***The First Line of Defense* - Episode 4 Transcript**
Kenner Family Research Fund

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This is The First Line of Defense - Primary Care Clinicians and Early Detection of Pancreatic Cancer. This podcast is brought to you by the Kenner Family Research Fund, focusing on collaboration and information sharing as a way to make earlier interception of pancreatic cancer a reality.

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In this special bonus episode, Chris Sander explains how his research on AI and machine learning are being used to help with early cancer detection. Here's Chris Sander to speak more on AI. I first was motivated to work on the cancer problem because of a family member who died of cancer. And since then, it's been a gradually rising consciousness of.

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This may be important in terms of using one's scientific effort to actually solve an important biomedical problem.

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I'm Chris Sander and the Department of Systems Biology at Harvard Medical School. I work in competition biology with a strong emphasis on artificial intelligence and machine learning, with applications to important medical and biomedical problems. There's nothing like working on a biomedical problem, a difficult problem that will gradually be of benefit not just to patients, but also the entire system.

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And so I'm very glad to have moved from computational biology, where we dealt with protein structures and genetic sequences. Yes, you said in the background, but now use the latest techniques of computational data sciences and move that into something that matters to patients, to their families. And I'm very glad that Barbara Kenner actually got us involved with the biomedical community and the patient community nationally and internationally.

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And that's really been an additional motivation for us to work on pancreatic cancer. And we'll move this forward also to other complicated, aggressive cancer types. How did you get involved in that? Very specific and important part of research in medicine. A few years ago, Phil Sharp, who is the chair of the advisory board of an organization called Stand Up to Cancer, organized a meeting of several experts in the medical and machine learning community and suggested that perhaps I could be used to assess the risk of pancreatic cancer.

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Initially, I was very skeptical in this meeting. I thought it was too ambitious. It was too hard. We didn't have the right kind of data, and this gradually grew on me. And particularly because of all the input from all the experts in the room, but also because I was aware of the importance of high quality medical data. And I knew that in Denmark, where we started, we had a very high quality data set of clinical records and also other sources.

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They gradually became aware of collaborating with the health center at Dana-Farber, for example. And so, we applied and I got funded by the Stand up to Cancer organization. And so it's really due to Phil Sharp and his initiative that got us involved. And it's now become the most important problem that I'm working on. So why did you pick pancreatic cancer?

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Pancreatic cancer is a very aggressive cancer. 80% of patients when the cancer is detected have a very bad prognosis. Only 20% survive approximately five years and only half of those. So it's very important to move the needle from late detection to early detection. And this would be a benefit both to patients as well as to the medical community overall, because it will simplify and make the treatment less aggressive and early and more effective in assembling this collaboration.

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It was very important to involve teams at several institutions and across continents. So we collaborated, with a group in Denmark led by a systems biologist, Sharon Bruno, and funded by the Novo Nordisk Foundation. And then in the US, we collaborated with the Dana Farber Cancer Institute, the Hale center. They're led by Brian Halpin, involved the Harvard School of Public Health, Harvard Medical School, where I am as the overall coordinator of this project, and the Veterans Administration, who have a very well organized national database of patients.

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And so the two key ingredients were one, assembling an international collaboration between Denmark and the US with access to high quality data, sets, funding from different organizations such as the Stand Up to Cancer Organization, the Novo Nordisk Foundation in Denmark, the Hale center for Pancreatic Cancer led by Brian Open at Dana Farber. And then bringing this together in a very collaborative way, which was facilitated but also made more difficult by the pandemic, facilitated because we were able to actually easily connect to people by zoom nationally and internationally.

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We made it more difficult, but we couldn't actually meet in person. So the project took longer than I thought it would be. But after three years and some difficulties solving a lot of problems along the way, we managed to get a reasonable assessment of the pancreatic cancer risk from clinical records using AI. The use of AI in the research community has gradually increased over the last 10 or 15 years, in ways that are quite amazing.

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We know this natural language processing well. Recently the ChatGPT and other tools. I publicly only hit the news and everybody else, everybody's perception quite recently, but it's actually been a long term development. So in research, it's Harvard Medical School in particular. We were aware of a lot of different methodologies that are used in AI that we could use to address this difficult problem of predicting the risk of cancer from a collection of very complex data sets.

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So it's true that AI has recently been in the news, but the actual scientific development has gone on for some time. And so it was important for us to be able to use the existing methods three years ago and apply them in a new way to this important biomedical problem. So applying AI to clinical records that define the risk of pancreatic cancer, most importantly, it was initiated using pancreatic cancer.

