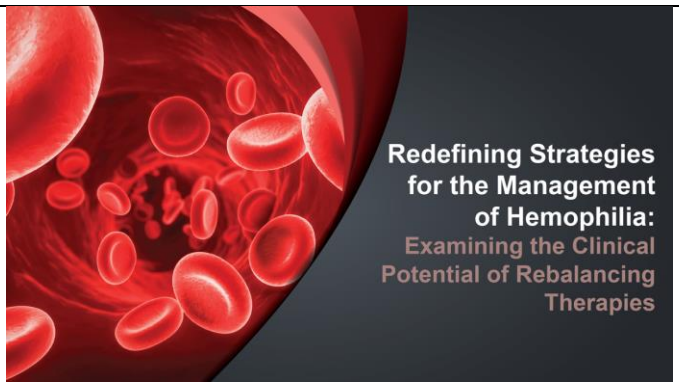
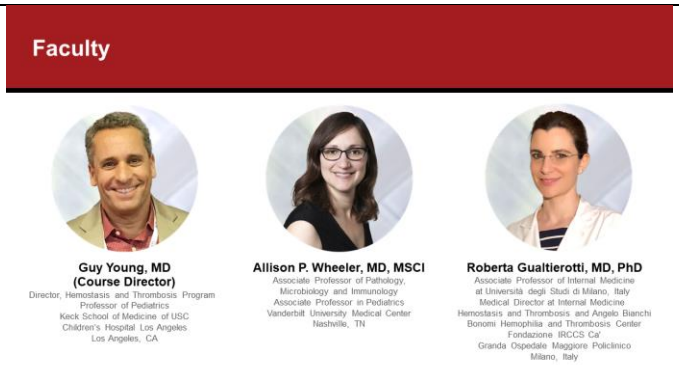
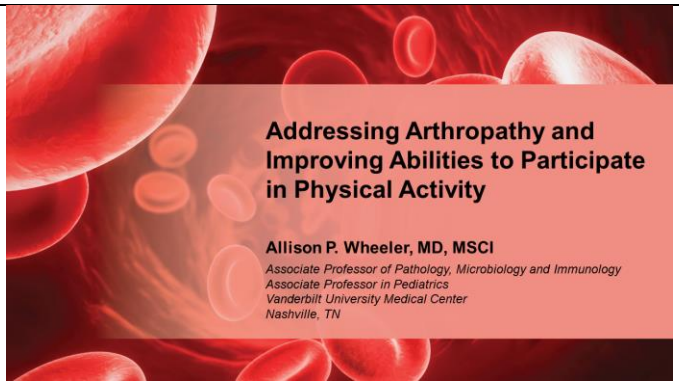
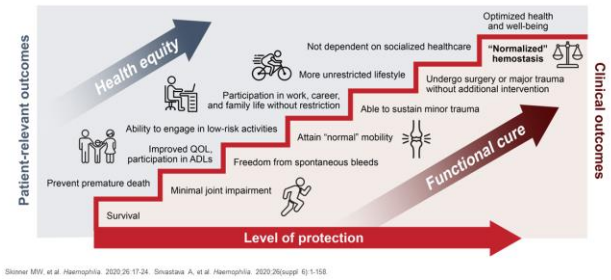
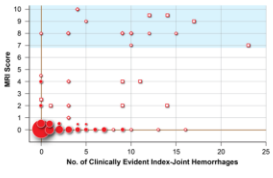
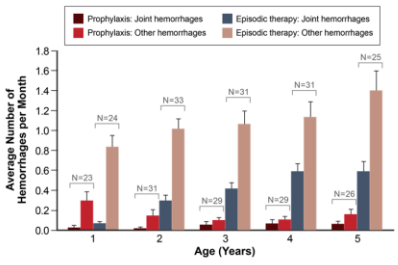
1.		***[Guy Young, MD]*** Hello, my name is Guy Young and I'm happy to introduce this program to you called "Redefining Strategies for the Management of Hemophilia: Examining the Clinical Potential of Rebalancing Agents."
2.		This is the second of a 2-part activity. This one is called "Improving Quality of Life for People Living With Hemophilia: Strategies to Stratify Joint Damage Risk and Allow Increased Participation in Physical Activity."
3.		So, I introduced myself already. I'm joined in this activity by Professor Allison Wheeler. Allison is an associate professor of pathology, microbiology, and immunology and an associate professor in pediatrics at Vanderbilt University Medical Center. And also by Professor Roberta Gualtierotti. Dr. Gualtierotti is an associate professor of internal medicine at the University of Milan, and she also works in the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center in Milan, Italy.
4.		So, first Dr. Wheeler. Please take it away. And you're going to give us the information about addressing arthropathy and improving abilities to participate in physical activity. ***[Allison P. Wheeler, MD, MSCI]*** Thank you, Dr. Young. So, we're going to spend a little time now addressing arthropathy and

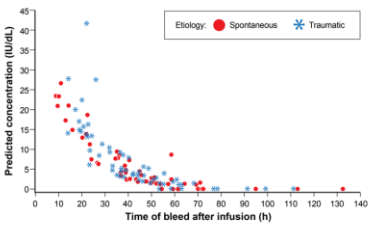
		improving abilities to participate in physical activity for our patients with hemophilia.
5.	**Patient Outcomes and Response to Innovation**  Skinner MW, et al. *Haemophilia*. 2020;26:17-24. Srivastava A, et al. *Haemophilia*. 2020;26(suppl 6):1-158.	So, I've really come very much to love this image (which came out of an article in 2020 that Mark Skinner authored), really looking at patients with hemophilia and how we can think about their care, both in the context of health equity and functional cure. So, as our ability to protect our patients with hemophilia from bleeding and thus protect their joints and muscles from sustained damage has improved, we've really been able to move from just looking at survival and prevention of premature death or improving joint health, to the point that patients are able to participate in of daily living and have an improvement in their quality of life to moving up the staircase, to the point where our patients with hemophilia can participate in their work, their career, their family life with minimal restriction. They can participate in various physical activities that, years ago, we probably never thought they could participate in and really optimize their health and well-being, as we get to the point where the medications that we have for our patients can reach the level of normalized or normal hemostasis. And so, I love the optimism in this image, and I love what it presents for our patients and the possibilities. So, with this in mind, let's talk a little bit about where we've been and what we know and where we're going to.

6.	**Poor Correlation Between Arthropathy and Bleeding Rates** ▪ Arthropathy is detected even in patients with few or no apparent bleeds[1-5] ▪ In patients with established joint damage, joint deterioration often progresses even if few or no further joint bleeds occur[6] ▪ These findings indicate that patients may have unrecognized bleeding episodes, which could contribute to the development of hemophilic arthropathy  MRI score for index joint according to the number of hemorrhages in that joint for episodic and prophylactic treatment groups.[1] MRI: magnetic resonance imaging 1. Image reproduced for educational purposes only from Manco-Johnson MJ, et al. *N Engl J Med*. 2007;357:535-544. 2. Oliveri M, et al. *Haemophilia*. 2012;18:369-374. 3. Kraft J, et al. *J Thromb Haemost*. 2012;10:2494-2502. 4. Di Minno MND, et al. *Haemophilia*. 2013;19:e167-e173. 5. Srivastava A, et al. *Haemophilia*. 2020;26(suppl 6):1-158. 6. Rodriguez-Merchan EC, et al. *Haemophilia*. 2011;17(suppl 2):1-23.	One thing that we know is that there's a very poor correlation between arthropathy or joint arthropathy and bleeding rates. So, arthropathy is detected even in patients who have few or no bleeds. And you can see on the image on the right side of this screen, data from Marilyn Manco-Johnson's pivotal paper on the benefit of prophylaxis. And you can see on the horizontal part of the graph, the number of clinically evident index joint hemorrhages, and that it goes from 0 to 25. And then you can see on the vertical aspect of the graph the magnetic resonance imaging (MRI) score. And although the majority of patients who had no clinically evident joint hemorrhages also had low MRI scores, you can see that there are patients with no clear joint hemorrhages who had higher MRI scores, indicating more damage. And you can see that there are patients with 15 to 20 joint hemorrhages who had very low MRI scores. And so, this poor correlation is something that we've always seen and is really important to demonstrate our lack of understanding—or lack of clear understanding—about what's going on in the joints of our patients. We know that there are patients with established joint damage and joint deterioration who have worsening of their disease even though there are no further joint bleeds that are occurring. And so, we know that there's something going on. There's something under-recognized, either bleeding episodes or micro-bleeds that are contributing to hemophilic arthropathy that we still need to understand more about.

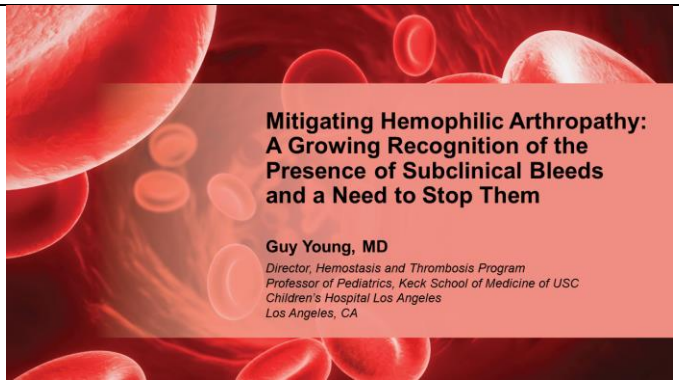
7.	**Joint Health Is a Contributing Factor to QOL** ▪ QOL scores in people with hemophilia vary based on multiple different factors: Age, severity of hemophilia, history of long hospitalizations, frequent visits to doctors, and joint health ▪ QOL is significantly decreased by —≥2 target joints —Higher frequency of joint pain —History of joint surgery ▪ Moderate-to-vigorous physical activity has been documented as decreased in people with hemophilia compared with controls (34.6 min/d vs 65.2 min/d) Carroll L, et al. *Patient Prefer Adherence*. 2019;13:941-957. Putz P, et al. *Haemophilia*. 2021;27:e268-e266.	We also know that joint health is a significant contributing factor to quality of life. Quality-of-life scores in people with hemophilia vary based on a number of different factors, or a number of different components: their age, the severity of their disease, their history of hospitalizations, how often they're going to their doctors, and what their overall joint health is. But we also see significant changes, specifically decreases in quality of life, when patients have 2 or more target joints, have a higher frequency of joint pain, or have a history of joint surgery. And what we know is that as you have this increase in joint damage and this increase in joint pain, you're going to have decreases in physical activity. And, specifically, when we look at moderate-to-vigorous physical activity, there are decreases in this activity in patients with hemophilia compared with controls. So, patients with hemophilia experience 34.6 minutes per day of moderate-to-vigorous physical activity compared with 65.2 minutes among control patients. So, again, impacting quality of life and what our patients are able to do. NOTE: Consequences of decreased activity = increased mean body fat, decreased lower extremity muscle mass. Decreased activity is postulated to be secondary to overcautiousness and pain.

