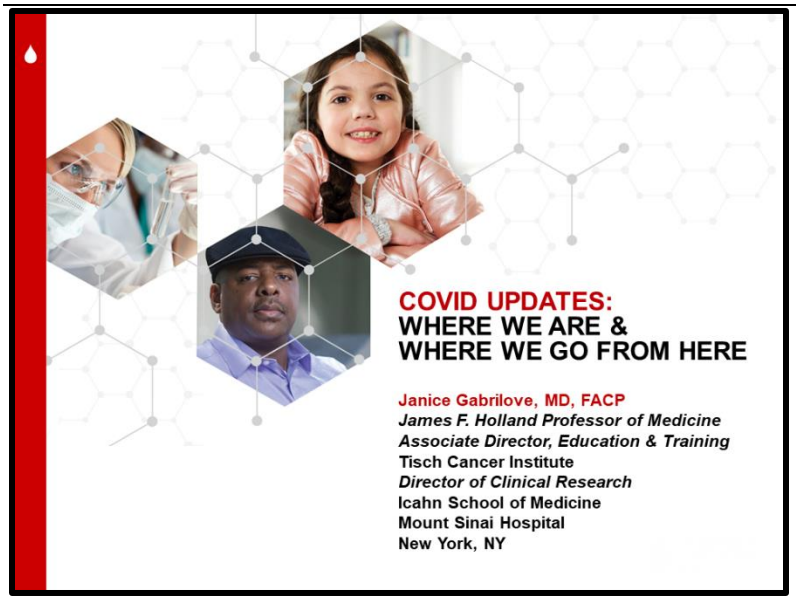
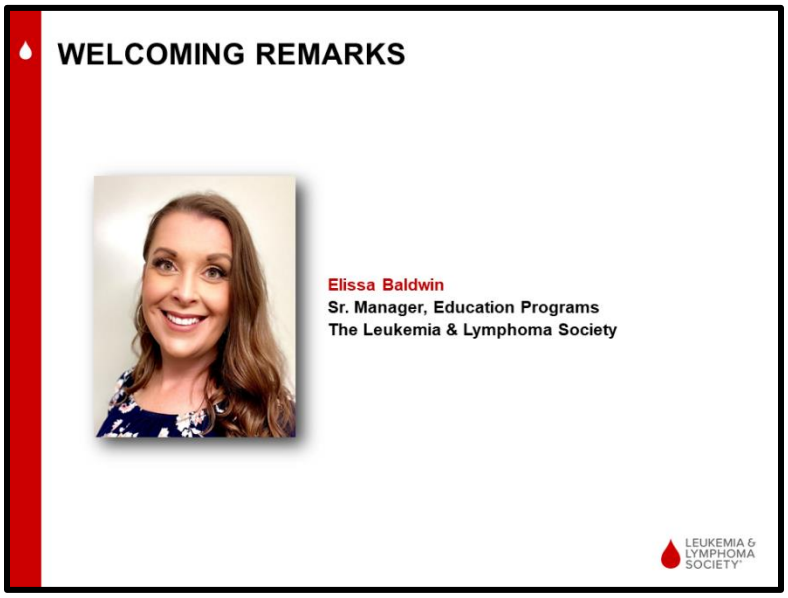
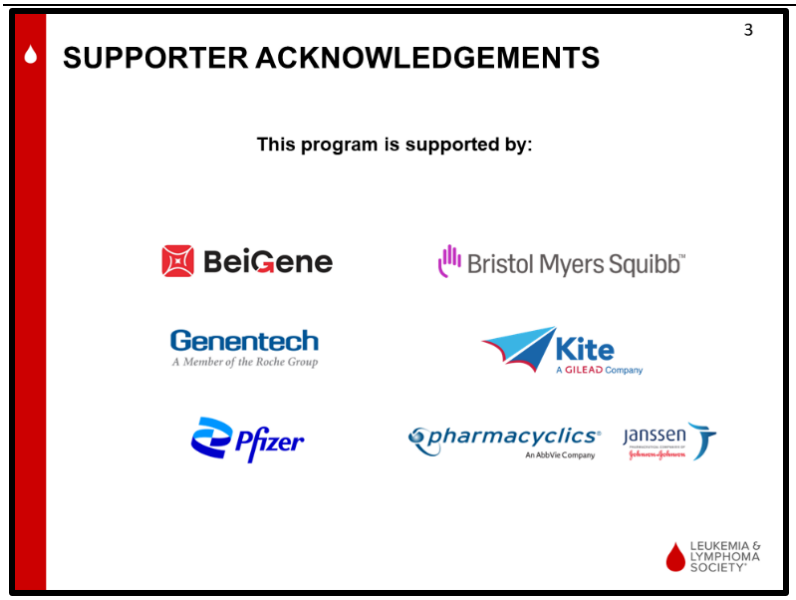


Elissa Baldwin: Hello everyone and welcome to "COVID Updates: Where We Are and Where We Go From Here.

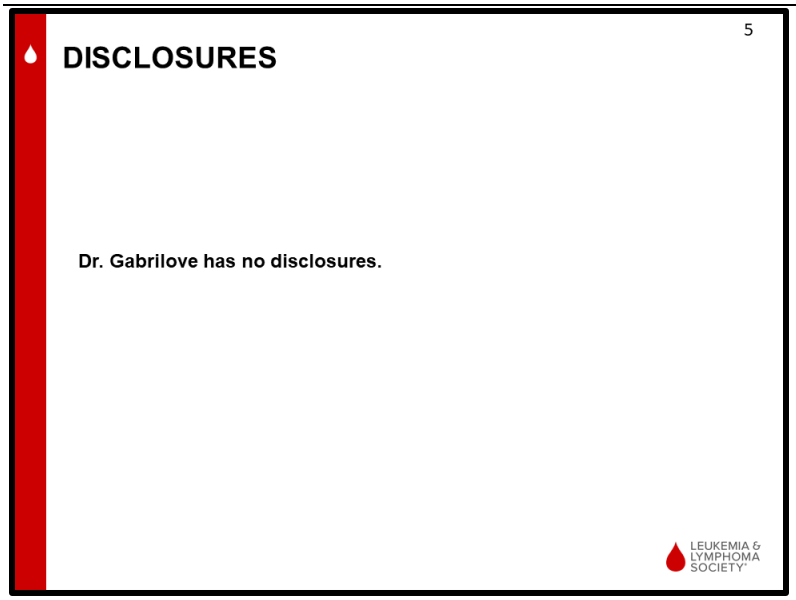


My name is Elissa Baldwin with the Patient Education team at The Leukemia & Lymphoma Society. Following a short presentation by our key opinion leader, we will have a facilitated discussion, where we will cover the most common questions asked of our LLS Information Specialists, as well as questions that have come in through our online Community.

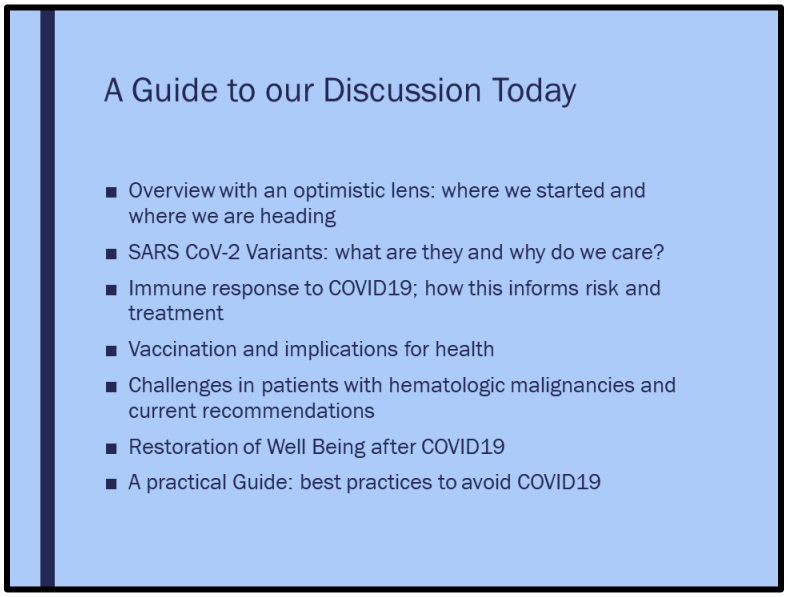


We would like to acknowledge BeiGene; Bristol Myers Squibb; Genentech; Kite, a Gilead Company; Pfizer; Pharmacyclics, an Abbvie company and Janssen Biotech for their support of this program.

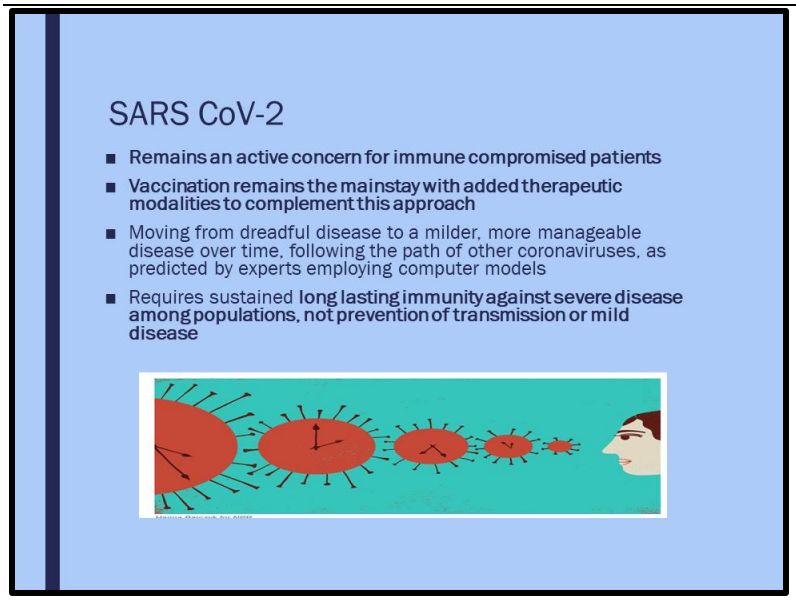
I am now pleased to introduce Dr.Janice Gabrilove, the James F. Holland Professor of Medicine and Associate Director of Education & Training for the Tisch Cancer Institute. She is also the Director of the Clinical Research Education Program at the Icahn School of Medicine at Mount Sinai Hospital in New York City. Dr. Gabrilove works on the development of novel therapeutics for leukemia and has been awarded multiple patents for drugs approved by the FDA to treat myeloid leukemias and alleviate harmful effects of chemotherapy. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise.