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But there are other very aggressive cancers which present late with very bad prognosis. For example, ovarian cancer. What other cancer research areas are employing this type of approach for detection? So we're actually very interested in working next and in parallel to the next development of pancreatic cancer on a variant cancer. There are others like triple negative breast cancer, a positive breast cancer that's very aggressive, certain subtypes of colorectal cancer.

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And so we and others are positioned to broaden the scope of this kind of investigation to look not just at pancreatic cancer cells, ovarian cancer and other aggressive cancers, and to define popular patients at highest risk so they can be looked at more precisely with better methods. And then the cancer could be detected early and treated early. So this is really something where machine learning and AI, with the right kind of data and the right kind of methods, could be applied very broadly to the problem of cancer detection early and cancer treatment early.

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We're working on that. And I think over the next 3 to 5 years, I expect a number of different investigators and groups collaborating with clinicians to develop methods like this that are applicable across the board, beyond the initial, most aggressive cancer types of pancreatic cancer and ovarian cancer.

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So it's obvious that this is a potentially powerful tool for early detection. How do you perceive this actually moving forward into an institutional system? What steps need to be taken? It's one thing to be able to do research and publish in one of the accepted journals the results of the investigation of how accurate a prediction of cancer risk.

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It's another thing to actually be able to apply this now in clinical practice, and this will require very close collaboration with the AI experts, clinicians and the health care systems, including hospital leadership. And very important aspect of that is initially not to focus on the entire population in terms of who gets the close surveillance for early symptoms, but to only take people at highest risk who are detected not just using standard risk factors, but the ones the risk factors that are detected by the entire corpus of clinical records in AI.

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So our focus in applying this in hospitals will be to identify populations just at the highest risk for example, 1000 out of 1 million. And then nominate collaborating very closely with the hospitals, with clinicians and with providers actually to have expensive detailed tests applied that have a chance of detecting the cancer early and then subsequently, then once it's detected, of course, to proceed to early treatment.

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So this requires collaboration between AI researchers, clinicians, hospital systems and providers. And applying this and in reality, it's very important to to involve the entire community, including clinicians, hospital systems and patient advocates to make sure that a we get this right

in terms of benefiting patients, too, to make this affordable, in terms of actually applying these advanced tests to people who then might get cancer detected early.

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And number three, to actually have it tested in a clinical context, to make sure that it holds up and improves over time and becomes more broadly available. Do you have any sense of this algorithm needing to be adapted for different groups, taking, for example, location, age, or gender into consideration? Or is it an algorithm that could work for all groups in developing this algorithm?

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Further and applying it in different countries, in different locations, it's going to be very important to be aware of the ethnic differences of the socioeconomic differences and other population differences, because there are maybe important differences in the clinical histories of patients that are predictive of cancer, that depend on various environmental factors, socioeconomic factors, ethnic factors have already seen some evidence for that.

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By looking at the databases in Denmark, as opposed to the VA, different national and different backgrounds. And so we can and will refine the method so we can actually assess the accuracy across different population groups, in particular different socioeconomic status, so that one can actually draw conclusions as to how best to apply this and make sure disadvantaged groups are not left out.

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The method as such with appropriate care, can actually be applied to these different groups in ways that doesn't require a lot of methodological adoption, but very refined data sections. And then assessing the accuracy for these different parts of the population, and applying these methods for prediction of cancer risk in different health care systems. There are two important aspects.

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One of them is the level of coordination among different sections of the health care community. In Denmark, we have a national health care system, which makes things much easier both in terms of coordination as well as the quality of data in the US or North America in general. It's a bit more complicated. So the community has to come together to do something like the VA has done with the national database with reasonable coordination, and we have to overcome, I think, the fragmentation between different providers, different health care systems for two reasons.

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One is we have to make sure that the data on which these predictions are based are sufficiently accurate and can be improved further. Number one. Number two, in applying this, each institution will have different conditions. And so to apply this methodology, once you have the software that works, you will have to work with each location and each health care system to make sure it can be number one, retrained and adapted to the particular health care system.

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And number two actually would work as intended for the different populations. And so that's a major challenge. It's one important thing is to make sure that the AI methods are improved and the accuracy. And we are working on that as well as are others. The other important aspect is to make sure that the AI method is applicable to different locations and is implemented in different health care systems.

