ReFlections

RGA's Global Medical Newsletter

Volume 53, May 2021

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FROM THE EDITORS

Hello and welcome to the May 2021 issue of *ReFlections*! As always, we hope you and your loved ones are safe and well. With COVID-19 vaccine options and accessibility increasing, there is hope for cautious optimism and the ability to anticipate a possible return to a yet-to-be-defined new normal.

This issue features articles from two senior Mumbai-based members of RGA's excellent Global Underwriting Manual (GUM) development team. Sandeepan Basu, Deputy Chief Manager, Research and Manual Development, returns to our pages with a detailed piece about pulmonary and thyroid nodules and their underwriting challenges. We also welcome to our pages Dr. Reema Nathwani Jani, Chief Manager, Global Underwriting, Research and Manual Development, who for her first *ReFlections* article provides an in-depth look at gestational diabetes, a rising risk worldwide.

A Brief Report on gene therapy by *ReFlections* editor Dr. Daniel D. Zimmerman, Senior Vice President, Head of Global Medical, rounds out the issue. Once the realm of science fiction, this rapidly-developing class of therapies is working near-miracles in how clinical medicine can treat various diseases and disorders.

The Longer Life Foundation, RGA's research collaboration with Washington University School of Medicine in St. Louis, continues to make news, expanding its visibility via sponsorships of Internal Medicine Grand Rounds, the first of which this year featured the cutting-edge research of Grant Challen, Ph.D., as well as sponsoring podcasts by epidemiologist Dr. Michael T. Osterholm. Dr. Osterholm is known worldwide for his understanding of infectious diseases and pandemics, and we are proud to be sponsoring two of his weekly podcasts focused on the COVID-19 pandemic. (See article on page 20 for information about accessing these podcasts.)

We hope you find the information in this issue relevant and informative. Please don't hesitate to let us know how we can continue to improve *ReFlections* for you.

Dan and Adela

DEMYSTIFYING RISK STRATIFICATION OF PULMONARY AND THYROID NODULES

Abstract

Underwriting pulmonary and thyroid nodules has always been a distinct challenge. Pulmonary nodules are one of the most common incidental findings on a chest X-ray or a computed tomography (CT) scan. Thyroid nodules, on the other hand, are primarily found on ultrasounds, and are presumed to be present in more than half of the global population. In this two-part article we aim to provide information about both types of nodules, which may help simplify their underwriting challenges by identifying factors that can help quantify their risks and provide precise and appropriate guidance.

Part I: Pulmonary Nodules

Background

Pulmonary nodules are characterized as having a focal rounded or irregular opacity, and measuring <3 cm. They can be well or poorly defined, are generally surrounded by lung parenchyma, and are not associated with lung atelectasis (collapse), lymphadenopathy, or pleural effusion.[1]

A study published in 2015 that tracked incidental pulmonary nodule trends in the U.S. noted that of the 4.8 million study participants who had had a computed tomography (CT) scan between 2006 and 2012, one-third (1.57 million) had an incidental finding of a pulmonary nodule. It was further observed that of these 1.57 million, approximately 4% developed lung cancer within two years of the initial finding.[2]

Evolution of Solitary Pulmonary Nodule Detection and Diagnostic Capabilities

Chest X-rays, historically, have been the test yielding the most frequent discoveries and diagnoses of incidental pulmonary nodules. The advent of CT scans, however, has led to more precise and accurate diagnoses, as it enables smaller or indistinct pulmonary nodules to be detected and then identified with more precision. The growing global frequency of CT scan utilization has been contributing to a marked increase in incidental pulmonary nodule diagnoses over the last two decades.

Studies indicate that prevalence of malignant pulmonary nodules can vary widely, depending on the means of detection. Initial lung screenings, such as CT scans, yield a rate of incidental nodule findings of between 2% and 24%, whereas for malignant nodules the rate is between 2% and 13%. Advanced tests or follow-up exams such as positron emission tomography (PET) scans result in a much higher discovery rate (46% to 82%).[3, 4]

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Sandeepan Basu is Deputy Chief Manager, Research and Manual Development at RGA. Based in Mumbai, India, his focus is on researching medical advances impacting life insurance and incorporating that information in RGA's Global Underwriting Manual.

His experience in life insurance encompasses underwriting, audit, training, and analytics in India, Southeast Asia, and the Middle East, as well as underwriting automation. Sandeepan earned his Bachelor of Pharmacy degree from Manipal College of Pharmaceutical Sciences, Karnataka, India.

Classifying Malignancy Risk
Several frameworks have been developed to classify malignancy risk for pulmonary nodules.

The American College of Chest Physicians (ACCP) guidelines, first published in 2007 and then revised in 2013, utilizes a calculation method developed by investigators at the Mayo Clinic as one of the methods that assesses a nodule's malignancy risk. It takes into account factors such as age, smoker status, location and diameter of the nodule, presence of spiculation, and history of cancer.[4, 5]

In 2015, the British Thoracic Society (BTS) published a set of widely used guidelines from which risk calculators were developed to ascertain the malignancy risk of pulmonary nodules.[6]

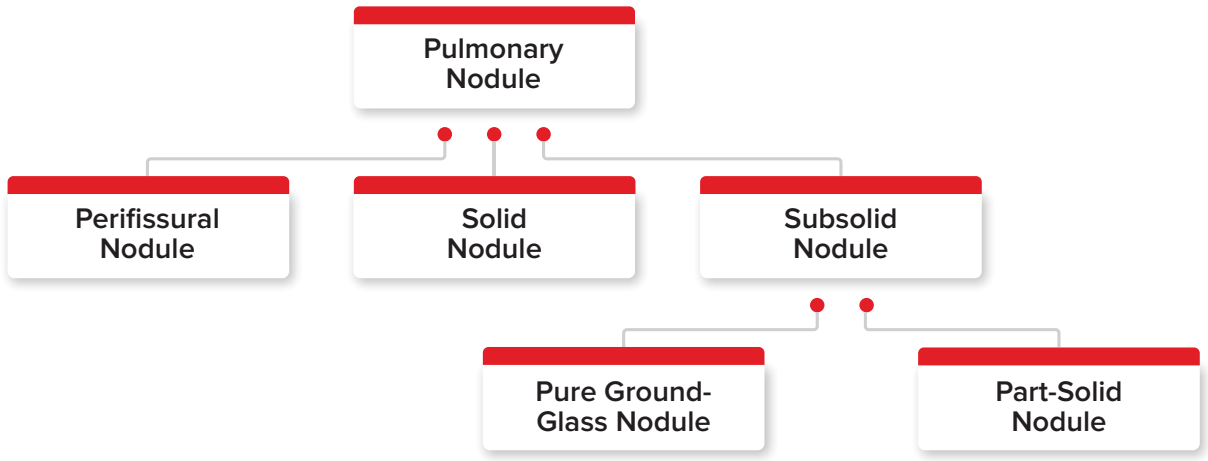
The Fleischner Society's recommendations, which were first published in 2005 and then revised in 2013 and 2017, are today the most widely accepted guidelines for classifying pulmonary nodule risk.[7]

