Advancements in Understanding Breastmilk: Learning from the BEGIN project

Webinar Transcript, March 23, 2022.

Elena Mieszczanski

Hello and welcome, everyone, thank you for joining today's webinar on Advancements in Understanding Breastmilk: Learning from the BEGIN project. My name is Elena Mieszczanski, and I am a project coordinator with USAID Advancing Nutrition and I will be supporting today's webinar. This webinar will present the findings of the BEGIN project and provide an opportunity for a conversation about its implications moving forward with our panel. Before we get started, I would like to review our zoom webinar environment. Today, we will be using zoom as the platform for this webinar. If you run into any technology questions or issues during today's webinar, you can reach out to me via email. If you are unable to hear please make sure you have connected your audio by selecting the headphone icon at the bottom of your Zoom window. You are also welcome to send a message to everyone to introduce yourself, send your comments or ask for tech support during today's webinar with the chat function. If you are unable to hear the presenters or see the presentation, please try leaving the meeting and joining it again via the link sent to you in your registration confirmation email. Like I said before, you can use the chat box to type in comments and click send. And we also have closed captioning enabled on this meeting so you can select closed captioning on the bottom of the screen to view that. Now I would like to introduce Lindy Fenlason, Senior Nutrition and Capacity Building Advisor at the USAID Agency for International Development, who will be providing an introduction on the Epics Nutrition subgroup.

Lindy Fenlason

Hi and welcome to all, thank you for joining us today. This webinar is a contribution of the US Government Global Nutrition Coordination Plan and its new subgroup Epic Nutrition, a name which refers to the ecology of parent, infant and child nutrition. This group's efforts will focus on human nutrition science including the biology, assessment, translation and context or ecology of human nutrition. Today's webinar is an illustration of those goals. To introduce our content and speakers, I will now hand over to my colleague Dr. Daniel Raiten from the NIH.

Dr Daniel Raiten

Hello everybody and welcome to this first and what will hopefully be a series of exciting webinars and interactions with you vis-a-vis the epic group. We are going to talk about a project today

called Breastmilk Ecology-Genesis of Infant Nutrition. You can see that term ecology. This project was initiated in response to a growing need for additional information in the US as it relates to our ability to make dietary guidance for the thousand days and certainly globally to address issues that continue to challenge us in the realm of infant feeding. Before we get started, I want to introduce two people who are instrumental in playing a leadership role in BEGIN and supporting BEGIN. Firstly, I would like to introduce Drew Grammer. I hope that he has been able to get connected; Drew are you on? I know he was having some challenges. Alright, well, he'll join us later and probably have a few words to say. The next person I would like to introduce is Dr Allison Steiber, the chief science officer for the Academy for Nutrition Dietetics, our partner in BEGIN and other projects without whom none of this would have been possible. Allison.

Dr. Allison St.

Yes, thanks Dan. I just want to say hello from the Academy of Nutrition and Dietetics. It has been our extreme pleasure to be able to work with Dan and Drew on this project, and all the experts that have really shaped the content that you are about to see represented in today's presentation. You know, it's in projects like these that when we get to be a part of it, we get to really see what we know, what we don't know and we begin to think about a strategic agenda on how to fill those gaps. We were pleased to be a part of it, and to be able to support the work. Thank you.

Dr Daniel Raiten

Of course, the community represents the sort of boots on the ground in many ways that interface between the patient and the care community; they are essential to everything that we do so they are great partnerships, and we really value their input.

First, slide please.

This is just a quick representation of all sort of aspirations and goals. In doing these projects in the NICHD under Drew's leadership and with the support of NICHD's leadership. We recognize that NIH is a Biomedical Research Organization and our primary job is to support the efforts of our constituent groups in the research community. But while we recognize that we are in the continuum of evidence-based programs and policies where we're responsible for the evidence generation, we also recognize that the generated evidence needs to be translated in a meaningful way to support the community, the caregivers and the end users. That will be reflected in the design of this project and the other projects that we have done.

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Just briefly, why do we need BEGIN? You would think at this point in time we need to know about human milk and breastfeeding and its role in human development. But the fact is that, there is a lot of questions that remain unanswered and there's a lot of questions that are emerging. There are questions about nutrient requirements for infants during this critical period of development. There are questions about the role of various types of feeding modalities; whether

it's express milk, donor milk, the duration of exclusive breastfeeding, the timing composition complementary foods etc. We also need to have a better idea about the biology of human milk because we have situations that we have experienced recently with the COVID-SARS survey and the COVID pandemic. where something like that hits the community really hard, and we had a hard time getting messages, communications out to everybody up and down the support chain about what's the best approach and how do we respond to these things. Part of the challenge is understanding the biology, so that's another motivation for this project.
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Just briefly, I want to make it clear what BEGIN is and what it is not. Starting with what it is not. We are not making guidelines, we are not making recommendations, we are not making policy, we are hopefully supporting all those agencies and organizations that do and you will hear from some of them later on. That is clear. This was not intended to enlist a bunch of people to write a funding opportunity announcement to the extent that the information developed by this project can be used by programs like NICHD and other funding agencies to support the development of funding opportunity announcements that's great, but that's not our motivation here. What we are motivated to do is to try to engage the community, to get a better understanding of what human milk biology is. In this case, perhaps there is a new paradigm in addressing that.
Next slide, please.
Just briefly, when we talk about an ecology, the working definition we use for an ecology is the interaction of a complex biological system and its environment. We have designed this project to explore that ecology. The complex biological system in this case is human milk composition.
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There is an internal ecology in this case; these are some of the factors that influence that internal ecology; the biology, the genetics of the parent and the child, the health context of the parent and the child, obviously the biology of nutritional status and various exposures on their impact on that biology. That will be the internal ecology.
Next slide.
The external ecology will represent those factors outside, above the skin as one of my colleagues likes to say, that influence the internal biology and influence what people do with regards to how they make choices in the kind of context in which they live. These are some of the factors, the physical environment, social behavioral demographic issues, equity issues etc.
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When we put this picture together this is sort of a cartoon representing how we view this complex system. There are various aspects of it, there is the role of the mode of infant feeding and how that affects it. There is the biology of the infant, the parent and there are exposure scenarios such as xenobiotics drugs, recreational drugs, therapeutic drugs, toxins etc. all of those affect this ecology and this project was designed to study that.
Next slide quickly.

These are some questions that we were hoping if we accept the fact that this is a biology then what does that actually mean? How do we study it? What is the nature of the crosstalk between these components of the ecology? What is the nature of the crosstalk between the lactating parent and human milk composition? What is the nature of the impact of the infant on human milk composition? What is the role of the actual matrix? We tend to think of human milk as a composite of components but there is actually a biology and an interaction that occurs within that matrix. What does that matrix mean? What are the implications of that matrix to the health of the infant?

There are many open questions, and one of the key issues is the coronal biology issue. What happens over time not just from of a traditional view or within a feeding, but also over the course of the day and certainly over the course of the lactation period? Out of this how does this composition change? And how does this ecology interact to affect those changes?

