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Venture capitalists address NICU need

At a Glance

Opportunity

Renowned researcher Katherine E. Gregory sought to improve bedside care for preterm infants to anticipate the onset of necrotizing enterocolitis, a potentially fatal condition.

Action

Gregory partnered with Philadelphia-area venture capitalists Astarte Medical Partners to launch NICUtrition, a software platform that includes a bedside feeding dashboard and a way to assess gut-inflammation risk.

Result

Ben Franklin Technology Partners of Southeastern Pennsylvania provided Astarte Medical with critical seed capital. The company is currently raising a $4 million Series A round of financing, and forecasters predict revenue of $25 million by 2020.

Medical research, financial partnerships yield breakthrough products to improve care, survival for premature infants

By M. Diane McCormick

Tracy Warren and Tammi Jantzen are experienced investors, comfortable in the health care space. They're accustomed to providing the venture capital that ushers products from research lab to market.

But a meeting with renowned researcher Katherine Gregory, steeped in the vital but mysterious matter of nutrition for premature babies, prompted an entrepreneurial shift. It was time to investigate the problem first and develop solutions second.

"We didn't know what the product would be," Jantzen said. "We were very interested in her work and specifically in working with her."

Fifty years ago, babies born too soon had little hope of survival. Science and technology have heightened the chances, but they have not delivered a mechanism to optimize nutrition and monitor the crucial factor of gut health. A sudden and devastating intestinal condition called necrotizing enterocolitis, or NEC, can deal setbacks leading to developmental consequences and death.

From a restored stone mill in a Colonial-era town outside of Philadelphia, Warren and Jantzen have partnered with Gregory, also an experienced neonatal intensive care nurse, to give hospitals the software and analytic tools to monitor preterm infant gut health, scrutinize the nutritional data collected at bedside, and assess the risk of NEC. On the brick walls of their office, artful photos of premature babies, in doll-like but very human dimensions, remind them why they're doing what they do – saving lives one at a time, while capturing and using data to improve survival chances for preterm babies.

Challenges and opportunities

Since 2001, Warren and Jantzen have worked together at three venture capital funds around Princeton, New Jersey. They have targeted health care and, in 2013, decided to focus exclusively on women's and children's health.

"It's an area that's totally underserved," Warren said from the Yardley office of their firm, Astarte Medical Partners. Traditional venture capital struggles to address health needs "that are very specific to women. You can't imagine them talking about menopause and vaginal dryness. It's not as easy to talk about as cancer or heart disease."

With the difficulty of the conversations, "those companies struggled to get money, even though we knew from our networks that the market was real and large," Warren said. "It's an opportunity we saw."

For several years, Warren and Jantzen invested directly in companies addressing this underserved market. They visited women's and children's hospitals, seeking insights into their varied clinical needs.

Along the way, they met Katherine E. Gregory, Ph.D., RN, executive director of women's and infant health and Haley nurse-scientist at Brigham & Women's Hospital, and assistant professor of pediatrics at Harvard Medical School.

Gregory's early-career work as a registered nurse at the bedsides of premature infants led her to recognize the lack of insight into the essential practice of feeding. In particular, it was time to pull back the veil blocking the ability to predict NEC and its consequences.

Warren and Jantzen knew researchers. They had worked with many on prior venture fund efforts, typically of the institutional spinout variety. Gregory inspired confidence from that first meeting.

"She was the kind of person who makes you say, when you walk out of the room, 'We'll figure out what the product is,'" Warren said. "She was worth spending that time and energy and effort on."

From the investors' perspective, Gregory paired academic and research credentials with hands-on clinical experience. She was a nurse, trained in primary caregiving and deft with on-the-spot solutions. In the NICU, Gregory dealt with the inexplicable onset and effects of NEC, but "instead of just being frustrated, she went and got her Ph.D. and decided she was going to solve it," Warren said. "That's the kind of person you want."

Added Jantzen, "Her passion was clearly evident, and she's very easy to understand. She can talk to laypeople, she can go toe to toe with experts in the field, and she does great in every circumstance. That all came through when we met her the first time."

Gregory's clinical and research experience revealed a tandem need – to improve bedside care and to anticipate the onset of NEC. That revelation led to the creation of NICUtrition, a platform for two products. One was NICUtrition Guidance, a bedside feeding dashboard. The other was the development of a gut health score, called NICUtrition MAGI, collating data from individual electronic health records into a kind of vital-sign reading that indicates the risk of gut inflammation.

The preterm gut and NEC

Every year, 450,000 preterm infants are born in the U.S., and 55,300 of them have very low birth weight, born at less than 3 pounds and requiring an average NICU stay of 77 days. With NICU costs averaging $6,000 a day, care for babies born before 32 weeks of pregnancy accounts for $13 billion in annual hospital charges.

