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INSIDE THIS ISSUE

BING NEEL SYNDROME

Jorge J. Castillo, MD
Dana-Farber Cancer Institute, Boston, MA, USA

Dr. Jorge Castillo

Jorge J. Castillo, MD, is Associate Professor at Harvard Medical School and Clinical Director of the Bing Center for Waldenström's Macroglobulinemia at Dana-Farber Cancer Institute.

Dr. Castillo was born in Peru and received his medical degree at the Universidad Autonoma Metropolitana in Mexico City. He completed his residency in internal medicine at the University of Massachusetts and his fellowship in hematology and medical oncology at Brown University.

Dr. Castillo specializes in the treatment of Waldenström macroglobulinemia. His research focuses on the various risk factors associated with an increased risk of developing hematologic malignancies. He currently is the principal investigator in a series of innovative clinical trials evaluating highly effective non-chemotherapeutic approaches for patients with Waldenstrom macroglobulinemia. Dr. Castillo has authored more than 250 peer-reviewed articles and has published his research in The New England Journal of Medicine, Lancet Oncology, Journal of Clinical Oncology, *and* Blood.

In 1936, eight years before Dr. Jan Gosta Waldenström described the case of two patients with severe anemia, a large, heavy protein in their blood (hyperglobulinemia), and a bleeding disorder, Drs. Jens Bing and Alex Valdemar von Neel described the case of two patients with hyperglobulinemia who presented with a rapid neurological deterioration. In 2022, we have a better understanding not only of Waldenström macroglobulinemia (WM), but also of Bing Neel syndrome (BNS), the associated neurological condition named for Drs. Bing and von Neel. Before focusing on BNS, I would like to review the diagnosis, indications to treat, and treatment options in patients with WM, as these have a direct impact on further understanding the choices available to manage BNS.

WM is a lymphoma, a lymphoplasmacytic lymphoma to be precise, in which the lymphoma cells produce a large monoclonal protein called IgM that accumulates in the patient's serum. In over 90% of patients with WM, the malignant cells will harbor an acquired (not congenital) mutation in the gene MYD88. A diagnosis of WM is therefore established by the presence of a lymphoplasmacytic lymphoma in the bone marrow, an excess of serum IgM protein in the blood, and the detection of the MYD88 mutation. Once a diagnosis is established, a decision should be made to treat or not. Some patients with WM are asymptomatic at the time of diagnosis and, as these patients can have a life expectancy similar to that of individuals of the same age and sex without WM, monitoring without intervention is the most reasonable approach. However, most patients with WM will develop symptoms during the course of the disease. Only when these symptoms affect the patient's activities of daily living or quality of life should treatment be instituted. Anemia (low hemoglobin causing symptoms of fatigue, shortness of breath), constitutional symptoms (fever, night sweats, or unintentional weight loss of unknown origin), neuropathy

Bing Neel Syndrome, cont. on page 3

IWMF
International Waldenstrom's Macroglobulinemia Foundation

6144 Clark Center Avenue
Sarasota, FL 34238

Telephone 941-927-4963
Fax 941-927-4467

E-mail: *info@iwmf.com*
Website: *iwmf.com*

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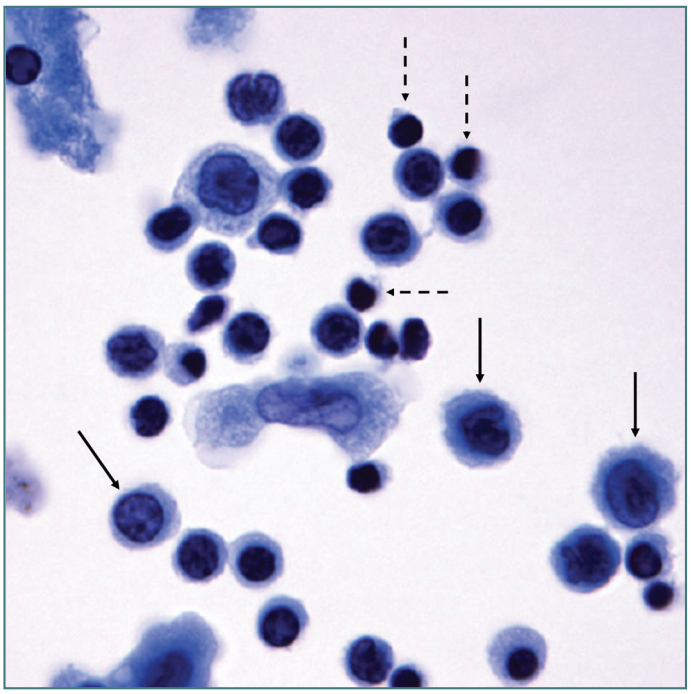

Figure 1. *Representative image of WM cells in spinal fluid showing lymphoplasmacytic cells (thin arrows), which are larger than the typical mature lymphocytes (dashed arrows).*

(numbness in feet and hands) are among the most common reasons to treat patients with WM. Treatment options include chemotherapy (bendamustine, cyclophosphamide, fludarabine) and non-chemotherapy agents. The latter include monoclonal antibodies (rituximab), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), BTK inhibitors (acalabrutinib, ibrutinib, zanubrutinib), and BCL2 antagonists (venetoclax). The choice of drug should be personalized based on patient's comorbidities (other medical conditions), other drugs taken by the patient, symptoms, and genomic profile.

BNS is a rare development described in 1% of patients with WM. Despite the rarity and given the high impact of BNS on the patient's quality of life, the 7th International Workshop for WM developed guidelines for the evaluation, diagnosis, and treatment of patients with BNS. In BNS, the WM cells gain access to the brain and spinal cord (central nervous system, or CNS) and can cause symptoms associated with this involvement. How or why the WM cells access the CNS in some patients but not in others is not well understood. In some patients, BNS can occur as the first manifestation of WM, and in others, BNS can occur as a late development after the patients have received multiple treatments for the WM. Very rarely, BNS can be present in the absence of WM. The symptoms of BNS are diverse and can include brain-related symptoms (headaches, facial paralysis, seizures), spine-related symptoms (weakness or numbness in limbs, unsteady gait), or a combination of these. Rarely, the optic nerve can be involved causing visual disturbances. The definitive diagnosis of BNS is made by detecting WM cells in the patient's spinal fluid (see **Figure 1**), and a lumbar puncture (spinal tap) is needed.

The spinal fluid should be evaluated using a technology called flow cytometry, aimed at demonstrating that the abnormal cells in the spinal fluid are monoclonal (belong to the same family) and share characteristics with the WM cells from the bone marrow. Other tests that can be done to investigate monoclonality in spinal fluid include molecular tests looking for immunoglobulin gene rearrangements and the MYD88 mutation. Imaging tests needed include a brain and spine MRI (see **Figure 2**), which can show a linear enhancement in the lining of the brain or spine (more common, also called diffuse), or suspicious masses (less common, also called tumoral). In 10-20% of patients with suspected BNS, the brain and spine MRI might not show abnormalities, and the diagnosis is made solely on the presence of malignant cells in the spinal fluid. In a portion of patients suspected to have BNS, the spinal fluid might not show abnormalities, and in this situation, the diagnosis of BNS is not definitive.

Once a diagnosis of BNS is established, we should evaluate the need for therapy, as we do in WM. In rare cases, the symptoms that prompted the initial evaluation resolve, and it is reasonable to observe without intervention. For patients who are symptomatic from BNS, treatment options should be discussed. In theory, any treatment option for WM should be beneficial in BNS. However, the vessels in the CNS have an additional layer of protection called the blood-brain barrier (BBB), which prevents specific molecules in the blood from reaching the CNS (think of expensive wines being protected from the environment in

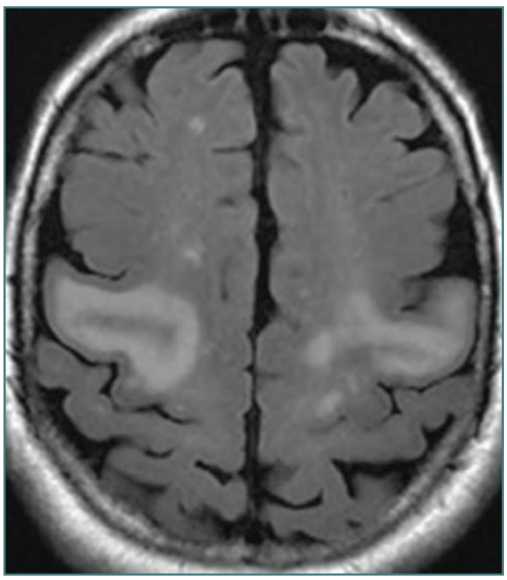

Figure 2. *Representative brain MRI from a patient with BNS showing abnormal enhancement in the temporal lobes.*

Bing Neel Syndrome, cont. on page 4

temperature and humidity-controlled cellars). Medications like cyclophosphamide, rituximab, and the proteasome inhibitors bortezomib, carfilzomib, or ixazomib do not access the CNS and therefore are not suitable to treat BNS. Treatment options for BNS are limited to other chemotherapy agents with easy access to the CNS but with a higher toxicity profile (methotrexate, cytarabine, fludarabine), and BTK inhibitors (ibrutinib is the one most studied in this setting).

The choice of therapy in BNS, as in WM, should also be personalized. Medications like methotrexate and cytarabine are administered intravenously in a hospital setting with close monitoring, given potential toxicity. Fludarabine is given intravenously (it is available orally outside of the United States) in an outpatient setting but has been associated with a risk of serious infections and the development of other bone marrow diseases such as myelodysplasia and leukemia. BTK inhibitors are oral agents with high efficacy in BNS and are not associated with developing other bone marrow diseases but do come with an increase in the risk of infections, bleeding, hypertension, and atrial fibrillation. It is possible that venetoclax has penetration to the CNS, but additional studies are needed. Marizomib is a unique proteasome inhibitor with good penetration into the CNS that is being evaluated in multiple myeloma and could be of use in BNS.

The goal of treatment is to decrease, and hopefully eliminate, the symptoms associated with BNS. As with WM, BNS is likely incurable but long remissions lasting for several years have been reported. Upon disease relapse, typically heralded by a recurrence of the neurological deficits or the development of new neurological deficits, along with changes in brain or spine MRI, a different treatment can be chosen after a careful discussion with the treating physician. Given the rarity of BNS, the outcome of these patients is not well studied. However, it seems that patients have a better outcome if the BNS is diagnosed earlier in the course of WM, with excellent outcomes in patients who have never received treatments for WM before developing BNS. In a recent study, the five-year survival rate from BNS diagnosis was 80%.

Unfortunately, BNS patients are typically excluded from clinical trials. However, future multicenter collaborations should focus on developing prospective studies in BNS patients, which will be of special interest for the Bing Center for WM. As more attention is drawn to BNS, I am hopeful that the number of treatment options available for BNS patients will further increase over time.

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MY JOURNEY WITH WM AND BING NEEL SYNDROME

By Julie Davidson

On February 14, 2011, I was diagnosed with both WM and Stage IIIA breast cancer followed by ten months of chemotherapy, a double mastectomy, and radiation. The chemotherapy aimed at the breast cancer had the added effect of reducing my IgM by over 50% and raising my hemoglobin to normal. Nothing like getting two for the price of one! In May of 2012 the marked fatigue returned, now accompanied by lower body weakness. My local oncologist, who had never heard of Bing Neel syndrome (BNS), did not recognize these symptoms as significant. My husband and I made the decision to go to Dana-Farber Cancer Institute (DFCI), where Dr. Steven Treon diagnosed Bing Neel in June 2012. He and my neuro-oncologist, also at DFCI, prescribed 11 rounds of high dose methotrexate, a chemotherapy. In October 2013 I had a recurrence of WM with elevated IgM, anemia, enlarged lymph nodes, an area of bone damage on the jaw, and a tumor on the kidney. This was successfully treated with fludarabine (selected because it crosses the blood-brain barrier) and rituximab. This is a short synopsis of my initial story published in the September 2016 issue of the *Torch*.

Since then, I have done very well with my Bing Neel, with a partial resolution of my symptoms after the treatment in 2012 and 2013. I went nine years without needing treatment again.

I have not returned to work since losing my job in 2011. My higher executive functioning and my memory are markedly affected, which I attribute to all of the chemotherapy, especially for the breast cancer. I still have issues with balance, strength, and some fatigue. My IgG and IgA are chronically low, and I experience frequent infections, requiring IVIG about every other month. However, and most importantly, I continue to have a very positive attitude. I spend very little time thinking about cancer and instead enjoy every day and just assume that I will be here tomorrow. We have no idea what the future holds for each of us, so I focus on making the best of my time.

I spend my extra time sewing and gardening. I do have help around the house and in the yard, as I find I do not have the stamina and endurance I had before 2011. I also have had a lot of physical therapy to improve some of my issues and have since begun working with a trainer who has really helped me improve my balance and stamina. I have been able to quit using my cane in most situations and am able to walk further distances. We discovered that much of my lower body nerve pain was attributable to severe spinal stenosis, or nerve compression from narrowing of the spinal canal, and I had decompressive laminectomy surgery to enlarge the canal in November 2020.

I had gone since the 2012/13 treatment without another Bing Neel problem. However, in June of 2021 I began experiencing increased fatigue, marked lower body weakness, and symptoms of cauda equina syndrome, which can cause incontinence and/or pain, numbness, or weakness in the lower body. Spinal MRIs and a lumbar puncture indicated that my Bing Neel was once again active. I am now doing well on zanubrutinib (Brukinsa), 160 mg twice a day, with minimal side effects, and the symptoms have subsided.

I think it is so important that ***Bing Neel*** *patients have a physician well-versed in this* ***rare condition*** *to oversee their treatment...*

My husband Wade is my greatest supporter and my best friend. He has been with me every step of the way, taking over or helping with day-to-day activities whenever I have felt less than my best. I couldn't have asked for a better partner through the ups and downs.

I am thankful that I have Dr. Jorge Castillo of DFCI on my treatment team, as he had guided my local oncologists through the bumps in the road. I think it is so important that Bing Neel patients have a physician well-versed in this rare condition to oversee their treatment, as information on this disease is changing rapidly.