The Fleischner Society guidelines are based on the following factors:

- **Type of nodule**
  Several types of incidental pulmonary nodules are found on chest X-rays or CT scans. Figure 1 shows the three main pulmonary nodule types – perifissural, solid, and subsolid – and the two types of subsolid nodules (pure ground-glass nodule and part-solid nodule). Each of these types are important to understand and differentiate among, as each has its own bearing on the applicant's malignancy risk.
  - **Perifissural nodules (PFNs):** These well-circumscribed nodules usually have smooth margins and are found near pulmonary fissures. Generally, no malignancy risk is associated with these nodules.
  - **Solid nodules:** These are the most common type of pulmonary nodules found on chest X-rays or CT scans. These nodules completely obscure the lung parenchyma. They present the most distinct underwriting challenge when assessing their malignancy risk, as the assessment depends on the nodule's features and associated risk factors.
  - **Subsolid nodules:** These nodules have two subtypes – pure ground-glass and part-solid. They are found more rarely than solid nodules and both carry a higher malignancy risk than solid nodules (Odds ratio [OR] 1.4).
    - Pure ground-glass nodules are nodules without opacity that do not obscure bronchial structure or pulmonary vessels. They generally grow slowly in size over a period of many years.
    - Part-solid nodules contain both ground-glass and solid components. Part of the nodule can completely obscure the lung parenchyma.

      Part-solid subsolid nodules have the highest malignancy risk of all nodule types. Their malignancy rate was 63%, whereas the rate for pure ground glass nodules was 18%.[3, 6, 7, 8, 9]

Figure 1: Classification of Types of Pulmonary Nodules



- **Nodule Size**
  The size of a pulmonary nodule plays an equally important role in determining probability of malignancy, with larger nodules indicating greater malignancy risk.

  For example, according to the Fleischner Society guidelines, a solid nodule of less than 6 mm and associated with factors considered to be low-risk (see Table 1, below) is generally benign and needs no further surveillance or follow-up. On the contrary, a solid nodule exceeding 8 mm may represent a poorer prognosis and would require more frequent surveillance, determined by the risk category with which it is associated.[7]

- **Number of nodule(s) found**
  Multiple pulmonary nodules are also common incidental findings on X-rays or CT scans. Malignancy risk is not necessarily higher if multiple nodules are found. However, closer monitoring may be required in certain cases, based on the "dominant" nodule identified. The dominant nodule is the one that may signify higher risk of malignancy. This may not always be the largest nodule.

  The Fleischner guidelines recommend close surveillance of the dominant nodule, especially when different types and sizes constitute the mix of multiple pulmonary nodules. For example, if a solid nodule and a part-solid nodule are found, the risk assessment should consider the part-solid nodule the dominant nodule due to its higher malignancy risk, even if the solid nodule is slightly larger in size.[7]

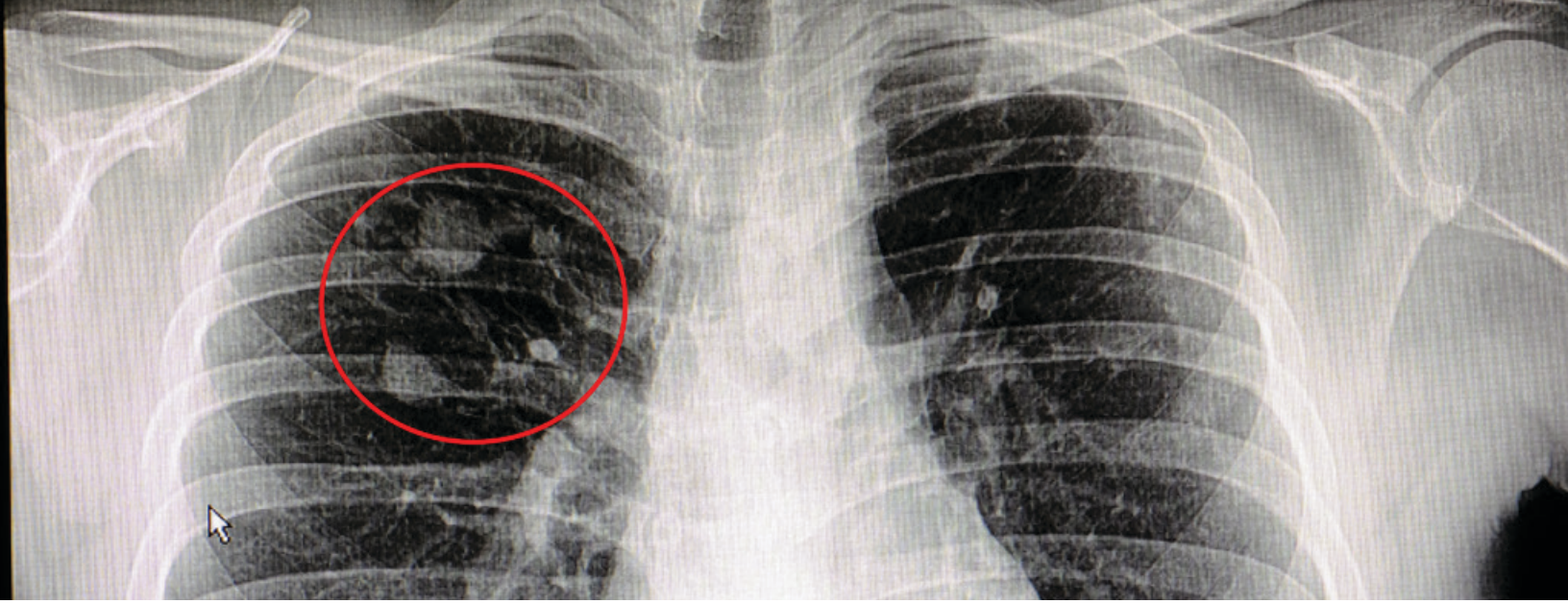
Prevalence of malignant pulmonary nodules can vary widely, depending on the means of detection.