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This is a sort of a stepwise progression of how we've designed the project from the biology to the science of how we study this, and we wanted to make sure again going back to that earlier model to include a strong consideration of what you do with this new evidence. If in fact what we are hypothesizing is true that this is a complex ecosystem, how do we convey that information in a meaningful way to all users in the continuum of support for infant being? Whether it's policy makers folks like Allison's group at the dietetic community, people who are providing care, people who are making policy and obviously the end user, the lactating parent and that family environment. How do we convey messages in a beautiful way? I think it's the end.

Thank you for the time. That was just a quick and dirty overview but I think you'll get a much deeper appreciation of the complexity of the situation, what we tried to do in the project by the following presentation starting with Dr. Peggy Neville who led working group 1, focusing on the parent inputs to composition thank you.

Dr. Peggy Neville

Thank you. Can you hear me all right? I'll be talking today about Parental Factors that Influence Mammary Development Milk Secretion and Composition. I was the chair of working group one. This is a diagram which comprises everything that we talked about. It's very complex but I want to just take you through it briefly before I go to some of the specific factors. Parental influence on mammary development is very important for breast development if you will. We have the pre-pubertal nipple if you will. During puberty, the hormones of puberty cause development of branches, of ducts. Finally, during pregnancy, the alveoli that actually do the milk secretion are developed. Then we go through a process called secretory activation mentioned here to the cell that actually secretes and synthesizes all the components of milk which are labeled here.

What are the factors that influence this?

There are social structural determinants of parental health, and I use the term parental because it is possible for men to breastfeed too. With the proper hormonal environment, men can develop their glands to actually secrete milk and provide sufficient milk for the infant for several months. In general however, it is the women that we're talking about and there are social determinants; the household housing breastfeeding supply support employment education, maternal health status and behavior, psychosocial stress; I'll come back to some of these in just a minute, then, interaction with the infant which is extremely important. Here we have the biological environment, placental factors, the maternal microbiome, nutrient availability, pollutants, medications/drugs and the 24-hour daily cycle, because there are indeed changes in milk output and to some extent composition during the 24-hour daily cycle of the circadian rhythm. Hormones and immunology are very important, inflammation and the immune system. We don't understand these as well as we should but sex steroids, prolactin, growth hormone, insulin, thyroid hormone, oxytocin, serotonin, human placental lactation and glucocorticoids are all important.

Finally, there are Genomic variations that can influence the development of the mammary gland and milk secretions. Factors that influence mammary development include genetics, puberty where estrogen promotes the ductile development, pregnancy hormones both the placenta and the ovaries are involved in promoting alveolar development and differentiation of the milk secreting organ i.e. estrogen, progesterone and growth factors. One thing about progesterone is that, it inhibits milk secretion during pregnancy and its fall at the end or at the birth of the child is what brings about secretory activation. Immune factors influencing this whole process are really quite poorly understood and are an area where we need more research.

We're going to talk about Maternal Health next.

The effects of Maternal Health Status on lactation are quite important. Preterm birth which is becoming more complicated, what are its effects on mammary development milk composition and milk volume? Let me diverge for just a minute to say, we need to be able to measure the amount of milk that is transferred to the infant. That is how we get the right amount of every nutrient and other milk component into the infant. It is extremely hard to measure; you really need a test weighing before and after a feed, preferably over a day or more. One of the questions here is; do the causes of preterm birth inflammation, drugs, smoking etc. alter breast development? Other things that alter breast development are obesity, gestational diabetes or pre-diabetes. We need to know their effects on mammary development, on milk composition, on milk volume. Dietary alterations in serum nutrients, hormones, growth factors, milk composition, and milk volume are linked to stress, depression, physical activity, mastitis or other inflammatory conditions. How do these conditions alter mammary development and lactation competency?

Infant Interactions are very important. Here, we need to work with a neurobiologist because suckling and skin contact cause oxytocin release from neurons which I depict on these green

circles. In the hypothalamus there are two directions; oxytocin goes into the brain and interacts with receptors like the opioid receptors, to give a pleasure/reward calm feeling very important in the bonding between mother and infant. This is the thing we've known about for quite a bit longer, oxytocin goes to the pituitary secreted into the bloodstream and hits the mammary gland, causing the myoepithelial cells to contract and producing milk letdown which pushes the milk out of the breast.

One of the things that we really don't know enough about is the effects of medications, environmental agents and drugs. There are quite a few questions that came up in the working group about medications. How much gets into breast milk? that's what people normally look at, but they also need to know how much of the dose in the breast milk is absorbed by the infant? What are its effects on the infants? Do psychoactive medications, antidepressants, antipsychotics, antihistamines and narcotics affect mother infant bonding? Very important these days. What are medication fit effects on maternal lactational physiology? How do recreational drugs affect milk composition and transfer to the infant?

With the increase in marijuana use throughout the United States, we need to understand that marijuana is transferred very efficiently to the infant. The question is, what does it do to infant development? To what extent do environmental toxins - of which there are a lot- alter mammary development, milk secretion and milk composition? All of these questions need more research so that we really have an understanding of human lactation. I would like to thank all the members of this audience, as well as the members of my working group Ellen Damarath, Jennifer Hahn-Holbrook who focused on the chronobiology of lactation, Russell Hovey, a dairy scientist, Jayne Martin-Carly, Mark McGuire, another dairy scientist who had little information that was useful to us. Edward Newton who really focused on environmental agents, Kathleen Rasmussen who has contributed to the human lactation field for many years, and Michael Rudolph, he and Ellen Damarath, are particularly interested in the effects of obesity on lactation. We couldn't have done much of a good job without Daniel Raiten. I'm now going to pass this to Jennifer Smilowitz if I can. I'm going to stop… no I'm just going to… Jennifer is on and I'm going to quit.

Jennifer Smilowitz

Hi everyone! Can you see me? Can you hear me? Can you see me? Oh! I have to start my video, I'm sorry I have to go to another screen. Elena can you share my video or start my video?

Elena Mieszczanski

Let me try. Jennifer that's something you'll need to do yourself.

Jennifer Smilowitz

Ok. Ok. Sorry my mouse will go over to the next monitor hold on.

Elena Mieszczanski
You can just start the presentation without your video Jennifer.