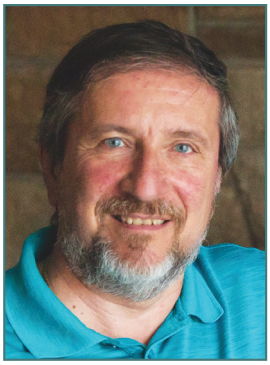
We have a small IWMF group of Bing Neel patients who share email addresses and are there to support each other. We also use this group to disseminate new articles or videos about our unusual disease. We put together periodic Zoom support meetings open to any BNS patient or caregiver and anyone who suspects they might have this condition. I am one of the IWMF LIFELINE volunteers for Bing Neel. If you would like to be added to the group or just want to talk about any concerns about life with BNS, please feel free to contact me at *jefdavidson@icloud.com* or by text or phone at 615-429-2017.

THE TORCHBEARER REPORT

By Peter DeNardis, Chair of the IWMF Board

EDITOR'S NOTE:

This new feature replaces the CEO's previous quarterly column; it will be written by Board members and others who tirelessly work to support the IWMF and its vision.



Peter DeNardis

Dealing with the enormity of living with a rare, incurable form of cancer is a daunting task under normal circumstances, and the ongoing global COVID-19 pandemic has made that journey even more complex for all of us. Whether you're a patient, caregiver, or medical professional, these are challenging times, and we are all called upon to do our utmost to be mindful of how our bodies are behaving because of WM and whether COVID-19 is having an impact on us.

For the past year or so, it has been my honor to be Chair of the Board of Trustees, and when I reflect on what the IWMF has accomplished despite the pandemic, I continue to be gobsmacked by the dedication of CEO Newton Guerin, the IWMF staff in our headquarters in Sarasota, FL, and my fellow Board members. All are vigilant in their focus on serving the global WM community, including the leaders and boards of the IWMF international affiliates tending to their country-specific needs; support group leaders doing their best to utilize electronic communication and online meeting tools to maintain vital connections; and the vast array of caring and committed volunteers giving of their time and talents to help provide the most current educational information and to advance cutting edge research.

To be honest, for my part, the call to action to help others dealing with WM is made more rewarding when I see fellow WMers around the world finding ways to communicate their appreciation to us, whether by phone call, email, social media posting, generous monetary donation, or some combination thereof. Truly, we are all dedicated to work even harder when we see the trust placed in us by the WM community by way of donated financial resources, despite the financial impact that the disease and the pandemic may have had. In such situations, I find that volunteer activities are not burdensome but become acts of love, compassion, and thanks for this trust.

For 2022, the IWMF is committed to ensuring that the 27th Annual Educational Forum will take place at the end of August. As you know, the 2021 Ed Forum was completely virtual due to the pandemic, and every effort is being made to ensure that we have a safe environment where we can all meet to learn from top-ranked researchers and clinicians, and from each other, on how best to deal with the physical and emotional aspects of living with WM. This may mean that we will once again go fully virtual or perhaps have a hybrid format of online and in-person sessions in Seattle, WA, that weekend. Ultimately, the health and safety of WMers is foremost in any planning, and it will continue to be the primary goal that guides planning for the event.

Largely because of the generous financial support of WMers around the world and the dedication of our Board, staff, and volunteers, new items will be seen this year in addition to the IWMF's "usual" array of education, support, and research activities:

- online webinars touching on a wide variety of WM-specific topics;
- new engaging online support opportunities that target specific manifestations of WM and specific communities of WMers;
- new IWMF-LLS Strategic Research Roadmap projects (read more at: *https://iwmf.com/research-strategy/*);
- new Robert A. Kyle Career Development Awards for young investigators (this will help create a community of younger investigators who can build upon the groundbreaking research that has already been achieved by folks like Dr. Steven Treon, Dr. Stephen Ansell, Dr. Meletios Dimopoulous, Dr. Véronique Leblond, and others);
- new IWMF Research Seed Money Grants to help investigators develop and explore new hypotheses concerning WM and how best to treat it.

Despite the pandemic, there is much to be excited about in 2022 if you're part of the WM community and much to look forward to as we collectively seek out and share information on how best to deal with diagnosis, treatment, and survivorship challenges. And I encourage every one of you to consider giving back in whatever way you can. If you have a specific skill or talent you think can benefit others, complete the form at: *https://iwmf.com/volunteerism/*. If you would like to help provide financial resources by giving to the IWMF, see: *https://iwmf.com/ways-to-give/* or to fundraise for the IWMF, see: *https://iwmf.com/fundraise-for-iwmf/*. Working together, we can help ensure that the IWMF accomplishes its vision of "A World Without WM"—and sooner rather than later!

Wishing all of you much good health and good fortune in 2022,

Pete DeNardis, Fellow WMer and
Chair of the Board of Trustees

WM RESEARCH HIGHLIGHT FROM THE 63RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY (ASH):

WNK2, A TUMOR SUPPRESSOR

BY GLENN CANTOR, SCIENCE EDITOR AND IWMF TRUSTEE

Presented by Maria Luisa Guerrera, Bing Center for WM, Dana-Farber Cancer Institute, Harvard University, Boston, MA, USA

Summary:

- Altered (mutated) genes such as MYD88 and CXCR4 can cause or drive WM.
- Alternatively, tumor suppressor genes normally keep cancers under control. But if tumor suppressor genes are mutated or not functioning correctly, the control is gone and cancers can progress more quickly.
- WNK2 is a tumor suppressor gene that may be involved in WM. Many WM patients have defective or silenced WNK2.
- Restoration of normal WNK2 function could be a new approach to control of WM.

Each year, the Annual Meeting of the American Society of Hematology (ASH) is a hotbed of presentations of new WM research. One of the most interesting, in my opinion, was from Dr. Maria Luisa Guerrera, who is a 2021 recipient of the IWMF-funded Robert A. Kyle Career Development Award.

WM patients who follow the research are well aware of altered (mutated) genes that **cause** or **drive** cancers such as WM. These include the mutated MYD88 and CXCR4 genes. That is one reason why it is currently recommended to test for MYD88 and CXCR4 mutations in the bone marrow when a patient is first diagnosed. But what about the opposite—defective or silenced genes that normally **prevent** cancer? Dr. Guerrera presented work from the Bing Center for WM on one of these tumor suppressor genes, called WNK2.

You can imagine two different types of genes involved in cancer. Genes that cause or drive cancer, such as mutated MYD88 or CXCR4, are like skilled, wily robbers. They can break into your house and cause mischief. In contrast, tumor suppressor genes are like your front door lock and your alarm system. When operating properly, they keep robbers out. But when they don't operate properly, the front door is left wide open and robbers can walk right in. WNK2 may be one of these tumor suppressor genes. When WNK2 is absent or defective, WM can progress more easily.

But then—as is often the case in biology—things get more complicated. There is increasing recognition that there may be different kinds of WM. Some patients have mutated MYD88 but normal (wildtype) CXCR4. Others have mutated MYD88 and also mutated CXCR4. There are other categories as well: patients with mutated MYD88 and normal CXCR4 but missing other genes (these are called deletion 6q, which refers to a portion of the 6th chromosome that is missing), or patients with normal (wildtype) MYD88 and normal CXCR4.

*WNK2 is a **tumor suppressor gene** that may be involved in WM. Many WM patients have **defective** or **silenced** WNK2.*

One could predict that when a person starts to develop WM (think of a robber trying to get into your house), tumor suppressor genes such as WNK2 would be on high alert and might even increase their expression (more WNK2 available). This strategy might keep the robber out. Unfortunately, in the MYD88 mutant/CXCR4 mutant (double mutant) patients that Dr. Guerrera studied, that didn't happen. Instead, the tumor suppressor gene WNK2 was silenced. It was hardly detectable at all. Dr. Guerrera and her group are still investigating the consequences of this, but it is easy to imagine that the absence of WNK2 makes WM worse. It's as if your door lock was completely removed. The door swings wide open.

Meanwhile, the patients with MYD88 mutant/CXCR4 wildtype have a different problem. Many of these patients express high levels of WNK2, but they express a particular type of WNK2 that is defective. The door lock is there, but it is jammed and doesn't work. So, despite having lots of WNK2, the door still swings wide open.

Dr. Guerrera and the Bing Center group are trying to figure this out. What causes WNK2 to be silenced in the MYD88 mutant/CXCR4 mutant (double mutant) patients? And what causes WNK2 to be expressed yet defective in the MYD88 mutant/CXCR4 wildtype patients?

In the double mutant (MYD88 mutant/CXCR4 mutant) patients with silenced WNK2, the answer may lie in what is called a promoter. Genes have a nearby region, an area of DNA called the promoter, that acts as a coach. When the coach says "You go!" the gene turns on—it gets off the bench and takes the field. In the case of the double mutant patients, Dr. Guerrera found that their coach, the promoter, was

WNK2, a Tumor Suppressor, cont. on page 8

sleeping on the job and not telling the WNK2 gene to turn on when it is supposed to. The reason is that the promoter has sections that are coated with a small chemical called a methyl group. Excessive methyl groups keep the promoter inactive.

The patients with MYD88 mutations but wildtype CXCR4 may face a different problem. If one looks at the DNA that encodes WNK2 in more detail, it looks like a large baseball team with a big roster. There are many players on the bench, but only a certain number of them are selected to play at any one time. The individual players, or pieces of DNA, are called "exons," and the team on the field at any one time, composed of a selected number of players, is called an "isoform." Depending on which players are selected to play, the team can perform better or worse. If a key player, say the pitcher, is totally incompetent, then the team can't possibly win a game, even though the team is obviously present on the field. That seems to be the problem with the patients with MYD88 mutations and wildtype CXCR4. They have lots of WNK2 (the team is on the field), but one of the key players (called a "regulatory domain") isn't working properly.

Most important for WM patients, what can be done about this? To my knowledge, there are no drugs available to directly restore normal production of WNK2. On the other hand, there may be ways to alter how WNK2 is regulated. For the double mutant patients (MYD88 and CXCR4), what makes the coach so sleepy? And for the patients with MYD88 mutations and wildtype CXCR4, why is WNK2 made with defective parts? A number of research labs and companies are trying to understand this. Drugs to change the faulty regulation of WNK2 may provide opportunities for a different approach to WM therapy in the future.

LEGISLATION TO ADDRESS US HEALTHCARE COSTS AND ACCESS

By Bonnie Beckett, IWMF Public Policy Liaison

The high cost of healthcare, especially of prescription drugs, and barriers to access remain concerns for the estimated 400 to 700 million patients with one of an estimated 7,000 to 10,000 rare diseases worldwide. Having a rare disease places a variety of financial and other burdens on patients, families, and the healthcare system. Several recent studies have attempted to capture these costs in the United States, where between 25 and 30 million Americans live with one or more rare diseases. However, US legislation to address these costs and to improve access to healthcare is stalled as of the February drafting of this article.

The costs of rare diseases in the United States are high, but their extent is unknown

Studies recognize a variety of factors that contribute to the overall cost burden of rare diseases. These factors include:

- the diagnostic odyssey before a rare disease is diagnosed, lasting an average of 16.5 years with visits to multiple providers;
- direct medical costs, including inpatient and outpatient care and prescription drugs;
- indirect costs for transportation, caregivers, education, modifications to make homes accessible, lost earnings and productivity, and quality of life.

The overall cost burden remains challenging to estimate both for individual rare diseases and collectively for all rare diseases. Attempts to estimate these costs are complicated by the sheer number of healthcare systems and databases, the lag between symptoms and ultimate diagnosis, the lack of International Classification of Diseases (ICD-10) codes for many diseases, the lack of a systematic way to capture many of the direct nonmedical and indirect costs, and other factors. The US Government Accountability Office's (GAO) recent study reviewed 36 peer-reviewed studies on the costs of rare diseases published on or after January 1, 2000. GAO noted the wide differences in costs included in these studies and the challenges in obtaining complete data on the total costs of rare diseases to both individuals and the healthcare system. Despite the limited data, GAO concluded that the available evidence suggests that medical and other costs for rare diseases can be substantial. The report is "Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial" (*https://www.gao.gov/products/gao-22-104235*).

Two other recent studies provided more detailed cost estimates for limited numbers of rare diseases. First, in February 2021 the EveryLife Foundation's "The National Economic Burden of Rare Disease Study" estimated that the overall economic burden for just 379 rare diseases affecting 15.5 million people in the US in 2019 exceeded $966 billion. The study attributed about one-third of the costs ($418 billion) to direct medical costs, another $111 billion to non-medical and uncovered healthcare costs absorbed by families, and the largest portion ($437 billion) to loss of income and productivity. (For more, go to *https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf*).