8.	**Known Variables That Influence Joint Damage** **Gene mutations** ▪ *F8* or *F9* genes → inversion, deletion, insertion, and nonsense mutations are associated with increased risk for a severe phenotype ▪ Genes encoding for homeostatic iron regulator protein (HFE) → increased number of hemarthrosis and number of affected joints ▪ Inflammatory and immune genes (*NOD2*, *TLR10*, *HLA B27*) → increased risk of range of motion abnormalities or greater risk of synovitis **Non-modifiable genetic changes have influences that can alter phenotype** Gooding R, et al. *J Blood Med*. 2021;12:209-220.	So, what variables influence joint damage? Well, some things we just can't do anything about. And that's genetic mutations. So, patients with more significant factor VIII or factor IX gene mutations: inversions, deletions, insertions, and nonsense mutations that result in an increase in severe phenotype. These are things that we haven't been able to control up to this point. We also know that there are genes that encode for other hemostatic components, such as iron regulator proteins and inflammatory and immune genes that are going to increase the number of hemarthrosis events that patients have, the number of affected joints that patients have, or the abnormalities in their range of motion and thus increase their risk of synovitis. So, overall, these nonmodifiable genetic changes can alter patients' phenotypes. Although we can't do anything about these genetic mutations, what can we think more about? NOTE: Although we cannot change the disease severity or genetics of a patient, we can intervene with prophylaxis in an effort to minimize bleeding and improve activity (and, thus, perhaps bone mineral density). →
9.	**Known Variables That Influence Joint Damage (cont)** **Disease severity/factor trough** ▪ Joint bleeding is the hallmark of severe hemophilia, and repeated joint bleeds lead to inflammation and arthropathy in joint(s) ▪ Approximately 30% of patients with moderate hemophilia experience clinically significant joint bleeds —Factor activity of 1%-3% is now considered insufficient to prevent bleeding ▪ Patients with mild hemophilia and those with a single *F8* gene mutation have a higher rate of arthropathy than the general population Gooding R, et al. *J Blood Med*. 2021;12:209-220.	Well, we can think a little bit more about the disease severity in our patients and what their factor troughs are and how we can optimize factor replacement to minimize joint bleeding. So, joint bleeding being the hallmark of severe hemophilia, we know that repeated joint bleeds lead to inflammation and arthropathy. And we know that patients with hemophilia are going to experience significant joint bleeds, about 30% of patients. We used to have this aim of a factor activity level of 1% to 3% as the trough to sort of be the base that we're looking for to help prevent joint damage. But we now know that

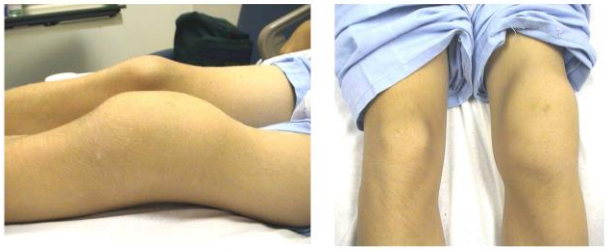
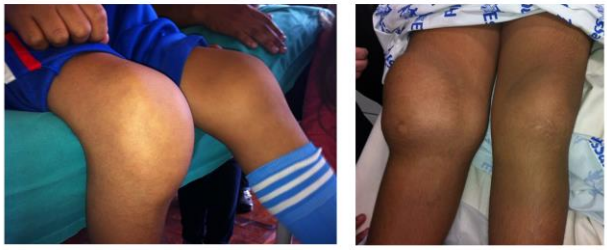
		that's probably insufficient. And we know that these patients with moderate or mild hemophilia or those with a single factor VIII gene mutation, historically referred to as carriers, are going to have a higher rate of arthropathy compared with the general population.
10.	**Known Variables That Influence Joint Damage (cont)** **Prophylaxis** ▪ Starting prophylaxis early (aged 2-3 years) reduces the risk of arthropathy ▪ Continuing prophylaxis throughout life and remaining adherent to prophylaxis have been associated with decreased joint changes  Gooding R, et al. *J Blood Med.* 2021;12:209-220. Image reproduced for educational purposes only from Manco-Johnson MJ, et al. *N Engl J Med.* 2007;357:535-544.	So, what are some known variables that influence joint damage, and how can we prevent it? Prophylactic therapy has been demonstrated to help minimize joint hemorrhages in patients with hemophilia. And this improves if we start prophylaxis at a younger age and continue prophylaxis throughout the lifetime. So, the table on the right side of this slide depicts data from Marilyn Manco-Johnson's pivotal paper in 2007. The horizontal side of the table indicates how old each patient is in years. So, 1, 2, 3, 4, or 5. And then the vertical side looks at the average number of hemorrhages per month. You can see the joint hemorrhages in patients on prophylaxis in the dark red and other hemorrhages for patients on prophylaxis in the brighter red. And then in the blue, joint hemorrhages for patients on episodic therapy versus other hemorrhages for patients on episodic therapy in the tan. As we look horizontally throughout this table, you can see that the patients who were receiving prophylaxis are starting with fewer bleeds and are continuing to have fewer bleeds in the joint and other hemorrhages when compared with those patients receiving episodic therapy. And, specifically, the other hemorrhages for patients receiving episodic therapy and joint hemorrhages are really increasing throughout each age of the patient groups in this study. So, again, starting prophylaxis early and continuing it and having patients be adherent to it is going to be something that improves joint damage.

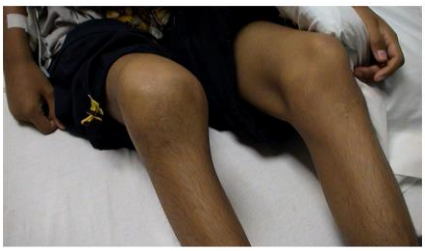
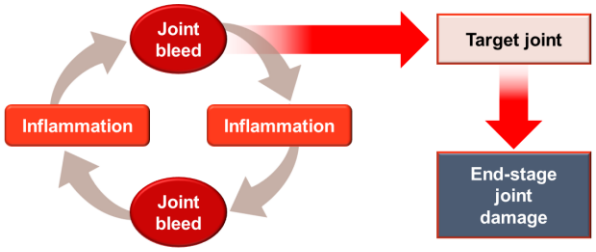
11.	**Protection From Bleeding** ▪ Initial prophylactic goal of >1% factor activity is inadequate for all patients with hemophilia. ▪ WFH defines prophylaxis as regular hemostatic agent use to prevent bleeding and ensure a QOL similar to non-hemophilic individuals. ▪ Optimal factor dosing is individual; population PK studies indicate >20% FVIII activity offers greater protection from bleeding.  FVIII: factor VIII; PK: pharmacokinetics. Nilsson IM, et al. *J Intern Med*. 1992;232:25-32. Image reproduced for educational purposes only from Valentino LA, et al. *Haemophilia*. 2016;22:514-520.	What about more general protection from bleeding, and how do we protect our patients from bleeding? How do we think about prophylaxis? So, factor activity. Again, historically, greater than 1% was the goal of prophylactic therapy. And that was what we were targeting. But the World Federation of Hemophilia has given this new definition of prophylaxis: "The regular administration of a hemostatic agent or agents with the goal of preventing bleeding in patients with hemophilia, while allowing them to lead active lives and achieve quality of life comparable to non-hemophilic individuals." So, this is impactful. This is telling us that we really want our patients with hemophilia to be living lives similar to those without hemophilia, and we can do that by giving them prophylaxis. But it's more difficult than one might have assumed. The image on the right side of this slide shows data from population pharmacokinetic studies that have indicated that even though we give patients our infusions and we expect bleeding—both spontaneous and traumatic bleeding—to occur after the infusions, bleeds are occurring in patients very close to their time of infusion—within 10 hours of their infusion. And we can see that as patients are experiencing factor activities that are higher for longer, they're doing better, but we're still seeing bleeds in those earlier time points. And so, the exact factor level that patients are at or the exact time that they've been at higher levels, although helpful and a good goal, is something that we need to think more about. NOTE: As seen in the figure, patients experienced spontaneous and traumatic joint bleeds at various factor activities, including spontaneous bleeding at more than 10%.

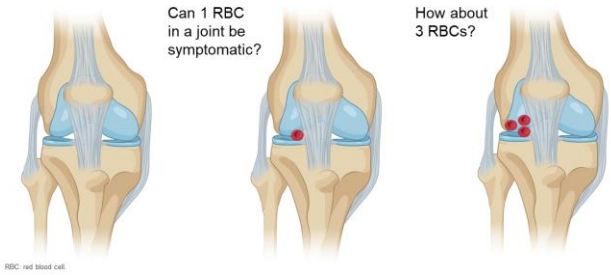
12.	**Increased Protection From Bleeding Can Lead to Increased Physical Activity** ▪ Providers do make recommendations to increase factor dosing or time factor dosing with higher intensity activities ▪ Case series of patients on Fc-fusion proteins allows for individualization of factor dosing to facilitate various sporting activity ▪ Patients in Explorer7 clinical trial demonstrated 30 minutes of additional moderate-to-vigorous physical activity per day (12 hours awake) on concizumab compared with pre-concizumab prophylaxis Negrier C, et al. *Haemophilia*. 2013;19:487-498. Wang M, et al. *Blood Coagul Fibrinolysis*. 2016;27:737-744. Villamail Martinez L, et al. *Blood*. 2022;140(suppl 1):5634-5636.	So, we know that increased protection from either factor or nonfactor products and increased protection from bleeding can lead to increases in physical activity. Providers have historically been making recommendations to increase factor doses or time factor dosing to allow higher-intensity activities, such as giving factor doses immediately prior to sporting events or dosing potentially on consecutive days because of the intensity of sporting events. There are case series that look at extended half-life products. Specifically, one looking at Fc-fusion proteins that allows for careful individualization of factor dosing, both amount and frequency, to facilitate various sporting activities that we maybe have not allowed patients with hemophilia to participate in in the past. And looking at the explorer7 clinical trial, patients wore an activity tracker both prior to the trial and during an observational period as well as during the trial for a number of weeks, and patients demonstrated an increase in moderate-to-vigorous physical activity each day. Specifically, 30 minutes of increased activity if people were awake for, say, a 12-hour day when they were receiving concizumab prophylaxis compared with when they were receiving alternative prophylaxis in the pre-concizumab portion of the trial. NOTE: Optimal factor replacement for physical activity is not well defined.

13.	**Modern Therapy for Patients With Hemophilia** ▪ As prophylactic therapy has been more readily adopted and newer/easier prophylactic options have become available, patients with hemophilia have experienced life-changing benefits – Bleeding prevention → protection from joint damage and life-threatening bleeding → decrease in missed school/work, increased physical activity, and QOL improvements → normal life expectancy ▪ Increases in physical activity include ADLs as well as sports/physical activity participation ▪ Complete understanding of optimal prophylaxis is not fully established	So, as we think about modern therapy for patients with hemophilia, we need to think about prophylaxis as being something that we need to individualize for each patient. Prophylactic therapy has to be readily adopted. It has to be easy for patients if that's what they need to be able to participate in the activities they want, and they need to be able to choose their prophylaxis based on the life experiences that they're having. So, as we think about first preventing bleeding, then we're going to protect from joint damage and life-threatening events. We're going to decrease the amount of missed school, missed work. We're going to allow for increased physical activity and quality-of-life improvements, and then we're going to move to more normal life expectancy as each of our prophylactic options is improving and individualized for patients. Increases in physical activity can include activities of daily living as well as sports or physical activity participation depending on the patient, their goals, and what other limits they have in their life. And we really need to optimize our understanding of each individual patient and those goals to optimize their prophylaxis. But it's not quite fully established yet. And this optimal prophylaxis is something that we're still working on to reach all of these goals.
14.		***[Guy Young, MD]*** Well, thank you, Allison. That was an excellent introduction to our program. And I'm now going to jump in here and talk about subclinical bleeding. So, Mitigating Hemophilic Arthropathy: A Growing Recognition of the Presence of Subclinical Bleeds and a Need to Stop Them.

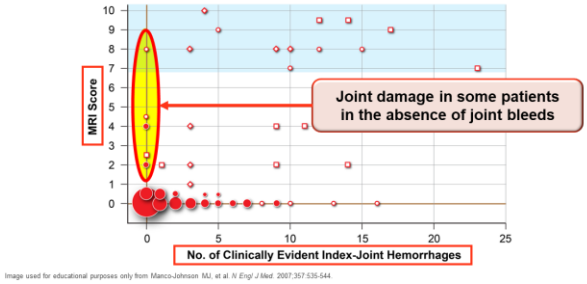
15.	**What Is the Goal of Hemophilia Treatment?** ▪ Is it to prevent bleeding? — Studies of new drugs use bleeds/ABR as the primary endpoint ▪ Is it to maintain healthy joints? — Sure, this is perhaps more important goal, but… — Not all damaging bleeds are in the joints ABR: annualized bleeding rate.	Now, what is the goal of hemophilia treatment? You might think, what a silly question to ask, but sometimes it helps me level-set thinking about my patients. Is it to prevent bleeding? All studies of new drugs use bleeds/annualized bleeding rate (ABR) as the primary endpoint. Or is it to maintain healthy joints? Now, of course this is an important goal, but not all damaging bleeds are in the joints.
16.	**What Is the Goal of Hemophilia Treatment? (cont)** **My thoughts:** ▪ Hemophilia treatment should be aimed at preventing the permanent sequelae of bleeding in any part of the body — While preventing overt bleeds is a big part of this and is what studies measure, we must be aware that subclinical bleeding can also result in joint damage — We also need to be able to prevent overt and subclinical ICH • How often due small brain bleeds occur and are they "damaging"? ICH: intracerebral hemorrhage.	So, my thoughts are that hemophilia treatment should be aimed at preventing the permanent sequelae of bleeding in any part of the body. So, of course, the goal of hemophilia is to prevent bleeding—I was being a little bit facetious. 'Thought provoking,' maybe, is the right word to make you think about what really is the goal. So, obviously, we want people with hemophilia to live a normal life, as normal as possible. And so, therefore, these are my personal opinions that hemophilia treatment should be aimed at preventing the permanent sequelae of bleeding in any part of the body. That could be preventing intracranial hemorrhage in babies who are more at risk of that. Preventing joint bleeds, preventing muscle bleeds, any type of bleeding. Now, importantly, although preventing overt bleeds is a big part of this, which is what the studies measure, right? Bleeds that you can see, overt bleeds. We must be aware that subclinical bleeding can also result in joint damage. And this is really what my session is going to be all about. I also want to say that we also need to be able to prevent overt and subclinical intracranial hemorrhage. How often do small brain bleeds occur in hemophilia? And are they damaging? And I think there's very little evidence to help us with that. So, I think any strategic goal in hemophilia needs to at least have that in the back of our mind as well.

