Biomarker Testing: Beyond Oncology

Substantial progress has been made in the fight against cancer in recent decades, resulting in a 33% reduction in the cancer death rate since its peak in 1991.[i] As patients are living longer, and some cancers become more of a chronic condition, cancer patients and survivors are often living with one or more comorbidities (additional diseases or medical conditions) due to shared risk factors and side effects of cancer treatment.

- A recent study found that nearly 2 in 3 patients diagnosed with colorectal cancer, lung cancer, or Hodgkin's lymphoma had at least one comorbidity at the time of their diagnosis, and about half of patients had multiple comorbidities.[ii]
- According to the National Cancer Institute, the top four most commonly diagnosed cancers—lung, colorectal, breast, and prostate—have rates of comorbidity at 52.9%, 40.7%, 32.2%, and 30.5%, respectively for patients over age 66. [iii]
- **The most common comorbidities cancer patients and survivors face include diabetes, COPD, cardiovascular diseases (e.g., congestive heart failure, cerebrovascular disease, peripheral vascular disease), renal failure, and rheumatological conditions (e.g., osteoarthritis and rheumatoid arthritis).[iv]**
    - Anxiety is also more common in cancer patients, and patients with cancer are five times more likely to suffer from depression compared to the general population.[v]

While most current applications are in cancer, biomarker testing is becoming increasingly important to the treatment of other disease areas including rheumatoid arthritis, other autoimmune conditions, organ and tissue transplant, rare diseases, preeclampsia. Pharmacogenomic biomarker testing also guides treatment across a wide range of conditions. There is biomarker research happening in many other areas including Alzheimers, other neurological conditions, cardiology and more. Current non-oncology biomarker testing applications could be used to address common comorbidities in cancer patients and survivors and as personalized medicine continues to evolve, non-oncology biomarker testing applications will likely have an increasing role in guiding treatment for patients with and without a cancer diagnosis.

Biomarker Testing and Autoimmune and Autoinflammatory Arthritis Diseases

One in 10 people are living with autoimmune and autoinflammatory arthritis diseases.[vi] The average age of onset in adults is 20 – 40.[vii,viii,ix,x] Age of juvenile onset disease varies, but can happen in early childhood.[xi] While it is recommended to initiate treatment within six months of disease onset to increase the probability of remission[xii], it takes several years to get an accurate diagnosis for a majority of patients.[xiii] Due to several factors, including clinical trials that do not represent real world populations, comorbidities, and disease heterogeneity, only 40-60% respond well to existing treatments.[xiv,xv, xvi, xvii] It is estimated that as many as 70% of patients develop comorbidities (including dual diagnosis and conditions such as heart disease or Alzheimers).[xviii,xix] The standard arthritis treatment approach of trial-and-error further complicates therapy response. Biomarker testing can be an important tool to pinpoint diagnosis, understand prognosis, and develop treatment plans that improve quality of life and increase chances for remission.

Biomarkers are not new in the autoimmune and autoinflammatory arthritis disease space. For example, doctors often refer to elevated rheumatoid factor, anti-CCP, and antineutrophil cytoplasmic antibodies (ANCA) to assist in diagnosis and to predict worse outcomes in rheumatoid arthritis (RA).[xx] Some tests, like multi-biomarker disease activity (MBDA) blood tests, test for several biomarkers at one time to monitor disease activity and predict joint damage. While there are current applications, recent research continues to advance the use of biomarkers in rheumatology, which can aid in detection, diagnosis, and determining treatment response.

Current applications of biomarker testing for arthritis patients include:

Anti-CCP Antibody Testing for Rheumatoid Arthritis (RA)

Molecular signature response classifier (MSRC) tests monitor levels of specific antibodies and gene expressions which can help indicate a patient's likelihood to respond to tumor necrosis factor inhibitors (TNFi), a specific class of medications used to treat inflammatory conditions. A low score means the patient will be less likely to respond to these types of therapies. Ninety percent of RA patients are prescribed TNFi biologics as first line therapies, and better access to predictive biomarker testing could potentially improve health outcomes and lead to cost avoidance for millions of patients.[xxi]

Polyglutamate Testing

This testing measures the effectiveness of one of the most commonly prescribed drugs for RA. This test allows a provider to determine if the dose needs to be adjusted, or if the patient needs to be prescribed a different medication.