Later that same month the Office of Rare Diseases Research,

Legislation to Address US Healthcare, cont. on page 9

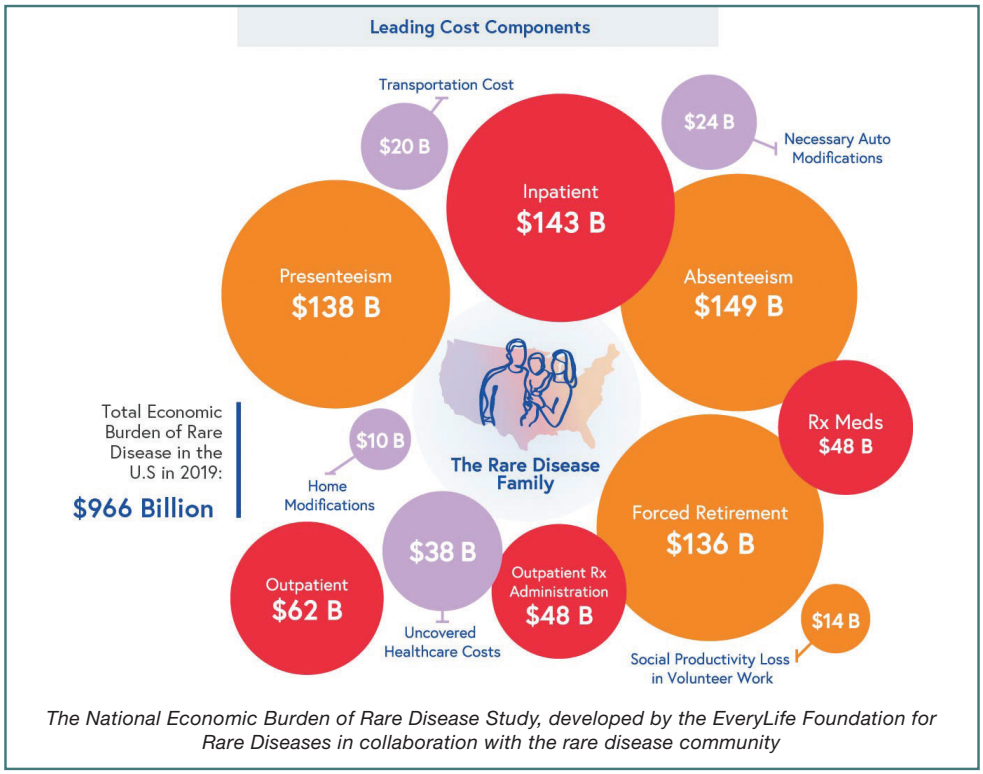


Figure 1: *Types of Disease-Related Costs Incurred by Different Payers*

National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) and others released a study of the impact of rare disease on patients and healthcare systems. The study found that healthcare costs for rare disease patients are underestimated, and that they are three to five times higher than costs for individuals without rare diseases. The study used patient medical records to estimate average medical costs for rare disease patients and to track the diagnostic journeys for four patients. The study estimated that direct medical costs alone averaged $17,000 per year for rare disease patients vs. $6,000 for patients with more common healthcare needs. They extrapolated this to an estimated 25 million rare disease patients in the US, which would result in total yearly direct medical costs for rare diseases in the range of $400 billion. This would make the cost burden comparable to other high-cost diseases such as cancer and heart failure. See "The IDeaS Initiative: pilot study to assess the impact of rare diseases on patient and healthcare systems" published October 2021 in *Orphanet Journal of Rare Diseases* (*https://doi.org/10.1186/s13023-021-02061-3*).

US legislation to lower health care costs and improve access remains stalled

As IWMF's Public Policy Liaison, I attend policy meetings or briefings held by several key groups that advocate on behalf of rare disease patients. The EveryLife Foundation for Rare Diseases, the PAN Foundation (Patient Assistance Network), and the National Organization for Rare Disorders (NORD) closely track US legislative proposals and offer comments to Congress to improve legislation. They also formulate guiding principles that recognize the unique needs of rare disease patients and are designed to foster the development of rare disease therapies that are safe, effective, and affordable.

Legislative provisions to lower costs and improve access to healthcare have been included in the Build Back Better Act as well as in individual bills. With US Congressional attention focused initially on passing an infrastructure bill in November 2021, much healthcare legislation was delayed to see which provisions might be included in the Build Back Better legislation. Build Back Better did not pass, and a more limited version is under consideration as of February 2022, along with individual bills covering many of the same healthcare issues. President Biden placed renewed emphasis in February on the need to reduce prescription drug and other healthcare costs. National polls show widespread and bipartisan support for lowering drug prices, and Democrats and Republicans have differing proposals to accomplish this goal. One concern raised by rare disease advocates is that legislation may opt for quick wins by lowering prices for commonly used drugs like insulin and Epi Pens, while doing nothing to reduce the high costs of drugs used by fewer people.

Several options for lowering healthcare costs discussed in my July 2021 *Torch* article remain in consideration, primarily for Medicare. The top options include capping (limiting annual out-of-pocket costs for medications and copays), smoothing (spreading out-of-pocket costs in installments across the calendar year), and allowing Medicare to negotiate

Legislation to Address US Healthcare, cont. on page 10

prescription drug prices. A December 2020 GAO study found that the Department of Veterans Affairs (VA) paid, on average, 54% less per unit for a sample of 399 brand-name and generic prescription drugs in 2017 than did Medicare Part D, and 106 of the drugs were at least 75% cheaper. The study is called "Prescription Drugs: Department of Veterans Affairs Paid About Half as Much as Medicare Part D for Selected Drugs in 2017" (*https://www.gao.gov/products/gao-21-111*). Two other options have less support and are less likely to be included: international reference pricing (setting individual drug prices comparable to their costs in 10-12 other developed nations) and allowing the importation of drugs from other countries where costs are lower.

Rare Disease Legislative Advocates (RDLA), a program of the EveryLife Foundation, is also advocating on behalf of three other options for lowering healthcare costs:

- **Strengthening the Medicare Part D low income subsidy:** Medicare has programs that can lower premiums and/or copays and deductibles for patients with very low incomes and assets. However, the income and asset levels are so low that many elderly people on limited, fixed incomes with even modest assets cannot qualify. Raising the levels would allow for more participation. (H.R. 2464, H.R. 3831)
- **Oral parity:** Infusions provided at healthcare facilities are covered by Medicare Part B. In contrast, oral cancer medications are covered by Medicare Part D and are subject to copays and out-of-pocket expenses with no cap. As of 2019 the District of Columbia and 43 states had passed oral parity laws. However, these laws only cover oral chemotherapy drugs with intravenous equivalents, and most of the oral chemotherapy drugs developed in the last 20 years have no intravenous equivalent. This leaves patients taking oral drugs a difficult choice between the high cost, convenience, and lower side effects of many of the newer oral drugs and the inconvenience of older infusion-based therapies, some of which have more side effects. Full oral parity would cover all cancer drugs as equivalent under Medicare Part B. (H.R. 4385, S. 3080)
- **Eliminate copay accumulators:** Copay assistance is generally only available for specialty medications used by people with serious, complex, or chronic illnesses. These include manufacturer assistance programs and rebates, as well as financial assistance available from such organizations as the PAN Foundation and the Leukemia & Lymphoma Society. Copay accumulators prevent financial assistance from counting toward a patient's deductible or out-of-pocket costs. Several rare disease organizations are suggesting changes to the Affordable Care Act and other insurance to require that insurers and Pharmacy Benefit Managers count all copayments made by or on behalf of an enrollee toward the annual deductible and out-of-pocket limit.

Bonnie Beckett (left) lobbying at her US Representative's office during Rare Disease Week on Capitol Hill

Several options are under consideration for increasing access to care and clinical trials:

- **Lowering the eligibility age for Medicare:** Currently the eligibility age for Medicare is 65. Lowering it to 60 would make it possible for seriously ill patients who cannot afford to retire because it would mean losing their employer-provided health insurance to transition to Medicare.
- **Increasing the use of telehealth:** Telehealth options were broadened during the pandemic and proved very popular. There is bipartisan support for allowing expanded use of telehealth focusing on key federal programs—Medicare, Medicaid, and the Children's Health Insurance Program. The hope is that private insurers, who frequently follow and mirror changes to these programs, will follow suit. However, for telehealth to be adopted more widely, patients, doctors, states, and the federal government need to be willing and have laws in place. RDLA has compared proposed telehealth bills to determine which ones measure up to the group's suggested criteria: remove arbitrary restrictions on a patient's location, empower the Center for Medicare and Medicaid Services to determine appropriate telehealth providers and services, extend the telehealth waiver authority to any public health emergency, and allow rural clinics and community health centers to offer telehealth. H.R. 2903 and its companion bill S. 1512 contain all four provisions and currently have the most bipartisan, bicameral support.
- **Broadening and diversifying access to clinical trials:** The majority of participants in clinical trials are white and live in more urban areas. Both federal agencies and rare disease groups have recognized problems with access to care by minorities and those who live in rural areas. Efforts to encourage more participation in clinical trials include, for example, providing for transportation costs, broadening locations for clinical trials, and using local healthcare providers, traveling nurses, or telehealth to follow patients after initial intake.

Legislation to Address US Healthcare, cont. on page 11

- **Fostering innovative drug research:** In 1983 The Orphan Drug Tax Credit was created to provide pharmaceutical companies with financial incentives to develop treatments for rare diseases. The law encouraged companies to consider whether existing drugs for a specific disease might be appropriate for treating a rare disease. The law originally provided a 50% tax credit to offset the cost of clinical trials for the rare disease. The credit was very successful and spurred an increase in the number of drugs for rare diseases from 38 approved prior to the Act to 468 indication designations covering 373 drugs approved by 2014. Following the 2017 tax bill, the credit was cut to 25%. The Build Back Better Act proposed limiting the credit to the first approved drug. This provision is strongly opposed by RDLA, NORD, and many of the individual rare disease groups.

Appropriations

Progress on the development of treatments and cures for rare diseases requires adequate funding both for research and for the agencies that review proposed treatments. When this article was drafted, the US government was operating on a continuing resolution slated to expire on March 11, 2022. This means that agencies operate at last year's funding levels and have received none of the increases proposed to cover inflation, staffing costs, new programs, etc. The Food and Drug Administration (FDA) reviews the safety and efficacy of new drugs. The Office of Orphan Product Development within FDA is slated to increase its funding by $5 million to over $35 million. The Center for Biologics Evaluation and Research, which reviews the applications for biologics, is slated to receive a funding increase to over $300 million needed to field sufficient staff to review the deluge of applications received. The NIH is part of the Department of Health and Human Services and falls under its budget request. NIH's National Center for Advancing Translation Science (NCATS) is slated to receive a $42 million increase in funding to $955 million. NCATS does cutting-edge research and helps translate new technologies from research to actual medications that help people with diseases. CRISPR gene-editing technology is one of the best-known technologies to emerge bringing hope and a potential cure to those with diseases such as sickle cell anemia. Progress on rare disease research and approvals will be slowed until these programs are fully funded.

DR. STEPHEN ANSELL RECEIVES THE ERNEST BEUTLER LECTURE AND PRIZE FROM THE AMERICAN SOCIETY OF HEMATOLOGY

Dr. Stephen Ansell

Dr. Stephen Ansell, IWMF Board member and WM expert, a hematologist in the Department of Medicine at the Mayo Clinic, and a distinguished leader in the Mayo Clinic Comprehensive Cancer Center in Rochester, MN, was recognized by the American Society of Hematology (ASH) for his work on understanding the tumor microenvironment in lymphoma and for developing treatment strategies that block inhibitory signals or deplete suppressive cells to eradicate cancer.

During the IWMF Ed Forum Month, November 2021, Dr. Ansell discussed the topic of current treatment options, and his video has received over 350 views on the IWMF YouTube Channel. The recording of this presentation is at *https://www.youtube.com/watch?v=DTeaAxQBDBo.*

Dr. Ansell shares the Ernest Beutler Lecture and Prize with Margaret Shipp, MD, of Dana-Farber/Harvard Cancer Center. According to the American Society of Hematology, Drs. Ansell and Shipp have brought their breakthroughs in understanding the lymphoma tumor cellular environment out of the research lab and into the lives of patients through more effective immunotherapies.

Named for the late Dr. Ernest Beutler, a past president of ASH and physician-scientist for more than 50 years, this two-part lectureship is intended to recognize major translational advances related to a single topic. Each year, ASH presents this award to two individuals: one who has enabled advances in basic science and one who has made achievements in clinical science or translational research.

The awards were presented during the 63rd ASH Annual Meeting, December 11–14, 2021.

Thanks to Joe Dangor and the Mayo Clinic News Network

MEDICAL NEWS ROUNDUP

By Sue Herms, IWMF Research Committee Member

CDC Issues Updated Guidelines for COVID-19 Vaccination in the Immunocompromised – The US Centers for Disease Control and Prevention has again updated its COVID-19 vaccination guidelines for moderately and severely immunocompromised adults. A number of immunocompromised patients have reported difficulty obtaining the booster (fourth) shot of Pfizer or Moderna because of confusion among vaccine providers over the guidelines, and the CDC has indicated that it is working to resolve the problem. To view the full recommendations, go to *https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised.* To briefly summarize:

- For those who receive Pfizer or Moderna vaccines initially, the total number of recommended shots is four—three primary shots plus one booster shot. Following the initial two-shot primary series of Pfizer or Moderna, a third primary shot of Pfizer or Moderna should be received at least four weeks afterward, with Moderna dosing at full strength (100 µg in 0.5 mL). A single booster shot, preferably of Pfizer or Moderna, should be received at least three months (timing now reduced from five months) after the third shot, with Moderna dosing at half strength (50 µg in 0.25 mL).
- For those who receive J&J vaccine initially, the total number of recommended shots is three—two primary shots plus one booster shot. Following the one-dose primary shot of J&J, a second primary shot of Pfizer or Moderna should be received at least four weeks afterward, with Moderna dosing at full strength (100 µg in 0.5 mL). A single booster shot, preferably of Pfizer or Moderna, should be received at least two months after the second shot, with Moderna dosing at half strength (50 µg in 0.25 mL). The CDC notes that, because the second primary shot following the J&J vaccine is a new recommendation, many recipients of the initial J&J shot may have already received a booster shot without having had the second primary shot. In this special situation, regardless of the type and timing of the second shot, a third Pfizer or Moderna shot should be received at least two months after the second shot, with Moderna dosing at full strength (100 µg in 0.5 mL). The CDC currently prefers the use of Pfizer and Moderna vaccines over J&J, although the latter is still available.

Evusheld Dosing Increased by the US FDA – The US Food and Drug Administration (FDA) has increased the dosing of Evusheld, a two-drug injectable monoclonal antibody regimen authorized to prevent COVID-19 infection in patients who are moderately or severely immunocompromised and may not mount an adequate immune response to COVID-19 vaccines or who have a history of severe adverse reactions to the vaccines. It is only authorized in those who are not currently infected with COVID-19 or who have not recently been exposed to an infected individual. Dosing was increased because data indicate that a higher dose of Evusheld may be necessary to help prevent infection by certain omicron subvariants of the virus. The new authorized dose is 300 mg of tixagevimab and 300 mg of cilgavimab (increased from 150 mg each). Patients who have already received the previously authorized dose of 150 mg each should contact their providers to return for an additional dose of 150 mg each as soon as possible. Any subsequent repeat dosing will be timed from the date of this additional Evusheld dose. The volume of each injection will be higher under the new authorization of 300 mg and should be administered in large muscles of the body that can accommodate the volume, such as the gluteal muscles.

