosting.

Figure 1: A CART model

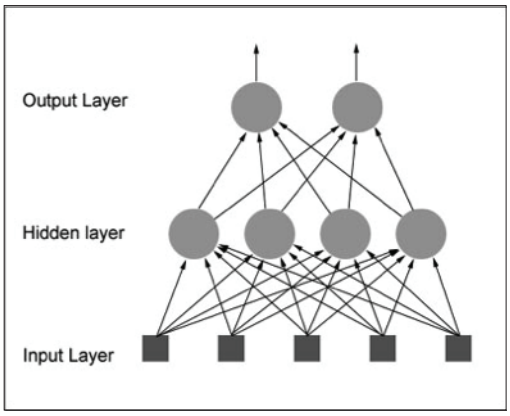


Other models

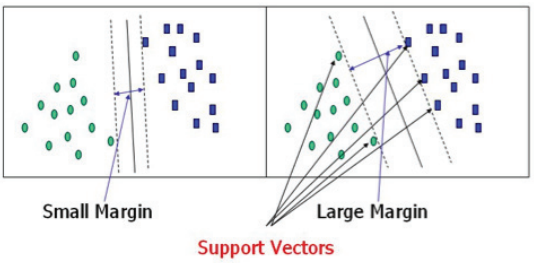
The advance of statistics has brought us more sophisticated models than are discussed above that will potentially find their ways to the insurance applications. Many of them have been utilized in other industries under such names as "business analytics", "big data", or "data mining". Some of them may well be suitable for applications in insurance, and a few examples are presented here for illustration.



Clustering. This algorithm is used to organize data points into groups whose characteristics in each group share similar distributions. It is an ideal candidate model for applications in classification, especially when the target variable is unknown or not certain. There are many different algorithms to form cluster, but the most popular and simplest is based on Euclidean distance in multidimensional space. One may apply the clustering for market segmentation to find group of customers that will buy similar merchandises, for identification of effective advertisement for different consumer groups, for recommender systems, etc. In actuarial science, clustering is a very useful tools for in-force cells compression or scenario reduction, especially when a detailed seriatim study is needed or a large number of scenarios have to be simulated.



Neural Network. Also called artificial neural network, the neural network model has its deep root in biological neural networks. The algorithm mimics the interconnected biological neural cells and uses weights for each connection to model patterns in data or relation between inputs and outputs. This model is very powerful in mathematics such that it can replicate any distribution in theory. Its applications dated back to the 1990s and today one can find its usage in almost every industry. The neural network is essentially a black-box approach, and it is very hard to interpret the model once it is built. Although its effectiveness and predictive power have been proved in practice, the model cannot help to better understand the business and provide insightful clues to improve it, which limits its practical applications.



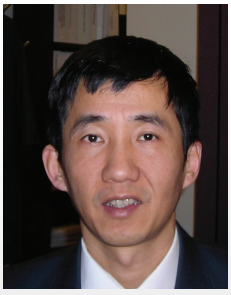
SVM. This refers to support vector machine. The basic idea is to split data into two groups in such a way that the separation margin between them is at a maximum. The real algorithm is much more complicated than the simple idea, with multidimensional non-linear feature space mapping and inclusion of regression as well as classification. This model is generally more accurate than most other models, and is very robust to noise and less likely to have an over-fitting problem. Although it is not totally a black-box algorithm, it is still hard to interpret the model and may take long computing time for a complicated model. Nevertheless, it has great potential in applications in insurance where applicants are segregated into different premium classes based on their risk profiles.

The choice of a model that is the best fit to a specific business purpose does not have to be limited to the models that have been briefly discussed here. There are certain rules to follow when selecting a model, but there is also a combination between science and art when one has the freedom to choose between varieties of options. The most advanced and sophisticated model is not necessarily the best choice for a particular business situation. More often than not, some simple models such as GLM may well meet the accuracy requirement and produce desirable results. As long as a model can meet the demand of real business, it will be much more effective to choose a simple model than a complicated one.

Conclusion

It should be clear by now that predictive modeling provides a wide range of potential applications for insurance companies. Whether it is a logistic regression model of fraud risk, a Cox proportional hazard model of mortality or a CART model of disability claims, the same core objectives are sought – maximizing the value of data to improve business processes and customer experiences.

The statistical concepts described in this article, although technical in nature, provide some of the background needed for understanding, developing and deploying these models. Far too often the statistical nature of the models creates uneasiness for those without a rigorous training in statistics. Similarly, statistical experts often lack the topic specific experience of the businesses for which they are developing models. Fruitful predictive modeling efforts will require a high degree of collaboration between the statistical modeling teams and the business unit experts in order to maximize the respective skills and knowledge of both. While successful development of predictive models will require access to statistical and analytical capabilities, it also ultimately requires a cultural evolution at the highest levels of the organization to embrace data-driven analytics as a source of competitive advantage. ■

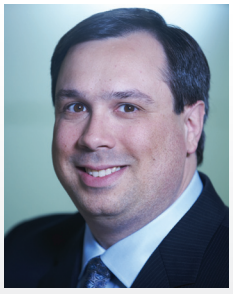


Richard Xu PH.D., F.S.A.
rxu@rgare.com

Richard Xu is Senior Data Scientist and Actuary, Global Research and Development, RGA Reinsurance Company. He leads the company's Global Research and Development's efforts in predictive modeling.

Scott Rushing F.S.A., M.A.A.A.
srushing@rgare.com

Scott Rushing is Vice President and Actuary, Global Research and Development. In this role, he participates in many of the company's large research projects and coordinates predictive modeling projects around the globe.



Tim Rozar F.S.A., M.A.A.A., C.E.R.A.
trozar@rgare.com

Tim Rozar is Vice President and Head of Global Research and Development. He oversees the company's experience analysis, predictive analytics, research and innovation activities worldwide.

By Sheetal Salgaonkar M.D.
Medical Director, Medical Services
RGA Services India Private Ltd

> "The greatest disaster that can happen to a patient with tuberculosis is that his organisms become resistant to two or more of the standard drugs. The development of drug resistance may be a tragedy not only for the patient himself but for others. For he can infect other people with his drug-resistant organisms."
>
> From *Chemotherapy of pulmonary tuberculosis*, by John Crofton BMJ 1959, 5138(1):1610–1614).

Introduction

Tuberculosis, or Koch's disease, has remained a challenge to mankind for centuries. More than a century after the *bacillus* responsible for the disease was first identified and decades after the first antibiotic-based treatments appeared, TB continues to thrive. It is ironic that it continues to be a serious threat well into the antibiotic era. Every aspect of pathogenesis is known and the scientific strategy is well-defined. The helplessness of the medical profession is not due to paucity of knowledge but probably due to lack of cohesiveness. To add to this vulnerability is the complexity of multi-drug-resistant TB. In recent years, global attention has turned toward the evolving burden of drug resistance. Multi-drug resistant tuberculosis (MDR–TB) has emerged in alarming proportions partly fuelled by the HIV epidemic especially in the poverty ridden nations. MDR has led to a significant health dilemma in some countries and is a major impediment to effective global TB control. Extensively drug-resistant TB (XDR–TB) was first reported in 2006 but has now been documented on six continents. These trends are critically important for global health, since drug-resistant TB mortality rates are high and second- and third-line agents for the treatment of drug-resistant TB are less potent and less tolerable than first-line therapies. This article discusses the various aspects of multi-drug resistant TB.

