



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Magnetic Resonance Spectroscopy (MRS)**

**Effective Date..... 11/15/2010**  
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## Hyperlink to Related Coverage Policies

Functional Magnetic Resonance Imaging (fMRI), Brain  
Genetic Testing for Canavan Disease

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

## Coverage Policy

**CIGNA covers magnetic resonance spectroscopy (MRS) as medically necessary for ANY of the following indications:**

- distinguishing recurrent brain tumor from radiation necrosis following radiation treatment of a brain tumor
- for evaluation of a brain tumor in a child when additional information is needed to plan treatment (e.g., biopsy is not a desired choice)
- inborn error of metabolism (e.g., leukoencephalopathy of childhood)

**CIGNA does not cover magnetic resonance spectroscopy (MRS) for any other indication because it is considered experimental, investigational or unproven.**

## General Background

Magnetic resonance spectroscopy (MRS) utilizes the principle that nuclei in different chemical structures have different characteristic resonance patterns, depending on the neighboring chemical structures and the interactions between these various chemical structures. MRS detects the chemical composition of the tissue under study, and the associated software displays a waveform with peaks that correspond to the

various chemicals detected. MRS, therefore, allows visualization of molecular processes as opposed to structural and anatomic imaging of tissues and organs. Thus, MRS provides direct biochemical information. Common metabolites studied with MRS include N-acetylaspartate (NAA), choline (Cho), myo-inositol (mI), glutamate (Glu)/ glutamine (Gln) and creatine (Cr), adenosine triphosphate (ATP), phosphocreatinine (PCr), phosphomonoesters (PME) and phosphodiester (PDE).

It is proposed that “MRS provides therapeutic impact in brain tumors, metabolic disorders such as adrenoleukodystrophy and Canavan disease, Alzheimer’s disease, hypoxia, secondary to trauma or ischemia, human immunodeficiency virus dementia and lesions, as well as systemic disease such as hepatic and renal failure”(Lin, et al., 2005). Lin et al. also proposes that MRS enhances routine neurological practice and treatment because: “1) there is added value from MRS where MRI is positive; 2) there is unique decision-making information in MRS when MRI is negative; and 3) MRS usefully informs decision-making in neurotherapeutics.”

### **U.S. Food and Drug Administration (FDA)**

Magnetic Resonance Spectroscopy Systems are approved by the FDA as a magnetic resonance diagnostic device (MRDD). MRDDs are Class II devices and intended for general diagnostic use to present images which reflect the spatial distribution and/or magnetic resonance spectra which reflect frequency and distribution of nuclei exhibiting nuclear magnetic resonance.

### **Literature Review and Professional Societies/Organizations**

#### **Brain Tumor**

There is sufficient evidence in the published, peer-reviewed scientific literature to support the use of MRS in distinguishing recurrent brain tumor from radiation necrosis in adults and children and in children with brain tumors for treatment planning. MRS is particularly useful in cases where MRI is unclear whether it is radiation necrosis or recurrence, as MRS is capable of distinguishing between residual or recurrent tumors and pure radiation necrosis (Prat, et al., 2010; Herholz, et al., 2007; Zeng, et al., 2007; Palumbo, et al., 2006; Weybright, et al., 2005; Lin, et al., 2005). For example, compared to follow-up or histopathology, Cho/NAA and Cho/Cr ratios were significantly higher in recurrent tumor than in regions of radiation injury ( $p < 0.01$ ) (Zeng, et al., 2007).

MRS improves the assessment of pediatric brain tumors by adding biochemical information beyond that obtained with gadolinium-enhanced MRI. This is important because although most childhood brain tumors are low grade and respond to therapy, their diagnosis and treatment are often complicated by their frequent location adjacent to crucial structures, restricting diagnostic biopsies. Biomarkers of tumor biology and metabolism aid in the choice of treatment of pediatric brain tumors. Although not a proxy for histology, MRS provides noninvasive biomarkers for preoperative characterization of focal brain lesions and this is especially helpful when obtaining a biopsy is not feasible. Tzika et al. (2002) demonstrated that MRI with gadolinium enhancement did not correlate with choline (Cho)-containing compounds (indicating tumor) and lipid levels (indicating necrosis) obtained with MRS. Comparing metabolite findings with histologic findings of unclear focal brain lesions in children for preoperative characterization, Wilken et al. (2000) found MRS to be correct in 14 (82%), wrong in one (6%), and of no added value in 2 (12%) of 17 patients. Astrakas et al. (2004) states that Cho and lipids and/or lactate can serve as independent prognostic indices of tumor grading, especially when obtaining a biopsy is not feasible. Compared to histology, Astrakas et al. logistic regression analysis demonstrated that both Cho and lipids and/or lactate biomarkers are significant independent predictors of tumor grade ( $p < 0.001$ ). Compared with histology, combined Cho and lipids and/or lactate biomarkers demonstrated an accuracy of 91% ( $n=60$  of 66).

