GUTHY JACKSON® Charitable Foundation

Series: ***Do You Know NMO ?***
Module: 1

▶ *NMO Biomarkers & You…*

Today, more than 7 billion people call planet Earth home. Yet, each one of us interacts with the world in a different way. Over time, we gather experiences that form unique signatures of our lives… ups & downs… setbacks & successes. Each one of us is an individual signal of how we adapt to the world — and how we change the world.

In a similar way, each of us contains billions of cells & molecules… and everyone has a purpose. When studied over time, their patterns can help us to understand health and disease. When cells or molecules are proven by research to explain a healthy state, disease cause, or treatment response, they are called *Biomarkers*. For example, in NMO, the anti-AQP4 antibody is a biomarker which signals that the immune system has reacted to AQP4.

With help from the GJCF, researchers are exploring cells & molecules that offer new insights into NMO causes and cures. From the T cells that govern the immune response, to B cells that make antibodies, to other cells and molecular causes of inflammation — finding the biomarkers of NMO and how they can be used to prevent, diagnose & treat disease are keys to the cure.

GJCF drives laboratory & clinical research to find new biomarkers in NMO. Projects focused on predicting relapses, identifying cells or molecules that wax or wane in response to effective therapies, and defining causes and genetic risks of NMO are priorities. In turn, applying such biomarkers to NMO patient care holds promise to predict & stop relapses before they occur, target therapies to the cells or molecules that cause disease, and prevent NMO from beginning at all.

Each of us can play a unique part in NMO biomarker research. Through the GJCF *CIRCLES* project, simply donating a sample of blood and medical data every 6 months can speed understanding — and solving NMO together.

What part do you play in the *NMO Story* ?

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▶ *Test Your Knowledge: NMO Biomarkers*

Q1. True or False: An NMO biomarker can be a cell or molecule ?

A1: True. A biomarker can be a type of cell or molecule — and may be found in some places in the body but not others. For example, certain types of cells and molecules pass through the *blood brain barrier* and into the *cerebrospinal fluid* (CSF), while others do not. So, particular biomarkers may be present in the CSF, while others are found only in the *peripheral bloodstream* (e.g. blood drawn from a vein in the arm). If proven to reliably indicate or predict the diagnosis, disease status or severity, or a response to therapy, NMO biomarkers can be important tools in preventing, treating or curing NMO. Proving that a biomarker is specific to NMO or a key signal of the disease is a process called *validation*. This process must be carefully performed, and eventually approved by regulatory agencies for a biomarker test to be certified for use in the clinic.

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Q2. True or False: To date we know only one biomarker in NMO ?

A2: True. To date the only validated biomarker in NMO is the anti-AQP4 antibody, or NMO-immunoglobulin G (*NMO-IgG*).

Antibodies are large, complex proteins that target and bind to other molecules, or *antigens*: anti-AQP4 antibody is meant to only bind to the water channel protein, *aquaporin-4*. When antibody targets a molecule normally present in the body, it is called an *auto-antibody* — and its target is called an *auto-antigen*. B lymphocytes (or *B cells*) make antibodies, but only when approved by T lymphocytes (or *T cells*). In this way, NMO-IgG or other auto-antibodies can serve as breadcrumb trails to guide research back to the types of B cells that made them, and the types of T cells that approved them. In turn, these cells may be targets for new or improved therapeutics. Today, there is interest in antibodies other than NMO-IgG that may exist in patients diagnosed with NMO or NMO spectrum disorder (*NMO/SD*).

The GJCF accelerates research to address these questions and help find safe and effective solutions to NMO/SD.

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Q3. True or False: All NMO patients test positive for NMO-IgG antibody ?

A3: False. The NMO-IgG test result is positive in only ~ 75% of patients diagnosed with NMO or NMO/SD. Because *serum* is most often used to test for the presence of NMO-IgG antibody, a positive result is termed *seropositive*, while a negative result is termed *seronegative*.

There are several reasons for a seronegative result, including:

- **the type of test (called an *assay*) used to detect the antibody was not effective (did not detect the antibody even though it is present)**
- **the type of biospecimen assayed (e.g. blood vs. CSF) did not contain any detectable amount of NMO-IgG**
- **no NMO-IgG exists, suggesting an autoimmune process and/or auto-antigen different from AQP4 or NMO-IgG may be involved in the cause of disease in that patient.**

Although uncommon, the assay results for NMO-IgG may change over time in some individuals. For example, certain types of therapies may affect the ability to detect NMO-IgG. Likewise, as assays improve, NMO-IgG may be detected in some patients who tested negative in the past. This area of research may help uncover the causes & cures of NMO/SD.

An area of related research focus is that of seronegative patients. New evidence suggests that antibodies to antigens other than AQP4 may exist in this group of patients. For example, antibody targeting myelin oligodendrocyte glycoprotein (or *MOG*) appears to be present in some patients in whom NMO-IgG cannot be detected. This pattern suggests that *anti-MOG* antibodies may be new biomarker candidates in some NMO/SD patients.

The GJCF supports breakthrough research to improve assay accuracy & reliability understand where biomarkers are best found in the body, and explore *immune pathways* that may drive NMO/SD disease regardless of whether it involves AQP4, MOG or other targets of autoimmunity.