Biomarker Testing for Organ and Bone Marrow Transplants

Biomarker testing is used in bone marrow transplants to match patients and donors. A close match between a donor's and a patient's tissue markers is essential for a successful transplant outcome.[xxii] Biomarker testing is also critical in organ transplant to assess risks and monitor for rejection, with research happening on methods to utilize non-invasive biomarker testing to monitor for rejection and ultimately improve outcomes. While bone marrow transplants are best known for their use in the treatment of blood

cancers, biomarker testing is also essential for other disorders. For example, bone marrow transplants are used in the treatment of non-malignant chronic diseases such as Sickle Cell Disease.

Organ Rejection Status Testing

This type of testing analyzes donor derived cell-free DNA (dd-cfDNA) present in the bloodstream of a patient to determine if rejection of the transplanted organ is occurring. It is used to monitor a transplant patient for signs of rejection, allowing for modification of immunosuppressive therapy to maximize longevity. The cost for managing a failed transplant may be up to 500% more than a patient with a functioning transplant.[xxiii]

Sickle Cell Disease

Sickle cell disease is a chronic disorder which causes the body to make unhealthy red blood cells, causing organ damage, and need for a bone marrow transplant as a life-saving treatment. Beyond the implications of biomarker testing for bone marrow transplants to treat the disease, there is ongoing research in using biomarker testing to predict the risk of a patient with sickle cell disease experience vaso-occlusive crisis, which can result in severe pain and organ damage.[xxiv]

Biomarker Testing and Rare Diseases

A rare disease is defined in the United States as a disease or condition that impacts fewer than 200,000 people. There are more than 7,000 known rare diseases, affecting about 1 in 10 people in the United States.[xxv] Of the newly FDA approved personalized treatments in 2022, 35% were for the treatment of rare diseases[xxvi]. Personalized treatments often require biomarker testing prior to use to determine patient eligibility. Often, patients with rare diseases suffer while going undiagnosed or misdiagnosed for years. Biomarker testing often plays a critical role in rare diseases to establish or confirm a diagnosis and monitor disease progression and treatment effectiveness.

Biomarker Testing and Preeclampsia

The United States is the only developed country in the world where maternal morbidity and death rates are increasing.[xxvii] Hypertensive disorders of pregnancy, like preeclampsia, are a leading cause of these preventable deaths. Preeclampsia manifests with heightened maternal blood pressure and organ dysfunction, leading to severe complications like kidney and liver failure and cerebral edema. If left untreated (and in rare cases without preeclampsia symptoms), it can escalate to eclampsia, a condition categorized by seizures or a variant called HELLP Syndrome which can cause liver rupture, bleeding/clotting issues, and other morbidities.[xxviii] There is a disparate impact when it comes to maternal morbidity, with black women three times more likely to die from pregnancy-related complications compared to white women.[xxix]

Preeclampsia can vary in severity. Patients with a diagnosis should be monitored closely, but those at high risk of severe preeclampsia will likely remain in the hospital until delivery.

Prognostic sFlt1 and PlGF testing

This test measures two proteins in the blood to identify those at highest risk of developing severe preeclampsia.[xxx] The test helps providers to develop the appropriate treatment plan. Low-risk patients can

be monitored from home, alleviating financial and emotional burdens and reducing healthcare costs. Those at higher risk receive appropriately intensified care, increasing the likelihood of positive outcomes for both mother and baby.

Pharmacogenomic (PGx) Biomarker Testing

Pharmacogenomic (PGx) testing (also known as pharmacogenomic biomarker testing) is a component of precision medicine that involves examining a patient's inherited genes to detect variations that may impact the way a drug is broken down, absorbed and used within the body. Sometimes these variations can impact the safety and effectiveness of treatment. The same treatment given to patients with the same disease can produce different responses based on each person's inherited genes. There are a significant number of drug-gene pairs that can impact a patient's response to a medication, thus making PGx testing beneficial. These interactions are most common in oncology, neurology, cardiology, and infectious disease.

