The NNE-CTR Quarterly Newsletter

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NORTHERN NEW ENGLAND CLINICAL & TRANSLATIONAL RESEARCH NETWORK

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A Message from Our PIs

Clifford Rosen, MD

Dr. Gary Stein, Ph.D.

The NIH Investment in NNE-CTR Data Science

There is rapidly evolving recognition for the necessity of data science to support clinical and translational investigation. The public health response to the COVID-19 pandemic decisively demonstrated the importance of data for life-saving decisions with immediate and broad-based impact. Capturing the analytical power and enormous potential of medical informatics, we are poised to provide guidance for health and healthcare practices and policies that are consequential for prevention, early detection, treatment, and survivorship of both acute and chronic diseases that we encounter in rural northern New England.

To accelerate NNE-CTR capabilities in data science, our program recently received several NIH grants that are significantly expanding our data-driven capacity and capabilities. The multimillion-dollar investment in data science is supporting partnerships of our Vermont and Maine NNE-CTR scientists, physician investigators, and clinicians to innovatively utilize Electronic Health Record data for clinically informative investigation. The investment will enhance development of novel dimensions to a cancer surveillance screening network that provides guidance for cancer prevention, early detection, and initial indications of disease recurrence. Support will be provided to guide strategic approaches for community engagement through development of messaging that addresses the challenges of rural healthcare hesitancy including vaccination, testing, and support of care. And, through our collaboration with the Northern New England Co-Op Practice and Community-Based Research Network, data science-based initiatives that emphasize rural northern New England primary care practices will be a priority.

The investment in data science has been slow in coming. But contributions that are emerging for clinical decision making and public health policy provide evidence-based confidence in the value added by the NIH data science investment for immediate and long-term acceleration in the clinical translational research mission of our NNE-CTR.

--Gary & Cliff

Washing Away the Acronyms

Flood debris gathered by volunteers in Waterbury, VT

The medical-research-public-health world we work in is full of acronyms, starting with the very title of our organization, NNE-CTR. But names carry power and create connection. While the drenching Vermont experienced on July 10-11, 2023, lacked the sudden drama of a tropical storm such as Irene, it has nonetheless picked up a name: The July Flood. The flood's victims all have names, too, and they have individual stories, something you realize when you dig out your worst clothes and sign up to help those who found their lives suddenly afloat in silty water.

In our daily commutes or errand runs, we all pass by countless houses, but how much do we know about what's going on inside? Then comes the flood, the uninvited visitor. Then comes the volunteer, the invited one. And everything changes the moment you walk across the threshold. You arrive with a floor squeegee and muck shovel, but you soon understand that part of your work involves another set of tools—your compassion, your ears, and whatever kind words you can muster that don't sound like platitudes. You find yourself speaking human again, leaving behind the professional patois that pervades our work lives.

As you fish memories out of spaces that threaten to turn into swamps, or, squat in a hot yard rinsing off the hundreds of tiny guitar parts that comprised someone's hobby; as you reassure the woman who wants to help but is nursing a swollen knee from too many trips up and down a set of narrow, rickety basement steps, or as you look for some direction from the man who paces aimlessly in the drizzle as he admits he doesn't know where to start … you're smacked with the embarrassingly simple revelation that everything is about each individual human story, and that none can be described in shorthand.

It's a reminder that in our public health work, it's perhaps too easy to float in our own shorthand, deadlines, degrees, and arcane particulars, to talk more with each other than with the community at large. To think about people as statistics. To substitute terms for names. So, for example, the elderly woman with the swollen knee becomes a person with "co-morbidities" when, in truth, she's a person with a name and a story that's over 76 years long.

Maybe the space you enter is redolent of a years-long smoking habit. Maybe there are dusty stacks that threaten to topple over into scarce free space. Maybe political leanings and accents differ. But these are neighbors, and communities are made up of them far more than the relative few of us in our academic-medical world. They vote, they volunteer, they patronize local businesses, they have life stories—and ultimately, their tax dollars support much of what we do.

The definition of neighbor shouldn't be reduced to the concept of mere physical proximity – the houses we drive past.

In this issue of the NNE-CTR newsletter, you'll read about research that affects our communities for the better. This work often requires us to communicate in the language of acronyms and data but in the end, what we do is about people with names. Our work, as well as our ability to speak human, will be increasingly needed in the years ahead—because we can't expect support from people who don't know what we do, and we can't learn what they need unless we know how to listen, and we can't expect them to accept our help unless they understand how we're helping.

In these times, no matter where our brains or bodies live, the floodwaters eventually touch us all. This is a chance to do better. Together, we face intersecting issues of climate, planning, housing, resilience and more. The common thread running throughout is health. It will take all of us, pulling on the same oar, to address these challenges. And so, the definition of "neighbor" shouldn't be reduced to the concept of mere physical proximity—the houses we drive past. It should be about shared goals and opportunities.

