So it’s a pleasure to introduce Jeremy Warner, who actually I first met this year when I was chairing a panel at ESMO and he was one of the speakers who we invited. Jeremy is the director of the Brown Lifespan Center for Cancer Bioinformatics and data science and associate professor technically pending I guess, at Ed Brown. His clinical focus is hematology and he received his medical degree from Boston University and also in a Masters in
Photonics and Electrical and Computer Engineering from UC San Diego.

In addition to his focus on malignant hematology, Dr. Warner is a leading expert in the clinical and translational cancer informatics research, including high dimensional data analysis and visualization, natural language processing of narrative oncology texts, and the creation and implementation of health data standards.

Before coming to Brown, Jeremy was at Vanderbilt.
University Medical Center, where he was an associate professor of medicine and biomedical informatics.
And I should also note that he is the deputy director of Escos Clinical Cancer Informatics Journal and a founding director of the New Brown University Center for Cancer Bioinformatics and Data Science.

So without further ado, you're going to speak to us about using and improving real world ecosystem in cancer.
Hey there. Ecosystem in cancer. Thanks. Look forward to it.
Thank you. Thank you so much for having me.
And if anybody wants to come up to Providence, just one stop away on the Acela, so. Really nice that we’re so close here.

In New England, so I just have a few disclosures first before I get started. So I have some grant funding, some consulting. I do have ownership in hemlock.org LLC, but has no monetary value unless one of you wants to be an Angel investor and we can talk after the presentation. So what I’m going to talk about here is you know why, why do we need real world data and real world evidence in oncology and I’m going
to focus on electronic health records.

There are other sources of real world data of course, but you know most of this talk will really focus on the ER, in particular interest in mine which is standardizing systemic anti cancer treatment representations and then I’ll spend some time talking about our COVID and COVID-19 and cancer consortium. Which is a bit of a culmination, if you will, of some of these thoughts.
So there are some learning objectives here. If hopefully this is a CME, so we'll cover, you know, some aspects of natural language processing and how it can be used to get information out of EHR’s, why we need formal representations for complex concepts. Such as systemic anti cancer therapy and then learning about how these these ideas went and propelled the COVID, the COVID registry. OK, so first of all, you know, probably everybody might be already
familiar with these definitions, but I think it’s always helpful to go over, you know, what is real world data, what is real world evidence. And you know, it’s nebulous a little bit and depending on where you, you know, the resource you look at, you’ll get a different definition. But this is my definition, which is really based on something called the I kW pyramid. Has anybody heard about this? Heard of the DKW? OK great. So teach you a little bit here. So the idea here is that it’s a pyramid where you’re climbing a
00:03:53.980 --> 00:03:57.179 levels here from a base of data.

00:03:57.180 --> 00:03:58.640 The next step is information.

00:03:58.640 --> 00:04:00.320 The next step is knowledge.

00:04:00.320 --> 00:04:01.360 The next step is wisdom.

00:04:01.360 --> 00:04:02.608 You’ll know there’s 5 levels here.

00:04:02.610 --> 00:04:04.938 There’s a little tiny level at the top

00:04:04.938 --> 00:04:07.540 which some people use you for understanding.

00:04:07.540 --> 00:04:10.242 But basically the idea is no matter

00:04:10.242 --> 00:04:12.719 what where the data comes from.

00:04:12.720 --> 00:04:13.698 What it is,

00:04:13.698 --> 00:04:15.654 whether it’s from a randomized control

00:04:15.654 --> 00:04:18.524 trial or case control registry,

00:04:18.524 --> 00:04:19.160 etcetera,

00:04:19.160 --> 00:04:21.020 the idea is that as you move up this pyramid,

00:04:21.020 --> 00:04:22.792 you’re generating real-world evidence,
whereas real world data is really that base.
On the right here you see the sort of traditional pyramid of evidence based medicine.
So if you look at this from another dimension kind of looking from above, when we think about cancer in particular, you know I think about sort of three big aspects of cancer, there’s the genotype, the phenotype and then the environment and sort of for each of these you have these layers.
So, so if you think about the data level for genotype that might that’s just the sequence right, just the somatic tumor sequence.
For phenotype, it might be just a histologic type, a cell, you know what, what is that? And for environment, it might be pollutant levels. Now this is data, but it’s not really telling you anything, right. So we need to kind of walk up this pyramid. The next level for for these three buckets would be for genotype and environment. You might talk about pathogenicity. What does that change mean in terms of is it, is it a driver mutation? That’s sort of the next level information
cancer behavior on the phenotype.

Side so is it, is it aggressive, is it a high grade malignancy or is it something indolent kind of stepping up further? For genotype knowledge, the knowledge level is actionability. What can you do with this information? Can you actually prescribe a medication that will change the outcome for a patient? Phenotype, same, you know, just generally speaking what are the treatment options and then the
environment are there risk modifications that can be taken and then really getting to that top level wisdom, you know this is really complicated now. So in phenotype you’re thinking about what are patient values and preferences and how do those influence what treatment options you might consider for genotype, what’s the tumor going to do once it gets exposed to treatments, how is it going to evolve under treatment pressure and an environment you’ve got issues about social justice.
And structural racism.

So those are all kind of like.

The ideas of climbing this pyramid alright,

hopefully I've convinced you the difference between data and evidence as we kind of step up.

Now, why do we need this real-world evidence?

Well, clinical trials are wonderful, but they're also expensive, slow to conduct, and they don't always represent the full population. At risk also trials, prospective trials, collect some but not all potentially pertinent information. And our space is huge.
Oncology, the treatment space and oncology is huge. And then lastly, I think last but not least is that we’ve got this enormous data source, which is the electronic medical record. So just a few words about each of these items. So when you think about trials and disparities, this is a paper we just published very recently and this one was earlier this year and we just published another one in Jim Oncology looking at prostate cancer.
This one looks at immune checkpoint inhibitors across cancers.