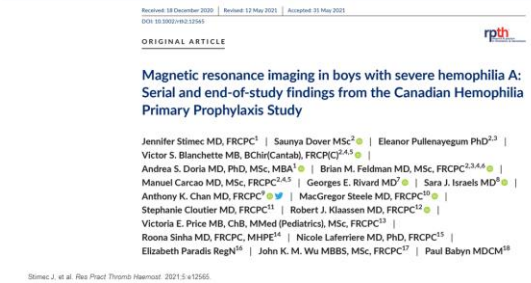
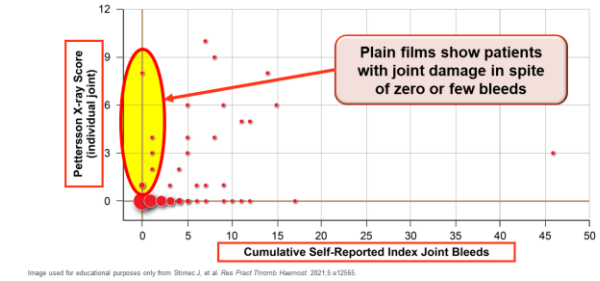
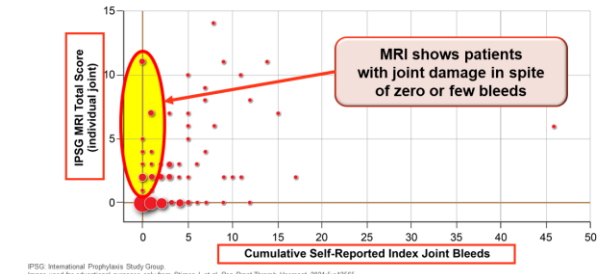
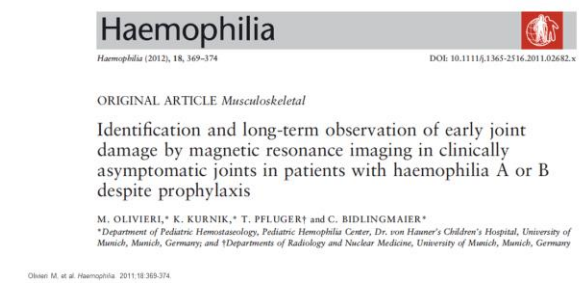
17.	**So Why Is ABR the Outcome of Choice?** ▪ It is relatively easy to measure ▪ It takes months to years to get meaningful results with subclinical bleeding as an outcome measure	So, why is ABR the outcome of choice? Well, it's relatively easy to measure. And patients can basically subjectively tell you "I have a bleed" or "I don't have a bleed," and they can feel what the bleeds are. So, ABR has become the de facto outcome of choice. We all complain about it: "Oh, it's too subjective" and all this, but really, nobody's come up with a better one. Subclinical bleeding as an outcome is also important. However, subclinical bleeding as an outcome measure takes months to years to get meaningful results, and this is one of the reasons why it cannot be used in clinical trials where we want to have results in 6 months, a year, or 2 years. Longer-term observational studies are what it will take for us to really understand the subclinical bleeding effects of any sort of new treatment strategy.
18.	**Acute Hemarthrosis**  Images provided courtesy of Guy Young, MD, for educational purposes only.	So, here's an acute hemarthrosis. I think it's pretty obvious to you looking at this about this type of bleed.
19.	**Synovitis**  Images provided courtesy of Guy Young, MD, for educational purposes only.	And that type of joint bleed, in that case, happened to be a target joint. These are all my patients and images or pictures that I took. If you have recurrent target joint bleeding, that can then lead to synovitis. As you see here, these are actually not acute bleeds in either one of these patients. Those patients walked into this workshop, but they have this spongy-feeling, swollen knee. And that's because they have synovitis. They could get an acute bleed on

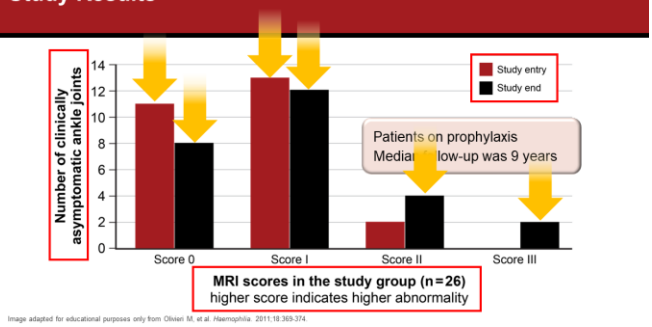
		top of that, of course. And they do. But in this case, what you're looking at is synovitis.
20.	**End-Stage Arthropathy**  Images provided courtesy of Guy Young, MD, for educational purposes only.	So, we go from joint bleeding, or current joint bleeding, to target joint, and then that can evolve into synovitis, which ultimately evolves into end-stage arthropathy—which I think is clearly visible here in this young man in his right knee where you cannot see any of the typical landmarks. You see the atrophy below the knee. And this guy was essentially wheelchair bound until he had his knee replacement.
21.	**The Classical View of Joint Disease in Hemophilia**  	So, the classical view of joint disease in hemophilia is you have a joint bleed, which leads to inflammation. It makes the joint more prone to bleeding, more inflammation. And you enter this vicious circle, which ultimately results in the pictures you saw before. Target joint synovitis, end-stage joint damage. Just like that.
22.	**Are All Bleeds Symptomatic?** Let's do a thought experiment	Now, are all bleeds symptomatic? Well, let's do a thought experiment to try to answer that question.

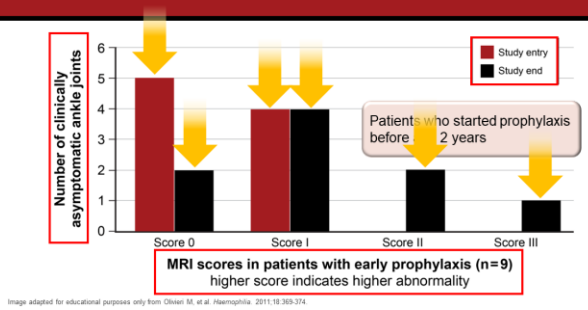
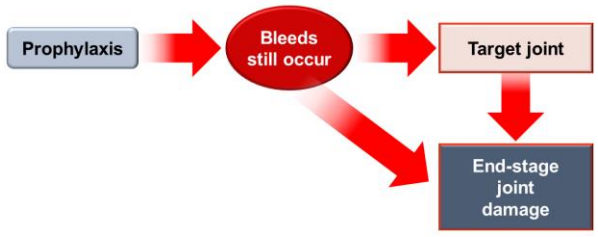
23.	**Are All Bleeds Symptomatic? (cont)** 	So, here's a cartoon essentially of a knee. And let's say this is our thought experiment. Let's say 1 red blood cell enters the joint. I know that might sound silly, but that's why it's called a thought experiment, because we're just thinking about it. Do you think a patient would feel 1 red blood cell in their joint? No, there's no chance. These are so small, there's no way they would feel 1. What about 3? Would they feel 3 red blood cells? And we can take it to the next degree. What about 1 µL, 10 µL? What about 1 mL? I mean, how much blood in the joint is required before a patient has a sensation? So, I think you'll agree with me that minuscule amounts of blood can enter the joint, which really is a joint bleed. But it would not be felt. Well, that's what I mean by subclinical bleeding.
24.	**Are All Bleeds Symptomatic? (cont)** *What is the threshold amount of blood that results in a bleed being symptomatic?*	So, what is the threshold amount of blood that results in a bleed being symptomatic? We don't really know the answer.
25.	**Symptomatic Bleed Threshold** ▪ Different between patients (different pain threshold) ▪ Different for each patient over time — Changes as patient grows from a child to an adult ▪ Different for every joint bleed within each patient ▪ Other reasons	And I'm sure that it is different between patients. Patients have different pain thresholds. Patients have different sensitivity to whether they're bleeding in their joint or not. It could be different for each patient over time. You know, for a 4 year old versus a 12 year old versus a 40 year old. They might feel things differently and they may recognize bleeding earlier, or maybe after enough joint damage, they'll recognize bleeds later. It's really hard to know. It's different for every joint bleed within each patient. It could be that 1 joint bleed is going to not give you symptoms. And then it could be

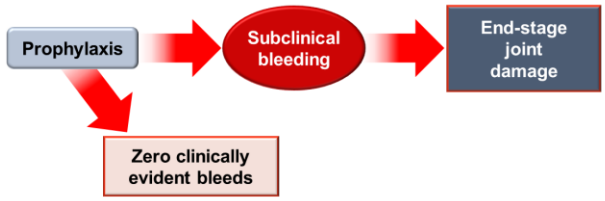
		that maybe the same amount of blood enters the joint, and it does give you symptoms. And there may be other reasons. These are all areas that we're still learning about and hopefully will be able to learn more about over the years.
26.	**How Much Blood Is Needed to Result in a Bleed?** ▪ We don't know ▪ This has not been, and with our current technology cannot be, studied	So, how much blood is needed to result in a bleed? Well, we don't know. This has not been studied and, with our current technology, it cannot be studied.
27.	**Subclinical Bleeding** ▪ There is no direct evidence for this, but that would be difficult to prove ▪ We do, however, have indirect evidence for the existence of subclinical bleeding	Now, there's no direct evidence for subclinical bleeding, but that would be difficult to prove. But we do have a lot of indirect evidence for the existence of subclinical bleeding. And that's what I'm going to share with you next.
28.	**Joint Outcome Study** The NEW ENGLAND JOURNAL of MEDICINE ESTABLISHED IN 1812 AUGUST 9, 2007 VOL. 357 NO. 6 Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia Marilyn J. Manco-Johnson, M.D., Thomas C. Abshire, M.D., Amy D. Shapiro, M.D., Brenda Riske, M.S., M.B.A., M.P.A., Michele R. Hacker, Sc.D., Ray Kilcoyne, M.D., J. David Ingram, M.D., Michael L. Manco-Johnson, M.D., Sharon Funk, B.Sc., P.T., Linda Jacobson, B.S., Leonard A. Valentino, M.D., W. Keith Hoots, M.D., George R. Buchanan, M.D., Donna DiMichele, M.D., Michael Recht, M.D., Ph.D., Deborah Brown, M.D., Cindy Leissinger, M.D., Shirley Bleak, M.S.N., Alan Cohen, M.D., Prasad Mathew, M.D., Alison Matsunaga, M.D., Desiree Medeiros, M.D., Diane Nugent, M.D., Gregory A. Thomas, M.D., Alexis A. Thompson, M.D., Kevin McRedmond, M.D., J. Michael Soucie, Ph.D., Harlan Austin, Ph.D., and Bruce L. Evatt, M.D. Manco-Johnson MJ, et al. *N Engl J Med.* 2007;357:535-544.	Let's start with this very famous study. This is the Joint Outcome Study published in the *New England Journal of Medicine.* It's hard to believe, 17 years ago now.