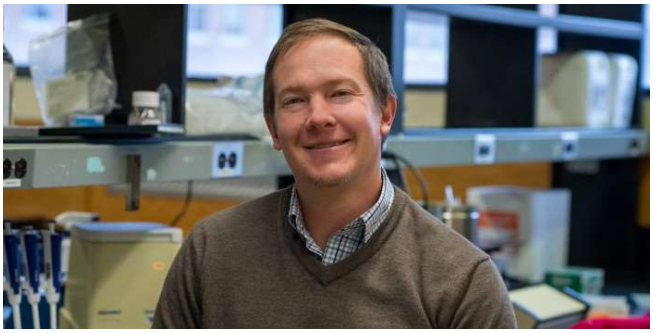
The July Flood of 2023 was an opportunity for us to learn names and listen to stories, to de-acronym our work, to remember why we do what we do. And it serves as a reminder that, the next time we get the opportunity to step across that threshold, we should gratefully accept the invitation. We'll all be better for it.

Investigator Spotlights

Editor's Note:
Beyond highlighting the terrific work of NNE-CTR pilot project investigators, we have a nakedly ambitious goal: We want you to picture yourself in their shoes. All great projects start with an idea, and your NNE-CTR is here to support and promote the kind of research that makes for a healthier northern New England. If you have a great idea that could use a boost, consider our pilot projects program.

We hope you enjoy meeting two pilot project investigators, Dr. Seth Frietz, and Dr. Constance van Eeghen. We think you'll find their work most interesting and inspiring (and we hope it inspires you to consider an NNE-CTR collaboration as well!).

Collaboration and the Cancer Counteroffensive



Seth Frietze considers himself a lucky guy. Spend a few minutes with the University of Vermont researcher and one thing is clear: He understands the value of support--both in building careers and in conducting potentially life-changing research. We recently chatted about Seth's NNE-CTR pilot project and his work around the gene CDK12 and breast cancer.

Matt: So, you're an 18-year-old and you're heading off to college in Las Cruces. What was in your brain back then? What were you interested in?

Seth: I was never really a strong student in high school, but [after] getting my first organic chemistry course as a sophomore. I made the switch from pre-med to becoming a scientist and my professor introduced me to research and that was a great opportunity.

I just fell in love right away and I remember the time I told my mom that I wanted to be a biochemist and how impressive that sounded. … And then I liked science from there, and I got good grades and all my science classes.

Matt: What keeps the fires burning there? Is it the chemistry of it or is it what the chemistry can do?

Seth: Well, I think the chemistry was like the fundamental training and the way of thinking about interactions and molecules … But then, as a graduate student, I was more interested in the how you can apply the chemistry or the quantitation of different molecules to more systematic approaches and so work as a graduate student focused on breast cancer and applying more genomic approaches--comprehensive analysis of some of the characteristics of the cells--and then trying to study that which requires computers. In chemistry, I liked the use of computers to do some modeling and I think there's some similarities there in the biology side of things, too.

I've been interested in breast cancer for some time, mostly from the biological perspective. In cancer, we want to understand how we can target specific vulnerabilities of different types of cancer cells. You can take a population of people and group them into different types of breast cancer and some of the most common ones have some signatures that are directly targetable, and drugs have been made and it's really improved those patients' life based on this precision medicine approach.

And I've been lucky thanks to collaborations with Gary and Janet Stein and Jane Lian. We have an exciting NCI NIH program project grant together that looks specifically at breast cancer and I've learned so much from that. Interacting with their research groups closely [and with] breast cancer pathologists and physicians actually treating patients [such as UVM oncologist] Peter Kaufman … has really helped make me more of an expert in the area of breast cancer.

Matt: I wonder if you could just talk for a moment in general terms about how cancer is this thing that people are scared of but actually has a lot of weaknesses.

> *"If we could solve a basic problem, we might open up a new set of doors for understanding this mechanism and maybe exploiting it as a potential therapeutic vulnerability for a specific group of patients."*

Seth: One of the research focuses of my lab is to systematically and comprehensively characterize patterns of molecules in certain types of cells. [We use] a large cohort of many different types of breast cancer patients, collect all that information and then group them to identify underlying mechanisms that drive those diseases by comparing them with each other and seeing what's different or what's similar.

This process is one way in which we search for targets, and we look for things that might be important to consider as an idea to go after. And there might be some interesting underlying biology in that pathway too, that, if we could solve a basic problem, we might open up a new set of doors for understanding this mechanism and maybe exploiting it as therapeutic vulnerability for a specific group of patients.