Global Burden of TB

Since Robert Koch's 1882 discovery of Mycobacterium tuberculosis, substantial progress has been made in tuberculosis (TB) control. Nevertheless, in the latter part of the 20th century, a long period of neglect of both quality program implementation and research led to persistently high TB incidence rates and failure to develop new tools to adequately address the problem. Today, most of the world continues to rely on the same diagnostic test invented by Koch approximately 125 years ago and on drugs developed 40 years ago. While both preventable and curable, TB remains one of the world's major causes of illness and death and is one of the most frequent causes of death in people infected with HIV in resource poor countries. Overall, one-third of the world's population is currently infected with the TB bacillus.

5-10% of people who are infected with TB bacilli become sick or infectious at some time during their life. Someone in the world is newly infected with TB bacilli every second.

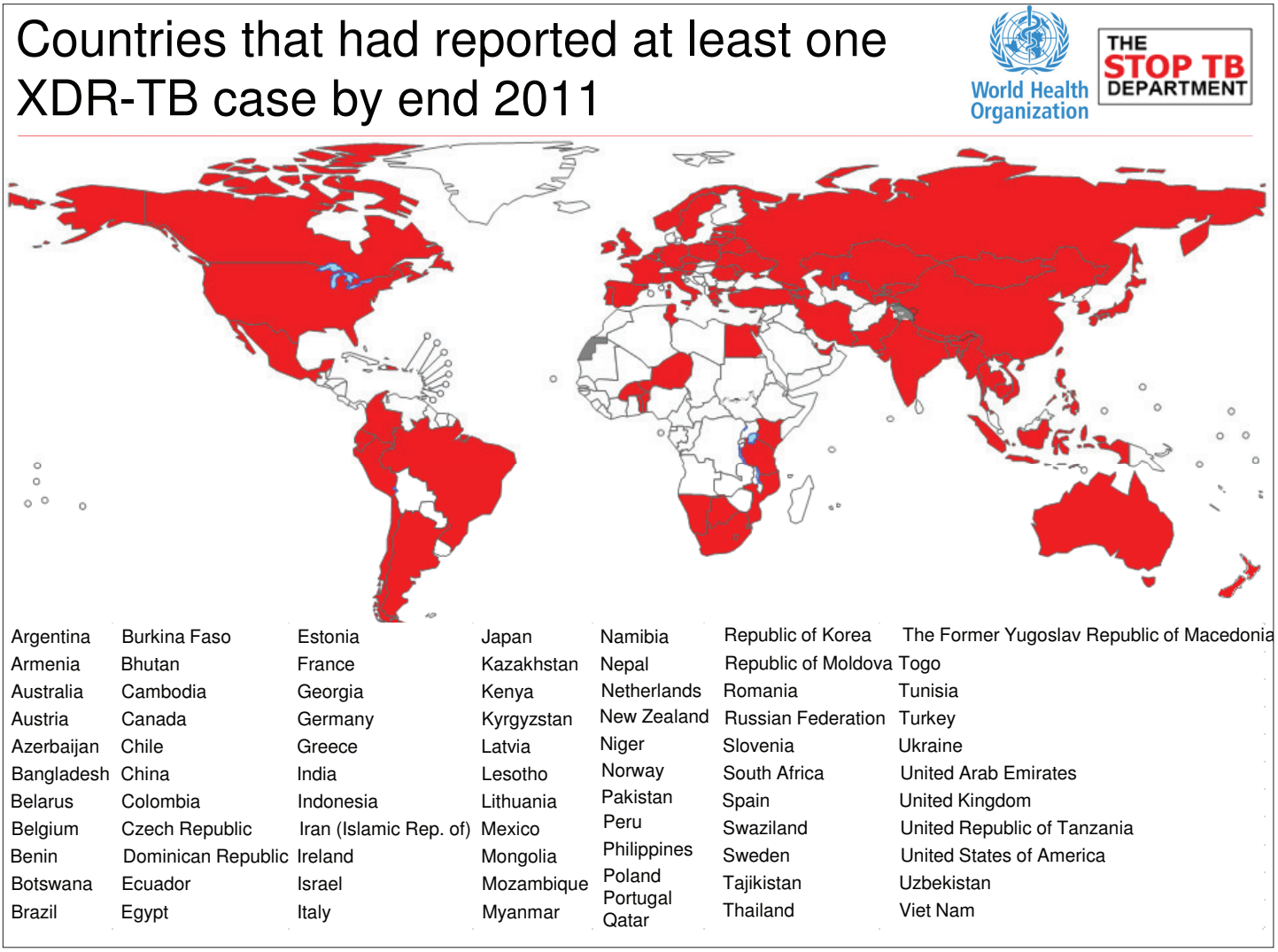
On average, someone dies from TB every 15 seconds and over 2 billion people carry strains of Mycobacterium tuberculosis.

As per Global tuberculosis control: World Health Organization (WHO) report 2010, there were an estimated 9.4 million new cases of TB and 14.0 million prevalent cases causing death to 1.3 million people in 2009.

TB burden is not evenly spread and TB disproportionately affects people in resource-poor settings, particularly those patients whose immune systems are weakened by HIV especially those in Asia and Africa. Twenty-two countries are considered "high-burden countries (HBCs)", which account for approximately 80% of new TB cases each year; most HBCs are in Africa and Asia. India, China, Indonesia, South Africa, and Nigeria have the highest number of new TB cases in the world.

Magnitude of Multi-drug Resistant Problem

Drug-resistant TB has been reported since the early days of introduction of chemotherapy, but the emergence of multi-drug-resistant tuberculosis (MDR-TB) with ominous progression to extensively drug-resistant tuberculosis (XDR-TB) and recently extreme form of XDR–TB has been an area of growing concern. Though unfortunate, yet a reality is that M/XDR TB are iatrogenic problems – the result of mismanagement of antituberculosis drugs through poor TB control, drug-prescription errors and no adherence of patients to treatment. However, the extent of the problem remains underestimated or unknown in many settings owing to insufficient laboratory capacity and inadequate policies to detect drug-resistant TB patients accurately and in a timely manner. Multidrug-resistant TB (MDR-TB) has become a serious threat to global control as a result of the difficulties in diagnosis and treatment and the associated high cost to TB control programs. In 2009 only 11% of the estimated MDR-TB cases among notified TB cases globally were enrolled on treatment. Alarmingly, WHO estimated 650,000 MDR-TB cases in 2010. By the end of 2011, 77 countries have reported at least one case of XDR-TB. Over 85% of the world's estimated number of incident MDR-TB and XDR-TB cases occur in 27 countries. Nearly 50% of the world's burden of MDR-TB cases is found in China and India (highest absolute numbers). In parts of north-west Russia, and in some eastern European countries, up to 25% of new TB patients have MDR-TB. Treatment failures are higher among new multi-drug resistant TB cases [10%] than among new susceptible cases [0.7%].



Classification of Drug-Resistant TB

Drug resistance can be simply defined as the temporary or permanent capacity of organisms and their progeny to remain viable or to multiply in the presence of the concentration of the drug that would normally destroy or inhibit cell growth.

Drug resistance can be classified according to:

A] Prior exposure to drug.

1. Primary Drug resistance: The presence of drug resistance to one or more anti-TB drugs in a TB patient who has received either no or less than one month of prior TB chemotherapy.

2. Secondary Drug Resistance: Resistance to one or more anti-TB drug which arises during the course of treatment usually as a result of non-adherence to the recommended regimen or faulty prescribing. This is found in a patient who has received at least one month of anti-TB treatment.

B] Specific drugs to which TB bacilli are resistant: The below case definitions are used to allow proper patient registration and notification; to facilitate case allocation to appropriate treatment categories and case evaluation.