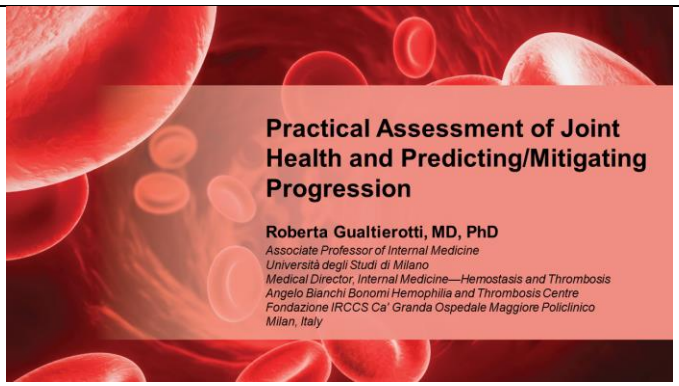
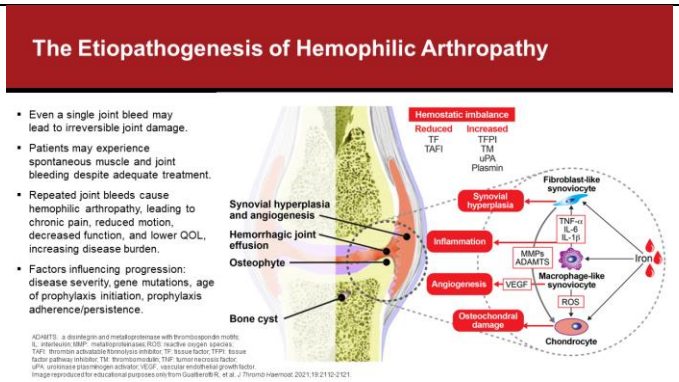
29.	**Joint Outcome Study (cont)** ▪ Patients on prophylaxis from ~1 year of age ▪ Joint bleeds collected over time ▪ MRI at start and conclusion of the study at ~6 years of age Manco-Johnson MJ, et al. *N Engl J Med.* 2007;357:535-544.	And we're going to take a look at one of the really famous figures from that study. So, the Joint Outcome Study was where patients were put on prophylaxis from about 1 year of age. They had joint bleeds collected over time, and they had an MRI at the start and the conclusion of the study at 1 year and 6 years of age.
30.	**Joint Outcome Study (cont)**  Image used for educational purposes only from Manco-Johnson MJ, et al. *N Engl J Med.* 2007;357:535-544.	So, this is this famous figure called the bubble plot, where you have the number of clinically evident index-joint hemorrhages on the x-axis. So, in other words, clinically evident bleeds—overt bleeds. And on the y-axis is the MRI score. The higher the score, the worse the bleed. So, of course, many of the patients are at 0-0. They didn't have any bleeds because they were on prophylaxis, and their MRI score is 0. The larger the bubble, the more patients are in that box. But I do want to call your attention to this [yellow-highlighted] box. Here we have patients who had 0 bleeds. Notice the x-axis, they had 0 clinically evident joint hemorrhages. And yet you've got at least 5 patients in this grouping who have MRI scores that are abnormal. In fact, some of them are very abnormal. Look at the one with an MRI score of 8. He's similar to patients who had 15 evident joint bleeds, 10 to 15. So, what's going on here? How can somebody have such a terrible MRI score and yet have never had a joint bleed? I know that Dr. Manco-Johnson, the author of this paper and the leader of this study, feels that this is a representation of indirect evidence of subclinical bleeding.

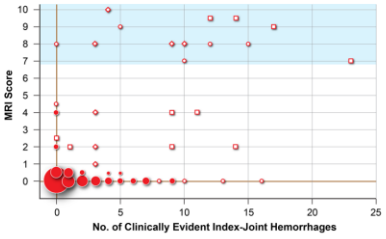
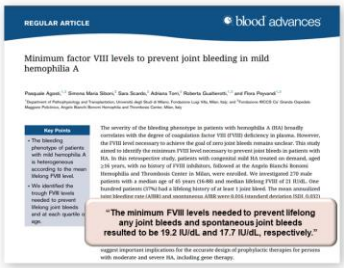
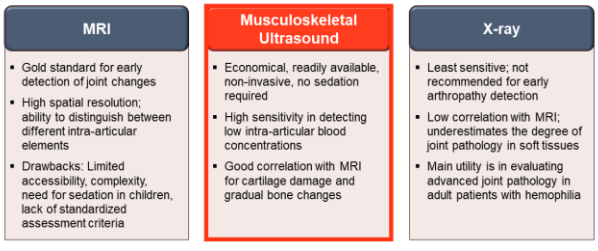
31.	**Joint Outcome Study (cont)**  ORIGINAL ARTICLE Magnetic resonance imaging in boys with severe hemophilia A: Serial and end-of-study findings from the Canadian Hemophilia Primary Prophylaxis Study Jennifer Stimec MD, FRCPC[1] | Saunya Dover MSc[2] | Eleanor Pullenayegum PhD[2,3] | Victor S. Blanchette MB, BChir(Cantab), FRCP(C)[2,4,5] | Andrea S. Doria MD, PhD, MSc, MBA[1] | Brian M. Feldman MD, MSc, FRCPC[2,3,4,6] | Manuel Carcao MD, MSc, FRCPC[2,4,5] | Georges E. Rivard MD[7] | Sara J. Israels MD[8] | Anthony K. Chan MD, FRCPC[9] | MacGregor Steele MD, FRCPC[10] | Stephanie Cloutier MD, FRCPC[11] | Robert J. Klaassen MD, FRCPC[12] | Victoria E. Price MB, ChB, MMed (Pediatrics), MSc, FRCPC[13] | Roona Sinha MD, FRCPC, MHPE[14] | Nicole Laferriere MD, PhD, FRCPC[15] | Elizabeth Paradis RegN[16] | John K. M. Wu MBBS, MSc, FRCPC[17] | Paul Babyn MDCM[18] Stimec J, et al. *Res Pract Thromb Haemost*. 2021;5:e12565.	So, there are other studies that took a look at this in a little bit of a different approach.
32.	**Joint Outcome Study (cont)**  Image used for educational purposes only from Stimec J, et al. *Res Pract Thromb Haemost*. 2021;5:e12565.	And I know this plot looks exactly the same as the last one, but it's not. On the x-axis, you have the cumulative self-reported index joint bleeds, and the y-axis is the x-ray score. That's not MRI, that's an x-ray score. And again, you see things are clustering at 0-0. Or people who have very few bleeds have no abnormal x-rays. But there are some patients here who do have an abnormal x-ray. So, plain films can show joint damage in spite of 0 or very few bleeds.
33.	**Joint Outcome Study (cont)**  IPSG: International Prophylaxis Study Group. Image used for educational purposes only from Stimec J, et al. *Res Pract Thromb Haemost*. 2021;5:e12565.	But in the same study, they also did MRI. Again, this looks just like the Joint Outcome Study plot, but this is a Canadian study. And again, you've got this MRI total score. It happens to be a little bit of a different scoring system, but that's really irrelevant to the discussion. Again, you see the same idea here. MRI scores that are terrible in some of these patients with either 0 or 1 bleed or maybe even 2 bleeds. But you see, most of this in the yellow box is 0 or 1 bleed.
34.	**Somewhat More Direct Evidence**  Haemophilia *Haemophilia* (2012), **18**, 369–374 DOI: 10.1111/j.1365-2516.2011.02682.x ORIGINAL ARTICLE *Musculoskeletal* Identification and long-term observation of early joint damage by magnetic resonance imaging in clinically asymptomatic joints in patients with haemophilia A or B despite prophylaxis M. OLIVIERI,* K. KURNIK,* T. PFLUGER† and C. BIDLINGMAIER* *Department of Pediatric Hemostaseology, Pediatric Hemophilia Center, Dr. von Haunner's Children's Hospital, University of Munich, Munich, Germany; and †Departments of Radiology and Nuclear Medicine, University of Munich, Munich, Germany Olivieri M, et al. *Haemophilia*. 2011;18:369-374.	There's more evidence. This is I would call somewhat more direct evidence. This is purposefully looking at long-term observation of early joint damage by MRI in what are called clinically asymptomatic joints in these patients. And this a study coming out of Germany.

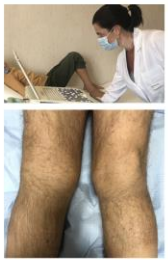
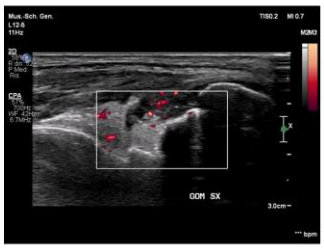
35.	**Study Design** ▪ Patients on prophylaxis who had joint bleed data and serial MRIs performed over a 10-year span Olivieri M, et al. *Haemophilia*. 2011;18:369-374.	So, in this study, patients were on prophylaxis. They recruited patients on prophylaxis who had jointly data and serial MRIs over a 10-year span. So, that's much, much longer than, double the length of, the Joint Outcome Study.
36.	**Study Results**  Image adapted for educational purposes only from Olivieri M, et al. *Haemophilia*. 2011;18:369-374.	And here're the study results. It's a little confusing, so let me walk you through this. We have the number of clinically asymptomatic, in this case, happens to be ankle joints. Just for illustration. And here we have the MRI scores. The MRI scoring system here, again, is different. And I apologize that each of these studies uses different scores; we really do need to harmonize that. But basically, score 0 means no joint damage. Score 3 means significant joint damage, and 1 and 2 are in between. So, study entry is the reddish color; study end is the black color. All these patients were on prophylaxis. And they were followed for a median of 9 years. Here is the study entry. You can see that about half the patients have a score of 0, about another half have a score of 1, and just 2 patients have a score of 2 in this ankle. But by the end of the study, after 9 years, you can see that fewer patients have a score of 0; it's gone from 11 to 8. And fewer patients have a score of 1. And things have shifted—to having more patients (double), with a score of 4 and even 2 patients with a score of 3. So, basically, the shift from the red to the black or from the left to the right, if you will, is worsening MRI scores in patients who've all been on prophylaxis and had no joint bleeds. Right? The definition here is these patients had no joint bleeds. Again, MRI scores are getting worse despite no joint bleeds.

37.	**Study Results (cont)** 	Again, looking at the same number of clinically symptomatic ankle joints, slightly different way of looking at the data and the MRI scores. Again, this is patients with early prophylaxis. So, these patients started prophylaxis before the age of 2. So basically, the same figure, but for those who started very early in life, before the age of 2. And again, here's the study entry, and in black is the study end. Once again, you see more patients shifting to the right, meaning worse MRI scores. Again, despite no bleeds and despite starting prophylaxis at a young age.
38.	**Study Conclusion** *"Using MRI, it is possible to identify early and subtle joint changes in patients with haemophilia A and B. Early arthropathic changes are apparent even in patients with clinically asymptomatic joints that have not yet experienced a clinically evident bleed and who were receiving adequate prophylaxis."*	What did they conclude from this? They said: "Using MRI, it is possible to identify early and subtle joint changes in patients with hemophilia A and B. Early arthropathic changes are apparent even in patients with clinically asymptomatic joints that have not yet experienced a clinically evident bleed and who were receiving adequate prophylaxis." Right—the joints are getting worse on MRI, yet they're asymptomatic. They're not causing pain or decreased range of motion, and they haven't bled in patients who are on prophylaxis from an early age.
39.	**The Modern View of Joint Disease in Hemophilia** 	So, if I take all of this together, here's my more modern view of joint disease in hemophilia. You can be on prophylaxis as most patients are, but bleeds still occur. And those bleeds can lead to a target joint, which will lead to end-stage joint damage like I showed earlier. However, it could also skip the target joints where you have bleeds that are occurring and then result in end-stage joint damage.

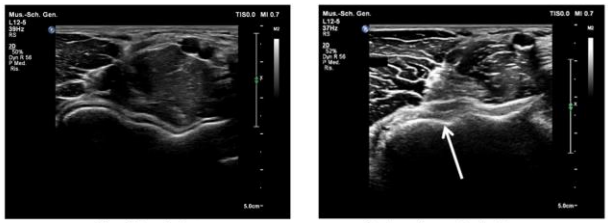
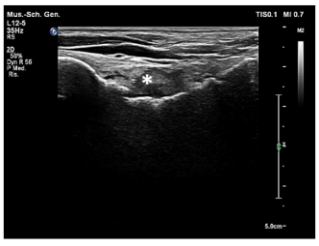
40.	**The Modern View of Joint Disease in Hemophilia (cont)** 	But in addition to that, we have to add this part that despite prophylaxis, subclinical bleeding happens. And that subclinical bleeding could result in end-stage joint damage, and prophylaxis, even in patients with 0 clinically evident bleeds, can result in end-stage joint damage.
41.	**Data Summary** ▪ Logically, subclinical bleeding must occur ▪ Data from long-term studies of patients on prophylaxis using bleed data and imaging strongly suggest that subclinical bleeding resulting in joint damage occurs ▪ All these studies were on patients using factor for prophylaxis *Why might this occur?*	So, to summarize logically in my thought experiment I showed earlier, subclinical bleeding must occur. There's no way every patient feels every amount of blood in their joint. Data from long-term studies of patients on prophylaxis using bleed data and imaging strongly suggest that subclinical bleeding resulting in joint damage occurs, and all of these studies were in patients using factor for prophylaxis.
42.	**What Can We Do?** **Aiming for zero bleeds has been a goal of hemophilia treatment, however...** ▪ Zero clinical bleeds is not enough to prevent arthropathy ▪ Eliminating subclinical bleeding should be a goal of prophylaxis ▪ Taking data from mild hemophilia, we know that levels >5% or certainly 15% are likely to prevent subclinical bleeding ▪ Future therapies should be aimed at preventing both clinical and subclinical bleeding	So, why might this occur? Well, aiming for 0 bleeds has been a goal of hemophilia treatment. However, 0 clinical bleeds are not enough to prevent arthropathy, coming back to that ABR. ABR of 0, well, it's great. We definitely want an ABR of 0, but that is probably not enough to prevent arthropathy. We really need to think about eliminating subclinical bleeding as the goal of prophylaxis and taking data from mild hemophilia. We know that levels above 5%, and certainly above 15%, are likely to prevent subclinical bleeding. There are very few patients with mild hemophilia above 15% who end up with permanent joint damage. So, that probably suggests that there's a threshold somewhere in there where subclinical bleeding does not happen. Therefore, future therapy should be aimed at preventing both clinical and subclinical bleeding.