Matt: OK, so you have the therapeutic target. What would you be targeting that with?

Seth: We take a two-pronged approach. We take a pharmacological approach where we can try to target that pathway using commercially available small molecules that we just buy and solubilize and the goal is to measure if the cells respond to the treatment--the drug--and then try to get some controls and understand if that's true for this specific subtype of breast cancer or maybe other breast cancer types as well. The genetic approach is to take those same cell lines that you know are making these targets [and] you might want to manipulate that pathway genetically.

We've also been implementing a methodology in large part thanks to the NNE-CTR—it's called chemical genetics--and we can use both genetic approaches and a chemical to inducibly remove a target from a cell within minutes and then test the impact on the proposed function of that target pathway.

By comparing the genomics of different breast cancer patients, we found that this gene CDK12 was highly expressed in HER2-positive breast cancer, which is interesting because it may mean that [cancer cells] have developed some sort of dependency on it for their growth … and so this could represent an obvious target but we don't really understand how CDK12 may function to give those types of breast cancer cells a growth advantage.

So, one question we can ask is does making more of this protein in these cells make them more aggressive? You know, is this part of a pathway that that confers some of these cancer properties? We have the experiments for this one particular project ongoing and we've made a lot of progress. We've actually generated a lot of the data; we just need time.

Matt: Would be an optimal outcome for your pilot project?

Seth: Pilot projects are an opportunity to generate preliminary data for a grant application and hopefully publish a paper. So those would be the two best outcomes. I know we'll publish a paper and I know this data is gonna go into a grant application, so already I think we've scored because we've been able to help generate some of the data.

In the best-case scenario, we're able to study this in HER2-positive breast cancer cells and show that specifically in those cells that there is a vulnerability. We can learn that not only is it a target, but learn how it's acting as a regulator to promote breast cancer. And so [UVM Health Network oncologist] Peter Kaufman, our clinical partner, is going to be really helpful with the translational results.

Matt: Localize your work for me. The NNE-CTR's focus is on the health of rural northern New Englanders, and as we know, cancer outcomes are generally worse in rural areas than in urban ones in the U.S. What comes to mind when you think about your work and the population our CTR serves?

Seth: It does affect our population quite significantly compared to others. We've been able to the curb the disease a bit, but we still need to figure out how we can better do that. I believe we'll be able to greatly improve the outcome and the quality of life for many cancer patients.

Matt: What would you say about the NNE-CTR to other experienced or early-career investigators?

Seth: I'd say it's been great to be part of the NNE CTR as a member. They provided a lot of support through pilot funding, which you know is critical for establishing preliminary data to do further research. The process has been straightforward. The applications are easy and the administrative process is great, which is really important. I'm thankful for the administrators both at UVM and Maine. They've been really patient and helpful.

Pilot Projects Program

A Careerlong Passion for Making Things Work Better

To understand Dr. Constance van Eeghen's NNE-CTR pilot project, you want to start with a term that is bandied about in different contexts and that even means different things to different people: "clinical and translational science."

Now hold on. Before you think, "Yeah, got it" and move on, linger here a moment--because in our complex healthcare world, it's not only that the left hand often doesn't know what the right hand is doing; there might be a hundred right hands and five hundred left ones all trying to do the right thing—and often getting frustrated when the results are less than ideal.

Enter Connie. As she explains, she's been interested in getting hands to work together for a long time …

Connie: I was a healthcare administrator (in Vermont) for over 20 years. I worked at Fletcher Allen Healthcare, now UVM Medical Center and I also worked at the Copley Health System. And so, my interest was, so we have all these great ideas; how can we make them happen? And I went back to school (for a Ph.D. in 2012) to try to understand that--not knowing it was already a field called clinical and translational science, or how do you take what you know you should do and make it what you do do?

Matt: What does that look like in your current day-to-day life?

Connie: I teach in the program called Clinical and Translational Science, which is graduate students from a diverse set of backgrounds that are interested in understanding how these things all connect together and also teaches clinicians to be scientists and to look at their work from a not just a how do you care for a person perspective, but how do you do that in a way that also adds to the field of knowledge? … So, I went from being an administrator to being a researcher and educator in one kind of idealistic jump. I [wanted to] find the key that would help people actually do what it is they think they should be doing and not have to keep doing the things that they know are ineffective, which is in so many industries in so many places and just eats the heart out of people and their willingness to keep trying.

So you have to know what to do, but also have to know how to implement that and there is another whole field of science called Implementation Science, which is part of CTS (clinical and translational science) in a sense that says we are going to study not just the good clinical practice we should have, but the implementation methods that make those practices actually work and make a difference. So, I call myself an implementation scientist. I am a sort of people organizer.