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Nationally, we have a challenge to improve the coordination and the accuracy of data across the board. One element of hope in this direction is actually the All of Us program by the federal government that is going to nominate patients for close investigation in terms of a blood test sequence of the genome, and then opt in to actually make your healthcare data available.

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And that then in a very protected way, will be made available for researchers. Once we have that initially 1 million that could then cover larger fractions of the population, we will have at the national level, hopefully one database that's very good for this kind of research, based on which can then develop a method to develop the practice of actually rolling this out in clinical surveillance trials.

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That will be then hopefully applicable across the board. One important caveat that this method, as currently worked out and published, is not yet directly applicable in clinical settings. We'll have to do another round of improvement of the methodology, and then work with conditions at selected hospital systems to actually try this out or work it out in a clinical trial in a hospital setting.

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Having said that, going forward, there's a major opportunity to go beyond the cancer centers or the hospital systems around cancer centers, which are high quality and where clinicians often

are very good at detecting the symptoms, such as unspecified jaundice or abdominal pain, and many others. Clinicians in advanced hospital systems may actually find that the patients, which are identified by the AI system at higher risk are people who they themselves would have identified at high risk.

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But there are many more that they might have missed. Now, if you go across the board in the country to local health care centers, community hospitals and so on, the expertise there, even though they are well trained, may not reach as far as in the more advanced centers. So to apply this in the future, I think that the community hospitals and in fact, local health care practices could benefit substantially for having software that is trained on selected populations initially, where there is high quality data, but then applied in a local setting where both the expertise and the background data is not as as complete.

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So I can make a contribution to help, especially locations where perhaps the medical expertise is not quite as advanced as it might be in the neighborhood of cancer centers. One important aspect of applying this in practice is the fact that the software once is developed and clinics get tested. It's actually quite inexpensive in applying it to people's health care records.

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That's the inexpensive part. So in a certain location could be any state. You might have a million patients, and it takes a very small amount of resources to then run this software and apply it to them. And then you take the ones with highest risk and nominate those for a surveillance program with more expensive tests. So the first part, and this is the good news, once they have the software is quite inexpensive.

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The application then to do surveillance programs is more expensive. And that's where the local communities and the hospital have to work with providers. Also to gradually move to a situation where those tests for the populations at higher risk are covered by insurance companies and national providers, including, of course, Medicare and Medicaid, which in my view would be great to expand.

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But that's just my personal opinion of how we get to a more efficient health care system in the future. The cancer problem is obviously a worldwide problem, and we've learned from the recent pandemic where we've also done some work that is very important to keep in mind the benefit of

the population on the entire planet. We think that these methods of using AI in cancer research will be applicable in many different countries, adapted to different locations.

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We've already worked with Denmark and with the U.S. health care systems, and in the future, we hope that this will be broadly applicable also to other countries where we started to talk to clinical researchers in the UK that have a national organized health care system, the NHS, that the UK Biobank. But they've already sequenced half a million genomes and genetic information is important.

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I've talked to people in Germany as well with their health care system that also suffers from fragmentation. So in the future we hope to assemble collaborative networks between different countries, to strengthen the research and make sure that these methods are broadly applicable beyond national boundaries, because cancer is a global problem, and I think we can be of benefit doing this kind of work to benefit patients anywhere.

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There are indications that there is increasing interest and international collaborations beyond what the NIH is funding in the US or the upper age, which is a new program in the US. beyond what happens in the UK with the Cancer Research UK or what happens in Denmark with the Novo Nordisk Foundation. These are all very interesting, powerful, philanthropic and national funding systems.

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There's indication that there's interest in both funding and collaboration across national boundaries. So we're talking now to sign up to cancer, the NIH, Cancer Research UK, the Novo Nordisk Foundation and others to see whether or not we can find an international funding mechanism. And based on that, collaborations beyond national boundaries that would advance this in a major way.

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Regarding some risks and concerns around AI. How are patients' health records and medical data being protected? So there's a substantial discussion, especially now, about the risk of AI in general. And it's true that, if I use social media beyond what we saw in 2016 and what we saw in the Brexit situation, it could actually be quite risky.

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Having false information being generated. And yes, there is a risk of AI in general that we have to mitigate and deal with and perhaps legislate and regulate. However, in the medical community, the good news is, number one, the patient data is very well protected through the HIPAA law. And to ongoing practice in hospital systems and medical practices. So health care data is one of the best protected kinds of data that we have nationally and internationally.