Dr. Gabrilove, I am now privileged to turn the program over to you.

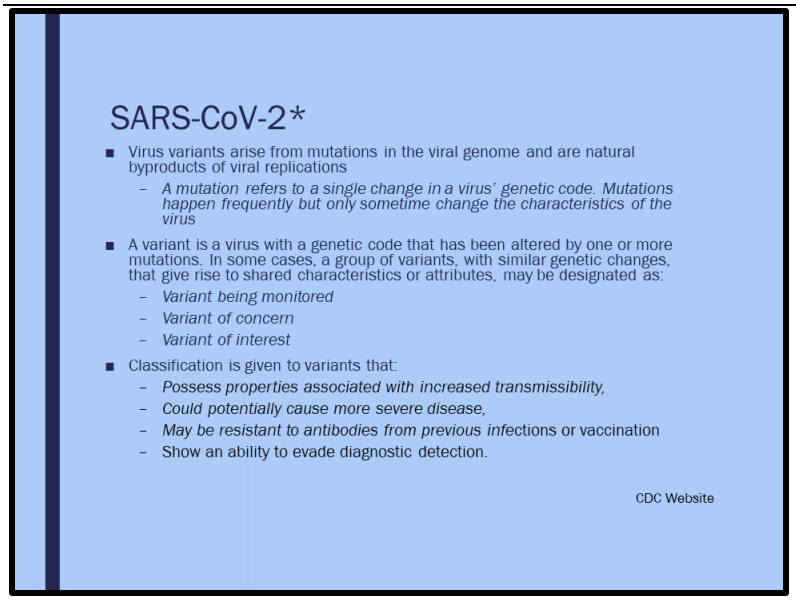


Dr. Janice Gabrilove: Welcome everyone. It's absolutely my pleasure to be here today with all of you to discuss this really important topic. I thought I would first start with a guide for our discussion today. I'm going to start with an overview, with an optimistic lens about where we started and where we're heading with COVID-19. We'll talk a little bit about SARS CoV-2 variants and what they are and why do we care. We'll then move into a little bit of an understanding of immune responses to COVID-19 and how that actually informs our concerns regarding risk and treatment interventions, moving on to vaccinations and their implications for health and well-being. Challenges, specifically in patients with hematologic malignancies, and current recommendations. And we'll spend a little time talking about the restoration of well-being after COVID and a practical guide for best practices to avoid contracting COVID-19, if possible.



So, it's obviously clear that SARS CoV-2 remains an active concern for patients with immune, or immune compromised, including patients with hematological malignancies and those receiving stem cell or cell therapeutic approaches. Vaccination remains the mainstay with added therapeutic modalities to complement this approach. And we'll talk a little bit about why vaccination is so important. It's also, as we think about the challenges we are confronted with in the realm of COVID-19 and the pandemic, it's important to take a step back and realize that actually we are, over time, moving from a dreadful disease to a milder, more manageable disease over time.

Following the path of other coronaviruses such as the common cold, which many think a thousand years ago actually started as a more severe infection. And this pathway of moving from a severe disease to a much milder, more manageable condition is really predicted by experts employing computer models recently published in "Nature Medicine". For this to really be realized, this requires sustained long-lasting immunity against severe disease among a significant component of the population. And that may not actually prevent transmission or mild disease, but the most important goal is to prevent severe disease among all of those who might come in contact with this infection.

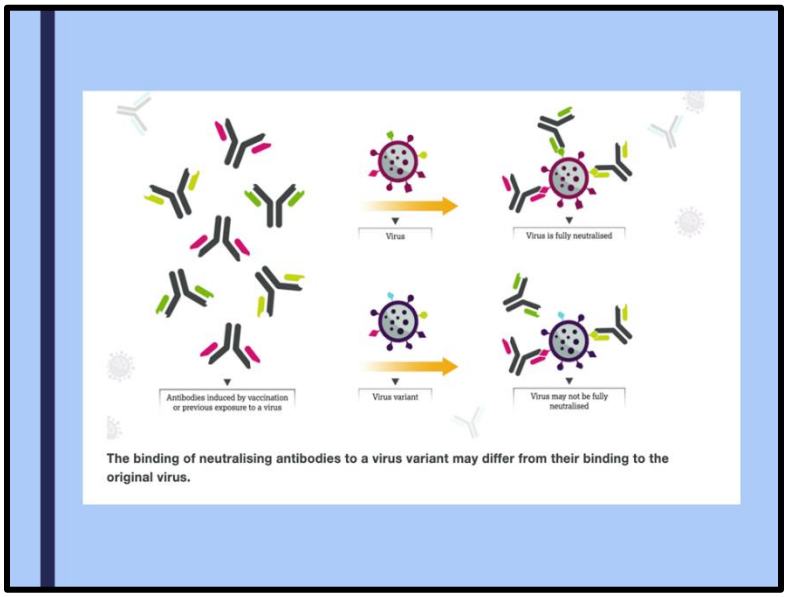


So let's spend a little time about talking about COVID-19 and the hot topic of variants. So, first and foremost, it's important to remember that not just for COVID-19, but for most viruses that exist, variants arise from something called mutations in the viral genome or the blueprint, the code for how that virus should behave, replicate and give rise to more of itself. And it's really a natural product of viral replication. If you think about it, you need to get a flu vaccine every year because the flu virus changes each year. It has a different mechanism that it uses to change than what we know for COVID, but nevertheless, it changes. And so that's why we need to get vaccinated every year with a slightly different flu vaccination.

When we talk about how these variants arise from mutations, it's important to think about what is a mutation? A mutation refers to a single change in the virus' genetic code in that blueprint that gives instructions, that set of instructions that the virus has for how it should behave. And those mutations happen frequently, but only sometimes actually change the characteristics of a virus. So again, these mutations are part and parcel of every virus. In this instance, those mutations seem to occur a bit more frequently, but they don't always result in characteristics that are of concern. Only in some instances are the changes consistent with characteristics of a virus that we need to be more prudent about.

So, a variant is a virus with a genetic code that has been altered by one or more mutations. In some cases, there are a group of variants, as we'll come to in a moment. We sometimes call those groups lineages that have similar genetic changes that give rise to shared characteristics or attributes. And as a result, they may be designated by experts in the field and organizations like the NIH [National Institute of Health] or the CDC [Centers for Disease Control and Prevention] within this country, as variants to be monitored because they have certain characteristics that make us a little more worried about them or characteristics that we really are not that concerned about. And so we might not label them at all in this instance.

So variants to be monitored, variants of concern or variants of interest. And that classification of a variant in those respective categories really relates to the following; does the variant possess properties that are associated with the likelihood it would be more transmissible? Could it potentially cause more severe disease? Could it be resistant to antibodies from previous infections or vaccination or therapeutics that we've already developed? Or does it show an ability to evade diagnostic detection? So these criteria are what are used to determine by national organizations and experts in the field to consider whether a variant is worthwhile following, monitoring, be of concern or be of interest.



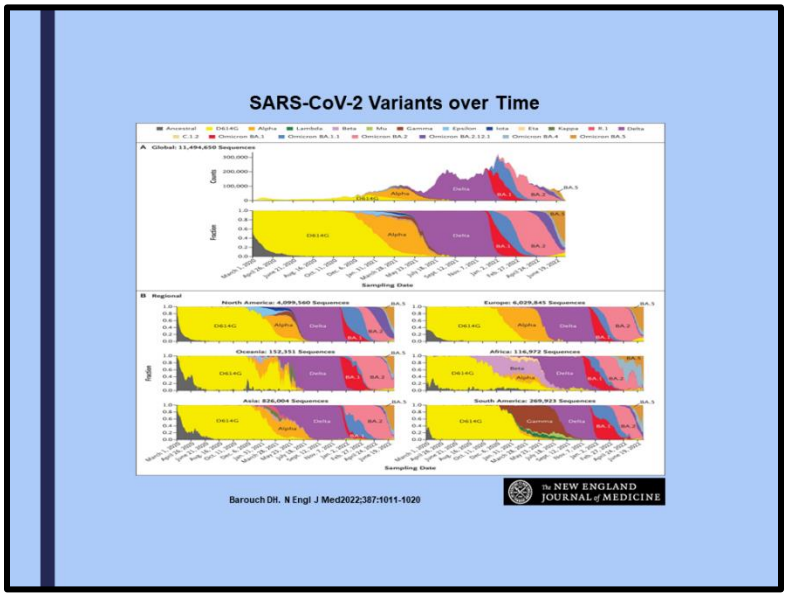
And just to understand this a little better, here's just a cartoon that shows antibodies that might be induced in your body when you're exposed to COVID or any virus and that those or you've been vaccinated, such as with the current vaccines or the flu vaccine. You make a variety of antibodies that recognize in our standard responsive virus a number of special features here indicated by this pretty pinkish red feature or this green feature. These become the features that the antibodies will attack and as a result of binding to those features, will neutralize the virus fully. When a variant comes around, they may still have some features that are approachable, but they may have some new features as indicated in blue or black here.