Four categories have been identified:

1. **Mono-resistant TB:** resistance to one anti-TB drug; INH monoresistance is more common than rifampicin or pyrazinamide. Rifampin monoresistance may be more likely to develop in HIV-infected patients with advanced immunosuppression (e.g., CD4 cell counts <100/microL) and treated with intermittent antituberculous therapy (i.e., once or twice weekly) rather than daily therapy.
2. **Poly-resistant TB:** resistance to more than one anti-TB drug, other than both isoniazid and rifampicin.
3. **Multi-drug resistant TB (MDR-TB):** TB caused by strains of Mycobacterium tuberculosis that are resistant to at least isoniazid and rifampicin (the most effective anti-TB drugs); with or without resistance to other first-line drugs.
4. **Extensively drug-resistant TB (XDR-TB):** resistance to isoniazid and rifampicin (i.e., MDR-TB) as well as any fluoroquinolone and any of the three second-line injectables (amikacin, capreomycin, and kanamycin).

Totally Drug Resistant TB (XXDR–TB) – refers to TB strains that are resistant to all the first- and second-line TB drugs. However, the lack of drug susceptibility testing often made it unclear whether it was just some or all of the second-line drugs to which these strains were resistant. The term "totally drug resistant" tuberculosis is not yet recognized by the WHO and is now still defined as extensively drug resistant tuberculosis (XDR-TB). These cases are extremely difficult to treat.

C] Site of MDR-TB: according to pulmonary or extra-pulmonary involvement:

Pulmonary MDR-TB refers to disease involving the lung parenchyma only.

Extra-pulmonary MDR-TB refers to organs other than the lungs, e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges. The definition of an extrapulmonary case with several sites affected depends on the site representing the most severe form of disease.

The treatment strategy is the same for patients with pulmonary and extrapulmonary MDRTB. However, drugs should be prescribed according to the site e.g., cerebrospinal fluid: in central nervous system MDRTB involvement, the regimen should use drugs that have adequate penetration into the e.g., isoniazid, pyrazinamide, rifampicin, protionamide/ethionamide and cycloserine, and avoid p-aminosalycilic acid and ethambutol which have poor or no penetration.

Factors Responsible for Resistance

One of the most important factors for developing resistance is the prescription of inadequate treatment regimens which entails giving lesser drugs or adding a single drug to a failing regime.

Defaulting on treatment regimes by the patient is also another important factor for drug resistance.

Table 1: Various factors contributing to drug resistance

Factors Leading to Drug Resistance	
Type of Factors	**Factors Associated with Drug Resistance**
1. Clinical Factors	Unreliable treatment regimens by doctors ▪ Lesser number of drugs ▪ Inadequate dosage duration
	Addition of a single drug to a failing regimen
	Easy availability of drug in private sector
	Poor drug supply
	Poor quality of drugs
2. Biological factors	Initial bacillary population
	Local factors in host favorable for multiplication of bacilli
	Presence of drug in insufficient concentrations
3. Sociological factors	Irregular intake/ inadequate duration
	Neglect of disease
	Ignorance
	Lack of health education

Source: Suryakant et al, BioScience Trends. 2010; 4(2):48-55

Mechanisms of Resistance

The tubercle bacilli have unique characteristics which endow them with natural resistance to many commonly used antibacterial agents which explains why only a few drugs are effective against M. Tuberculosis, and why they can develop resistance to anti-TB drugs through chromosomal mutations.

- The hydrophobic cell envelope of Mycobacteria is a natural barrier to many drugs.
- The bacilli also have transporters which flush out the drugs.
- Moreover, they can hydrolyze or modify the drug by synthesizing necessary enzymes.
- Resistance to isoniazid can occur due to mutations in the katG, InhA, and kasA genes, resistance to rifampicin can be affected by mutations in the rpoB gene. Others include gyrA and gyrB leading to ofloxacin resistance and rpsL and rrs leading to streptomycin.

Diagnosis of MDR–TB

MDR-TB cannot be differentiated from drug-susceptible TB through physical examination alone. No form of TB can be diagnosed solely through symptom review and physical exam as clinical signs and symptoms of TB and MDR-TB are often non-specific. A confirmed diagnosis of MDR-TB, however, can only be made by demonstrating in vitro resistance to isoniazid and rifampicin through drug susceptibility testing (DST) or rapid molecular test of the M. tuberculosis isolate from the patient; therefore, MDR-TB is a laboratory diagnosis.

A careful history must be obtained prior to initiation of treatment, for clues that drug resistance may be an issue of concern, e.g., demographic and historical features that should raise the suspicion of drug-resistant TB.

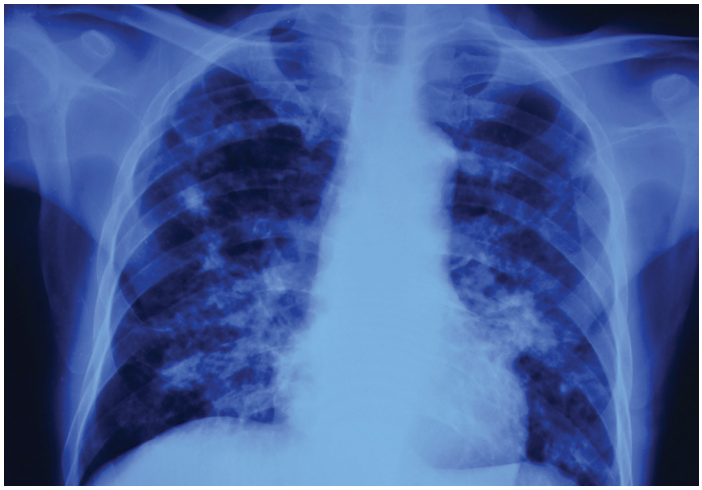


Table 2: Risk Groups for MDR-TB

S.No	Risk Groups for MDR-TB
1	MDR-TB suspects may include:
	Failures of retreatment regimens
	Failures of new patient regimens
	Failures of TB treatment in the private sector
	Relapses and defaulters who are smear-positive at month 3 of retreatment
	Symptomatic contacts of a known MDR-TB case
2	They also may include (depending on national guidelines):
	Patients with HIV
	Patients who remain AFB sputum smear-positive at month 3 of new patient treatment
	Patients who have exposure in institutions that have MDR-TB outbreaks or live in a high MDR-TB prevalence setting such as a prison
	Patients who live in areas with high MDR-TB prevalence
	Patients with a history of using TB drugs of poor or unknown quality
	Patients receiving treatment in programs that operate poorly (especially recent and/or frequent drug stock-outs)
	Co-morbid conditions associated with malabsorption or rapid-transit diarrheas

Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008

There are several tests that can assist the diagnosis of TB and extent of drug resistance. Among them are:

- Smear microscopy
- Liquid and solid culture
- Drug susceptibility testing
- Molecular Tests
    - Line probe assay
    - Xpert MTB/RIF
    - MTBDRplus

Smear Microscopy

M. tuberculosis is classified as an acid-fast bacilli (AFB), meaning that, once stained, the bacteria cannot be decolorized by acid alcohol. In most many settings, TB diagnosis can be made by the presence of AFB in sputum smear specimens as it is highly specific for the M. tuberculosis complex in high TB prevalence settings. Smear microscopy cannot distinguish viable from non-viable organisms, nor differentiate between drug-susceptible and drug-resistant M. tuberculosis or between different species of mycobacteria. Sputum acid-fast bacilli (AFB) smear examination misses the diagnosis of TB in 50-70%.

The main uses of smear microscopy in the management of drug-resistant TB are therefore limited to:

- Assessing the initial infectiousness of patients;
- Deciding which specimens can be used for different culture and drug susceptibility testing methods (i.e., smear negative specimens cannot be tested using certain molecular DST methods); and
- Confirming that organisms growing on (or in) culture media are mycobacterium rather than contaminants.