Preterm infants "come into the world too soon," and health consequences follow, Gregory said. Proper development of brain and body depends on the area of the body that clinicians and researchers call "the gut." It can be synonymous with the gastrointestinal tract traveling the length of the body, but typically the term zeros in on the small and large intestines.

"We are most interested," Gregory said, "in the small intestine." In particular, she is attuned to the gut's microbiome, that ecosystem of microbes interacting and promoting the infant's health or illness. The gut microbiome has the power to break down food, manufacture vitamins, and ward off allergies. When the microbiome goes wrong, gastrointestinal disease "can be associated with poor neurodevelopmental outcome — poor growth and developmental outcome," Gregory said.

Just like full-term babies, preterm infants require constant feeding, about eight times a day, Gregory said. But that's where the similarities end. The preterm infant's feeding — and its impact on the baby's immediate and long-term development — proceeds according to an "enormously complex" system that determines the type of feeding, quantity, and nutritional fortification each time.

"The software we're developing," Gregory said, "is helping to expedite all of that."

Introducing technology will help hospitals adhere to feeding protocols — the lengthy and complex decision-making procedures relied on to determine the how and what in each feeding. Hospitals develop their own protocols, "but these guidelines are not always followed," Gregory said.

Research is clear on the value of hewing to protocol.

"The truth is, we don't really know the very best way to feed a preterm infant," Gregory said. "What the literature has shown is there may not be a perfect way to do it, given all the complexities, but if you follow a standardized approach in your clinical setting, the outcomes are better.

"NEC is really, really catastrophic for families and also for the clinical team taking care of these kids because they've survived that early period of immaturity, only to develop this complication," Gregory said. "Sometimes we talk about it as a disease of survivorship."

NEC survivors face "greater risk for neurodevelopmental impairment," Gregory said. "It's a disease of the gut, but we also need to consider it a disease of the brain, because these babies don't have all the same advantages. They have often-interrupted growth and never grow the same way that their unaffected counterparts do."

In the NICU, apprehension over NEC's appearance can cause clinicians to veer from protocol and make suboptimal feeding decisions, including the use of antibiotics. "Sometimes we're concerned about whether the baby is progressing OK," Gregory said. "We think the baby is getting sick, but it's not really getting sick."

About 7 percent of very-low-birth-weight babies get NEC, "but that means 93 percent are not going to get NEC," Jantzen said. "Yet we're treating them all as if they could. If we knew which ones were trending toward NEC, or the ones not trending toward NEC, then we could be making better nutritional decisions."

In this atmosphere, the NICUtrition software is designed to institutionalize the delivery of feedings according to hospital protocol. Of course, it's good for babies and the clinicians who care for them. But from there, the team pushed its thinking to straddle Gregory's intertwined clinical and research lives by striving to answer all those questions about optimal feeding and the prediction of NEC.

Linking "all the disparate information" in the infant's medical record to umbrella measures of intestinal inflammation can help clinicians and protocol writers "better understand how we might use microbial interventions in the ICU," such as pre- and probiotics, Gregory said. "We know there is likely a place for microbial interventions, but we're not sure how it should be deployed."

Product development

After their initial meeting with Gregory, Warren and Jantzen spent about nine months reading research, attending conferences, and talking to experts. They discovered numerous but disconnected papers on clinical nutrition, NEC, gut inflammation, and other factors. All influence or are influenced by the microbiome, but they are separated into siloed buckets of research. Enough data points emerged to show that the team could create an intersecting tool.

Then came the investment questions – how to create, commercialize, and make money from a proprietary product?

"It'd be great to solve this problem, but unless you're a social enterprise, you have to figure out how to make money," Warren said. "That was where we spent the bulk of our time, both validating the need but also figuring out how you put a business around this. We had, far too many times, seen inventors or CEOs or companies come in with great solutions, but they couldn't make money. As investors at heart, that's where we started."

Warren and Jantzen founded Astarte Medical Partners in 2016 to commercialize the NICUtrition platform. Building a global brand around Astarte, the goddess of love, fertility, and defense of children, the initiative launched with $1.2 million raised from the founders and Astarte Ventures. Astarte Medical is currently raising a $4 million Series A round of financing. By targeting Level III and Level IV NICUs, the two highest levels of neonatal care, forecasters predict revenue of $25 million by 2020, with positive cash flow in the fourth quarter of 2019.

Ben Franklin Technology Partners of Southeastern Pennsylvania recognized Astarte's potential from the beginning. Ben Franklin, a state-related program, partners with venture capital for the public-spirited purpose of leading the region's technology community to new heights, creating jobs, and changing lives for the better.