Other than to distinguish recurrent brain tumor from radiation necrosis, there is limited evidence supporting the use of MRS in adults with brain tumors. Additional, larger clinical trials are needed to validate the usefulness and role—in addition to other imaging and diagnostic procedures—of MRS in the diagnosis and treatment planning of adults with brain tumors.

A Technology Assessment conducted by Tufts-New England Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ) evaluated the use of MRS in brain tumors (2003). The conclusion stated that “human studies conducted on the use of MRS for brain tumors demonstrate that this non-invasive method is technically feasible and suggest potential benefits for some of the proposed indications. However, there is a paucity of high quality direct evidence demonstrating the impact on diagnostic thinking and therapeutic decision making. In addition, the techniques of acquiring the MRS spectra and interpreting the results are not well standardized. In summary, while there are a large number of studies that confirm MRS’ technical feasibility, there are very few published studies to evaluate its diagnostic accuracy and whether it can positively affect diagnostic thinking and therapeutic choice. Those studies that do address these areas often have significant design flaws including inadequate sample size, retrospective design and other limitations that could bias the results.”

The Blue Cross Blue Shield Technology Evaluation Center (TEC) evaluated MRS for suspected brain tumor (2003). The assessment was conducted to determine if MRS might aid in the diagnosis and treatment of brain tumors and improve patient outcomes, in particular, by reducing the number of unnecessary biopsies. The assessment formulation considered patients with brain lesions that were indeterminate on conventional imaging (e.g., MRI or computed tomography [CT]) and required differentiation between neoplasm and non-neoplasm. This included patients who initially presented with new brain lesions for which brain tumor was a differential diagnostic consideration, as well as patients who had undergone radiation treatment for brain tumors and had persistent or progressive brain abnormalities that were suspicious for either recurrent brain tumor or delayed radiation necrosis. The Summary of Evidence stated that “the overall body of evidence does not provide strong and consistent evidence regarding the diagnostic test characteristics of MRS, and those reviewers were unable to determine whether MRS provides sufficiently high sensitivity, specificity, or positive or negative predictive values to avoid brain biopsy safely.”

**National Comprehensive Cancer Network (NCCN):** NCCN Central Nervous System Cancers (v.1.2011) states the following regarding MRS, under heading “Principles of brain tumor imaging”:

- assesses metabolites within tumors and normal tissue
- optimal use is to differentiate tumor from radiation necrosis; may be helpful in grading tumors or assessing response.
- area most abnormal should be the best place to target for a biopsy.
- limitations; tumors near vessels, air spaces or bone.

**American College of Radiology (ACR)/American Society of Neuroradiology (ASNR):** A collaborative practice guideline was developed by the ACR and the ASNR (revised 2008). It states that MRS “is a proven and useful method for the evaluation, assessment of severity, and follow-up of diseases of the brain and other regions of the body. MRS should be performed only for a valid medical reason. While MRS can be useful in the diagnosis and management of patients, findings may be misleading if not closely correlated with clinical history, physical examination, laboratory results, and diagnostic imaging studies.” The American College of Radiology Practice Guideline for the Performance and Interpretation of MRS of the Central Nervous System lists indications for MRS. When conventional imaging by MRI or computed tomography (CT) is inadequate to answer specific clinical questions, indications for MRS in adults and children include, but are not limited to, the following:

- evidence or suspicion of primary or secondary neoplasm (pretreatment and post-treatment)
- grading of primary glial neoplasm, particularly high grade versus low grade glioma
- evidence or suspicion of brain infection, especially cerebral abscess (pretreatment and post-treatment) and human immunodeficiency virus (HIV)-related infections
- seizures, especially temporal lobe epilepsy
- evidence or suspicion of neurodegenerative disease, especially Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease
- evidence or suspicion of subclinical/clinical hepatic encephalopathy
- evidence or suspicion of an inherited metabolic disorder
- suspicion of acute brain ischemia or infarction

