Vitamin D Dosing Policy Update – Transcript Cleanup Draft

JEN >> Welcome everybody to a very special event brought to you by Grassroots Health and IPAC edu. We will be discussing vitamin D dosing policy and updates with an expert panel discussion and thank you everybody for joining us today. So we are bringing together the world's leading researchers and clinicians to examine the current state of vitamin D science in comparison to existing vitamin D guidelines and its implications for public health and policy. Our objective is to explore key vitamin D policy issues alongside the current evidence suggesting necessary and immediate changes to vitamin D guidelines and policy. This is a two and a halfhour event. We may go over as a lot of us love to talk about vitamin D. I'll be starting with our opening and introduction followed by individual speaker presentations and I will introduce each of our speakers just prior to their presentation. We'll follow those up with key takeaways and action items and then our open Q&A with the audience. So just very briefly for those of you who are new to Grassroots Health, Grassroots Health was started in 2007 by Carol Baggerly. We are a 501c3 nonprofit organization. And Carol began Grassroots Health along with 40 senior vitamin D researchers based on a consensus and a call to action that really called out that vitamin D deficiency and insufficiency was incredibly common and contributes to increased risk of many diseases beyond bone health.

Our vision is to eliminate the worldwide vitamin D deficiency. Everything we do at Grassroots Health is really keyed into that vision and our tagline is moving research into practice. We work with these amazing researchers who will be speaking today. And we're really here to implement that research into practice. There is is more than enough research now to make change happen. And I am incredibly honored to work alongside the world's top vitamin D scientists and experts, many of whom have spent decades researching vitamin D and incorporating their findings into practice. Each of these scientists brings an incredible amount of expertise and credibility to the work of grassroots health and to this presentation today. And I want to exp extend my deepest thanks to each and every one of you. So with that, I would like to turn the floor over to Dr. James Lyons Weiler.

DR LYONS WEILER >> So I'm James Lyons Weiler. I'm the president CEO of IPAC, the Institute for Pure Applied Knowledge, and I founded IPAC edu. We had something like two or three thousand two 2500 to 3,000 people take courses as a result of COVID so they could learn immunology and statistics and keep up with the bad guys as they were lying with statistics and lying about public health policy.

So you know vitamin D problems with vitamin D dosing actually first came to my attention when I saw a friend of mine a colleague of mine Keith Baggerly give a presentation about it online. I knew Keith from many many years ago when I worked with the early detection

research network in cancer and I was really pleased to see that he was advancing the knowledge of the problem with vitamin D mistakes. So that's what my talk is going to be about today. I'm just going to share some slides. I probably won't even take up the whole five minutes. I'm not going to go to great detail, but you can bet that you can find more detail about this at popular rationalism on Substack. I've written one article. I'm going to write another article about it. And of course, you can find a lot of articles there. We're transitioning everything at IPAC o edu over to IPAC edu online. So it's a social media platform that that we're creating to bring about four or 5,000 people together to do great work. But let's get underway here and talk about the the one of the mistakes or many mistakes. We're going to hear from the many of the speakers here about all the mistakes that have been made over the years, but in vitamin D dosing so everybody who's speaking today will probably go over this and clarify it, but the the RDA, the recommended daily allowance right now is somewhere around 600 800 international units a day.

And we want to distinguish that from the tolerable upper limit intake level or the upper level. And part of the mistake that was made and I'm going to make it very very painfully clear about how and why they made the mistake. It was a inferential error. It wasn't a mathematical error or a statistical error. It was just looking at statistics wrong and doing analysis wrong. And this is un this is documented. It is not controversial. This mistake is absolutely you know published in the peer-reviewed literature. The institutes of medicine 100% you know now the national academy of sciences and have validated it but what they did was they said that the lower 95% prediction interval for the upper limit not the RDA but the upper limit of of exposure was determined using something that allowed that level to be too low and the way that it was too low is is that they they handled individual study averages as if they coverage they cover the entire distribution of diversity among individuals. And it's really obvious u when you think about it if you know about statistics is it's called regression to the mean. The idea that 97.5% of individuals, you know, might actually be above a certain level based on inferences based on what the averages are telling us is is patently false.

You can't get there from here to quote my friends from New England. And so I came up with this cartoon. It's if you want to copy it, go to popular rationalismstack.com. So, let's say that my job as I'm an engineer and I'm going to make you know bridges in my town and I know that there's diversity among the trucks and so I want to be sure that the trucks aren't too high and an acceptable risk so that we can have to reroute a certain amount of traffic is 2.5% of trucks will have to be rerouted right and so because the variation among the trucks what I do is I go to the literature and I look at the the average of different kinds of trucks that maybe different categories of shipping needs or companies or produce or something and and I take those averages and I go well listen on average the average of all these trucks are lower than this and so I can actually have the bridge a certain height or maybe they're higher than this and so you know I can have I can have my bridges a certain height and so if I get that wrong and I don't look at all the diversity of trucks that are out there then the the math that you do when you take look at the average of distributions rather than the the

average of all individuals in the population is you're going to have a lot of trucks that are hitting the bridge, right, that you don't anticipate.

And so you're going to have to reroute a lot more traffic. And that's what's happening here. So I won't go through it in great detail, like I said, but there's more variation among individuals in the population than there is variation among averages among studies. That's the problem. So they they they really made a a silly mistake and it's not controversial. Another example of how to understand what they said about that upper limit is by taking the average. If I said to you that most classrooms averaged above a passing grade, it's certainly not the same thing that saying that 97.5% of students passed. Those are two different inferences. And so the institutes of medicine they they try to release some new DRRI limits re recommended intake. Katherine Ross u a Katherine Ross shared that and and and they still are very very very low compared to what the data would actually support. Here's one of the studies that that got it started and some Canadian scientists looked at the statistical error and said, "Hey, we published this. This is in the journal Nutrients in 2014. Now it's 2026, so it's been a while." and because of that statistical error that I told you about then it was confirmed if you look at independent data and this is some people associated with u grassroots health data they analyzed it at all they said hey look it's it's it's actually you have to have higher intake than we thought and Carol is on there and so on.

So, you know, this is a problem that's very well known to this particular group. Our job today is to make sure that the institutes of medicine, I'm sorry, I misspoke, that HHS understands that there are consequences for them. They're continuing to distribute the wrong information. There's never been a revision of the RDA. There's never been a revision of the upper limit based on fact. Even though we know that the problem was was there. The data are published and I can now determine what a more reasonable limit would be. And it's been the the frustration of everybody that's going to be presenting today for years and years that no one seems to be able to move the needle. And Robert F. Kennedy Jr. Is the secretary of HHS and I spoke with him about this problem and I wrote up something for him which he ended up distributing across HHS and hopefully there'll be some action but we're not seeing that action yet and so we got to keep the heat on. We want to bring it to the public and say there's a problem here that the science as it stands is not being translated into policy and really basically boils down to correcting the website here and there across HHS. For the most part in other publications, but there are other consequences that we're going to recap at the end like maybe we need to update medical education and maybe we need to study the consequences of you enroll somebody in a clinical trial for research and they have low vitamin D.

I mean why would you do that? You you want to increase the health of the population then you should take a look at what's happening when you know doctors are practicing ethical medicine let's call it that. So there have been debates, there have been positions on it. There are health consequences for pregnancy and maternal. We're going to get into all of this. I'm sure people are on the call are much more expert than I am. Children and adolescent

deficiencies, very important. Geriatric population, very important. But let's just say that there's a problem because the while the knowledge base has shifted, the policy hasn't changed and we we know the health consequences, but we need to talk about it. So, I'm happy to turn it back over to you, Chen, and stop sharing and we're going to move right on to the next one.

JEN >> Thank you, James. Yeah, so Dr. Michael Hollik will be speaking next. Dr. Dr. Michael Hollik is a pioneering physician, scientist, and one of the world's leading experts on vitamin D, whose decades of research have helped shape modern understanding of vitamin D metabolism, deficiency, and its impact on human health. As professor of medicine, pharmarmacology, physiology, biopysics, and molecular medicine at Boston University School of Medicine, Dr.

Dr. Hollik has authored more than 900 scientific publications and has been actively involved in the development and discussion of vitamin D guidelines and public health recommendations over the course of his career. Welcome Dr. Hollik.

DR HOLICK >> Thank you so much for that kind introduction Jen. So I'm going to give you a very broad overview of the 2010 M guidelines, the 2011 and 2024 endocrine society guidelines, history and shortcomings and a 2026 perspective. People worry about conflicts of interest and so I do consult and speak and I also get support from NIH. Now, you might think I'm an idiot because what am I going to tell you about vitamin D that you don't already know about from the Institute of Medicine report and the 2024 guidelines? And it turns out that the Institute of Medicine in 2010, they realized something that the 200 units a day was inadequate and they recommended 600 units a day. So, the RDA was increased three-fold. They also realized that 2,000 units a day, it's intoxic. And they've recommended the upper limit can now be 4,000 units a day. That's amazing when you think about this. I'm constantly asked, "What do I think about this?" And I have only one word for it.

Wow. Right. Because no nutrient has been increased by that amount in such a short period of time. The question is, did they get it right? In 2011, the Endocrine Society practice guidelines. I was fortunate to chair that committee. All the members are experts in the field of vitamin D. And it turns out that the guidelines were specifically for prevention treatment of vitamin D deficiency. The M guidelines was not intended for physicians. It was recommended that professional associations should make those guidelines for patient care and they used a population model not a medical model. So the recommendation in 2011 from endocrine society 400 to a,000 unit for neonates 600 to a,000 for children and adults 1,500 to 2,000 units a day and if you're obese two to three times more safe upper limit based on the literature 2,000 units for infants 4,000 units for children 10,000 units for teenagers and adults 2024 guidelines. You need to understand that those guidelines were not for patient care. They were guidelines for those that were vitamin D sufficient and could

take additional vitamin D for having other health benefits. But a priority decision that they made, they said that generally the population is healthy and therefore the RDA should be the M recommendations which is 600 units a day for most children and adults.

Therefore, the 2024 guidelines assume the healthy population that's vitamin D sufficient. And what do they recommend? 1 to 18 years, 600 units a day. 18 to 70, 600 units a day. 75 and plus 900 units a day. Obesity, they don't recommend anything. And they don't recommend anything for the first year of life. Again 2011 guidelines for infants and for children and for adults and obesity all were recommended. Is vitamin D deficiency a health issue? It estimated 40% of the world's population is deficient 60% insufficient. Here a national health survey data from US population showed less than 50% of the US population is vitamin D sufficient and some in the ages of 10 up to 30 no more than about 30% are sufficient. Recommendation 12 from the 2024 guidelines healthy adults we suggest against routine screening for vitamin D status. So why should you care? Well, it turns out that vitamin D is important for pregnancy. And we showed with Lisa Bodner many years ago, the higher the 25 hydroxy D in pregnancy, lower is the risk for preeacclampsia. A very nice study looking at gestational age and 25 hydroxy D. 60% reduction in premature births. If your blood level is greater than 49 grams per ml, mom, thanks for taking your vitamin D.

Recommendation 8 from the 2024 guidelines. We suggest empiric vitamin D supplementation during pregnancy given the potential lower risk of preeacclampsia interuterine mortality pre-term birth small for gational age. That's fantastic. And they recommend 2500 units of vitamin D a day. However, again go back to the a priority decision. The panel said healthy population and so even pregnant women they recommend 600 units of vitamin D a day. 2024 guidelines pregnancy 600 units a day even though they appreciated from the literature that a higher dose will marketly re improve birth outcomes. Obesity is associated with vitamin D deficiency. The higher your BMI, lower is your vitamin D status. And so a study was done by IURU many years ago. And what he did was he looked at serum concentrations of 25 hydroxy D and how much vitamin D they were taking and to see what would happen if you're normal weight, underweight, and obese. And he showed very nicely to get to the same level as a normal person, you would need to take 2.5 times more vitamin D to satisfy an obese person's requirement. They need two to three times more. Recommendation 14 from 2024 guidelines. They say adults, we suggest against routine screening for 25 hydroxy vitamin D, especially with obesity.

The guidelines recommend obesity. They don't have any recommendation for obesity. M re had u used this study as a way of defining vitamin D status for bone health. And the endocrine society looked at the study as well and talk about another error in u calculation. This is 675 German adults ages 20 to 90 years of age and bone biopsies and blood was taken and the authors concluded to see no evidence of vitamin D deficiency bone disease you needed to be greater than 30 nanogs per ml but and in fact the institute of medicine said wait a second not really because if you take the number between 21 and 29 for those that have osteomalia over all that are deficient or insufficient and only about 1% have bone disease. So that's of no consequence, right? But the problem is they made an error, right?

Typically when you're going to do a analysis, you want to have this as your numerator and this as your denominator. 21 to 29. And if you do that, 22% of otherwise healthy German adults were found to be vitamin D deficient in the sense that they had osteomalia, bone disease. None had greater than 30 nanogs per ml. And that's why the endocrine society in 2011 recommended 30 should be your minimum. 40 to 60 is preferred especially because of the vagaries of the assays that were out there.

Up to 100 is perfectly safe. Also working with Bob Heene years ago, we showed 10,000 units of vitamin D a day to healthy adults is safe. And also a nice study again by Aquaru showed four to 5,000 units a day blood level around 40 20,000 units a day about 60 in 22,000 observations no toxicity. What about COVID? When COVID hit because vitamin D does play a role in your immune system. I worked with Quest Diagnostics looked at over 190,000 patient samples and what did we find? We found that if you were vitamin D sufficient 25 hydroxy D of at least 34 nanogs per ml 54% likelihood of having COVID. We also look at our hospital and we're shocked to find if you walk in the hospital vitamin D sufficient overall decreased odds of death was 67%. Overall odds of death ratio 82% if you were sufficient and you had normal weight. Recommendation one from the 2024 guidelines. They say that empiric supplementation for children can potentially help in reducing risk of respiratory tract infections. Right? And they said about 1,200 units a day, which is fantastic, except that they don't make any recommendations for children or adults to increase your vitamin D intake for anything. They just say 600 units a day.

Vitamin D supplementation and diabetes, a paper came out, the D2-D study originally said doesn't work. However, when you do and look at the data more carefully and you look at those that had a blood level of at least 50 nanogs per ml compared to 20 to 29 nanogs per ml, they had a 76% with a three-year absolute risk reduction of from pre-diabetes to diabetes, which is truly remarkable. CDC estimates that more than about 50% of the US population has either pre-diabetes or diabetes recommendation 10 from again the 24 guidelines adults with high risk of pre-diabetes in addition to lifestyle modification they recognize 3500 units a day can help but again what do they say they assume that it's a healthy population and they make no recommendations for adults that are obese or have pre-diabetes. Also, vitamin D supplementation mortality. Here, a study showed 25% reduced risk. Cedric Garland showed very nicely. The higher your 25 hydroxy D, lower is your risk for mortality. What is recommendation six from the 24 guidelines? If you're age 75 and older, they automatically now say don't take just 600, but 900 units of vitamin D a day because that is going to help your survival rate. Your survival is based on everything that you've done as a child, young adult, middle-aged, and older adult.

Not all of a sudden taking some vitamin D is going to make a difference for your mortality. Right? They recommend 75 plus and over 900 units a day. Age adjusted studies. Again, look at this. This is Garland's data. 40 to 50 nanograms per ml maximum benefit. You would have to take 4,000 to 5,000 units of data to achieve that level. And a study done many years ago by Lux Wald showed that these hunter gatherers have blood levels of 40 to 50 nanograms per ml. And they would need to take, like I said, you would 4,000 to 5,000 units a day.

Vitamin D deficiency is a disease of neglect. Don't think about a normal level, but a healthy level, right? How much vitamin D do you need? We know based on studies we did with Bob Heeney, you need a 100 units will raise your blood level by about 6 to 1 nanogram per ml. If you're not taking a supplement, your levels are in this range. So, you think you can get it from your diet. There's essentially no vitamin D in your diet. You cannot get it from your diet. Right? We did a study in healthy adults in Boston at the end of the winter. 1,000 units a day. Essentially, no one was vitamin D sufficient. I recommend minimum 2,000 units for adults. Children, 1,000 units a day.