And basically the take home message here is that when you look across Childs, there is really a lot of disparity in who enrolls in trials. And it can be different by cancer type, but it’s pretty consistent across the board. Sometimes it’s over representation, as you can see from the bottom row.

In this case, gender, age, race and ethnicity, and a cancer type where the enrollment is as you’d expect.
00:07:48.640 --> 00:07:50.296 If it’s green, it’s sort of more than
00:07:50.296 --> 00:07:52.240 you’d expect, and if it’s red, it’s.
00:07:52.240 --> 00:07:53.360 It’s less than you’d expect.
00:07:53.360 --> 00:07:55.230 So. So you know this,
00:07:55.230 --> 00:07:57.270 this gets that generalizability and there
00:07:57.270 --> 00:07:59.289 might be statistical ways around this,
00:07:59.290 --> 00:08:03.298 but you know, essentially.
00:08:03.300 --> 00:08:05.355 Our knowledge from clinical trials
00:08:05.355 --> 00:08:08.082 is primarily coming from younger.
00:08:08.082 --> 00:08:12.410 White men, OK, so.
00:08:12.410 --> 00:08:14.386 How about the information that gets left out?
00:08:14.390 --> 00:08:16.700 So this is, this was amazing.
00:08:16.700 --> 00:08:18.674 This is the recovery group that
00:08:18.674 --> 00:08:20.679 really geared up during the early
00:08:20.679 --> 00:08:22.863 days of the COVID pandemic and found,
you know, pragmatic trials that they ran in the UK and they found some really important treatment options for COVID. This is one of their papers. This is probably the most impactful look, showing that dexamethasone could help hospitalize patients with COVID. And I've excerpted a table from that paper.

So this is a table of previous coexisting diseases in the patients who have COVID. Is there something missing?

From this table.
00:08:58.170 --> 00:09:02.237 Something that’s the topic of this talk.

00:09:02.240 --> 00:09:03.114 Cancer, right.

00:09:03.114 --> 00:09:05.736 There’s no cancer in the stable.

00:09:05.740 --> 00:09:07.426 They did not collect cancer and

00:09:07.426 --> 00:09:09.170 and or they didn’t report it.

00:09:09.170 --> 00:09:11.319 Well, we actually, we actually went and

00:09:11.319 --> 00:09:13.718 you know got their case report forms,

00:09:13.720 --> 00:09:14.816 they didn’t record cancer.

00:09:14.816 --> 00:09:16.830 So here they enrolled 10s of thousands

00:09:16.830 --> 00:09:18.410 of patients in these trials.

00:09:18.410 --> 00:09:19.970 And they don’t know if these

00:09:19.970 --> 00:09:21.270 patients had cancer or not.

00:09:21.270 --> 00:09:23.130 And so I mean, amazing work,

00:09:23.130 --> 00:09:26.834 but we’re missing a key piece of information.

00:09:26.840 --> 00:09:29.036 And then sort of the last item you know
that I met that I mentioned before is

this idea that our treatment space

is huge but head-to-head comparisons

of important drugs are mostly absent.

And I’ll just give you one example.

So this is the space of PD1 inhibitors

which have changed our obviously changed

our fields from our hemac knowledge

We have 137 trials that have been published

using 64 different regimens of of various.

This includes XUS by the way.

If you’re like they’re not 13 P you

want to have actually there are,

but many of those are only approved in China.
So 83 of those are phase three trials. The take home point is one of those 83 actually compared to PD1 inhibitor to a PDL 1 inhibitor kind of it. It’s compared to Kobe matanov and atezolizumab and that’s the grand total. Of zero of these trials compared 1PD1 inhibitor to another PD1 inhibitor so. You know, maybe I’m missing some trials that are ongoing now that have yet to be published. But at this point in time, we don’t have any data at all on whether 1PD1 inhibitor is better than another except for indirect treatment comparisons.
so. Hopefully I've convinced you that we should at least think about using real-world data. But they are messy, ambiguous and unpredictable. So let me talk about some challenges that we have once we start delving into the real world. This is real-world data from the Medline. OK, so did you know that there were 21 clinical trial institutions in New Haven? Did you know that?
That’s amazing, right? Here they are.

Smilow Cancer Center, Smilow Cancer Hospital, Smilow Cancer Hospital at Yale University, Yale Cancer Center, Yale Medical school.

Alright, I think you get the idea, right? So I mean this is real world.

I mean, a computer is not going to know, I mean you have to do something.

I mean, if you want to use this data in some way, you’ve got to do some work to actually fix this, right?
That is a big part of working with real world data.

There's the 21st, OK?

So how about, so that's bibliometrics to some degree, how about treatments, how many tyrosine kinase inhibitors are there?

And so this is a little project that a student of mine undertook where they mapped out how many letters you'd have to switch around or basically misspell.

So that one tyrosine kinase inhibitor would actually be another one.
than you think and.
You know, these drugs get misspelled all the time in a pretty amazing ways.
I see that the net, there's a little bit of formatting issue with the next slide, but. So this is real data. From the Vanderbilt University Medical Center. So this is from our text list of medications. Now you might say, oh, let’s just, you know, we’ve got to be able to get these medications from structured data. That may or may not be true.
It depends. We can talk more about that.

But these are real misspellings of the drug or Latino BI.

Think you can tell looking at this that all of these are or lot in him.

But again, I mean if you don’t have some sort of system to harmonize all those misspellings.

You’re not going to know which patient got what drug.

You’re not going to know that’s you know, that’s a real world issue with real world data.