- evidence or suspicion of a demyelination or dysmyelination disorder
- evidence or suspicion of traumatic brain injury
- evidence or suspicion of brain developmental abnormality and cerebral palsy
- evidence or suspicion of other neurodegenerative diseases such as amyotrophic lateral sclerosis.
- evidence or suspicion of chronic pain syndromes.
- evidence or suspicion of chromosomal and inherited neurocutaneous disorders such as neurofibromatosis and tuberous sclerosis.
- evidence or suspicion of neurotoxicity disorders.
- evidence or suspicion of hypoxic brain injury.
- evidence or suspicion of spinal cord disorders such as tumors, demyelination, infection, and trauma.
- evidence of neuropsychiatric disorders such as depression, post-traumatic stress syndrome, and schizophrenia.
- differentiation between recurrent tumor and treatment related changes or radiation injury.
- differentiation of cystic lesions, e.g., abscess versus cystic metastasis or cystic primary neoplasm.
- evidence or suspicion of cerebral vasculitis, systemic lupus erythematosus (SLE), and neuropsychiatric systemic lupus erythematosus (NPSLE).
- evaluation of response to treatment of neurological disorders.”

### **Inborn Errors of Metabolism**

Inborn errors of metabolism refer to inherited defects that produce metabolic abnormalities in the human body (e.g., lysosomal disorders, peroxisomal disorders, mitochondrial disorders, white matter disorders, and disorders of amino and organic acid metabolism). MRS provides complementary information to an MRI. Due to the rare nature of these disorders, evidence supporting the use of MRS for this group of diseases is limited, primarily in the form of single case reports and small case series (Bizzi, et al., 2008; Cecil, 2006; Oz, et al., 20005; Lin, et al., 2003). Cecil (2006) reviewed the use of MRS in metabolic disorders and identified case reports on the following disorders:

#### **Lysosomal Disorders:**

- Sjögren-Larsson's syndrome
- neuronal ceroid lipofuscinosis
- cerebrotendinous xanthomatosis
- Niemann-Pick type C disease
- mucopolysaccharidoses
- metachromatic leukodystrophy
- globoid cell leukodystrophy (Krabbe's disease)
- Sandhoff's disease
- Tay-Sachs disease

#### **Peroxisomal Disorders:**

- Zellweger syndrome
- rhizomelic chondrodysplasia punctata
- X-linked adrenoleukodystrophy

#### **Mitochondrial Disorders:**

- pyruvate dehydrogenase deficiency
- cytochrome oxidase deficiency
- Complex I deficiency
- mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

#### **White Matter Disorders:**

- infantile Alexander's disease
- Canavan's disease

- vanishing white matter disease
- Pelizaeus Merzbacher disease

#### Disorders of Amino and Organic Acid Metabolism:

- phenylketonuria
- maple syrup urine disease
- L-hydroxyglutaric aciduria, methylmalonic aciduria, propionic aciduria

#### Miscellaneous disorders:

- Wilson's disease
- galactose-1-phosphate uridylyltransferase deficiency
- defects in creatine synthesis and transport

In lysosomal disorders, MRS is useful in monitoring therapeutic interventions. In peroxisomal disorders, markedly elevated concentrations of Cho, ml, and glutamine in affected white matter suggest active demyelination and glial proliferation as seen in X-linked adrenoleukodystrophy (ALD). The detection of MRS abnormalities before the onset of neurologic symptoms may help in the selection of these patients for bone marrow transplantation and stem cell transplant. Detection of CNS lactate by MR spectroscopy is useful in the diagnosis of mitochondrial disease. In patients with disorders of amino and organic acid metabolism, for example nonketotic hyperglycinemia, elevated cerebral glycine can be measured with MRS. Additionally, MRS seems to be useful for examining patients who suffer from maple syrup urine disease (MSUD) in different metabolic states. MRS is able to predict underlying pathophysiology across a relatively wide spectrum of hereditary leukoencephalopathies.

#### Unproven Indications

There is insufficient evidence in the published, peer-reviewed scientific literature defining a clinical role for MRS for applications other than its use in brain tumors and inborn errors of metabolism. Small cohort studies suggest that MRS is promising for other specified indications; however, it remains unknown if results will be reproducible in larger studies. More importantly, although MRS can accurately define the chemical composition of the tissue under study, the impact of MRS on health outcomes for other applications has not yet been determined through well-designed clinical trials.

**Breast Cancer:** The use of MRS in breast cancer is generally found in the research setting. Varying metabolic findings have been identified in malignant versus non-malignant tissue; however, more study is needed to determine if the use of MRS in the diagnosis and/or management of patients with breast cancer can have impact on clinical outcomes (Sardanelli, et al., 2009; Bartella, et al., 2006).

**Dementia:** The use of MRS in dementia is currently limited to the research setting. Brain metabolic abnormalities in Alzheimer's disease and dementias have been identified; however, more study is needed to determine if the use of MRS in the diagnosis and/or management of patients with dementia can have an impact on clinical outcomes (Westman, et al., 2010; Kantarci, et al., 2007; Jessen, et al., 2006).