- **Other risk factors**
  There are other risk factors which may play a significant role in modifying the malignancy probabilities of a pulmonary nodule. For example, a smaller nodule associated with the high-risk factors listed in Table 1 (below) would need to undergo further surveillance and monitoring, as its malignancy probability is enhanced.[7]

Table 1: Pulmonary Nodule Risk Factors

	Low-Risk	High-Risk
Age*	Younger (age <40 years)	Older (age >50 years)
Smoking status	Never smoked OR quit >15 years ago	Current smoker OR quit 15 or fewer years ago
Family history of lung cancer	None among first-degree relatives	Present among first-degree relatives
Location of the nodule(s)	No upper lobe involvement	Upper lobe involvement
Nodule characteristics	Round, smooth margins; presence of cavity	Irregular, spiculated margins; absence of any cavity
Personal history of any cancer	No	Yes

**Between ages 40 and 50 is considered moderate risk.*



Additional Points for Underwriting Consideration

Apart from the primary risk modifiers for pulmonary nodules noted above, the presence of the following secondary risk factors must not be ignored:

- selected occupations, e.g., asbestos industry workers or individuals who work with radioactive substances
- presence of other pulmonary diseases such as emphysema, infections, or fibrosis
- periodic growth of nodule(s) observed on chest X-rays or CT scans on follow-up exams

The presence of these additional risk factors augments the malignancy risk further. Such cases would require complete and detailed up-to-date reports about the nodules for any consideration at the underwriting stage.

On the other hand, a benign nodule often exhibits all or most of the following characteristics:

- diffuse calcification (hamartoma, popcorn calcification), with smooth margins
- absence of any high-risk factors
- no growth of the nodule over a period of two years
- complete absence of any changes in the nodule that would indicate increased malignancy risk

Conclusion

Underwriting pulmonary nodules continues to pose a challenge for underwriters. Although a significant percentage of pulmonary nodules are benign, the fact that lung cancer has one of the highest mortalities among all cancers remains a definitive concern. Thus, a judicious approach to selectively quantify the risk, based on collective features of each nodule and its associated risk factors, is recommended.

Part 2: Thyroid Nodules

Background

Thyroid nodules are solid or fluid-filled masses that form within the thyroid gland. They are one of the most common types of nodule found in the human body, with estimates suggesting that approximately half of the global population is likely to develop a thyroid nodule during their lifetime. The estimated worldwide prevalence is between 19% and 67% on ultrasonography (USG), depending on geographies.[10, 11, 12]

Over the past few decades, the rapid growth in the use of ultrasound scans globally has led to an exponential increase in the number of incidentally found thyroid nodules, with only 3% to 7% of these nodules discovered upon thyroid palpitation alone.[12]

There has also been a significant rise in thyroid cancer rates. In the U.S. alone, thyroid cancer incidence increased overall by an alarming 211% between 1975 to 2013, reflecting an average annual incidence increase of 3.6% as well as an annual 1.1% increase in overall mortality rates.[13]

Growth in the number of thyroid ultrasound scans has led to an exponential rise in incidental thyroid nodule findings.

Risk Classification Methodologies

For underwriters, reports of incidental thyroid nodules found on USGs are common. However, assessing the prognosis of such nodules based on a single USG report has continued to challenge underwriters. A methodical approach to assessing the malignancy risk would be highly beneficial.

Several groups have sought to classify thyroid nodules based on their features. A recent study outlined the differences in relative risk among thyroid nodules by comparing three sets of guidelines: the 2016 guidelines from a consortium of the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and Associazione Medici Endocrinologi (AME); the 2015 American Thyroid Association (ATA) guidelines for management of thyroid nodules and differentiated cancer; and the 2014 British Thyroid Association (BTA) guidelines for management of thyroid carcinoma.[10]

The study looked at thyroid nodules based on features found on USGs and categorized them as:

- Low-risk thyroid lesions (benign or low suspicion of malignancy)
- Intermediate-risk thyroid lesions (intermediate or indeterminate suspicion of malignancy)
- High-risk thyroid lesions (high suspicion for malignancy or malignant)

Today, however, the American College of Radiology's Thyroid Imaging Reporting and Data System, known as ACR TI-RADS (or just TI-RADS), is one of the most accepted thyroid nodule risk classification methodologies.

ACR TI-RADS: A New Chapter for Risk Classification of Thyroid Nodules

Risk classification frameworks for thyroid nodules are not a new development. Several, including Europe's EU-TIRADS, published by the European Thyroid Association in 2017 and the Korean Society of Thyroid Radiology's (KSThR) K-TIRADS, published in 2016, assessed malignancy risk using features of the nodules.[14, 15]

In 2017, the ACR TI-RADS model was introduced, which paved the way for a new classification framework wherein the focus shifted to assigning point values to nodule features and using them to compute a holistic risk score to predict malignancy.[16]

Table 2 (below) provides a snapshot of the ACR TI-RADS method of risk classification.

Table 2: ACR TI-RADS Scoring System for Thyroid Nodule Classification From USG Images

Composition	Echogenicity	Shape	Margins	Echogenic Foci
Cystic or almost cystic	Anechoic	Wider than tall	Smooth	None or large comet-tail artifacts
Spongiform	Hyperechoic	Taller than wide	Ill-defined	Macrocalcifications
Mixed cystic and solid	Hypoechoic		Lobulated or Irregular	Peripheral (rim) calcifications
Solid or almost completely solid	Very hypoechoic		Extrathyroidal extension	Punctate echogenic foci

Risk Increases

**Table adapted from ACR TI-RADS, Reporting and Data System (TI-RADS): White paper of the ACR TI-RADS committee.[16]*

Each component in the table has been assigned a specific point value, with higher values assigned to more suspicious features. For example, a solid hypoechoic nodule with rim calcifications would have a significantly higher malignancy risk than would a smooth cystic nodule, which is often benign. Thus, each component – solid, hypoechoic, and rim calcification – would have a higher individual point value than would the cystic and smooth components.

The goal is to then calculate a cumulative risk score for each nodule, based on the presence of characteristics indicating a specific TI-RADS category, thereby enabling a more precise assessment of a nodule's potential malignancy risk. TI-RADS categories can range from 0 to 5, with 0 signifying a benign nodule and 5 representing highest risk of malignancy. For example, a cumulative risk score of 2 would indicate TI-RADS 2, a relatively benign prognosis, whereas a cumulative risk score of 7 or more would indicate TI-RADS 5, a more malignant pathology.