Again, looking at the Edwar study, 5,000 units a day for a normal weight person, 50 nanogs per ml. 10,000 units a day gets up to about 60 nanograms per ml. And if you're obese, you need two to three times more. Right? I was asked to review the 2024 guidelines and pointed out there's a mountain of evidence linking vitamin D deficiency with increased risk for cancer, mortality, autoimmune diseases, etc., and showed that essentially all of these chronic illnesses can definitely be improved risk if your level is at least 30 and sometimes 40 to 60 nanogs per ml. Adequate vitamin D is critically important from birth until death. Vitamin D can help improve your health and I thank you for your

JEN >> Thank you. That was fantastic as always. I love how animated you are, Dr. Hollik. All right. Next up, we have Dr. Wimalawansa is director of the cardiometabolic and endocrine institute and a former chief of endocrinology. A distinguish distinguished professor of medicine and human nutrition at Rickers University. He is a respected clinician researcher and innovator, a philanthropist and he has served as a board member and consultant to multiple scientific organizations. He holds multiple academic credentials and has authored hundreds of peer-reviewed scientific publications and several books spanning vitamin D physiology, osteoporosis, endocrine disorders, immune health, and chronic disease prevention.

So, I really appreciate that you are here with us today, Dr. Wimalawansa. I hope that your presentation goes well.

DR WIMALAWANSA >> Thank you, Jen. And so the next 18 minutes or so I'm going to produce discuss with you 15 key issues related to vitamin D which would help you to understand better the presentation in this particular program as well as any publication you're going to read related to vitamin D in the future. Firstly, vitamin D the D3 is the one we preferred and should be used in supplementation as well as it's one which is generators on the in the skin casol is 25 hydroxy vitamin D and 125 is one produced in the skin as well as a peripheral target tissues. There are synthetic analoges based on both 25 and 1/2 hydroxy vitamin Ds which should not be used as a supplementation for vitamin D. So what is vitamin D? It's a firstly it's a threshold nutrient which is very important and it has nothing to do with the pharmacutetical agent. They are very different. It's a it has many

physiological functions. That's a very shallow dose responses compared to pharmaceutical agent and beyond that being a thresh nutrient beyond that there's no added benefit by adding more nutrients. Secondly it also a network nutrient but it means none in fact the none of the micronutrient work on their own to benefit us.

Micronutrient always work as a clusters of nutrient what we used to call what we call them as co-actors for in the case of vitamin D you need magnesium omega3 K2 and in fact there are several more other co-actor necessary to get the maximal benefits of vitamin D. So these co-actors are essential. So vitamin D deficiency can also occurs in the presence of co-actor deficiencies. In addition, it also affect about 2,000 of our key vitamin D genes which may have already mentioned in this presentation. Now there are some of the outdated concepts has been mentioned. I'm going to mention couple more here. When you expose the fair fair skin person about one/ird of the upper body to the midday sun, people can generate anything from 10 to 15,000 units of vitamin D in the body. So that's supposed to be the general safe generation of vitamin D. Okay. Governments, agencies and even some scientific societies recommending 400 to 800 interactions per day as you have already heard. However, as Professor Holik mentioned 1,000 international unit we recommend for infants but that cannot this cannot be correct for recommending for adults. There's something wrong in the entire system. Similarly, targeting the 20 nanogas mill based on the 1980s recommendation we only designed to prevention of written and oy Malaysia in adults but nothing whatsoever to do with the other benefits of vitamin D.

What the blue be is vitamin D physiology sun exposure generates in vitamin E. However, over exposure of UVB and also UVA can cause arythema and skin damage. Therefore, overexposure must be avoided. Nevertheless, exercise never causes over production of vitamin D or or causes hypocalcemia because there are in inherent mechanism to prevent that happening in the skin. So why do we need functions? The one of the key things in the recent days of important is that twothirds of the immune system function is driven by the vitamin D. Of course, it need the other core factors and other other sub supplementary evidence is supporting factors to go in. So as magnesium before the escalating you know vitamin doses with the vitamin D may working maybe because not insuffion vitamin D magnesium is present in the system. So not necessarily the vitamin D discharge itself. So vitamin D also has additional physiological and biological function lot more than what we discussed including the DNA repair in a generation and lot more. I'll discuss that in this particular slide very briefly. So as you see on the left side it has got a many other component and the different system and as you see these slides will be appear on the video will available which I'm not going to dwell.

However, there as you see in the right side, there's no downside with the vitamin D treatment. It's economical and there's no adverse effect on the recommended doses by this panel and there's not a pharmacological agent. It is a nutrient and there's a very safe wider margin as I mentioned co-actors are essential part of the vitamin D physiology and for biological actions. So magnesium don't forget the sufficiencies necessary for vitamin D action. In fact, some of the so-called vitamin D resistant syndrome could be due to these co-

actor deficiencies. Similarly, vitamin A deficiency can also caused by proton pump inhibitors like a gastric acid inhibitors, inflammatory bowel diseases, fatty liver disease, chronic disease, kidney disease, etc. Can also lead it to vitamin D deficiency. So don't underestimate those areas. The next one is the increased utilization of vitamin D in the presence of active diseases especially any active infections or any indication for admittance to ICUs. So as any race condition with the CRP is almost equivalent to increased requirement of vitamin D. In other words, it's in the utilization of vitamin D goes up. So demands also rises in autoimmune diseases, fractures, pregnancy as well as in lactation.

So the bottom line is rapid lipation occurs without supplementation. So in this scenarios if the patient admitted to the hospital even with the normal vitamin D if the patient is acutely ill if they don't supplement with the vitamin D and magnesium they can rapidly become insufficient or deficient within few days and the hospital length will length of stay increases therefore the cost of healthcare will actually increases. So let's look at the blood levels again very briefly. So vitamin D stasis is measured only by the 25 hydroxy vitamin D level. 125 hydroxy level is only is a specific mark for renal diseases and should not be usedful as vitamin D status measurements. So human physiological and nutrition threshold do not change between healthy versus sick as well as young versus old. So what is changing then is what is changing is vitamin D intake required to achieve and maintain the optimal blood level that changes between people disease prevention and the management. Let's look at that little bit more details. Why the same dose of vitamin D leads to different serum 25 hydroxy level in different people? Number of reasons. One gastrointestinal absorption issues varies from person to person.

It's not the same. Different individual had the different medication body mass indexes which we discussed in previous presentation. High the fat mass, high the sequestration so as muscle mass. Similarly, differences in utilization in infection as I just mentioned, pregnancy, physiology, lactation as well as enhancement of a metabolism as well as some medication like anti epileptic drug causing increase catabolism. Therefore, one cannot expect that same medic same dose to have the same efficacy of vitamin D. Similarly, why can two people have the same serum level of but have a two different biological outcome? These are the questions a lot of people asking me. So, I think it's the same question asking from you all. So, that's why I put these two here. So one commonest and hidden thing is the genetic differences. We don't address this commonly because it's a costly somewhat costly to get the answers. These are the gene variants particularly the gene pomeism particularly the gene holding of the vitamin D binding protein as well as the vitamin D receptor abnormalities. These are not that uncommon by the way. And secondly, as I mentioned, it's very common to have a magnesium and other co-actor variabilities, the levels as well as combination can lead to significant alteration of the sensitivity of the vitamin D to the body system.

So that's one of the reason some people are categorizing low versus high responders indirectly. It's not the responders. What we are having is these variables influencing the system consequencely that's why they having we need to have the wider normal range like

40 to 100 nanogs per mill or in the lab point of they are even considering 30 to 100 nanogs mill as a way wider range in vitamin Here are some practical guidelines in clinical trials. One should not rely on intakes of vitamin D. Instead, we need to chain a culture to measure the rely on the measurement of serum 25 hydroxy measured 3 months into the clinical study. In other words, stable blood levels achieved. We have been preaching this for almost 10 10 15 years but not no study has been done this yet. Similarly this process can be accelerated by giving loading dose of vitamin D. In practice we have been doing this in our clinic for at least 20 years probably not longer than this. It has a significant benefit for the patient advancing the benefits of vitamin D in this patient by several weeks if not several months. So technically this principle can be accept adapted to in clinical practice and clinical trials especially for high-risk patients to maximize the benefits clearly we need to individualize the treatment for patients.

So no nothing no single dose applicable to all patients. So let's look at the blood levels of vitamin D. Simplify calculations on what what you can use to approximately get get into the very close doses necessary for all everybody without exception. So which is based on the body weight or BMI. Similarly there's a calculation you can get through this publication based on the serum 25 haroxy vitamin D level both give the equal very approximate but very good proximity correct amount of vitamin D necessary for the individual patient as you see the non-obese patient about 70 to 90 international unit per kilogram body weight as the body weight increases the amount necessary for kilogram body basis increases. Therefore, it automatically increases the amount needed to the dosage needed to that given patient. So, this is what generally you need to remember in this situation. So, what should be the minimum serum 25 hydroxy? This confusion going on for multiple publication. In my opinion, consideration levels 20, 30, 40 is silo mentality is misleading and is clearly unhelpful for patient care. But will maintain the blood blood serum 25 hydroxy level between 50 and 80 nanogs per milll as shown in the multiple recent studies.

It encompasses 99.5% of the disorders that is.5% disorders. These are the rare disorders vitamin D resistant disorders. This amount to about 0.55% soda requiring much higher level of vitamin serum level like 100 nanogas mill but it's a very very small component of patient. Lastly the various tissues and diseases respond to different serum tissue levels. This is another important factor we need to keep an eye on. So in on the background also we need to remember that the freely living human typically having a serum 25 level above 25 nanog per milll not 30. So adequate adequate him minimum level must be satisfy the functions of vitamin D to cover maximum amount of disorders. Why not? So this we recommend that in the range of 50 to 80 nanog per milliliter. This range reduc the cardiovascular diseases reduce the cancers improve the pregnancy related better outcomes as well as the least amount of neurogenerative disorders include the Parkinson's and other neurovvascular disorders. This does not vary by the age, race, ethnicity, skin color or the latitude. So this is the human inherent genetic issue. So higher target needs however specific disease condition. So the rare disorder as I said like disorder were like drugresistant migraine cluster headaches drug resistant psoriasis some genetically acquired vitamin D resistant disorders those are requiring much higher level.

Nevertheless, this treatment for this synd disorder should not be treated by the general practitioner or even by the endocrinologist but should be treated by the specialist supervision under experienced clinical centers because this can this can develop into problem unless these patient are managed very carefully with the calcium free diets and that kind of things under specialist management. Here's a slide I I could generate long time ago based on about five more than 500 different published studies to summarizing different levels of vitamin D required to overcome the different system or system based disorders. Again I'm not going to go through this one. But as you see that this slide will be available in the in the video but as you see that on the right side column you can see that the symptomatically you can see that the amount of benefit occurring on these symptoms and the correlation between the amount of CM level and the symptomatic benefit of these disorders to achieved. So, so with the sun exposure plus supplements, knowing the levels and enjoying the better health with vitamin D, there's every reason to have vitamin D. It is simple, safe, essential, and as I shown and others shown that there's no downside.

So to summarize last couple of slide transform US health care better care with a low cost. Let me show you couple of slides on my thoughts. We have a fundamental failure in United States and industrialized countries in general in the west. We have a high burden of chronic diseases across all stage group from infancy to death. This is because our pharmaceutical modeldriven clinical care. We treat the symptoms and we forget the root cause analysis and treatment. This happened as you know some remember that reflection report going back to 1908. I think that changed the entire health system in the United States to the negative. We need to change that. This is the opportunity of the new administrator to change it. So without changing that mindset to changing back to the pharmaceutical model to root case root cordriven model we cannot change the healthare system at all. So we need to go back to the root cause largely unadressed micronutrient deficiencies and its toxic burden food issues are partly being addressed right now. I'm very pleased to see that the final slide what's need to happen in addition we need to integrate the nutrition and medical and nursing education into the curriculum which is still not happening.

Some of the medical curriculum still has only two hours of nutrition treatment. Vitamin D perhaps 20 minutes for the entire education curriculum. Revise the vitamin D guideline using current evidence. Guidelines are 30 years outdated. Avoid RCT approaches in nutrition research. And Dr. Grant has mentioned we need to use the prospective studies instead of the RCTs for evaluation of all micronutrient not necessarily vitamin D. So shift from the symptomdriven care to root cause medicine. And then finally the most important prioritize the primary care and chronic disease management instead of the specialist care and the hospitalized medicine. Thank you for your attention. Appreciate. Have a great day.

JEN >> Thank you Dr. Wimmelansa. That was excellent. And I hope you get some rest after this. All right. Next up, we have Dr. William Grant, who is an internationally recognized researcher and the founder of Sunlight Nutrition, and Health Research Center, where he has spent decades studying the relationships between vitamin D, sunlight exposure, nutrition,

and chronic disease prevention. He is widely known for his extensive work in epidemiology and ecological health research, authoring hundreds of scientific publications examining the role of vitamin D and UVB exposure in reducing the risk of conditions such as cancer, cardiovascular disease, diabetes, autoimmune disorders, and respiratory infections.

As a worldwide recognized expert writing about vitamin D and sunlight, Dr. Grant has been an important contributor to scientific discussions surrounding vitamin D guidelines and public health recommendations. So let's see if we can't get Dr. Grant up.

DR GRANT >> Okay, thanks for the introduction. So the advantages of observational studies include that they they include large numbers of participants useful for minor diseases and accuracy for major diseases. Some studies can be conducted quickly using existing databases such as the national health and nutrition examination surveys in Hannes in the US and the UK bioank. They generally include participants with large ranges of 25HD concentrations values for confounding factors are generally available at the same scale as the serum 25HD concentration data. Now there are two types of ecological studies temporal and geographical. Geographical were important in cancer to show that UVB and vitamin D reduce risk of cancer as started shown by the Garland brothers starting 1974. The temporal ones show the seasonal variations and here we have for the death rates from 1979 to 2004 showing a 27% increased death rate in winter compared to summer. And that's correlated primarily with the solar with UVB with vitamin D which is in the lower the blue the dash line on the in the right due to solar UVB.

Now there is primarily due to cardiovascular disease but also infectious diseases and you see two extra bumps one in about February or March one about September when they're more infectious diseases. It's interesting that wintertime 25 hydroxy vitamin D levels are about 70% as high as summer values. That's because u of 25 LD stored in muscle cells and released into the serum as shown by our colleagues Mason and Ription in in Australia. So the advantage of observation okay sorry the prospective cohort studies are what's generally used for observational studies in these participants are enrolled variables are measured and health outcomes noted over a follow period of years the results are analyzed according to serum 25 concentration or vitamin D level at baseline with adjustments ments for various confounding factors. These are very useful but subject to regression dilution due to changes in the variable values over the time and this was first demonstrated in 1999 by Clark at all. So Michael Hollik just showed his response to the demay at all new endocrine society guidelines for 2024. This is our similar reaction to those those awful guidelines. And what we did was we took obser findings from observational studies for eight for the top 10 cause of death in the US and found that serum 25 hydroxy vib concentrations above 30 nanogs per milliliter could significantly reduce the burden of disease for eight of these top 10.

And these eight accounted for 90% of all deaths in 2021 and 2022 which was the COVID area era. So these are the diseases I'm going to show the results for in the order we'll be presenting them. First there's cardiovascular disease. This is a metaanalysis of 19

independent observational studies of CVD as known as of 2012. And what you see here is that for those with 25 hydroxy vitamin D less than 8 nanogs per milliliter, there was about a a factor of two increased risk compared to sufficient 25 hydroxy vitamin D. And there was a deflection point around 25 or so nanogs per milliliter, which means above that point you were not seeing any increased benefit of vitamin D supplementation. Here's another example for cardio colorctal cancer. This is for a number of groups. This for 17 cohorts as originally reported by McCullen in in 2019. What we did was we plotted the the reduction for high versus low 25 for doxy ID versus median years to diagnosis. And what you see is that for men you have a a a a a sharper more steeper change with time they do for women. That's because men spend more time out of doors and have higher 25 for oxytocration. But in consistent consistent with with the results from Garland at all, there's about a 25% reduction for high versus low.