PGx Testing in Depression

Depression is the number one cause of disability in the United States for individuals ages 15-44.[xxxi] PGx biomarker testing can be used to inform the selection of prescription drugs to treat patients. This type of testing can help a provider to understand the way a patient's genomic make up may affect an individual's response to certain psychiatric drugs – including those used to treat depression. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used drugs to treat depression in adults.[xxxii] There are several genetic variants that may impact the effectiveness or safety of SSRIs.[xxxiii]

PGx biomarker testing made the difference for Julie, who was suffering from postpartum depression. After having an adverse reaction to the antidepressant that she was prescribed, an SSRI, she underwent PGx biomarker testing. The results showed that SSRIs may not be a good fit for her. Her doctor prescribed a different medication, and Julie credits that new medication with helping her feel like herself again:

> *"I felt defeated because these medications worked for others; why didn't they work for me? Now I know that's not how this works! Since being on a medication that is working for me, I am motivated, optimistic, and thriving – rather than trying to survive.*
>
> *-Julie L., Indiana*

[i] American Cancer Society. Cancer Facts & Figures 2023. Atlanta: American Cancer Society; 2023.
[ii] Fowler, H., Belot, A., Ellis, L. *et al.* Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers. *BMC Cancer* 20, 2 (2020). https://doi.org/10.1186/s12885-019-6472-9

[iii] National Cancer Institute. (2016). Annual report to the nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast or prostate cancer: Questions and answers. Retrieved from https://www.cancer.gov/news-events/press-releases/2013/ReportNationDec2013QandA#que12

[iv] Fowler, H., Belot, A., Ellis, L. et al. Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers. BMC Cancer 20, 2 (2020). https://doi.org/10.1186/s12885-019-6472-9

[v] Naser Abdallah Y., Hameed Anas Nawfal, Mustafa Nour, et al. Depression and Anxiety in Patients With Cancer: A Cross-Sectional Study. Frontiers in Psychology, 12 (2021). https://www.frontiersin.org/articles/10.3389/fpsyg.2021.585534

[vi] International Foundation for Autoimmune & Autoinflammatory Arthritis. What is AiArhtritis? Retrieved from https://www.aiarthritis.org/whatisaiarthriti

[vii] Hmamouchi I, Bahiri R, Hajjaj-Hassouni N. Clinical and radiological presentations of late-onset spondyloarthritis. ISRN Rheumatol. 2011;2011:840475. doi:10.5402/2011/840475

[viii] SarcoidosisUK. What is sarcoidosis? Accessed December 1, 2023. https://www.sarcoidosisuk.org/information-hub/what-is-sarcoidosis/.

[ix] Rubén Queiro, Patricia Tejón, Sara Alonso, Pablo Coto, Age at disease onset: a key factor for understanding psoriatic disease, Rheumatology, Volume 53, Issue 7, July 2014, Pages 1178–1185, https://doi.org/10.1093/rheumatology/ket363

[x] Crohn's & Colitis Foundation. Crohn's Disease Diagnosis and Testing. Retrieved from https://www.crohnscolitisfoundation.org/what-is-crohns-disease/diagnosis-testing.

[xi] Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases?. Autoimmune Dis. 2012;2012:251730. doi:10.1155/2012/251730

[xii] Demoruelle, M.K., Deane, K.D. Treatment Strategies in Early Rheumatoid Arthritis and Prevention of Rheumatoid Arthritis. Curr Rheumatol Rep 14, 472–480 (2012). https://doi.org/10.1007/s11926-012-0275-1

[xiii] International Foundation for Autoimmune & Autoinflammatory Arthritis. "Early Symptoms of AiArthritis" Retrieved from https://irp-cdn.multiscreensite.com/8f027529/files/uploaded/Final%20ESS%20from%20website%2003.2019%20.2.pdf

[xiv] Kayal M, Ungaro RC, Bader G, Colombel JF, Sandborn WJ, Stalgis C. Net Remission Rates with Biologic Treatment in Crohn's Disease: A Reappraisal of the Clinical Trial Data. Clin Gastroenterol Hepatol. 2023;21(5):1348-1350. doi:10.1016/j.cgh.2022.02.044

[xv] Wang R, Dasgupta A, Ward MM. Predicting Probability of Response to Tumor Necrosis Factor Inhibitors for Individual Patients With Ankylosing Spondylitis. JAMA Netw Open. 2022;5(3):e222312. doi:10.1001/jamanetworkopen.2022.2312

[xvi] Mehta, P and Manson, JJ (2020) What Is the Clinical Relevance of TNF Inhibitor Immunogenicity in the Management of Patients With Rheumatoid Arthritis? Front. Immunol. 11:589. doi: 10.3389/fimmu.2020.00589

[xvii] Moss A. Approach to Treatment Failure in Inflammatory Bowel Disease. Gastroenterology & Hepatology. 2022;18(6):360-363.