Culture

Bacteriologic culture is the most sensitive method for confirming TB diagnosis. Both solid and liquid cultures are used in microbiology laboratories for TB. Liquid cultures deliver quicker results than solid (2-4 weeks vs. 6-8 weeks) and have higher sensitivity. However, they are more costly and require a higher degree of laboratory capability.

Drug Susceptibility Test (DST)

DST is performed to confirm MDR-TB or any type of drug resistance in a patient. Generally DST is done from a cultured specimen. Conventional DST methods can take an additional 9-12 weeks after smear. If the strain grows in the presence of a given drug, it is said to be resistant to that drug but if growth is inhibited by that drug the strain is said to be susceptible to that drug. The reliability of DST for second-line drugs is not as good as for first-line drugs and its limitation must be kept in mind when interpreting DST results.

For resource-limited settings, WHO has recommended interim use of microscopic observation of drug susceptibility (MODS) and nitrate reductase assay (NRA) for direct testing of sputum specimens, and colorimetric redox indicator methods, MODS and NRA for indirect DST of M. tuberculosis isolates.

Molecular Tests

These assays are very important for early and rapid detection of drug resistance. Since the assays do not depend on culture, they yield results even in specimens that were contaminated or had no growth. Molecular testing is successful even when the AFB smear was negative. Limitations include cost, identification of only rifampin or isoniazid resistance, and inability to identify which patients are "sputum smear positive" for infection control and treatment monitoring purposes.

- **Linear Probe Assay (LPA):** A molecular line probe assay or DNA polymerase chain reaction (PCR)-based test can be directly on smear–positive sputum and provides molecular resistance results within 48 hours. Data from systematic reviews and meta-analyses evaluating LPA against conventional DST methods showed that LPAs are highly sensitive (>=97%) and specific (>=99%) for the detection of rifampicin resistance, alone or in combination with isoniazid (sensitivity >=90%; specificity >=99%), on isolates of M. tuberculosis and on smear-positive sputum specimens.

  WHO has recommended the use of commercial LPA in direct testing of smear-positive sputum specimens and on isolates of M. tuberculosis complex for early detection of MDR-TB.

- **Xpert MTB/RIF:** The Xpert MTB/RIF test was approved by WHO for use in December 2010. The assay provides results directly from sputum within 100 minutes. Xpert MTB/RIF is a TB-specific, automated, cartridge-based nucleic amplification assay that uses a real-time PCR method involving short segments of single-stranded DNA called molecular beacons. In comparison with microscopy, the use of Xpert MTB/RIF is expected to increase the diagnosis of drug-resistant TB by three times, and double the yield of TB/HIV diagnoses.

  The development of the Xpert MTB/RIF assay for the GeneXpert platform marks the first time a molecular test is simple and robust enough to be introduced outside conventional laboratory settings. Xpert MTB/RIF detects M. tuberculosis as well as mutations which confer rifampicin (R) resistance with a high degree of specificity. The test has been recommended for use in all MDR-TB suspects and HIV-positive patients as the first diagnostic test and other suspects when resources permit. Xpert MTB/RIF detected rifampicin resistance with 99.1% sensitivity and excluded resistance with 100% specificity.

- **MTBDR plus** is a molecular probe capable of detecting rifampin and isoniazid resistance mutations (rpoB gene for rifampin resistance; katG and InhA genes for isoniazid resistance).

  Despite the availability of rapid culture and molecular assays, we still need conventional microscopy, culture and DST in solid medium for confirming diagnosis, monitoring treatment, and epidemiological studies.

HIV and MDR – the cursed duo

- Worldwide, tuberculosis is the most common opportunistic infection affecting HIV-seropositive individuals.
- TB is the leading cause of death among persons with HIV infection and almost one in four deaths among people with HIV infection is due to TB.
- There is a grave concern regarding the increase in HIV-associated TB and the emergence of MDR-TB in both magnitude and severity of the TB epidemic. Mortality from MDR-TB and XDR-TB in the high HIV-prevalence region is alarming, with one-year rates reaching 71% and 83%, respectively.
- HIV co-infection is an important challenge for the prevention, diagnosis and treatment of MDR-TB. 15% of people with HIV will have a false negative result from a TB sputum smear test/negative tuberculin test. This can result in a large number of cases of active TB disease going undiagnosed.
- The symptoms and screening of HIV-positive patients are the same for TB as for MDR-TB but more vigilance is required due to worse

outcomes in co-infected patients with DR-TB. People living with HIV are more likely to have smear-negative TB or extrapulmonary TB.

- HIV infection also requires an adjustment of diagnostic steps and reasons for treatment. The diagnosis of TB in an HIV-positive person is more difficult due to lower bacillary burden, extrapulmonary presentations and difficulty in differentiating from other pulmonary or systemic infections.

- WHO recommends that all HIV-positive patients with a suspicion of TB receive an Xpert MTB/RIF test as the first diagnostic test where possible. If resources are not available to test all patients, prioritizing DST for patients with increased risk of MDR-TB or low CD4 count may be considerable.

Principles of Chemotherapy of TB

The goals of treatment of TB are to ensure cure without relapse, to prevent death, to impede transmission, and to prevent the emergence of drug resistance.

Long-term treatment with a combination of drugs is required.

A] **Treatment of drug susceptible TB** uses the first line drugs [Group 1] these have the greatest bactericidal activity when used for TB treatment. Treatment of pulmonary and extrapulmonary TB typically consists of 6 months with 2 phases.

1. An **initial intensive phase** of rifampicin (RIF), isoniazid (INH), pyrazinamide (PYZ), and ethambutol (ETB) daily.
2. A **continuation phase** of RIF and INH for a further 4 months, either daily or 3 times per week, to be administered.

B] **Treatment of multi-drug resistant TB** (MDR-TB) is more difficult than the treatment of drug susceptible TB, and it requires the use of second-line or reserve drugs. [Group 2, 3, 4]

Compared to first-line anti-TB drugs, second-line drugs for the treatment of MDR-TB

- Are much more expensive
- Are less effective
- Have more side effects/toxicities
- Have shorter shelf life

Cure rates for MDR-TB are lower, typically ranging from around 50% to 70%.

Grouping	Drugs
Group 1: First-line oral anti-TB agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2: Injectable anti-TB agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin V(Cm); Viomycin (Vm)
Group 3: Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lvx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
Group 4: Oral second-line anti-TB agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizadone (Trd); para-aminosalicylic acid (PAS)
Group 5: Agents with unclear efficacy (not recommended by WHO for routine use in MDR -TB	Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/ Clavulanate (Amx/CLv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high dose isoniazid (high dose H); Clarithromycin

A total treatment duration of at least 20 months is recommended in patients not having previous MDR treatment.

- During the **intensive phase of treatment**, an MDR-TB patient should take at least four drugs deemed effective (including a parenteral agent), as well as pyrazinamide, which should be included.
- During the **continuation phase**, the patient takes at four oral drugs deemed effective.
- During both phases the drugs are taken daily.

- Patients with MDR-TB can have very high mortality rates, even on treatment.
- If MDR-TB patients are left to take drugs by themselves, a large proportion will not take treatment as directed and predicting who will or will not comply is virtually impossible.
- Healthcare workers or a treatment supporter must take an active role to ensure that every patient takes the recommended drugs, in the right combinations, on the correct schedule, for the appropriate duration by observing each patient swallow the drugs.