Jennifer Smilowitz
Ok. You people can see me as a panelist Ok. Hi everyone! I'm sorry you can't see me. It's an honor to be here and to represent the BEGIN project working group 2 on Human Milk Composition. I am one of the lead authors of the report and I'm here to represent my group and our project. Before I get started, I would like to share with you my disclosure. I received a grant funding from the NIDDK, USDA/NIFA and Reckitt to conduct research at UC Davis in the past 12 months. I'm also a Technical Advisory Committee member of BIOMILQ, a lab-grown milk company, and I'm also the director of the International Milk Genomics Consortium. It's a non-profit organization; our scientific society that aims to advance the fields of milk and lactation. We are given this huge task to address human milk composition and so our overarching objectives of the project is to characterize the state of the science in terms of what we know and what we don't know on human milk composition, structure and their functions in the infant. We propose a paradigm shift in researching human milk then rather to look at human milk components individually to think of milk as a biological system, and to think of human milk composition with an ecological basis. What explains human milk composition from an ecological perspective? How does that influence human milk variation and influence infant health? Identifying gaps in knowledge related to human milk components and how these gaps could be filled. I don't have a lot of time to go over all these objectives so I'm going to give you a high-level summary of this project.
We know human milk is universally recognized as the optimal exclusive food for infants for the first six months of life and more than one thousand unique biologically active complex supramolecular structures in human milk synergistically support infant health by nourishing, communicating with and protecting infants. As you can see from this figure, human milk components may target one or several of these functions. What we see in orange is nourishment. We know that human milk components are the most digestible bioavailable sources of nutrients. Examples include total concentrations of protein or essential fatty acids or micronutrients and these support the growth and development and metabolism of infants. However, milk also communicates important information as to how to best respond to a particular environment. A really good example of this are flavor compounds in human milk. We know that human milk flavor compounds might actually educate or imprint the infant's palate and prepare the infant for the flavors of the cultural diet that may impact later feeding and food acceptance in life. We all know that human milk components deliver protection to the infant and a great example are antibodies. Immunoglobulins are upregulated when infants are exposed to pathogens, and these immunoglobulins bind and neutralize pathogens. Milk delivers structural complexity in a matrix whereby the components themselves are bound together. Many of them are, and as a result they target multiple functions in the infant and this characteristic makes human milk unique from any

other food on the planet. One example is milk fat globules. You can see that milk fat globules are in the sweet spot between providing nourishment, communication and protection. Milk fat globules deliver essential fatty acids but are also precursors for eicosanoids. They are important for signaling and glycolipids that bind and neutralize pathogenic toxins. Despite decades of research on human milk composition, the multifaceted impact and the mechanistic understanding of all the various human milk components on infant health are far from being understood. One main reason is that historically milk components have often been studied in isolation as mixtures of independent molecules. For example, researchers might study proteins of in human milk, and other researchers may study micronutrients, vitamins or minerals, but not many researchers come together with multidisciplinary tools from other fields to understand the complex matrix; how does milk work as a matrix. So, in our report, we propose to research human milk as a biological system, to understand how its complex matrix of interacting molecules synergistically target infant health. We propose investigating the role of human milk component function through their interactions as a biological system. We provide three types of interactions or examples of interactions that could be instrumental in supporting infant health. The first type of interaction is that, the presence and or concentration of one human milk component will impact the presence or concentration of another human milk component. Therefore, a possible example would be a specific complex human milk oligosaccharide profile shown in green that nurtures a specific complex human milk microbiome profile. Another type of interaction, type 2 shown in blue, is that human milk components are physically associated with each other, and that their impact on infant health depends on their physical connection. A possible example shown in this cartoon is that, selected proteins that are embedded in the milk fat globule membrane exert an effect on infant only when they are consumed as part of the membrane rather than as individual proteins. The third type of interaction, type 3 shown in orange, is that the impact of one human milk component on infant health can be modified by another milk component. A possible example would be the effect of a specific protein on infant health only if that protein is also consumed with a milk borne protease, an enzyme that helps the infant digest that protein and utilize it for its function. Understanding the complex interactions among human milk components requires a systems' biology approach with diverse tools from multi-disciplinary fields ranging from chemistry, nutrition, mammary biology, genomics, immunology, microbiology, bioinformatics engineering, infant development lactation, medicine etc. the list goes on and on. Even the lactating parent infant dyad we need to include them as important stakeholders in our discoveries.

Let's understand how these components vary and how this variation may impact infant health. Human milk components vary among individuals, populations, they vary across lactation and even in the course of the day. So, all of these variations, the dynamic way that milk responds to the environment can confound our understanding of their functions in the infant. These types of variation are attributed to inputs from the infant, the lactating parent and their shared environment. Our group focused on the variation of human milk components in response to

ecology. We are defining ecology for human milk basically as the relationship between the infant, their lactating parent and their shared environment. We propose that ecological variation might differentially support optimal health and survival of infants living in varying ecological contexts; this is shown in blue and orange. These are related to differences in parenting and infant genetics, nutrient and food availability, environmental exposures, for example exposure to commensals and pathogenic microorganisms that differ, cultural practices that differ and even sunlight exposure. Rather than think about milk composition with normal ranges in mind, we propose the concept of a shift to variable normal to support health in a particular ecosystem, and this is referred to eco-homeoresis, which was originally coined in 2017 by McGuire et al. Eco-homeoresis is basically homeoresis that supports optimal health in a particular ecosystem. Homeoresis is basically homeostasis in a dynamic or physiological state such as lactation. An example of eco-homeoresis might include the upregulation of secretory IGA in milk that targets specific pathogens that the infant and the lactating parent are exposed to or could include secretor sugars versus non-secretor milk. Thus, there may not be a normal one-size-fits-all construct for human milk composition and we propose the need to research human milk composition and function in the infant with an ecological lens. Let's not ignore ecology.

We have many gaps that we talked about in our manuscript or our report and I only have one more minute left, but here are some general gaps in research with respect to human milk components and their impact on infant health and well-being, which also impact infant feeding; which I would be happy to discuss later with the panel. But we want to know more about how does human milk variation influence infant health? Does it really make a difference? What are the ranges that we need to think about with the various environments that different individuals live in? How does chronobiology impact human milk components on infant health and development? Is there a big difference between day milk and night milk? This applies specifically with bottle feeding human milk. How does the matrix influence digestibility, bioavailability and protective functions in infants and what are factors that could impact the matrix? Freezing, thawing, pasteurization. We need to think of other factors that influence the matrix. How do antimicrobial components in human milk selectively target pathogens but spare commensals and symbiotes? How do fix factors, modifiable factors and even external factors, influence human milk functions. So, from diet, environment, but also pasteurization, handling for a donor milk for example. How does human milk respond to the infant health state? How does human milk know to increase immunoglobulins when the infant is exposed to a pathogen? We don't know. How do human milk components interact with each other and within the infant's developing system to exert function? In summary, we know human milk components offer a myriad of benefits including nourishment, communication and protecting the infant. All of these functions are in part related to the interactions among the various components in a complex matrix. There is high variation due to ecology, that is between the infant, the lactating parent and their shared environment. We propose rather than focusing on normal ranges of components we should think about a variable

normal to embrace the echo-homeorhesis. Not every baby lives in the same environment with the lactating parent. We believe that we should change our ideas about how to study milk, we should look at it from an ecological lens, using a systems biology approach with multi-disciplinary tools to identify the synergistic interactions that support infant feeding and health. I wish my team were here with me, I would love to thank them, introduce them. We seamlessly collaborated together to approach human milk with a sort of a different creative lens. I would like to thank the chair of the project and senior author of the manuscript Shelley McGuire from the University of Idaho, who worked tirelessly to lead and inspire our group. Finally, big thanks to Mary Rozga, Alison Steiber, Andrew Bremer and Dan Raiten for their leadership and collaboration. Thank you all for your attention. I am now going to pass the baton to Mandy Belfort.