This is work that we did some years ago on staging.
Here is what I call manageable ambiguity.

All right, so.

And again and maybe you know during sort of discussion we can talk about the value of structured versus unstructured data, but the idea here is that we would take data from progress notes from clinical text to all these notes. And figure out if a patient had stage 123 or four. So just forget ABC. The problem that we knew ahead of
time is that these things are going
to be recorded variably in different
notes by different types of doctors.
But you know we did a pilot
with about 1000 patients with
lung cancer with over 460,000
clinical documents across them.
Now if you pause for a minute and you think
about. A chart review.
Think about how long it would take you to
go through 460,000 documents, right so.
Here’s my pitch for natural
language processing.
You can actually automate this kind of
thing and do this kind of work at scale.
So cutting to the chase a little bit here.
First of all, we found that out of those 964 patients, 99% had some kind of stage freeze in their note. At least one. And we also had a gold standard which was the tumor registry data. So we were able to compare our system to the subset. You’ll notice only 790 out of those 964 had tumor registry data, but we were able to do a comparison and you know our system worked really pretty well. The green, you know, basically the matches are in the green, and we got some things wrong.
but we didn’t usually get things really wrong most of the time. So if it was stage one, we called stage four, that was a big mistake. Only happened once. This shows actually, so again 460,000 documents. And you have to look at all of those or can you just look Right after a patient was diagnosed you know with if you think of some of this inspiration for this project came from the copi measures.
And if any of you have done that work you'll remember I believe and they may have changed but at one point the coping measure was recorded in one of the first two progress notes written after diagnosis. So it kind of makes sense that you would look for stage early on but if you look at this black line towards the bottom. So does this. Are you seeing my? You don’t see the arrow, are you? I don’t think you’re seeing the error, OK. If you look at the black line towards the bottom, you’ll see that.
If you look at the notes in the first five weeks from diagnosis, actually there’s a pretty high rate of unknown stage. Like we couldn’t determine it. It wasn’t until we got to five weeks and out that we had enough mentions of stage that we could sort of make that determination. So we saw this kind of inflection point. And so that’s another thing just to note when you’re working with real-world data is that, you know, time matters. time can matter a lot. And the other thing that really matters is,
I mentioned we found stage in 99% of the records.
What I didn’t mention is that most of those are 84% had more than one stage in their records,
OK and some degree of discordance.
And we constructed a network graph on the right here you see like every possible combination was present,
every possible combination including more terms that are more generic like early stage,
advanced stage.

Everything you know happens and you

here you can see a histogram of Co

occurrences of various stage information.

But I do think that so that

really potentially ambiguous.

One take home point from this

though is that we use a

really simple decision rule on,

you know, what is the actual stage?

We just chose the phrase that showed up

the most OK and that seems to work.

So if stage three shows up

in the notes 100 times,

in stage one shows up twice.
Chances are at stage three now, just sort of a practical rule and it worked. Now getting back to that, you know, whole idea of. You know unknown or sort of lack of information and missingness which is a major issue with real world data. This is another mini project we did looking at colon cancer and we wanted to say could you find patients with stage 3 colon cancer and patients with stage 3 colon cancer and this was for the OCM project, the oncology care model. So you know really important as a metric to know if these patients
got appropriate treatment within appropriate period of time.

But again what we saw here. Is this sort of crossover at about seven weeks, at which point?

You know, the the stage was changing or it was or is missing in the records and it wasn’t until about seven weeks after diagnosis that you get to a kind of steady state where you can definitively say a patient has stage three or we don’t know the stage so.

Here’s some really interesting work from here, actually from Yale, from the Radiation Oncology department, where they they actually looked at
missingness as a variable, if you will. So they took the National Cancer database, the NCDB data, and they split patients into whether they had complete records or had some missing data from their record. Now the NCDB is not EHR data, right? But it is based on EHR data. And you know the punch line here is that missing this is an independent prognostic factor for survival which is really an interesting thing to think about, right. And and it kind of depends on what kind
of what kind of cancer you have as well. So they found for instance on the left. If you have non small cell lung cancer, it’s the non metastatic patient who had a real difference in their prognosis if they were missing data. Whereas with prostate cancer it was the metastatic group that sort of split apart. But either way, I mean this is. Yeah, just think about it for a minute while I get my water bottle.

It’s certainly not something that we conventionally use as a metric. That’s certainly not something we conventionally use as a metric.
because there’s it’s not an issue, right?

Case report forms are complete, but missing this itself can be informative as in real world data.

So what I wanted to do now is actually take us down a little different path briefly, which is a brief diversion into the history of medical records.

Anybody know what this is? It’s a local local. It’s kind of cool if you never been there. It’s still there. Doesn’t exactly look like this anymore, but you’ll see why I'm showing.
this in a couple slides, so.

So this is also this is a real thing.

OK, so this is one of my favorite vehicles from the Lane Motor Museum in Nashville.

Which is Doctor Weiner mentioned, I was there for about a decade and so this is a real vehicle.

There’s they actually have a collection of these and it makes me think of electronic medical records because it it works, right?

It actually this person’s actually driving this car.

But we don’t exactly see propeller driven cars on the roads these days, right?

So our ER, but it works.
So MR’s are functional, but are they fit for the purpose that we want to use them for? I think many of us have, some ideas about that, but you know, when you think about medical records, this is obviously a little bit before the computer, you know, medical records have been around for. Almost, you know, 3500 years in one form or another. But what’s interesting to me? Is that they were primarily used for teaching or didactics. Until very recently,
that was the only purpose of medical records.

And then sort of the second purpose that arose, if you will, didn’t arise until the 1880s. It’s not that long ago if you think about it.