And the antibodies that were generated from prior infection or from vaccination may still neutralize or may still have some impact, but not as fully. So, when we talk about a variant not being responsive more or less, it's the degree to which there is some retention or lack thereof, of the ability of an antibody to actually neutralize or partially neutralize a given virus variant. And we'll come back to that in a moment.

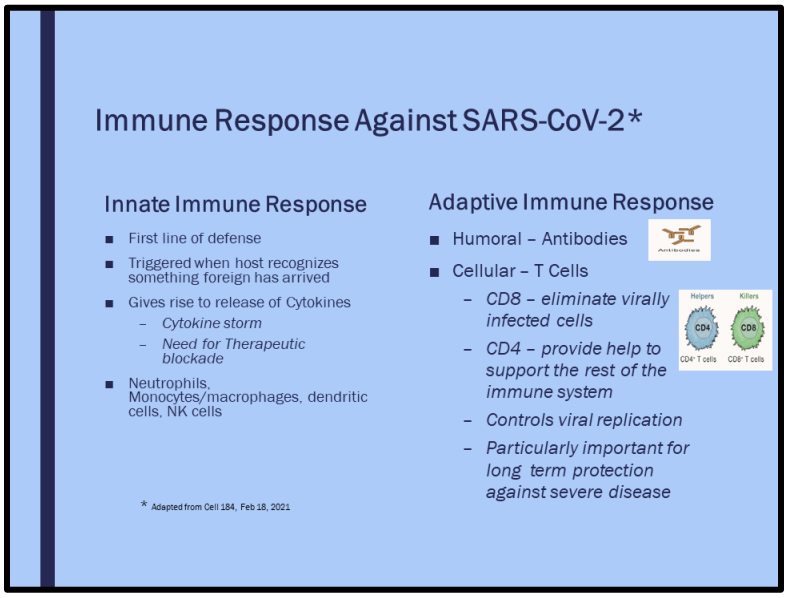
Lineage	Variant	Time Appeared	Transmissibility	Severity of Disease	Break-thru Infections
	Ancestral	2019			
B1.1.7	Alpha	November, 2020			
	Beta	End of 2020	50% more than Alpha	More likely to result in hospitalization & mortality	
B.1.617.2	Delta	Late 2020	Twice as much as Beta	More severe in unvaccinated	Some
AY.4.2	Delta+		10-20% more than Delta		
BA.1, BA.1.1, BA.2, BA.3, BA.4 BA.5	Omicron	November, 2021	More than others		More
BQ.1, BQ.1.1,			More than BA strains		
BQ.1.1					

Other: XBB (emerged from prior BA variants), *Gamma, Epsilon, Eta, Iota, Kappa, Mu, Zeta, 1.617.3.*

So, this is not a quiz to really know the different variants, but you certainly are all familiar with the major variants from the ancestral original strain of COVID-19 appearing in 2019 at the end of the year, all the way from Alpha through Omicron, most recently. And you can see that of the Omicron, there are many similar types of variants. They're not really variants, they're lineages within that variant of Omicron. And we've heard about many of these BA.4, BA.5, and more recently the BQ versions. And this has to do with how transmissible they are. So, the Omicron BA versions were more transmissible than some of the earlier variants and there was more of a response, more of an infection breakthrough, largely with mild disease as opposed to severe disease with earlier variants. And then with the BQ variants of Omicron, they appear to have an even greater advantage of transmission. There are a number of other variants that we'll hear about that are actively monitored by the CDC and the NIH and other regulatory groups to really, some of which, as I mentioned, will be important and some of which will not. A recent version XBB emerged from prior BA variants and appears to not be as much of a concern as originally thought.



This just shows you, for those of you who are visual learners, the wave of these variants globally over time. You can see the original strain all the way through to the current BA.5 version of Omicron. And this is depicted for North America. And you can see that the lifespan of the variant changes and is reduced as a function of some of the interventions that we've had in terms of how quickly these come and go and why we leave it to authorities to really let us know which variants to be most concerned about. But you can see that the lifespan of these variants really becomes less and less over time.



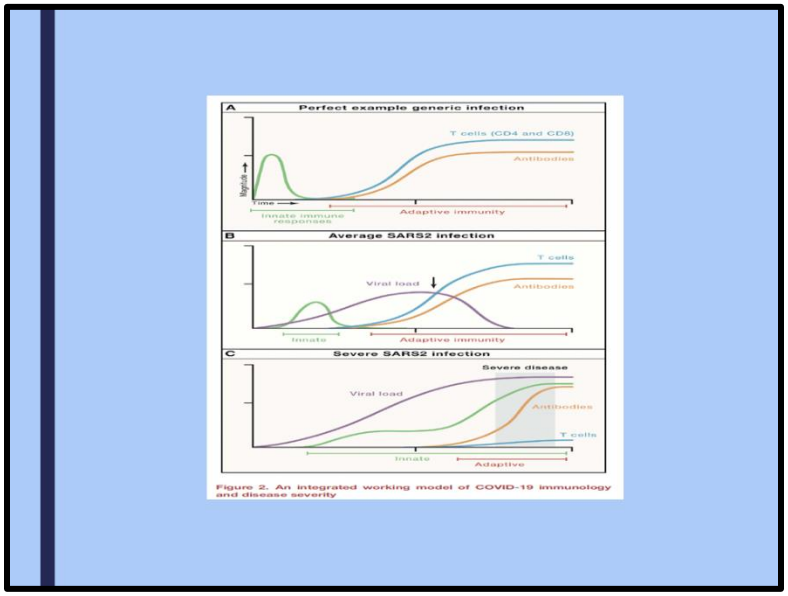
So, when an individual is actually exposed to COVID, CoV-2, or COVID-19, there are two parts of our immune system that are activated and we're just going to talk about this briefly because it helps us understand some of the risk factors and it also helps us understand the role of immunization and vaccination. So the first response to any infection and absolutely important in exposure to COVID-19 is what we call the innate immune response. This is the first line of defense. It is triggered when a person, a host recognizes that something foreign has arrived and needs to be gotten rid of.

And this includes a number of cellular elements such as neutrophil granulocytes, which are a special type of white cell that fight largely bacterial infections but are also important for viruses, monocytes and macrophages which are like little Pacmen. And they are major garbage collectors. Even lobsters have monocytes and macrophages and they eat up anything foreign in sight. And a variety of other lymphoid elements, dendritic cells and NKs and natural killer cells. In addition, epithelial cells, which are barriers in our mouth and our nose and our intestinal tract also serve as a first line of defense.

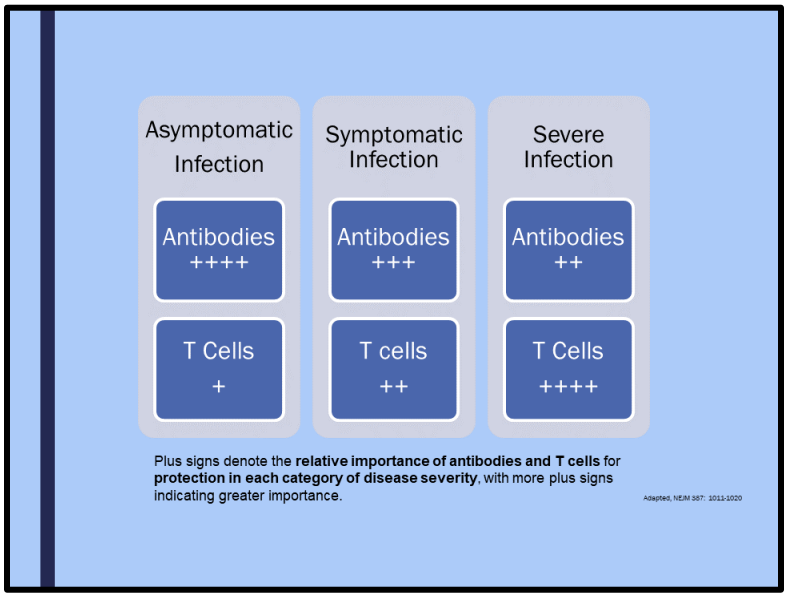
And one of the ways they defend us is by releasing a variety of proteins, which are called cytokines. And this can be very beneficial, but in some cases, if there is too much or an excessive amount of those cytokines produced, that can give rise to a cytokine storm. And some of the therapeutic approaches that have been instigated have included a blockade of these cytokines when they are too abundant and too strong. In addition, you can see that since the innate immune response is important at the start to try to prevent viral entry, patients who are neutropenic or have low neutrophil counts in the setting of both treatments for non cancer.As well as treatments for solid tumor malignancies and blood cell cancers have an increased risk initially when their neutrophil count is low, because they don't have the same capacity for mounting this full innate immune response. Although there are other cells that can help with that.

The second part of the immune response is the adaptive immune response. And this is the educated portion of the immune system, which involves cells called B cells and T cells. And the job of B cells are to make antibodies and the job of T cells are to eliminate virally infected cells or to provide help to the support the rest of the immune system. And this is the job of two different types of T cells called CD8 and CD4, respectively. And their overall role is to control

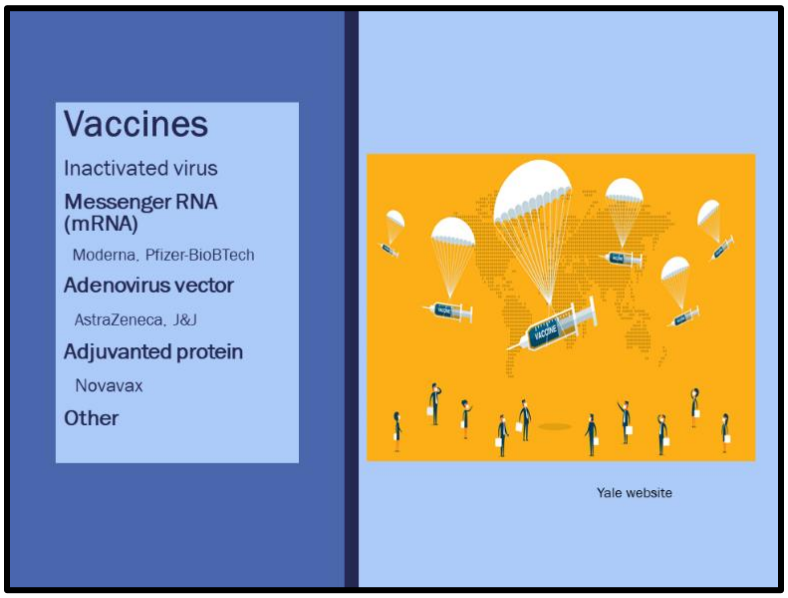
not viral entry but viral replication. And it's particularly important for long term protection against severe disease which is what we care about most.