Mandy Belfort

All right can you see and hear me? Ok. Great. All right, well, thank you so much for the opportunity to present today on behalf of working group 3 and in particular on behalf of our chair, Dr Nancy Krebs, as well as the other members listed here Paula Meier, Julie Mennella, Deborah O'Connor and Sarah Taylor. We also received amazing support from Deepa Handu. I'm a practicing Neonatologist at Brigham and Women's Hospital and an Associate Professor of Pediatrics at Harvard Medical School in Boston. I'm going to be covering the work that our group did on Infant Inputs to Lactation and related issues.

Ok. Here are my disclosures. I'll just give you a minute to read it. Our group really started with the idea that the infant is not just a passive recipient, but rather actively drives many lactation processes. This idea was a foundational point and really our inspiration. From this idea, we were able to delve into specific ways in which the infant phenotype plays a dynamic role and contributes to the human milk ecology again in an active way. The focus of our group was on the parent-infant dyad, but specifically through the lens of the infant contribution to this dyadic relationship, as it pertains to lactation.

Another foundational concept that we came up with early in our work was the idea that gestational or fetal experiences can drive both infant conditions and lactation processes. Here, we were thinking about disruptions in gestation that could influence both the infant phenotype and the process of lactation from the parent side, and we were also interested in continuities that might exist between the fetal environment and the postnatal environment that are relevant to lactation. We focused on four major specific ways in which the infant contributes to lactation. When we talk about lactation, what we mean is milk letdown, milk volume and milk composition. I'll start with a brief overview of each of these and then provide a bit more detail as well as highlight some of the key research gaps that we identified. However, milk removal and resulting mammary gland stimulation is the overarching dynamic mechanism by which the infant contributes to lactation. Milk removal, whether by the infant or through milk expression such as; by a pump or manual expression, is really fundamental for both the initiation and maintenance of

lactation. Net we looked at chemosensory factors and this is cross-cutting a bit from what we heard from working group 1 and 2 but we really delved into this; so chemosensory factors are tastes, smells and other aspects of the infant sensory environment that influence the infant's behavior related to lactation. Xenobiotics meaning drugs and other substances fit here as well. Here, there are some particularly interesting continuities between the prenatal and postnatal environments that I'll cover in a moment. We thought about microbial interactions, so human milk contains its own unique microbiome as most people are aware. This drives and colonizes the infant's oral and gastrointestinal microbiome. However, we consider this relationship in the opposite direction; the idea that the infant influences the microbiome of the milk in addition to the other way around.

Lastly, we consider disruptions in gestation such as fetal growth restriction and preterm delivery and how these conditions might influence different aspects of lactation, including milk composition, feeding behavior and alternative methods of milk removal.

Ok. First milk removal. I think you know a key point that we centered our work on was that, milk removal is really essential for adequate infant intake and for continued milk synthesis. I first want to highlight that milk removal has a specific definition and can be measured accurately and feasibly through the test weighing method. I saw some chatter about other methods to measure milk removal, but in our group, we talked mainly about test weighing method, acknowledging that there are others as well. The concept of standardizing milk meaning examining milk removed as a proportion of available milk in the breast is an important one in part because, the caloric density is lowest when the breast is fullest and highest when the breast is nearly drained. Milk removal includes both milk removed by an infant feeding at the breast and milk removed by either hand expression or mechanical pumping. In both cases, milk removal should be effective, efficient and comfortable for both the parent and the infant.

Some research gaps that we identified on the topic of milk removal include, the interactions of infant and maternal factors on milk removal and composition, innovations in measuring milk synthesis and removal that could be scaled in clinical or field settings. The impact of milk removal on milk composition and the optimal frequency and duration for milk extraction by pumping and how these might differ between people; which is important for individualizing recommendations.

Ok. Now onto chemosensory factors. Individualized chemosensory signals are exchanged between the lactating parent and the infant through the milk. The senses of taste and smell are mature enough at birth to allow the infant to detect and respond to a variety of stimuli including the parent scent or body odor, which can facilitate recognition and flavors that the infant may have experienced in utero. Here, we also considered substances that pass through the breast milk such as alcohol and nicotine as well as exposures such as cannabis for which data are unfortunately still quite limited, particularly in this recent era of legalization and the diversity of products that are currently available. Again, this is a topic that's cross-cutting with some of the other working groups.

Research gaps here with respect to chemosensory signals include, how chemosensory properties of milk affect infant feeding behaviors such as sleep, as well as longer term effects on neurodevelopment. Other research gaps include new methods for detecting chemosensory properties of milk and a gap in pharmacokinetic data. Now on to microbial interactions.

As I mentioned, the breastfeeding infant contributes to milk composition by its influence on the milk microbiome. One way in which this appears to happen is through the transfer of microbes from the infant mouth to the mammary gland ducts. It is interesting to note that, when the infant has an infection this may actually stimulate white blood cell concentrations and alter cytokine content in the milk. This may alter the infant microbiome and feedback to influence milk microbial composition. Gastroesophageal reflux and treatments for reflux such as proton pump inhibitors also alter the infant microbiome. This is another situation in which infant factors may influence milk microbial composition. There are many research gaps on this topic such as; what are the favorable microbial patterns with respect to infant health and development? How do other components of milk such as human milk oligosaccharides drive microbial profiles and infant outcomes? How do interventions such as probiotic, prebiotic and micronutrient supplementation act in this way? Finally, the role of pre-term birth and the hospital environment?

Lastly, we covered this idea of the infant phenotype and disruptions in gestation. Disruptions in gestation such as fetal growth restriction and preterm delivery influence both the infant phenotype and lactational processes. Pre-term delivery for example affects milk composition in that, pre-term milk is substantially higher in protein than full-term milk. Although this makes sense from an evolutionary standpoint, the mechanisms driving these differences are unknown. Aligning with the theme of milk removal, another important point is that small sick pre-term infants are not able to feed at the breast. This means that, the lactating parent becomes pump dependent either in part or in full and this can have a strong influence on milk production and removal.

Fetal growth may be disrupted, either too little growth, intrauterine growth restriction or excess growth; fetal macrosomia. Both of these conditions affect the postnatal nutrient requirements and may also influence infant feeding behavior. For example, infants of diabetic mothers who experience excess fetal growth, often have immature sucking patterns even when born full term. Research gaps identified by our group include many factors related to human milk and how to meet the unique nutrient requirements of preterm infants as well as the fetal programming of appetite signaling and how that might influence feeding behavior and drive lactation.

Here's a summary of the key points from working group 3 Infant Inputs and I also want to emphasize that there are many knowledge gaps that remain within each of these areas. Milk removal is essential for adequate infant intake and continued milk synthesis; individualized chemosensory signals are exchanged between the lactating parent and the infant through the milk. The breastfeeding infant contributes to milk composition by its influence on the milk microbiome. Finally, disruptions in gestation such as fetal growth restriction or excess and preterm delivery influence infant phenotype and lactation processes. Thank you again, for the

opportunity to present today on behalf of our chair, Dr. Nancy Krebs, as well as the entire working group 3 listed here. With that, I will pass it over to Meghan Azad.