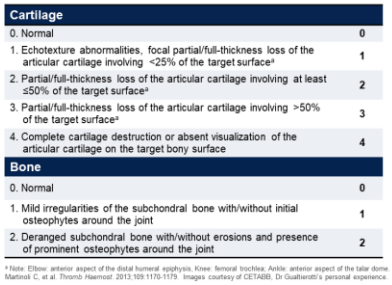
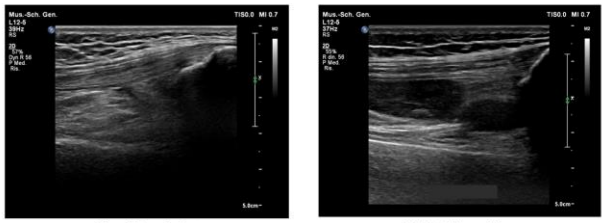
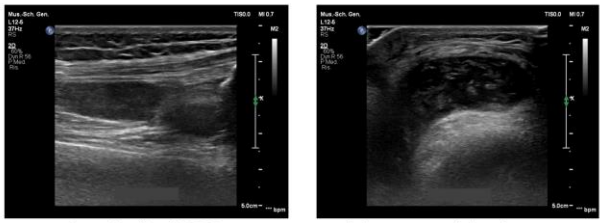
43.		And so with that, I'm going to pass it on to Professor Roberta Gualtierotti. I introduced her earlier. And she's going to take the discussion to practical assessment of joint health and predicting/mitigating progression. So, Professor Gualtierotti, please take it away. ***[Roberta Gualtierotti, MD, PhD]*** Thank you, Dr. Young.
44.		So, we know that the etiopathogenesis of hemophilic arthropathy depends on recurrent joint bleeding and that even a single joint bleed may lead to irreversible joint damage. And patients with hemophilia experience spontaneous bleeding into muscles and joints, even despite adequate treatment. The repeated joint bleeding results in hemophilic arthropathy, which is characterized by chronic pain, reduced range of motion, decreased function, and eventually disability. There are different factors that may influence progression of chronic arthropathy: disease severity, mutation, the age at prophylaxis, initiation, and adherence, or persistence on prophylaxis. Over the last few years, the improvement of treatment availability and efficacy and the comprehension of the underlying mechanisms leading to chronic hemophilic arthropathy have allowed us to understand the importance of prophylaxis over an on-demand regimen and the importance of early recognition of synovitis as a proxy of clinically overt or subclinical bleeding. NOTE: Over the last few years, the improvement of treatment availability and the comprehension of the underlying mechanisms leading to hemophilic arthropathy have allowed us to understand the importance of 1) prophylaxis over an on-demand regimen and 2)

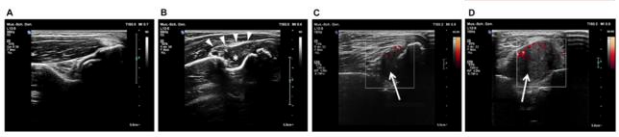
		early recognition of synovitis as a proxy of clinically overt or subclinical bleeding.
45.	**Rationale for Joint Health Monitoring** ▪ Patients treated with FVIII prophylaxis >1% trough levels may still experience subclinical joint damage →3%-5% FVIII trough levels recommended ▪ FVIII up to 15% may not be enough to prevent arthropathy (lifestyle, joint status, etc) →Need for personalization  Image reproduced for educational purposes only from Manco-Johnson MJ, et al. *N Engl J Med*. 2007;357:535-544. Peyvandi F, et al. *Haematologica*. 2020;105:2038-2043. den Uijl IEM, et al. *Haemophilia*. 2011;17:41-44. Soucie JM, et al. *Blood Adv*. 2018;16:2136-2144.	Despite these improvements and these acknowledgments, patients treated with factor VIII prophylaxis, around 1% trough levels, still experience subclinical joint damage. So, this is why the current recommendations aim for a 3% to 5% factor VIII trough level, the international recommendations. And still, factor VIII up to 15% may not be enough to prevent arthropathy, as recently showed by several groups. And this is why we really need to personalize the prophylaxis regimen. NOTE: However, many groups have demonstrated the importance of higher trough levels, leading to the need for a personalized approach based on patient features.
46.	**Minimum FVIII Levels to Prevent Joint Bleeding in Mild Hemophilia A**  Agosti P., et al. *Blood Adv*. 2023;7:7209-7215.	Also, our group has recently confirmed this finding and found that the minimum factor VIII level needed to prevent lifelong joint bleed and spontaneous joint bleed is around 17%. NOTE: Our group recently confirmed these findings: a minimum trough factor VIII level of approximately 17% is needed to prevent spontaneous bleeding.
47.	**Imaging Modalities to Assess Arthropathy**  Rodriguez-Merchan EC, et al. *Haemophilia*. 2011;17(suppl 2):1-23. von Drygalski A, et al. *J Ultrasound Med*. 2018;37:1945-1956. Cuesta-Barriuso R, et al. *J Blood Med*. 2022;13:589-601.	We have several imaging techniques available. Compared with the more traditional MRI and x-ray, musculoskeletal ultrasound has several advantages. It allows evaluation of multiple sites. It is sensitive in detecting lesions in soft tissues. It has a high sensitivity in detecting low intra-articular blood concentrations, and it needs no sedation in children. It is noninvasive, it is economical, and it showed a good correlation with MRI for cartilage damage and gradual bone changes.

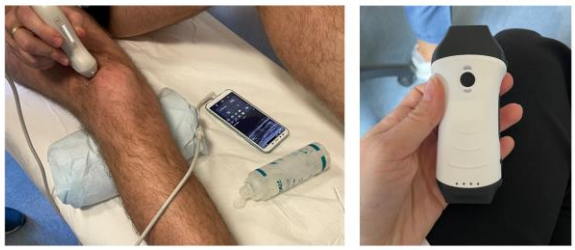
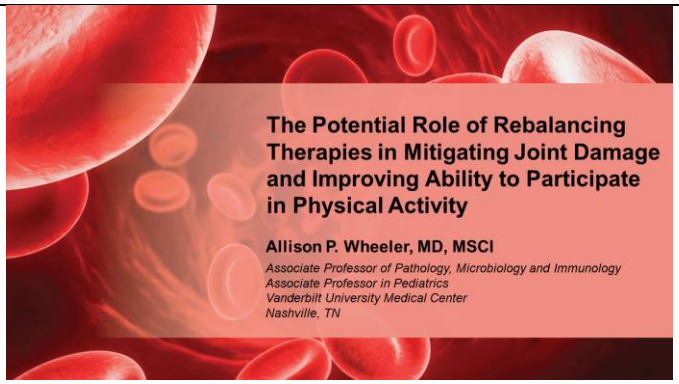
48.	**Musculoskeletal Ultrasound** ▪ Patient perception of bleeding and physical examination are inaccurate in >50% of cases in identifying bleeding in painful joints ▪ Musculoskeletal ultrasound is a non-invasive and easily accessible diagnostic tool for joint health assessment ▪ Differently from MRI, it can be performed in multiple joints and in children without sedation; useful for long-term follow-up  Images courtesy of CETABB, Dr Gualtierotti's personal experience. Bakeer N, et al. *Res Pract Thromb Haemost*. 2021;5:e12531. Martinoli C, et al. *Thromb Haemost*. 2013;109:1170-1179. Volland LM, et al. *J Ultrasound Med*. 2019;38:1569-1581.	Why is it important to implement musculoskeletal ultrasound in the evaluation of patients with hemophilia at our center? Because we have evidence that the patient perception of bleeding and also the physical examination by the physician are inaccurate in more than 50% of cases in identifying bleeding events in painful joints. Musculoskeletal ultrasound is a noninvasive and economical imaging technique that allows joint health assessment. Not only for chronic damage monitoring, but also in a point-of-care way of evaluating patients whenever they come to the center experiencing a painful joint. One advantage is the fact that we can perform musculoskeletal ultrasound in multiple joints at the same time, and there is no need for sedation in children. And it is readily available at the center.
49.	**Synovitis** **Synovitis** ▪ Presence of a hypoechoic SH, regardless of the presence of effusion or any grade of Doppler signal **SH** ▪ Abnormal hypoechoic synovial tissue within the capsule ▪ Not displaceable and poorly compressible ▪ May exhibit Doppler signals  SH: synovial hypertrophy. Images courtesy of CETABB, Dr Gualtierotti's personal experience. Bruyn GA, et al. *J Rheumatol*. 2019;46:351-359.	What can we study with musculoskeletal ultrasound? We can study the presence of synovitis, which is a reaction to a noxious stimulus such as iron. It appears as a hypoechoic synovial hypertrophy with or without effusion or any grade of Doppler signal. This is a standardized definition in the rheumatological field. And synovial hypertrophy is an abnormal hypoechoic synovial tissue within the capsule that is not displaceable and is poorly compressible and may exhibit Doppler signals. And this is very important: we need to better understand the clinical significance of a power Doppler signal whenever we find it in our patients with hemophilia. On the right-hand side of the slide, you can see a video showing this Doppler signal in the joint of a patient with severe hemophilia

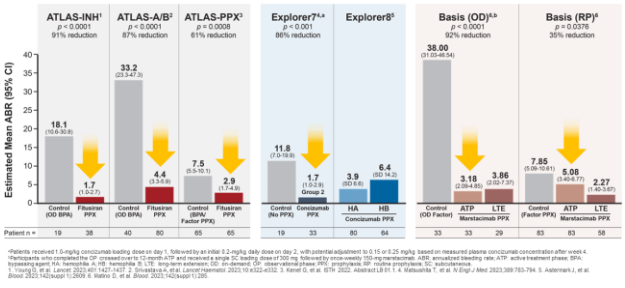
		experiencing a painful joint, and an important differential diagnosis must be made against joint bleeding, against hemarthrosis. NOTE: Outcome Measures in Rheumatology (OMERACT) definitions of elementary lesions in ultrasound for rheumatology. Synovitis is the reaction of the synovial membrane to a noxious stimulus, in this case repeated bleeding and iron inside the joint. Inflammation leads to synovial hyperplasia with prominent vascularization. We can go beyond the concept that there could be bloody effusion, but there should be no blood inside the joints.
50.	**Ultrasound Features of Synovitis** | Synovitis	SH (grayscale)	Doppler (PD)	Combined Score (grayscale SH + PD) | |---|---|---|---| | Grade 0 (normal) | No SH independently of the presence of effusion | No Doppler signal | No SH and no PD signal | | Grade 1 (minimal) | Minimal hypoechoic SH[b] up to the level of the horizontal line connecting bone surfaces between the metacarpal head and the proximal phalanx | Up to 3 single Doppler spots **or** up to 1 confluent spot and 2 single spots **or** up to 2 confluent spots | Grade 1 hypoechoic SH and ≤grade 1 PD signal | | Grade 2 (moderate) | Moderate hypoechoic SH[b] extending beyond joint line but with the upper surface concave (curved downward) or hypertrophy extending beyond the joint line but with the upper surface flat | >Grade 1 but ≤50% Doppler signals in the total grayscale background | Grade 2 hypoechoic SH and ≤grade 2 PD signal **or** grade 1 SH and a grade 2 PD signal | | Grade 3 (severe) | Severe hypoechoic SH[b] with or without effusion extending beyond the joint line but with the upper surface convex (curved upward) | >Grade 2 (>50% of the total grayscale background) | Grade 3 hypoechoic SH and ≤grade 3 PD signal **or** grade 1 or 2 SH and a grade 3 PD signal | • PD signal could be used to identify acute synovitis • PD signal is not sensitive for SH [a]EULAR-OMERACT combined score. [b]Independently of the presence of effusion. EULAR: European Alliance of Associations for Rheumatology; OMERACT: Outcome Measures in Rheumatology; PD: power Doppler. Terslev L, et al. *RMD Open*. 2017;3:e000427. Di Minno MND, et al. *J Clin Med*. 2017;6:77. Zhang N, et al. *Insights Imaging*. 2021;12:132.	The European Alliance of Associations for Rheumatology (EULAR) and OMERACT, which are rheumatological scientific societies, have defined different degrees of synovitis based on the gray scale and the presence of power Doppler signal. And in hematology, in the study of hemophilic arthropathy, we still need to standardize these definitions and understand the different meaning of synovitis with or without power Doppler signal. So, the absence of a power Doppler signal does not necessarily mean that there is no synovitis. NOTE: EULAR-OMERACT scoring based on gray scale/power Doppler system.