Special practices are a must when feeding premature infants

Feeding an infant is a delicate exercise. However, feeding a preterm infant requires additional precautions.

Full-term infants can be sustained with breast milk or formula. Neonatal intensive care units (NICUs) use parenteral feeding for preterm infants for several weeks before introducing enteral feeding.

Preterm infants are afflicted with gastrointestinal immaturities such as an inability to coordinate breathing, sucking, and swallowing. Enteral feeding a preterm infant from birth can have negative health impacts, such as necrotizing enterocolitis. Through parenteral feeding, NICUs meet the infant's energy needs and prevent catabolism and other detrimental health issues. Many NICUs use gavage feeding to provide breast milk or formula to the infant.

The common practice of feeding preterm infants is early parenteral nutrition, followed by combined parenteral and enteral nutrition, before phasing to complete enteral nutrition. Many NICUs will not allow a preterm infant to be discharged until it successfully latches on to the mother's nipple or a bottle.

Ben Franklin provided Astarte with critical seed capital – and more, Warren said. It introduced the Astarte team to The Innovation Partnership (iPart), a consortium of Pennsylvania economic development and business assistance organizations aiding Astarte's quest for federal Small Business Technology Transfer support. Ben Franklin Director of Investments, Health & Digital Health Jennifer H. Hartt "has been a good reference with angel groups, and we have received press and exposure due to them," Warren said. "We are huge fans of Ben Franklin and hope to continue to leverage their expertise and introductions."

Ben Franklin saw the value of Astarte's work, Hartt said. The unmet medical need in gut health "can have lifelong consequences for those born preterm. This approach is informed by a newer understanding of the role of the microbiome as nearly a vital organ in its own right. Astarte's system will also allow clinical staff to track feeding and nutritional status with much greater granularity and management in the digital health record."

With the investment, Warren and Jantzen realized that software and data science could merge into a product when Gregory demonstrated a NICU nurse's entry of feeding information into each patient's electronic health record. It looked like a spreadsheet but was "terribly laid out," Warren said. "For them to just document feeding a child took 15 steps."

A software engineer brought into the process delivered the happy news that creating a dashboard for entering and managing all that information was a simple matter.

NICUtrition Guidance

For preterm infants, complex protocols start with determining the volume of feeding the baby can tolerate, followed in time by amping up caloric density.

"When you start life as a 500-gram infant, we only feed based on weight," Gregory said. "All of this is an evolving target every day. The nurses do this by second nature, but we know there are places and ways in which we can make this easier."

Complicating the process is that information inputted into what Warren called "the bowels of the EHR system" is very difficult to retrieve. In the NICU, clinicians might not know what happened and why from one feeding to the next. And from one week to the next, administrators can't connect the dots from protocol adherence to outcomes, whether on the basis of individual babies or institutionally.

The NICUtrition Guidance dashboard hurdles above those clinical and administrative challenges by bringing standardization — based on the hospital's own protocol — to feeding through the gut.