*Dosing was increased because data indicate that a higher dose of **Evusheld** may be necessary to help **prevent infection** by certain omicron subvariants of the **virus.***

US FDA Authorizes Another Monoclonal Antibody Treatment for COVID-19 Infection – The US Food and Drug Administration (FDA) has issued emergency use authorization for a new intravenous monoclonal antibody treatment for COVID-19 infection, called bebtelovimab, that retains activity against the omicron variant and the BA.2 omicron subvariant of the virus. Bebtelovimab is for the treatment of mild or moderate infection in those with a positive COVID-19 test who are at high risk for progression to severe disease, including hospitalization or death. The authorization came as the result of a Phase 2 trial that included high-risk individuals. Reported side effects of bebtelovimab were itching, rash, infusion-related reactions, nausea, and vomiting. The Department of Health and Human Services will distribute 600,000 doses of the treatment to state health departments that will, in turn, determine which healthcare facilities receive the drug.

Ongoing Study Reports Preliminary Results of COVID-19 Vaccination in WM and Multiple Myeloma – According to a poster presentation from the 2021 American Society of Hematology (ASH) Annual Meeting, patients with

Medical News Roundup, cont. on page 13

Medical News Roundup, cont. from page 12

WM and multiple myeloma showed impaired antibody responses following COVID-19 vaccination with Moderna, Pfizer, or J&J vaccines. At the time of the presentation, 141 patients were enrolled in this study, 46 of whom had WM. The primary endpoint was the detection of COVID spike protein antibodies 28 days after two doses of Pfizer or Moderna or one dose of J&J, with secondary endpoints to include neutralizing antibody assessments and T cell responses at 28 days, six months, nine months, and one year following vaccination. This presentation discussed antibody responses after 28 days. A spike antibody titer of 0.8 U/mL was defined as a positive result, and a titer greater than 250 U/mL was co nsidered to be a stronger indication for effective antibody neutralization of the virus. The spike antibody was detected in 56% of WM patients, but with a median antibody titer of 3.92; only 26.1% achieved the optimal antibody response. Vaccination with Moderna resulted in significantly higher antibody response rates than Pfizer or J&J. Higher responses also occurred in untreated WM patients or those who were less than 75 years old. The most significant low antibody responses occurred in patients who received rituximab (Rituxan) within 12 months or were on active BTK inhibitor therapy. Overall, WM patients showed more severe impairment of antibody responses than multiple myeloma patients, of whom 91% achieved a positive antibody response and 47.3% reached the optimal antibody response. The study, conducted at Massachusetts General Hospital Cancer Center and Dana-Farber Cancer Institute, will be updated as the trial proceeds.

French Study Examines Antibody and T Cell Responses to COVID-19 Vaccination in WM – A research study from the French Innovative Leukemia Organization (FILO), published in the *British Journal of Haematology*, also examined responses to COVID-19 vaccination in WM patients. In this study of 168 participants, almost all received two doses of the Pfizer vaccine, with a third dose added if a patient tested antibody negative. After two doses of vaccine, the antibody response rate for the whole group was 67.5%. Treatment-naïve patients had the highest response rate of 94.7%, compared to previously treated patients at 66.7% and to currently treated patients at 38.2%. Patients currently on BTK inhibitors or anti-CD20-based regimens achieved vaccination response rates of 43.5% and 27.5%, respectively. Participants who had three doses of vaccine because they were antibody negative after two doses achieved a response rate of 35% after the third dose. The researchers also evaluated T cell responses in 29 WM patients; among those patients, all who were antibody positive after two vaccine doses also exhibited a T cell response, while 50% who were antibody negative after two doses and then achieved an antibody response after the third dose exhibited a T cell response. Of interest, two patients who did not have an antibody response after three vaccine doses did, however, exhibit a T cell response.

Streamlined Pneumococcal Vaccine Recommendations Issued by the CDC – The US Centers for Disease Control and Prevention (CDC) has streamlined its recommendations for pneumococcal vaccination for adults who have not previously received a pneumococcal vaccine or whose previous vaccination history for pneumonia is unknown. The guidelines apply to those who are 65 years and older or who are 19-64 years old and have underlying conditions such as leukemia or lymphoma, multiple myeloma, diabetes, chronic heart or liver disease, HIV, or other immunodeficiencies. Either of two recently approved vaccines, PCV15 from Merck or PREVNAR20 from Wyeth, can be used; if PCV15 is chosen, a subsequent dose of PPSV23 from Merck should also be provided, at least one year later.

***Tirabrutinib** is a second-generation **BTK inhibitor** designed to improve its safety and effectiveness over **ibrutinib (Imbruvica)**...*

Japanese Researchers Present Two-Year Follow-Up Data from Phase 2 Tirabrutinib Trial for WM – Two-year follow-up data were reported from a Phase 2 study of the oral BTK inhibitor tirabrutinib (Velexbru) in 18 treatment-naïve (cohort A) and nine relapsed or refractory (cohort B) WM patients in Japan. Of the 27 enrolled patients, five discontinued therapy because of adverse events. The major response rate in cohort A was 94.4% and in cohort B was 88.9%. The rate of very good partial responses was 33.3% in both cohorts. The most common adverse events were rash, low neutrophil count, and nasopharyngeal infection; two patients experienced atrial fibrillation, and nine experienced bleeding. Tirabrutinib is a second-generation BTK inhibitor designed to improve its safety and effectiveness over ibrutinib (Imbruvica) and was approved for WM in Japan based on earlier results from this study. These two-year follow-up results were presented during the 2021 ASH Annual Meeting.

Impact of Ibrutinib Dose Reductions in WM Patients Presented at ASH – A 2021 ASH Annual Meeting abstract from the Bing Center for WM at Dana-Farber Cancer Institute retrospectively looked at 385 WM patients treated with ibrutinib (Imbruvica) at its clinic from May 2012 through October 2020 to study the effects of dose reductions related to adverse side effects. Approximately 25% these patients required at least one dose reduction, with 6% requiring a second reduction. Patients requiring

Medical News Roundup, cont. on page 14

dose reductions tended to be older when they started ibrutinib therapy. Median time to first dose reduction was 7.3 months, and median time to second dose reduction from the start of treatment was 23 months. Of the 95 patients requiring dose reductions, 42% saw improvement in at least one of the medication's side effects after the first dose reduction, with 23% achieving complete disappearance of side effects. Additional dose reductions were required in 10.5% of patients, with half of these achieving improvement or disappearance of symptoms. A one-year follow-up of 48 patients for whom data were available indicated that 21% experienced improvement in their hematologic (blood test) response, while 73% maintained their response despite dose reduction. Only 6% experienced worsening of their response after dose reduction.

*Both **CXCR4** mutations and platelet counts of 100 K/uL or less were associated with worse **progression-free** survival in WM patients [on ibrutinib].*

Article from Dana-Farber Cancer Institute Discusses Predictors of Response and Survival in Large Study of WM Patients Treated with Ibrutinib – An article in the journal *Blood Advances* by researchers at the Dana-Farber Cancer Institute discussed predictors of response and survival in a large group of 319 WM patients treated with ibrutinib (Imbruvica) only. Major and very good partial responses were attained in 78% and 28% of patients, respectively. The presence of CXCR4 mutations was associated with lower rates of major responses at 67% vs. 86% for CXCR4 unmutated patients and lower rates of very good partial responses or better at 16% vs. 35% for CXCR4 unmutated patients. Both CXCR4 mutations and platelet counts of 100 K/uL or less were associated with worse progression-free survival in WM patients.

Italian Clinical Trial Group Presents Final Phase 2 Study Results of Combination Bendamustine, Rituximab, and Bortezomib in Relapsed or Refractory WM – The Italian clinical trial group Fondazione Italiana Linfomi (FIL) presented final results at the 2021 ASH Annual Meeting from its Phase 2 study of the combination therapy bendamustine, rituximab, and bortezomib in 38 relapsed or refractory WM patients. The treatment plan consisted of intravenous rituximab (Rituxan) on day 1, followed by intravenous bendamustine on days 1 and 2 and subcutaneous bortezomib (Velcade) on days 1, 8, 15, and 22, repeated every 28 days for six months. Thirty patients completed all cycles of the BRB combination, with seven stopping for toxicity and one for progressive disease. The overall response rate at the end of therapy was 82%, including 11% complete and 39% very good partial responses; of note, the complete and very good partial response rates from this combination were significantly higher than typically observed with treatments for WM. At 18, 24, and 30 months, progression-free survival was 84%, 81%, and 79%, respectively. Fifty percent of patients experienced moderate to severe blood count side effects, primarily low platelet count, while approximately 16% developed bortezomib-related nerve disorders but did not require treatment discontinuation.

Chinese Researchers Discuss Safety and Effectiveness of BTK Inhibitor Orelabrutinib for Relapsed or Refractory WM – Researchers from China reported on the safety and effectiveness of the BTK inhibitor orelabrutinib in relapsed or refractory WM during the 2021 ASH Annual Meeting. A Phase 2 study of 47 patients presented data after a median treatment follow-up of 10.5 months, at which time the overall response rate and major response rate were 87.2% and 74.5%, respectively. The major response rate was higher in patients who were MYD88 mutated and CXCR4 unmutated. The most commonly reported adverse events were low platelet count, low neutrophil count, low total white blood cell count, upper respiratory infection, weight increase, influenza-like disease, and rash. There were no serious adverse events of atrial fibrillation or diarrhea, and only one adverse event resulted in drug discontinuation.

Study from Researchers in Singapore Compares Frontline Treatment Regimens for WM – A study by Singapore researchers presented at the 2021 ASH Annual Meeting looked at frontline treatment regimens for WM from past clinical trials to analyze and compare their effectiveness. The regimens were designated BR for bendamustine and rituximab; IR for ibrutinib and rituximab; BDR for bortezomib, dexamethasone, and rituximab; and CRD for cyclophosphamide, rituximab, and dexamethasone. Progression-free survival at one and two years was higher for BR (91% and 87%, respectively) and IR (93% and 82%), compared to BDR (87.5% and 66.8%), and CRD (82% and 64%). Combined complete response and very good partial response rates were also superior with BR (35%) and IR (26%), compared to BDR (9%) and CRD (7%). As expected, bleeding and atrial fibrillation were more common with IR, while neuropathy was more prevalent with BDR.

Small Study Evaluates Use of BTK Inhibitors for Treatment of AL Amyloidosis in WM – A small retrospective study from the Cleveland Clinic, published in the journal *Advances in Hematology*, evaluated the tolerability and effectiveness of the BTK inhibitors

Medical News Roundup, cont. on page 15

ibrutinib (Imbruvica) and acalabrutinib (Calquence) in four WM patients with IgM-related light chain (AL) amyloidosis. This is a disorder in which the light chain fragments of monoclonal immunoglobulin, in this case IgM, deposit in tissue and organs, leading to organ dysfunction. All patients in this study had the MYD88 mutation, but their CXCR4 status was unknown. All achieved an improvement in their amyloidosis status, with reduction in free light chains and improvement in organ function. Atrial fibrillation led to the discontinuation of ibrutinib in one patient, and acalabrutinib caused significant bleeding under the skin in another, necessitating a temporary dose reduction. The authors suggest that BTK inhibitors should be further investigated in larger prospective studies for the treatment of AL amyloidosis in WM patients.

Dutch Researchers Develop Questionnaire for WM Patients to Aid in Discussion of Treatment Preferences – A study from The Netherlands suggested that a better understanding of WM patients' treatment preferences could aid physicians in developing an individualized treatment plan, as well as helping to direct future clinical trials in WM. A standardized questionnaire was developed and distributed online via patient organization websites and on paper to participants at outpatient clinics in The Netherlands. The resulting data were collected from 214 questionnaires. Dutch patients reported that five-year progression-free survival followed by the risk of secondary malignancies were the most important factors for making treatment decisions. Of the adverse events associated with treatment, patients disliked being at risk for neuropathy the most—more than nausea, vomiting, and extreme fatigue. Fixed-duration treatment options with IV or subcutaneous administration at the hospital were preferred over an ongoing daily oral regimen at home. During their oral presentation of this abstract from the 2021 ASH Annual Meeting, the researchers noted that the Dutch do not pay for cancer treatment, so that factor was not included in the questionnaire for decision-making. They hope to do an international study involving the US, the UK, and Australia.

*The authors suggest that **BTK inhibitors** should be further investigated in larger prospective studies for the treatment of **AL amyloidosis** in WM patients.*

US FDA Approves First Therapy for Cold Agglutinin Disease – The first therapy for cold agglutinin disease (CAD) has been approved by the US Food and Drug Administration (FDA) and is called sutimlimab-jome (Enjaymo). Cold agglutin disease is a rare condition caused by antibodies binding to the surface of red blood cells, which starts a process that causes the body's immune system to mistakenly attack healthy red blood cells and cause their rupture (hemolysis); this can lead to severe anemia, which is often treated by blood transfusions. CAD occurs in a small percentage of WM patients. The new therapy is a monoclonal antibody that targets one of the complement pathways, a part of the immune system activated during CAD. Approval was based on the Phase 3 CARDINAL trial of the drug in 24 patients; 54% achieved normal hemoglobin levels or an increase of at least 2 g/dL and did not require blood transfusions. The most common adverse reactions were respiratory tract infection, viral infection, diarrhea, stomach upset, cough, muscle ache, arthritis, and swelling of the legs.

ASH Abstract Discusses Safety and Effectiveness of Zanubrutinib in Patients with B Cell Malignancies Intolerant to Other BTK Inhibitors – An ongoing multicenter Phase 2 study presented during the 2021 ASH Annual Meeting looked at the safety and effectiveness of zanubrutinib (Brukinsa) in 64 patients with B cell malignancies who became intolerant to prior BTK inhibitor therapy because of side effects. Patients were divided into two groups before receiving zanubrutinib: group one patients were intolerant to ibrutinib (Imbruvica) only, and group two patients were intolerant to acalabrutinib (Calquence) only or both acalabrutinib and ibrutinib. Nine WM patients were included in group one and one WM patient in group two of this study. Overall, 73% of patients receiving zanubrutinib did not experience recurrence of the side effects they previously had with the other two BTK inhibitors; if the side effects did recur, 79% of those side effects were at lower severity. Patients on zanubrutinib also maintained (41%) or improved (53%) their responses compared to their reported best overall responses from prior BTK inhibitor therapies.