If you extrapolate to zero follow-up time, Michael Hollix's already shown this for for the virus associated with COVID. Here's an interesting study from Israel reported in 2022. For those with mild COVID, the mean 25 for deconstration is around 35 nanograms per milliliter. For moderate COVID, it was around 20. For severe is around 12 and critical around 10 10. What's interesting is that this paper was retra retracted in 2025 on the basis that the inclusion of only patients for whom vitamin D determination had been performed before COVID 19 infection introduces bias. Well, that's just this was really redacted because big pharma doesn't like publica publicity or natural compounds that are inexpensive and have strong health benefits. What we've seen is that if vitamin D were a patentable drug and could be sold for profit, it would be the most popular drug in the world. But since it isn't, it's it's it's sort of languishing. And and and and co vitamin D was was blocked from for co was blocked from mass media and even from the social media because big pharma and the system wanted to sell vaccinations and and drugs for treating COVID. Here's for stroke. You see that for those with greater greater than 30 nanogs per milliliter versus versus less than 20 nanogs per mill milliliter, there's about a 60% reduction in risk of stroke for one year follow-up.

By 10 years, there's there's no correlation. Again, this shows that the the the studies are all consistent if you count for follow-up period. Here's for COPD, chronic obstructive pulmonary disease. What we find here is the kink is around 18 nanogs per milliliter with a very steep rise before for lower values. For dementia we have over a factor of two increase at five years of followup for less than 20 versus greater than 30 nanogs per milliliter. And note that Alzheimer's disease accounts for about 70% of dementia. Now, Michael Hollik also mentioned this study from the from the from Tus University. Again, what it shows is that there's a very significant reduction for those with higher versus greater than 50 NOGS per milliliter versus less than 20 to 30 NOGS per milliliter. And here we have new onset chronic kidney disease. This study used data from the UK bio bank without prior CQ data CQ KD at baseline and during median median followup at 12.1 years there was about a 30% reduction for those with diabetes and no significant reduction for those without diabetes. So that that's the our results from these observational studies. Now here's a study from the holic group which shows that the well first of all many of the vitamin D's effects are due to

the hormonal metabolite of vitamin D which is 125 dihydroxy vitamin D or calcatrial binding to a vitamin D receptor in cells thereby affecting gene expression what they showed when they randomized 30 healthy adults to re receive 600 400,000 or 10,000 IU per day of vitamin D for six months There was a dose dependent 25 each concentrate alteration in broad gene expression with 162 320 and 1289 genes up or down regulated in their white blood cell.

And the the assumption is that if vitamin D causes the changes it must be beneficial. So observational studies suggest the following points. First randomiz randomized control trials and vitam vitamin D supplementations supplementation studies even in observational studies should be based on participants with serum 25HD concentrations below 20 nanogs per milliliter participants in the treatment group should be supplemented with variable vitamin D doses up to 10,000 IU per day with a loading dose in the first one to two weeks as to jumpstart the the study. If you did not jump start it, it would take up to three months to get them up to whatever the satur saturation level would be. Participants in the control group should not be supplement with vitamin D. Unfortunately, it's considered unethical not to supplement people in the control group with vitamin D because that's considered the normal basis of treatment. However, there was a study Michael Hollis, Bruce Hollis conducted with colleagues in Iran where the baseline was 11 nanog grams per milliliter and they showed very very good results for achieving greater than 20 nigs per milliliter for pregnant women. Outcomes should be analyzed according to achieve 258 junk deconentrations and BMI categories.

That's because there are many ways that that the vitamin D concentration changes with respect to vitamin D concentration includes BMI, it includes genetics, etc., etc. And so you cannot assume that that one dose has the same result for all participants. And as found in a number of studies, people with higher BMI do not get as much benefit, if any, from vitamin D supplementation. Now I just found this paper today at PubMed. It shows that based that that median serum 25HD or vitamin D concentrations among Americans in a cross in cross-sectional studies as measured by NHANES now inhanes sends trailers to the southern United States in winter and the northern hemisphere northern states in summer. And what they found is that from 2000 2001 the mean value was 25 nanogs per milliliter by 2022 and 2022 or 20 23 24 it was up to 31 nanogs per milliliter and this is about a a nanogram per milliliter change. This is likely due to reports from observational studies since most of the clinical trials most of the RCTs have not reported beneficial effects. So I think this this shows that we've been doing a very very beneficial service over the past 1015 years. It's been sort of I call the golden age of vitamin D in which the nonskeeletal benefits of vitamin D have been recognized and and studied.

Now normally it said that association is not causality. Okay. But AB Hill in 1965 gave a talk to the Royal Society of Medicine in London in which he outlined his criteria for a causality in a biological system and as appropriate for vitamin D. They include strength of association, consistent findings in different populations, temporality, biological gradient, plausibility such as mechanisms, coherence with known science of the day, experimental verification

such as randomized control trials or other vitamin D supplementation studies, analogy, and adjusting for confounding variables. There have been over 20 such analyses with vitamin D for health outcomes reported in PubMed. Nearly all of them showing that causality that the criteria for causality are generally satis satisfied. Now not all criteria need to be satisfied or causality be claimed but the more that are the better and most of these said that well the randomized control trials are are missing. Hopefully that'll be rectified the next few years with better studies. Thank you for your attention.

JEN >> Thank you so much for that Dr. Grant. It's such a important topic to really emphasize the importance of the totality of evidence especially when randomized control trials are very poorly designed for nutrient studies.

Something that Dr. Robert Haney spoke about quite frequently. So next up we have Dr. Edward Giovanucci who is a physician, epidemiologist and internationally recognized nutrition research researcher whose work has significantly advanced understanding of the relationships between vitamin D, diet, lifestyle and chronic disease prevention. He serves as professor of nutrition and epidemiology at Harvard Thchan School of Public Health. His extensive research has focused on cancer epidemiology, metabolic health, and the role of vitamin D and other nutritional factors in long-term disease risk. And he has authored hundreds of scientific publications contributing to substantially to the scientific evidence informing public health recommendations related to nutrition, lifestyle, and vitamin D status. And today he will be discussing insights from randomized control trials and mandelian random randomization. Thank you Dr. Giovanucci.

DR GIOVANNUCCI >> thank thank you thank you Jen. It's a pleasure for me to be here. I will talk u mostly about RCTs very little about mandelian randomization studies. And I you know I will be talking about RCTs but most of my work well over 90% is from observational data. So just a little bit of a background now like randomized trials are critical part of the evidence of course and and for some people that's all they accept.

But I think that's a little bit simplistic. Now the for chronic disease the randomized trials there's really an imbalance in how you interpreted the data. Now, a positive result in a in a strong well done randomized trial is very strong evidence for a causal effect because it's the most definitive way to exclude confounding factors. But a null result needs to be carefully interpreted in the context of many factors that push the tendency towards a false negative. And I can't go through all of these. This this would be a lecture on onto its own but this is a list of nine there I'm sure there are more factors that I have been documented u in my course that you know each one of these I can spend a lecture on that impact randomized trial so unless you really mess up a randomized trial and like the you know the randomization process or something if you do a reasonably well done randomized trial you could still get a false negative because of all these factors And for vitamin D or for any

nutrient, it's particularly important to take into account the status of the population for that nutrient. It's different from a drug where you either, you know, you take the drug or not, but for a vitamin, it's we all have an underlying status, which makes it important.

Now, the the biggest trial and and the one I mean, I was peripherally involved in this, but it was led by Drs. Manson, Julie Burring. And this is probably the most well-known large trial was was vital. And this had about 26,000 men and women. You can see the ages and they they randomized to vitamin D or placebo. They also had fish oil, but we don't have to consider that. You can just look at the vitamin D. And so about 13,000 got 2,000 units of vitamin D and 13,000 got a placebo. And this is about a five-year study and and looking at major end points. Now, the results started coming out about 2019 and the one of the first reports was for major cardiovascular events and as you can see not much going on up to five to six years. The placebo and the active group had the same cumulative incidence. And for invasive cancer, pretty much the same. Not much difference, a slightly lower risk, 4% non-significant lower risk in the vitamin D group. Now, results like this led some to be very skeptical of vitamin D. I I'm sure people here are aware of and and there were some editorials saying results from vital and other studies really put a dent in the vitamin D even making very strong statements like we stop recommending vitamin D supplements.

But we really have to look at the details of the trial. And so in this slide we show this is from UK bio bank for for cardiovascular endpoints and for fractures and you can see the dose response these are observational data. So in these studies when you get around up to maybe 30 nanom moles vitamin D you know 10 to 50 nanogs you get most of the benefit then it's pretty flat and in vital to people as as Dr. Grant, you know, mentioned in trials for for ethical reasons, you don't often start with deficient. That would be the good scientific question, but you know, for for we already acknowledge that people, you know, shouldn't be very deficient in vitamin D. So in vital essentially, you can interpret what's going on from the the mean of the population was around 30 and increase to about 42 nanogs. So, so these are averages and then we averages don't tell the whole story but at least this gives you a sense of what's going on and you can see here that if you look at vital so so this is roughly what the control group achieved and this is the intervention and you can see like you would predict no response based on the observational data the most of the response would be in the in the lower levels of vitamin D.

Now having said that there are I think some very positive results from vital that sometimes get ignored. So for for cancer mortality which was a prespecified endpoint u you can see that there is a reduction and you know and it's biologically plausible because you wouldn't necessarily expect a reduction you know at time zero or start taking vitamin D today. I don't think your risk goes down immediately for an endpoint like cancer mortality and you see very plausible after three three to four years reduction that actually got stronger when we excluded the first two years of followup which was prespecified and you had a 25% reduction in total cancer mortality. That's a pretty remarkable reduction. And when we actually looked at the the the end points in these large trials, it's hard to get very clean end points, but when we get the very clean end points, looking at medical records and making

sure these are cancers, there was a statistically significant 37% reduction in total cancer mortality. That's pretty impressive. Now vital was the largest trial but there were a few other trials and we did a metaanalysis looking at total cancer mortality and if you put there like three trials that had daily dosing you actually get a 13% reduction that was statistically significant and not much seen u with the trials that had large bowl of supplementation which is a an issue unto itself but the daily dosing did actually you know so so the available trial evidence do support a reduction in cancer mortality another area where vitamin D is potentially important is immunity and in vital when you looked at total confirmed autoimmune diseases you actually did see a reduction 22% reduction that actually was stronger when you excluded the first two years.

Again, you wouldn't necessarily expect an immediate benefit on a chronic disease. So, there was about almost a 40% reduction that was highly statistically significant. I view that as a positive result. Now, for for diabetes, there were this actually is not vital. These are three trials combined data from three trials that were in individuals specifically with pre-diabetes. And the trials gave that the doses were 3,000 IU daily 4,000 IU and then this is an analog of of vitamin D elder calcitol and you can see there was actually statistically significant reduction about 15 % 17% if you exclude participants who basically were not taking the medication. So but the intent to treat which is the most conservative result did give a positive result. And interestingly in those with pre-diabetes this is 10 trials and one endpoint was that they regressed from pre-diabetes to normal glucose and you can see every trial was in the right direction. I mean some were small and had wide confidence intervals but you put the studies together and there was a highly significant statistically significant reversion to from pre-diabetes to no indication of diabetes normal glycemic. So so these are you know pretty impressive.

Now we talked a lot about body mass index previously. You need higher vitamin D. In vital you can see when you stratify by BMI these are the baseline levels of vitamin D. You can see that the leaner people had higher levels. And so that the leaner people actually were were already above 30 on on average. And you can see they levels went up and a little bit higher in the vitam in the the lean group. Now it's become evident that for lots of endpoints we see benefits mainly in the leaner. So BMI 25 this is for any type of metastatic cancer highly statistically significant very highly significant and interaction that's significant a 44% reduction in total cancer metastatic cancer. Now, remarkably for invasive cancer, we actually did not see a reduction in overall in vital, but there was a 24% reduction in those that are lean. So, even for incident, not just cancer mortality for autoimmune diseases, which I showed that most of the benefit were was in people with BMI under 25. And then in the diabetes data that I just showed, they also stratified by BMI under 31, which was the median. And that's where they saw all of the benefit. So, it's actually quite remarkable that in these four separate analyses, highly significant interactions show up, which I don't think it's chance.

The the other point briefly I think that's an important finding from vital that I think is sometimes ignored is that in in terms of toxicity like sometimes the you know studies show

that there's no toxicity at high levels but you know one counterargument is that like well these studies are shortterm you know like in 6 months you may not see toxicity but maybe for long-term high levels but in vital there was absolutely no evidence for toxicity, hypercalcemia, anything. So, so essentially it shows long-term up to 6 years going from around 30 to like 40 to 50 nanogs. There's no evidence of adverse effect. So, so that does away somewhat with the long-term you know things that we're missing if with long-term relatively high levels. And then this is actually the only slide I have for mandelian randomization. Mandelian randomization you know it's a complex to process to interpret. I think it could be useful but sometimes over interpreted sometimes under interterped but the the main point I wanted to make is we actually did a a summary of all the the mandelian randomization studies in vitamin D and multiple end points and believe me there's a lot of interest in this. We had to go through over a hundred articles.

And I list here where where there are positive signals. And this is I'm not claiming that this proves a a causal effect, but the the nice thing about Mandelian randomization is that it's complimentary. It's not perfect, but because it's looking at genetic factors, it's not confounded by lifestyle or other factors. So, so does give independent evidence and it's a genetic factor that gives you some indication of long-term status because your genes don't change over life. So, so this is kind of like looking at individuals with genetically slightly higher levels of vitamin D. And for all of these endpoints, there was evidence of of benefit. So just in summary so RCTs are an important component of the evidence for vitamin D but I think we need to interpret results cautiously and many factors can cause a false negative. The actions of vitamin D are likely to be pleotrophic. For some conditions like CVD or fracture you know perhaps all you need to do is to avoid severe deficiency. For others cancer, autoimmune disease or diabetes, high levels and doses are likely needed. Emerging evidence suggests high atyposity blunts the actions of vitamin D's and benefits of supplementation are are clear in those without obesity.

And long-term RCT show that attaining levels up to 50 nanogs for for multiple years show no evidence of harm. And I think through the time I will end at this point. Thank you.

JEN >> Thank you very much Dr. Giovanucci. So now we get to enter the realm of vitamin D and pregnancy. And up next is Dr. Dr. Bruce Pollis who is a nationally recognized vitamin D researcher and was professor of pediatrics at the Medical University of South Carolina where his work has helped shape modern understanding of vitamin D metabolism during pregnancy, lactation, and early childhood development. Over several decades, Dr. Hollis has authored hundreds of scientific publications and especially well known for his research demonstrating the importance of adequate vitamin D supplementation during pregnancy for maternal and infant health outcomes. Dr. Hollis has played an influential role in advancing scientific and clinical discussions surrounding prenatal vitamin D recommendations, helping to build the evidence base supporting higher maternal vitamin D intake and routine monitoring during pregnancy. Welcome Dr. Hollis. And you wanted me to share your slides for you. So, let me pull those up.

DR HOLLIS >> All right. So, this is work that's been going on for at least 30 years.