Fine Needle Aspiration's Role in Thyroid Nodule Diagnostics

The 2017 Bethesda System for Reporting Thyroid Cytopathology, a revision of the system first introduced in 2007, has been universally adopted as the system for classifying thyroid nodules following Fine Needle Aspiration (FNA) evaluation.

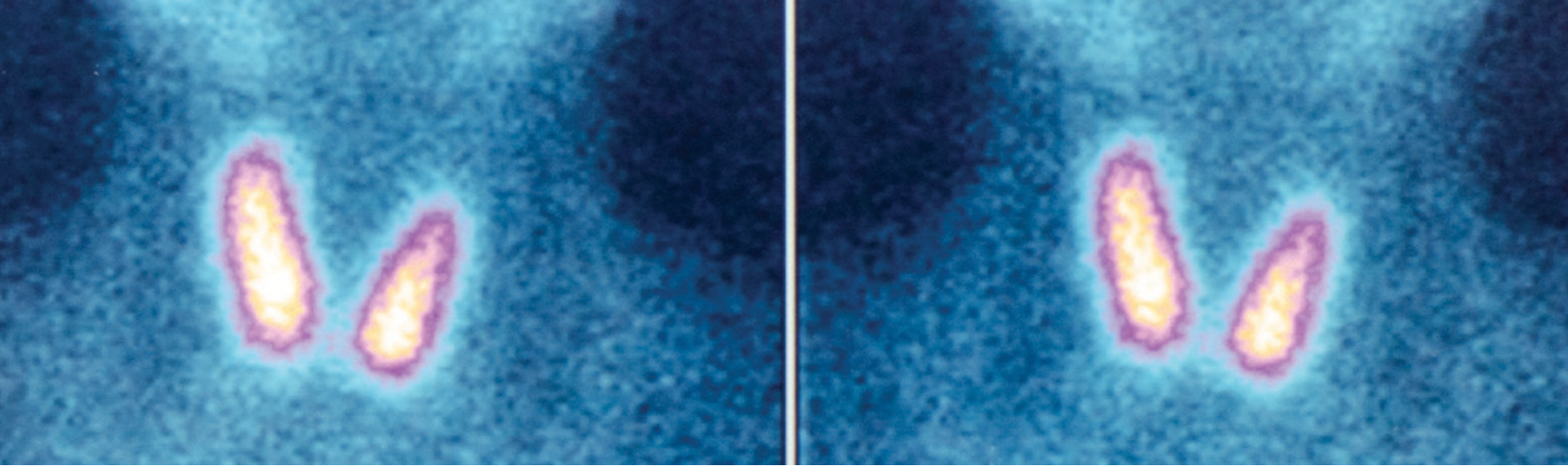
Table 3 (below) shows the different diagnostic categories of FNA results and illustrates the corresponding malignancy risk with usual management strategies.[17]

Table 3: Bethesda System for Classifying Thyroid Nodules Using FNA Results

Bethesda class	Diagnostic category	Malignancy risk (%)	Usual management
I	Non-diagnostic or unsatisfactory	0% - 5%	Repeat FNA with ultrasound guidance
II	Benign (e.g., benign follicular nodule)	0% - 3%	Clinical and sonographic follow-up
III	Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	10% - 30%	Repeat FNA, molecular testing, or lobectomy
IV	Follicular neoplasm (or suspicious for follicular neoplasm)	25% - 40%	Molecular testing, lobectomy
V	Suspicious for malignancy	50% - 75%	Near total thyroidectomy or lobectomy
VI	Malignant	97% - 99%	Near total thyroidectomy

**adapted from 2017 Bethesda System for reporting Thyroid Cytopathology: Cibas A, et al.[17]*

It must be noted that there are few predefined criteria for carrying out the FNA tests. Clinicians generally rely on a combination of the TI-RADS score and the size of the nodule to determine if an FNA is warranted. For example, an FNA may be recommend for an EU-TIRADS 5 category nodule when its size is greater than or equal to 1 cm. However, an EU-TIRADS 4 nodule might be considered for FNA if the nodule is 1.5 cm or larger, and an EU-TIRADS 3 nodule considered for FNA if it is 2 cm or larger. In cases where multiple nodules are found, FNA is recommended for not more than three nodules, according to risk and size criteria.[14]



Risk Modifiers

The factors listed below can be used in conjunction with both ACR TI-RADS scores and FNA results, when available, to determine the prognosis of the nodule. The presence of any of these factors may lead to a poorer prognosis, indicating a prudent underwriting approach.[10]

- Age at onset, particularly adolescence or older ages (age >70 years)
- Presence of first-degree family history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2, or papillary thyroid carcinoma
- Periodic growth of nodule(s), i.e., nodule growth observed in follow-up USG or PET scans
- Associated symptoms such as persistent dysphonia, dysphagia, or dyspnea
- A personal history of head and neck irradiation, particularly during childhood and/or adolescence
- Presence of cervical adenopathy

There remains an ongoing debate whether intranodular vascularity is determinant of malignant potential of a thyroid nodule. A 2017 U.S. study based on more than 20 years of follow-up of 698 individuals noted that intranodular hypervascularity is associated with adenoma/adenomatous (benign) thyroid nodules, whereas a lack of vascularity was found to be indicative of thyroid carcinomas.[18]

Another study, conducted on 1,024 hospitalized patients in South Korea, found that vascularity discovered upon ultrasonography, in isolation or in combination with gray-scale ultrasound features, was not useful in predicting thyroid cancer. Intranodular vascularity was present in 31% of the individuals with benign nodules compared with 17% with malignant nodules.[19]

From these studies, it appears that utilization of intranodular vascularity as a factor to predict malignant thyroid nodules may not be always accurate, and it remains controversial. Further studies are warranted to explore this aspect.

Role of Other Tests in Evaluating Thyroid Nodules

The diagnostic process for thyroid nodules can frequently involve additional tests. Here are a few, and their implications.