Matt: Let's talk about how all this applies to your NNE-CTR pilot project.

Connie: So, in opioid prescribing patterns … we're trying to say, "How do we make it easy for people [to] help their patients manage unmanageable chronic pain? What are the tools that a medical provider has to try to help that person regulate their life in a way that they can enjoy it and do productive things with it?"

Now it happens that measuring pain is impossible to do from the clinicians' perspective without asking the patient. There's no pain-o-meter. The only person who can tell you is the person who's experiencing the pain, and with that the relationship between the provider and the patient becomes paramount. You know, do you trust the person? And does the patient trust you? What this project is about is what kind of data can we give [healthcare providers] that is factual, that is objective, that will help you have a conversation.

> *"How do we make it easy for people [to] help their patients manage unmanageable chronic pain? What are the tools that a medical provider has to try to help that person regulate their life in a way that they can enjoy it and do productive things with it?"*

In our world today, every single state in our country has created a Department of Health database called a prescription drug monitoring program, or PDMP. The PDMP allows providers to look at their patients from a perspective of what did they actually pick up from the pharmacy? Not what did [the doctor] prescribe, but what did they receive? And not just the pharmacy … prescribed to them, but any pharmacy in the state of Vermont and prescribed by anybody in the state of Vermont. So, if they're getting their help from more than one provider, that's easy to see, too.

So, one way to use the PDMP is for the prescriber to say, "Well, you're coming into my office; let's take a look at your prescription record and see how that's been going" as a way of starting a conversation like, "Did you pick up the medications, you know, did you not?" [This is the] part of the conversation that builds that relationship.

The data can also be used in another way that's allowable by state law, and that is for the providers to say within a practice, "I want to see my history of how I prescribe. Am I prescribing this patient a lot overall or not that much?" All those different things that say, "Am I doing a good job helping this patient or not?"

[A provider could] say. "Ohh, I'm this kind of prescriber and if I and my colleagues and my practice did that together, we could look across each other's practices … and the story could unfold of a practice essentially doing a quality improvement project around how they prescribe opioids, which in these days is a hot issue because people who can't get their pain managed one way will seek to figure out how to manage unmanageable pain in a different way.

Our team is theorizing that we'll make it easier for providers and their surrounding practice members to say, "Ohh, this is how we're doing." There are different variables that we can get out of the electronic health record that helps us map, not the drug itself, but the behavior around the drug use. So, in that way we can see whether or not currently the practice is following CDC guidelines and we can report that back to practices and say, "Does this matter to you, does this make a difference, do you think it's helpful?" without ever violating patient confidentiality or the rules around using the PDMP.

Matt: You've done a lot of projects in your life. How does this one feel compared with those in terms of the support you've gotten from the NNE-CTR?

Connie: The NNE-CTR has been fantastic. They're good people. They respond quickly. They meet with us on a quarterly and half year basis and are super supportive and helpful and did a lot to help us move forward. So, I really, really appreciate the support that we got from them.

Matt: Let's put your project in the context of rural helping rural communities from a public health perspective in northern New England.

Connie: We are mostly going back to the idea of how to help people make changes happen. It takes the chaos out of life when you can manage pain and you don't have to [ask] relatives and loved ones try to do the impossible. It's it really is about that it's making people's lives manageable and fun and enjoyable and rewarding.

Matt: And you're talking about both patients and the providers?

Connie: Absolutely.

Benefits of Your NNE-CTR Membership
(And a call for new members!)

The NNE-CTR was founded in 2017 with the mission of improving the health of rural northern New Englanders. Like any six-year-old, your NNE-CTR is growing by the day--learning, exploring, meeting people, making connections, and getting better at what we do. So, what is it that we do?

We bring together community members and organizations, researchers, advanced equipment, mentorship, and administrative assistance to address the unique health challenges of rural northern New England.

See yourself in any of these roles? Thought so.

As we look toward year seven, we want to hear more from communities about their needs. We want to hear more from early-career researchers interested in generating new knowledge. In short, whoever you are, we want to hear more from you. This is how we build our organization and help the communities we serve.

If you are receiving this newsletter, you are likely already a member of the NNE-CTR. So here is what we'd like to ask of you:

- If you have been on the periphery and would like to know more or do more, get in touch!
- If you know someone who would benefit from joining the NNE-CTR, forward them this newsletter or send them here: Learn more about NNE-CTR membership **HERE.**
- If you have questions you've always wanted to ask, email us **HERE.**

Let's grow a great NNE-CTR together!

What Are You Up to These Days?

Do you have a story to share or work you would like us to highlight? An idea that our members should know about? Let's put it in our newsletter. Email matthew.j.dugan@med.uvm.edu