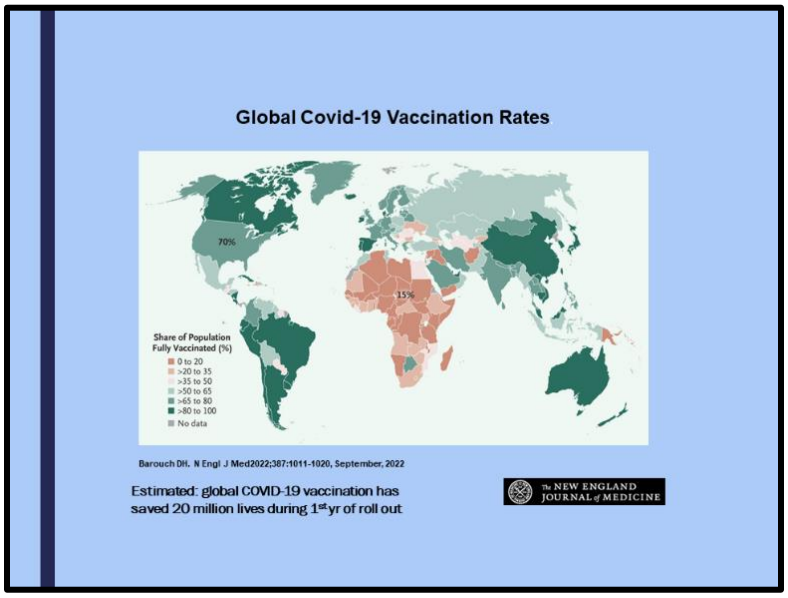
This is a cartoon taken from that same paper published in *Cell* that just gives you a feeling for the time course of how your immune system gets activated. Here we're looking at the magnitude of the response and here we're looking at the time factor for the immune response and in a characteristically ideal situation, you're exposed to a virus your innate immune response immediately comes into action and allows that viral load to be reduced. And then subsequently, your adaptive immune response comes into play to really prevent viral replication. In a typical COVID-19 infection, you can see that you're exposed to virus. The innate immune system comes into play that somehow slowly affects the entry of the virus, which continues to come into the system. And then the adaptive immune system comes into play, which will diminish viral replication and render a reduction in the overall severity of the infection. In severe infection, and these are all idealized for a non-vaccinated individual. In a severe infection, the viral load gets ahead of us and the innate immune system, while trying very hard to catch up is not able to really effectively block entry and the adaptive immune system may be delayed. Again, not able to catchup with disease that is severe already.



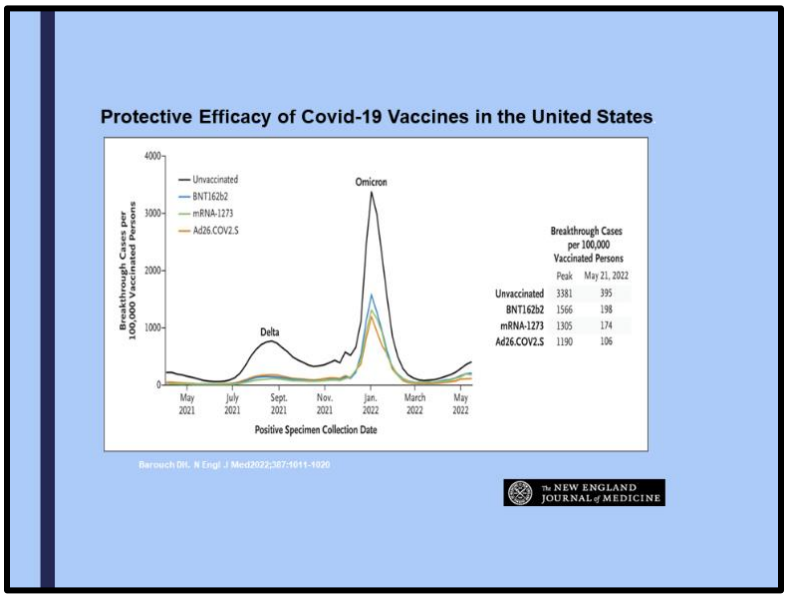
So in general, there are, in terms of infection and if we put aside the innate immune system, the adaptive immune system plays an important role and probably one of the most critical roles in the severity of infection. In asymptomatic individuals, the antibody production plays a greater role in rendering that asymptomatic status than T cells. On the other hand, as we move through amore clinically significant infection, T cell function actually is more important in preventing and alleviating severe infection, which is something that we greatly care about.



So, if we keep those thoughts in mind, that little brief tutorial in mind, let's move into the realm of vaccination and, of course, we have the speed at which vaccine development came about is a marvel in and of itself. And there are really three major types of vaccination. In this country, we only have the Messenger RNA virus vaccine, the Messenger RNA virus and the adjuvanted protein virus of Novovax, which is the new player on the block. The adenovirus vector vaccinations, while used abroad, are no longer being used in the US. The FDA has no longer allowed them to be used in the US.



So, if we look globally at what's happening with vaccination rates, and this is taken from a recent paper published in the *New England Journal of Medicine* in September of 2022.This looks at, is color coded for the degree of vaccination of populations. And you can see that within Canada, many regions in South America, China, Australia, New Zealand, the vaccination rates are extraordinarily high. In the US, we have about 70% of the population being vaccinated. But you can see that in pockets in Eastern Europe and Asia and in Africa, there is a large percentage of individuals who remain unvaccinated. And this is one of the challenges for the continued emergence of variants of COVID-19 in the absence of vaccination. At the same time, it's estimated that globally, COVID-19 vaccination in its first year of rollout saved 20 million lives.



So, when we think about vaccination, we of course, are concerned about the recent breakthroughs. And I alluded to this in terms of breakthrough cases, but you can see that with both Delta and with Omicron, that this largely occurred in individuals who were unvaccinated. And it's the unvaccinated population that remains the greatest issue and concern in the current

environment. That's not to say that we haven't seen breakthrough cases in vaccinated individuals, but for the most part, these have been considerably milder.

Protective Efficacy of Coronavirus Disease 2019 (Covid-19) Vaccines against the Ancestral Viral Strain in the United States and against the Omicron Variant in South Africa.

Table 1. Protective Efficacy of Coronavirus Disease 2019 (Covid-19) Vaccines against the Ancestral Viral Strain in the United States and against the Omicron Variant in South Africa.

Vaccine (Dose)	Efficacy against Symptomatic Disease	Efficacy against Hospitalization	Efficacy against ICU Admission
	United States, Ancestral Strain*	South Africa, Omicron Variant†	
	percent	*percent*	
Pfizer BNT162b2 (two shots)	95	70	70
Moderna mRNA-1273 (two shots)	94	ND	ND
Janssen Ad26.COV2.S (two shots)	94	72	82
Janssen Ad26.COV2.S (one shot)	72	ND	ND

* Data on protective efficacy of vaccines against symptomatic Covid-19 in the United States are from randomized, placebo-controlled phase 3 clinical trials.[14-17] Interim efficacy data before the emergence of the omicron variant are shown for each vaccine. The global efficacy of Ad26.COV2.S was lower, at 66% for the one-shot vaccine and 75% for the two-shot vaccine, as a result of the beta, lambda, and mu variants in Africa and South America.
† Shown are data on clinical effectiveness of BNT162b2 and Ad26.COV2.S against hospitalization and admission to the intensive care unit (ICU) during the omicron surge in South Africa (November 15, 2021, to January 14, 2022).[18] Data are for effectiveness 1 to 2 months after the second immunization. ND denotes no data.

Barouch DH. N Engl J Med2022;387:1011-1020

The NEW ENGLAND JOURNAL of MEDICINE

And this just demonstrates if we look at Pfizer, the Pfizer for which there is the most data, the efficacy against symptomatic disease, including severe disease, hospitalization and ICU admissions were really in the 95%. With the Omicron, that did drop, but still there was considerable protection with 70% efficacy against hospitalization or against ICU admission.