**Encephalopathy:** It has been suggested that, for diagnostic assessment, MRI should include MRS if single-voxel proton MRS is available for term infants with neonatal encephalopathy (American Academy of Neurology/Ment, et al., 2002, reaffirmed 2005). The small, preliminary studies that have been conducted have not yet demonstrated that the use of MRS has an impact on the clinical outcomes in patients with encephalopathy (Thayyil, et al., 2010; Da Silva, et al., 2006; Robertson, et al., 2001). The AAN guideline Neuroimaging of the Neonate (reaffirmed 2005) states, "for diagnostic assessment, MRI should include MRS if single-voxel proton MRS is available for term infants with neonatal encephalopathy" (Ment, et al., 2002).

**Epilepsy:** Willmann et al. (2006) conducted a meta-analysis and concluded that "much research work remains to be done to standardize, integrate and understand the possible additional role of MRS in the presurgical evaluation of intractable epilepsy. Unilateral MRS abnormalities and the absence of bilateral

spectroscopic abnormalities might be valuable to select patients with good outcome, but this might depend on the underlying pathology or population. Larger studies with a specific question, for example, in patients with non-localizing ictal scalp EEG and/or MRI should be obtained.”

**Multiple Sclerosis (MS):** Although MRS can identify chemical features of MS (e.g., reduction of NAA), the impact of MRS on treatment planning and health outcomes has not yet been determined through well-designed clinical trials. Filippi et al. state that “non-conventional MRI techniques (such as magnetization transfer MRI [MT-MRI], diffusion tensor MRI (DT-MRI); functional MRI [fMRI], and MRS) were considered but not recommended” (European Federation of Neurological Societies [EFNS] guidelines on the use of neuroimaging in the management of multiple sclerosis) (2006). Frohman et al. 2005 (American Academy of Neurology/Utility of MRI in Suspected Multiple Sclerosis) states under future research discussion: “New imaging technologies, such as magnetization transfer ratios (MTR), MRS, diffusion tensor imaging, tractography, and brain atrophy measurements will undoubtedly facilitate a better understanding of the extent and dynamic aspects of disease pathology in MS.” The use of MRS in MS is currently limited to the research setting (Steen, et al., 2010).

The AAN guideline entitled Utility of MRI in Suspected Multiple Sclerosis (reaffirmed 2005) states, “new imaging technologies, such as magnetization transfer ratios (MTR), MRS, diffusion tensor imaging, tractography, and brain atrophy measurements will undoubtedly facilitate a better understanding of the extent and dynamic aspects of disease pathology in MS. Each of these new MRI techniques will need to be evaluated for sensitivity and specificity in detecting tissue injury in MS and for predicting the development of MS in the future” (Frohman, et al., 2003).

**Myocardial Ischemia:** The use of MRS in individuals with myocardial ischemia is primarily seen in the research setting (Hudsmith, et al., 2009; Johnson, et al., 2004).

**Parkinson’s Disease:** The use of MRS in the diagnosis and/or treatment of Parkinson’s Disease is generally limited to the research setting. In a review article, Rango et al. (2007) state that MRS is a tool for investigating many pathophysiological aspects of Parkinson’s (i.e., alterations of brain energetics, brain biochemistry and brain biophysics). Clinical studies have concentrated mainly on metabolites containing hydrogen (<sup>1</sup>H MRS) and phosphorus (<sup>31</sup>P MRS), studying single, localized volumes of brain tissue. Rango notes that through further exploration of its possible clinical and pathologic correlations, MRS “will be fundamental in furthering understanding of Parkinson’s disease and parkinsonian syndromes.”

**Prostate Cancer:** Umbehr et al. (2009) conducted a systematic review and meta-analysis to establish the current role of combined MRI and MRS in the diagnosis of prostate cancer and to explore risk profiles with the highest benefit. The meta-analysis contained a total of 581 patients (seven studies on men with suspected prostate cancer and nine studies analyzing correlations of parts of the prostate within men with proven cancer). The authors noted they found limited evidence indicating a potential role of this technique in the future. Umbehr et al. stated “At this stage, clinical implications of our results remain limited for several reasons. Studies tended to be of limited size, applied different methods, and investigated a broad spectrum of patients. Moreover, study quality and reporting was limited.” Their authors stated there were substantial variations in the way spectroscopy findings were used for the identification of prostate cancer indicating a lack of consensus regarding diagnostic criteria and thresholds. The authors stated “it is too early to call for broad application of this method in clinical practice”. Further improvement of the technology may increase its role in the future.