Meghan Azad

Thanks Mandy and hello everyone. I'm happy to be here to share on behalf of working group 4, our review of research approaches for investigating human milk as a biological system. I want to acknowledge the entire working group and in particular our chair Sharon Donovan. It's been a pleasure working with this group to brainstorm and think about how we could actually accomplish research to address all of the gaps that my colleagues have presented in the previous few talks. As you've heard we need to be studying Milk as a Biological system and there are a whole lot of research gaps still to be addressed. Our job was to think about what approaches we could use to fill those gaps. I'll start with my disclosures, sources of research funding and affiliations. What I want to get through in my talk today is to briefly touch on human milk as a biological system. You've heard a lot about that from my colleagues in BEGIN already. Touch on the limitations of previous human milk research and talk about how we could use a systems biology approach to address those limitations. I'll end with some specific recommendations that our group wants to put forward to researchers in the field.

This beautiful graphic is from humanmilk.com, a great group of science communicators, looking at ways to share the wonders of human milk with the world. I love it because it shows what I want us all to think about, which is human milk as a biological system. As you've heard, milk contains many different bioactive components. Some of them nutrients, some of them not nutrients and these are all present together in a complex matrix and so, we need to be thinking about new ways to study those components all together as a system. As you heard, past research has often focused on a few components or maybe just one bucket of these components but we need to think of them all together. It's not just that human milk itself is a system, but it exists within another system, which is the parent infant milk triad. So many of us in maternal child health are used to thinking of the mother infant dyad, but what we're proposing and what has been proposed by Bodhian colleagues in this perspective a couple of years ago is that, we need to be thinking about the entire triad which you've heard about today. The mother has inputs, the parent has inputs on milk composition, so does the infant. This is very important for the formation of the infant gut microbiome and other body systems. How can we study that?

We also need to think that this system within a system exists within an environment; and so, both the physical and the social environments are influencing this triad. That triad all together as one collective system within a system, is what's influencing these many different health outcomes in infants and children, which inner of themselves are systems. You have for example, the microbiome of an infant, which has impacts on many of these other body systems. The microbiome is going to influence how much energy is extracted for food and that's going to influence growth, it's also going to help educate the immune system. The microbiome can also

affect brain development through the gut brain axis. All of these systems are interconnected and we need to be thinking about new ways of studying them in order to really move the field forward. Some of the Limitations of Previous Research on Human Milk and Lactation are firstly at a very simplified level before we even start looking at the milk. The definition of infant feeding practices to begin with. However, if you look in different studies, they have different approaches to defining infant feeding practices and breastfeeding. Sometimes, they're looking at the exclusivity of breastfeeding and their different ways of defining that. Many studies ignore the mode of human milk feeding which could be at the breast or pumped and fed from a bottle, which is increasingly common. As you've heard a little bit in previous talks, it can have an impact on the milk composition and the chronobiology, the timing of feeding milk. Also, thinking about the source of human milk, is it the parent's own milk, or is it particularly in the instance of premature infants donor human milk? All of these are important nuances and elements of infant feeding that are often not captured in research.

Equally, there is heterogeneity and outcomes, so just taking growth as one example when you find studies on infant feeding or human milk and growth outcomes, you'll find a mixture of body weight, linear growth, body composition, z-scores, weight velocity. These are all important, but having some standardized definitions of what we need to be measuring, as the most important outcomes, would go a long way to helping us harmonize resorts results across studies. There's also inconsistent reporting of human milk nutrient composition and volumes ingested. You heard in one of the previous talks, how important it is to consider not just the composition but also the volume. You need both elements of that to understand the dose that the infant is receiving. Volumes in particular are often not recorded in research and even looking at the nutrient components there are different methods used to analyze and report them.

Many previous studies as I mentioned have focused on single human milk components or perhaps single human milk component types. Studies on individual components, lactoferrin as one popular example, or component types, maybe macronutrients as a whole or oligosaccharides as a whole, but this is really not capturing the entire milk system where all of these components exist together. Many studies also focus on a single outcome which is understandable, but that's not thinking about the infant system. As I mentioned, the systems influence each other. The microbiome is influencing growth; it's also influencing brain development. Growth is influencing brain development. So, thinking of the entire infant system, is also important. Many studies are observational and this is not easily avoidable when you're speaking about breastfeeding and human milk but, these observational designs can introduce bias. It's important to think about that at the design phase and do as much as we can to avoid that.

There are some important studies that have been done; adding human milk components or human milk-based components to infant formula, which does give us some useful information. When you look at a formula with a particular component, compared to the same formula without it, you can get some important information. But there are big limitations to that type of evidence,

because it ignores the human milk matrix. Therefore, when you add a particular component to a formula, it may have a very different activity in that matrix as compared to when it's contained and ingested within human milk. Wanting to do research about these different systems: the milk system, the triad system, thinking about its environment, it's one thing to capture all this data. That is step one. Capture all the data about the milk, the mother infant triad, the infant outcomes, and the environment. But then what do we do with it all? That's a huge challenge. I think the field is at a point where the easy part is getting the data almost and the hard part is what do we do with it all? Here is where we need systems biology approaches and this is going to include methods for data integration, so just integrating all those different types of data sets. Statistical analysis methods like Bayesian modeling network analysis, deep learning. I'm not going to stand here and pretend I understand all of these in depth but I work with some great data scientists and we had some of them on our working group, informing us about how these methods which are being used successfully in other fields could be applied to human milk research. These are useful for two broad purposes, one being predictive models. By integrating all this data and using these approaches, we can then predict a health outcome for a group of infants that can be very useful particularly in the context of developing personalized feeding protocols for pre-term babies. Also, for identifying mechanisms, so many of us human milk scientists really want to understand how does human milk work, how does this matrix work, how does it affect infant health? and so by combining these data sets and using systems biology approaches to pull out the most important factors and combinations of factors, we can start to identify mechanisms by which human milk is affecting infant outcomes. So, this is one example by Nima Agupur's group. Nima is on our working group where they applied a systems biology approach to predicting and understanding preterm labor. And so, this is one of the omics that they measured; the metabolome, and they generate very pretty pictures all of the dots in this figure are different elements that can be measured and then they can use systems biologies approaches and machine learning to see how they're all interconnected. What can be done with this type of data is, it can be combined with other omics for example, in this study the proteome, the immunome, these were all analyzed in plasma or blood samples from pregnant women and through this machine learning approaches. Those data sets were integrated, combined and used to actually predict preterm labor at a quite impressive rate of accuracy. This is just one example of where this approach is being used in other domains of health research. We can learn from this to apply it to human milk research as well.