[xviii] Helga Radner, Viewpoint: how to measure comorbidities in patients with rheumatoid arthritis – clinical and academic value, Rheumatology, Volume 62, Issue SI3, October 2023, Pages SI282–SI285, https://doi.org/10.1093/rheumatology/kead436

[xix] Coghlan A. Autoimmune disorders linked to an increased risk of dementia. New Scientist. March 1, 2017. Accessed December 1, 2023. https://www.newscientist.com/article/2123274-autoimmune-disorders-linked-to-an-increased-risk-of-dementia/.

[xx] Sewell, C. ANCAs in patients with early RA. *Arthritis Res Ther* **3**, 66828 (2000). https://doi.org/10.1186/ar-2000-66828

[xxi] https://www.prismra.com/wp-content/uploads/2023/04/PrismRA-Strand-CU1-Clinical-Summary.pdf

[xxii] BeTheMatch.org. Transplant Basics. Human Leukocyte Antigen (HLA) Typing and Matching. Retrieved from https://bethematch.org/transplant-basics/how-blood-stem-cell-transplants-work/hla-basics/#:~:text=HLA%20basics-,HLA%20basics,body%20and%20which%20do%20not.

[xxiii] United States Government Accountability Office. End-Stage Renal Disease: Characteristics of Kidney Transplant Recipients, Frequency of Transplant Failures, and Cost to Medicare. In:2007.

[xxiv] Bryson, S. Red Blood Cell Biomarkers May Predict SCD Severity, Crisis Risk. Retrieved from ://sicklecellanemianews.com/news/red-blood-cell-biomarkers-predict-scd-severity-crisis-risk/#:~:text=The%20FA-WB-VCAM%20test%20is%20based%20on%20the%20known,the%20surface%20of%20cells%20that%20line%20blood%20vessels.

[xxv] Fermaglich, L.J., Miller, K.L. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet J Rare Dis 18, 163 (2023). https://doi.org/10.1186/s13023-023-02790-7

[xxvi] Personalized Medicine Coalition. (2023, February 22). Personalized medicine at FDA. Retrieved from https://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/report.pdf

[xxvii] Munira Z. Gunja, Evan D. Gumas, and Reginald D. Williams II, "The U.S. Maternal Mortality Crisis Continues to Worsen: An International Comparison," To the Point (blog), Commonwealth Fund, Dec. 1, 2022. https://doi.org/10.26099/8vem-fc65

[xxviii] The American College of Obstetricians and Gynecologists. Preeclampsia and High Blood Pressure During Pregnancy. April, 2023. Retrieved from https://www.acog.org/womens-health/faqs/Preeclampsia-and-High-Blood-Pressure-During-Pregnancy?utm_source=redirect&utm_medium=web&utm_campaign=otn

[xxix] Samantha Artiga et al., "Racial Disparities in Maternal and Infant Health: An Overview," Kaiser Family Foundation, November 10, 2020, https://www.kff.org/report-section/racial-disparities-in-maternal-and-infant-health-an-overview-issue-brief/.

[xxx] Thadhani, Ravi, et al. “Circulating angiogenic factor levels in hypertensive disorders of pregnancy.” NEJM Evidence, vol. 1, no. 12, 2022, https://doi.org/10.1056/evidoa2200161.
[xxxi] Anxiety and Depression Association of America. What is Depression. Retrieved from https://adaa.org/find-help/treatment-help/medication-options.
[xxxii] Anxiety and Depression Association of America. Medication Options. Retrieved from https://adaa.org/find-help/treatment-help/medication-options.
[xxxiii] Campos, A.I., Mulcahy, A., Thorp, J.G. *et al.* Understanding genetic risk factors for common side effects of antidepressant medications. *Commun Med* **1**, 45 (2021). https://doi.org/10.1038/s43856-021-00046-8