Surgery for MDR–TB: Surgery should be considered in patients with persistent culture positive MDR-TB despite effective medical treatment. Surgery mostly benefits those who have localized disease and reasonable lung function with susceptibility to only 2 or 3 drugs. Resection surgery is done as an adjunct to medical treatment. Patients with MDR-TB should continue antituberculous therapy for 18 months following surgery. Published data has shown that the overall cure rate was substantially higher (81-56%) when surgery was more-frequently and aggressively applied. Feasibility and success of surgery appears to be substantially enhanced by nutrient support.

Prevention of MDR–TB: The best way to prevent multidrug-resistant tuberculosis (TB) is by prompt institution of appropriate therapy with efforts to guarantee adherence to therapy.

There are two main approaches to prevent multi-drug resistance:

(a) Identification and treatment of patients with multi-drug resistant tuberculosis. The aim is to identify their disease and to prevent further transmission.

(b) Identification of persons with tubercular infection and their prophylactic treatment. The aim is to prevent the 5-10% risk of subsequent development of disease.

The accepted guidelines for preventing the transmission of tuberculosis in health care settings with special focus on HIV-related issues are:

1. Patients with active tuberculosis must be identified quickly by using the most sensitive and rapid laboratory methods available.
2. Isolation of confirmed or even suspected infectious tuberculosis patients.
3. All diagnosed patients to be started on effective antitubercular therapy by identifying the appropriate regime. Treatment should be in a specialized center with standard laboratory facilities. Never add a single drug to a failing regimen.
4. Patients and health care workers exposed to multi-drug resistant infectious tuberculosis patients should be evaluated regularly for the presence of infection/disease.
5. Patterns of drug resistance should be evaluated regularly in the community.
6. Intermittent therapy is usually not effective and should be avoided in multi-drug resistant tuberculosis.
7. No drug should be kept in reserve and the most powerful drugs (bactericidal) should be used initially and in maximum combinations to ensure that the first battle is won and won permanently.
8. Surgical treatment should be considered as an adjunct to chemotherapy wherever applicable, as results of chemotherapy are very unpredictable.
9. All measures should be taken to persuade and encourage patients not to stop treatment despite all its discomfort as it is the last treatment that stands between the patient and death.
10. WHO has recommended the Three 'I's for TB/HIV: intensified TB case finding, Isoniazid preventive therapy [IPT], and infection control for TB.

Global efforts and Stop TB strategy

- Ambulatory treatment supervision, the origin of directly observed therapy (DOT), was first explored in the 1960s to enhance treatment adherence. It soon became the cornerstone of TB management.

- In response to the resurgence of TB, WHO declared TB as the first global emergency in 1993, and coined DOTS to emphasize DOT with short-course combination chemotherapy using first-line drugs for treatment. Given proper implementation, DOTS can achieve cure rates of at least 90% and prevent MDR-TB.

- However in populations where MDR-TB is endemic, the outcome of the standard short-course regimen remains uncertain. Unacceptable failure rates have been reported and resistance to additional agents may be

induced. As a consequence, there have been calls for well-functioning DOTS programs to provide additional services in areas with high rates of MDR-TB. These "DOTS-plus for MDR-TB programs" were introduced and they consist of a comprehensive approach including the major DOTS principles but technically devoted to the intensive diagnostic and therapeutic management of MDR-TB.

i. The treatment may need to be individualized rather than standardized;
ii. Laboratory services may need to provide facilities for on-site culture and antibiotic susceptibility testing;
iii. Reliable supplies of a wide range of expensive second-line agents;
iv. Operational studies would be required to determine the indications; and
v. Financial and technical support from international organizations and Western governments would be needed in addition to that obtained from local governments.

- WHO has established a Working Group on DOTS-Plus for MDR-TB, to develop policy guidelines for the management of MDR-TB and to develop protocols for pilot projects intended to assess the feasibility of MDR-TB management under program conditions

- The World Health Organization (WHO) has also established a unique partnership known as the Green Light Committee [2000] to lower the prices of and to increase control over second-line anti-TB drugs.

- WHO and its partners have pledged to achieve universal access to diagnosis and treatment of M/XDR-TB by 2015.

Conclusion

The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multidrug-resistant TB (MDR-TB), has become a significant public health problem in a number of countries and an obstacle to effective TB control. Quality-assured culture and DST are indispensable for the diagnosis of M/XDR-TB. M/XDR-TB must be managed very effectively with careful use of second-line drugs to reduce morbidity and mortality and transmission of multi-drug resistant tuberculosis and to prevent the development of XDR-TB. Sound infection control measures to avoid further transmission of M/XDR-TB and research towards development of new diagnostics, drugs and vaccines should be promoted to control M/XDR-TB. WHO emphasizes that good TB control prevents the emergence of drug resistance in the first place and that the proper treatment of multi-drug resistant tuberculosis prevents the emergence of XDR-TB. Multi-drug resistant TB as of now appears to spare the "insured population" as it is a disease of poverty and low socioeconomic status; however, the future remains uncertain. A watchful approach and encouraging response by many countries jointly to battle this mammoth problem may ensure the insurance fraternity will never have to tackle this health dilemma.

> "Fortunately we can prevent the emergence of drug resistance in virtually all cases if we take enough trouble to ensure that the best drug combinations are prescribed and that the patient takes them as directed…If physicians come to apply thoroughly the present knowledge about preventing drug resistance, this [drug resistance] should steadily diminish".
> **Sir John Crofton (1912–2009)**

Sheetal Salgaonkar M.D.
ssalgaonkar@rgare.com

Dr. Sheetal Salgaonkar works from RGA's India office, providing opinion and medical reviews of facultative applications referred from all regional offices in the international division.