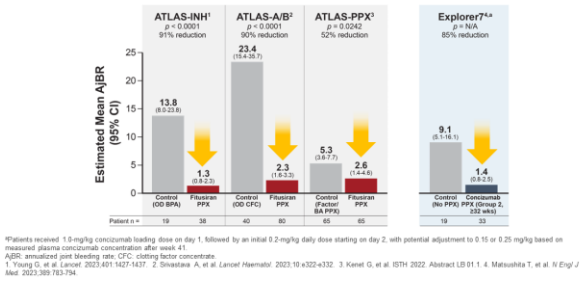
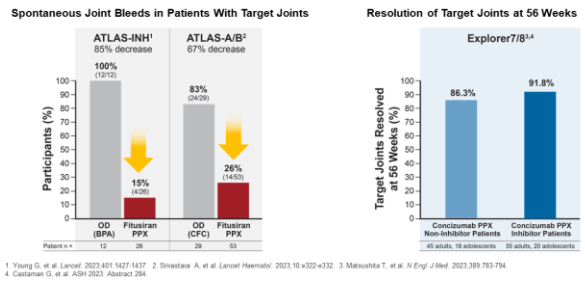
51.	**Osteochondral Damage**  Healthy joint Osteochondral damage Images courtesy of CETABB, Dr Gualtierotti's personal experience.	With musculoskeletal ultrasound, we can also detect the presence of osteochondral damage. And on the left-hand side of the slide, you can see a healthy joint with the presence of an anechoic band of a uniform thickness over the subchondral bone, which appears hyperechoic and smooth and regular. On the right-hand side of the slide, you can see that this appearance is different. The hypoechoic thickness is lost, and there is some irregularity in the subchondral bone. So, even though ultrasound cannot investigate the deeper parts of the joint, the position of iron is ubiquitous. So, it induces modifications in easily accessible sites that can be studied and are a proxy of the general situation of damage inside the joint. NOTE: › Iron deposits, which may be ubiquitous in the joint cavity, induce modifications since the first episode › Presence of an anechoic band of uniform thickness over the subchondral bone, which appears hyperechoic and smooth
52.	**Osteochondral Damage (cont)** ▪ Variable degree of loss of thickness of the cartilage ▪ Variable degree of irregularity of subchondral bone ▪ Anterior aspect of the distal humeral epiphysis, femoral trochlea, and anterior aspect of the talar dome  Image for educational purposes only. Hoovield MJJ, et al. *Rheumatology (Oxford).* 2003;42:784-790. Manco-Johnson MJ, et al. *N Engl J Med.* 2007;357:535-544. von Drygalski A, et al. *Haemophilia.* 2021;27:e298-e301. Martinoli C, et al. *Thromb Haemost.* 2013;109:1170-1179.	Also, in the case of osteochondral damage, a variable degree of loss of thickness of the cartilage and irregularity of the subchondral bone have been described in the currently used ultrasound scores for hemophilic arthropathy. The sites used to look for these alterations are the anterior aspect of the distal humeral epiphysis for the elbow, the femoral trochlea for the knee, and the anterior aspect of the talar dome in the ankle.

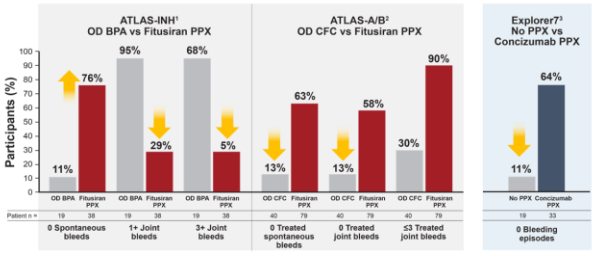
53.	**Osteochondral Damage (cont)**  **Cartilage** 0. Normal — 0 1. Echotexture abnormalities, focal partial/full-thickness loss of the articular cartilage involving <25% of the target surface[a] — 1 2. Partial/full-thickness loss of the articular cartilage involving at least ≤50% of the target surface[a] — 2 3. Partial/full-thickness loss of the articular cartilage involving >50% of the target surface[a] — 3 4. Complete cartilage destruction or absent visualization of the articular cartilage on the target bony surface — 4 **Bone** 0. Normal — 0 1. Mild irregularities of the subchondral bone with/without initial osteophytes around the joint — 1 2. Deranged subchondral bone with/without erosions and presence of prominent osteophytes around the joint — 2 [a] Note: Elbow: anterior aspect of the distal humeral epiphysis. Knee: femoral trochlea. Ankle: anterior aspect of the talar dome. Martinoli C, et al. *Thromb Haemost*. 2013;109:1170-1179. Images courtesy of CETABB, Dr Gualtierotti's personal experience.	Despite these different degrees of osteochondral damage described, we must consider that this kind of damage is irreversible. So, when we try to modify a prophylaxis regimen, we should not expect a difference in this kind of modification of lesions, but we can in synovitis, which is a reversible kind of damage. NOTE: However, damage is irreversible, so we should focus on reversible lesions.
54.	**Joint Bleeding (Hemarthrosis)**  Healthy joint — Joint bleeding Images courtesy of CETABB, Dr Gualtierotti's personal experience.	Another important application of musculoskeletal ultrasound is as a point-of-care study for the differential diagnosis of painful joints, and in particular for the detection of joint bleeding. So, with ultrasound, we can describe acute joint bleeding. And you can see on the left-hand side of the slide a normal joint with a virtual space inside the joint. No capsule distension. This is a knee. And on the right-hand side we can see a capsule distension of the subquadricipital recess of the knee of a patient with severe hemophilia. This capsule distension is due to acute joint bleeding. NOTE: With ultrasound, we can describe acute joint bleeding. On the right-hand side, capsule distension due to acute joint bleeding.
55.	**Joint Bleeding (Hemarthrosis) (cont)**  Longitudinal SQR — Transverse lateral recess SQR: subquadricipital recess Images courtesy of CETABB, Dr Gualtierotti's personal experience.	On the left-hand side of the slide, you can see that with the probe, we can try to move the fluid inside the joint, and the capsule distension is due to dislocable fluid. And in particular, it is a complex effusion, which is even more evident in the video on the right-hand side of the slide. It is possible to see a fluid that contains fibrin, clots, cells, and debris and has this kind of movement, which is different from synovitis. Synovitis appears as synovial hyperplasia, a thickening of the capsule, and clots, which are adherent to the

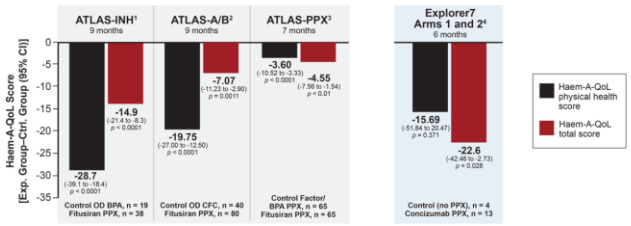
		capsule and do not move inside the joint with this stormy appearance. NOTE: On the left hand-side, the capsule distension is due to dislocable fluid and is a complex effusion, which is even more evident on the right-hand side in a transverse lateral scan as fluid containing fibrin and clots. Here you can see the distended knee capsule of a patient with hemophilia experiencing hemarthrosis, and you can see the corpusculated appearance of the effusion that corresponds to fibrin and erythrocytes that move inside the joint, compared with synovitis, which appears as synovial hyperplasia and clots that adhere to the capsule and do not flow or move inside the joint.
56.	**Standardization of Ultrasound Definitions of Hemophilic Arthropathy Is Still Lacking…** **The most frequently used scoring systems and protocols for the ultrasound evaluation of hemophilic arthropathy** | First Author	Year	Synovial Membrane Hypertrophy	PD Signal	Hemosiderin Deposition	Articular Cartilage Damage (Partial or Full Loss of Thickness, Thinning)	Subchondral Bone Damage (Surface Irregularity, Bone Cysts, Erosions, and Osteophytes)	Investigated Joints | |---|---|---|---|---|---|---|---| | Klukovska | 2001 | Yes | Yes | No | Yes | Yes | Knee, ankle | | Zukotynski | 2007 | Yes | Yes | Yes | Yes | Yes | Knee, ankle | | Melchiorre | 2011 | Yes | Yes | Yes | Yes | Yes | Elbow, knee, ankle | | Muça-Perla | 2012 | Yes | Yes | No | Yes | Yes | Knee, ankle | | Martinoli | 2013 | Yes | No | No | Yes | Yes | Elbow, knee, ankle | | Doria | 2015 | Yes | No | Yes | No | Yes | Knee, ankle | | Kandagaddala | 2019 | Yes | Yes | Yes | Yes | Yes | Knee, ankle | | Volland | 2019 | Yes | Yes | No | Yes | Yes | Elbow, knee, ankle | Gualtierotti R, et al. *J Thromb Haemost*. 2021;19:2112-2121.	This table shows the currently proposed scores for musculoskeletal ultrasound evaluation of patients with hemophilia. And so, you can see that a standardization is still lacking. We really need to thoroughly study the different stages and clinical significance of synovitis and osteochondral damage to find a standardized and shared definition of these lesions. NOTE: We need standardization of the currently available joint scores based on ultrasound.
57.	**Standardization of Ultrasound Definitions of Hemophilic Arthropathy** Received: 14 September 2023 | Revised: 25 December 2023 | Accepted: 27 December 2023 https://doi.org/10.1016/j.rpth.2023.102314 FORUM rpth **Ultrasound evaluation of hemophilic arthropathy: a proposal of definitions in a changing landscape** → Call to action for a joint project of standardization in the ISTH SSC Subcommittee on FVIII, FIX and Rare Coagulation Disorders, EAHAD, and OMERACT  EAHAD: European Association for Haemophilia and Allied Disorders. ISTH: International Society on Thrombosis and Haemostasis. Images for educational purposes only from Gualtierotti R, et al. *Res Pract Thromb Haemost*. 2024;8:102314.	This is why our group has recently proposed a call to action, a joint call to action to reach a consensus on standardized definitions of the lesions that are typically found in patients with hemophilic arthropathy.

58.	**Ultrasound in the Era of Telemedicine**  Images courtesy of CETABB, Dr Gualtierotti's personal experience	Finally, in the era of telemedicine, we can use home-based ultrasound imaging systems that can be performed by caregivers, by the general practitioner, or the patients themselves to identify joint bleeding early and to provide the correct treatment for joint health protection. We also need to study in the future the limitation of this type of imaging technique for the detection of subclinical joint bleeding, which is now very, very frequent in our patients. NOTE: In the era of telemedicine, we can use home-based ultrasound performed by patients, caregivers, or general practitioners for the early identification of joint bleeding and joint health protection.
59.	**Conclusions** ▪ Long-term monitoring of joint health is crucial in an era of availability of novel drugs and improved survival and QOL of patients with hemophilia ▪ Musculoskeletal ultrasound offers a cost-effective, readily available, and non-invasive modality for assessment of arthropathy ▪ Standardization of the currently available biomarkers for joint damage and joint bleeding will further improve the management of patients with hemophilia in the near future	So, in conclusion, the long-term monitoring of joint health is crucial in an era of availability of novel drugs, improved efficacy, and improved survival and quality of life of patients with hemophilia. Musculoskeletal ultrasound offers a cost-effective, readily available point-of-care, noninvasive modality for the assessment of arthropathy, both in the follow-up and as a point-of-care way of studying joint health. And finally, the standardization of the currently available biomarkers for joint damage and joint bleeding will further improve the management of patients with hemophilia in the near future.
60.		***[Allison P. Wheeler, MD, MSCI]*** In this section of the program, we're going to talk about the potential role of rebalancing therapies in mitigating joint damage and improving ability to participate in physical activity.