And I'd like to thank help NIH for the funding that they pro provided and so let's go to the next slide. So here you have the current recommendations that go back years. So what we were told essentially by the M and before that the requirements for the subject on the left were identical or or slightly different than the person on the right and that if you supplement it to these levels which was 2 to 400 units a day that everybody would be okay. So if you give the infant 400 units of vitamin D and you measure 25 hydroxy in in their circulation, you get a profound increase in circulating levels. However, if you give that same dose to to Mr. Atlas here on the right, you don't even see a response. Next slide. How toxic is vitamin D? And unfortunately, you're going to have to hit these to advance the slide. The guidelines state that the prior to 2000 that you could not take more than 2,000 units of vitamin D a day. This is from 1997 M recommendations or it would be it would be toxic and those are ridiculous statements. That was an error an impediment to health. The new that has been talked about is 4,000 units a day which is much better. And the truth is intakes of 10,000 we know today are totally safe.

So the M position reported that an optimal circulating level of 25D would be 50 nanomles or 20 nanogs. The N also states that a level of 120 nanomoles are potentially harmful and that this this is odd in the human beings for millennia 25 hydroxy set levels have far exceeded this. So public health issue for vitamin D in during pregnancy. So, Carol Wagner and I, this is going back in 2001, looking at the recommendations, looking at what we saw in the clinics, looking at what we saw in our our our bu babies, it was evident in our minds that vitamin D deficiency during pregnancy was a serious health issue that affect both mother and fetus. And we needed to establish the vitamin D requirements of pregnant women as seen as vital to preventing vitamin D deficiency. Yet the institute of medicine made only slight slight changes in in the recommendations for vitamin D. So let if we go to fast forward or go a rear to 2002 we devised we wanted to do a randomized trial in pregnant women. So we designed this study and at the time we basically it was designed as a safety study. How much vitamin D did women pregnant women need to normalize their circulating levels? We looked at a few things like we were looking at the maternal skeletal integrity in infant because to be honest with you all the things that are important that we know today like prevention of pre-term birth preeacclampsia gestational diabetes asthma which is going to be talked about later by Dr. Weiss. We didn't even know if ask those questions. So not so we we had to go with the data and the information that we had and we divine this define the study wrote in an NIH grant big clinical grant for the time got a great score and when we came back from the study section we got the comments back that they said well this is all great but you know at the time the UL was 2,000 units and you want to give pregnant women 4,000 you wait a minute. Okay, so they forced us to go to the FDA and write a an application that essentially drug comp pharmaceutical companies had to write to conduct pharmaceutical studies and so we had we had to get an IND number from the FDA. Never had anybody been required to do that for vitamin D but we were required to do it. So, this initial study that was

started in 2002 or 2003 was a randomized trial of 400 2,000 or 4,000 units of vitamin D per day. Women, this is all published if and and anybody has any questions, they can contact me and and I'll go over this, but this was published in 2011, I believe. It's been cited well over a thousand times. So we we can did this study it was monitored like a hawk by the FDA. All right. And we had this IND number which was accessed by many people after to do many clinical studies outside of pregnancy because we had this I we had this this drug approval number to do these studies.

So we as I said it was monitored for safety efficacy with monthly 25DS 125 there was data monitoring committees that had to watch over all this and for adverse events go to the next slide. Okay, so we we published the the initial data, okay, in 2011. All the safety data, all the blood levels, all the the adverse events which were zero attributable to any vitamin D supplementation we were doing. So we found out what women, you know, what what the levels of of 25 would do during pregnancy. These women end started in the study in the first trimester which is about 12 weeks or so because that's when you see women coming in for pregnancy. The truth of the matter is that's really a weakness in these studies because a lot goes on in that first trimester where these all of these women with vitamin D deficiency when adverse events could be happening due to vitamin D deficiency and you have no control over it because they haven't entered your study. But when we went back a couple years later when when we knew that we could ask these questions, we went back and looked at the data and lo and behold in a so in a randomized trial although it was not in an intent to treat fashion because they weren't these out endpoints were not defined in the original study.

Again we didn't even know to ask these. So we went back and did this and so we if you look at the blue numbers on here, okay, those were significantly different when women got higher doses of vitamin D. These complications of birth we saw were actually real in a randomized trial. Okay, I I think I presented this maybe in in initially in 2009 and at a vitamin D meeting and was brutally attacked. How can vitamin D have anything to do with this? You know, why are you even asking these questions? So, this is this is the kind of hostility that we faced when we first started presenting this data that vitamin D really would have an effect on on complications of birth. Next slide. This slide was a study that was done by Dr. Sodlock in India. And as mentioned earlier, if you want to do vitamin D studies in our country or largely in Europe, you have to have the control group has to be in it has to meet standard of care. Okay? Which means pregnant women have to be prescribed a certain amount of vitamin D that they would get if they were being followed by a a a OB and which is 4 to 600 units. Okay. You can't do a study and give anybody zero. All right? Even though in as it stands in our medical care system, many people especially minorities are going through pregnancy exactly in that fashion.

They're not being treated. They're not taking their supplements. So what happens if you conduct studies where you have a deficient population? And this particular study was run in India. This was published in 2015 in clinical endocrinology by an Indian group and what they did was that they took a population of women half of them got supplemented with

vitamin D. It was bola supplementation which wasn't ideal but it has its advantages because it's 100% compliance versus compliance problems when we did our study that are largely unavoidable. But in the end when they looked at this simplistic looked at these groups okay of placebo which means there was ongoing vitamin D deficiency the entire pregnancy okay as opposed to the supplemented group which were intervened and there was a massive decrease in gestational diabetes preeacclampsia and pre-term labor. All right totally ignored by the by mainstream media. Next slide. This study was published in in 2018 after and it was it was done in Iran the s the under the same type of protocol that was that was performed in Indian study meaning you had a a a large group of women who were uniformly vitamin D deficient who entered a study half of which got treated half of which did not.

It was a very complicated field trial essentially a randomized trial. The results were frankly just incredible. Okay, next slide. So when this paper was was done and submitted to the places where people want to put high impact, New England Journal, Journal, Jamama, British Medical Association, one universal thing happened. They all rejected it. They said, "Nope, we're not publishing that." But if you look at the results from this Iranian dis study and this hazard ratio and if you look down here it's it's preeacclampsia pre-term delivery. Every single one of these things was dramatically decreased. If you look at at the effects of true supplementation into a vitamin D depopulation and I would relate this back, you know, I don't I don't have any evidence per se, but this would be what our our minority populations who get very poor nutritional care and prenatal care. This is what it would look like if you ran a study in our country where you gave no vitamin D supplementation to that group and then intervened in the other group. Unfortunat I mean you know we we just can't run that kind of study in in in our country. Lactation it's well known that human milk is a poor source of vitamin D for their nursing infant.

This goes back forever. Okay. It's true in a fact that it is human milk is supposed to be the perfect food except if a nursing infant is solely it was his sole source of nutrients they could get ricketetts and so we asked the question how how can this happen how how can human milk be replete in other nutrients but in vitamin D it's deficient to the point that the infants can get infants from infants could ricketetts from consuming only vitamin D breast milk. Next slide. So to Carol Wagner and I again conducted this study which led to getting another big NIH grant and what we did was we gave how much vitamin D would would women have to get to to make their milk adequate. So the the common practice was a nursing infant would get 400 units of of vitamin D orally and nurse from the mother. But what if you could give the mother enough vitamin D? How much would that be so that you wouldn't have to do that? The woman could take it herself, enough vitamin D would pass into her milk and she would pass it to the infant. So we carried that study out and this is measured levels of milk in a mother and a baby. So next go to the next slide. And what we found was when we gave women 6400 units of vitamin D, she passed plenty of vitamin D into her milk.

So you no longer had to supply the nursing infant with supplemental D. That infant was getting plenty of vitamin D just through the mother's milk. So, next slide. We designed

another NIH study that was carried out at our place in the University of Rochester. There were four, you know, we had three different groups again 400 a day to the mother, 6 2400 6,400 again is the FDA monitored study. Next slide. By two months the maternal 25D differed significantly among treatment groups. And what we found was the the infants that were getting their milk from mothers who had had higher levels of intake of 6400 to replete their milk did just fine. They they were the same as a standard of care which a infant would get 400 units. So it gave pediatricians an option to either recommend supplementation directly to the infant and nursing or the mother could take substantial amounts of vitamin D and supply the infant directly with her milk. And actually that's in use today. I don't think it's in use as much as it should be, but I know in certain practices in pediatric practices the pediatrician is giving that option. It just it has never made any headway in any of the recommend official recommendations in say in pediatric society that they go that route.

It's still just give it to the baby the mother don't worry about her and and so and and in that in this study again we never saw one single adverse event due to vitamin D supplementation. It was totally safe and I I always thought it was much better to go this route than give it because often times mothers stop giving the vitamin D to the infant nursing infant because it's a pain. Infant doesn't like it. They just don't do it. So, and there's real risks to not doing that. Next slide. So, the conclusions mothers currently taking 400 units of D will not provide Adam adequate vitamin D at her mop for nursing infant. You need intakes up to 10,000 when you give a I mean my own family has done this 10,000 units kids were great you know had infants have plenty of vitamin D and vitamin D is essentially during pregnancy not only for skeletal integrity which is relatively requires minor amounts but also the complications of birth such as preeacclampsia preterm birth neural development which I think Dr. Wagner. But I just want to relay one additional thing. You know that we've said that vitamin D really could be used to prevent preeacclampsia or preterm birth. And several years ago, it was more than 10 years ago, a small drug company came out with a injectable called 17 hydroxy progesterone.

It was used to prevent preterm birth. It was given preliminary FDA approval. So, it became used in in in clinics when women would go into pre-term labor. And there was only one problem. It didn't work. But this company, which was purchased by a bigger company for $700 million, continued to market this until about maybe two or three years ago when they promised to give more data, never showed up, and the FDA actually pulled the plug and wouldn't let them do it. So there's currently no treatment to stop pre-term labor. I'm I'm I I don't think I'm mistaken in that. But there is currently no approved treatment where this is looking physicians in the face and saying if you do this, especially to high-risisk populations, you will you will prevent a lot of that pre-term labor in preeacclampsia. Thank you.

JEN >> That was great. Thank you, Dr. Hollis. Dr. Carol Wagner is a neonatlogist, researcher, and professor of pediatrics at the Medical University of South Carolina, whose research has focused extensively on maternal, fetal, and infant vitamin D health. Working closely with Dr. Hollis, Dr. Dr. Wagner has co-authored numerous landmark studies examining vitamin D

supplementation during pregnancy and its impact on maternal outcomes, infant development, immune health, and pregnancy related complications.

Through her decades of clinical research and scientific publications, Dr. Wagner has become a leading voice in the field of prenatal vitamin D research and has contributed significantly to ongoing discussions regarding vitamin D recommendations and maternal child public health policy. Welcome Dr. Wagner.

DR WAGNER >> That my talk is entitled vitamin D deficiency in pregnancy and overlooked modifiable driver of maternal and infant outcomes. And I thank you for this opportunity to speak today. About something that obviously Bruce and I have been working on for a few decades and I'd like to focus on what happens clinically and biologically when vitamin D requirements during pregnancy and lactation are or are not met. Next slide. So as you've just heard from Dr. Hollis, vitamin D requirements during pregnancy and lactation are higher than historically recommended. And importantly, these levels are safe and achievable. The question I'd like to address is what happens when those requirements are not met. And so, biologically and clinically, vitamin D deficiency remains common among pregnant women in the United States. It disproportionately affects racial and ethnic minority populations and it is associated with meaningful clinical outcomes.

So we see increased risks associated with vitamin D deficiency linked with preterm birth, pregnancy complications such as preeacclampsia and certainly altered immune and placental function. Importantly for this audience, vitamin D status and deficiency are measurable and the whole aspect of deficiency is modifiable. So, who's most affected by vitamin D deficiency? So, black women, they're 20 times more likely than white caucasian women. Hispanic and obese women also have are at higher significant risk of vitamin D deficiency. These same populations already are at higher risk for adverse pre pregnancy outcomes. So vitamin D deficiency may be compounding existing disparities. Next slide. In a realworld cohort of over 15,000 pregnancies that were women that were followed at the Medical University of South Carolina, we see a consistent pattern that vitamin D status is strongly associated with preterm birth. Next slide. In this cohort of over 15,000 pregnancies, we observed a clear and consistent relationship between vitamin D status and preterm birth. So women delivering pre-term had significantly lower 25 OD concentrations and those with severe deficiency as you can see less than 12 nanogs per ml had nearly double the rate of pre-term birth.

Importantly, this follows a dose response relationship which strengthens the biological plausibility of this association. And as Dr. Grant said earlier, you know, looking at association does not translate into causality. But there certainly is a strong association. Next slide please. So taken together with earlier randomized trials and these combined data sets which we've we have listed here and we've published extensively we now see a consistent inverse relationship between vitamin D status and preterm birth across more than two decades of research. These findings really support the screening and addressing vitamin D

deficiency that that the effect it could have and it represents a cost-effective strategy to reduce preterm birth and as Dr. Hollis mentioned there really is not I'm a neonatlogist and so there is no at this time we have drugs that may delay you know contractions and so forth but we really do not have treatment for preterm birth. Next slide please. So the next question is whether there is biological plausibility between this association. Next slide. To step back and take a broader view, the data from the Kellogg studies and others suggest that vitamin D is not acting through a single mechanism.

Instead, it operates across three major biological systems that are central to pregnancy. First, at the level of the placenta, we see effects on angioenic signaling and placental development. Second, in the immune system and microbial environment, vitamin D influences immune mediators and is associated with differences in the vaginal microbiome. And third, at the level of fetal programming, there are epigenetic effects that may influence developmental trajectories. So rather than thinking of vitamin D as a single nutrient with a single function, which I think we're led to think that because we measure 25 hydroxy vitamin D or 125 and we see this association or this you know this tendency of one one measurement one single function. The evidence suggests it is acting across interconnected systems that are directly relevant to pregnancy outcomes. Next slide, please. So, vitamin D, as we've re recently argued in the American Journal of Clinical Nutrition editorial, vitamin D in pregnancy is better understood not as a single nutrient or dose, but as part of a developmental system that's operating across maternal, placental, and fetal biology. Next slide, please. One of the questions I increasingly find myself asking is what from an evolutionary perspective actually represents physiologic normality during pregnancy?

And we've heard about these studies and so Lux Walda and colleagues published looking at traditionally living East African populations in a sunrich environment and found that pregnant women naturally maintain substantially higher vitamin D concentrations than are typically observed in western populations. And following giving birth there's a rapid postpartum decline and to me and others these findings suggest that pregnancy itself may represent a unique developmental and physiologic vitamin D state and I think that we have to apply that through the lifespan. Next slide please. So if we extend this premise beyond pregnancy, the next question is whether these effects continue into lactation and early life. And what we see emerging data suggests that vitamin D does not just transfer into milk. It may influence the composition of milk itself. In particular, we see differences in human milk olosaccharides which are critical for immune development and the infant microbiome. And this raises the possibility that maternal vitamin D status is shaping early life biology through human milk. We've also seen differences in the proteomic profiles of women who are vitamin D replete versus those who are deficient over time.

Next slide please. And importantly these effects do not appear to stop at birth. Next slide please. So beyond pregnancy, the effects appear to extend into early brain development across multiple cohorts, including our own and international studies. Higher early life vitamin D status is associated with better neurodedevelopmental outcomes using validated objective measures of neurodedevelopment. Conversely, maternal deficiency during

pregnancy particularly later in pregnancy is associated with suboptimal neuro development. Next slide, please. So what we're beginning to see is that vitamin D deficiency may influence a developmental trajectory extending from pregnancy and into tr into early childhood. And I also opine that it extends throughout the lifespan. So beyond pregnancy itself, maternal vitamin D status appears to affect human milk composition including components involved in shaping the infant immune system and microbiome. And across multiple cohorts, higher early life vitamin D status has been associated with better neurodedevelopmental outcomes. So when we combine these findings we it suggests that vitamin D is acting across interconnected developmental systems during critical early life windows that persist across the lifespan.