Clinical dashboard

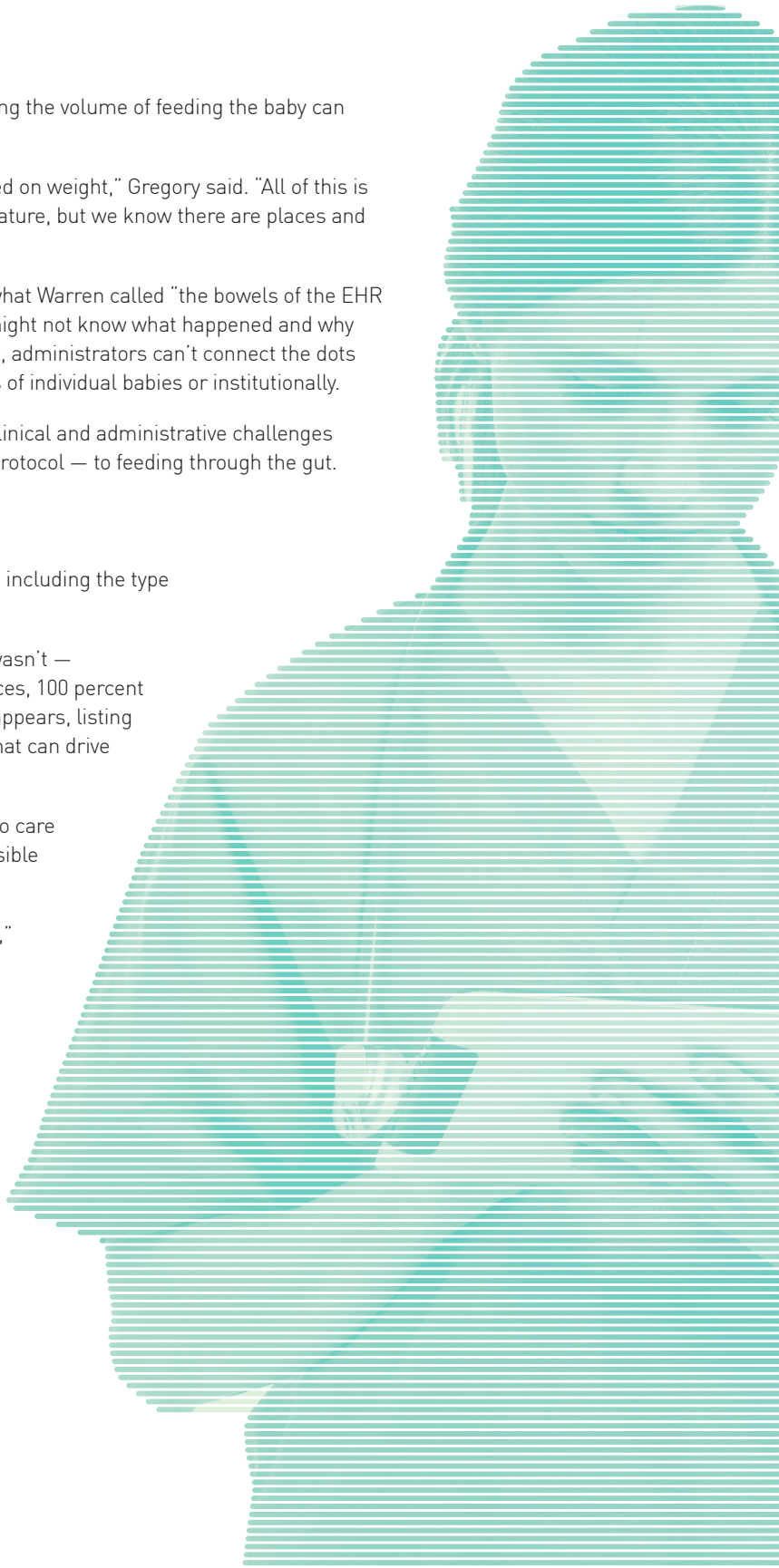
On the clinical dashboard, a nurse enters a range of details, including the type of nutrition and calories delivered at each feeding.

The nurse then enters whether protocol was followed. If it wasn't — and with each patient's complexity and evolving circumstances, 100 percent compliance is considered impossible — a clickable screen appears, listing all the possible contraindications and signs of intolerance that can drive the decision.

All the data immediately populate the EHR, freeing nurses to care for patients and providing the next shift with instantly accessible documentation of previous feedings.

"We were joking that we are replacing a Post-it, but it's true," Warren said. "We've resoundingly heard from hospitals that they know this is what they want to do, but it's impossible in their current EHR environment. We have very quick sales meetings. The nurses love us. The nutritionists love us. The neonatologists love us."

One neonatologist told them, "When I do rounds, there are all these things in my head I'd like to do, and when I'm looking at the screen, I'm seeing everything I've wanted to see."



Administrative interface

As real-time data accumulate, NICUtrition Guidance generates analytics for hospital use. Administrators can pinpoint the complex patients showing the most variability in outcomes. They can access a graphic showing where protocol is most frequently veered from, raising the possibility of revisiting and revising those sections. They can see staff varying from protocol, with or without reason.

"Modified is one thing, but modified without reason is where we have opportunities for education and training," Warren said.

With the advent of value-based care, NICUtrition Guidance shows measurable improvements in outcomes as health systems strive to meet quality metrics. Perhaps most powerfully, it represents "the first time an institution will ever be able to look at how its kids are being impacted by its ability to follow or not follow its own protocol," Warren said.

After pilot testing that includes data integration and vendor security review, the software is expected to be commercially available by the end of 2018.