In a prospective study, Weinreb et al. (2009) assessed the value of combined endorectal MRI and MRS as compared with endorectal MRI alone for cancer localization, in 110 patients scheduled to undergo radical prostatectomy. Weinreb et al. found the accuracy of combined MRI/MRS for sextant localization of peripheral zone prostate cancer is equal to that of MRI alone.

In a literature review, Lawrentschuk et al. (2009) sought to determine the efficacy of MRI for targeting cancer, compared with biopsies, in patients with previous negative prostate biopsies and persistently elevated prostate-specific antigen (PSA) levels. Included studies were prospective and in all, 215 patients

were assessed across the spectrum of prostate cancer. The number of cores taken at initial biopsy was 6-10. In these studies, the cancer-detection rate at repeat biopsy was 21-40%. For MRI or combined MRI/MRS the overall sensitivity for predicting positive biopsies was 57-100%, the specificity 44-96% and the accuracy 67-85%. In five studies, specific MRI-targeted biopsies and standard cores were taken, with a significant proportion of patients (34/63, 54%) having cancer detected purely because of the MRI-targeted cores. In none of the studies were clinicians taking the biopsies unaware of the MRI results. It should be noted that this review included six studies and MRS was utilized in four of the studies.

The National Comprehensive Cancer Network® (NCCN®) Prostate Cancer guideline (v.3.2010) states the following under Post-irradiation Recurrence: “A negative biopsy following post-radiation biochemical recurrence poses clinical uncertainties. Observation, ADT, or enrolling in clinical trials are viable options. Alternatively, the patients may undergo more aggressive workup, such as repeat biopsy, MR spectroscopy, and/or endorectal MRI.”

**Psychiatric Disorders:** The use of MRS in psychiatric disorders is also primarily found in the research setting. Brain metabolic abnormalities in psychiatric patients versus healthy controls have been identified; however, more study is needed to determine if the use of MRS in the diagnosis and/or management of patients with psychiatric disorders can have an impact on clinical outcomes (Dager, et al., 2008; Yildiz-Yesiloglu and Ankerst, 2006).

### Summary

Magnetic resonance spectroscopy (MRS) provides unique information that can aid in distinguishing recurrent brain tumor from radiation necrosis, and provide additional information in pediatric brain tumor treatment planning. Also, case reports and small case series suggest that MRS provides valuable information in the diagnosis of inborn errors of metabolism. For other proposed indications, there is insufficient evidence in the published, peer-reviewed scientific literature defining a clinical role for MRS. Although MRS can accurately define the chemical composition of the tissue under study, the impact of MRS on health outcomes for other applications has not yet been determined through well-designed clinical trials.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

### Covered when medically necessary:

CPT®*	Description
76390	Magnetic resonance spectroscopy

ICD-9-CM Diagnosis Codes	Description
191.0 – 191.9	Malignant neoplasm of brain
225.0	Benign neoplasm of brain and other parts of nervous system, Brain
239.6	Neoplasms of unspecified nature, Brain
270.0 – 270.9	Disorders of amino-acid transport and metabolism
271.1	Galactosemia
272.7	Lipidoses
275.1	Disorders of copper metabolism
277.5	Mucopolysaccharidosis
277.86	Peroxisomal disorders
277.87	Disorders of mitochondrial metabolism
330.0	Leukodystrophy

330.1	Cerebral lipidoses
742.9	Unspecified anomaly of brain, spinal cord, and nervous system
757.1	Ichthyosis congenita
V10.85	Personal history of malignant neoplasm of brain

**Experimental/Investigational/Unproven/Not Covered when used to report any indication other than what is covered in this policy:**

ICD-9-CM Diagnosis Codes	Description
217	Benign neoplasm of breast
290.0-290.9	Dementias
332.0-332.1	Parkinson's disease
340	Multiple sclerosis
345.0-345.91	Epilepsy
348.8	Other demyelinating diseases of central nervous system
414.8	Other specified forms of chronic ischemic heart disease
414.9	Chronic ischemic heart disease, unspecified
V16.42	Family history of malignant neoplasm, Prostate
	All Other codes

**\*Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.**

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21. National Comprehensive Cancer Network<sup>®</sup>. Clinical Practice Guidelines in Oncology<sup>™</sup>. Prostate Cancer v.3.2010. Accessed October 2010. Available at URL address: [http://www.nccn.org/professionals/physician\\_gls/PDF/prostate.pdf](http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf)

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	11/15/2007	0244	Magnetic Resonance Spectroscopy (MRS)

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.