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Q4. True or False: Genes may be useful as biomarkers in NMO ?

A4: True. Genes and the codes they contain carry all the instructions necessary to cause autoimmune responses, make auto-antibodies or *complement* proteins, control T or B cell function, and so on. Genes also encode signals needed to repair tissues damaged by NMO/SD.

Genes are composed of a special type of molecule, called deoxy-ribonucleic acid, or *DNA*. Think of genes as the software of a cell: they are the code of instructions for creation of proteins that are the hardware of the cell. Humans have two copies of every gene; each copy is called an *allele*. Maybe even more important than composition is the *sequence* in which units of DNA are organized in a given allele. Gene *transcription* converts information it encodes into a messenger molecule called ribonucleic acid, or *RNA*. Transforming the instructions of a messenger RNA molecule into a functioning protein is called *translation*. Some sequences of a gene store the instructions for specific *amino acids* that form its protein. Other sequences control when the gene is turned on or off. Regulating when and where a gene is expressed can also be as important as what protein it encodes. Sequences of DNA, RNA or amino acids, and patterns of their expression, hold secrets into causes and effects of NMO or NMO/SD. With careful research, each aspect of these gene fingerprints may serve as biomarkers to prevent, diagnose, treat and cure NMO and NMO/SD.

The GJCF is leading new and exciting efforts to find genes, decode their roles and solve their functions or dysfunctions that contribute to NMO/SD.

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Q5. True or False: Biomarker research only examines blood samples ?

A5: False. In addition to blood, many diverse types of biological materials (called *biospecimens*) may be used in biomarker research or development. For example, research is actively being performed to discover new NMO biomarkers that may be present in saliva, urine, skin perspiration and other biospecimens.

The GJCF is supporting basic and clinical research to identify biomarkers in blood or CSF, as well as in other biospecimens such as saliva or urine that can easily be obtained and tested — even at home.

Discovering and validating biomarkers are the key steps to the important goal of identifying new and better ways to prevent, diagnose, treat and cure NMO/SD. Exciting new and smart technology is also emerging that can perform biomarker tests quickly and easily, and even transmit results from home to the clinical care team. All of these advances focus on serving patients and their *caregivers*, and will be strengthened the more the *NMO community* actively joins in the research. The GJCF is here to help.

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▶ *Test Your Knowledge: NMO Biomarkers*

Q6. True or False: Only patients may participate in biomarker research ?

A6: False. Understanding and solving NMO or NMO/SD will result from two very distinct groups: 1) patients diagnosed with NMO/SD; and 2) comparative control individuals who are not.

In biomarker research, ideal controls are individuals not affected by NMO or NMO/SD, but closely matched in age, gender, race, or other relevant *demographic* features, as well as treatment history and relevant clinical care. Control participants may have an autoimmune disease other than NMO or NMO/SD, may be affected by a chronic disease that is not autoimmune in nature, or may be healthy. Controls may also be related or unrelated to NMO patients. By understanding what NMO is — and what it is not — we can make great strides in preventing, diagnosing, treating and curing NMO or NMO/SD… and contribute to improved care for patients affected by other diseases as well.

GJCF is sharply focused on curing NMO/SD. Even so, the quantum leaps it is pioneering are likely to help patients who are affected by other autoimmune diseases, such as multiple sclerosis, lupus, myasthenia gravis, psoriasis, and beyond. Exciting GJCF research into *immune system checkpoints* also has the potential to discover promising new ways to prevent or treat other important diseases, including cancers.

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Q7. True or False: The CIRCLES project enables NMO biomarker discovery ?

A7: True. The *CIRCLES* project is a living and breathing research effort. The name is short for the Collaborative International Research in Clinical and Longitudinal Experience Study of NMO and NMO/SD. This type of study occurs over an extended period of time (*longitudinal*). The research focuses on participants who are diagnosed with NMO/SD, as well as control participants who have other autoimmune diseases, unrelated chronic illnesses, or no known disease (healthy). Participants work with their *CIRCLES site* doctor to donate a small sample of blood or other biospecimen, and a defined set of medical data, every 6 months. The set of biospecimens and medical data create a *biobank*, which is already being used to drive discovery research in NMO biomarkers.

The GJCF is truly grateful to all the patients, relatives, caregivers, healthcare professionals and other individuals who have joined us in this groundbreaking study. We invite all stakeholders to consider being part of this bold new effort on the mission to cure NMO.

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▶ *Here to Help*

- **The Guthy-Jackson Charitable Foundation (GJCF) supports efforts directed at solving NMO and NMO/SD. It promotes involvement of all stakeholders in facilitating clinical advances to prevent, diagnose and treat patients — and ultimately cure NMO and NMO/SD.**

- **The GJCF serves to facilitate education of all NMO stakeholders. The views and information herein are intended to aid education of the latest research and clinical advances in NMO and NMO/SD, and heighten awareness for advocacy. This information is provided solely to assist in self-education and informed decision-making by each individual of the NMO community as they deem best for themselves.**

- **The GJCF welcomes comments and suggestions regarding this educational module and overall program. Feel free to contact Derek Blackway, Manager - Communications, at the following venues:**

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