The Rise of Autoimmunity and the Role of IQuity

Recognizing and diagnosing an autoimmune disease at the earliest clinical time points can be a difficult process for both the patient and provider. The quote "I knew there was something wrong, but didn't know what it was or where to go," sheds light on a common experience at the beginning of the autoimmune disease patient story. These types of stories are all too familiar for patients who live for years with vague, recurring symptoms without any clear diagnosis until they eventually discover that their immune system—the very system meant to protect them from harm—is now a chronic problem.

This statement of uncertainty draws attention to the need for additional diagnostic tools in the field of autoimmune disease. The long-term uncertainty felt by these patients compounds the physical problems with emotional stress. While many patients can experience a long and complicated diagnostic process starting at the earliest symptoms, there are technological advancements that can change this reality. Here, we will close our three-part series by looking at autoimmune disease directly and then explain how specific autoimmune diseases can be detected leveraging the power of RNA diagnostics.

The reality that patients with autoimmune disease often live for years with vague, recurring symptoms and no clear diagnosis draws attention to the need for additional diagnostic tools.

The incidence and prevalence of autoimmune disease are increasing in the Western world. Though generalized numbers are somewhat difficult to find, a publication from 1997 put the number at 3% of the US population suffering from an autoimmune condition. In 2005, the NIH put that number at roughly 5-8%, and a recent meta-analysis showed a steady increase in the incidence and prevalence of autoimmune diseases since the mid-80s across the Western world. Obtaining a specific number of individuals suffering from an autoimmune disease is difficult because different organizations include different numbers of autoimmune diseases (24 or 80 being two common standards) in their analysis, and many of these conditions are challenging to diagnose. The AARDA uses a broader list of diseases (80+) and says that at least 17% of the US population should be included. Regardless, more people suffer from one or more autoimmune disease than we have historically recognized.

Autoimmunity is the body responding to a perceived problem within itself. While this can be helpful for attacking cancer cells or responding to a pathogen, it's devastating when the immune system becomes dysregulated and attacks the body's healthy cells and tissues. These are complex situations, and in virtually all cases, it's not clear how dysregulation arises. Genetics play a role, but researchers believe a large driver of the increasing incidence is environmental and lifestyle changes, especially in developed countries.

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Furthermore, symptoms are sometimes vague or nonspecific. Fatigue, malaise, and rashes, for instance, may be the outward indicators that something is wrong. So, how long does one go before knowing there is a real problem?

Eventually, when a person decides to seek medical care, these symptoms become the starting point for the diagnostic process. If the provider determines the problem requires a work-up, extensive clinical examinations, laboratory analyses, and multiple office visits are standard. Referral to diagnostic and autoimmune specialists can be delayed due to lack of awareness of a particular autoimmune disease or the nonspecific nature of the symptoms. The case of multiple sclerosis in Brain Health: Time Matters in Multiple Sclerosis, published by Giovannoni late last year documents this claim. The report suggests that multiple sclerosis patients are often delayed up to two years before being referred to a neurologist or MS specialist. Also documented in this report is the need for biomarkers of disease activity that can be used to identify presence, absence, or activity of disease at the earliest time points to best manage patient care.

In 1948, Hargraves and colleagues described an early marker for autoimmune disease. They wrote about two types of cells (LE cells and Tart cells) found in bone marrow samples that contained a second nucleus. In fact, these cells were leukocytes that had engulfed the nuclei of other cells to break them down. While Tart cells were present in most samples, with increased numbers of various cancers, LE cells were restricted to patients with systemic lupus erythematosus (SLE). For many years, then, the presence of LE cells was used as an indicator of this autoimmune disease.

More recently, researchers have uncovered changes in any number of molecular and cellular markers that may be present depending on the disease. Initial blood work may find aberrations in white or red blood cells, as well as platelets. In serum, metabolic markers will show up at abnormal levels. Enzymes related to muscle cell function may be elevated, and markers of kidney function are often examined.

So, if there are known markers for basically any autoimmune disease, why is it so difficult to get a positive (or negative) diagnosis? For one thing, those markers are not binary and can show up in the absence of an autoimmune condition. Additionally, other diseases may present the same molecular or cellular characteristics. In these latter cases, the presence of a marker - in serum or urine, for example – simply indicates a problem that then requires more testing and clinical examination to obtain a differential diagnosis. Only recently has the medical community begun to have access to tests that provide the highly sought after ‘yes’ or ‘no’ determination for a specific disease.

In the mid-2000s, RNA profiling studies found specific patterns in patients with autoimmune conditions. Some of these patterns were similar across different diseases, but individual diseases also had unique signatures. Another step forward in differentiating between conditions came in 2007. At that time, IQuity Chief Science Officer, Dr. Tom Aune, led a group that used gene transcripts to get an even more accurate read on multiple sclerosis, a disease that is often difficult to diagnose in its earliest stages. The team started with microarrays

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to narrow down the list of candidate genes that could be relevant to MS. Unlike other studies using microarray to look for differential gene expression in patients with autoimmune diseases, the Aune group went a step further. Once the list of candidate genes was narrowed using microarray, they isolated RNA from blood samples and used qPCR (quantitative real-time polymerase chain reaction, or Q-RT-PCR) to determine the levels of nine relevant transcripts. The final results allowed the group to not only distinguish patients with MS from healthy controls, but from individuals suffering from other autoimmune diseases as well.

Since that first paper, the work on which IQuity was founded has continued to advance and includes the use of new technologies including RNA sequencing. The product of these endeavors is a suite of algorithms used to identify and quantify gene expression enabling us to distinguish between autoimmune and related conditions by analyzing RNAs found in whole blood. Our process, as described in peer-reviewed papers from 2012 and 2013, is to rule out other conditions. This can be done very effectively using machine learning techniques to analyze data collected from our library of patient samples across multiple medical disciplines. Our investigations have now examined three different branches of medicine including neurology, gastroenterology, and rheumatology. For instance, in neurology, we have focused on identifying gene expression signatures that are consistent with multiple sclerosis. We found that patients at the earliest clinical time points exhibit differences in expression of certain RNAs. These RNAs are distinct from other neurological diseases and healthy patients. Harnessing this information, we can now provide data to healthcare providers indicating presence of gene expression signatures consistent with MS early in the course of disease.

Our technology will be among the first to provide RNA expression information to healthcare professionals who refer, diagnose, and treat patients with suspected autoimmune and related conditions. Our current focus is on multiple sclerosis and IBS/IBD – Crohn's and ulcerative colitis - and our first tests will launch in late spring 2017. In addition to MS and GI, IQuity plans to expand its offerings to include rheumatologic diseases like rheumatoid arthritis, lupus and fibromyalgia syndrome.

Even while acknowledging IQuity's stake in the field of RNA diagnostics, the inclusion of RNA-based technologies will provide science and medicine with a quantitative tool for identifying an ever-growing list of human diseases. The specificity and accuracy of RNA technologies, like those IQuity has developed, will provide timely and accurate information for healthcare providers as they either rule in or rule out a suspected autoimmune diagnosis. This actionable information speeds time to treatment, which leads to optimal patient outcomes and a better quality of life for patients.

IQuity's suite of algorithms identify and quantify gene expression patterns enabling us to distinguish between autoimmune and related conditions by analyzing RNAs found in whole blood.

For any questions regarding the IQuity IQIsolate™ tests, please contact us at info@iquity.com or

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