And, you know, essentially to have a written record of what happens in case there was a lawsuit around medical malpractice. And we’ll skip that and sorry about the there’s some Mac to PC changes here with the font. So it’s a little bit hard to read some of this,
but you know how about billing that's billing is the major driver rate of how our medical records look like today. But that only really happened in 1960s is really not long ago and until you know not so long ago physicians were paid with food and lodging. This is a picture from the Confucian medical system where there's at least some cases where the the court physician was basically executed if the if the emperor did not get better. So that's a pretty harsh payment
or penalty if you will.

But you know what really changed things was the Medicare Act of 1965, which basically established this profile.

You know, quote usual customary and reasonable fees which.

And sorry about the font that’s messed up here, but there’s a quote from the AMA, the American Medical Association, that said that the 1965 Medicare Act was the most deadly challenge ever faced by the medical profession.

That’s actual quote.
It certainly changed things a lot. And then what I’d argue also changed was really more recent was in the 90s when the physician fee schedule was introduced and then something called the evaluation and management guidelines, which I think. A lot of us know more than we ever wanted to know about, but those really changed how medical records were written. Noticed that haven’t yet used the word electronic, right? So now what about patient care, which I think all of us want that to
be the primary purpose of medical records. This kind of dates back to the 1800s in some ways. The case records of the Massachusetts General Hospital introduced some ideas like history of presenting illness, past medical history and so forth, medical record numbers. The whole idea that you would track a patient by a number was introduced at the Mayo Clinic in the early 1900s, where they also introduced the chief complaint and the review of systems. And then the American College of Surgeons,
00:24:32.390 --> 00:24:33.914 this is amazing bit of history
00:24:33.914 --> 00:24:37.900 if you didn’t know in 1918, they.
00:24:37.900 --> 00:24:39.657 There was no federal mandate of any.
00:24:39.660 --> 00:24:41.276 They basically mandated as
00:24:41.276 --> 00:24:42.488 a professional organization.
00:24:42.490 --> 00:24:45.298 They mandated that hospitals had to
00:24:45.298 --> 00:24:47.344 keep records including a discharge
00:24:47.344 --> 00:24:49.552 summary that basically said was the,
00:24:49.560 --> 00:24:50.202 you know, patient,
00:24:50.202 --> 00:24:52.419 you know alive or dead at the time they left.
00:24:52.420 --> 00:24:55.588 And at that time fewer than 20% of
00:24:55.588 --> 00:24:58.260 physicians kept any kind of record at all,
00:24:58.260 --> 00:25:02.830 which is like. Amazing, right?
00:25:02.830 --> 00:25:05.143 Now this is tying back to that Eli Whitney.
00:25:05.150 --> 00:25:06.950 So this is, you know,
for those that did take records, this is kind of what they looked like as these are called case books. I'm not sure where this one is from, but it’s basically a handwritten. And what’s really interesting about this is that it’s physician centered, right. This is not, this was written as. The doctor saw patients, so if you ever wanted to go back and say OK, Mr. Smith or whoever, like put their case together, good luck.
So really the most recent innovation if you will in medical records was this one and that from Austin from the mid 1960s which is the problem oriented medical record which which was conceived as a quote medical record that guides and teaches. So kind of back to that idea of didactics in a way and I'm sure everybody's familiar with this, this idea, this soap notes, right. What I like from the paper when doctor we'd introduced this idea. This is a quote which I think actually forecasts the ER right so,
and it’s worth reading it.

It can be readily, readily be seen that all narrative data presently in the medical record can be structured, and in the future all narrative data may be entered through a series of displays guaranteeing a thoroughness, retrievability, efficiency and economy important to the scientific analysis of a type of datum that has hitherto, been handled in a very unrigorous manner. It’s an amazing quote. I mean, this is essentially before any
electronic medical record, right?

But he basically saw it, saw it coming.

I think the most important part of this quote is this to be concluded.

We're living through the evolution of these electronic medical records.

This is actually a two-part paper, that’s why it says this.

But I think, you know,

he could have been like OK,

we don’t know what’s going to happen.

It’s worth taking a step back

and saying what you know what.

So now I’m going to say electron what

is the electronic health record for?
And it’s got primary uses and secondary uses. So the primary uses are patient care and delivery, financial billing. But it’s this, when you talk about real-world data and real world evidence, that’s a secondary use, as it’s conceived here in this model, which the Institute of Medicine put forward. At that time there was issues around funding to you know roll out electronic medical records and. What I like on the bottom here is in
2003 the mass medical society did a survey where 89% of physicians wanted EHR data, but 48% refused to use an ER. So little bit of a disconnect there and by 2004 hardly anybody was using medical records. So what changed? Arguably this is, you know, one of the events that really changed things. Is everybody familiar with Katrina and what happened in New Orleans? Does everybody know why the? Record so there’s a picture there on the right.
were in the basement.

That flooded.

It’s the they are so heavy that the building literally would have collapsed under the weight of the paper if they’d been up on higher floors.

So that’s why they have their medical records in the basement and they were all destroyed, right?

So, so fast. We’re a little bit the High Tech Act in 2009, which Obama signed this this is what really gave a lot of money for institutions to really start putting any Mrs.
but what is interesting is if you look at sort of the adoption curve and there's a couple, I won't get into the details here. There's a couple ways of like what is an EHR basic versus complete and so forth, but you actually see them starting, so here's E&M coming out in the mid 90s. Here's Katrina in 2005. There's the High Tech act. By the time the High Tech Act comes out, actually we're like well on the adoption curve and so, you know, definitely help things along, but you know,
the process is already starting.

And then you know where. So this is already five years old, but I think, you know it's it's.