Bibliography

1. Global tuberculosis control: WHO report 2010. Geneva, Switzerland: World Health Organization; 2010. (WHO/HTM/TB/2010.7)
2. Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs: World Health Organization Geneva 2008: WHO/HTM/TB/2008.392
3. Salmaan Keshavjee, M.D., Ph.D., and Paul E. Farmer, M.D., Ph.D.N Engl J Med. 2012 Sep 6; 367(10):931-6.: Tuberculosis, drug resistance, and the history of modern medicine.
4. 2010 Global report on surveillance and response:Multidrug and extensively drug-resistant TB (M/XDR-TB)4.Confronting Multidrug-Resistant Tuberculosis: Richard E. Chaisson, M.D., and Eric L. Nuermberger, M.D.N Engl J Med 2012; 366:2223-2224June 7, 2012DOI: 10.1056/NEJMe1204478
5. Global tuberculosis control: WHO report 2010. Geneva, Switzerland: World Health Organization; 2010. (WHO/HTM/TB/2010.7)
6. Prasad R, Garg R. XDR-TB: An emerging threat. Chest India. 2007;8:3–4.
7. Multidrug and extensively drug-resistant TB (M/XDR. TB): 2010 global report on surveillance and response. Geneva, Switzerland: World Health Organization; WHO/HTM/TB/2010.3.
8. Caminero JA. World Health Organization; American Thoracic Society; British Thoracic Society. Treatment of multidrug-resistant tuberculosis: Evidence and controversies. Int J Tuberc Lung Dis. 2006;10:829–37.
9. Surya Kant, Anand K. Maurya, R. A. S. Kushwaha, Vijaya L. Nag, Rajendra Prasad Multi-drug resistant tuberculosis: An iatrogenic problem BioScience Trends. 2010; 4(2):48-55.
10. S.K. Sharma & A. Mohan:Multidrug-resistant tuberculosis: Indian J Med Res 120, October 2004, pp 354-376
11. CDC. MMDR TB: MMWRs. http://www. cdc.gov/tb/publications/guidelines/ MDR_TB.htm
12. 1Kwok-Chiu Chang*, Wing-Wai Yew Management of Difficult Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis: Update 2012:2012 Asian Pacific Society of Respirology
13. Chaisson RE, Martinson NA. Tuberculosis in Africa–combating an HIV-driven crisis. N.Engl. J. Med. 2008; 358: 1089–1092.
14. Espinal MA, Dye C. Can DOTS control multidrug-resistant tuberculosis? Lancet 2005; 365: 1206–1209.
15. Chang KC, Leung CC, Grosset J et al. Treatment of tuberculosis and optimal dosing schedules. Thorax 2011; 66: 997–1007.
16. multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009;9: 153–161.
17. Migliori GB, Besozzi G, Girardi E et al. Clinical and operational value of the extensively drug-resistant tuberculosis definition. Eur. Respir. J. 2007; 30: 623–626.
18. Shah NS, Pratt R, Armstrong L et al. Extensively drug-resistant tuberculosis in the United States, 1993-2007. JAMA 2008; 300: 2153–2160.
19. Mitnick CD, Shin SS, Seung KJ et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N. Engl. J. Med. 2008; 359: 563–574.
20. Kim H-R, Hwang SS, Kim HJ et al. Impact of extensive drug resistance on treatmentoutcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clin. Infect. Dis.2007; 45: 1290–1295.
21. Eker B, Ortmann J, Migliori GB et al. Multidrug- and extensively drug-resistant tuberculosis, Germany. Emerging Infect. Dis. 2008; 14: 1700–1706.
22. Keshavjee S, Gelmanova IY, Farmer PE et al. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet 2008; 372: 1403–1409.
23. Gandhi NR, Shah NS, Andrews JR et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. Am. J. Respir. Crit. Care Med. 2010;181: 80–86.
24. World Health Organization. Global tuberculosis control: WHO report 2011.WHO/HTM/TB/2011.16. 2011.
25. Zhao Y, Xu S, Wang L et al. National survey of drug-resistant tuberculosis in China. N.Engl. J. Med. 2012; 366: 2161–2170.
26. Gler MT, Macalintal LE, Raymond L et al. Multidrug-resistant tuberculosis among previously treated patients in the Philippines. Int. J. Tuberc. Lung Dis. 2011; 15: 652–656.
27. D.W. Connell*, M. Berry*,#, G. Cooke" and O.M. Kon* Eur Respir Rev 2011; 20: 120, 71–84 Update on tuberculosis: TB in the early 21st century
28. WHO. The World Health Report 2004: Changing History.World Health Organization, Geneva, Switzerland, 2004.
29. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. JAMA. 1999;282:677-686.
30. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003; 163:1009-1021.

31. WHO. Global Tuberculosis Control: Surveillance, Planning, Financing. World Health Organization, Geneva, Switzerland, 2006; p. 242
32. Singla R. Management of drug resistance pulmonary Tuberculosis in India. The Cardiothoracic Journal. 1995; 1:312-316.
33. Guidelines for the programmatic management of drugresistant tuberculosis. WHO/HTM/TB/2006. 361
34. Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004: Drug-Resistant Tuberculosis: A Survival Guide for Clinicians.
35. Paramasivan CN, Bhaskaran K, Venkataraman P, Chandrasekaran V, Narayanan PR. Surveillance of drug resistance in tuberculosis in the state of Tamil Nadu. Ind J Tub. 2000; 47:27-33.
36. Trivedi SS, Desai SG. Primary TB drug resistance and acquired Rifampicin resistance in Gujarat, India. Tubercle. 1988; 69:37-42.
37. Jain NK, Chopra KK, Prasad G. Initial and acquired Isoniazid and Rifampicin resistance to M. tuberculosis and its implications for treatment. Indian J Tuberc. 1992; 39:121-124.
38. Datta M, Radhamani MP, Salvaraj R, Paramsivan CN, Gopalana BN, Sudeendraa CR, Prabhakar R. Critical assessment of smear positive pulmonary TB patients after chemotherapy under the district TB programme. TuberLung Dis. 1993; 74:180-186.
39. Crofton J, Chaulet P, Maher D. Guidelines for the management of drug resistant tuberculosis. Geneva WHO, 1997 (Document WHO /TB/96:210).
40. Mukerjee JS, Rich ML, Socci AR. Programmes and principles in treatment of multidrug resistant tuberculosis.Lancet. 2004; 363:474-81.
41. Iseman MD. Treatment of multidrug resistant tuberculosis.New Eng J Med. 1993; 329:784-791.
42. Iseman MD, Madsen L, Goble M, Pomerantz M. Surgical intervention in the treatment of pulmonary disease caused by drug resistant mycobacterium tuberculosis. Am Rev Respir Dis. 1990; 141:623-625.
43. Takeda S, Maeda H, Hayakawa M, Sawabata N, Maekura R. Current surgical intervention for multidrug resistanttuberculosis. Ann Thorac Surg. 2005; 79:959-963.
44. DOTS-Plus Guidelines. Revised National Tuberculosis Control Programme March 2006.
45. Prasad R.Management of multi-drug resistant tuberculosis: Practitioner's view point. Indian J Tuberc. 2007; 54:3-11..
46. Arora VK , Arora Raksha (1st. ed.). Practical Approachto Tuberculosis Management. Jaypee Brothers Medical Publishers (P) Ltd. New Delhi, India, 2006.
47. Singla R. Management of drug resistance pulmonary Tuberculosis in India. The Cardiothoracic Journal. 1995; 1:312-316.
48. World Health Organization. Policy statement: Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). 2008.
49. World Health Organization. Policy statement: automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. WHO/HTM/TB/2011.4. 2011.
50. World Health Organization. Tuberculosis diagnostics: Xpert MTB/RIF test. Available a http://www.who.int/tb/features_archive/factsheet_xpert_may2011update.pdf.
51. World Health Organization. Policy statement: Noncommercial culture and drug-susceptibility testing methods for screening patients at risk for multidrug-resistant tuberculosis. WHO/HTM/TB/2011.9. 2011.
52. Kiet VS, Lan NTN, An DD et al. Evaluation of the MTBDRsl test for detection of second-line-drug resistance in Mycobacterium tuberculosis. J. Clin. Microbiol. 2010; 48:2934–2939.
53. Van Deun A, Martin A, Palomino JC. Diagnosis of drug-resistant tuberculosis: reliability and rapidity of detection. Int. J. Tuberc. Lung Dis. 2010; 14: 131–140.
54. R. Prasad Multidrug and extensively drug-resistant tuberculosis management: Evidences and controversies Lung India. 2012 Apr-Jun; 29(2): 154–159.
55. Zarir F. Udwadia, Rohit A. Amale, Kanchan K. Ajbani, and Camilla Rodrigues : Totally Drug-Resistant Tuberculosis in India :Clin Infect Dis. (2011) doi: 10.1093/cid/cir889.

By Susan L. Wehrman F.L.M.I., A.C.S.
Vice President, Electronic Health Record Initiatives
RGA Reinsurance Company

One of the primary goals of Meaningful Use and the advancement of health information technology (including electronic health records, or EHRs) is that the information is interoperable – that it can be shared among patients and providers. Without interoperability, we are merely trading paper silos for electronic silos.

Currently, paper-based information is exchanged primarily via mail or fax. When we make the leap to exchanging electronic healthcare information (specifically, **Protected Health Information**, or PHI) the likelihood and frequency of data breaches and interceptions increases. Further, many providers do not have the technical or financial resources to deal with encrypting and decrypting data, etc. How can we level the playing field for everyone? Enter the Direct Project.

What is the Direct Project?