- **Thyroid function tests** (TSH, T4) are commonly carried out during investigations of thyroid nodule(s). A hyperfunctioning nodule is less likely to be malignant.
- **Blood thyroglobulin tests** are not clinically mandated for the evaluation of thyroid nodules, as their reliability to predict malignancy remains controversial. In fact, it has been observed that in few cases, thyroglobulin was found to be elevated for eventual benign nodules.
- The presence of **calcitonin**, which is produced by parafollicular (C) cells, is considered more reliable as a serum marker for medullary thyroid cancer but may not necessarily play a role in the initial clinical evaluation of a thyroid nodule.[20]
- A diagnosis of indeterminate thyroid lesions presents an ongoing challenge for most radiologists and cytologists. The evaluation of morphological features alone is not always adequate. The application of **ancillary molecular testing** for indeterminate thyroid FNA specimens has provided better stratification and triage for some of these instances. Research continues to further refine and improve molecular tests, making them more accurate and less expensive, anticipating that they could provide the basis to solve some of the challenges surrounding these types of nodules.[21]

Conclusion

Thyroid nodules are one of the most common incidental findings seen at underwriting. Although the features of a nodule play a significant role in determining its malignancy risk, it is important not to underestimate associated risk factors, as they also serve as potential risk factors for malignancy. Thoughtful guidance supported by research-based underwriting tools would help an underwriter classify and assess a nodule's malignancy risk and yield prudent decision-making.

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CURRENT TRENDS IN GESTATIONAL DIABETES MELLITUS

Abstract

Gestational diabetes mellitus (GDM) is a condition in which maternal hyperglycemia develops during pregnancy and usually resolves post-partum. It is one of the most common endocrinopathies in pregnancy and its global prevalence is on the rise. In most cases, hyperglycemia in pregnancy is due to impaired glucose tolerance resulting from pancreatic beta-cell dysfunction and chronic insulin resistance.

GDM is associated with maternal morbidity and fetal mortality if left untreated, with consequences that can include increased risk of future cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) in the mother and macrosomia and birth complications in the infant. Although the immediate impact of GDM may be very minimal on maternal mortality, there can be significant long-term consequences. Screening and appropriate management of GDM are therefore of the utmost importance for the health of both mother and child.

Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy in which women without previously diagnosed diabetes develop chronic hyperglycemia during gestation. GDM can occur at any stage of pregnancy but is more common in the second or third trimester.[1] This definition applies whether insulin and/or diet modification is used for treatment, and whether or not the condition persists after pregnancy. It also does not exclude the possibility that unrecognized glucose intolerance may have preceded or begun concomitantly with the pregnancy.[2]

Epidemiology and Risk Factors

Worldwide prevalence estimates for GDM are difficult to interpret due to inconsistency in its screening and diagnosis.

The prevalence of high blood glucose (i.e., hyperglycemia) in pregnancy is known to increase rapidly with maternal age. In 2019, it was estimated that globally, one of every six mothers who gave birth to a live infant (20 million) had experienced some form of hyperglycemia in pregnancy, of which an estimated 84% of the cases were GDM. Currently, approximately 10% to 15% of all pregnancies are complicated by GDM, with the highest prevalence seen in Southeast Asia at around 27%.[3]

The ongoing obesity epidemic, coupled with rising maternal ages and sedentary lifestyles, are also major contributors to the global increase in GDM. Most cases of hyperglycemia in pregnancy are in low-and middle-income countries, where access to maternal care is limited.[4]

Any woman can develop GDM during pregnancy, but the risk is higher if certain maternal factors exist, such as: obesity before pregnancy or excessive gestational weight gain; advanced maternal age; presence of diseases of insulin resistance (e.g., polycystic ovarian syndrome [PCOS]);

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a personal history of chronic hypertension and/or of low or high birth weight babies; a family history of insulin resistance or any form of diabetes; ethnicity (prevalence rates are known to be higher in Black, Hispanic, Native American and Asian women);[5] and genetic polymorphisms.

Signs, Symptoms, and Prognosis

Diagnosis of GDM is often through prenatal screening rather than through reported symptoms. However, symptoms such as polydipsia, polyuria, dry mouth, or fatigue may develop with poorly controlled maternal blood sugar levels.[6]

GDM is associated with multiple short-term adverse maternal and perinatal outcomes and is known to have long-term adverse health effects on the mother and child.[7]

GDM risk is higher if certain maternal factors exist.

During pregnancy, short-term risks include spontaneous abortion, premature birth of the fetus, and stillbirth. GDM may also be associated with fetal anomalies and complications such as macrosomia, shoulder dystocia, neonatal hypoglycemia, or hyperbilirubinemia. Neonatal respiratory distress syndrome is commonly seen as well.

Operative delivery (caesarean section or instrumental assist) is frequently needed and may also be necessitated by maternal factors such as pre-eclampsia or gestational hypertension. Antenatal depression is also frequently experienced by GDM mothers.

Post-pregnancy, GDM can be an indicator of future diabetes and cardiovascular disease (CVD).[8] Long-term maternal risks associated with GDM include:

- **Impaired glucose tolerance.** Approximately 30% of women with GDM experience impaired glucose tolerance during the early postpartum period.
- **Metabolic syndrome.** Approximately one-third of women with mild GDM (i.e., one normal fasting glucose during an oral glucose tolerance test [OGTT]) develop metabolic syndrome within five to 10 years of delivery.
- **Type 2 diabetes mellitus (T2DM)**. GDM is often indicative of underlying maternal pancreatic beta-cell dysfunction, which increases maternal risk of development of T2DM.[9] According to a 2018 study, approximately 60% of women with a history of GDM develop T2DM later in life. The yearly risk of conversion to T2DM is approximately 2% to 3%.[1] A more recent study noted that for women with GDM, longer duration of lactation was associated with a lower risk of T2DM and a favorable glucose metabolic biomarker profile.[10]
- **Cardiovascular disease.** Women with GDM are at higher risk of not only developing CVD, but of also developing it at a younger age than women with no history of GDM. Some studies suggest that GDM permanently alters female vasculature, causing increased CVD risk. A recent study also reported increased risk of CVD and lower HDL levels among women with a history of GDM.[11]
- **Recurrence.** GDM usually resolves post-delivery, but there is a high risk of recurrence in subsequent pregnancies. Recurrence is seen more among advanced age pregnant women and among women who gain more weight between their pregnancies. Approximately one-third to two-thirds of women with GDM will have GDM in subsequent pregnancies. Women who had GDM also have a threefold risk of developing T2DM with each additional pregnancy compared to women without additional pregnancies.[8]

There are also hazards for children born to mothers with GDM. These children are at increased risk for obesity, T2DM, CVD, and associated metabolic diseases. In some of these children, impaired glucose tolerance can first be noticed at a very young age. GDM in mothers could also establish a propensity for GDM in their female children, who may be more likely to experience it in their own future pregnancies.[1]

Investigation and Diagnosis

There is currently not just a lack of uniform strategy for screening GDM, but also an absence of an accepted, evidenced-based, gold standard for diagnosis of GDM during routine antenatal screenings.