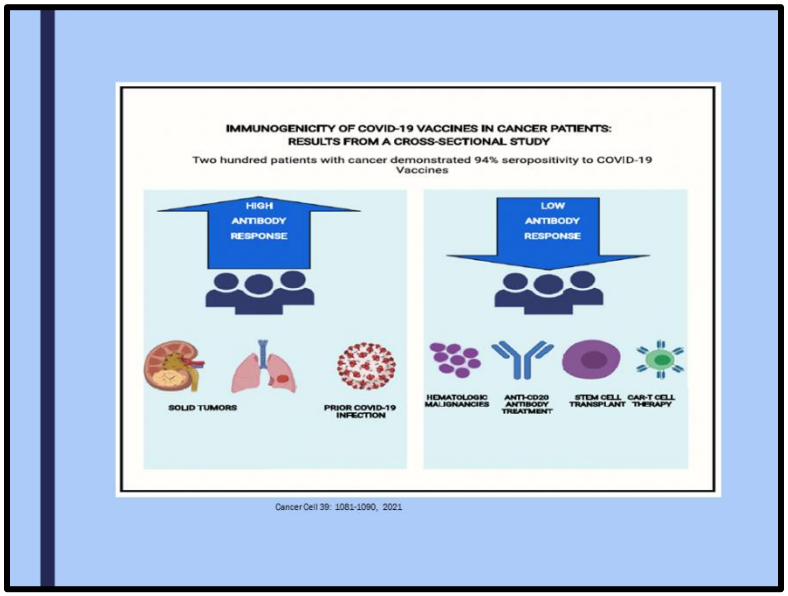
Immunologic Impact of Vaccination

- Prior boosting increases neutralizing antibodies to omicron but wane over time
- T cell responses induced by vaccines have > 80% cross reactivity to omicron and to prior variants
- Hybrid immunity from both vaccination and infection provides greater and more durable protection than either alone
- Role of specific mucosal humoral and cellular immunity at site of inoculation may play an important role

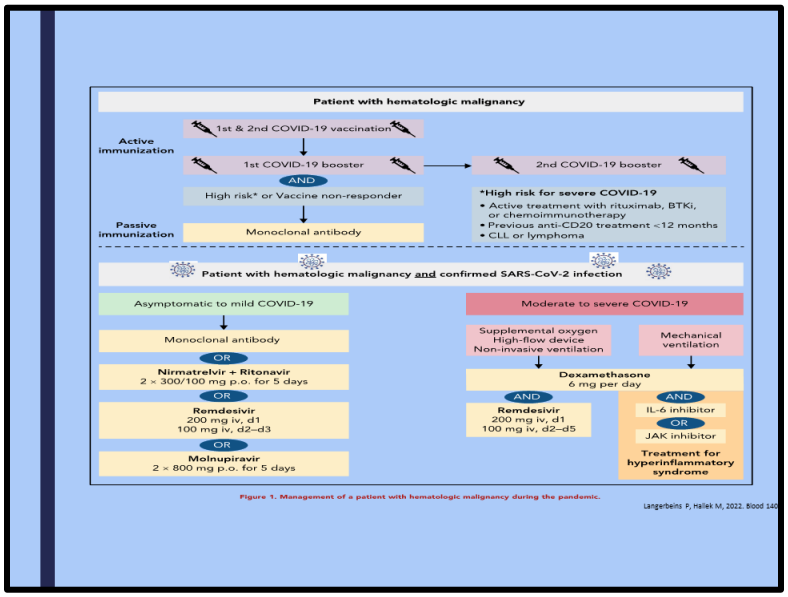
Cell 184, Feb 18, 2021

So, the immunological impact of vaccination has been that prior boosting certainly increases neutralizing antibodies to Omicron, but they do wane over time and ergo, the reason for the newer bivalent vaccinations to boost neutralizing antibodies that will be protective against a broader range of variants. The good news, however, is in those who have that capacity, T cell responses that are induced by vaccines have more than 80% cross-reactivity to Omicron and to

prior variants. So, it's the T cell response, that I mentioned, becomes really the most important for protection against severe disease, which is what we are really most worried about. And so vaccination appears to have a significant impact and a prolonged protective impact on preventing severe infection across a broad range of variants and likely against variants for the future. There is evidence that hybrid immunity from both vaccination and infection provides even greater and more durable protection than either alone. And ergo, the reason for the recommendation for vaccination. Even in individuals who have previously encountered infection with COVID-19. And additional promising research is ongoing that may inform therapy of the role of specific mucosal, the lining of our airways, the lining of our nose and cellular immunity at the site where the virus tries to enter, may play an important role. And there are already nasal sprays under development, in this regard.



So, if we move to patients with malignancy, we know this is what's published in *Cancer Cell*. And we know that patients with solid tumors are in general have the ability to have high antibody responses to COVID-19 vaccination. However, patients with hematologic malignancies, patients who have received anti-CD20 antibody treatment, which includes not only patients with lymphoproliferative disorders, but patients with autoimmune disease, in particular. Those who have been exposed or have received stem cell transplant for a variety of indications, and CAR T-cell therapy in general have a lower antibody response. Now, as you now know, antibody response is not the whole story, and LLS is actively supporting research to really look at whether patients with these conditions are able to mount a T cell response, which we know is equally, if not more so important over time.



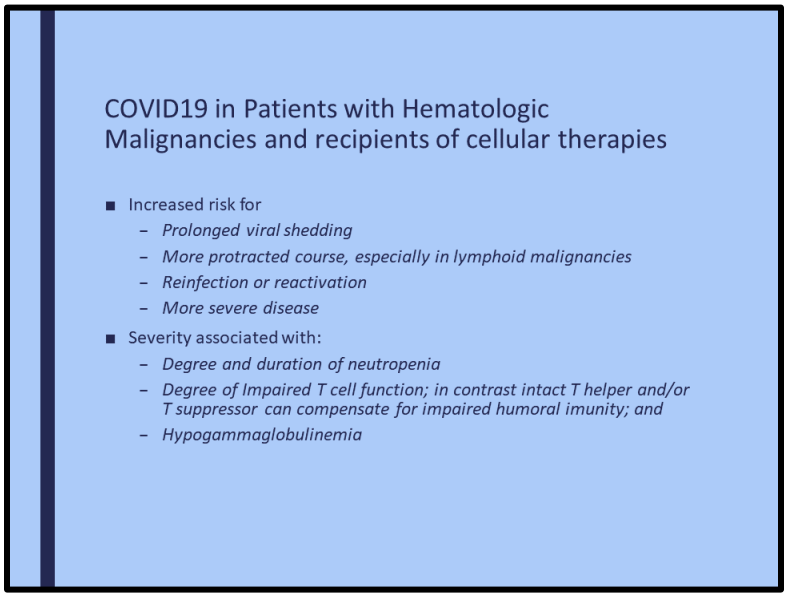
This is a little busy, but it's taken from a recent publication in *Blood* by Langerbeins and Michael Hallek, looking at the current standing of therapeutic guidelines for vaccination and therapeutic intervention for COVID-19. I say this was published in July of this year. But we know that this is a constantly changing role of guidelines and recommendations, and it's important to be aware that we are all surrounded by experts. I have patients who come to me with a question and I will tell them that I need to check with my infectious disease colleague and I get back to them. The recommendations are changing, and the good news from that is that there are experts paying attention, revising recommendations and optimizing strategies to keep us all safe and as well as possible.

And having, maintaining that active conversation with your healthcare providers is critical to really optimizing the care and the approach of patients with hematologic malignancies. So currently, of course, there are COVID-19 vaccinations, both first and second and the two boosters, now followed by the bivalent booster that are recommended for those patients who do not mount an antibody response, even though it's possible that they may have a T cell response which we haven't measured.

And the data is just beginning to come to the fore, the recommendation is still to provide passive immunization with medication, treatments such as Evusheld™, even with the newer Omicron strains that appear to be less impacted by Evusheld. Haunting back to the cartoon I showed you, ineffective does not mean that or less effective does not mean that it is completely ineffective. And since we don't know for sure and since there is a possibility that the variant's lifespan will change and a new variant will come along that will be more responsive, the recommendation still, as of November 14, to administer Evusheld. Even if its efficacy may not be as great as what it had been in the past. I'm confident that there will be newer, passive immunization approaches in the not too distant future.

For those patients with hematologic malignancies, who actually develop COVID-19, again, the treatment paradigm has changed. Some of the monoclonal antibodies that we had are currently not active against the current strains, but are held in reserve for future if needed, and the antiviral agents have really come into play. There are also recommendations for moderate to severeCOVID-19, which involve both remdesivir, as well as inhibitors of il 6, the whole cytokine cascade that I mentioned, and inhibitors of JAK2,again to block that cytokine cascade. And

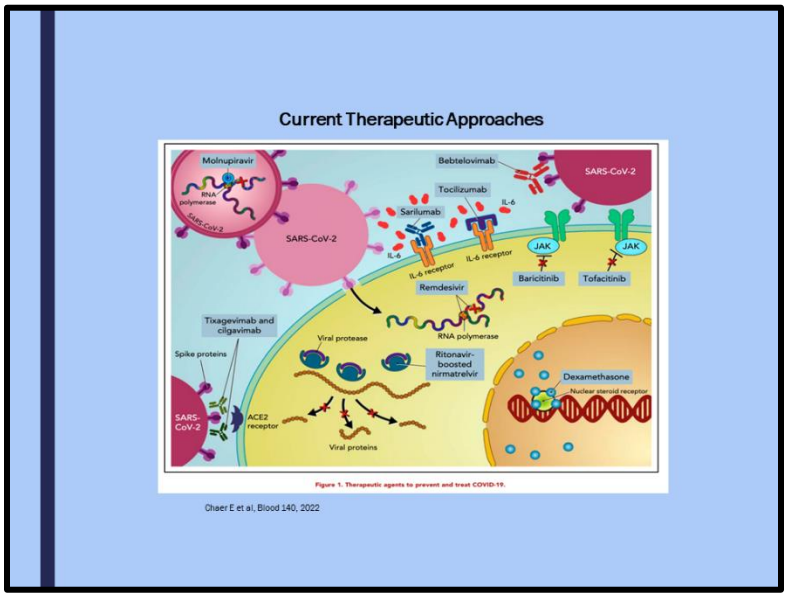
these, of course, are done in concert with a range of healthcare providers and experts, along with patients and their families.



Some of the additional challenges for patients with hematologic malignancies and recipients of cellular therapies is that these patients are at increased risk for prolonged viral shedding. We do not know whether that viral shedding is consistent with infectious virus or whether it's footprints related to elements of the virus, but in general it is assumed that that prolonged viral shedding may include some active virus.