Phase 2 Three-Drug Combination Trial Results Reported for CLL/SLL Patients – A three-drug regimen of zanubrutinib (Brukinsa) combined with the anti-CD20 monoclonal antibody obinutuzumab (Gazyva), and venetoclax (Venclexta) was tested in a Phase 2 trial of 39 treatment-naïve patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). After a median follow-up of 25.8 months, 89% of evaluated patients achieved undetectable minimal residual disease in the peripheral blood and bone marrow, meeting the trial criteria to stop therapy and monitor. This response occurred with a median treatment time of ten monthly cycles. All patients achieved a response; median progression-free survival was not reached, with only one patient developing progressive disease. The most common adverse events were low platelet count, fatigue, low neutrophil count, and bruising. The trial data were reported in the journal *Lancet Haematology*.

Medical News Roundup, cont. on page 16

Results Discussed from Phase 2 Trial of MK-1026 (Formerly ARQ-531) in B Cell Malignancies – A multicenter US Phase 2 study of oral MK-1026 in 118 patients with B cell malignancies was reported during the 2021 ASH Annual Meeting. MK-1026 was formerly known as ARQ-531 and is a noncovalent BTK inhibitor intended to also be effective in patients who have developed resistance to other BTK inhibitors because of C481 mutations in the BTK binding site or PLCγ2 mutations downstream from BTK. This presentation focused on data from patients with chronic lymphocytic leukemia and small lymphocytic lymphoma, although four relapsed or refractory WM patients participated in the study. The overall response rate was 57.9%, with a drug-related adverse event rate of 66%. Common drug-related adverse events included taste distortion, nausea, fatigue, and decreased neutrophil count.

Phase 1 Trial Results Evaluated for Novel BTK/FLT3 Inhibitor in Relapsed or Refractory B Cell Malignancies – A multicenter US Phase 1a/b dose escalation trial assessed the safety and tolerability of oral luxeptinib, a noncovalent inhibitor of BTK and FLT3 (also known as "fms-like tyrosine kinase 3") in 23 patients with relapsed or refractory B cell malignancies, including two WM patients. Drug-related moderate to severe toxicities included low neutrophil count, low white cell count, low platelet count, anemia, increased ALT liver enzyme levels, diarrhea, high blood pressure, and headache. Twelve patients were able to be evaluated for treatment response, and eight, including one WM patient, achieving varying degrees of response. The data were represented during the 2021 ASH Annual Meeting, and the trial is continuing. The identification number on *www.clinicaltrials.gov* is NCT03893682.

Bispecific Antibody Phase 1 Study Results for Relapsed or Refractory NHL Presented During ASH – Also presented at the 2021 ASH Annual Meeting were preliminary data from a multicenter international Phase 1 study of the bispecific antibody plamotamab in 80 relapsed or refractory non-Hodgkin lymphoma (NHL) patients. Bispecific antibodies target two different molecules, in this case CD20 on B cells and CD3 on cytotoxic T cells; the advantage of such antibodies is that the body's own T cells are recruited to kill any malignant cells expressing CD20. Weekly infusions with stepped-up dosing were used; treatment was continued for two cycles or longer if any benefit was seen. The most common treatment-related adverse event was cytokine release syndrome, in which the immune system causes an excessive release of inflammatory signaling molecules called cytokines, with potentially serious consequences. To help prevent cytokine release syndrome, patients were treated with dexamethasone, antihistamine, and acetaminophen prior to each administration of plamotamab. The overall response rate to treatment was 43.4%. On *www.clinicaltrials.gov*, the identification number of this ongoing trial is NCT02924402.

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Have Your Say

The *Torch* welcomes letters, articles, or suggestions for articles. If you have something you'd like to share with your fellow WMers, please contact *IWMF Torch* editor Shirley Ganse at *shirleyganse@hotmail.com*

MARIA CATANIA, MEMBER OF THE 30+ CLUB

By Ron Ternoway

"Maria (Contino) Catania of Marshfield, MA and Palm Bay, FL passed away on January 18, 2022, with her loving family at her bedside. She was 91 years old."

That was not the opening I had planned to write when *Torch* Editor Shirley Ganse asked me last fall to write a profile about a member of our Waldenstrom macroglobulinemia (WM) community. But man plans and God laughs...

When I called Maria for the first (and last) time, she and her daughter Vivien were watching the ocean come up over the sea wall in their coastal Massachusetts town, waiting for the power to be restored as a storm raged.

I learned that she had WM for 32 years—diagnosed in 1989 and given five years to live. She was a patient of Dr. Jorge Castillo, and had been a patient of Dr. Steven Treon. She had known IWMF founder Arnie Smokler and said he was a wonderful person. She went to one of his first WM patient meetings in Boston, and a very young Dr. Treon spoke at that meeting.

Eventually she sent me four carefully handwritten pages about her life since her diagnosis. But first, a little about the first 60 years of her life.

Maria Contino was born in Brooklyn, NY, and attended public schools in Brooklyn. She was always interested in investigations and newspapers. She was an avid reader, loved mysteries and history novels. At the age of 15, she went to work for Hooper Holmes Investigation Bureau five days a week, and two days a week she worked at the *Brooklyn Eagle* as a classified ad taker and as a proofreader. In 1947, she met the love of her life, Raymond Catania; they married in June of that year and settled in Maynard, MA. While raising her children, she took art classes, for she always had a passion for painting and drawing.

When her children were in school, she went to work for Beacon Publications, part-time as a proofreader. She learned many other things about the printing business, including running the Linotype machines. Maria later became a classified ad manager for the company's ten weekly papers. She met many interesting people, such as the governors of Massachusetts and Senator Edward Kennedy. After 30 years in the newspaper business, she retired to their summer house in Marshfield, MA, and bought a winter house in Palm Bay, FL.

It was soon after retirement that Maria was diagnosed with WM. Faced with the prognosis of five-year survival, she was heartbroken, as her retirement plans included spending as much time as possible with her son and grandchildren in Florida. Once she recovered from the shock and disappointment, she was determined to learn as much as she could about her malady.

She telephoned Arnold Smokler, who was living in New Jersey at the time. "He was just wonderful," she said, "He spoke to me for over an hour, giving me courage to find out more about this disease. I spoke to him several times, and when he organized a New England support group, I became one of the 30 to 40 patients who met regularly at the Dana-Farber Cancer Institute in Boston. One of the first speakers was a very young doctor named Steven Treon, who clearly explained this very rare disease called WM."

Maria Catania with her children, Vivien, Francis, Joseph, and Vincent

Over the years Maria received a variety of therapies, both in Massachusetts and in Florida. She always arranged for a volunteer driver to take her to her appointments, except, to her chagrin, one time.

She drove to what she thought would be a regular check-up, only to be told by the doctor that she must have chemotherapy before she left. Her inner voice said, "No, Maria, go home NOW!" but the doctor assured her that if she sat for an hour or so after treatment, she would be fine. By the time her treatment was done, the office was closing, and she was obliged to leave immediately. On her way home, detours and accidents greatly lengthened her time on the road. She collapsed with fatigue upon arrival, and "never went back to that doctor."

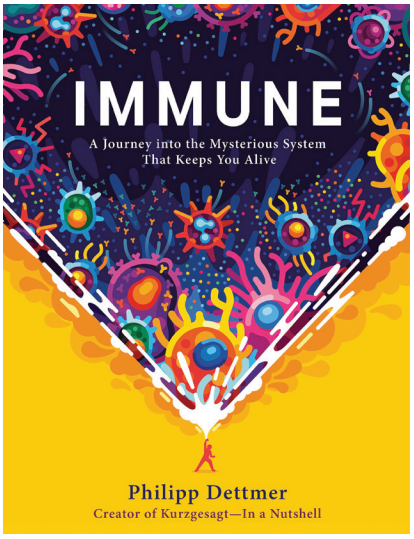
Five years ago, another relapse led to Maria's return to Dana-Farber, this time under the care of Dr. Castillo. She was prescribed Imbruvica, which successfully controlled her WM. As will be the case for many of us, Maria Catania died with WM, rather than because of it.

As I follow the IWMF Facebook page, I regularly see newly diagnosed WM patients who have been told by Dr. Google that they have five years to live. Maria Catania and many other members of the "30+ Club" belie that dated statistic. My good friend Dr. Charles Schafer, who has chronicled the origins of our Nova Scotia, Canada WM support group elsewhere in this magazine, traces his disease back to 1989, the same year Maria was diagnosed. And many other members of the 30+ Club are regular contributors to IWMF Connect.

As a 15-year veteran on the WM bus, I am hopeful that I, too, will one day be a member of the 30+ Club. I very much admire the optimism and spirit of a fellow traveller who has had WM for 32 years, for when he posts on IWMF Connect, he uses the tagline "Halfway to my Goal!"

IMMUNE: A JOURNEY INTO THE MYSTERIOUS SYSTEM THAT KEEPS YOU ALIVE BY PHILIPP DETTMER

BOOK REVIEW BY GLENN CANTOR, SCIENCE EDITOR AND IWMF TRUSTEE



The uncertainties of the COVID pandemic and our diagnoses of WM have forced most of us to learn something about immunology. How do vaccines work? What is an antibody? What does "protected" mean? How do antibodies made in response to a vaccine differ from antibodies made by WM cells? What is a virus anyway, and why don't we have better medications against viruses?

Philipp Dettmer's new book, published in November 2021, provides a remarkably accessible, easily understood guide to the immune system. Dettmer offers brilliantly creative explanations for the complex scientific terminology used by immunologists. Proteins are "really complex three-dimensional puzzle pieces," which "fit together…in specific ways." Antibodies are proteins that are "shaped like little crabs with two pincers," and they are "extremely good at grabbing on to the enemies they were made for."

But not all antibodies protect us equally or in the same way. What about "neutralizing antibodies" that we hope are made in response to COVID vaccines? Here's how Dettmer describes them: "Imagine your cells are a subway train and the virus a passenger that wanted to get inside. This is usually fairly easy for the virus, just pass one of the automated ticket barriers and enter through one of the doors. An Antibody* is basically grabbing and covering up the ticket of the virus, so it can't pass the ticket barrier and is stuck outside. The more Antibodies attach to the ticket, the more impossible it becomes to get to the train. And so it is neutralized, unable to do anything of consequence. A passenger stranded at the station."

Cancer is explained in easily understood generalities, including how the immune system responds to and often controls cancer. Dettmer describes cancer as "a group of people in Brooklyn [who decide] that they were no longer part of New York City but that they were now a new settlement called Tumor Town." Then, when the body senses "the commotion," the immune system kicks in. "NYC building inspectors and police show up" and Killer T Cells "scan the tumor cells' display windows…and order them to kill themselves." The immune response is not always successful: The tumor's "city council [may] forge all sorts of permits that confuse the NYC building inspectors." Although the chapter on cancer is too brief from my WM point of view, his description of cancer is a worthwhile introduction.

The book presents a comprehensive and remarkably up-to-date view of all parts of the immune system, how they interact, and what the immune system's consequences are to us. Each part of the immune system must work together in a tightly regulated system of checks and balances. The goal is not only to eliminate invaders, called "pathogens" (which appropriately mean "the makers of suffering"), but also to avoid such an excessive response that the body is torn apart.

Dettmer's account of how the immune system protects us reads like an exciting novel, not a traditional science book. Some of his descriptions are so entertaining that I couldn't help reading sections out loud to my wife. I even look forward to reading parts of the book to my 5-year-old granddaughter next time I see her.

The book is available as hardcover, Kindle, and on Audiobooks. The author also produces a series of widely viewed YouTube videos called *Kurzgesagt*. These include a series of cleverly illustrated videos about the immune system. See for example: *https://www.youtube.com/watch?v=lXfEK8G8CUI* ("How the Immune System ACTUALLY Works"). He also has a slightly out-of-date video about COVID, written before the availability of the vaccines but still informative: *https://www.youtube.com/watch?v=BtN-goy9VOY.*

*Dettmer capitalizes Antibody, as well as other immune system components, as if they were human actors (or even superheroes!) in his story of immunology.

INTERNATIONAL SCENE

EDITED BY ANNETTE ABURDENE

CANADA

The WMFC is pleased to announce the start of another new support group with Dennis Kornaga as leader. Dennis is no stranger to the WMFC, as he initiated the first Vancouver Support Group several years ago. He moved to Vancouver Island and has graciously agreed to lead a new Vancouver Island SG. The dates for this group will be posted on our website at *www.wmfc.ca.*

A national Zoom support group meeting was held on February 9 with Dr. Neil Berinstein from the Odette Sunnybrook Cancer Centre in Toronto. He provided an excellent update on the BRAWM trial of which he is principal investigator. *[Ed. Note: This Phase 2 clinical trial studies the combination of bendamustine, rituximab, and acalabrutinib.]* He also provided an update of COVID-19 and WM. The link to this presentation can also be found on our website.

Betty McPhee, WMFC, reporting

The Atlantic Canada Support Group: Then and Now
By Charles Schafer

Published statistics suggest that about four new cases of WM per million population per year can be expected to occur. So given Nova Scotia's current population at just under one million, I was a bit surprised when a dozen patients showed up for our first Nova Scotia Support Group (NSSG) meeting. The attendees were split almost evenly between males and females. Establishment of the NSSG was the result of an incidental meeting between Susan Gagnon, the NSSG's first leader, and me. Before its inception in 2005, I recall attending at least one IWMF Educational Forum in Boston and dropping in occasionally at several of the Sarasota, FL Support Group meetings to hear the latest news from Dr. Steven Treon and other emerging "top guns" in the WM research community of those days.

Charles Schafer, Atlantic Canada Support Group, and Susan Gagnon, previous Leader.

Susan and I agreed that a notice advertising the NSSG should be prepared and posted in several of the evaluation rooms of the Halifax Queen Elizabeth II Hospital's Dickson Cancer Centre (DCC), which was being used by WM patients, as well as those having other forms of blood cancer. Both of our respective hematologists agreed and fully supported the initiative.

Some of the more important reference material that was consulted in designing the poster included an information document prepared by a US-based company called Ortho Biotech. It had been distributed to a beginning support group by none other than Arnold Smokler way back in IWMF twilight time, when Arnold first convened several WM conferences in Springfield, VA.

Susan once told me, "As a woman at age 51 at the time of diagnosis, I felt so alone. I needed to meet other people living with WM and, especially, other women. At the time, it was said that women with WM were very rare. The group has always held a very warm place in my heart."