So you know, it's problematic. But OK, here's a few other challenges. So.
And I'm sure everybody who's clinical knows these things already. But carry forward a copy pasting is ubiquitous in medical records and there's just a ton of redundancy. Here's a paper that basically shows that. Umm. You know, large, large portions of any note you particularly look at have been copied forward from previous notes. In particular, note material is copy pasted. This is a different study looking at you
00:30:30.614 --> 00:30:32.566 know how many progress notes have a manually
NOTE Confidence: 0.861171268571429
00:30:32.566 --> 00:30:34.207 entered text versus copied in any kind.
NOTE Confidence: 0.861171268571429
00:30:34.210 --> 00:30:37.720 And you can see again like very few progress
NOTE Confidence: 0.861171268571429
00:30:37.720 --> 00:30:40.448 notes have have fully written text.
NOTE Confidence: 0.861171268571429
00:30:40.450 --> 00:30:43.510 Which you would say is fully original, but.
NOTE Confidence: 0.861171268571429
00:30:43.510 --> 00:30:44.973 So I think it’s a legitimate question
NOTE Confidence: 0.861171268571429
00:30:44.973 --> 00:30:46.708 to say what are we dealing with here?
NOTE Confidence: 0.861171268571429
00:30:46.710 --> 00:30:47.851 Is it a giant pile of paper
NOTE Confidence: 0.861171268571429
00:30:47.851 --> 00:30:49.099 or is there actually meaning.
NOTE Confidence: 0.861171268571429
00:30:49.100 --> 00:30:51.500 So this is a little little tiny project
NOTE Confidence: 0.861171268571429
00:30:51.500 --> 00:30:54.032 I did and when during fellowship where
NOTE Confidence: 0.861171268571429
00:30:54.032 --> 00:30:56.699 I basically took one of my patients
NOTE Confidence: 0.861171268571429
00:30:56.700 --> 00:30:59.150 charts and I counted up like how
NOTE Confidence: 0.861171268571429
00:30:59.150 --> 00:31:01.569 many data points are in that chart.
NOTE Confidence: 0.861171268571429
00:31:01.570 --> 00:31:04.810 And you can see the blue bars are all the
NOTE Confidence: 0.861171268571429
structured data elements like billing codes or vital signs or lab values. And then these red bars are the words in the clinical documents and you see that that just drowns out right, so there's a lot of data there but. So in this chart. And this is small these days, right? So this was more than 10 years ago, there was another 277 pages of scanned documents with 69,000 words in them that were basically inaccessible, but and the take home point here.
Is that this is what it all boils down to, OK? Patient with diffuse large B cell lymphoma. It was a complete remission after getting 6 cycles of our chop. I think that’s enough for most research. OK now how can we, how can we boil things down like that because that’s that’s kind of maybe what we’re talking about here. So and of course there’s more to it right. But you know when you think about what’s in ER’s or EHR’s and and what is not. Umm. You have to know what you’re,
you have to know what you’re going to find,
right.
So let’s say you know you’ve unlocked this medical record,
but it’s not necessarily going to have what you want.
So here’s, here’s some big buckets, right.
So you’re going to find the person’s date of birth, no problem, right.
You know they won’t have lived

00:32:15.090 --> 00:32:16.467 you have to know what you’re going to find,
NOTE Confidence: 0.861171268571429
00:32:16.470 --> 00:32:16.794 right.
NOTE Confidence: 0.861171268571429
00:32:16.794 --> 00:32:19.062 So, so let’s say you know you’ve unlocked this medical record,
NOTE Confidence: 0.861171268571429
00:32:20.690 --> 00:32:21.760 but it’s not necessarily going to have what you want.
NOTE Confidence: 0.861171268571429
00:32:21.760 --> 00:32:22.830 to have what you want.
NOTE Confidence: 0.861171268571429
00:32:22.830 --> 00:32:25.050 So here’s, here’s some, you know, basically some big buckets, right.
NOTE Confidence: 0.861171268571429
00:32:28.010 --> 00:32:29.536 So you’re going to find the person’s date of birth, no problem, right.
NOTE Confidence: 0.861171268571429
00:32:31.003 --> 00:32:32.629 But you’re not going to find
NOTE Confidence: 0.861171268571429
00:32:33.968 probably where they were born,
NOTE Confidence: 0.861171268571429
00:32:35.170 the circumstances of their birth,
NOTE Confidence: 0.861171268571429
00:32:36.880 where their complications.
NOTE Confidence: 0.861171268571429
00:32:39.036 Very unlikely, because they will have.
NOTE Confidence: 0.861171268571429
00:32:40.560 You know they won’t have lived

60
their whole system with their life within the electronic air, and they won’t have all that data. You might find their biologic sex, no problem, but are you going to find their gender orientation, that sexual identity? You’ll find race in this city, but are you going to find other social determinants of health? You’ll find the medications that they are prescribed, but will you find what they actually took, the medication that they took and the
regimens and we’re going to get into

NOTE Confidence: 0.861171268571429

that next you’ll find laboratory tests,

NOTE Confidence: 0.861171268571429

but you want necessarily find images.

NOTE Confidence: 0.861171268571429

And so forth.

NOTE Confidence: 0.861171268571429

So kind of you know as moving

NOTE Confidence: 0.898628412727273

forward. Thinking about what you know,

NOTE Confidence: 0.898628412727273

the low hanging fruit.

NOTE Confidence: 0.898628412727273

You know it’s the cancer type,

NOTE Confidence: 0.898628412727273

it’s easy like we don’t need to create

NOTE Confidence: 0.898628412727273

a new system to get cancer type.

NOTE Confidence: 0.898628412727273

You can get that from billing codes,

NOTE Confidence: 0.898628412727273

registry data.