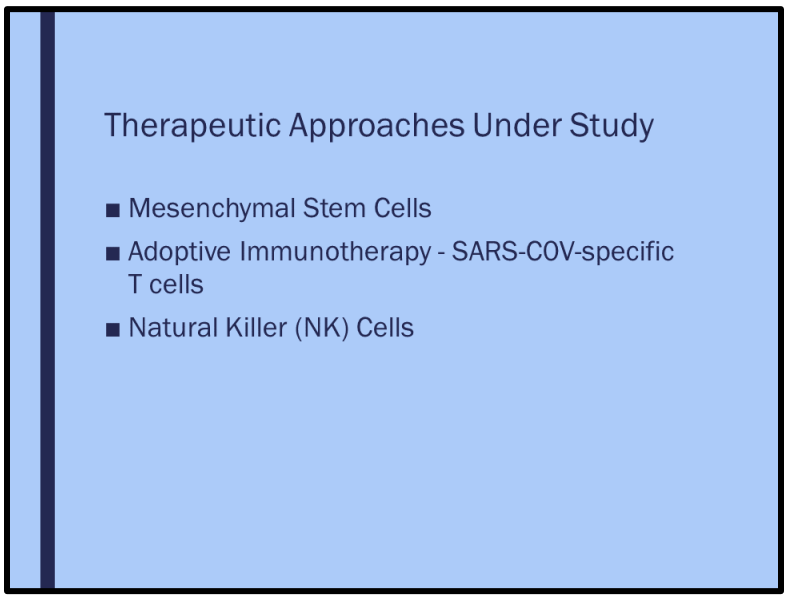
And so for patients with hematologic malignancies, the recommendation is that really, at least for our own facility, they are not seen in a usual environment for at least 21 days, but can be seen in an environment where we see patients who have had exposure to COVID-19. These patients often have more protracted courses, especially in lymphoid malignancies. They may be at risk for reinfection or reactivation. May still be at risk for more severe disease. And so, monitoring of symptoms and intervention with appropriate modalities, as I mentioned on the previous slide, becomes very important. So remaining vigilant, aware, sharing your symptoms with your care provider or as family members, being advocates for early intervention is really key.

Severity of infection may also be correlated with the degree and duration of a low white count, the degree of impaired T cell function, and also the presence of low immunoglobulins or low production of antibody. I will just say that there are patients who have low antibody levels and are what we call hypogammaglobulinemic, but they are still able to mount an antibody response to a vaccination. So, if you are hypogammaglobulinemic, it does not automatically mean that you cannot mount an appropriate response to vaccination, which is why we recommend vaccination for everyone, unless there is a medical contraindication to doing so.



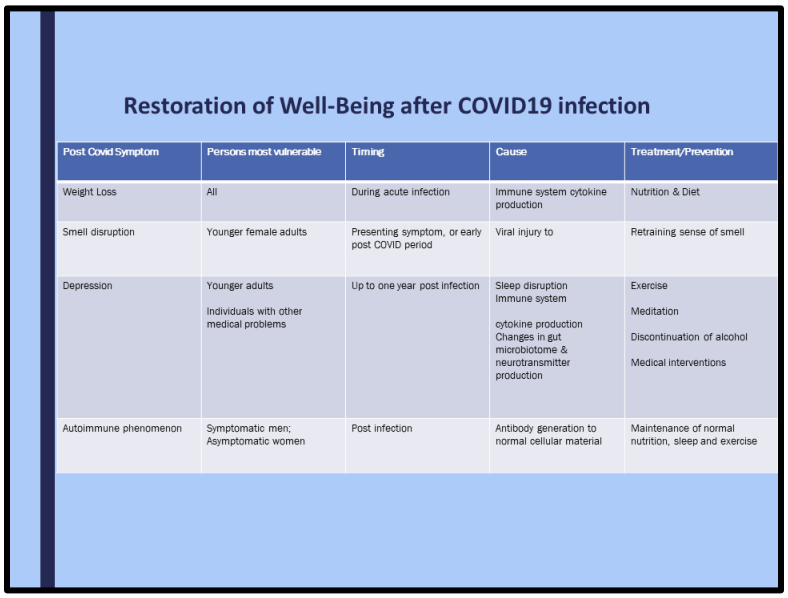
This is a nice cartoon that just kind of summarizes the current therapeutic interventions just from an understanding perspective. There are antiviral medicines that attack the virus itself. There are medications, antibodies that block some of the cytokine storms, specifically against interleukin 6, which is one of the proteins made by the immune system to fight viral infection, but can also cause harm when produced in excess.

There are antibodies against the spike protein itself, which currently are being put on the shelf, since the current strains are not as responsive to these antibodies to signaling cascades that pass on the message from a viral infection. And we have effective medications to block those. Antiviral medicines that prevent viral replication and then steroids that are used for non-specific inflammation at the level of the genetic code.



Some new treatments that are on the horizon include the use of mesenchymal stem cells. These are cells that possess immunomodulatory and anti-inflammatory properties. They're also

inherently resistant to COVID-19, which makes them quite attractive, since they lack receptors for the virus. But this is still an investigational strategy as are adoptive immunotherapy, looking at infusions of COVID-19 specific T cells and natural killer cells, but you'll be hearing more about this in the not too distant future.

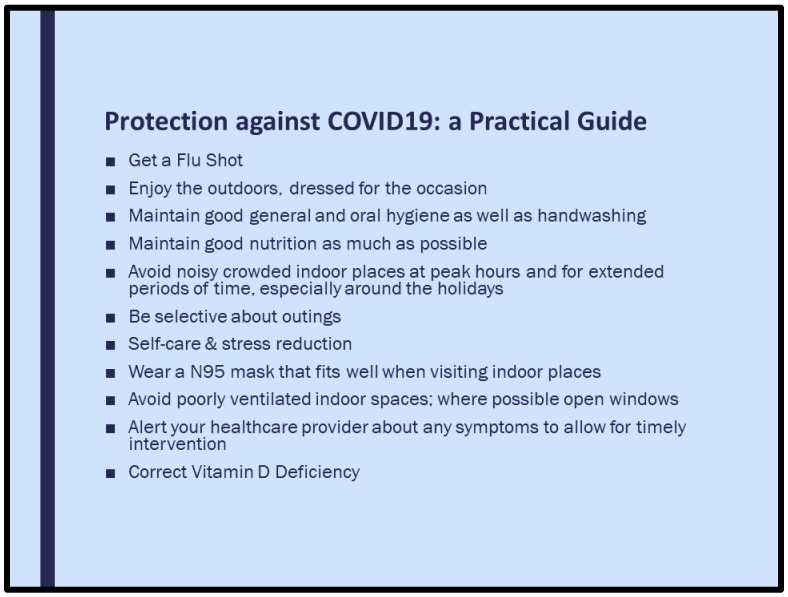


Restoration of Well-Being after COVID19 infection

Post Covid Symptom	Persons most vulnerable	Timing	Cause	Treatment/Prevention
Weight Loss	All	During acute infection	Immune system cytokine production	Nutrition & Diet
Smell disruption	Younger female adults	Presenting symptom, or early post COVID period	Viral injury to	Retraining sense of smell
Depression	Younger adults Individuals with other medical problems	Up to one year post infection	Sleep disruption Immune system cytokine production Changes in gut microbiotome & neurotransmitter production	Exercise Meditation Discontinuation of alcohol Medical interventions
Autoimmune phenomenon	Symptomatic men; Asymptomatic women	Post infection	Antibody generation to normal cellular material	Maintenance of normal nutrition, sleep and exercise

So, in our last few minutes together, I wanted to focus on really looking at restoration of well-being after COVID-19 infection, in both healthcare family, caregivers, friends and patients. I've indicated here that there are a number of symptoms that can occur after COVID, including weight loss, disruption of smell, changes in morale, with depression that may actually be related to il 6 production and then a variety of autoimmune phenomena. I've also listed here persons that are most vulnerable with weight loss being all patients, smell disruption and depression being more in younger adults and younger female adults in the realm of smell disruption, in particular.

The treatment prevention for each of these, we have a number of approaches for weight loss, nutrition and diet. So I would certainly advocate that, in working with your healthcare providers, really enlisting the help and support of nutritionists, physical therapists to promote exercise and meditation to counteract depression. Sometimes there is a time and place for medical interventions and encouraging the discontinuation of alcohol, if that's something that's being pursued. Maintenance of normal nutrition, sleep and exercise, also important.



So finally, how can we protect against COVID-19? Just give you some practical guide here. First and foremost, it may sound odd, but get a flu shot. There is some compelling data to say that the enhancement of the immune system, especially the adaptive immune system, through a flu shot, may actually confer protection against COVID-19.So getting a flu shot is extremely important. Probably enjoying the outdoors dress for the occasion, of course, since the outdoors seems to be a safer environment. Maintain good general and oral hygiene, as well as hand washing. Good nutrition as much as possible. Avoid noisy, crowded, indoor places at peak hours and for extended periods, especially during the holidays, and be selective about outings.

Really focus on those that are important to you and your family. Self-care and self stress reduction. Wear an N95 mask that fits well when visiting indoor places. Avoid poorly ventilated indoor spaces and where possible, open windows. Alert your health care provider about any symptoms to allow for timely interventions. Don't depend on your own ability to test and keep your symptoms a secret. And then correct for Vitamin D deficiency. The Vitamin D is very important for both innate and adaptive immune responses and, although not clearly been shown to be correlated with severity of disease, is an important constituency in your overall immune response. So it's important to correct this, especially since Vitamin D deficiency is something that is not uncommon in patients with lymphoid malignancies, in particular. So with that, I think we'll go back to our host and engage in discussion.

Elissa Baldwin: Well, thank you, Dr. Gabrilove, for your informative presentation. As you know, blood cancer patients and their families have significant concerns as we move into our third winter of the COVID-19 pandemic. Hopefully today, we will be able to answer the most pressing questions that our patients have about COVID and staying safe as we move into the holidays. So, as we approach cold and flu season, we are now looking at four respiratory viruses the cold, flu, RSV and COVID. How can patients know the difference between the symptoms of these viruses and whether or not they should be concerned it's COVID? And also, would you explain what RSV is for our viewers who don't know?