Advances in feeding and caring for preterm infants:

1890s — Drs. Pierre-Constant Budin and Stephane Tarnier advocate early feedings of breast milk and popularize gavage feeding

1903 — Martin Couney treats premature infants with incubators and displays the babies in a Coney Island sideshow

1913 — Dr. Julius H. Hess establishes the first U.S.-based unit for premature infants in Chicago

1922 — Hess publishes the first book on premature infants and advocates for delayed feedings with breast milk from a wet nurse or through gavage

1940-1965 — Hess and others advocate for delaying fluids and feedings to premature infants through the first 96 hours of life

Post-World War II — Hospitals begin to create Special Care Baby Units, precursors to modern NICUs

1947 — A study finds that feeding premature infants a diluted "half-skimmed cow's milk formula" helps them gain weight faster

1950s — Necrotizing enterocolitis is first named

1960s — Total parenteral nutrition (TPN) is first used in premature infants, as well as advocating early provision of fluids/feedings because of severe health concerns

1970s — A new study stressing protein quality, not quantity, provokes interest in using breast milk in premature infant care

1980s — Special formulas for very-low-birth-weight (VLBW) infants are commercially developed

1990s — TPN becomes the standard of care for very-early-in-life VLBW infants

The MAGI score

In October 2016, Astarte launched a study, with Gregory as principal investigator. Called BabyBiome, it began at Brigham & Women's Hospital in Boston and onboarded Massachusetts General Hospital in summer 2017. The study characterizes the preterm infant intestinal microbiome "based on measures of intestinal inflammation and specific clinical factors related to the preterm infant," Gregory said. By study's end, the goal is completion of "an analytical model that will predict the intestinal microbiome of the infant based on clinical factors and measures of intestinal inflammation."

In noninvasive form, the project collects naturally occurring urine, fecal matter, and blood spots from preterm babies born under 34 weeks of gestational age. Since completion in November 2017, Gregory's team is sequencing the biomarkers from the samples. Then, she cross-checks them against more than 200 metadata fields in the EHRs of 80 babies, including factors about the mothers, modes of birth, antibiotic use, feedings, and growth information.

It all goes into a "giant data set that will form the basis of MAGI," Warren said. After analysis by industry and academic experts, followed by data science and machine learning experts, they will launch BabyBiome II. The second phase will be much larger, targeting 300 infants in two or three additional, large labor-and-delivery hospitals.

After the thorough validation of BabyBiome II, MAGI should be available for clinical use by late 2019 or early 2020. As envisioned by its founders, MAGI will cull from its "phenomenal library" of data to provide a gut health score and inflammation profile for each individual infant.

"Our vision is that it's sitting on the patient profile dashboard, just like your blood pressure and heart rate," Warren said. "It's sitting as your gut health measure."

Though it's "a work in progress," Gregory sees the MAGI score putting the research-revealed biomarkers of NEC — the early signals, essentially — into clinical practice. "Using all this data through a big science manner would give, not quite a test, but a profile that would say this baby is increasingly at risk for getting NEC, so you should do this." The hope is that NEC can be averted if the signs are spotted and acted upon, she said.

Potential customers for MAGI include clinicians seeking bedside guidance and their health systems seeking better outcomes for NICU patients. Plus, "by default," payers want to see healthier preterm infants and a drop in the average NICU stay of 77 days, Warren said. "That's a big target."

Other potential customers are nutritional companies developing early infant nutrition, seeking assurance that their sophisticated formulas relate to the baby's environment and individual circumstances. Finally, microbial therapeutics companies are seeking tools like MAGI to connect their therapies with the right patients at the right time, for ultimate personalization. Better outcomes to show the Food and Drug Administration, Warren noted, promote shorter time to market.

> "...there may not be a perfect way to do it...but if you follow a standardized approach in your clinical setting, the outcomes are better."

NICUtrition "started with this vision of gut health, and now that we are looking at the space more clearly, we realize that standardizing the practice of care is the first step in personalizing medicine," Warren said. In clinical settings, understanding the microbiome can elevate development of nutrition guidelines and delivery beyond the old concepts of calories and volume.

"We know now that people are very different in how they can accept one or both of those, and that's the new level of sophistication and nutrition that we're going to see across the lifespan," Warren said. "I think it's most important for our babies."

Building knowledge

Heads nod when Warren and Jantzen share with potential investors and customers the research showing the detrimental impact of gut inflammation on neurodevelopmental outcomes.

"By attenuating that, you would see better physical and immune-mediated outcomes — asthma, allergies, obesity," Warren said.

Ideally, Gregory said, the NICUtrition approach will "trim days from the hospital length of stay and ultimately improve growth outcomes and prevent gastrointestinal disorders. With all of that taken together, our thought is to improve their long-term neurodevelopmental outcome."

From her lab in Boston, Gregory puts the issue in historical perspective. In 1963, the nation grieved along with President John Kennedy and first lady Jacqueline Kennedy when they lost a baby boy born slightly prematurely.

"That baby, who would have been a very straightforward child to care for today, didn't survive," Gregory said. "The truth is, we've made huge strides in not that long a period of time, but we are still learning about the nutritional needs of these babies. There's still a lot we don't exactly know."

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