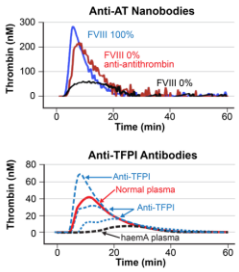
61.	**Subclinical Bleeding and Rebalancing Agents** ▪ Factor levels achieved by conventional prophylaxis are insufficient to address all joint bleeds, particularly subclinical bleeds, supporting treatments that can achieve at least near normal, if not normal, hemostasis[1,2] ▪ Because non-factor therapies restore hemostasis without elevating FVIII or FIX levels, efforts to understand factor equivalence of each of these therapies is needed[3] ▪ A recent model determined that the AT level of 10%-35% (target therapeutic range of fitusiran prophylaxis) corresponds to 10-20% FVIII[2] AT: antithrombin; FIX: factor IX; FVIII: factor VIII. 1. Mancuso ME, et al. *Haemophilia*. 2023;29:619-628. 2. Malec L, Matino D. *Haemophilia*. 2023;29:1419-1429. 3. Kaddi C, et al. *Blood*. 2022;140(suppl 1):5686-5687.	Let's think a little bit about subclinical bleeding and rebalancing agents. So, factor activities that are achieved by conventional prophylaxis are insufficient to address or prevent all joint bleeds, particularly subclinical bleeds, which we are continuously learning more about. So, we want our supporting treatments to achieve near-normal or normal (potentially) hemostasis. And we're still working on that when it comes to factor prophylaxis. As nonfactor therapies are being used to restore hemostasis in the absence of factor VIII or factor IX, we really want to understand and learn more about factor equivalents of each of these therapies, so we can understand how much or what level of therapy is needed. Recent modeling has shown that antithrombin levels of 10% to 35%, which is a target therapeutic range for fitusiran prophylaxis, correspond to 10% to 20% factor VIII activity. So, again, working toward near-normal, not-quite normal in terms of hemostasis.
62.	**Fitusiran vs Concizumab vs Marstacimab: Estimated Mean ABR Across Pivotal Clinical Trials**  	So, what do we know about the clinical trial programs that have been looking at rebalancing therapies? The fitusiran clinical trial program—or ATLAS program—data are shown here. You can see the ATLAS-inhibitor and ATLAS-A/B trials comparing patients on fitusiran prophylaxis with those receiving on-demand therapy and a significant decrease in the estimated mean ABR. The ATLAS-prophylaxis study compared patients receiving either bypassing or factor prophylaxis versus fitusiran prophylaxis and, again, demonstrated a significant reduction in the estimated mean ABR. The explorer trials looked at concizumab prophylaxis. explorer7 is looking at patients with hemophilia A or B with inhibitors.

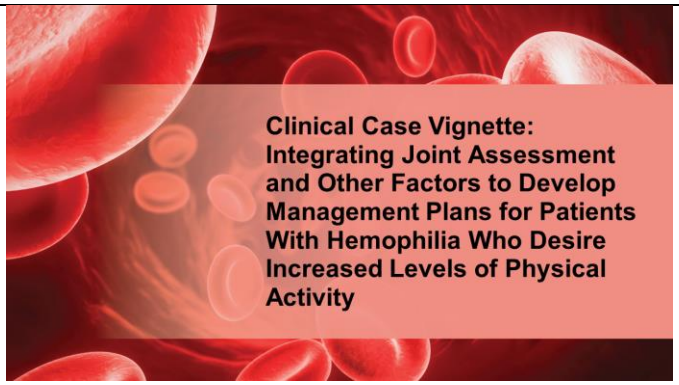
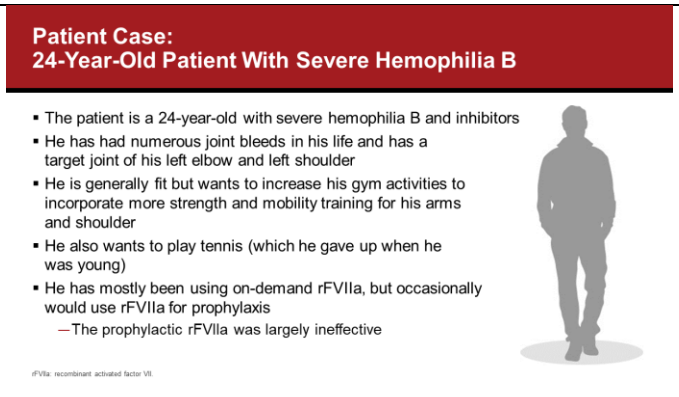
		Comparing patients without prophylaxis with those receiving concizumab prophylaxis, it is demonstrating a statistically significant decrease in the estimated mean ABR. The explorer8 trial is looking at patients with hemophilia A or hemophilia B receiving concizumab prophylaxis, demonstrating similar ABRs to what we've been seeing in the other clinical trial programs that have been described. Finally, the marstacimab clinical trial program, referred to as the BASIS trial, compared patients receiving on-demand therapy with those receiving marstacimab prophylaxis or those receiving factor prophylactic therapy, compared with those receiving marstacimab prophylaxis. It showed reductions in ABR in the marstacimab groups in both comparisons.
63.	**Fitusiran vs Concizumab: Estimated Mean AjBR Across Pivotal Clinical Trials**  [a]Patients received 1.0-mg/kg concizumab loading dose on day 1, followed by an initial 0.2-mg/kg daily dose starting on day 2, with potential adjustment to 0.15 or 0.25 mg/kg based on measured plasma concizumab concentration after week 41. AjBR: annualized joint bleeding rate; CFC: clotting factor concentrate. 1. Young G, et al. *Lancet*. 2023;401:1427-1437. 2. Srivastava A, et al. *Lancet Haematol*. 2023;10:e322-e332. 3. Kenet G, et al. ISTH 2022. Abstract LB 01.1. 4. Matsushita T, et al. *N Engl J Med*. 2023;389:783-794.	When looking at estimated mean annualized joint bleeding rates, we have data from both the fitusiran and the concizumab clinical trial programs. And as you can see here, all 3 comparisons showed reductions in the joint ABR when patients were receiving fitusiran prophylaxis. And you can see in the explorer7 trial looking at patients with inhibitors, a reduction in the annualized joint bleeding rate in patients receiving concizumab, compared with those patients receiving no prophylaxis.
64.	**Fitusiran vs Concizumab: Target Joint Bleeding in Pivotal Clinical Trials**  1. Young G, et al. *Lancet*. 2023;401:1427-1437. 2. Srivastava A, et al. *Lancet Haematol*. 2023;10:e322-e332. 3. Matsushita T, et al. *N Engl J Med*. 2023;389:783-794. 4. Castaman G, et al. ASH 2023. Abstract 284.	What's another way that we can look at joint health and joint bleeding when looking at these clinical trial programs? Well, we can look at target joints, and we can look specifically at the number of spontaneous bleeds in patients who have target joints. Or, we can look at resolution of those target joints. And different clinical trial programs are looking at different endpoints. And so, we have to sort of have that shift when looking at these data. So, the ATLAS

		trials, again looking at fitusiran, compared spontaneous joint bleeds in patients with target joints. And as you can see, for the patients who had inhibitors, there was an 85% decrease in the spontaneous joint bleeds for those receiving fitusiran prophylaxis. And when looking at patients who don't have inhibitors, there was a 67% decrease in spontaneous joint bleeds for patients receiving fitusiran prophylaxis. In both cases, these are compared with patients who are receiving on-demand therapy. The concizumab trials look specifically at resolution of target joints at 56 weeks. And this is both patients in explorer7 and explorer8. So, patients with and without inhibitors. You can see an 86.3% resolution of target joints in patients without inhibitors and a 91.8% resolution of target joints in patients with inhibitors.
65.	**Fitusiran: Patients With Bleeding Episodes in Pivotal Clinical Trials**  1. Young G, et al. *Lancet*. 2023;401:1427-1437. 2. Srivastava A, et al. *Lancet Haematol*. 2023;10:e322-e332. 3. Matsushita T, et al. *N Engl J Med*. 2023;389:783-794.	Looking at the patients without inhibitors in the ATLAS-A/B trial, the data were looked at a little bit differently. This is looking at patients with 0 treated spontaneous bleeds, 0 treated joint bleeds, or fewer than 3 treated joint bleeds. As you can see, in each of these categories, there were more patients in the fitusiran prophylaxis group than those in the on-demand group who met these criteria of lower numbers of either spontaneous or joint bleeds. Finally, in the explorer7 clinical trial program, they looked at patients with 0 bleeding episodes in general, and you can see that there was a larger percentage of patients with 0 treated bleeds in the concizumab prophylaxis group than in the no prophylaxis group.

66.	**Fitusiran vs Concizumab: Haem-A-QoL Scores Across Pivotal Clinical Trials[a,b]**  [a]Change in health-related quality of life in ATLAS-INH, ATLAS-A/B, and ATLAS-PPX was assessed using LSM change from baseline in physical health score and total score. [b]Change in health-related quality of life in Explorer7 was assessed using estimated treatment difference in physical health score and total score. Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; LSM, least squares mean. 1. Young G, et al. *Lancet*. 2023;401:1427-1437. 2. Srivastava A, et al. *Lancet Haematol*. 2023;10:e322-e332. 3. Kenet G, et al. *Blood*. 2022;140(suppl 1):7977-7978. 4. Wheeler A, et al. HTRS 2023. Abstract HTRS2023.P2.15.	So, we see throughout the clinical trial programs a reduction in bleeding events, as well as a reduction in joint bleeding events across both clinical trial programs. But we can also look at changes in quality of life throughout the clinical trial programs. And so, this graph is looking at the Haemophilia Quality-of-Life Questionnaire for Adults (Haem-A-QoL) scores across the pivotal clinical trial programs. The Haem-A-QoL is a quality-of-life questionnaire that's hemophilia specific and looking at various aspects of quality of life. And we see here in the blue bars the physical health score for the Haem-A-QoL questionnaire and in the red bars the total score. We're demonstrating negative changes in these scores, indicating improvements in quality of life throughout all 4 clinical trials that have reported these data to us looking at patients receiving both fitusiran and concizumab throughout the clinical trial programs. And indicating those improvements in their quality of life, not necessarily 100% saying to us "This is because of the decrease in joint bleeding," but the implication being decrease in bleeding, decrease in joint bleeding, and decrease in spontaneous bleeding also being associated with that improvement of quality of life.
67.	**Fitusiran and Concizumab: Thromboembolic Risks** **Both fitusiran and concizumab were safe and well-tolerated in phase 3 clinical trials, but carry a potential risk of thromboembolic events** See table below [a]The period during which patients were exposed to OD treatment with BPAs or concizumab treatment. [b]The period during which patients were exposed to OD treatment with BPAs or concizumab treatment, with the exclusion of the data on the initial concizumab regimen. DVT: deep vein thrombosis; TEAE: treatment-emergent adverse event; VTE: venous thromboembolism. 1. Young G, et al. *Lancet*. 2023;401:1427-1437. 2. Srivastava A, et al. *Lancet Haematol*. 2023;10:e322-e332. 3. Kenet G, et al. ISTH 2022. Abstract LB 01.1. 4. Matsushita T, et al. *N Engl J Med*. 2023;389:783-794. 5. Astermark J, et al. *Blood*. 2023;142(suppl 1):2609.	So, what else do we have to think about with these drugs? We have to think about the risk factors associated with them, and how we need to consider those risk factors in our patient populations. So, both of the fitusiran and concizumab clinical trial programs have experienced thromboembolic events throughout the programs. In the fitusiran clinical trial program, there were 4 treatment-related adverse events of special interest. Specifically, suspected or confirmed venous thromboembolic