After the NSSG became operational, meetings were often held in a conference room in the Bethune Building, a doctor's office complex that lies adjacent to the DCC. At that time there were about 15 WM patients attending regularly. In later years, the meeting venue was often shifted to a variety of locations. These "remote" meetings often attracted patients who were unable to attend the Halifax meetings.

The typical format of those early meetings focused mainly on presentations and interchange by NSSG patients about their personal experiences with WM in relation to their other comorbidities, with an occasional guest speaker drawn from among the DCC's staff. Discussions also included subjects such as which drugs were currently approved in Canada, the Rituxan "flare" effect, maintenance Rituxan treatments, clinical trials, and some NSSG advocacy initiatives aimed at the office of the Nova Scotia Minister of Health. After several active years, Susan passed the leadership to me in 2005.

Many of the NSSG meeting topics discussed during those early years were derived from a typed handout list of particularly informative postings that I captured from the IWMF Talklist, now known as IWMF Connect. One posting that comes to mind is an April 27, 2009, note by an unknown Talklist

International Scene, cont. on page 20

member regarding a proposed WM theme song called "Hunk of Burning IgM." It was said to be based on the lyrics of an old Elvis tune, "Hunk of Burning Love." Other activities were a bit more on topic, such as the distribution of a handout, "Brief Summaries of Some of the 3710 Abstracts," that were published in that year's Proceedings of the American Society of Hematology (ASH) Conference.

I recall one presentation from those early NSSG meeting days. It was an opinion by Betty McPhee that found its way into my May 5 to April 14, 2009, Talklist handout. Betty's post was an observation to the effect that the "Canadian health care system's worst problem is the lack of communication between doctors and patients, doctors and doctors, institutions and other institutions. That and pure cheapskate mentality (long waiting lines for many services)." This precautionary statement was taken very seriously by NSSG attendees and provoked quite a bit of discussion—they loved it. Of course, since then, many of those medical system weaknesses have changed for the better here in Nova Scotia, but there is still much to do to improve the standard of care, especially for seniors.

My second fond memory of those pioneering days is a PowerPoint presentation, "Access to Treatment and Supportive Drugs," that was delivered by a local DCC Medical Resource Specialist, Mary Lou Robertson, at the October 21, 2013, NSSG meeting. It focused on drug development trends, impact of access to drugs in Canada, the "Journey of a Drug" in Canada, and the Canadian drug approval process. That speaker was of particular help to me personally in arranging for co-payment relief for some of my very expensive ancillary drugs that became necessary during the course of my chemotherapy treatments. One example is a drug called Neulasta that is a post-chemotherapy treatment used to rapidly rebuild a patient's white blood cell count.

In 2014, Ron Ternoway assumed leadership of the NSSG and was soon joined by Co-Leaders Jim Mason and Paul Kitchen. In October 2015, Dr. Robert Kyle of the Mayo Clinic spoke to NSSG meeting attendees. The topic of his presentation was "Understanding Blood Tests." Having the world's greatest living hematologist sharing his knowledge and experience with NSSG attendees was an unforgettable experience. There are now about 40 active patients plus their caregivers in the NSSG, representing all four Atlantic Provinces: New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador. In recognition of that expansion, the NSSG's name was changed to the Atlantic Canada WM Support Group (ACSG) in 2018. In October of that year, the ACSG hosted a most successful one-day Educational Forum, featuring Dr. Zachary Hunter from The Bing Center for WM and Dr. Shirley D'Sa from University College Hospital London.

Nova Scotia's WM treatment policies have come a long way since those early NSSG days when drugs such as Cytoxan (cyclophosphamide) and 2-CdA (2-chlorodeoxyadenosine or cladribine) were in vogue. Now, for example, there is the story about the first Nova Scotian non-Hodgkin's lymphoma patient who was sent to Boston for a CAR-T treatment in 2019. He somehow (obviously using some sort of magic) was able to persuade the Nova Scotia government to cover his US$900,000 costs. That is probably about as good as it will ever get in our economically challenged "have not," but otherwise beautiful, province that does its very best to support the many demands on its socialized medical system.

Since the start of the COVID-19 epidemic, the ACSG has been coming together via regular Zoom meetings hosted by its very enthusiastic, knowledgeable, and hardworking support group Co-Leader, Ron Ternoway.

CHINA

China WM Online Group Reaches 500 Members

In-person gatherings have become difficult since COVID-19 broke out. With weak immune systems, our WM patients prefer to keep socially distancing and avoid going out. Therefore, more and more patients and their family caregivers joined the WECHAT online group (similar to a Facebook group) to exchange information and experiences and to get psychological support from each other.

The WECHAT online group was established by Roger Yao, Leader of the China WM Support Group (CWMSG), in January of 2018 after Roger's father, Yao Yongpin, was diagnosed with WM. He named the online group "We (WM) together," "我们WM在一起." The letters "w" and "m" are also the two first letters of *wo men* (In Chinese pinyin characters, *wo men* means "we"). By the name, we wish all WM patients could be together as a warm family to support each other.

Since then, many WM patients and caregivers have joined this online group. "We (WM) together" has become the biggest online communication group in China. Apart from patients from mainland China, the group also attracted members from Taiwan, Hong Kong, Germany, and the US.

In this group, members frequently share educational material, WM research outcomes, information about medical insurance policies, the experience of going to the doctor, and their own stories. We comfort the newcomers, inspire the fighters, and pray for the ones who left. Many patients said they felt lucky to find this group and appreciated this warm online WM platform; they felt really assured after joining this group.

Some hematologists and doctors have also joined this group to give free advice. Hence, patients in the group have the chance to reach well-known hematologists for WM and get preliminary advice before meeting doctors in person. Some doctors also recommended our group to their WM patients to get educational material and psychological support.

International Scene, cont. on page 21

International Scene, cont. from page 20

On January 26, 2022, member #500 joined the group, a 37-year-old WM patient from Shandong province, just newly diagnosed. According to the regulation of WECHAT, 500 members is the limit for an online group, so we decided to establish another group for new WMers, naming it "We (WM) together-2."

Roger Yao, China WM Support Group, reporting

*Funds raised for the WM cause in Australia are being used in a collaborative effort to support research projects under the **IWMF-LLS Strategic Research Roadmap Initiative**.*

AUSTRALIA

IWMF-LLS Strategic Research Roadmap Initiative

Funds raised for the WM cause in Australia are being used in a collaborative effort to support research projects under the IWMF-LLS Strategic Research Roadmap Initiative. The total raised since the effort began in 2020 is A$153,184, $95,737 through WMozzies and $55,447 from a generous donor. A sum of A$62,000 has already been transferred to the IWMF to support Dr Zachary Hunter's project. The Leukaemia Foundation will be committing a further $100,000 over two years (commencing in September 2022) toward the IWMF-LLS Strategic Roadmap Initiative.

Evusheld

On 4 January 2022, the Therapeutic Goods Administration (TGA) in Australia granted a provisional determination to AstraZeneca in regard to the use of Evusheld, for the prevention and treatment of COVID-19 in adolescents and adults aged 12 years and older. The original determination of 4 November 2021 was for prevention in adults 18 years and older.

This treatment consists of two monoclonal antibodies, tixagevimab and cilgavimab, which bind to the spike protein of the SARS-CoV-2 virus at two different sites. By attaching to the spike protein, the medicine is expected to stop the virus from entering the body's cells and causing infection.

Provisional determination is an early step in the drug's approval process and means AstraZeneca can now submit further data to the TGA from human trials about how the treatment works and its safety. Once the TGA has scrutinised the data and is satisfied with it, it may grant Evusheld "provisional approval" for use in Australia in limited circumstances.

The Australian Government has ordered 5,000 doses of Evusheld. How these will be prioritised is not known. There are WM patients who, after three vaccine doses, still have no immunity. Hopefully, they will be at the head of the queue.

WMozzies Team Leader David Young Recognition Statement

David Young has received recognition from the NSW Parliament for his advocacy for the WM community in Australia. He was diagnosed in 2012 and soon discovered there were no support groups in northern New South Wales where he lived. His solution was to establish one. He also took on the role of team leader of WMozzies and actively urged that zanubrutinib (Brukinsa) be made available free of charge to cancer patients under the Pharmaceutical Benefit Scheme.

Michael van Ewijk, WMozzies Committee, reporting

*Once the TGA has **scrutinised** the data and is satisfied with it, it may grant Evusheld **"provisional approval"** for use in Australia in **limited** circumstances.*

FRANCE

On November 20, 2021, our annual patient-doctor day was held online for the first time. This first webinar represents an important progress for Waldenström France to reach and inform a maximum number of WMers. Of the 155 members who registered for this event, 116 showed up online and others accessed the replays. The replays are currently available online on the association website: *https://portail.waldenstromfrance.org/rencontre-francophone-patients-medecins-du-20-novembre-2021*. The program included three talks followed by questions. The exchanges were particularly rich and intense, with the total number of questions in the chat reaching 150.

The first talk was given by Dr. Damien Roos-Weil of Salpêtrière Hospital, Paris. It dealt with therapeutic targets in WM and provided information about anti-COVID vaccination for WMers.

The second speaker was Prof. Véronique Leblond, also of Salpêtrière Hospital, Paris, who provided an up-to-date survey of the therapeutic options for WMers. From the same hospital, Dr. Sylvain Choquet then presented current research on family cases and the genetics associated with them.

At the end of the meeting, Mrs. Paulette Gérard, President of Waldenström France, briefly presented the association, its current activities, and its projects. Emphasis was put on the sharing of information between doctors and patients and among patients.

International Scene, cont. on page 22

The Waldenström France website is *https://portail.waldenstromfrance.org*.

On January 11, 2022, the Waldenström France association offered Prof. Véronique Leblond a guestbook containing a collection of testimonials and thank you messages from WMers on her new professional activity. They thus wished to pay tribute to Prof. Leblond who, alongside the greatest international specialists, dedicated her career as a haematologist to the study of Waldenström and its treatment.

As Honorary President of Waldenström France since its creation in 2009, Prof. Leblond provided WM patients with information about multiple aspects of WM and how to take control of their care. Her research on this disease, notably with the French Innovative Leukemia Organization (FILO), led also to significant advances in treatment.

Professor Leblond was Head of the Clinical Hematology Department, Pitié-Salpêtrière Hospital, Paris, since 2010. In July 2021, she was succeeded by Dr. Sylvain Choquet and she became Professor Emeritus at the Sorbonne-University Faculty of Medicine, where she pursues her research career. Although she no longer sees patients in consultation, V. Leblond wishes to maintain her ties with WMers and the association.

Prof. V. LeBlond

On the occasion of her change of activity, the Waldenström France association was pleased to thank her for her empathy, her kindness, and her commitment to patients by producing this guestbook. Peter DeNardis, Chairman of the IWMF Board of Directors also expressed his immense gratitude in a letter to V. Leblond *(See his letter in the January 2022* Torch*)*. These testimonies deeply touched our physician.

Cover of the 36-page book, Rencontres au fil du temps (Encounters over time)*, presented to Prof. LeBlond and illustrated with photos of the patients-doctors meetings*

We wish you a nice new life, Professor Leblond, and keep in touch.

Annie Rialland, Waldenström France, reporting

UNITED KINGDOM

In November we launched our very own Walk for Waldenstrom's to help fund the new WMUK Support Line. Over 40 participants registered, and we are delighted to say that they have not only raised the £17,000 needed to launch the line, but they have also raised a further £8,000 to keep it going for many months more. We have pledged to use anything over the £25,000 target to fund this year's support programmes, so that no WMer feels in the dark or alone in their diagnosis. A huge thank you from the bottom of our hearts to everyone who joined the event, whether they have already walked, or plan to walk, in the months to come. You are all amazing!

When it comes to support, our phone line will not be the only new addition to our services in 2022. We have ambitious plans for the upcoming year, including launching a peer-buddy system to support WMers needing one-to-one support; healthcare professional education to help clinicians, nurses, and allied healthcare professionals to learn more about this rare disease; sponsoring community events; and more. Every project we are planning has been informed by feedback from WMers, their friends, and families, and we are excited to be able to grow this community even more.

Information is also an important part of our work. We have continued our hard work in informing the community about the ever-changing COVID-19 situation. This was especially key over the new year and in January, when many WMers could not get crucial priority PCR tests that would allow them access to treatment if they tested positive.

We are aiming to grow our range of information in the next few months by expanding our website, creating more videos and podcasts, and publishing our first patient booklet for newly diagnosed patients. The booklet should be available in spring or summer 2022 for download or order, and we hope it will help WMers feel less alone and more informed when they receive their diagnosis.

In December 2021, the British Society for Haematology published new guidelines for the diagnosis and management of WM. This important document gives doctors guidelines on how they should treat their WM patients, ensuring that WMers, no matter where they're being treated in the UK, can expect the same care. We have condensed this clinical document into a factsheet for people living with WM and their families. It can be downloaded here: *wmuk.org.uk/resource/wm-guidelines-patient-factsheet/*.