Launched in March 2010 as a component of the Nationwide Health Information Network (NHIN), the Direct Project was created to specify a simple, secure, scalable, standards-based way for participants to send authenticated, encrypted health information directly to known, trusted recipients over the Internet. Because using Direct does not require that providers implement software, the platform dramatically lowers costs and barriers to secure health information exchange. Several EHR vendors have developed products that are Direct-ready, enabling providers to send structured health information directly from their EHR using Continuity of Care Document (CCD) standards. That said, it is not necessary to have an EHR in order to use Direct. When users have computer and Internet access, they have the ability to use Direct.

The core mission for the Direct Project is to enable secure transport of information between known parties. Direct users have to establish their own policies and standards for deciding which other Direct addresses to trust:

- The receiver assumes the sender has obtained the patient's consent to transmit the information;
- The sender ensures that it is clinically and legally appropriate to transmit the information;
- The sender and receiver have agreed the purpose for the exchange of information and know the appropriate addresses, etc.

The beauty of the Direct Project lies in its simplicity, in that it is essentially 'secure messaging'; it allows two healthcare entities the ability to directly exchange electronic information via secure e-mail. For example, since the exchange of information is based on a simple point-to-point concept, the sender and receiver do not require common or pre-negotiated patient identifiers. Similar to the exchange of fax or paper documents, there is no expectation that a received message will be automatically matched to a patient or automatically filed in an EHR. Additionally, Direct providers do not have to share or expose their data or establish pointers to specific patient data.

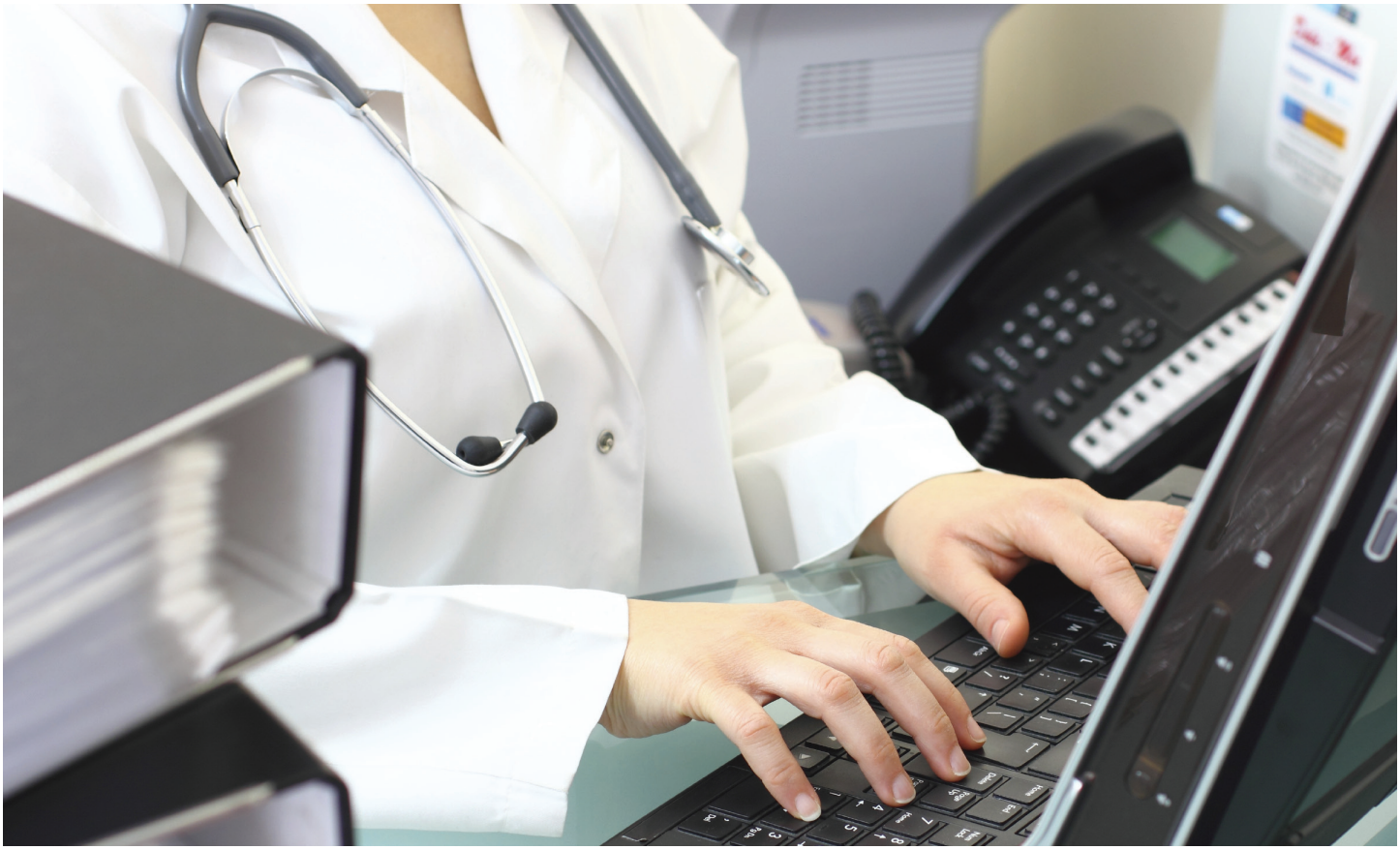
However, it is important to note that one trade-off for this level of simplicity is that the Direct Project alone does not meet the Interoperability Requirements for Meaningful Use.

Interoperability enables two or more disparate systems to communicate information meaningfully, and it requires three prerequisite predefined components: Transport, Content, and Vocabulary. In order for systems to interoperate, they must determine:

- How they will send and receive their messages (e.g., Direct Project-specified transport),
- The structure and format of their exchanged content (e.g., a Continuity of Care Document), and
- What terms they will use within their content (e.g., SNOMED Clinical Terminology).

The Direct Project provides only the first of these three prerequisite components.[1] However, if a provider uses the Direct Project as a means to exchange a

[1] *The Direct Project Overview, October 11, 2010.* http://wiki.directproject.org/file/view/DirectProjectOverview.pdf