Agent	Clinical Trial	Thromboembolic Events
Fitusiran	ATLAS-INH[1]	4 TEAEs of special interest, suspected/confirmed VTE, in 2 (5%) patients: • DVT (non-serious), subclavian vein thrombosis (serious), superficial thrombophlebitis (non-serious) • AT activity before onset: 11.9%, 7.8%-11.6%
	ATLAS-A/B[2]	No suspected/confirmed thromboembolism
	ATLAS-PPX[3]	2 suspected/confirmed thromboembolic events in 2 (3%) patients • Cerebrovascular accident and thrombosis (suspected thrombosis on papilla of left eye) • After treatment restart, no thromboembolic events were reported
Concizumab	Explorer7[4]	During "on-treatment" period[a]: • Groups 1-4: 1 event in 1 (1%) patient (renal infarction; non-fatal) During "on-treatment, without data on initial regimen" period[b]: 0 events
	Explorer8[5]	4 thromboembolic events in 2 (1.3%) patients • DVT, pulmonary embolism, superficial vein thrombosis in 1 patient; acute myocardial infarction in 1 patient; all non-fatal

		events in 2 patients in the ATLAS-inhibitor trial, none in the ATLAS-A/B trial, but 2 suspected or confirmed thromboembolic events in 2 patients in the ATLAS-prophylaxis trial. And in the explorer clinical trial program, we saw 1 thromboembolic event in the explorer7 program and 2 thromboembolic patients with thromboembolic events in the explorer8 program. Now, you'll note that there's no marstacimab in this table. And that's because there have not been any thromboembolic events that have been reported in the marstacimab clinical trial program. These thromboembolic events led to assessments of why this happened and risk mitigation strategies for both of these clinical trial programs (and those risk mitigation strategies have been discussed in other portions of this program).
68.	**Factor Equivalence of Rebalancing Agents** ▪ Thrombin generation allows for comparison of hemostatic potential of factor compared with rebalancing agents — Fitusiran: 20% AT corresponds to 30% FVIII equivalence — Anti-TFPI is likely 20% FVIII equivalence ▪ In *theory*, these equivalence should provide hemostatic benefit for spontaneous, traumatic and potentially subclinical bleeding TFPI: tissue factor pathway inhibitor. Lenting PJ. *Blood Adv.* 2020;4:2111-2118. 	So, what about the factor equivalence of rebalancing agents, and how we can think about these drugs? We see the improvements in ABR, in joint annualized bleeding rates. But why do we think we see these improvements? So, we don't have clear measurements of hemostasis that are standardized and available for testing in various laboratories throughout the country. But what we do have are research-based assays, specifically the thrombin generation assay that allows us to have some sense of the hemostatic potential of each of these agents. What's been demonstrated using thrombin generation studies is that for fitusiran, about 20% antithrombin activity corresponds to about 30% factor VIII equivalence. And anti-tissue factor pathway inhibitor, when in therapeutic dosing, is likely equivalent to about 20% of factor VIII equivalence. You can see examples of the thrombin generation assays on the right side of this graph, where spiked samples were used and

		thrombin generation studies were conducted to try to determine these factor VIII equivalents. So, in theory, these thrombin generation studies should demonstrate the hemostatic equivalence of each of these agents, and we should be able to determine from that what the risk or the potential benefit is in the context of spontaneous bleeding, traumatic bleeding, and potentially subclinical bleeding. But hopefully what's come through in this discussion is that we're still learning a lot about that, and we still don't completely understand why all bleeds happen—why bleeds happen necessarily when they happen and how we can prevent them. So, although these data are really helpful and can help us guide considerations in terms of treatment, we do need to understand that those limits still exist.
69.		***[Guy Young, MD]*** All right. Well, now it's time to discuss our clinical case vignette after you've already heard from all of us about the importance of maintaining medications to protect patients from bleeding. But we also want patients to be able to achieve normal types of activities. So, be able to have increased levels of physical activity because we know it's healthy in general, but also particularly healthy for patients with hemophilia.
70.		So, the patient I have here is a 24-year-old patient with severe hemophilia B. He happens to have inhibitors. He has had numerous joint bleeds over his life, particularly a target joint of his left elbow and left shoulder. He's quite fit. He wants to increase his gym activities. He wants to increase his strength and mobility because he feels that although he's aerobically fit, he doesn't have enough strength. So, he

		wants to do some strength and mobility training because he plays tennis. He used to play when he was a kid. He then started to have a lot of issues with bleeding. He started to have these target joints. He kind of gave it up. But he's really sad that he gave it up because he really would like to get back to it. Throughout his life, he's mostly used on-demand factor VIIa. He's occasionally used prophylactic factor VIIa, not that it's approved for this indication. But we tried that, and it was largely ineffective because he would still have bleeds despite that.
71.	**Patient Case (cont)** ▪ He had an opportunity to participate in the fitusiran (ATLAS-INH study) and decided to take part, hoping that with fewer bleeds and improved prophylaxis that, he could increase his gym activities and his tennis ▪ He was initially randomized to the on-demand arm that he had to stay on for 6 months, but after that started fitusiran at 80 mg subcutaneously monthly – This was before the new dosing strategy—he is currently on 50 mg every other month	Then he had an opportunity to participate in the fitusiran trial, the ATLAS-inhibitor study, which you've heard about before. And he decided that he wanted to take part, hoping that with these fewer bleeds and improved prophylaxis, he could increase his gym activities and really get back to playing tennis. His initial randomization was with an on-demand arm, so you have to stay on that for 6 months. And then he moved to the fitusiran arm, where he was getting 80 mg subcutaneously once a month. I do need to point out here that there's a new dosing strategy, which is lower doses to have fewer side effects, as you've heard already in the earlier presentation. So, currently he's on 50 mg every other month.
72.	**Patient Case (cont)** ▪ He remained on fitusiran at 80 mg monthly for about 1 year and then was switched to the new dosing regimen of 50 mg every other month ▪ He did well without any bleeds during the 80-mg/mo time and continued to increase his gym work and tennis ▪ After switching to 50 mg every other month, he did have 2 bleeds over the first 6 months with activity—1 in the left shoulder and 1 in the left elbow ▪ However, in the subsequent year, he has had no further bleeds 	He remained on fitusiran, around 80 mg monthly, for about a year. He then switched to the new dosing regimen that was required by the protocol. Now on 80 mg per month, he did great. He was able to increase his gym work and his tennis activities. And he really wasn't having bleeds. When he switched to 50 mg every other month, he did have 2 bleeds in the first 6 months. One is target left shoulder, and one is target left elbow. But

		thankfully after that, whether his body adjusted to that or whether his antithrombin levels got even lower while he stayed on the same dose, he actually has done really well and he's not had any further bleeds.
73.	**Patient Case (cont)** ▪ Fitusiran allowed this patient to resume activities he had enjoyed until he developed his target joints ▪ Now, his target joints have resolved and following a proscriptive exercise regimen to build up his strength and mobility, he has been able to go the gym regularly on his own and to play tennis with his friends 	So really, in this case, fitusiran allowed this patient to resume activities he had enjoyed in the past until he developed his target joints. And now that his target joints have resolved and following a proscriptive exercise regimen, we really wanted to get him into a proper strength and mobility so that he could go play tennis. We had a specifically designed program for him, particularly with the shoulder and the elbow, which are his problem joints. They are also really important joints in hemophilia to allow him to get back to the gym regularly and to play tennis with his friends and to not have to worry about bleeding with that.
74.	**Panel Discussion** **What strategies can be employed to increase activity levels for patients with hemophilia, irrespective of their current treatment?** ▪ Collaborate with physical therapists to design individualized strength training or aerobic programs ▪ Emphasize gradual reintroduction to activities and consideration of target joints to prevent injury **How can patients be supported to participate in their desired activities or sports while ensuring effective protection against bleeding?** ▪ Tailor treatments to enable safe engagement in activities, including sports ▪ Telemedicine programs with ultrasound imaging may allow for prompt bleeding detection and management **What target FVIII or FIX level is recommended for active patients participating in sports, especially those with a history of joint bleeds?** ▪ Aim for factor levels of at least 20% during sports activities ▪ Adjust dosage or timing to maximize clinical benefit	So, with that discussion, I'd like to bring in the panel and ask, perhaps, Dr. Wheeler first. Have you had situations with your patients where you have worked to increase the activity levels for them? And what have you done in those situations to try to increase activity, regardless of which product the patient might have been on? ***[Allison P. Wheeler, MD, MSCI]*** Yes, absolutely. I've had patients similar to this, although not specifically tennis. I think one of the things that I find really important in these circumstances, as we get patients who are on what we hope to be an improved prophylactic regimen, is also helping them to slowly get back into their activities, to work with our physical therapists in the clinic. And as you pointed out at the end, really design an individual program so that they can improve

		their strength and can end up meeting their goals without hurting themselves by following a more generalized strength training or generalized aerobic program. And I think that as somebody has improvement in their prophylaxis, as your patient did, and really thinks about how to improve their strength considering their target joints, we can make some really nice strides. And I've seen that happen in a number of my patients. ***[Guy Young, MD]*** Thanks for that, Allison. Professor Gualtierotti, you're very much an expert in joint health, which goes even beyond hemophilia. How do you think about various types of activities that people might do, as it relates to their hemophilia? From your point of view, what are the important things to allow people to participate in whatever activity or sport they want and, at the same time, obviously protect them from bleeding? ***[Roberta Gualtierotti, MD, PhD]*** Thank you for the question. I think that patients with hemophilia are now allowed to reach a higher protection compared with the latest decades because we see the very important evolution in treatment efficacy and availability. So, even the recent evidence shows that probably 3% to 5% trough levels are not enough to prevent spontaneous bleeding. And for posttraumatic bleeding, we have data that show that 15% factor VIII trough levels might not be enough. I think we really need to start personalizing the treatment of patients and reach for as normal as possible activities. So, not only physical activity, but also sports activity, because we now can achieve this goal. And I think that in the future, a telemedicine program

		with ultrasound imaging might allow patients to recognize bleeding, joint bleeding early, and treat themselves as soon as possible in the case this bleeding is confirmed. ***[Guy Young, MD]*** Thank you for that. Dr. Wheeler, when it comes to factor VIII or factor IX levels, what do you think the trough should be? If you have somebody who's active in, let's say, a noncontact sport like tennis and somebody with a history of joint bleeds, is there some target that you're aiming for that you think would be best for them? ***[Allison P. Wheeler, MD, MSCI]*** A little bit of a loaded question because I think there's a lot that we don't know. I'd love for my patients to be close to or in the normal range when they're participating in sports. But I do find that a lot of patients do very well on nonfactor therapy or factor therapy. That has me knowing that they're probably closer to, 15%, 20%, 25%. So, I generally try to maximize the potential for the therapy that the patient's on and then really respond carefully to what their body is doing. If somebody is having bleeds with a specific prophylactic program, making sure that we think about increasing or that we adjust their dose or the timing of their dose to really maximize that clinical benefit for the individual patient. But if you're really going to make me put a number on it, I would probably say at least 20%. ***[Guy Young, MD]*** Okay, thanks. Thanks for that. I think one of the other things to consider is that with a lot of the rebalancing agents, we don't really have a laboratory parameter that we can easily

		measure. Although we will see thrombin generation data provided to us from the trials, it's going to be much more challenging to think about a level, for example, that makes it safe for patients to participate in sports if they choose to be on a rebalancing agent. So, I think that one of the challenges for us going forward in the future—from the companies and academically speaking as well—is to figure out how do we know where a patient is in terms of their hemostatic profile when they're using a drug that doesn't really have something to measure that equates to the hemostatic efficacy? For fitusiran, the level of antithrombin might equate to that. For concizumab, it'll be a little bit more challenging. For marstacimab, it'll be a little bit more challenging. I think we're going to be facing some of those challenges and questions going forward. I'll just open it up to the panel for any last comments about the discussion surrounding activity and hemophilia. ***[Allison P. Wheeler, MD, MSCI]*** Well, I think your patient that you described really demonstrated the potential for some of these therapies, especially for our patients with inhibitors. You're right that it's going to be hard to know exactly where each individual patient is, but it's also going to be really exciting for this improvement in quality of life and activities and hopefully longevity for our patients. ***[Guy Young, MD]*** I will ask the final question to Professor Gualtierotti, which is: you talked about ultrasound and home ultrasound, and I know you've done some really excellent work in this area. Do you see the potential for at least, let's say, active patients—maybe not every patient—having the ability to have a small handheld

		ultrasound in their home so that when they finish activities or before they go to activities, they can evaluate themselves essentially with those tools to help determine should they go and play a sport, or do they have a bleed after their sport? What are your thoughts on that going forward? ***[Roberta Gualtierotti, MD, PhD]*** Thank you. I think now we have the technology available to think of that as a very near future option. And not just ultrasound, but also combining the data from the patients. So, patient-reported outcomes, patient-reported pain, quality of life. They might be used to put together a profile that is a risk profile or a lower risk profile for patients before starting a sports activity or a physical activity. So, I think in the near future, we will be able to use all these data coming from the patient and from the remote ultrasound imaging to personalize the treatment and also personalize the target of the treatment for each patient. ***[Guy Young, MD]*** All right. Thank you very much. Well, I think that this case really brings home everything that we've learned earlier, which is that it does come down to the patients. And every patient is an individual, as you heard, and will have lots of different treatment options that we can use to individualize our care for patients, including those who want to be physically active and have had some joint issues. So, I think it's a bright future for us, both diagnostically, as you've heard, and ultrasound treatment wise. I think one area we will need to figure out a little bit better is the laboratory testing.

75.		Well, thank you. That'll close this portion of the program.