Next slide please. So again taken together these data suggests that vitamin D deficiency in pregnancy is not simply a nutritional issue. It is common. It is disproportionately affects vulnerable po vulnerable populations and it's associated with outcomes that matter from pre-term birth to early childhood development and most importantly it is measurable preventable and treatable and addressing vitamin D deficiency represents a safe lowcost opportunity to improve maternal and child health outcomes. Next slide please. So in closing, vitamin D deficiency, as we've seen and is shown, is common in maternal infant health. Ultimately, this represents an opportunity to improve maternal and child health, not only through the treatment of deficiencies, but also through earlier support of biology during critical periods of human development. Next slide. Thank you. All right, that was fantastic. Probably my favorite subject when it comes to vitamin D. Thank you, Dr. Wagner. All right, so we now have Dr. Scott Weiss, who is professor of medicine at Harvard Medical School, co-leader of the systems genetics and genomics unit, and associate director of the Channing division of network medicine at Bringham and Women's Hospital.

He has been continuously NHLBI funded for 48 years with more than 1,000 publications in H index of 190 and he has been recognized among the top 0.004% of biomed researchers for his scientific impact. He is also an international expert on clinical trials in asthma including the de the dart trial. All right, welcome Dr. Weiss. My presentation and Human Makani's presentation are sort of coordinated. I'm going to present sort of what we learned from Vart and then he's going to talk about what what the next trial in pregnancy might look like. So next slide please. So in 2004 I was doing asthma genetics and genomics and we identified the vitamin D receptor as a gene for asthma. Then we did two observational studies where we demonstrated that maternal intake of vitamin D mostly from supplements was associated with about a 50% reduction in asthma and the offspring of the mothers. And after those observational studies, we designed and got funded by NHLBI the vitamin D antiatal asthma reduction trial. The scheme of which is shown on this slide where we enrolled women between the 10th and the 18th week of pregnancy. Had blood draw at entry and at 32 to 38 weeks. Randomized the women to 4,000 IU plus 400 IU in prenatal vitamins versus prenatal vitamins alone, which was 400 IU.

Followed them to make sure that they didn't have any adverse complications from the treatment. Looked at the mother at one year and the child at one and three and six years.

There were absolutely no complications whatsoever of the 4,400 dose. Why did we use 4,000? Bruce explained it in his talk. He had the IND for 4,000. If we had tried to use a higher dose, we would have had to go through the FDA and get a separate IND. His paper dosing paper had not yet been published when a vart started. So the path of least resistance was to go with the 4,000 IU. Next slide. So what did we learn? Well the effects of vitamin D treat treatment were statistically significant at 3 to six years for both asthma we for lung function at age six when we did a level stratified intent to treat analysis. What's a level stratified intent to treat analysis? It's basically considering the amount of vitamin D in the control group and controlling for that and then doing the standard intent to treat analysis. If you do just the standard intent to treat, the results were borderline significant at 3 years, not significant at six. But if you do the levels stratified intent to treat, which controls for the amount of vitamin D in the control group, the results were statistically significant.

We did a metaanalysis where we actually showed that the we could recover exactly the same effect a 50% reduction as was seen in in the observational studies. We also showed that the earlier in pregnancy u that the people women enrolled in the trial and got on treatment that there was an effect. Obviously, nutrient trials are fundamentally different from drug trials because there's contamination of the control group in nutrient trials. You see this in vital as Ed presented that the level of vitamin D in the control group in vital is exactly the same as in the treatment group at the start of the trial. They they never did an intent a level stratified intent to treat in a vital but it would be a useful exercise to carry that out. This method of analysis was initially proposed by the late Bob Heene as a way of overcoming the effects of the the effects of vitamin D in the control group. So next slide. Time of enrollment matters. The the the the window for airway development in the fetal lung is between the fifth and the 10th week of pregnancy. So in in Vard we were enrolling people between 10 and 18 weeks but ideally you would get them at conception. I I agree with what Carol said you you know this is a continuum.

Vitamin D is necessary at every stage from the point of conception right through the first few years of of life. Dose matters. The higher the dose the better. At the 4,000 IU dose, 70% of the women in Vart achieved u a level of 30 nanogs or better. But the ones who did not were the women who were obese. And that was 30% of the women who never got to 30 nanogs per ml despite the 4,000 IU. So BMI matters. It it matters in pregnant women. BMI is associ higher BMI is associated with preterm birth. It's associated with preeacclampsia. A and these adverse pregnancy outcomes both pre-term birth and preeacclampsia are major risk factors for childhood asthma and also for neurocognitive development. So all of these outcomes are interrelated and part part of more of a systems approach to these health outcomes. I would like to point out that each one of these is about a12 billion a year cost to the health care system. Child asthma we 40% of kids we in the first year of life that's down to 20% by age six of half of those are actually diagnosed as having asthma and then obviously the collection of omix samples is critical to the interpretability and the biologic understanding of clinical trials. And so that was something that we did in Vart has been very important.

Paid off in a in a big way. Next slide. So 50% reduction you could probably at a suboptimal dose we could probably get to 85 production percent reduction in asthma if we were at an optimal dose. The risk of asthma is a continuum. It's not categorical. The higher level of vitamin D, the earlier in pregnancy, the lower the risk. Long-term protection is linked to change from the baseline level with the intervention and prevention is directly linked to early intervention with preconception being the the optimal and this optimal serum level is 60 not 30. To give you an idea the magnitude of the problem 70% of pregnant women have levels in the United States have vitamin D levels less than 30. 99 to 100% have vitamin D levels less than 60. I think that's my last slide. Just want to acknowledge the people who were worked on Vard and Bruce who was on our me key member member of the control data safety group at the Channing. So I'll end there and turn it over to Human.

JEN >> All right. I'll I'll introduce him first real quickly and thank you for that. Dr. Humman Mir Zakani is assistant professor of medicine at Harvard Medical School and faculty investigator at the Channing division of network medicine at Bringham and Women's Hospital.

His research focuses on maternal and child health particularly adverse pregnancy outcomes, early life respiratory disease and modifi modifiable prenatal exposures such as vitamin D. Today he will discuss trial design considerations for optimizing vitamin D supplementation in pregnancy to improve maternal and child outcomes. Right, welcome.

DR MIRZAKHANI >> Thank you so much. I appreciate and thanks for having me and I just mentioned that I had the honor of working with Dr. W last 13 years and glad to present here. So previous talks paved the way for me make it easier to summarize things and approach about the future vitamin D supplementation during the pregnancy and how we can optimize that and what are the practical issues that we should consider that. So the key question about the trial is that we know that why do we need another vitamin D trial in pregnancy? There is no doubt that pregnancy is a key window during the life and because of the placentation and fetal development in different areas. Dr. Weiss talk about the early effect of vitamin D on early lung development and also the brain development and neurodedevelopmental development in fetus. So we know that supplementation could reliably increase vitamin D even with low doses.

But different trials tried different doses and the outcome was remained still mixed. Some of them they got the results, some of them after doing the secondary analysis and some of the studies were solely just like observational. As mentioned prior trials try different and they start at different time they target different population and also the primary end point was different too. So that makes it a key point for the next trial to answer an optimization question meaning that who and when and what level and which outcome should be considered and to be approached. Definitely there are different outcomes to be considered

for the effect of vitamin D supplementation and based on the current evidence adverse pregnancy outcome child asthma and neurodedevelopmental the disorders are the on the top layers that they have evidence in support of the preventing of them. Definitely for a short trial design presentation, we can have two competing concept which one could be a pragmatic approach and the other one could be a mechanistic approach and gives us more information that how vitamin D works. Prior we in presentations before it was very helpful that the do what discussed about the reliable dose and what is they're based on the different recommendation like M and society and ACOG all has different recommendation between 600 up to 5,000 and it was well pointed well pointed that up to 10,000 international unit per is safe and no toxicity has been reported in terms of the vitamin D supplementation in adults and pregnancy.

But in trial design there is one key point that those alone should not be the central controversy. There are so many other factors early initiation body mass index as Dr. Wise mentioned baseline vitamin D level and early target attainment all of these factors that could be considered aligned with the applied dose. Definitely doing the intent to treat analysis as primary is important. However, there are so other studies have already shown including radar the achieved level and prespecified stratified analysis by EMI could be very important too. One key as I mentioned before that maternal adverse pregnancy outcome and also Carol mentioned to and Dr. Hol is that all of them could be as a composite outcome or individual outcome pre-term birth and preeclampsia has a specific importance because they also increase the risk of other type of offspring health issue related such as asthma and put them at neurodedevelopmental disease risk. Overall, we know that the prior studies had been either underpowered for the right end point or they applied low dose or they applied different doses or started too late during the pregnancy or if all of the these factors were considered they failed to account for differential target attainment.

I want to give you two Dr. Wise talk about the BMI and this is slide that you can see that those who in vart those who received high dose of the vitamin D at least one-third of them among the obese obese pregnant women they remained u vitamin D insufficient at the cutoff of 75 nanom mole per liter which equals to the 50 nanog per ml if we consider the cutff of 20 by this drops to the 15% still it's a very considerable rate that they did not reach to the sufficiency based on both of the cutoffs and one interesting point that I want to share is about the as a cumulative exposure so that's a very important factor that we did a pharmaccoinetic analysis in reart and we assess the cumulative exposure to vitamin D during pregnancy as you can see that K U Z area under the curve at Z at zero it corresponds to 30 nanog per ml or 70 nanom mole per liter and each standard deviation above this level decreases decrease the asthma and recurrent we in offspring by 25% and by six years it was 70%. So the point is that the trial design should also consider just in addition to to the dose not only the dose late pregnancy level is important but cumulative exposure across pregnancy is very important too.

This could be also important because even if that they are receiving the supplementation for other factor genotypes and other things there might be some fluctuations across the level

due throughout the pregnancy. So based on these factors that we discussed we can just introduce two concept or approach for a supplementation trial. The first one I call it a pragmatic trial for feasibility which we provide prenatal supplementation and we consider the maternal primary outcome for the trial. The population target will be planning those who are in planning of the pregnancy. That's the ideal population or enrolled less than 30 weeks of the gestation and design will be double brand double blind randomization which will they will be randomized to standard prenatal versus higher dose vitamin D similar to vart but definitely possible higher dose will be desired and also based on the two approach could be considered based on the BMI one approach with the single to high dose across Ross all BMI categories. The other one is to stratify the doors across the normal pregnancy, overweight and obese. The primary outcome as I highlighted the adverse pregnancy outcome import importance specifically also Carol and Bruce mentioned highlighted the pre-term birth and pre-clansio.

Have similar results in vart or also Bruce mentioned about the composite adverse outcomes which there was a significant in one of the studies in the trial that he had as a comp in association with vitamin D level in such a trial secondary child outcome child outcome will be secondary which include asthma and the neurocognitive development and we can consider that autism a spectrum disorder as a exploratory long-term followup because they need to be tested at 8 or 10 years after the supplementation and the trial. Definitely, it's important to follow up maternal for hypertension and cardioabolic outcomes. These are another area that vitamin D has shown some efficiency in prevention of them and affecting the maternal health. One key point that I want to mention in var that we have shown that pre-term birth and preeclampsia increase the risk of offspring asthma and recurrent we and also affecting the neuro developmental assessments. So these are all supporting aapo focused maternal trial design. However, if we want to have a more comprehensive approach, more mechanistic and just understanding which which exposure window might be important comparing prenatal versus post-natal then we should just consider a trial design of by maternal child supplementation kind of a factorial design and we have four arms two arm as a control child maternal two arms as a supplementation or treatment.

On in child and maternal. In such a trial, primary outcome will be child outcomes, child health which include child recurrent we and all asthma and also the cognitive and neurodedevelopment assessment and disorders at ages of four and six years continued by 10 years for rarer outcomes such as ASD. And here maternal APOS will be considered as a secondary outcome for the pren and and all other prenatal disorders that we might just see during the pregnancy. BMI should be considered in the and planned as a level stratified anal along with the level stratified analysis and intent to treatment approach. Regardless of whatever any any one of these two approaches that we consider, there are some key elements that should be harmonized and included in both of them. We should just start supplementation as early as possible. I mentioned that ideally preconception or at least less than 20 weeks of the gestation. Definitely we should measure the baseline of vitamin D 25 hydroxy in all participant and we talk about the importance of the BMI and stratify based on the BMI include that either with different dose supplementation or we include it in the

analysis. One other key point is that accounting for the baseline and 20 f hydroxyd level because as discussed by other presenters it might not be ethical to only enroll those who have deficiency into the trial and there might be some controls with higher level of the vitamin D levels and also adherence we have shown in readart could be important factor at the level of the for 10% percent change in adherence.

We might have one or two unit differences in the level of the vitamin D. However, this level is different across the BMI category too. Another key point to consider is defining the target that we want to attain and this is important from two aspects not only by the level by the timing. As soon as possible we achieve the sufficient level ideally we want to be more than 40 nanog per ml. The result could be much much different from just like a later some some of the pregnant women with even with a high dose they might reach after three or four months to that level. We also talk about the considering the cumulative exposure and that that we should be included in as a pre-specified exposure metric in the trial because it could just show how much on average during the pregnancy women has been exposure to the vitamin D level throughout the pregnancy from the beginning to the end of the supplementation and it's very helpful consider putting that in aligned with the adherence concept and the key point is that not only how much vitamin D level is achieved but it's important that we know how early and how sustained it is and I put here a comparison of two approaches side by side but regardless of either of them a more comprehensive approach a more pragmatic approach the final message is that the next pregnancy vitamin trial should determine for whom, when, what level and toward which outcome supplementation works best.

So here I just want to acknowledge all those whose work and just inform all these ideas and also Dr. Weiss Dr. Leon we collaborated in Voc for the last 13 years. Thank you so much.

JEN >> All right well we are going to be going over time. I hope everybody can stick with us. We still have a few presentations and they should be pretty short. But if not, it's all good, right? We're all here to learn from each other and this is going to be recorded and shared afterwards. So next up, we have Dr. Le frame who is chief well-being officer at good bacteria executive director of the GW office of integrative medicine and health associate professor of clinical research and leadership and physician assistant studies at the George Washington University School of Medicine and Health Sciences. A translational health leader and microbiome researcher. Her work focuses on the microbiotic gut brain immune access and nutritional immunology, including a big focus on vitamin D. She co-hosts the GW Integrative Medicine podcast and co-founded the GW resiliency and well-being center. Dr. Frame also serves as chief medical officer of Reondite Consulting and advises multiple healthc care and biotech organizations advancing integrative pathways to well-being and whole person health.

Welcome Dr. Frame.

DR FRAME >> Thank you so much. So while I do do a lot of things I have no relevant disclosures to this particular talk. I'm going to talk about vitamin D and immune health and particularly focus on stress testing those two components. Let's get moving here. All right. So, first vitamin D is really important in immune competence and physiological stress kind of stress tests those things. And what do we mean by that? So, hospitalization, surgery, acute illness, these things are stress tests for the immune and and metabolic system. And so at these time periods we see an increased inflammatory burden, an increased immune demand, increased tissue repair perhaps, and decrease decreased philosophical reserve. So we don't have as much leeway there, not as much resilience. And so basically what we're seeing here is the clearest consequences of low vitamin D status really emerge under these cases of physiological stress. So while a lot of the the studies that have been presented so far are very meaningful it may be that we could actually get a clearer picture by looking at these cases where there's this larger stress component. So vitamin D is really important for the immune system. It's important for a balanced immune response.

Why is that? Well, vitamin D is actually an immune regulatory hormone. So while it's a nutrient, it's also a hormone and affects the way that our immune system reacts. It makes it act in more of a homeostatic way. The balance idea, right? So, what's happening during balance is the immune system is surveilling. It's looking for pathogens. It's looking for cancer. It's it basically it's doing its job, but it's not raising alarm. Now, if you have insufficient vitamin D, what happens is your immune system is going to be disregulated. Now, what that means actually varies from person to person. It could mean autoimmunity. It could mean an inability to fight off infections. But every aspect of the immune system is really touched by vitamin D. So the innate immune system, that first line of defense, the adaptive response, those T- cells and B cells that get in there and learn what's going on and really come to the rescue. In the second line, regulation of inflammation, so resolution of inflammation after an appropriate immune response. It vitamin D is really important for that barrier integrity. So the ability of the different barriers inside our body to actually act as that first line of defense really important to have vitamin D in that immune tolerance.