The clinical criteria often applied are from the World Health Organization (WHO), the American Diabetes Association (ADA), the International Association of Diabetes in Pregnancy Study Groups (IADPSG), the American College of Obstetricians and Gynecologists

(ACOG), and the Canadian Diabetes Association (CDA).

WHO, for example, recommends that a diagnosis of GDM be made when one or more of the following metrics are found:

- Fasting glucose of >126 mg/dL (7.0 mmol/L)
- Two-hour plasma glucose of >200 mg/dL (11.1 mmol/L) following a 75-gram oral glucose load
- Random blood glucose of >200 mg/dL (11.1 mmol/L) in the presence of diabetes symptoms[12]

The American Diabetes Association (ADA), meanwhile, recommends the use of either a one- or two-step screening approach at 24 to 28 weeks of gestation in pregnant women not previously known to have diabetes.[2]

Table 1: ADA Screening Approach for GDM

75 gm OGTT*	100 gm OGTT* **
A diagnosis of GDM can be made when any of the following three plasma glucose levels are met or exceeded: • Fasting: 92 mg/dL (5.1 mmol/L) • 1 hour: 180 mg/dL (10.0 mmol/L) • 2 hours: 153 mg/dL (8.5 mmol/L)	A diagnosis of GDM can be made if at least two of the following four plasma glucose levels are met or exceeded: • Fasting: 95 mg/dL (5.3 mmol/L) • 1 hour: 180 mg/dL (10.0 mmol/L) • 2 hours: 155 mg/dL (8.6 mmol/L) • 3 hours: 140 mg/dL (7.8 mmol/L)

** Oral Glucose Tolerance Test*
***This test is performed after failing an initial screening with a 50-gm glucose challenge.*

GDM Management

Several treatments and healthcare practices can reduce the risks GDM can pose to pregnancy.

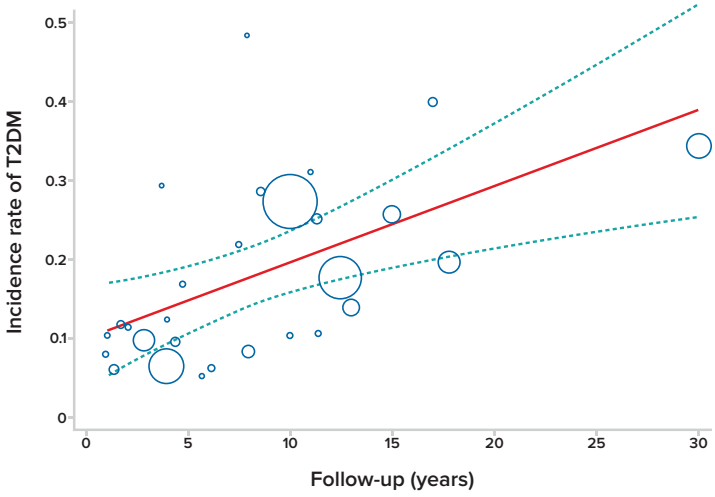
- Lifestyle changes are the first approaches recommended for management of GDM. Changes in diet and exercise habits are essential components of lifestyle change and may suffice for treatment of about 70% of those experiencing GDM. The changes should aim to limit the gestational weight gain and improve glycemic control.[13]
- Monitoring certain metrics can be beneficial. GDM patients are encouraged to monitor their blood glucose levels four-times per day, preferably prior to meals, as the risk of fetal macrosomia rises with increased maternal blood glucose following meals. Measuring glycosylated hemoglobin (HbA1C) can have some benefit, but due to the increase in red blood cell mass and turnover during pregnancy, frequent measurements of it might not be useful. However, in women with an initial HbA1C of more than 6.5%, regular assessments (one every three months) might be helpful.[14]
- Insulin is preferred for treating GDM as it does not cross the placenta to a measurable extent.[15] The type and timing of insulin doses depends on the blood glucose levels.

- Pharmacotherapy is the next line of treatment, but needs to be done with great care, as all oral agents lack long-term safety data.[16, 17, 18] Metformin and glyburide are not advised as first-line agents, as both cross the placenta to the fetus, but they are occasionally prescribed.
- Post-partum screening every three years to check for development of diabetes or prediabetes should be lifelong for women with a history of GDM.[19]

Insurance Implications

- **GDM and T2DM**
  In 2020, two meta-analyses were conducted. The first analyzed 20 studies containing a total of 1,332,737 participants and noted that the pooled relative risk (RR) of developing T2DM was almost 10 times higher among women with GDM than among the controls.[20] The second, in which 170,139 women with GDM participated, reported that the incidence rate of developing T2DM after GDM was approximately 26%. It also noted that the development of T2DM after GDM increased an estimated 9.6% per year of follow-up.[21] (See Figure 1, below)

Figure 1: Incidence of T2DM Among Women with GDM Over Time [21]



A 2018 study investigated the impact of GDM on long-term T2DM risk among women at different time periods post-partum. Findings indicated that the relative risk of developing T2DM was highest at three to six years after GDM and for women under 40 years of age.

This study also found that previous GDM was associated with a 7.76-fold risk of developing T2DM and that women with early-onset T2DM (under age 40) were at higher risk of experiencing diabetes as well as cardiovascular and microvascular complications than those with later-onset T2DM. Finally, Asian women, as well as women of advanced-maternal age and women with higher body mass indexes (BMI >30.0 kg/m2), were found to be at higher risk of developing T2DM.[22]

- **GDM and CVD**
  There is a distinct relationship between GDM and future risk of CVD. Women who had GDM have been found to be at more than twice the risk of future cardiovascular events during follow-up than women without GDM.[23] GDM is also associated with increased risk of myocardial infarction (MI), with a fully adjusted hazard ratio of 1.45 (95% CI; 1.05-1.99).[24]
- **GDM and Cancer**
  Diabetic individuals overall are known to be at higher risk of certain types of cancers. Women with GDM have been found to have a higher risk of developing cancers than women without GDM (2.24% vs 1.96%). Hence, regular cancer screening is warranted for women who have had GDM.[25]
- **GDM and Maternal Insurance Benefits**
  For maternal coverage products, it should be kept in mind that the cost of healthcare will be higher for pregnant women with GDM. The additional costs include GDM diagnosis and treatment, maternal complications, neonatal complications, and increased need for assisted deliveries. The cost of outpatient expenses will also be higher, as they may need to include additional physician visits, GDM screening, diet and exercise consulting, medical tests, drugs, and insulin.