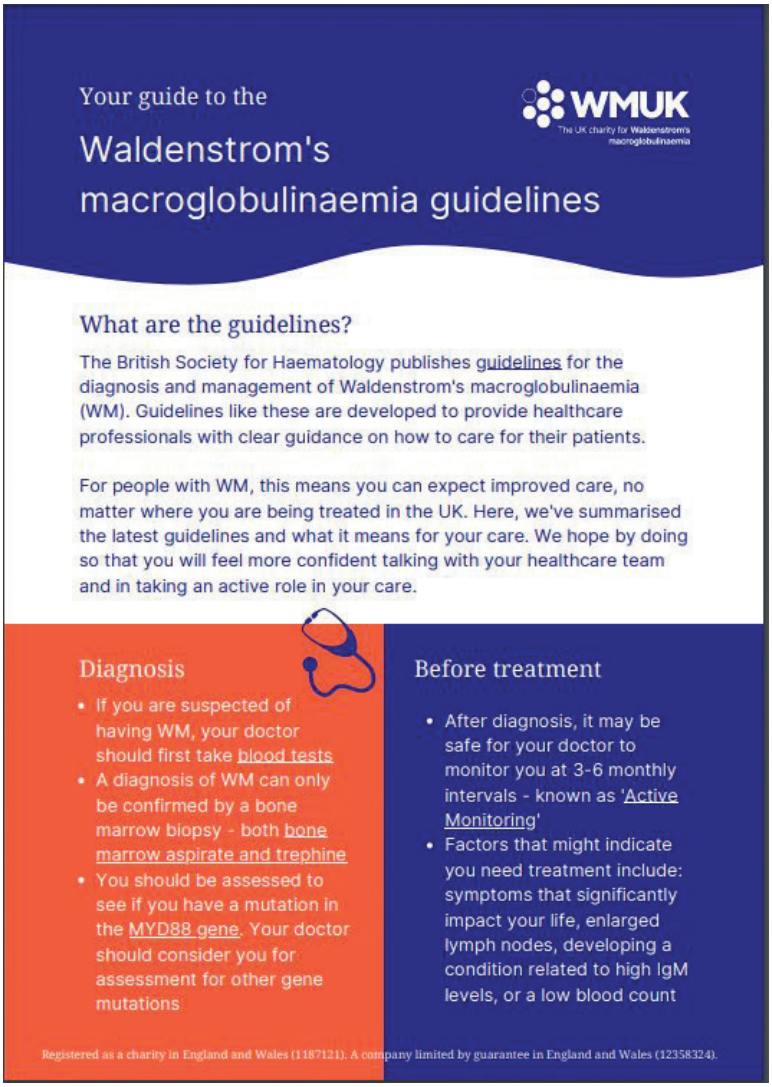
International Scene, cont. on page 23

Steve McGraw, a participant in the Walk for Waldenstrom's

We were disappointed to learn that the National Institute for Health and Care Excellence (NICE) has initially decided not to recommend ibrutinib for commissioning for patients in England and Wales. The drug has been available on the NHS as a second-line treatment for WM patients since 2020. The decision is just one step in an ongoing process and could be overturned. We are working hard with all parties to ensure that WMers can still get access to this important therapy, and we will be keeping the community up to date with new developments.

As always, we want to say a big thank you to all our fundraisers and donors, without whom we could not do any of our work. If you want to support us, find more information about our services, or join our thriving community, you can find more information at *wmuk.org.uk*.

Kat Tucker, Fundraising & Communications Manager, WMUK, reporting



FROM THE FACEBOOK WM SUPPORT GROUP: SPRING 2022

By Betty Ann Morton

The more I learn more about the IWMF and the multiple ways it serves the WM community, the more impressed I am by its responsiveness to the changing needs of the community and the varied preferences of its members. Information about WM is available by mail, directly accessible from the website, by phone from the office or LIFELINE volunteers, and by Zoom with local or national and international support groups. The IWMF has helped to set up special interest groups for young WMers, for WMers who are people of color, for those dealing with peripheral neuropathy, for those with Bing Neel, and even a yoga class. IWMF members can choose to receive the quarterly *IWMF Torch* magazine and a weekly email with news of interest to the community, as well as information about upcoming presentations by medical experts. Along with IWMF Connect, the Facebook WM Support Group allows WMers to connect directly with each other and the wider WM community.

Because Facebook posts can be automatically translated, communication between people from different parts of the world is relatively simple. Within the past week, I've read posts that were originally written in English, French, Italian, Dutch, and Greek. Recent new members include WMers and family members from France, Belgium, Australia, Great Britain, Canada, and the United States. Posts range from information about upcoming IWMF activities or links to research studies, to requests for information, to sharing of personal experiences with WM, and even to humorous anecdotes.

*The overall **consensus** was that, because WM is a rare cancer and most local oncologists do not have experience with treating it, **second opinions** are highly helpful.*

Did you ever lie awake at night, needing guidance or reassurance about a medical question? **MS** wrote, "I love that we can get our questions answered so quickly here. Awesome!" If the question is about a serious and emergent problem, seek medical attention from your doctor or an emergency room. But if it's simply a nagging question, the Facebook WM Support Group is active around the clock. With close to 4,800 members, any new post is likely to receive a response in less than an hour.

BS, a WM patient, recently asked how many WMers had received a second opinion from a WM expert regarding their diagnosis and treatment recommendations. Within three days, over 60 people responded, with most describing how positive their interactions with the experts had been. A particularly interesting response from **ML** said that his local oncologist had been the one who requested the second opinion because he wanted input regarding the treatment he planned to recommend. No one regretted getting a second opinion, although some had to travel long distances. The overall consensus was that, because WM is a rare cancer and most local oncologists do not have experience with treating it, second opinions are highly helpful.

WMers who are about to start treatment often wonder what to expect. **TF** asked how long it generally takes for bendamustine and rituximab to lower IgM and raise hemoglobin. **DH**, about to start treatment with those same drugs, asked about others' experiences with working during treatments. Many people shared personal experiences; suggestions included the possibility of taking FMLA (Family and Medical Leave), perhaps intermittently. Member **DGB** was concerned about the recommendation of ibrutinib for a family member who had previously had problems with atrial fibrillation (a-fib). Several WMers suggested asking the doctor about zanubrutinib, since it is also a BTK inhibitor but with a lower risk of afib. Along with relating personal experiences, members posted links to fact sheets from the IWMF website, detailing various treatments.

Life with WM isn't all serious. **BS** posted, "So don't laugh. Got Waldenstrom down pat. Need a way to pronounce the M word!" **JP**'s response was, "Slowly, lol. I googled how to pronounce macroglobulinemia." **MCM** posted a link to Tim Salz's "Waldenstrom's Song." It can be found at *https://www.youtube.com/watch?v=svySGKdjE7Y*. Have you ever before heard a song that includes the words "Waldenstrom's macroglobulinemia," the names of some of our expert WM doctors ("Docs Castillo, Morie Gertz, and Steven Treon") and even makes it all rhyme?

In a recent Facebook discussion about prescription drugs, **CC** suggested using *www.drugs.com* to check possible interactions between prescription drugs. Another suggestion was to inform our regular pharmacy about any specialty drugs we may be taking, such as ibrutinib or zanubrutinib.

As the COVID-19 pandemic progresses, the group's concerns have also changed. Recently, people have shared

From the Facebook WM Support Group, cont. on page 25

their experiences with Evusheld, a drug that helps to decrease the likelihood of contracting COVID-19 for an immunocompromised person. Many WMers, particularly those recently treated with rituximab, have not developed strong immunity from COVID vaccines. Evusheld is an injectable monoclonal antibody, not a vaccine or a treatment for disease. **PLD** wrote, "After disappointing test results this week that showed no antibody build up after a fourth Moderna vaccine injection, I got a lottery slot for antibody injections today (Evusheld) and will be better protected for the next six months. Never thought we'd be so excited for a couple of injections."

Unfortunately, there are problems with drug availability. **ZD** wrote, "My husband has WM. He had rituximab and Velcade for six months. His treatment was completed in October. Although he had three BioNTech [Pfizer shots], he had no antibodies. We are living in Turkey. And Evusheld is not available here."

*...it's **great** to have found a **space** where I don't have to **worry** about anyone close to me and their **feelings**...*

AC expressed the feelings many of us had when we were first diagnosed. "Thank you for letting me join the group. I am 51 and was given the diagnosis of Waldenstrom's macroglobulinaemia on 2/12/2021. Ninety percent of me feels like I've come to terms with the diagnosis, then there's this ten percent that thinks 'S___! I've got cancer!' To be honest I don't think that ten percent is ever going to leave me, but I'm OK with that. The diagnosis came as a relief after seven weeks waiting for results from blood tests, a bone marrow biopsy, and a CT scan. Knowing cancer in the blood wasn't secondary, that my major organs were clear, was a huge relief. Staying strong and positive, keeping my fears to myself in order to protect my three grown children was tough. Not knowing if I'd still be here next Christmas, thinking how losing me would devastate them, worrying how they would each cope and was there anything possible I could do to alleviate things? So you can maybe see how a diagnosis of WM was welcome when you consider the possibilities. On my worst days during the wait, I was mentally clearing-out my house; who would get what in terms of family, charity, and landfill! But that stage of things is over, and with a diagnosis I know where I stand, 'watching and waiting,' but feeling grateful for every day for so many reasons. XX"

AC was warmly welcomed by the group. **DH** wrote, "Like you, I felt a huge sense of relief when I finally knew what I was dealing with. I'm 54 and was diagnosed a few weeks ago. Right now I'm learning the lingo and keeping positive. So much to learn and realizing that everyone experiences this disease differently. Take care."

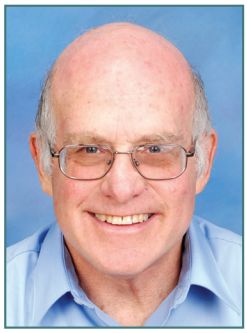
JJM responded, "Welcome! I know all those feelings so well. My doctor told me if you're going to get cancer you got a good one. Diagnosed 2017…been an up and down ride, and I'm still here ready to ride."

AC thanked everyone, commenting, "Funny, that's exactly what I've been telling people. I knew it was something serious, but of all the cancers, this is one of the kindest! Thank you for the welcome, it's great to have found a space where I don't have to worry about anyone close to me and their feelings—that's been exhausting...Thank you to all of you for making me feel so welcome. I am overwhelmed. I feel so lucky to have found you, and that I now have a safe space where I can be myself, to say what's bothering me without having to think before I speak for fear of upsetting my loved ones."

To join the Facebook WM Support Group, go to *https://facebook.com/groups/wmsupportgroup*. In order to join, people must answer two membership questions. WMers and their support people are welcome. Since the group is private, only group members are able to see the posts. If you need additional help with the process, please contact the IWMF office at 941-927-4963 or email *office@iwmf.com*.

EVER WONDER HOW A CLINICAL TRIAL IS GOING? I FOUND OUT BY ASKING PARTICIPANTS.

By Howard Sholkin



Howard Sholkin, Discussion Leader

They joined from Colorado, Florida, Massachusetts, Washington State, Michigan, Maine, Virginia, Georgia, Puerto Rico, and British Columbia. I also was contacted by a man who couldn't join the noon Eastern Standard Time meeting in February because he was in Australia. They learned of the meeting by my post to the Facebook WM Support Group page, to IWMF Connect, and a notice in the IWMF's Waldenstrom's Weekly email blast. The IWMF arranged the Zoom call.

Drawn together by a clinical trial

I had arranged the Zoom meeting with Waldenstrom patients; cancer wasn't our only connection, as all but a few are in a clinical trial of ibrutinib and venetoclax combined, run by Dana-Farber Cancer Institute in Boston. Two of the 16 Zoom participants weren't in the trial but were taking the combination. Of the 16 participants, 10 were male, six were female, and all were diagnosed as early as their 40s and into their 70s. I didn't expect this, because I had read that WM affected mostly men and people 60 and older. Some had multiple treatments before joining the trial.

I facilitated the discussion with the help of the IWMF because I wanted to share my experiences in the trial and learn about others. I was diagnosed in February 2021 only after my new primary care doctor, who trained at Dana-Farber, was suspicious of my prolonged anemia and certain blood test results. I didn't have any other significant symptoms.

Our varied stories

The meeting participants had been diagnosed from one year to 21 years ago. Trial patient #8 (almost 50 people are in the two-year trial) was diagnosed six years ago at age 54. The WM symptoms varied greatly, including fatigue, anemia, night sweats, leg cramps, osteoporosis, numbness and cold in extremities, and mood swings. What seemed uniform was that all participants had improved blood test results within months of taking ibrutinib and venetoclax. As for me, after five months of taking both medicines, cancer in my bone marrow dropped from 90% to 10%, and my IgM fell by almost half.

Of course, it's not only the effect on the cancer that's important, but also how one responds to the drugs. Participants reported digestive problems, muscle and joint pain, welts and sores, cracking nails, and heart issues. I developed atrial fibrillation (a-fib), an electrical signaling issue with my heart that causes irregular heartbeats, one week after I started ibrutinib, and, in my case, it's a chronic condition controlled with medication. One man lost 20 pounds before the trial but has gained most of the weight back.

Some said their reactions were too severe, leading to dosage changes. A few suggested that people try taking the meds at different times to lessen the side effects.

Dealing with COVID-19

Everyone said that they had limited or no response to COVID-19 vaccinations. One woman said she got COVID and was told to switch from Pfizer to Moderna. She said her reaction to Moderna was worse than COVID's mild congestion and that her husband was sicker than she was. Another said their T cell test was in a normal range after the first two shots. One person had received Evusheld by AstraZeneca without a negative reaction. Its two injections were approved last fall by the FDA under emergency use authorization for immunocompromised people to better resist COVID infection.

The future

One participant said he was told the trial drugs could lead to remission for three to four years. Others said prior treatments had lasted for up to five years, and one said the cancer seems to run in cycles leading to a relapse. Another said the trial "is working, and he's blessed to be on the trial," adding the Dana-Farber team "is fantastic." A woman said ibrutinib worked for five years but began to lose its effectiveness, and when venetoclax was added, the combination worked.

The participants agreed to meet again in three months on Sunday, May 15, at noon EDT. If you're in the ibrutinib and venetoclax combination trial or taking both drugs and would like to join our discussion, contact Howard Sholkin at *hsholkin@gmail.com*.