Here's one example where this is being attempted in human milk research; Kirsty Yarvin and Seppo et al. applied a system biology approach to look at clustering through partial least squares regression of different milk components. In this case, they're looking at fatty acids, HMOs, IgA and microbiota in two different populations of women. Women living in Rochester, New York and women of an old order Mennonite colony. They started to see that there are different clusters of milk profiles in these different populations. That was kind of a first step to understand

how the milk differs and how might that be related to allergy outcomes in their infants. One last example I'll touch on, is a study that I'm leading called the International Milk Composition Consortium. This is an international study where, we're comparing milk from women in four different geographic settings and then looking at all the different elements of the milk system. The nutritive factors macro and micronutrients, the microbial factors and the various different non-nutrient bioactives. This is where I was fortunate to meet Nima Agapor and his team, he's a collaborator on this project. We're using these types of machine learning approaches to understand how the whole milk system which is influenced by various different maternal factors is related to infant and child health, initially with growth and body composition as our primary outcome and then looking at others as well.

What we're also proposing in our group is that we probably need a new study, a new longitudinal systems biology study designed from the very beginning with all of these things in mind. This would involve recruiting lactating triads, collecting lots of information about the physical and social environments, the parent and infants inputs and the milk system of course. We think this study needs to really go for 10 years or longer because many of the outcomes we're interested in, do not appear until later in childhood. It is important to be mindful of the population we're recruiting from the outset. They're diverse and representing the population as well. So, we would then be collecting milk samples and other biospecimens applying omix technologies, as well as to the infant outcomes, to understand milk as a system within a system.

I won't go into detail about what we think needs to be collected, but suffice to say that we need to be collecting information on environmental and biological samples that would be collected; this would include both information about environmental samples, perhaps water, soil, house dust, samples from the lactating parent like milk but many others from the infant or child. We've suggested a range of physiological measurements or testing that would be ideal to include in such a study. This includes measures of growth, body composition, cognitive development, brain structure, endocrine, immune function, intestinal function for the infant and child, but also for the mother because wanting to understand how this influences milk. The other element of this study would be of course medical records, questionnaires and surveys. So, we've developed some recommendations around what type of information should be collected in this ideal study. This would include elements of the external ecology, of social determinants of health, lifestyle and so on, as well as information about both the parent and child. In some cases, these would be the same so, race and ethnicity, health history, medications and supplements as we've heard, can influence milk composition, sleep patterns and some elements unique to the parent and the child related to feeding practices, maternal health history and so on. Ideally, we'd want to be collecting a range of samples including not just milk, but also blood samples, saliva samples, nasal swabs, skin swabs and these would be used for a variety of analyses which are summarized here. These include the genome, the epigenome, the nutrients in milk, the microbiome of the milk and other sample types, the metabolome, proteome, all the "oms," to enable this systems biology approach.

In addition to this new study that we're proposing, there are some other important resources that need to be utilized and leveraged for human milk research going forward. First, we can have in mind is existing data sets. A lot of research has been done, a lot of milk samples have been analyzed and there's probably a lot we can learn from those data sets just by analyzing them with a different approach. We think human milk biorepositories have a role to play. I'll give some examples of those as well as online-data repositories. Once these studies are done, having a single repository where the data resides to enable them to be linked together and really accelerate research would be important. For other cohorts, we've proposed a new one but we recognize that there are lots of existing cohorts or new programs that will be planned. Being able to embed milk research and collection in those studies will be important.

I've highlighted just a few examples of these different types of resources here. I already mentioned the MILC study milk, is the interdisciplinary lactation center that I lead in Manitoba, Mommy's Milk is a repository in San Diego; LactaHub is a great resource in Australia. These are just a few examples certainly not an exhaustive list but these are the types of initiatives that we need to go forward and we need to integrate together to really maximize their impact. We already heard that human milk science is a team sport and very multidisciplinary, moving towards this type of systems biology approach, it's going to be really important to have members of various different disciplines. Again, not an exhaustive list to include parents, community members and stakeholders at all stages of this research.

Coming to our specific recommendations for the future of human milk research as a systems biology approach; first as I mentioned, establishing an online portal where researchers can upload demographic and biological data from completed and ongoing studies. Secondly, establishing a biorepository of human milk samples paired with other samples to enable systems biology research. Thirdly, developing a core list of metadata to be collected in studies of human milk lactation and infant feeding practices. I zoomed over what we think that list should look like, but having this so that people starting new studies can have a reference for what they should collect at a bare minimum using validated surveys and questionnaires about feeding practices for example and other outcomes.

Finally, this costs money. So, allocating supplemental funding to support milk research in general and also to supplement other studies that might be about to launch but maybe didn't think of collecting milk; if we can supply supplemental funding to those studies, it would be a great way of leveraging research that's already about to happen, to contribute to the milk space.

To summarize, we're proposing this new wonderful longitudinal study to tackle human milk as a biological system. We also want to leverage other resources to support this research. Together, we think systems biology approaches can be applied to both the new study and existing resources to generate new findings that will inform strategies and interventions, to ultimately support lactation and breastfeeding and improve parent and child outcomes. Multidisciplinary research teams as well as public private partnerships are going to be very important for advancing this

agenda. I want to thank all the members of working group 4 again and especially acknowledge Sharon Donovan, our Chair. I've listed on here, where you can find me if you have questions or input, we'd love to hear from you. I will pass the baton to our final speaker, speaking on behalf of working group 5, Laurie Nommsen-Rivers.

Laurie Nommsen-Rivers

Hello everybody. Happy spring to you all. I'm Laurie Nommsen-Rivers from the University of Cincinnati and I'm the chair of working group 5 of the BEGIN project. Here is my disclosure statement. As the fifth and final working group of the BEGIN project, we were tasked with developing a framework for translation and implementation of new knowledge in human milk and lactation. I would like to start by acknowledging our fabulous collaboration of NIH leadership, our support from the Academy of nutrition and dietetics. I'm sure you've noticed the fabulous graphics throughout all of these presentations. That was a really nice benefit of working with the Academy. Our work group had some guest contributions Kenneth Sherr, with expertise in implementation science and Stephanie Merlino Barr, for one of our case studies and I want to acknowledge the members of our group including Maureen Black, Parul Christian, Sharon Groh-Wargo, Jane Heinig, Kiersten Israel-Ballard, Julie Obaggy, Aunchalee Palmquist and Alison Stuebe. Our task is a little different from the previous work groups, it's less about identifying gaps in the fundamental questions and more about the lens we use to, identify high priority research needs and a framework for applying the science effectively and equitably. First, let me provide a brief introduction to Translational Research Frameworks. The National Center for Advancing Translational Sciences was established by the National Institute of Health in 2012, under the recognition that several barriers impede progress from basic science discoveries to impacting human lives. A translational research paradigm can accelerate progress. NCATS defines translation as the process of turning observations in the laboratory, clinic and community into interventions that improve health. The classic NCATS framework is viewed through a disease-curing lens, with a framework that proceeds in a uni-directional manner from bench to bedside. We have often heard of this 'bench to bedside' terminology. A lens of health optimization and disease prevention is more appropriate for human lactation and infant feeding. So, we want to look beyond the classic NCATS framework.