I kind of alluded that already. You know autoimmunity is a a problem of of immune tolerance, poor immune tolerance. So insufficient vitamin D really loses that immune tolerance aspect where we can, you know, attack ourselves or attack food antigens, things that are inappropriate for the intestine to respond to. And then this last box over here is the one that I get most excited about is it works in a system, right? We can't take this thing out and and look at it by itself. So it's part of our metabolism. It affects our microbiome and the environment that our bodies are in. Okay. When we're talking about hospitalizations, infection, acute care, what are we looking at in the literature? So we've seen associations. Lower vitamin E status has been associated with increased respiratory infections, particularly upper respiratory infections, the ones that we often get the most. Increased hospitalization risk, longer hospital stays, which I'm putting this asterk here because the longer you're in the hospital, the more you're having that immune and physiological stress.

So things can actually compound there. So this is one of those factors that we really want to put a pin in and say this one's really important to look at.

And similarly, we see an increased ICU severity and worse critical illness outcomes in those that have lower vitamin D status. With a big a big caveat. So, a lot of this is observational evidence, which we've talked a lot about today and some of the issues with that and the RCT findings. And they're not always consistent, the observational evidence and the RCT findings. There's been a lot of discussion as to why that is. So, I'm not going to beat a dead horse here, but just highlight a couple of potential reasons that really are important in this particular area. One being baseline variability. Where are these people starting? Are they coming into the hospital vitamin E deficient? That's likely going to increase their risk. And then a failure to achieve meaningful biological status. Right? So if you're not giving a large enough vitamin E dose to actually improve their baseline status, you might not see the same thing in an RCT finding as you would as in these observational studies. Surgical outcomes, recovery, and wound healing. This is actually what I did my doctoral dissertation on. So I'm a little bit passionate about this one. It's in many cases a factor that we can very quickly treat prior to surgery, especially if we're talking about elective surgeries like joint repair, beriatric surgery.

We have time to plan and we can replete people with vitamin D prior to prevent these complications. The biggest ones are wound healing and dehissance which is when the wound actually reopens after surgery. Surgical sight infection, recovery trajectory, so how quickly it takes them to get back up on their feet. Rehabilitation capacity, how much time can they spend in physical therapy or physiootherapy depending on what country you're in. The ability to spend sufficient time and effort in PT is a real big predictor of that recovery trajectory. So that's an important factor. And then overall resilience during recovery. So are we having these ups and downs? Are we be able to like bounce back from bad days? Vitamin D seems to be predictive of that. And overall recovery is actually a process, right? It's not just any one thing. And the immune system, our metabolism, the endocrine system, tissue repair, inflammation resolution, all of those are important factors and all of those are touched by vitamin D. So this is not simply about surgery as an event. Vitamin D status actually shapes the body's reaction to that event, right? The ability to overcome that acute injury and inflammatory and immune stress, metabolic demand, tissue repair and recovery are the three main components that are really driving that.

Okay, vaccine responsiveness. So, adaptive immunity is the the ability of the body to learn how to react to something. And that's the whole premise behind vaccines is we give it an antigen, the body learns to react to it, and then when it sees the real thing in real life, it will react in a positive way. Now, if you don't have sufficient vitamin D status, that doesn't work so well. We don't see a great adaptive immune response. We don't see a sufficient antibbody production or viral tighter production after vaccination. So essentially not getting enough vitamin D and getting vaccinated is is not getting the full dose of the vaccine in some ways. Then the immune response quality and coordination. So the ability of the immune system to kind of really learn that and then in followup to be able to actually swoop in and create that

acute immune response that will hopefully rescue you from the pathogen that can be affected with poor vitamin D status. So I just want to point out that I'm not saying this is necessarily a replacement for vaccination. Ideally you'd be doing both. Having a strong immune system is always going to help prevent you and then having your immune system learn how to protect itself with vaccines is also very important.

But it is a modifiable factor, right? So we know vitamin D status is really important and it's most relevant in groups that are aging, groups that have been hospitalized during that perioperative period and chronic disease. So these are definitely groups that we should be looking at vitamin D status in, right? They should be generally screened. The broader implication is that vitamin D actually right it's effectively shaping the immune system and how it's responding. So to me this really reinforces the value of this as a proacti proactive status assessment, right? We don't want to reactively look at vitamin D. We want people to have sufficient vitamin D kind of just regular before they get sick. That's really the ideal way to treat this because you don't know when you're going to get in a car accident and end up in the hospital. So having sufficient vitamin D status will really help protect you in the long run. Okay, clinical implications. So from the literature, it seems quite clear we need to have this proactive assessment. We need to actually test what the vitamin D status is and not just make assumptions, right? Not just saying, oh, the dose in your multivitamin is enough or on the flip side saying you need two or 4,000 international units without actually testing, right?

We need to know your number. Then we need to stratify by risk. We've identified many different factors that can really put you at risk for vitamin deficiency, adoposity, aging, medications, and gut health. All of those things are things that we can measure or can really come to actually understand relatively easily. Then these approaches need to be individualized. Because we're starting at different baselines, you have the different absorption rates, different metabolism, different synthesis when you go outside. So you really need to know what that individual person's status is and how they're reacting to the supplement. And so because of that, we need to treat the target model, right? We're not just picking a dose and giving it to everyone. Even if we know XYZ about them, it doesn't necessarily mean they're going to react like every other person that has XYZ category. So really looking at the serum levels as the driver. And I would I would use this as a a parallel to acute care. So it's very common for someone to be admitted for acute care where we routinely optimize their fluids, their glucose, oxygenation, hemodynamics, all of these elements. And I would argue that nutrition and therefore immune readiness deserve the same consideration.

So this would just be part of your checklist in acute care, making sure you have enough vitamin D status. And we did have some people talk about that earlier. So I was excited to see others thought so as well. So in my mind, the question is no longer whether variability exists, but how we incorporate variability into evidence-based personalized whole person care. So what does that mean? For me, it's really about timing. Timing is critical. A correction after the acute crisis is likely too late. Even though it's something we can also do, I would prefer us to be actually being proactive. The timing helps explain why we see mixed

findings in RCTs. A lot of times what we are having is an event and then we are treating vitamin D and seeing how the outcomes work and my argument is that is too late and while it's better than nothing it is not the optimum way to handle this. So looking at status before the stress drivers is really what's going to drive recovery and rescue dosing cannot simply reverse early dysregulation. It's it's the immune system takes a while to recover and so having that rescue dosing while beneficial is likely insufficient in many cases and so I would call for riskbased screening in public policy really identifying those high-risisk groups before surgery illness pregnancy we're really kind of just generally knowing at risk groups because anyone could get into a car accident and end up in acute care.

So the focus on preventative public policy moving from reactive treatment to proactive optimization across the life course. We talked a lot about how the it's important in the maternal fetal transition. It's also important you know in different parts of our life as we are growing bones and whatnot. So just kind of across the life course we need to know that we're getting sufficient vitamin D. And then finally at the population level we need to have equity and address modifiable status risk factors. Right? So, we know certain groups are at higher risk than other groups, and it it doesn't seem right to not treat those groups just because we're say, "Oh, most people are probably okay." and I would argue that today I think we've shown that most people are probably not okay because we spend too much time indoors. So in summary, please please think about proactive optimization instead of postcrisis rescue in the opportunity to translate vitamin D into better public health. And with that I will stop sharing.

JEN >> Excellent presentation Dr. Frame. Thank you. So next up we have Dr. Richard Chang who is an NIH trained physician scientist and practicing clinician focusing on nutritionbased systems approaches approaches to chronic disease.

He has been developing an integrative framework referred to as OM systems medicine that brings together orthomolecular, metabolic and systemsbased perspectives. His he serves as editor and chief of the orthomolecular medicine news service and as a board director of the Rordian clinic with his work centered on nutrient biology, chronic disease prevention and a systems level cont and systems level contributors to health and disease. Dr. Chang, are you ready?

DR CHENG >> Well, okay. Well, thank you, Jen, for the introduction. I would like to briefly discuss why clinical responses to vitamin D can vary so dramatically between individuals and why a systems oriented perspective may help explain these inconsistencies. From a systems medicine perspective, vitamin D should not be viewed as merely an isolated nutrient, but rather as part of a broader biological reg regulatory network. And for disclosure, I also serve as chief scientific officer of DORB, a nutrition company based in China. Well, most people have heard that vitamin D is important. Yet, clinical results are

often inconsistent as we discussed by many experts today. Some people respond dramatically while others show little improvement despite supplementation.

Some studies show remarkable benefits while others show minimal or mixed effects. Public health officials and the public are understandably confused. But perhaps the issue is not vitamin D itself, but how we understand human biology or systems biology as several experts alluded to today. Vitamin D is often discussed as if it affects only bones or calcium metabolism. But in reality, vitamin D influences multiple physiological systems simultaneously, including immunity, inflammation, metabolism, endothelial function and mitochondrial activity, neuroendocrine signaling and gene expression as many particularly Dr. Hollik in his first lecture mentioned. So this may help explain why vitamin D deficiency has been associated with such a wide range of chronic diseases. Importantly, it also suggests that vitamin D should not be viewed as an isolated nutrient but as part of a larger broader biological regulatory network as shown in this diagram. Now this is important. I think one missing concept in my view is biological barrier integrity. Vitamin D does not act on just one organ or on one disease. It helps support multiple biological barriers including the gut barrier as we know lung barrier, vascular endocy and more vascular barrier, skin barrier, the eye and even the bloodb brain barrier.

When these barriers become dysfunctional or leaky, the result may be chronic inflammation, increased infection, susceptibility, immune dysregulation, and a greater vulnerability to chronic disease. This systems level perspective may help explain why vitamin D responses so dramatically between individuals. So this is what I call systems level systems systemic leaky barrier syndrome framework. So this is a simplified illustration as we are very familiar with as the in the leaky gut. So what we mean bio I mean biological barrier healthy biological barriers are selective and protective. They help keep harmful substances out while allowing nutrient signals normal immune communication to function properly. But when these barriers become inflamed or dysfunctional, they become more permeable. Some sometimes we're referred to as leaky. This may allow toxins, pathogens, inflammatory triggers, and undigested particles to enter the bloodstream and activate chronic immune responses. As in the leaky gut. However, this doesn't happen to only leaky gut. We can have leaky brain bread I mean blood brain barrier causing brain problems. So importantly this concept is not limited to the gut. Similar barrier systems exist in the lungs the vascular endothelium skin and the blood brain barrier.

As I just mentioned, from a systems medicine perspective, vitamin D may help support the integrity and the resilience of these biological barriers throughout the body, protecting us from various diseases. So, two people may have the same blood vitamin D blood levels yet experience very different biological responses. Why? Because vitamin D biology is highly individualized. Response may depend on inflammation, metabolic health, nutrient co factors, different diets you eat, lot of ultrarocessed foods you eat, body composition, sleep, stress, genetics, and overall physiological resilience. Vitamin D does not function in isolation, which is critical. It functions within a complex biological system and the systems oriented perspective may help explain why vitamin D studies often produce inconsistent

clinical outcomes. As a clinician, this is particularly important. Clinicians should not treat a single symptom, a single issue, but a whole body. This concept may help explain why some individuals respond poorly to vitamin D despite apparently adequate blood levels. Inflammation, metabolic dysfunction, oxidative stress, barrier impairment I just mentioned, and other chronic physiological disruptions may interfere with vitamin D signaling pathways and the receptor responsiveness.

In this situation, the issue may not simply be vitamin D deficiency alone, but reduce the biological responsiveness to vitamin D itself. From a systems medicine perspective, improving vitamin D function may therefore require restoring the borrow broader physiological environment, not merely increasing supplementation. So traditional reductionist medicine often asks as illustrated by some of the earlier speakers Dr. Hollik, Dr. Grant and Dr. W, Dr. Sunnil and a few others. So the traditional like I mentioned medicine asks which nutrient affects which disease but but systems medicine asks a different set of questions. What impairs resilience? What increases inflammatory burden? What weakens biological regulation? What disrupts metabolic flexibility? As several experts on today's panel emphasize, vitamin D should not be viewed as an isolated single nutrient. Its biological effects depend on a much larger physiological networking involve magnesium, vitamin K2, metabolic health, immune regulation, mitochondrial function, inflammation status, and the biological barrier integrity. From this perspective, vitamin D is less a statalone molecule and more of an integrated systems regulatory network.

OOM systems medicine is one systems oriented framework that attempts to integrate root drivers, biological mechanisms and physiological resilience into a more unified understanding of health and disease. So from a public health perspective, this means we may need to think beyond isolated nutrient recommendations alone. Vitamin D likely works best within a healthy physiological environment, one that includes metabolic health, healthy diet, good sleep and circadian alignment, nutrition in sufficiency and lower inflammatory burden. Health is not linear. It emerges from the interaction of many interconnected biological and environmental factors. And this may be one reason why public health strategies focused on only one variable often produce inconsistent outcomes. So to summarize, first vitamin D is a systems regulator not just a nutrient. Second, biological context matters. Third, vitamin D resistance may be a rare may be rare and clinically important. Fourth, supporting the broader physiological environment may improve vitamin D responsiveness. And finally, a systems oriented approach may help improve long-term public health outcomes. Final message, the future of public health may depend less on isolated interventions and more on restoring human biological resilience.

This is the central philosophy of integrative also molecular medicine systems medicine also molecular medicine pioneered by Linus Pauling and colleagues over 50 years ago helped establish the principle that the body's nutritional and molecular environment profoundly influences health and disease. Today integrative or molecular system medicine expands upon this foundation by integrating nutrient sufficiency with metabolism, biological barriers, inflammation, endocrine regulation and systems resilience. The author Molecular

Medicine News Service or OMNS has served this field for two decades as an independent educational platform dedicated to science-based nutritional and systems oriented medicine. If interested, please get feel free to scan the code to subscribe to OMS Interactive. Thank you very much, Jen. Over.

JEN >> Thank you very much, Dr. Chang. Okay. We have our last speaker and then I will close and we will go into open Q&A. So hopefully you guys can all stick with us a little bit longer. I apologize for going over time. So I would love to introduce Dr. Beth Sanford who earned her BSN and MSN in rural health nursing with a specialization in nursing education from the University of North Dakota and completed her DNP in public health and policy.

Dr. Sanford later earned a post-graduate certificate in applied clinical nutrition to close the research practice gap to address vitamin D deficiency in patients and populations. Dr. Sanford is a full-time graduate nursing educator and is a director of education and clinical practice for grassroots health. She is the current president at the North North Dakota Nurses Association and the North Dakota Nurh Center for Nursing and she advocates for nurses and nursing students across the state and nation. Welcome Beth.

DR SANFORD >> Thank you everyone. I have really enjoyed listening to all the presentations of my distinguished colleagues and I wish I had time to edit every slide of my presentation just to reiterate the wonderful things that I've heard today. I'm going to be closing talking about the implementation of vitamin D science into policy, population health, and practice. So, we could see from all the presentations today, vitamin D science has grown significantly in the last decades. Vitamin D is crucial for genetic and cellular optimization. Current one-sizefits-all dosing recommendations are not effective to achieve optimal 25HD serum concentrations and improve patient outcomes and population health.

Vitamin D optimization is a modifiable risk factor and preventing health disparities. And evidence suggests that 25 optimization thresholds are body system specific ranging anywhere from 30 to 80 nanogs per milliliter, even higher for special conditions. You know, as I continue to in my career to review the vitamin D science, it's clear to me that we lack a framework that organizes risk in a way that patients and populations actually experience it and optimization best practices in a clear way for decision makers so that they can make the best decisions possible to support our population health and our clinical practices. So, I'd like to introduce something that's a work in progress that I'm calling the vitamin D risk ecology. And it's a framework that I developed to help understand and anticipate vitamin D risk and optimization of best practices. On this first slide, I'd like to address the three domains at the top of the model looking at environmental context, population health, u population vulnerability, and individual risk profile. These domains remind us that there

that risk is partially shaped by where people live, by where we work, by most of us within the same geographic area for most of our life.