Spotlight ON SUPPORT GROUPS

EDITOR'S NOTE:

As the support group section continues to evolve away from individual reports, we begin to spotlight certain groups, activities, or people. As always, for particular information about when and where meetings are being held, go to the Events Calendar for listings: ***https://iwmf.com/events-calendar/***

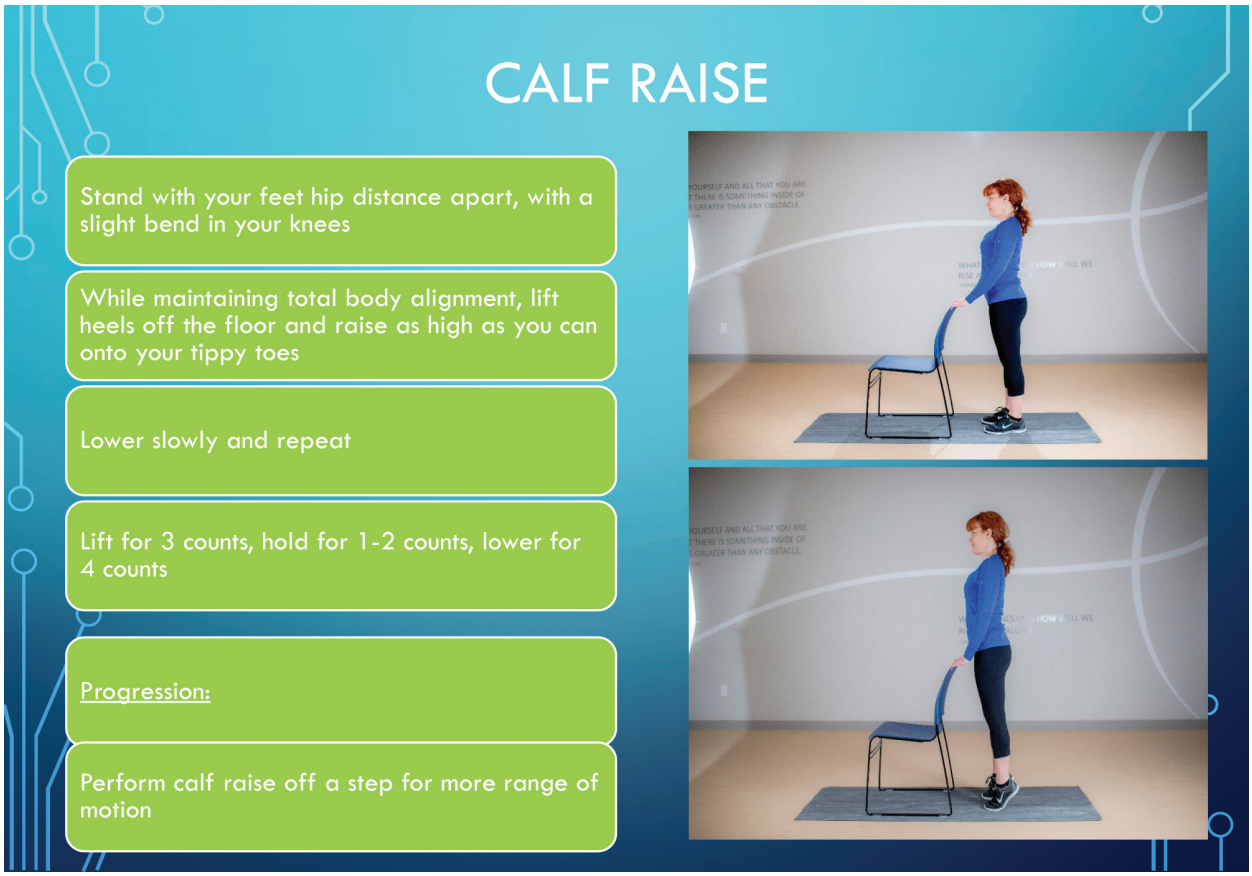
PERIPHERAL NEUROPATHY AND EXERCISE

By Steve Pine

On January 26, the Peripheral Neuropathy (PN) Support Group hosted a live Zoom presentation featuring Nancy Campbell, MS, Clinical Exercise Physiologist at the Dana-Farber Cancer Institute's Leonard P. Zakim Center for Integrative Therapies and Healthy Living. The session was attended by over 100 participants from North America, Europe, Scandinavia, and Oceania.

Nancy was tasked with explaining to the group how exercise might help with the symptoms of PN, and her presentation, "Neuropathy: How Strength and Balance Can Help," was right on target. She opened with an explanation of what an exercise physiologist is and then gave the group a brief rundown of common PN causes and symptoms. The benefits of exercise and a general exercise prescription were also presented.

Exercise is helpful, but only if you do it, and do it with consistency. To that point, Nancy shared two useful concepts, "habit stacking" and "the traffic light approach." Habit stacking is marrying exercise time with something you do every day, such as brushing your teeth or hand stretches. By doing this, exercise becomes part of your routine instead of something for which you have to set



Spotlight on Support Groups, cont. on page 28

aside time. The traffic light approach, (red, yellow, green), matches the type and amount of exercise done, according to how you feel that day.

For WMers, PN is either a symptom of their WM or a result of chemotherapy. Nancy provided some strength and balance exercises that can help counter the PN symptoms we experience. These came in the form of descriptive slides and live demonstrations, during which attendees were encouraged to join in the exercise.

Throughout the presentation, Nancy was able to address most of the 30+ pre-submitted questions related to PN and exercise. A Q&A followed during which additional questions from the attendees were answered.

The video of Nancy's presentation and Q&A can be found at the IWMF web site on the "Presentations for Peripheral Neuropathy" page (*https://iwmf.com/presentations-for-peripheral-neuropathy*). This newly created page also contains past PN-related presentations from the IWMF and WMUK (United Kingdom).

To join the PN Support Group mailing list, contact *office@iwmf.com* or call 941-927-4963.

WE'RE BACK!

NORTHERN VIRGINIA, WASHINGTON DC, AND WESTERN MARYLAND

By Mary V. Waleski

On the cold winter afternoon of February 6, 2022, the support group for Northern Virginia, Washington DC, and Western Maryland (NVA/DC/WMD) held its first meeting in over two years. In compliance with current IWMF COVID-19 policy, the meeting was held virtually on Zoom. The group has three new co-leaders who share responsibility for operations: Deborah Kelly, Suzann Albanese, and Chuck Ross. Suzann and Deborah are relative newcomers to the group and to WM. Chuck was at one of the group's first meetings in 2015, held soon after he was diagnosed.

***Dr. McMaster** has looked at the possible role of the environment, lifestyle factors, and genetic mutations that might result in a **WM diagnosis**.*

Chuck opened the meeting with greetings to everyone and introduced Deborah and Suzann to the membership. Next Chuck gave a special welcome to Lisa Wise, who chairs the Philadelphia/New Jersey Support Group, and to its members. The NVA/DC/WMD wanted to take advantage of virtual meeting capabilities and extended a warm invitation to our northern counterparts to join us in learning from our two guest speakers. Over 50 members from the two groups participated in the Zoom meeting!

Deborah introduced Lu Kleppinger, who founded the Northern Virginia group in 2014 and continued as the dynamic and much-admired leader of the combined NVA/DC/WMD group until her retirement in 2019. After the greetings, introductions, and a belated tribute to Lu *(see page 30)*, everyone settled in for the highlight of the winter meeting—presentations by two distinguished guest speakers discussing topics of immense interest to everyone.

Dr. Mary McMaster is an eminent research scientist in the National Cancer Institute (NCI) at the National Institutes of Health (NIH) in Bethesda, MD, where she has worked since the 1970s. Her presentation for us, entitled "A Familial Link for WM," is based on research she began in the early 2000s. Around that time her research focus turned to WM, specifically the biology of the disease rather than its therapeutic side, and whether there is a possible familial predisposition to the disease. Familial WM is rare, she explained, but not as rare as was once thought. Actually, today there are more than 150 families enrolled in NCI's Familial WM registry. There are also WM family registries in France and Sweden.

In her research, Dr. McMaster has looked at the possible role of the environment, lifestyle factors, and genetic mutations that might result in a WM diagnosis. It appears that the MYD88 mutation present in most WM cases cannot be passed on to offspring because it is in somatic cells rather than the germ (reproductive) line of cells. However, relatives of WM patients may be at risk for other B cell cancers, perhaps because of problems in the immune system. She added that even if a WM patient's relatives appear healthy, they should still be screened after the

Spotlight on Support Groups, cont. on page 29

age of 40 for monoclonal gammopathy of undetermined significance (MGUS).

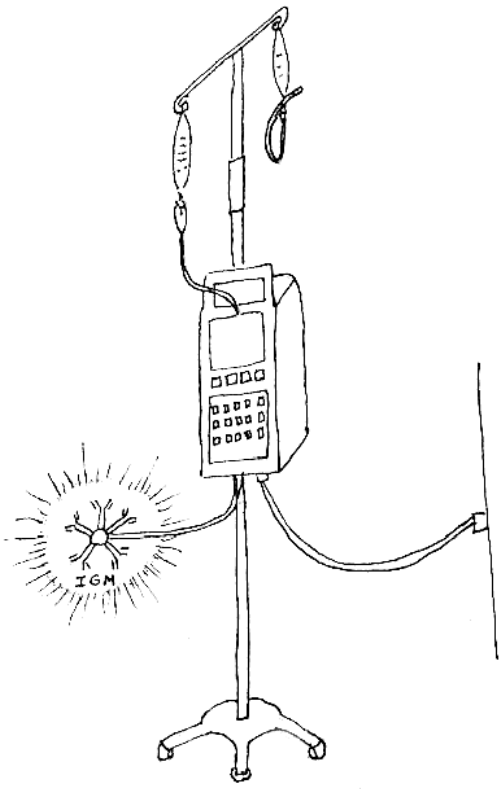
*...in the US, WM is by far a disease of White men. Black Americans are **more likely** to have multiple myeloma.*

In closing, Dr. McMaster agreed to an extended Q&A session and answered questions that were submitted prior to and during her presentation. One particular question submitted online was about ethnic background. Dr. McMaster explained that in the US, WM is by far a disease of White men. Black Americans are more likely to have multiple myeloma.

The meeting's second speaker was Dr. Bonnie Beckett. She is retired from a 25-year career with the Government Accountability Office in Washington DC. For the past ten years she has been a member of the NVA/DC/WMD Support Group and is now the Public Policy Liaison for the IWMF. She was diagnosed with WM/MGUS in 2012, but is still in the watch-and-wait phase. Dr. Beckett is very active in lobbying the US Congress for increased funding for WM research.

She also emphasized the importance of personal lobbying of government representatives, explaining that US Senators and Representatives are eager to meet with their constituents either virtually or in person and to hear their personal histories, needs, and ideas on upcoming or future legislation. They, or senior members of their staffs, do, in fact, listen carefully to their constituents, and these efforts are reflected in proposed legislation. That's the way it's supposed to work, Dr. Beckett said, and it does. Organizations such as the EveryLife Foundation and their Rare Disease Legislative Advocates also lobby on behalf of the WM community. *(See the legislative update article by Bonnie Beckett on page 8.)*

After saying farewell to the speakers and all of the guests, Suzann conducted a few items of business and future planning for the D/M/V Group and then ended the meeting.



Infusion stand: Drawing by Diane Mazza

Spotlight on Support Groups, cont. on page 30

LU KLEPPINGER'S RETIREMENT AS SUPPORT GROUP LEADER

On Sunday, February 6, two IWMF support groups, one from Northern VA, Washington DC, and Western MD (NVA/DC/WMD) and the other from Eastern PA and Southern NJ, met jointly via Zoom to hear Dr. Mary McMaster from the National Institutes of Health speak on familial WM. Before her presentation, the group honored Lu Kleppinger, who is stepping down from the leadership of the NVA/DC/WMD group.

Left to right: Jim Reed (IWMF Eastern Maryland Regional Contact); Elly Levie (Carl's wife); Tony Sablo (Lu's husband); Lu Kleppinger; Carl Harrington; Liv Grace (Arnie Smokler's granddaughter); and Dr. Mary Lou McMaster of NIH (inaugural speaker who attended in Carl's honor)

Carl Harrington, IWMF President Emeritus, and Lisa Wise, Vice Chair Information & Support, thanked Lu. Carl noted that Lu was a "gift" from Dr. Steven Treon and Chris Patterson from the Dana-Farber Cancer Institute, who had passed Lu's name along to Carl in 2014 as someone who could help. And help she did!

Among her many contributions, Lu:

- Established the Northern Virginia support group in 2014 and then continued as leader, as it grew to include Washington DC and Western Maryland (NVA/DC/WMD) in 2015. Ironically, the first group meeting she ran featured Dr. McMaster.
- Served on the IWMF Educational Forum planning committee for many years on both the publicity committee and the meal planning committee. With Lu in charge, there were always raves for the interesting, healthy food at the Ed Forum!
- Served as a joint IWMF-LRF (Lymphoma Research Foundation) ambassador. When LRF CEO Meg Gutierrez called, asking for a WMer to undergo media-training and act as joint spokesperson, Lu was the natural choice. And Lu helped strengthen the IWMF-LRF partnership immeasurably.

Now, Lu happens to be petite, so of course Carl never missed an opportunity to kid her for being "height challenged." Neither did he miss an opportunity to contrast her other characteristics: a big heart, no shortage of compassion, boundless energy, limitless enthusiasm. Carl ended by thanking Lu "for the giant impact she made on the lives of WMers."

Lisa then closed the thank-you segment by presenting Lu with a special glass vase with the inscription:

To Lu, With Love,

Your uplifting spirit touched so many!

In gratitude, The IWMF

Lisa also noted that Lu was the first person she met at the 2015 IWMF Ed Forum and that you always remember your first…WM friend.

Thank you Lu!

Dr. Steven Treon, Chris Patterson, Lu Kleppinger, and Dr. Jorge Castillo at the 2017 Ed Forum

The 2015 meeting of NVA/DC/WM Support Group when Dr. Steven Treon (back row, fourth from left) was guest speaker

BEN RUDE HERITAGE SOCIETY

The Ben Rude Heritage Society recognizes those who have made provisions for a future gift to the IWMF, such as a bequest, listing the IWMF as a beneficiary for a life insurance policy or qualified planned asset (such as a 401k or IRA), or a life income agreement, such as a Charitable Remainder Trust. Legacy gifts represent an important component of the IWMF's financial future. There are many ways to support the IWMF through a planned gift, but a bequest is perhaps the easiest and most tangible way to leave a lasting impact. The following supporters are members of the Ben Rude Heritage Society:

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For a commitment of $50,000 per year for a minimum of two years, or a lump sum of $100,000 or more, you can become a research partner supporting a specific IWMF research project approved by the IWMF's Scientific Advisory and Research Committees. Research Partners will have an opportunity to be kept informed of the progress of the research project and will be formally acknowledged by the investigators in their report of the project as well as in any resulting publications. Generally 10 to 12 research projects are underway with new projects under consideration each year. The following funds support current IWMF research:

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If you have discretionary giving power and would like to help move our research program forward in a special way, we invite you to join those listed above. For more information about Research Partners and Named Gift Fund opportunities and potential gifting options that might make that possible, please contact Director of Development and Communications Jeremy Dictor at JDictor@iwmf.com or 941-927-4963.

BETWEEN JANUARY 1, 2022, AND MARCH 1, 2022, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE AS TRIBUTE IN MEMORY.

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Sarasota, FL 34238

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