NOTE Confidence: 0.898628412727273

The treatments are hard like our chop

NOTE Confidence: 0.898628412727273

times 6, that’s hard determining that

NOTE Confidence: 0.898628412727273

the patients in a complete remission,

NOTE Confidence: 0.898628412727273

that’s really hard.
So what I go for the middle, I don’t go for the middle ground, right, I’m going to tackle the thing in the middle.

So now I’m going to switch gears here for a bit and talk about our work on standardizing systemic anti cancer treatment. And before I get into that, If you’ve not seen this XKCD cartoon, it’s a classic. And this is a challenge, right?

Whenever you decide to create a new standard or you actually just you know. Just creating more complexity or not. Hopefully we’re not.

Well, what we did in this space,
there really weren’t 14 existing standards.

There were none.

And so as everybody here knows,

Chemotherapy regimens are complicated and
given in cyclic fashion combinations.

This was the standard when

we got started on our work.

This is, you know,

one example of these things called
cancer chemotherapy handbooks,

kind of recipe books, physical books,

right.

With some some details here,

but maybe not enough.

Here’s another example from 2005.
Which if you kind of look in detail about what’s there. There’s a lot of optionality here, some of the references. Here’s a little excerpt from the Adenoma. I don’t know carcinoma of unknown primary section, but the references are to non small cell lung cancer so there’s sort of a mismatch there in the evidence base. So what we did is we. Really basically tried to collect all this information and put it into a computable format, which is our hemlock.org website and
the ontology that comes from it.

So he might.org is a website with the goal to collect all standard of care systemic anti cancer treatment. That's the goal.

It's a big goal and at the website has grown over more than a decade now. Of almost 1000 primary content pages, over 7000 references, and a large editorial board, actually members of which are from Yale. And many page views, so 1.4 million page views last year, we do get visitors from all over the world were primarily US based. I always like to throw in that we've
00:35:57.510 --> 00:35:59.590 had one visitor from North Korea.

00:36:00.810 --> 00:36:03.426 I don’t know who it is, but I don’t think I want to know.

00:36:05.810 --> 00:36:08.330 So what can we do with this website?

00:36:08.330 --> 00:36:10.360 over the past 11 years is create

00:36:10.360 --> 00:36:12.231 a structure such that we could actually take the content and develop a formal model.

00:36:12.231 --> 00:36:13.796 and

00:36:13.796 --> 00:36:15.260 And so this is the model?

00:36:15.260 --> 00:36:17.120 Or this is part of the model?

00:36:17.120 --> 00:36:21.070 And I don’t have time right now obviously to kind

00:36:21.070 --> 00:36:22.110 go through all these details,

00:36:22.169 --> 00:36:23.867 but it’s somewhat complex and enlarge

00:36:23.870 --> 00:36:27.188
we have over 100,000 concepts and 300,000 ways in which those are interrelated in the latest version. This is showing, you know, I don’t have time to actually show the website. This is a screenshot from the website showing basically that each regimen on the website is in such a way that we can take all those pieces and put them into the data model. And then we can start to do cool things with real world data.
with some folks in South Korea who basically had access to. Essentially medication level database. And remember I mentioned you know way back when that we might get medications, but to actually understand regimens we have to do something extra. And So what they did is they applied our model and they mapped medications through regimens and they were able to look basically over a decade of time 2008 to 18. And you can see here that you know the changing pattern of care in that country. So you see that for example of you know
bevacizumab wasn’t used really until 2014 and then it started getting popular. And by the year 2018, it’s, you know, full Fox and Bevacizumab Kappa, a good chunk of of the treatment regimens, whereas something like fluorouracil monotherapy essentially disappears off the scene by the time you get there. This is much more recent so that now we’re working with folks at the University of California System have a really cool combined database across all the UC’s and California is kind of a.
You know, country unto itself, once you start putting all this data together, this is just from UCSF and again we're taking medication exposure data including time stamps and we're mapping that to regimens. And so that's that alone is an interesting thing, right? You also see some funny things, right? Like so I didn’t know Leuprolide was a treatment for pancreatic cancer, did you? Is it? Not no, right. No.
00:38:53.842 --> 00:38:55.860 But these are real patients, right.
NOTE Confidence: 0.8194428005
00:38:55.860 --> 00:38:57.360 And they actually have second malignancies.
NOTE Confidence: 0.8194428005
00:38:57.360 --> 00:38:58.944 So these are people who have
NOTE Confidence: 0.8194428005
00:38:58.944 --> 00:39:00.402 also have prostate cancer and
NOTE Confidence: 0.8194428005
00:39:00.402 --> 00:39:01.810 they’re also getting leuprolide.
NOTE Confidence: 0.8194428005
00:39:01.810 --> 00:39:04.450 So you, you, you kind of have to you know,
NOTE Confidence: 0.8194428005
00:39:04.450 --> 00:39:06.450 it’s not enough to get that data out.
NOTE Confidence: 0.8194428005
00:39:06.450 --> 00:39:07.284 Y ou’ve got to,
NOTE Confidence: 0.8194428005
00:39:07.284 --> 00:39:08.873 you got to apply knowledge, right.
NOTE Confidence: 0.8194428005
00:39:08.873 --> 00:39:10.224 You’ve got to, you’ve got to determine,
NOTE Confidence: 0.8194428005
00:39:10.230 --> 00:39:11.787 you know, am I, what am I looking at?
NOTE Confidence: 0.8194428005
00:39:11.790 --> 00:39:13.926 Does it make sense, is it?
NOTE Confidence: 0.8194428005
00:39:13.930 --> 00:39:17.180 Is it relevant and and?
NOTE Confidence: 0.8194428005
00:39:17.180 --> 00:39:19.217 And so that that’s why we’re
NOTE Confidence: 0.8194428005
00:39:19.217 --> 00:39:20.599 seeing things like that so.
NOTE Confidence: 0.8194428005
00:39:20.600 --> 00:39:23.522 Umm. Here’s another kind of.
Here’s another.