The next area of population vulnerability reminds us that some groups may benefit from earlier intervention and targeted prevention strategies like I've heard from my colleagues today. Looking at pregnant women, those with darker skin tones, occupational risk, including college students who I work with, and finally that two individuals may live in the same city, eat similar diets, receive similar supplementation recommendations, but their biological response may differ substantially. These three domains make up the ecology of the vitamin D risk, vitamin D deficiency risk. And next I will address just reminding us of some symptoms of vitamin D deficiency. So some common symptoms. This isn't reflective of all the symptoms of vitamin D deficiency by any means. But it is a fairly significant list and it's important for patient followup and also important for insurance coding. I think probably the number one comment I get from clinicians is well vitamin D testing is not covered by insurance. Actually, it is depending on how we document. So, documentation and coding for insurance purposes is very important. So these are some of the symptoms that can that can clue a clinician that their patient may be vitamin D deficient, fatigue, generalized weakness, sleep disturbance, cognitive impairment such as impaired focus and memory, headaches, mood imbalance, for example, depression, anxiety, poor stress management, neuromuscular pain, postsurgical pain, frequent infection, infections, including hospitalacquired infections and postsurgical infections.

As I said, and I can't emphasize this enough, these need to be specifically documented in the patient's record and need to be followed up on. And this is so important for insurance coding because with these symptoms, you can justify presumed vitamin D deficiency. Now, let's go back to our optimization continuum and we'll look at what the next steps are. So this portion of the model is actually adapted from a 2022 cycle of best practices for addressing vitamin D deficiency that was developed by grassroots health executive director Jen Aliano and myself. After assessing risk in our patients which includes that environmental context, population var vulnerability and individual risk and identification of symptoms, then we would look at either coding as a screening or testing for our patients testing that 25HD. And then once we get that result, we can look at calculating that individualized dose. Now, this is where Grassroots Health has really done some great work is that they've developed evidence-based calculators where you can input your patients weight, current serum concentration, and you can come up with a personalized dosage recommendation. The clinicians that I've worked with that have implemented the use of this calculator have just said that it's taken so much stress off their shoulders.

It's just a really quick e tool that they can input that information in and they can boom they can have a recommended loading and maintenance dose so that they can not only achieve but like our presenter said but m sustain and maintain that that serum concentration for maximum optimization for their patients. And then the next step of course is to educate our patients. We want to empower them with that knowledge to address those modifiable risk factors and with what are practical strategy they strategies that they can do to optimize

their sun exposure and optimize their vitamin D with use in nutrition. Maybe their magnesium is not sufficient things like that. So how can we individually educate our patients for maximum obser optimization and then in addition it is our responsibility as that clinical team to help the patients with followup and to monitor that status so that it it stays in in consistently in that optimized fashion. I know for example you know if somebody has something come up it can change what their needs are. For example, I had my mom so that she was consistently hovering around 60 nanogs per mill. And I and you know, she only had to be tested a couple times and we knew, okay, this is the dose that keeps her about 60.

Now, she unfortunately got an infection from a tooth procedure cuz she didn't take her antibiotic like was prescribed and she ended up with sepsis. We had just had her vitamin D tested and I with within 30 days she rapidly was depleted from 60 to 30. So it shows how quickly under pressure under stress the body will utilize that vitamin D. And thankfully because of one of Dr. Wimluance's articles I was able to see that in action that my mom's vitamin D was over 60 she had a 97% chance of surviving sepsis and she did. So that's my personal recent great story about vitamin D. But in general we want to dose and monitor and follow up for that general recommendation like our panel said between that 40 and 80 nanogs per mill based on the spec the patient specific risk history and health concerns. I always tell my friends if you have a family history of breast cancer you don't want to be hovering around the low end right? We want to see what the research says and the research says if you have a family history of cancer you want to be higher than that and so just remember normal range is considered 30 to 100 nanogs per mill and that's with several of our big laboratories saying that these are normal and I want to make a note that these best practices are really for high resource countries and regions obviously this isn't practical across the globe but we're not covering that in this presentation today and that's something I cover in some of my other work that I've done.

But this is very practical and high resource regions and countries. So lastly I want to move back to the anticipated outcome section of the diagram that's to the right of the arrow. And if we follow this model and we look at precision public health, which identifies environmental risk, population vulnerabilities, it allows regions and communities to implement targeted prevention strategies that will strengthen their overall specific health. And that's going to look very different. And if if you live in the northwest part of the United States, for example, where you have a lot of cloud cover and a lot of rain compared to if you're in the southwest where it's very high heat, but people may be causing their own vitamin D winter by going indoors. So, just to give you a few examples, I live in the northern plains where it's so cold all the time, we don't even get UVB rays hitting the earth for 6 months of the year. So we have a very different strategy than our colleagues in the south of how we need to keep our population's vitamin D serum concentrations high. And so it's each different region of the US that that precision public health should be informing precision medicine how to improve their patient outcomes.

And then they can take that public health information and move that into individualized care and use targeted interventions to decrease the mod the modifiable risk of that

particular patient. These things working together then do help preserve healthcare resources, reduce waste, reduce medical spending because there are fewer complications in our patients and we have a stronger workforce and more s sustainable health care systems. And just remember vitamin D risk becomes more predictable when you have when you look at the environmental context, population vulnerability and individual risk profile and when they are considered collectively. Now how do we rapidly improve global vitamin D status? I just want to move to the globe just for a minute here. And if we look at this diagram, you can see this is a modified socioecological model that's surrounded by environmental and cultural context of the community that it's serving. So we'll move from healthc care policy to looking at population systems, the community and institutional perspectives down to interpersonal and where that cl that clinician relationship really sits and then individual levels. So rapid optimization of global vitamin D status could be accomplished very quickly and safely through multi-pronged precision public health and precision medicine approaches that would target every level of this socioecological model.

This modles this model is very practical. It helps us understand how to design interventions that can impact multiple levels at one time saving money. And this it's really for example it can be used in an updated national policy which is the purpose of this panel and what we are hoping for can be used to inform trickle down and inform every level of this model and it can be used as a foundation for public health initiatives. We don't need separate necessarily public health initiatives but we can incorporate vitamin D scientist science into every other public health initiative that we are really doing because vitamin D like Dr. Grant said is impacts eight out of 10 of the leading causes of death in the United States. We can use it to inform community health programming, workforce health initiatives, practice protocols, patient educa education, and inspire people like us for individual health decisions. So my final recommendations for today for policy we definitely need to update guidelines to regionally specific sun exposure and vitamin D dosing recommendations and enact and enact state specific concurrent resolutions like Alaska and North Dakota have done that are related to their environmental health and population risk factors.

It should be added to workforce and military health initiatives specifically for cognitive mental health, physical health initiatives to address stress and burnout in our workforce and in health health as well. And like I said added to specific public health initiatives like wick like cancer prevention programs targeting women's health and breast cancer can be easily integrated into those programs. Very cheaply and affordably for research and quality improvement. I think my colleagues covered this really well. Standardized research design per the Haney criteria is really important and if we had some homogeneity in our research design, it would really make the outcomes much easier for us to discuss in the literature. From education, we need to increase access to vitamin D knowledge. For example, physiology, consequences of deficiency, risk, symptoms, research design, and practice protocols for all decision makers and health care professionals in training programs and through continuing education. Now practice we need to look at increasing assessing patients screening testing and repletion and maintenance of every patient's 25d status to that minimum target of 40 which really like Dr.

Wimlon said is really pretty low. And using grassroots health calculator and etool protocol we can improve patient outcomes and preserve those healthc care resources. I'm taking note to that BMI sensitive dosing to the target. In my personal opinion, educa lack of education is the biggest barrier that we have to change this. That's why we're doing this webinar today. This is why we all work so hard to write and publish articles and do presentations. None of us are sitting around idle. I in my right beside me, I have two large textbooks. These are volumes one and two. And there are a lot of contributors on this panel to these large textbooks. And if you are concerned that maybe there isn't enough vitamin D signs, I encourage you to buy these and read them. I tell you what, there's so much information there. I really now carry them around to every presentation that I do so that people get it. The science is there, it just needs to be translated into practice. One of the other things that I'd like to just make a comment about is about barriers to successful projects because I personally have struggled with this in the vitamin D projects that I've done. We need to educate educate educate the people that are involved with our research and with our quality improvement products projects.

We need to share the research studies. I'm not kidding you. I drown people in research studies. You got a question? Boom. Here's a study. Boom. Here's a study. Boom. Here's a study. And a lot of people on this panel, I've emailed and said, "Hey, you got a study on this one?" Because I got somebody who needs to hear it. And I don't want to spend the time in PubMed, but I know that everybody has to at the tip of their fingers, right? Drown people in research cuz the research is there. People just need to read it and get it in their hands. Probably the top tip I have is to test the key stakeholders vitamin D concentrations cuz most of them are in the toilet. Then they really do see, oh, wait a minute, my personal level is bad. Maybe this is a priority. Negotiate the cost of the vitamin D test in any studies that you do. I in several projects I worked at, a facility came back with, we had this price, ABC price for each of the testing. Now, I happen to know that the actual cost of vitamin D testing is very, very low. Like the military cost for a vitamin D test is like $4 something, right? So, we don't need to be charging $300 a test, $600 a test. We don't even need to be charging $50 a test.

But, I've successfully negotiated the cost of 25 OD tests for some of my projects. So, negotiate follow up on your project people and progress frequently. I had one project to be honest that I kind of dropped the ball a little bit and didn't follow up. And I went back and followed up and found out that they had a new staff member who had quit doing vitamin D tests on all their brand new inpatients. Well, that really threw a nice wrench in my project. So, thankfully I have a couple years of data before that, but we actually had to stop the study because we had a new person who stopped doing testing upon admission at the facility. So again, if I didn't say it enough, it when you've educated, educated, educated, come back and educate again because that is really the key to a successful research and work project. That is all I have for you today. I want to hand it over to back to my executive director, Jennifer Aliano. Thank you everyone and thank you for your time here today.

JEN >> Thank you, Beth. And I do want to thank everybody else. Beth, I'm glad you brought up your concurrent resolution. Alaska and North Dakota are the only two states that have a vitamin D resolution, and I challenge anybody on this call or anybody who watches it to champion their own state's vitamin D resolution.

And if you have questions about that, just reach out to us at Grassroots Health. And I also want to just update everybody on a couple things coming up. Grassroots Health is in the process of building an online vitamin D consortium where we can all gather and we can all advocate together. We're going to have frameworks to share where anybody can participate from the individual level up to the policy level to really implement this research into practice at all levels. And so I'm going to just share a few closing slides to tie this all together and to give everybody some take-home actions. And before I do read through these, I I want to really emphasize an important point. We know that vitamin D is only one piece of the puzzle and we know that our diet that our environment pollution are also very important. Please remember vitamin D is an incredibly easy, safe, inexpensive way to really improve health. It's the lowest hanging fruit in my opinion and that's why we are focusing on vitamin D and everything else hopefully will follow. So vitamin D deficiency and insufficiency are common yet easily preventable and harmful and can result in long-term health consequences well beyond bone health.

Health policy and nutrition guidelines should be updated to reflect the current evidence. Based on this knowledge, we suggest the following changes. And I'm not going to read through all of these because they've already been reiterated by many of our presenters today. But number one, the minimal 25 vitamin D sufficiency range of 40 to 60 with upper normal optimal ranges up to 80 or even 100 nanogs per milliliter should be set. Higher serum concentrations may be necessary for specific conditions and individuals. 10,000 IU per day should be set as the safe upper limit as it was through the endocrine society previously instead of 4,000 IU per day. I can't tell you how many people I've heard online, they give amazing presentations about vitamin D, but where they really fall short is they say, "Don't take more than 4,000 IU per day." because that is the safe upper limit and anything above that could be toxic and that is just such bad misinformation that is contributing to the harm and the confusion surrounding vitamin D. You know calculating doses based on weight or BMI we've gone through that many times. The dosetotarget protocol of testing and retesting to ensure that a target level has been achieved.

And then also different protocols for hospitalization and that are included here. In addition medical education education in general is of utmost importance. Grassroots Health just had our online vitamin D education course which is built for practitioners to help move vitamin D research into practice but it's really anybody can take it. It was just approved for 11 CES continuing education units for nurses. So I really hope that you'll go to our website and check that out share it. And then also you know addressing all the places of misinformation or shortcomings when it comes to vitamin D on all government websites is important an important next step. And we covered a little bit about insurance but there's there's other things that are really acting as barriers to implementing the research into daily practice that

need to be addressed. Optimizing vitamin D status proactively is an important clinical and public health consideration that must be acted upon now, especially recognizing pregnancy and early infancy as periods of heightened vulner vulnerability to vitamin D insufficiency. And this is what I want to close on because we're affecting the lifetime of our infants. And really when it comes down to it, that preconception phase is when vitamin D deficiency and insufficiency really need to be addressed.

So and this is something that came from Dr. Wagner that I wanted to close with. Unlike many other stages of life, pregnancy and lactation involve dynamic maternal, fetal, and maternal infant interactions in which maternal vitamin D status directly impacts the developing fetus and infant. These early life developmental periods may represent some of the greatest opportunities for long-term health impact through prevention and optimization of vitamin D status. This has important implications for clinical guidance, preventative care, and public health policy. And with that, I thank everybody. Please feel free to email me, jengrasshealth.org if you have any questions. Especially if you have questions that we didn't get to today because I know that we are out of time but we will open up for discussions now for for our Q&A and I'm going to hand it back over to you James.

COMMENTS, QUESTIONS & ANSWER SESSION

JAMES >> Thank you Jen. That was amazing. I learned so much. So I just want to pick up on the thread for for a minute. There's actually it's little known fact that aluminum hydroxide causes hypopos phosph what is it phosphodmia and the initial use of aluminum hydroxide in medicine led to a condition that was acts that was actually misdiagnosed as ricketetts so there's your vitamin D connection I will actually been publishing an article on how aluminum hydroxide can cause vitamin D deficiency the mechanisms are very very clear and so this is a fantastic panel and, you know, it's great what you're doing.

You know, I'm a huge supporter and I want to be sure that you guys get as much material in front of HHS as possible. The pathways towards research funding, the pathways towards centers, center grants, and all of that. I'm very familiar with all of that. In in the groups that you're talking about in the consortia and all the rest. I've already offered to open up spaces on the new IPAC edu forum. They're private. You can do file sharing. It's all your material and I own it. So it's not like anybody's going to steal your information. So what I'd like to start with is Jen. We've come so far in the knowledge space and repeatedly everybody is repeating we we don't want to do randomized clinical trials. And yet the clinicians that become regulators it's beaten into their heads you know randomized clinical trials the gold standard you have to have it. What's the plan to convince them that the consilience of evidence from mechanism of action from improvement of health after the intervention of of vitamin D supplementation of testing people who need it and seeing that their health improves and testing people who don't need it and it their health doesn't improve anymore you know that consilience of evidence itself what's the plan on the pathway to have this

regulated in a way where insurance can actually give sufficient coverage not just for testing but also potentially for prescription.

JEN >> This is the plan, James. We're presenting the evidence right now and not just focusing on randomized control trials which when designed properly I think just like Dr. Weiss and Dr. Dr. Mir Zakani really pointed out in detail when it comes to pregnancy when these randomized control trials are designed around nutrients with specific criteria in place and we are enrolling people who are coming in with a baseline deficiency and treating to a to a sufficient level and and really monitoring that level throughout the study. Oh, then then we'll be able to see more reliable findings. And so, but I but the education piece is is what comes first. And when you talk about insurance as well, well, you know, that's where we're asking for help, right? That's where we're asking for our new connections or what is it we have to do? We've got the scientists, we've got the experts, they have the knowledge. What more do they need to to ensure universal coverage of vitamin D testing, of the education? How can we implement vitamin D protocols into prenatal standard of care or wick programs and other things like that?