Dr. Gabrilove: Of course, great question. So, first and foremost, RSV stands for Respiratory Syncytial Virus and it's a virus that has been around for a long time and causes inflammation in the airways, in the lung, in particular the tiny airways. A way to think about this is when we look at a tree, we know it has a large trunk and then it has many, many branches that branch into

smaller and smaller branches. Our lungs and our airways are very similar toa tree and the very distal, the very distants mall little airways are like the very tiny branches on a tree and they become inflamed with RSV. And we have a name for that, as we have a name for everything. It's called bronchiolitis, inflammation of the small tiny airways called bronchioles.

And this has largely been an infection of concern in children. It's particularly a concern for babies where infants can become quite ill with this, but also is a concern for our patient population, especially those undergoing stem cell transplants. And so in hospitals, infection control groups really monitor survey for RSV fairly regularly, to be sure that hospital floors are, and personnel on those floors, are free of infection and if not, something is noted and infection control moves in.

For during the winter, I think the safest advice I can give is if somebody has any, many of these symptoms in the beginning are very similar, so I would encourage people not to try to guess, not to rely just on a home kit. They really should call their healthcare providers and be tested. The tests that are most helpful are something called a respiratory BIOFIRE®, which looks at a panel of viruses that are known to cause respiratory infections and each may be treated really just symptomatically or with specific interventions, but not knowing your healthcare provider can't properly advise. The best and most reliable test for COVID is still the swab for PCR. While the diagnostic kits, the rapid kits, especially the Abbott kit (BinaxNOW™), appears to still be quite helpful in identifying COVID-19 infections, even with the new variants, it is hampered by the viral load. So a lot of our strategies to reduce infection, especially masking, have to do with reducing the viral load. If you're exposed to one virus as opposed to 100 viral particles, your ability to prevent entry and block replication is going to be more effective than if you're exposed to a million virus particles.

And, likewise, the home kits are very...depend on the viral load. If there's a lot of virus, they'll be very reliable. If there's very little, they may not be. But the PCR is much more sensitive. It can detect much, much greater one in a million particles. So I think the safest advice is if you are having any symptoms of an upper respiratory infection, you should really contact your healthcare provider and find a way to easily go to have a swab, a PCR swab, and a BIOFIRE test to know exactly what you're dealing with.

Elissa Baldwin: Yes, that is very good advice. It's good to, I agree, not guess, and just find out exactly what we're dealing with. Now, let's discuss current variants and how they affect us. We've heard for months that BA.4 and BA.5, but the virus has evolved rapidly and there are now more offshoots of Omicron, as you discussed in your presentation. Now, with these new variants, is there real concern about them becoming immune evasive, essentially defeating the protection of the vaccine, or natural immunity from prior infection?

Dr. Gabrilove: So at the current time, there is really no evidence that the variants of concern are likely to be able to escape immune surveillance, especially T cell immune surveillance, which appears to be really the more important in the long run for preventing severe infection. And there's very good data that in non immune-compromisedindividuals, that it's the T cell immune response that has remained consistent across variants to date. So, there's no a priori reason to think that that will suddenly change. It's possible that the antibody response will not be as optimal with additional variants, but not subtypes of Omicron.

So, the Omicron variants are not truly variants. They're really lineages within Omicron. They're very, very related, but they're still coming into the Omicron family. They're the Gabrilove family or your family. It's a family name. We haven't moved to a brand new family yet. Although, as I

listed, there are a number of other families that are utilized in the naming criteria that we haven't moved on to as yet. But I think that there is great hope that the T cell response really appears to be very important. And the humoral response is important for the initial entry and the initial ability to fight off infection. That might change over time and we might require a different bivalent, but that's an unknown. But there's nothing to suggest the current immediate variants are going to escape what we're currently doing.

Elissa Baldwin: That is very good to know because of course we hear all these different things and they do cause fear and anxiety, particularly with our blood cancer patients and their families. So, that is great to know. Now, with the virus changing so rapidly and being very different than it was in 2020, what about the people who haven't been vaccinated? If they have had COVID already, do they have some level of protection? Are there other ways for them to stay protected from severe disease?

Dr. Gabrilove: So, I cannot truly answer this reliably, but I'll tell you my thinking. So, I think that, while I respect each individual person's wish or lack thereof to be vaccinated, it's clear from the evidence we have that vaccination is the greatest opportunity to really make this viral infection become milder and milder over time. For individuals who have had COVID and subsequently get vaccinated, their protection is even greater. And so there is some and so we call that hybrid protection. So, there is some data that the specific protection they have to is very variant specific and may not extend to new variants with the proviso that their T cell response may actually help them. So, I think if somebody has a medical or religious reason for not being vaccinated, then I think the safest thing they can do is to still practice some degree of social distancing whenever possible. Wearing a mask.

We know that a mask may not prevent transmission, but it certainly absolutely reduces the viral load, which is critical. If you remember those curves I showed, if the virus gets a head start by having a huge viral load and it's doubling, it will be overwhelming very quickly, whereas if it starts off very low, we may be able to get on top of it with treatment interventions and other approaches. So, I think wearing a mask and then if you do have symptoms, paying attention and getting diagnosed properly and getting help from care providers early will be best for you and for the people around you that you love.

Elissa Baldwin: Absolutely. Now, going back to vaccines, we recently interviewed the LLS Chief Scientific Officer, Dr. Lee Greenberger on *The Bloodline with LLS* podcast and he shared how the virus seems to be evolving faster than we can keep up with the vaccine. Now, what is the current effectiveness of the new bivalent booster and also prior versions for those who may not have received the bivalent yet?

Dr. Gabrilove: So, I think, while I appreciate that the virus is changing rapidly, as I mentioned, all this is a natural process for all viruses, and COVID seems to be doing it a bit faster than some other viruses. On the other hand, it doesn't undergo changes that sometimes are even more problematic. In that sense, it's behaving itself. But I think that the current vaccinations, I think that what may require changes is this immediate antibody response. We don't have any evidence that that antibody response to the current vaccinations isn't optimal in an otherwise healthy individual, even those with comorbidities such as obesity or diabetes or heart disease.

The most protection are in older individuals over the age of 65, whose immune system is not quite as robust and are best served by getting a head start. So, I think the current vaccinations are certainly, have been very helpful and continue to be helpful. And as the data I shared with you and summarized in the recent *New England Journal of Medicine* paper have really

contributed to the reduction in severe disease. Severe disease really is largely occurring in patients who have not been vaccinated.

Even in our population of patients who don't mount an appropriate immune response to vaccination, because there is active engagement with healthcare providers and intervention quickly with treatment strategies we have, overall, our patients are doing better than they did at the start of this pandemic. But still, for a given patient, this is a very serious, potentially life-threatening infection. But I don't think that the fact that the virus is changing rapidly means that it is getting more severe, that we don't have evidence for that.

And I, personally, am comforted by the fact that in the population that is able to have a T cell response, that that is remaining protective against severe disease across all these variants. And it's the population as a whole that will help to protect those that are more immune compromised because there is this herd protection that we talk about that as the otherwise healthy population, including those who are vaccinated, who have comorbidities, but are vaccinated and appropriately respond, they will help to protect others around them.

So, I have a little more of a hopeful uptake on this. Hope is good. I definitely like the hope uptake, rather than a lot of fear and anxiety. Now, can we expect new vaccines in the future that would be effective for all potential variants? That's a great question. There has been considerable work by leading investigators, some of whom are actually at my institution, Dr. Palese and colleagues, who have been working on a universal flu vaccination. And some of the lessons learned from that I'm quite confident will go into better understanding how to vaccinate more comprehensively. We aren't there yet. I do think these approaches to really look at the site of entry. So again, there's a rich source of cells involved in adaptive immunity in our nose and our mouth.

Our tonsils, for example, our adenoids, for those of you who had them removed when we were children. That scientists are looking at strategies to deliver a vaccination, if you will, closer to those sites, because that may be even more useful. So I do think that one of the wonderful things. The upside I wouldn't say wonderful, the upside of the COVID-19 pandemic has been the rapidity at which scientific advances have been made that have impacted human health in a positive way. We aren't where we were three years ago. In general, patients do much better. And the wealth of knowledge and the sharing of information, I'm confident is going to inform newer approaches, newer vaccines that will be more efficacious and will anticipate how the virus might change next and stay ahead of it. Again, computer models being helpful to do that, but I'm hopeful that we'll be moving in that direction.

Elissa Baldwin: That's great. Now, we've also heard some about T cell vaccines, correct?

Dr. Gabrilove: Well, ways to activate T cells and make them educated as if they had COVID. So, that your adaptive immunity would come to fruition earlier. And so vaccination does that, but it takes a little longer for that to come into play. So if we wanted to readily allow that to occur, there are strategies ongoing and there are strategies to use cellular therapies, which I mentioned. These [SARS] CoV2-specific T cell infusions, but these are still investigational.

Elissa Baldwin: Right. Now, you discussed the recommendation for high risk patients or those who did not mount a response to the vaccine to get Evusheld in addition to the vaccine. If a patient is eligible for Evusheld, should they get it before or after vaccination?

Dr. Gabrilove: I think the recommendations have really been changing. I think now the recommendation is that there be a window of 14 days. Many patients who've had, many

patients have already received Evusheld and are waiting to get their next dose and want to know when to get the bivalent vaccine relative to that. I would say if you're getting Evusheld, the current recommendation is to wait at least 14 days before getting vaccinated. It used to be a much longer interval, but I believe that is the current recommendation. I would double check with your healthcare provider and their infectious disease colleagues that are often working in partnership with them to know specifically what the latest recommendation is.

Elissa Baldwin: Now, you discussed earlier about testing. So if a patient does test positive, what is the next step? We've heard a lot about Paxlovid™ and you did mention some of the other treatments. Should they be calling their healthcare provider to try to get Paxlovid?