Gives you a taste of what we can look at.

So that is looking at folfox.

So one of my long-term interests, as well as Doctor Zach here, is to understand treatment delays, dose reductions.

Removals of medications from a regimen drop.

You know, dropping a drug and this starts to get at that and you can kind of see, each of those bars represents cycle to cycle.

the cycle you see.
People. People dropping out, right. And so and then you can actually see why and you can see on the top here. These, these bands at the top are showing. You don’t think that you have a pointer or something. These bands at the top are showing. You know, these these are folks. You don’t think that you have a pointer or something. A pointer or something. Oh, actually, let’s see if this will. Yeah. So, so you see these bands coming across, those are basically patients that are progressing and going on to a second line treatment what’s not shown here. Just to spare you a little
bit on the visual side, our patients who are or stopping therapy and essentially transitioning to Hospice or some sort of end of life care and that’s this big bar here. And then some patients these little ones they’re going to a deescalated regimen. So they’re dropping the Arena taken or the oxaliplatin and so you can really start to see these patterns of care in the real world data so. This is my little advertisement for Humalog.
It’s available to you. You can download the whole thing and mess around with it if you’re an academic or non-commercial user and just Google Hemac dataverse and you’ll find it. Or you can use these links. It’s also available through something called the Odyssey Athena vocabulary. And yeah, I mean, we want more users. There’s a lot more that can be done with it. So along comes a pandemic. So, now I want to spend the last little bit here talking about the COVID-19 and cancer consortium.
Which yells a member and this is our mission statement, which has been the same since we were created in March 2020, which is our goal is to collect and disseminate prospective, granular, uniformly organized information on people with cancer who are diagnosed with COVID-19 at scale and as rapidly as possible. But what I want to talk about here for a minute is sort of what I call the ancillary goals of C19 or the unwritten goals.
can we build a consortium, can we build an airplane while also flying?
Just, you know, can we do it? That was the question. Convening a group of stakeholders was really in, you know, a goal including patients, really engaging patients and then.

pertinent to the talk today, can we demonstrate the additive value of real world data elements that are not easily obtained from structured EMR data? We knew that there were other efforts kind of getting rolling that were based on what was in that structured data.

If you remember that’s the.
The tiny little blue bars right on the graph I showed you. So we wanted to, you know, get more than that. So this is back in Rhode Island. Alright. Showed you Eli Whitney earlier. This is Slater Mill in Pawtucket which I think I pronounced correctly but I’m getting my New England shops. And what’s interesting to me about this story is that he earned this name, Samuel Shredder Slater and the reason he was branded as a traitor.
is that he was accused of stealing
the ideas for industrialization.
From England where he was born and grew up,
and then replicating it in America.
So this is really the beginning of
the American Industrial Revolution.
But what’s interesting about that is
that he didn’t exactly steal the ideas.
Like he didn’t steal blueprints
or things like that.
He just like memorized them and
brought the knowledge with him.
So it’s, you know, that’s what he did.
So. I think that that’s great actually.
And so you know when we think
00:43:47.719 --> 00:43:49.493 about C 19 and I certainly don’t
00:43:49.493 --> 00:43:51.420 have time to go through all this,
00:43:51.420 --> 00:43:55.158 but we have many inspirations he,
00:43:55.160 --> 00:43:58.060 the hemlock,
00:43:55.672 --> 00:43:58.060 what I just spoke about is one of them.
00:43:58.060 --> 00:44:01.300 But in all the domains of C19,
00:44:01.300 --> 00:44:04.000 we are borrowing best ideas,
00:44:04.000 --> 00:44:06.536 modifying sometimes and putting
00:44:06.536 --> 00:44:09.012 together this consortium and and
00:44:09.012 --> 00:44:11.760 this is just sort of a list of that.
00:44:11.760 --> 00:44:13.140 The other thing I wanted to
00:44:13.140 --> 00:44:14.060 say about you know
00:44:14.110 --> 00:44:15.466 the C 19. Work and just,
00:44:15.466 --> 00:44:17.501 you know, research in general
00:44:17.501 --> 00:44:19.886 is that sponsors are critical.

In a Samuel Slater’s case, he had a sponsor named Moses Brown who basically fronted him the money to build those mills. And our sponsor is Julie Klem at the NCI who didn’t front us any money but was very supportive and helped us kind of, you know, surface and socialize our ideas. So this is our data schema, and what I want to emphasize here related to this talk is that everything in red is not available in structured data, so as we sort of built this up.

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you know, in many different ways.

But the red items. And you'll see in a few slides that those turn out to be critical things like ECOG performance status, things like toxicity of cancer treatment pneumonitis. Items like that, that we really wanted to zero in on. We've done really pretty well on capturing what I would call elusive variables. So these are kind of the
things that they’re in the ER, but they’re in that unstructured. Leak of data, but we we got a lot of them. So cancer status is the patient. Getting better, getting worse or staying this, you know the same as before, a stable disease. We have that in over 95% of the patients. Even smoking status is hard to get right. We have that. Did COVID affects the patients treatment plants that’s not going to be unstructured data necessarily. We have over 90% on that on the ECOG
which is a notorious difficult thing to get and all the various efforts such as flat iron and so forth have had challenging and cancer link have had challenges with this. We have ECOG data on 88% although that does includes patients who just didn’t have any ECOG recorded but we that knowledge of no ECOG is still. Knowledge, And you know getting to our right? And you know getting to our results again in getting to our results again in
just focus on the red and what we found is that these factors, these elusive factors are really important. And so this is unadjusted just kind of descriptive. If you had progressing cancer at baseline you get COVID your 30 day mortality is 26% and if you had an ECOG of two or higher your mortality is extremely high. And we also found that immunosuppression which is a somewhat nebulous definition here which includes a lot of things you can’t easily get out of structured data.
So this is sort of the real world data is a huge driver of mortality. And if you look at the right, even younger patients have substantial mortality in our data set. Furthermore, if you add on top of that active cancer. Again, we have our definition for that.
Because if you’re not immunosuppressed and you have inactive cancer, in our data, at least you have a zero chance of dying in the 30 days, whereas if you’re older immunosuppressed, your chance goes all the way up to 30%. So really a huge spread here based on these data. And then if we start to look at. Multivariable adjusted analysis. Again, we see that these factors like ECOG or cancer status are highly associated with outcome, both mortality as well as severity, which means hospitalization, intubation and so forth.
We saw this as well more recently when we looked at vaccinated patients. So patients who are getting breakthrough COVID-19 after vaccine again we saw things like cancer status really you know being a, you know huge adjusted odds ratio there of six if you had an active and progressing cancer of of dying in 30 days.