Conclusion

The global burden of GDM has been on the rise with increases in obesity and changes to lifestyle. There is a well-established association between increasing hyperglycemia in pregnant women and the occurrence of adverse maternal and fetal outcomes. Women with GDM are at an increased risk of complications during pregnancy and at delivery. However, the risks can be reduced if the condition is detected early and managed effectively.

The impact of GDM may be very minimal on immediate mortality, but it may have significant long-term consequences for the health and well-being of the individual with GDM. For insurance purposes, it is important to consider the history, complications, and long-term outcomes of GDM on maternal morbidity, fetal mortality, and that it may be a precursor for increased risk of diabetes, CVD, and cancers. RF

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GENE AND CELL THERAPIES

Abstract

Rapid advances in medical science's understanding of the human genome have led to the recent development of novel gene-based therapeutic strategies. Only a short time ago, such approaches would have been considered technically difficult or impossible to carry out. While not yet common or widely used, new gene and cell therapies are being developed and approved for use today at an increasing rate and are demonstrating promise for diseases that otherwise have had few options for treatment or were deemed incurable. This Brief Report will define gene and cell therapies and provide some insights into these rapidly developing and impactful technologies.

What Are Gene and Cell Therapies?

According to the U.S. Food & Drug Administration (FDA), human gene and cell therapies seek to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. Gene and cell therapies fall into two main categories: replacement or inactivation of a disease-causing gene; or introduction of a new or modified gene.[1] Cell therapy products include cellular immunotherapies, cancer vaccines, and other types of autologous and allogeneic cells for certain indications, including hematopoietic stem cells and adult and embryonic stem cells.[2]

How Are Gene and Cell Therapies Delivered?

The several techniques and mechanisms for delivery of these new therapies can generally be categorized as either *ex vivo*, where the gene and/or cell modification is performed on cells removed from a person's body and the cells then transplanted back into the body, or *in vivo*, where the gene or cell modification is delivered either intravenously or conveyed directly to the affected tissue or organ in the body.[4] New genetic material can be transported to cells via engineered nanoparticles or adeno-associated virus vectors. The latter method can be problematic, as up to 50% of people have pre-existing immunity to these adenoviruses which excludes them from treatment. Research to circumvent this issue continues.[5]

Oligonucleotide therapies, which use synthesized nucleic acid polymers to treat or manage a wide range of diseases, are considered gene therapies for the purposes of this article but are often considered a separate treatment category in the medical literature.

What Diseases Have Approved Gene and Cell Therapies?

Several gene and cell therapies, including oligonucleotide therapies, have been approved for use, but this differs depending on the country. The U.S. FDA, for example, has approved gene and cell therapies for several diseases,[3, 9] including:

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Dr. Daniel D. Zimmerman is responsible for the global medical function at RGA which includes thought and medical leadership, case consultation, product development, client support, and internal and external education and he serves as editor of *ReFlections*. He is also Managing Director of The Longer Life Foundation, www.longerlife.org. Dr. Zimmerman received his medical degree from the University of Wisconsin School of Medicine and Public Health and his undergraduate degree in Medical Microbiology and Molecular Biology from the University of Wisconsin – Madison. He has held leadership positions with the American Council of Life Insurers (ACLI), participated in program committees of the American Academy of Insurance Medicine (AAIM), and frequently represents RGA to key industry professional organizations. He has also contributed several articles to the *Journal of Insurance Medicine*, *On The Risk, and Best's Review*.

- Spinal muscular atrophy
- Duchenne muscular dystrophy
- Diffuse large B-cell lymphoma
- Mantle cell lymphoma
- Acute lymphoblastic leukemia (ALL)
- Unresectable melanoma
- Hormone refractory prostate cancer
- RPE65 mutation-associated retinal dystrophy
- Neovascular age-related macular degeneration
- Hereditary ATTR amyloidosis
- Cartilage defects of the knee
- Cytomegalovirus (CMV) retinitis
- Homozygous familial hypercholesterolemia (HoFH)
- Acute hepatic porphyria (AHP)

Many additional diseases are being studied for possible applicability of gene-based therapies. Much success has thus far been achieved, especially for hemoglobinopathies such as sickle cell disease and beta thalassemia. Notably, a gene therapy treatment for beta thalassemia was approved in 2019 in the European Union and its application is currently under review in the U.S.,[7] and studies are ongoing to assess the potential of using gene therapy to prevent HIV from infecting T-cells.[5]

Gene and cell therapies fall into two main categories.

Regulators are, however, proceeding with some caution: although U.S. approval had been expected last year for the novel gene therapy Roctavian for hemophilia A, the FDA is requesting to see at least two years of follow up data from the manufacturer's Phase 3 trial before proceeding.[8]

Insurance Implications

Advances in gene and cell therapies have been extraordinary, and in many cases, life-changing. However, insurers have several potential challenges when assessing the risk of using these new therapies. Considering that more than 900 gene therapies are currently in development and more will be approved, they will be more frequently encountered in patient histories both during underwriting and claims adjudication. Also, as many of these therapies are so new, their long-term efficacy is still unknown. In addition, certain gene therapies require toxic conditioning regimens prior to administration of the actual therapy, imparting additional risk.

The overall safety profile of gene and cell therapies will need to be monitored closely since unlike other clinical studies, gene therapy studies are often performed on very small cohorts of patients. One pharmaceutical company recently halted the clinical trial for its gene therapy for sickle cell disease after receiving reports that a few patients had been subsequently diagnosed with

myelodysplastic syndrome and leukemia, although direct cause and effect are still being investigated.[10]

Finally, the cost of gene and cell therapies can be incredibly high, which may present a barrier for patient access as well as concern for insurers providing medical coverage. For example, one gene therapy for an inherited form of blindness costs U.S. $425,000 per eye and one for a type of spinal muscular atrophy costs U.S. $2.1 million in total.

Insurers have several potential challenges when assessing the risk of using these new therapies.

Conclusion

Multiple next-generation gene and cell therapy technologies are advancing quickly, and will ultimately improve the specificity, accuracy, efficiency, and applicability to different classes of disease. The rapid pace of these advances will dramatically broaden the scope of human disease to which these approaches can be applied.