>> Yeah, for sure. So the the other thing I wanted to say just before we get to some of the questions which I pulled aside for you it I really appreciate Dr. Riverman's caution about hedging on causality, but clinical science, nutrition science, so much of us, so many of us have been socialized to do that to hedge up causality, especially when we're speaking in public. But there are things that we know, right? There are things that we know about vitamin D supplementation. And we have things that we know based on the like again the consilience of the evidence which comes from Eio Wilson the evolutionary biologist that if there if there was a way to express policy and I want to congratulate Beth on her fantastic presentation on policy recap and and and Chen and your contribution to those ideas and everyone's but if there was one policy that HHS could implement right now what would it be? I mean, this is my personal opinion and I encourage anybody else to chime in. But I really think it needs to be the if we don't change the government recommended guidelines, people are always going to fall back on them as their excuse no matter what education they receive. I think that needs to be the number one item that we address. >> We're close. We're pretty close to that. So, fingers crossed. So Ed Kellogg has a good question here. If everyone in the United States simply had a year- round sufficiency of vitamin D, what kind of impact as a negative percentage do you believe that it would have in the overall revenue of the medical industry?

>> I believe that question was aimed at Dr. Grant. >> Dr. Grant, you want to weigh in? I have to ask him to >> Well, I I don't have an exact answer, but I I I do know I've done studies for various countries like Canada on the effect and and Europe. I'd have to go into it, but I'd imagine if you're going to have 20 to 30% reduction in in mortality rate, you you from raising vitamin D, you might have a 20 30% reduction on the cost. However, there are of

course fixed costs because the medical system wants you to come in for exams and and this procedure and that procedure and so on. So, it'd be difficult. So, this could be a something that might upset the the the medical system and medical system impires what hires what 20% of the population. So, it could be it'd be widely fought in in the by the system. >> Yeah. Thank you, Dr. Grant. There's no doubt about that. We do have an overbuilt medical system that's reliant on cell on sick people. Another question I thought was fascinating, came right out of the gate when we were discussing genetics. Comes from Christian B's VDR polymorphism question. Does anyone plan to look into this future to determine why certain genotypes are nonresponders?

>> I think Dr. Mirconi or Dr. Weiss might or any of you on the panel, you are more than welcome to step up here. >> I just have a quick comment on this. I I read a study and maybe this will trigger someone else's mind. That prenatal vitamin D exposure impacts the development of those VDR receptors. And so that if a mother has really low vitamin D serum concentrations, the infant won't even develop VDR receptors. Is that true? Maybe if Dr. Hollis or Musakani or Weiss is maybe they can address that. I think that would maybe have some ris respon would have some connection to adult response to vitamin D serum concentrations. >> A fascinating possibility. I'm not sure that it's been studied. So but Beth, >> may I make a comment here? >> Yeah. >> Yeah. Actually I I believe well I have a PhD in genetic molecular biology but I think the genetic component has been over emphasized and I made a category a study and I found a 10 categories of rude drivers and I believe lifestyles particularly dietary factors play a lot more important roles in these issues than the genetics particularly like the asthma and autism mentioned today you know you can't simply use genetics to to to explain for example cancer over the last 30 years cancer rate in the young people under 50 has increased by 80% it has nothing to do with genetics autism the same thing you know has increased so much has nothing to do with genetics so so yes genetics does play a role but it's at the bottom of my list >> okay well thank you for that Dr.

Chang and for thank you Beth for that fascinating I was going to say that there are some examples where environmental exposure say for endockinabonoids if you have too few of them you don't have enough receptors and so lowd dose endockinabonoids can cause an increase in receptor so there's precedent for that so yeah fascinating stuff another another good question Richard Smith Jr says, "Why not have recommendations for dosing that would be based on international units per kilogram body weight per day?" which is what ironically I criticize FDA of not doing when it came to aluminum hydroxide and vaccines in the pediatric schedule. They would just say, "Oh, oh, 800 mill micrograms." so yeah, what are your thoughts on that? Anyone? >> I think Dr. Hollik should address this because he has the most experience with interacting with those panels. >> Dr. Hollik. >> Yeah. So why don't you repeat the question? >> Yeah. So the question is the expression of dosing. You have international units as a base range. Why not express it? And this pro probably comes from environmental toxicology thinking. International kilograms dosing question sorry international units kilogram dosing might actually actually be expressed as international units kilograms body weight per day.

So based on body weight as a >> yeah so it so it turns out that what's curious is that you know even though there are these calculations out there what what is true is that you can have a a one-year-old getting 600 units a day and you can have a 10-year-old get 600 units a day and the blood level will be the same and the body weight is a lot different. Right? You have at least at least three different 25 hydroxilas and and one of the observations that I think we've all made is that if your blood level is around five even if you take just a couple hundred units of vitamin D one of the hydroxilases the cm is such that it rapidly converts as much as it can to 25 hydroxyd so as a result the 25xd will rise very rapidly to about 15 to 20 nanogs per ml and then for every 100 units it only raises by about 6 to one yeah nanog per ml. So, so it's nice to see for obesity, for chronic illnesses, including inflammation, you probably need more vitamin D, but for the most part, the body has been pretty good at at being able to regulate the level. I saw in one question that one person said that my levels a lot higher than I would have expected. It turns out that the 24 hydroxilase, right, is the major contributor for your 25 hydroxyd and and and there's a significant number of people out there that have a partial 24 hydroxy waste deficiency.

And as a result, the dose of vitamin D that they take, the 20x D is higher because it's not degraded as fast. Yeah, >> I did see Robin Robin Whittle raised raised her hand as well to address this question. Thank you, Dr. Hollik. By the way, are we able to unmute, Robin? >> I think so. Find her. >> It's nice to see your face, Robin. I've been on many threads with your name on it. >> There you go. Hey, >> here we go. Test one, two, three. Hi there. I'd like to thank everybody and also I just want to say hello to to Ronald Ve who wrote in 2004 that vitamin D is not a hormone and that we need to talk about the three compounds as separate compounds because they have different functions in the body. I just want to totally support that. I want to I want to speak about the value of Senil's recommendations for supplement supplemental vitamin D quantities as ratios of body weight. His is the only peer-reviewed journal recommendations along these lines. He has as one of his slides he recommends certain amount of IUs per kilogram a range of IUs per kilogram. For ordinary weight people and people are overweight and underweight but for obesity 1 and two he has a higher range and for obesity 3 he has another range.

Now I believe those recommendations are ideal and that's what should be the national policy. Because it suits everybody. It doesn't depend on race, doesn't depend on body body body weight. It just handles all that all that sort of thing. And and it doesn't require any further research because it will and the and the target is to achieve at least 50 nanogs per milll circulating 25 hydroxy vitamin D which is a really great target. This idea of aiming for 20 or 30 is just obviously wrong. You can look at research and see that the immune system dysfunction starts at 50 and anything below 50 you get more and more post post-operative infections. So 50 is a really good target 50 or higher. And the recommendation should be sils I can't think of anything better. The alternative is to try and modify the RDA and this is absolutely not the way to go. The RDA is just a a broken concept because it doesn't take into account body weight. If you had a target of 50 nanogs per milliliter 25 hydroxy vitamin D, I did some rough calculations last night and I wrote it in a comment a few hours ago to your

most recent James your most recent Substack article. I looked at the statistics for the the United States population.

Because all nutrients depend on body weight, the amount you've got to you've got to give them to achieve sufficiency. But in the case of 25 hydroxy vitamin D, it's made even worse by obesity because obesity reduces the ability of the liver to to hydroxilate vitamin D3 into 25 hydroxy vitamin D and also the excess adapost tissue seems to absorb the 25 hydroxy vitamin D and not give it back. So you really need to have high the high ratios that sil has with obesity. But anyway, if you want to do an RDA for 50 nanogs per milliliter, 25 hydroxy vitamin D, one way to do it is to find who are the people in the United States population who are at the within the the top 25 top 2.5% of the body weight because they're all suffering from obesity 3. And I try to calculate what that threshold is. What is the body weight? And I came up with 133 kilos, which is 290 lb. And reversing Sil's recommendation for obesity 3, I estimated that the RDA would to get those people up to 50 NOGS is about 18,000 IU a day. Now, that is ridiculous to recommend to the population because the RDA depends entirely on those on those top two and a half% of the body weight. So the RDA is not the way to go. I'm talking about say completely the phys the physiological dynamics of uptake, metabolism and clearance of vitamin D in all of its forms will be different based on all of those physiologic factors that you mentioned.

And that's why I like you know grassroots health's message. You need to test to know where you are. You need to test. It's not superfluous to test. If you are a person that suffers from chronic illness and you say, "Oh, I'm just going to up my vitamin D." You're shooting in the dark. It really depends on all of these other factors. So, your message is really heading home. But one of the things you can do is you can ask your doctor, "Hey, I'm curious about my vitamin D level. Do you know what it is? I don't know what it is. Let's test it." Okay? If they don't know how if they don't know how to get through the the paperwork for that, have them contact or better yet join Grassroots Health because send them this video because the education that's here is, you know, and and attend their their their their education for continuing education credits is just so fundamentally important. One of the policy changes that came up in question was, hey, we have to teach nurses. We have to change medical education and all the rest. You know, I I put out on Twitter today. I think the medicine has to stop treating the average patient. We ha they have to stop thinking that every the next patient that walks through the door is like the last six that they saw.

And and the individualized medicine approach has benefits for the doctors as well because they they have more to do with maybe fewer patients, but they'll have more to do. And nobody's ever done the economics of the trade-off of actually taking into attendance. When when you when I started doing cancer research, when I found out that vitamin D was a risk factor like Keith Bankerly really emphasized for for cancer, that that's what it really got my attention. But what I've learned since is the profound effect that it has on so many conditions and so much of the human health and the chronic illness that we see. It's a quick win to do something about increasing the general population's dose and I think you know

everything simplifies when you do HHS math right they have to have an RDA right but what is an RDA unless you consider these other factors is very good so >> you should consider vitamin D as a prevention right not to be intervening just when you have a chronic illness >> absolutely >> that should be the message >> that's the thing right how do you stay healthy if we transitioned our mental mindset from getting better when you're sick to staying healthy across the United States and across all around the world.

And you saw your doctor as a partner in maintaining your health and getting healthy and staying healthy, then you put then you empower the patient. There's a little bit of a language war going on in in in medicine. I don't know if you've noticed, but there's no such thing as insulin resistance. I mean, there is. You can say the body is resistant, but from the person's perspective in their day-to-day existence, it's really insulin dependence. But doctors don't want to say you're dependent on insulin because we're Americans and we're strong and we're robust and we don't want to be dependent on anything, right? Because then that will light a fire to say, I don't want to be dependent on that. I want to do something. No, no, no. Just take your insulin, you'll be fine. Is one message. Well, we're certainly not saying take your vitamin D and you'll be fine. They're saying you don't have enough of something that's fundamentally profoundly important to your biology, and that's a different message. So, yeah. Well, Robin, I'll let you have a close-up thought there. >> Great. Thanks. Sil's recommendations are intended for everyone. And it's not a medical matter, it's a nutrition matter because the natural source of vitamin D is ultraviolet B which raises the risk of skin cancer and it's not really available to most people.

So his recommendations are don't preclude the idea of of testing vitamin D and certainly anyone who's got any particular illness or is having consulting with doctors absolutely in western countries should have the 25 hydroxy vitamin D tested. But the value of Senil's recommendations is that they will safely achieve at least 50 nanogs per milliliter 25 hydroxy vitamin D after a few months all year round for the whole lifetime without the need for blood tests or medical intervention it's just a matter of getting your body weight estimating your obesity status and any child can calculate it and and away you go. And it's applicable to everyone in the world. And it doesn't involve tests and so on. >> I I totally appreciate that. I think you're exact I think you're exactly right. But here's what I one one thing that I've learned. If we do not incentivize Hang one a minute. If we do not incentivize doctors >> to behave differently with money, they won't behave differently. Right? So if they tested each of their patients in their practice for vitamin D who they suspected might be deficient, they then have some skin in the game. And I'm sorry, it's an economic argument. It's not a scientific or a medical one.

>> It's that the because they hold the authority of parents, especially new parents, with their infants, show me what to do because I've never done this before and I'm not getting along with my parents anyway. So, I'm entirely dependent on my doctor. If the doctor said, "Your your kid is constantly sick. I wonder what their vitamin D levels are." It gives the patient a data point >> to remember. >> Yeah. It gives the patient a data point to remember to supplement. So there's benefits to testing beyond just knowing that you

should do that. >> Look, if if you're seeing a doctor, you should ab absolutely get get things tested. But Sil's recommendations if are adopted by women of childbearing age would pretty much eliminate or or greatly reduce preterm birth, preeacclampsia, mental retardation, on and on it goes, you know. But but what I want the final thing I want to say is that our responsibility as vitamin D experts you know you know I'm not a researcher but you know I will be one day our responsibilities to the people and we somehow have to get to the people through the through the you know HHS and so on and if they're doing something wrong like think in terms of RDAs we need to say so RDAs a morabundant approach and and Sil's recommendations are the way to go and I totally support them.

>> Thank you. I'll take that seriously and I'll bring that up with Secretary Kennedy because there's another there's another factor that has to be considered just to throwing a number out there on the web. I'm just trying to stop them from distributing the wrong number, you know, like Oh, yeah. Yeah. So, let's have that conversation. I thank you very much, Rob, and and everyone else. >> So, listen guys, this has been great. The the video will be distributed to everybody who registered as a free video to share. Please do share the video and John I'm going to make sure that this gets a wide distribution and an audience with some people that we that we hope will watch it. They won't watch the whole thing, but I'll try to pull out parts of it that I think are very important. Could I ask everyone and make this into a working group final thing? Could you send me your slides? If you send me your slides, I can make them available. And maybe they'll maybe you'll see them in an HHS presentation. Maybe it'll result in a an invitation to you to come to the HHS. We still want to have that live that live workg group. And some final good news is I have it on very good authority that the vitamin D project to stop lying to the public about vitamin D dosing was taken out of the hands of the guy who decided that it wasn't an important thing and it's going that project is going to the hands of someone who does think it's an important thing.

So, I'm going to hold my friends accountable at HHS to to come through for the people. Robin, we do owe it to the people and to each other. John, I'm going to let you close out to your audience, but please, I want to pitch to ipac-edu.org for courses and IPAC online, ipacedu.online for a new social media experiment. It's just for people just like you from all different walks of of health concerns and integrative medicine and so on. IRB members will be there, editorial board members will be there from my journal. I'm bringing all of my community together into one social media experiment that will feel very familiar, but please, I developed it, so it's going to be slow. Just give me some time to work out some of the bugs. So, thanks, Jen. I'll let you close out. >> Actually, I would like to give all of our panelists a opportunity with any of their closing remarks or any last things that you would like to say. So, I'm going say have a delightful day. >> You too, Dr. Holland. And go outside. >> Yes. >> All right. >> All right, guys. Thanks so much. >> That's it. I very much appreciate all of you, your life's work, some of you. And for continuing to stay in the game as challenging as it's been for I I know I've heard stories that I and I appreciate the the disinformation playbook.

Dr. Grant I you know during COVID was witnessed to several attacks against vitamin D even just as minimal as sharing a paper in a social media platform and just the attack that that we received in return. So, I appreciate all of you, your life's work, the energy that you put into this and the passion that you continue to show and thank you for being a part of Grassroots Health and hopefully we can make some forward movement, not just baby steps but really big strides and leaps with joining new forces such as with you, James, and HHS. So, again, thank you everybody. >> Thank you. Bye.