In the absence of an existing framework specific to human lactation and infant feeding, we looked at other frameworks that are out there and this is an example from the National Institute of Environmental Health Sciences. They coordinated the development of this highly detailed and complex translational framework that was conceptualized through a lens of environmental exposures. In the broadest sense, human milk and lactation are exposures for the infant and the lactating parent. Thus, this framework was an attractive starting point for our work group, but we desired a simpler template to communicate and disseminate key concepts across an interdisciplinary landscape. Also, within the environmental health sciences field, Joel Kaufman and

Cynthia Curl proposed a more simplified Translational Research Framework with stages that span from discovery to outcome evaluation, but going in a uni-directional manner although the middle stages include integration and cross-fertilization. We were attracted to the Kaufman and Curl framework for its clarity. We also identified areas to revise and conceptualize our framework for human lactation and infant feeding. Thus, we did receive permission from the authors, to adapt their template for our report. Here is the translational research framework tailored to human lactation and infant feeding, developed by working group five.

The first stage is discovery. This stage addresses the fundamental questions of observing, identifying and understanding human lactation and infant nutrition at the discovery level. The approach includes both basic sciences and observational studies in human cohorts. The second stage is human health implications. At this stage, we are applying discoveries to understand health implications for lactating parents and their children. This approach includes highly focused human studies. This is where we're trying to establish causation, assess feasibility, develop methods for assessment or validate prediction tools. The third stage is the clinical and public health implications. At this stage, we are scaling up the promising research from the T2 stage. This approach includes intervention studies to determine clinical or public health implications of T2 research in real world context specific settings. Approaches include individual or cluster randomized trials, randomized crossover trials, patient-centered outcomes research and comparative effectiveness studies. The fourth stage is implementation. At this stage, we inform, develop and implement evidence-based protocols, guidelines or policies, in clinical, public health or community settings. Approaches include systematic reviews, meta-analyses and research, risk communication, shared decision making and implementation science. The fifth stage is impact. At this stage, we assess attainment of health goals within the health care system, within the community, the nation, region or even globally. Approaches include utilization, expansion, or development of epidemiologic surveillance infrastructures, to assess outcomes of relevant interventions and to evaluate unintended consequences and demographic disparities in meeting goals.

Our working group wanted to be sure to emphasize that, encompassing all phases of this translational research framework are overarching principles that our root group identified as central to equitable community gains translation of the discoveries in human lactation and infant feeding. Here is a brief summary of these principles and we do go into more detail in the report. Number one, research spans, the Translational Continuum and moving from one stage to another in a non-linear, non-hierarchical manner and thus the circular format, overlaying circles of our framework. Number two, projects engage transdisciplinary teams in continuous collaboration and crosstalk. Number three, priorities and study designs incorporate a diverse range of contextual factors; and we'll cover context in the next slide. Number four, teams include community stakeholders from the outset through purposeful ethical and adequate equitable engagement that fosters a foundation of trust to prioritize work and optimize impact across

translational stages. We can learn a lot in the development of our data collection forms, from how parents really interact in their families and in feeding their babies. Number five, research designs and conceptual models need to incorporate respective maternal care and address implications for the lactating parent. All the other work groups talked about the triad. Research implications for real-world settings account for contextual factors surrounding the feeding of human milk including exclusivity and mode of feeding. It is very important for research to take into consideration how exclusive and how the human milk was fed, that is our sixth principle.

As I mentioned, overarching principle three emphasizes the diverse range of contextual factors that should inform research study design at every stage. Contextual considerations are so huge that we have a separate graphic in our report to illustrate the numerous layers of context. Most often, our research efforts focus on the individual, but it is important to recognize that this is just the tip of the iceberg when it comes to its influence on health behaviors and health outcomes.

To close, I am going to provide a very condensed version of one of the six case studies that are included in our report. This particular case study focuses on applying a translational research framework to knowledge gaps in the provision of human milk to small sick newborns in low and middle-income countries. These are simply examples among a myriad of research needs. Number one at the discovery stage, there is a need to characterize how quality of donor human milk varies according to human milk banking, screening, pooling, pasteurization etc. in the context of low-cost systems. Number two at the human health implications stage, there is a need for innovative research to support long-term lactation for parents of small sick newborns in the low-income country context. Number three, there is a need for clinical trials in this same low-income context where, we scale up the most promising innovations to emerge from context appropriate T2 research aimed at improving lactation support exclusive breastfeeding at discharge and appropriate use of donor human milk. Number four at the implementation stage, there is the need for development of best in practice guidelines for small sick newborn care in low-income country settings, through systematic reviews, meta-analyses and implementation research. Finally, at the impact stage, there is a need for epidemiologic surveillance frameworks to monitor lactation support to the birthing parent, to the human milk donor and the human milk recipient with consideration for ethics and equity.

That was a very whirlwind tour through workgroup 5 report. When our report is published, I hope you get a chance to read it and see the entire nuance in these details. In conclusion, translational research frameworks were initially established to accelerate bench to bedside progress in curing disease. However, a framework oriented towards optimizing health has potential for accelerating reach and impact of human milk and lactation research and importantly, there are several overarching considerations that are integral to an ethical and equitable human milk and lactation research agenda. I will turn it back over to our leadership for the panel.

Lindy Fenlason

Thank you! Laurie, sorry my video is going on and off. Thank you so much for your presentation and thank you to all of our speakers for sharing your time and expertise with us today. We are now going to transition to the panel portion of this event. I would like to welcome our respondents. We have Nigel Rollins, he is a scientist in the Department of Maternal, Newborn, Child and Adolescent Health and Aging at the World Health Organization in Geneva, and his work focuses on Research and Guideline Development Related to Infant and Child Health, especially Infant Growth and Malnutrition. Fatimata Fatima Sesay is a Nutrition Specialist in Infant Feeding with UNICEF/HQ in New York. Jeniece Alvey is a Nutrition Advisor in USAID's bureau for Global Health and the Office of Maternal and Child Health and Nutrition. We have Dr. Jennifer Nelson who works as a Medical Epidemiologist in the Nutrition branch at the Centers for Disease Control and Prevention with the CDC. We are running a bit short on time just because of all the rich information that was provided and I want to be respectful of everybody's time. What I'm going to go ahead and do is put forward some questions for our panelists. What I want to do for our panelists, if you could take three minutes each to respond to these questions. I realize it's a very short amount of time so, any feedback that you have to offer would be very interesting to all of us. Let me go ahead and state the questions and then Jennifer, we'll start with you and let you go ahead and provide us with some feedback. Two primary questions I have for you all. One is after hearing these presentations, what particular aspect or question stood out to you and how might this knowledge be used by your organization to support your mission? The second question is what are your thoughts on how we might be able to build a resilient system that allows us to integrate our understanding of biology into evidence-informed programs policies and messaging that support safe and efficacious infant feeding practices? Those are big questions, but I will go ahead and hand it over to Jennifer for your feedback.