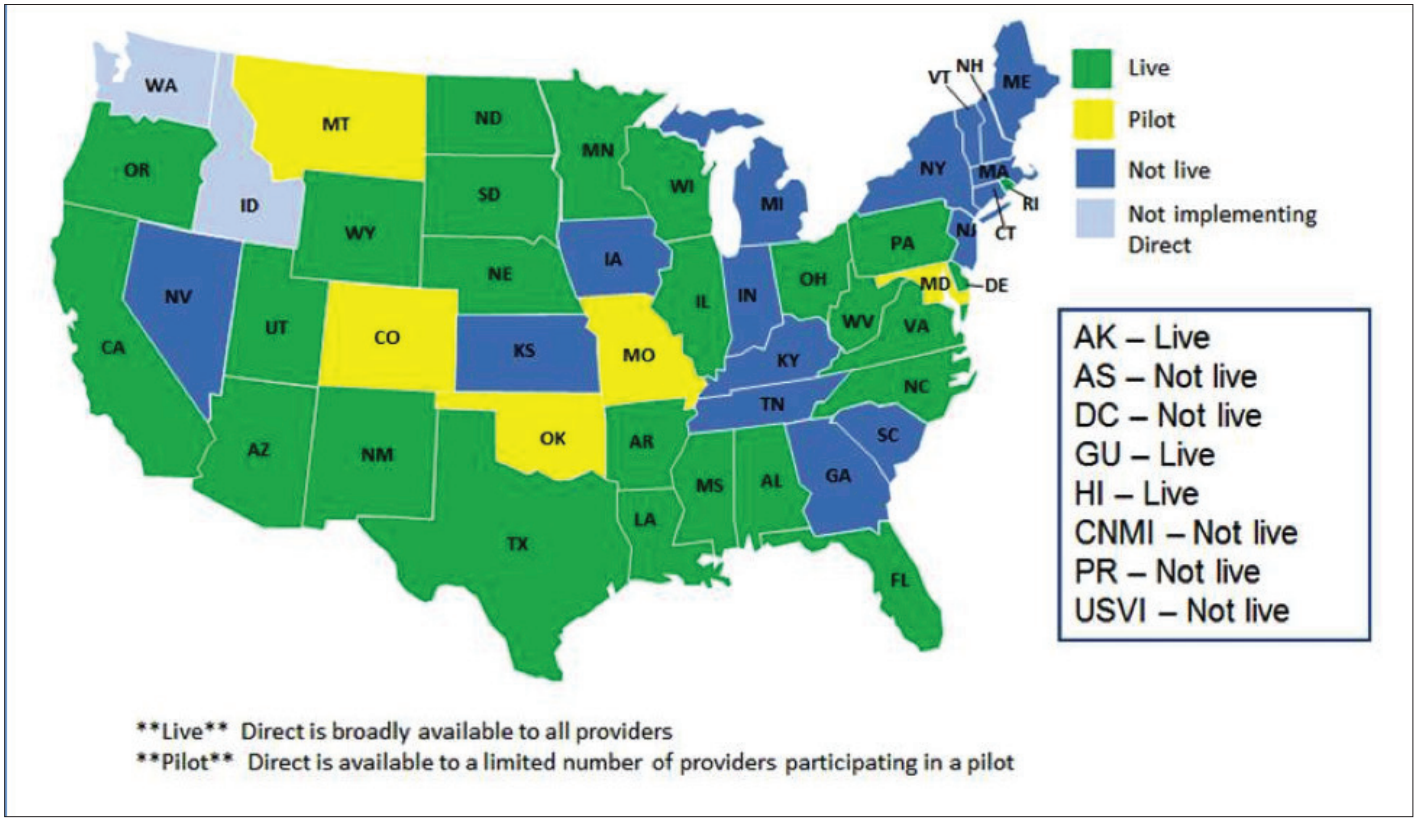
Continuity of Care Document (CCD) – which is a format approved for Meaningful Use – the combination of the two (Transport and Content) meets the criteria for interoperability. Further, when the requirements for Stage 2 of Meaningful Use were released in August 2012, actual use of the Direct Project was included. This means the rules of transport established by the Direct Project are now mandated for all providers, and all certified EHR systems must support it.

Direct is a simple "push" messaging function (also known as "directed exchange"). Therefore a provider could not use Direct to query other healthcare organizations in search of additional patient's information, for example. That would be a type of "pull" function (query and retrieve) and require a Health Information Exchange (HIE). Several U.S. states have built Direct into their HIE plans. In addition to simple messaging, files can be attached to messages for transport between providers. This can include communication of summary care records, referrals, discharge summaries and other clinical documents in support of continuity of care and medication reconciliation.

There are three primary deployment models for Direct. In the first model, an entity sends and receives Direct messages through a web portal offered as a service of a Health Information Service Provider, or HISP – the user experience is much like that of a web-based e-mail account. In the second model, an entity sends and receives Direct messages using a standard e-mail client which has been Direct-enabled, e.g., through a software plug-in or an upgrade to the e-mail client. In the third model, an entity uses an EHR system software that is Direct-compliant, through which it sends and receives Direct messages from within the application.[2]

---

[2] *Direct Project FAQ - State Health Information Exchange, www.statehieresources.org*



Source: www.healthit.gov

Rate of Adoption

Despite a slow start, doctors and hospitals currently share patient health information electronically and securely to support safe care transitions and informed referrals to other providers using the Direct Project services offered by ONC's State Health Information Exchange Program grantees in 40+ states across the nation. In July 2012, functionality of the Direct Project was expanded with new lab messaging capabilities; the Office of the National Coordinator released an implementation guide for electronically reporting laboratory results using Direct Project secure messaging protocols.

Susan L. Wehrman F.M.L.I., A.C.S.
swehrman@rgare.com

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

LONGER LIFE FOUNDATION

The Longer Life Foundation is approaching its 15th anniversary in 2013. The LLF has now funded 74 grants during its history. The results of these studies have helped researchers to sequester larger grants from other funding agencies. These projects have also helped physicians better care for their patients and this work has been useful for the insurance industry. These studies have led to more than 50 publications in peer-reviewed, internationally renowned medical journals that mention the Longer Life Foundation name in the credits section of the papers. This high publication rate attests to the interest, academic rigor and quality of the studies the LLF has funded over the years.

You can read more about these studies and their publications on the Longer Life Foundation website at http://www.longerlife.org/publications.html.

New Grants Awarded in 2012

Study details available at http://www.longerlife.org/current_research.htm

1. **"Long-Term Health Benefits of Calorie Restriction; Does a Low-Protein Diet Slow Aging, Protect Against Cancer and Inhibit Prostate Cancer Growth?" (3rd year)**
   Longevity Research Program: John Holloszy M.D., Director; Luigi Fontana M.D., Ph.D., Associate Director
2. **"A Randomized Control Trial of the Probiotic LGG for Prevention of Side Effects in Patients Undergoing Chemoradiation for Gastrointestional Cancer."**
   Matt Ciorba, M.D.
3. **"CD36 Variants and Stroke Risk Factors" (2nd year).**
   Latisha Love-Gregory, Ph.D.
4. **"A Pilot Study of Adipokines and Caloric Restriction in Patients with Multiple Sclerosis."**
   Laura Piccio, M.D. Ph.D.
5. **"Use of Alzheimer's Disease Biomarkers to Predict Longevity and Disability" (2nd year).**
   Catherine Roe, Ph.D.
6. **"Monomethyl Branched Chain Fatty Acids (mmBCFAs) as Potential Biomarkers for Risk of Obesity-Associated Metabolic Disease."**
   Xiong Su, Ph.D.
7. **"Effects of Iincreased Dietary High-Fructose Corn Syrup on Intrahepatic Triglyceride Content and Lipoprotein Kinetics in People with a Non-Alcoholic Fatty Liver Disease"**
   Shelby Sullivan, M.D.
8. **"Is Aging and its Associated Co-morbidities Due to Diminished Autophagy?"**
   Conrad Weihl, M.D. Ph.D.
9. **"Survival, Disease Co-morbidity, and Assessment of Novel and Genetic Variants for Risk Prediction in the NHLBI Family Heart Study (FamHS)."**
   Mary Kaye Wojczynski, Ph.D.

ON DEMAND WEBCASTS

RGA and industry experts discuss the topics below in our upcoming 2012 webcasts.

AVAILABLE NOW

Underwriting Fraud Prevention

Presenters
Rick Gordon, Second Vice President,
Mortality Management, Sammons Financial Group
Midland National and North American

Lynn Patterson, Chief Underwriter, ING

Moderator
Mark Dion
Vice President, Rules and Education
RGA Reinsurance Company

COMING SOON

Mortality Improvement

Presenters
Peter Banthorpe
Head of Actuarial Research
RGA UK Services Limited

Derek Kueker
Actuary
RGA Reinsurance Company

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

Electronic Health Records

Presenters
Dr. Carl Holowaty
Senior Vice President and Chief Medical Director
RGA Reinsurance Company

David Atkinson
Vice Chairman, Executive Vice President
RGA Reinsurance Company

Moderator
Dave Wheeler
Senior Vice President and Head of Global
Mortality Markets Underwriting
RGA Reinsurance Company

NOTES

RGA®

The security of experience. The power of innovation.