Indeed, many of these treatments address previously incurable diseases and could offer great hope to those suffering from them. While the benefits are very promising, much remains to be learned with regard to long-term efficacy, outcomes, and safety. Insurers will need to keep up to date with this technology and monitor the impact on mortality and morbidity as well as costs, especially to those providing health cover. RF

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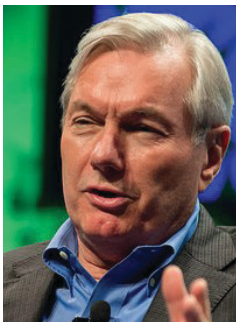
Longer Life Foundation

An RGA/Washington University Collaboration

The Longer Life Foundation (LLF), a collaboration between RGA and Washington University School of Medicine in St. Louis that is now in its 23rd year, continues to support and advance research benefiting clinical and insurance medicine as well as public health.

We recently resumed our successful program of sponsorships of Internal Medicine Grand Rounds. So far this year, LLF has sponsored Grand Rounds featuring Grant Challen, Ph.D. Dr. Challen, a recipient of LLF grants in 2018 and 2019, presented an update of his cutting-edge research into blood cancers and their prevention.

LLF has also sponsored two weekly podcasts by Dr. Michael T. Osterholm. Dr. Osterholm, the founder and Director of the Center for Infectious Disease Research and Policy (CIDRAP), is a world-renowned infectious disease epidemiologist and has been a leading public health advocate and a trusted source of useful advice and information throughout the pandemic.



We are proud to be sponsoring his podcasts, which focus on the latest trends and developments in COVID-19. Please click this link to listen.

We recently published the second edition of our LLF newsletter, which updates stakeholders and interested parties in our latest activities. Please click here to access.

LLF's Advisory Group also met in early April to review the initial Letters of Intent. This year we received 19 such letters from investigators in a broad range of disciplines and departments. From these, several have been invited to submit full application proposals to LLF's Scientific Review Committee for consideration of funding in 2021.

ReCite

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

Post-COVID Syndrome in Individuals Admitted to Hospital With COVID-19: Retrospective Cohort Study

Ayoubkhani D, et al.
BMJ. 2021; 372: n693.
https://www.bmj.com/content/372/bmj.n693

In this British study, almost 50,000 people hospitalized and discharged alive for COVID-19 were matched to controls. They were followed for hospital readmission, all-cause mortality, and diagnoses of respiratory, cardiovascular, metabolic, kidney, and liver diseases. Over the mean follow-up period of 140 days, almost one-third of the hospitalized COVID-19 patients were readmitted and more than 10% died after discharge. These rates were four and eight times greater, respectively than the matched controls.

Editor's Note: *Insurers need to review the literature and develop research-based guidelines in order to optimize their assessments of the risk of applicants previously infected with SARS-CoV-2.*

Fitness, Fatness, and Mortality in Men and Women From the UK Biobank: Prospective Cohort Study

Tarp J, et al.
Journal of the American Heart Association. 2021 Mar 16; 10(6): e019605.
https://doi.org/10.1161/JAHA.120.019605

Cardiorespiratory fitness was estimated from a submaximal bicycle test in 77,169 men and women from the UK Biobank cohort and combined with World Health Organization standard body mass index categories to develop cohorts of obese fit and unfit men and women. All-cause mortality was determined from death registries. During a median follow-up of 7.7 years, 1,731 participants died. In analysis stratified by sex that excluded individuals with prevalent major chronic disease and short follow-up and using direct measures of body composition, mortality risk was 1.78 (95% CI, 1.17-2.71) times higher in unfit-obese men but not higher in obese-fit men (0.94 [95% CI, 0.60-1.48]). In contrast, there was no increased risk in obese-unfit women (1.09 [95% CI, 0.44-1.05]) as compared with the reference (obese fit women).

Editor's Note: *Further research is needed to fully understand the complex relationships between body composition, fitness, and mortality outcomes. Insurers with wellness programs and dynamic underwriting approaches need to take all the medical literature into account when developing these specialized benefits and products.*

Suicide Risk in the First Year Following Dementia Diagnosis: A National Study of U.S. Older Adults

Schmutte T, et al.
The American Journal of Geriatric Psychiatry, 2021 Apr; 29(4): S118-9.
https://www.ajgponline.org/article/S1064-7481(21)00139-1/fulltext

This article presents results from a U.S. study of suicide risk in adults older than age 65 during the first year following newly diagnosed dementia. The suicide rate was 26.42 per 100,000 person-years. Compared with the general population, the overall standardized mortality ratio (SMR) for suicide was 1.54 (95% CI, 1.42-1.65) and was highest in the 65-74 year-old age group. Half of suicide deaths occurred within 90 days.

Editor's Note: *With greater screening and better diagnostic testing to identify those with dementia, it must be kept in mind that suicide risk assessment and support should be carried out at the time of diagnosing incident dementia.*

RGA THOUGHT LEADERSHIP PUBLICATIONS

RGA publishes content on many topics of interest to insurers. Here are links to some recent publications:

Metabolic U-Turn: Type 2 Diabetes Mellitus Remission and the Implications of a Turn in the Right Direction
By Dr. Heather M. Lund, MBBCh, Regional Chief Medical Officer, RGA Asia
https://www.rgare.com/knowledge-center/media/articles/metabolic-u-turn-type-2-diabetes-mellitus-remission-and-the-implications-of-a-turn-in-the-right-direction

Long-Term Disability in the Time of COVID-19: The Economic Impact of the First "Pandemic Recession"
By Jeff Schuh, FSA, MAAA, ACIA, Vice President and Actuary, Group LTD and CI, RGA
https://www.rgare.com/knowledge-center/media/covid-19/long-term-disability-in-the-time-of-covid-19-the-economic-impact-of-the-first-pandemic-recession

Physical Health, Obesity, and the Challenge to Stay Active During the COVID-19 Pandemic
By Gayathri Ravi Shankar, Knowledge Management and Information Specialist, RGA
https://www.rgare.com/knowledge-center/media/covid-19/physical-health-obesity-and-the-challenge-to-stay-active-during-the-covid-19-pandemic

The Good, the Bad, and the Ugly: Alternative Therapies in the Prevention and Treatment of COVID-19
By Hilary Henly, Global Medical Researcher, RGA International Reinsurance Company dac
https://www.rgare.com/knowledge-center/media/research/the-good-the-bad-and-the-ugly-alternative-therapies-in-the-prevention-and-treatment-of-covid-19

Global Claims Views: After the Storm, Long-Term Health Consequences of COVID-19
By Marilda Kotze, Vice President, Global Head of Claims, RGA South Africa
https://www.rgare.com/knowledge-center/media/covid-19/global-claims-views-after-the-storm-long-term-health-consequences-of-covid-19

The security of experience. The power of innovation.