Jennifer Nelson

Perfect. Thank you so much for inviting me to this panel. At CDC, our main objective is to ensure that all infants are optimally fed and that they have the support to be able to be optimally fed. Understanding both the maternal and parental inputs into infant feeding as well as with breastfeeding and the transition to complementary feeding it's super important. We are very excited that the 2020 /2025 dietary guidelines for Americans included young children for the first time. This is definitely the evolving science. It is important into informing those guidelines. We look at it from a population level and how we can ensure that all infants are optimally fed. I think understanding how to communicate the message that comes from the science is going to be very important. The work that is being done by the BEGIN group is laying the foundation for those messages and our job at the government level is to ensure that those messages are appropriately communicated.

The other big component is us gaining a better understanding of how maternal weight in the obesity and overweight epidemic play into lactogenesis and human milk. As we see, the numbers

of obesity continue to increase and understanding how that influences not only fetal growth, development and gestational weight gain, but also melt lactogenous and milk and so forth. This is an exciting time for the information in the science around the first 1000 days. There is a lot that we need to learn. Taking that basic science knowledge and translating it, is going to be critical in order to ensure that babies get the best nutrition and that, moms get support for their health as well.

Lindy Fenlason

Wonderful thank you so much for that. Nigel.

Nigel Rollins

Thanks. The whole systems biology approach is absolutely spoken on. Megan made reference to it, Jennifer made reference to it and the large boot paper was written. What was striking was that, it was written by five men and yet it was that sort of knowledge, it was great to see the presentations to get today, but our understanding of breast milk breast feeding as part of that system is a critical part to understanding the impact of breastfeeding on child health and maternal health. I don't think those perspectives are really commonly understood, accepted or just grasped by people. I think there is, as Jennifer said, there is a challenge in the communication of it and then seeing how the data helped to explain the clinical outcomes. I suppose that one of the impact of the systems biology is that, it would suggest that the impacts of breastfeeding are substantially beyond kind of the impact on diarrhea or the impact of pneumonia that we often associate with breastfeeding. I think it is also, understanding the extent of reach of breast milk composition, breast-feeding on child health that will be important in the future.

Again, we look beyond kind of maybe, historical areas of impact like morbidity and mortality. I suppose a final comment was that there is a danger however, in reducing this just down to breast milk composition and impact on biological outcomes. What is extraordinary about breastfeeding is that biopsychosocial interaction between mother and infant. There is something extraordinary about that interaction which does actually translate into biological and human milk composition changes and by a psychosocial interaction, also it has impact on health outcomes. I would urge that we don't reduce this down to an issue of composition, but that we also see breastfeeding in its entirety. I think there is something exceptional about the whole breast-feeding role and breast milk aspect of it. Thanks.

Lindy Fenlason

Thank you for raising that point Nigel. Fatimata?

Lindy Fenlason

I believe you are muted.

Fatimata Fatima Sesay

Can you hear me? Ok. Thank you. First of all, I'd like to thank the pioneers of the project for the great and inspiring presentations today. Of course, we all know and we have long established the value of breast milk and the evidence to date exists to advance our breastfeeding programs, but this additional analysis to address the existing gaps in evidence and knowledge and looking at the study of human milk from a biological approach is a welcome initiative. The approaches used to fill out the research gaps are also very good ones for me as well as the translational frameworks including the discovery, the implementation and the impact. The non-linear model for translation, as colleagues already alluded is key, because translating research, to messages, to implementation will be very important for this project. One of the speakers also mentioned about costs attached to some of those initiatives. I think it is also important if we can have costs attached to this because, it's important for fundraising.

Some of the key areas that are also of great interest include improving precision regarding the duration of exclusive breastfeeding and the understanding of the timing and composition of complementary foods. This area will continue to support our breastfeeding programs and help to better understand the importance and chronology of breast milk in the context of breast milk or expression. This resonates very well with key messages as well as breastfeeding counselling programs that, we implement across a number of countries and also developing the deep understanding of the role of donor human milk. This is an area that we have not programmed extensively enough to enable the design of safe and efficient interventions for breastfeeding support for women and families, particularly for those living in under nourish and infectious environment. While our mandate is universal and we work with all countries, it is important to know that most of our work is also focused on underdeveloped and developing context. This will be an important area of focus for us. Over. Thanks.

Lindy Fenlason

Thank you so much. Jeniece?

Jeniece Alvey

Thank you to all the speakers today and to everyone who's joined us from around the world. It has been incredible to see the participants. Thank you for being here and for inviting me to the panel. No-Breastfeeding has been part of USAID programming for maternal and child health survival programming for over 40 years because, we know it is a powerful intervention. It is exciting to see these frameworks and the BEGIN project in general. Looking for knowledge gaps to fill in this area, I think some things that stood out to me from the presentation particularly is that, this framework is not looking to establish a normal range of human milk composition, but

understanding and affirming that there are going to be variable ranges in humans we are, biological systems with variations ourselves.
Something that will really be important and that stood out to me from the working group five is that, all of the ethical considerations that will be necessary for every part of the Translational Framework, of all of the research that would be done across the working groups, especially the global communities, countries, governments and academic institutions that will work with engaging more local researchers in this conversation, is going to be critical having them lead research in countries where we'll need information to fill some of these gaps. It is going to be absolutely critical for filling some of this knowledge gap.
I also want to highlight that, these are interesting and very important gaps that we have about human milk composition, but there's still a number of gaps that we're seeing in how we close the support getting policies that enable environment. There is still so much research that needs to be done on how we can most effectively support families and maybe, some of that will come through this research. But I think there are other more socio-political things that we need to also be looking at, to be able to support the triad. Those are the things that have stuck out to me most and are relevant to the work at USAID. Thanks.

Lindy Fenlason

Thank you Jeniece. Thank you to all of our panelists, all of our speakers, all of our participants who have hung in with us over time. I am going to go ahead and hand it over to Dan who will go ahead and give closing remarks.

Daniel Raiten

Thank you, Lindy. I want to thank my partner Lindy Fenlason and the teammate in Advancing Nutrition. I want to thank everybody who has been involved in the bond project, the BEGIN project. You have reinforced the notion; Nigel is great at pointing out key aspects. It is not just about human milk composition but our ecological approach did highlight the environment and the importance of the context in studying how best to feed our babies and so, and that is our goal. Before we leave, I would like to quickly give Andrew Bremer an opportunity to say hello and goodbye on behalf of NICHD. He has been the force behind our ability to pull this project. Off. Dr. Bremer?

Dr. Andrew Bremer

Dan thanks. Thanks to everyone. I am sorry that I was having connection problems at the outset, but this really is a 'tour de force' from Dan and Alison. To all the speakers today, I want to say profound thanks. This project is extraordinary, but just like its name implies, it is just the beginning, we are committed to the science of supporting understanding of human milk, and that is a joy to work with such committed scientists and individuals on the ground to make this happen.

We are a little bit over time and I apologize but I want to thank everyone for tuning in. I want to thank all the working group members at BEGIN, the BEGIN leadership, for the opportunity to present today and to be a part of this global discussion. Please take care of yourselves, stay safe, be well and enjoy the rest of your day.