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Actually, that's one point of good news. The other point of good news is that medical researchers are sensitive to the fact that any kind of software can only provide decision support, not make decisions. So the software we're developing and we're going to make this point again and again, is not AI software that makes any decisions or generates any information that's spread out.

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It's only information based on patient records provided to the clinicians for decision support. The clinician will get the results of this, and then she or he will look and make a decision with other colleagues and with the patients as to a whether or not to nominate somebody for a surveillance program, and B, what are the consequences of that, and at the same time advise them as to what it means to be at high risk.

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So I use the clinical setting as decision support is a key aspect of that. And the risks that are currently broadly discussed in the community about the risks of AI are not relevant for the medical setting, with very well trained doctors who learn medical ethics through their entire medical school career. And so I think we're safe in terms of data protection for the HIPAA laws.

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And number two, we're safe in terms of clinical practice, building on the ethics in the medical community. Another aspect of identifying patients' high risk and then working with them to nominate them for surveillance programs is the fact that this is already happening for selected populations, for genetic risk, if somebody has a broken mutation or for a family history, somebody who has a history, a family history of pancreatic cancer.

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Important research has been done in the community, and there are surveillance programs for people with genetic risk and with family history. And this genetic counseling that takes place for people at highest risk. And this is a well known practice. Clinicians already have implemented surveillance programs for people at genetic risk and people with family history. And, we can connect to the existing ethical principles in those consultation sessions where clinicians

communicate the risk to patients, nominate the importance of its evidence program, and then draw conclusions from that which could be go home, no problem, or come back every six months for an MRI.

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No problem. Until we find it, there's a chance of finding the cancer early, and then we can treat you early. And so the message to patients is that this is something to your benefit. And if you're nominated for a surveillance program, this is not something to be afraid of. It's like PSA tests for men or mammograms for women.

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In current clinical practice, it's well established. The goal here is to actually find the cancer early and treated early. And if anything, this is of benefit to you. What are the steps in identifying patients that are at high risk for certain types of cancers? Medical practitioners is already very good when somebody has a nominal pain or some other indication to take a close look at them, and they know for the most part of how to look for early signs of cuts, and they know how to look for early signs of pancreatic cancer through MRI, CT scans and this Copic ultrasound.

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This is fairly routinely done. So the opportunity here is to nominate additional people in the population based on their clinical histories that are then looked at closely. And the way that medical practitioners already can do is just broadening this spectrum of who gets looked at finding ways of paying for that. And that gives us a chance to go beyond the family risk and genetic risk and now broaden gradually, more and more people who get looked at early and then have a chance of getting the cancer detected early, or we find that they don't have cancer.

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And then that, of course, is very reassuring as well. I research to look at clinical records and identify patients at highest risk for certain types of cancer. Really are the first step in the three step program. The first step is to identify the risk and identify people who would benefit from a surveillance program. A second step is in the surveillance program.

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The cancer would actually have to be detected early. And then the third step is once you detect it early to treat it early as well. So what researchers can contribute here is to make a contribution to that first step. And it has to be done in close collaboration. Then with the second step and the third step. So risk definition of risk number one.

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Number two early detection. And number three early treatment. And so the entire community are researchers, clinicians and people that developed biomedical technologies will have to work together to make this happen in the real world to move the entire spectrum of cancer care gradually. Earlier, to move it to earlier detection, which will be number one to patient benefit. And number two will also be economically important because earlier treatment tends to be less expensive than the very expensive late treatment.

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So that's the major opportunity and challenge to collaborate between AI researchers and people who develop early detection methods and clinicians who then would use this and would be able to treat cancer early. Currently, there are no population based tools to screen broadly for black hat, for cancer, only for people with family history and certain genetic mutations that predispose them to pancreatic cancer are screened in a targeted fashion.

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But such targeted screenings can miss other cases that fall outside of those existing categories. And so the opportunity of using the entire clinical history of patients, rather than just pointing to family risk or genetic modification, is to broaden the spectrum. And what I am particularly good at is to analyze a large amount of data and find the combined data items that indicate an early risk of cancer.

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So this is not just one individual risk factor, another individual risk factor that are added up. And they way you would, for example, in the clinical trial for late onset diabetes is people above age 50. But this is actually looking at 2000 different disease codes and the sequence of those in family history. And that's where I have additional power beyond what's already done for screening programs in limited populations based on family history and genetic mutations.