Dr. Gabrilove: So, I think if a patient has who's underactive treatment for hematologic malignancy or has completed treatment in the not too distant past or certainly within the first several years of having had treatment, they should be reaching out to their healthcare provider to discuss next what should be done and whether they should be seen. Paxlovid, in the current environment, is the first treatment of choice. Since the therapeutic monoclonal antibodies at the current time do not appear to be efficacious for the current variant. That changes moment to moment. It depends on which variant is present in your area. So, what is responsible for most of the cases in New York City may not be what's responsible for most of the cases in LA.

I, personally, am not up to date on that and was something that I would check if I had a patient of mine in California call me. I would check with my infectious disease colleagues, which I'm sure many of my other colleagues in hematology oncology would do the same. But we can't assume that the strain is always the same. But assuming that it is, those antibody treatments that we had have been shelved for the moment. And Paxlovid is the go to in someone who's relatively asymptomatic or has mild disease. Better?

Although, it said you can start this within five to ten days, it is better to start it sooner rather than later again to prevent the virus from having any replication. So, Paxlovid would be the treatment of choice. That, unless there was a contraindication to that, in which case other antivirals would be recommended. For most patients who are on medications that interact with Paxlovid, those medications can be safely held for the five day period. And that's currently our practice to withhold certain medications that might be used, for example hyperlipidemia. Those medications often interact with Paxlovid and can be safely held for a brief period of time.

Elissa Baldwin: Now, we are in our third year of the pandemic and a lot of people very much feel over COVID. Many people have already had COVID, at least once, and everyone's risk tolerance is different. So, for those who are not needing to be quite as strict as highly immunocompromised patients, what advice would you give to stay safe from severe disease?

Dr. Gabrilove: Vaccination. Vaccination is the mainstay for preventing severe disease. There's no question about that.

Elissa Baldwin: Now, speaking of staying safe around others, some patients would like to know if it's safe to go back to work in an office or setting that has other people. Should they be masking if they do this, or is it safe enough if they are vaccinated and boosted or just have natural immunity from a prior infection?

Dr. Gabrilove: So, excellent question. I think it's patient specific. It really depends on where you are in your treatment, how far along or how far out you are from having had therapy that might impact your immune system. It may depend on whether your doctor has monitored your ability to make an antibody response to the vaccination or not. In general, I would say if you're an

individual who has been able to make an antibody response to vaccination, then I think going back to the office is perfectly reasonable. I think in the RSV environment, one might consider wearing a mask at work, depending on the proximity you are to coworkers.

If you have a private office, obviously a mask in your own office is not needed. But when you go to congregation areas, you might consider a mask really focusing on RSV. Now, if you want to avoid that, if that's not a risk for you in consultation with your healthcare provider, then I think that using judgment, having good hygiene, being vaccinated, you know if you've responded to vaccination, avoiding huge crowds where possible. I think you do have to get back to living, for sure.

Elissa Baldwin: Yes, and speaking of living, it is December when we are recording this and holiday gatherings are right around the corner and patients have some real concerns. They want to see their families, but the highest risk patients, particularly those who didn't respond to the vaccine, want to hear if there are ways to do that while staying safe. What advice would you give to those blood cancer patients and survivors, as well as their family and friends, to stay safe during the holidays?

Dr. Gabrilove: So I think there are a couple of considerations. Again, I would say this should be in consultation with your healthcare team, because the specifics really do matter. I would say that there are a lot of techniques that have been used now that we know Zoom and a variety of other tools, social media tools, which I'm not a guru on, but that I would consider assigning some of the younger people in your family to put together a really fun filled Zoom interaction. If you're really not encouraged to be in person. I think if you want in-person gatherings, I think outside is still the safest environment, and a safe environment where you are together with family and friends. I think going for walks as a family during the holiday is something to consider.

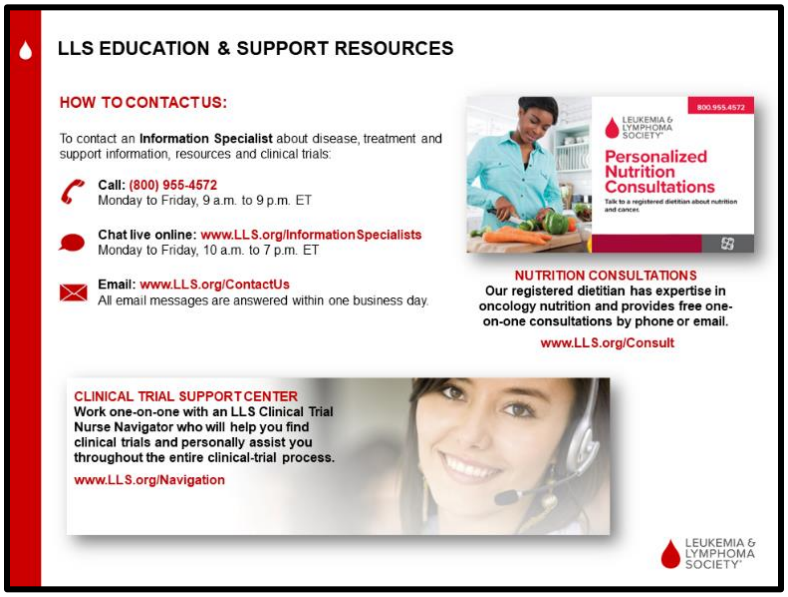
The biggest risk is really sitting over a table of food, drinking and eating together for long periods of time. Because as people drink, their voices become louder, they project more. And I think for patients at risk, that's likely not an ideal setting to participate in. But I think that there are lots of ways to enjoy the holiday with your family. You may need to be a little bit creative. You need to dress the part for the outdoors if you're in a colder environment. But I think celebrating outdoors, having a fun adventure outdoors that doesn't involve alcohol is probably the way to go.

Elissa Baldwin: Sounds like a good plan. Now, a question we often ask on *The Bloodline with LLS* podcast is about hope. As the final question for our program today, what would you say to patients and their families to give them hope for the future with regards to the COVID-19 pandemic?

Dr. Gabrilove: So first, I would say that I applaud the resilience, the fortitude, the courage, and the humanity of all of the patients that I'm fortunate to care for and to be a part of their lives and to all of you who are participating in today's call. So I think one of the reasons I love this field is it gives us a window into the strength of the human spirit. That being said, I think I've shared with you my perhaps sometimes more optimistic, glass half-full. I have great respect and faith in what can be accomplished when science and fortitude come together. If we take a step back, and while many may not feel that Dr. Fauci quite accomplished what he wanted to with this pandemic, the AIDS pandemic really changed rapidly. And while we're still living through COVID, relatively speaking, we have made enormous progress. It's hard to see that sometimes,

especially at the individual level, but I'm confident that we're going to make more and more progress.

I think the treatments we have for patients are so much better now and reduce the toxicity that patients experience that may make them more vulnerable to some of these viral infections. I'm hopeful about that as well. So I do think that where there's a will, there's a way. Science, with the support of fantastic organizations like LLS, that are contributing to the brain trust and the research that really impacts the well-being of all of our patients and families is really what I'm positive and hopeful about.



Elissa Baldwin: Thank you so much, Dr. Gabrilove, for sharing your expertise with us today and for your continued dedication to cancer patients. If we were not able to answer your question during this program, please contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572 from 09:00 a.m. to 09:00 p.m. EST or by visiting LLS.org/ContactUs.

LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, **moderated by oncology social workers**. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**

Education Videos

Community of blood cancer patients, survivors and caregivers supporting each other and giving trusted information and resources, please visit **www.LLS.org/EducationVideos**

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

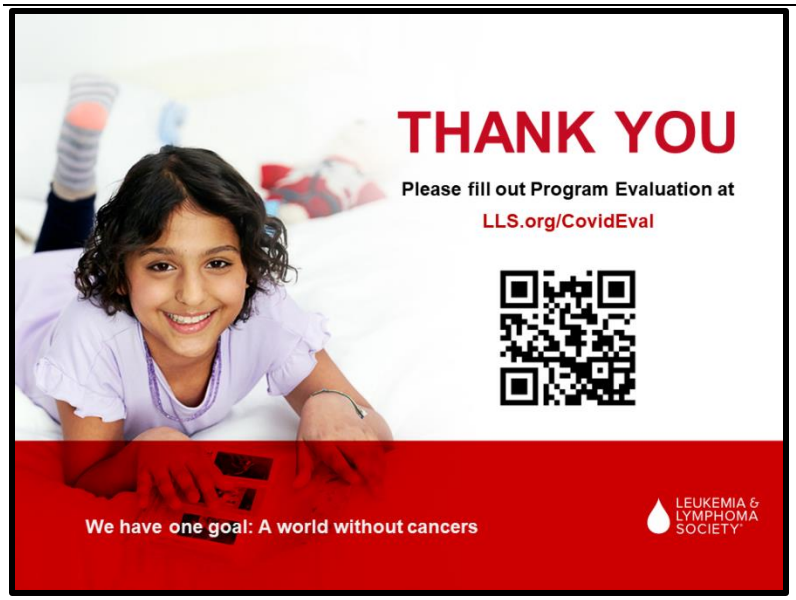
LEUKEMIA & LYMPHOMA SOCIETY

LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: **www.LLS.org/Finances**

To order free materials: **www.LLS.org/Booklets**

LEUKEMIA & LYMPHOMA SOCIETY



We also encourage you to please complete the program evaluation, which can be found at LLS.org/CovidEval or by scanning the QR code on your screen with your smartphone. Completing the evaluation will help us to continue to provide the engaging and informative programming that would benefit you the most. Dr.Gabrilove, thank you again for volunteering your time with us today and on behalf of The Leukemia & Lymphoma Society, thank you all for watching this program. Take good care.