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Once the methods have been improved and tested clinically, the AI approach for cancer risk could expedite detection of pancreatic cancer and other very aggressive cancers can lead to earlier treatment and improve outcomes. And this, of course, and this is our intent, is to the benefit of individual patients and their families, but also has some economic impact on the health care system because of reduced costs of treating cancer early, rather than treating cancer late and improving these methods and rolling them out to patient benefit and the benefit of early detection of cancer, it will be important to use not just the clinical histories as we currently have done with international disease codes, but also that add

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additional data like blood tests, the drugs people take, prescriptions, perhaps domino scans and other kinds of data that become available through wearable devices that are increasingly accurate and collect more data. So we look forward to improvement of these methods gradually, with availability of more data and basing it as well organized clinical data beyond just the disease codes, including medication and other kinds of information.

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That's actually very important to assess the health, state and disease state of a patient and the gradual emergence of cancer, because we know that cancer actually arises over many years, and it's only detected late after it's actually become a problem. So overall, the research and the application challenge is to find ways by AI and also by other methods to find ways of detecting the emergence of cancer.

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And then as soon as it's detected, treat it early. So I'm trained as a competition biologist and have helped form the field, in fact, over several decades. But recently, learning from our graduate students and interacting with the Michigan community. Over the last 5 or 6 years, we've increasingly learned methods which go beyond the typical computational biology methods and use AI adapted from natural language processing, adapted from other areas of AI research, and move them into the biomedical arena in ways that we hope will be productive.

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It turns out that AI is particularly good at dealing with large data sets that are complicated and sometimes noisy, and for sure, health data. Disease data is very complicated. It can be somewhat inaccurate, and we need large scale data with increasing accuracy, with good coordination to do even better. We learned this over the last 5 or 6 years, and I would like to encourage anyone in the biomedical research field to take a good look.

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Learn more of these methods, be critical in the way these are used, and then apply them intelligently. With all the caution that we need in clinical research. As clinical research moves into clinical practice, the success of the ultimate application of AI for this kind of biomedical problem, and the bigger contribution that the cancer problem will have to come from increasing collaboration between AI researchers, clinicians, and medical practitioners in a way that sometimes work.

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But we should make an effort, I think, to bring this community together in ways that Barbara Kenner has pioneered and others stand up to cancer, without collaboration across these different areas of expertise will be short of what we'd like to do, which is to benefit patients that suffer from cancer.

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Here, as doctors try to provide context on this study and how and where it's most applicable. In a recent article in Nature Medicine, Doctor Chris Sander and his group published a paper that applied machine learning to electronic medical records to predict subsequent development of pancreatic cancer. The strategy they used was to identify patterns in diagnosis that appear in a patient's medical record, and a sequence of diagnosis predicted pancreatic cancer development in the subsequent months to years.

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They use this in the Danish registry and in the Veterans Administration database in the United States, and both of these contain longitudinal medical records of patients and their respective populations, and so they were able to look at sequential appearance of diagnosis and use that to predict future development of pancreatic cancer. The disadvantage is that logical medical records are the bane of all of us trying to do research.

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United States people get fragmented care. They go anywhere and everywhere, and don't have logical records in one place. To me, it's incredible that the First Nation in the whole world doesn't have a health wallet where all the medical information of one person is spread, and so somebody can go and check that. And we struggle to put the pieces together because they've got four different hospitals and the records are scattered all over the place.

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And that's informing the VA. And the Kaiser is an exception to the rule. And even VA patients who are well off go outside and get care outside. So they're quite old pieces of information even in a VA patient can be missing because they've got elsewhere to get care. The Danish registry is way more contained. It contains every single interaction between the patient and the health care system.

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Within Denmark. And so it would be contained and you could track every single interaction between the patient and the healthcare field. Whereas in the United States this is uncommon. Integrated health care systems like Kaiser Permanente do have this available for those who stay within the system long enough. But for the majority of people in the United States, the

information is scattered across multiple institutions, and they still don't have a way to integrate this in a consistent manner. There are attempts being made to do this using software like Care Everywhere, etc. but it's still not a reality.

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And doing such studies when the records are scattered across multiple institutions is nearly impossible. So at this point, this study is best applicable to integrated health care systems, where patients get longitudinal care within the same system. Even with the multiple challenges inherent in AI, this study represents a much needed and valuable step in earlier cancer detection efforts.

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Thank you for listening to The First Line of Defense - Primary Care Clinicians and Early Detection of Pancreatic Cancer.

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