So I could talk about COVID-19 itself for an hour, but I’m going to pause and so I just want to share some parting thoughts.
I'm a believer here that real world data has a great potential to yield real-world evidence if. We approach it with an understanding about the completeness issues, the accuracy issues, and we anticipate them and we come up with either ways to adjust for or avoid certain data, certain variables in the first place. We need automated methods, right? Yes, we need automated methods, right? Like, it wouldn’t be great if NLP and a computer could do everything, but in reality a lot of real world data and real world evidence...
depends on human curators going into EHR’s pulling out that data. And to do that we need rigorous approaches. We have a paper published earlier this year describing the approach we used in ACR Genie. I encourage you to check that out. It basically gets into. You know you need directives. You need two people to independently curate the same record at a certain rate so you can see if you know there’s comparability between their results. And so forth.
If there’s widespread adoption of standards such as M code, hemac, omop and so forth, that will increase the usefulness of structured data markedly. I think NLP is having a moment. If you pick up the newspaper nowadays, like you’re going to see our other paper on chat, GPT, for example, which is generative NLP but sort of the other side of NLP, and then Umm. You know, really important though, and I didn’t get to touch on this at all except for the very beginning when I alluded to disparities and bias.
There’s a lot of concern that working with real-world data might actually make biases worse that are already present in that data. So we need new approaches to deal with that issue. New approaches to deal with that issue. Just have some acknowledgements here. So there’s two slides here. So this is my first acknowledgement slide. I acknowledge the himanka.org editorial board. Others that have worked on it are funding and and Dolly,
which is the creator of some of those graphics you saw. And here’s our acknowledgement for the C19, which is a huge endeavor that has more than 600 active investigators at this point. And with that, I will pause for questions.

So I’ll start. And can you see the ones that are online or not? I do see, yes, yes, I see. I don’t for a second dispute the value of real world data in terms of being able to answer questions, but I’m struck by the fact that we have these two extremes we have. Randomized controlled trials where
we spend a fortune to collect every last bit of data and you know they cost $15,000 per patient or more. And we get lots of useless data as part of it. And then we then say, well, we can’t do get everything from randomized controlled trials. So then we go to real world data where everything’s pretty messy and you have to make all these assumptions and clean up the data. And the the question is, is there a role for much simpler randomized trials done as part of standard?
00:52:28.940 --> 00:52:30.000 I mean sure, yeah,
NOTE Confidence: 0.839671244545455
00:52:30.000 --> 00:52:32.000 I mean I think the recovery trial,
NOTE Confidence: 0.839671244545455
00:52:32.000 --> 00:52:34.440 I mean that they they showed that you
NOTE Confidence: 0.839671244545455
00:52:34.440 --> 00:52:36.784 can do these huge pragmatic trials
NOTE Confidence: 0.839671244545455
00:52:36.784 --> 00:52:39.678 in 10s of thousands of patients with
NOTE Confidence: 0.839671244545455
00:52:39.680 --> 00:52:40.919 they didn’t spend a lot of money.
NOTE Confidence: 0.839671244545455
00:52:40.920 --> 00:52:42.696 I mean they used off the shelf drugs,
NOTE Confidence: 0.839671244545455
00:52:42.700 --> 00:52:45.780 right, dexamethason you know things.
NOTE Confidence: 0.839671244545455
00:52:45.780 --> 00:52:46.818 Some of the drugs we won’t,
NOTE Confidence: 0.839671244545455
00:52:46.820 --> 00:52:48.472 we won’t say the words but you
NOTE Confidence: 0.839671244545455
00:52:48.472 --> 00:52:50.159 know and things like oxygen right.
NOTE Confidence: 0.839671244545455
00:52:50.160 --> 00:52:51.707 But when you get into the you
NOTE Confidence: 0.839671244545455
00:52:51.707 --> 00:52:52.894 know the expensive drugs that
NOTE Confidence: 0.839671244545455
00:52:52.894 --> 00:52:54.079 are not yet FDA approved,
NOTE Confidence: 0.839671244545455
00:52:54.080 --> 00:52:57.480 I think that’s a whole other area but.
NOTE Confidence: 0.839671244545455
00:52:57.480 --> 00:52:59.730 I I think that FDA has got to lead
00:52:59.730 --> 00:53:02.224 the way in some ways here because they

00:53:02.224 --> 00:53:04.737 and I didn’t get to talk about this,

00:53:04.740 --> 00:53:05.808 but you know,

00:53:05.808 --> 00:53:07.588 there’s a high profile rejection

00:53:07.588 --> 00:53:09.230 of real-world data within the

00:53:09.230 --> 00:53:10.675 last month or two that.

00:53:10.680 --> 00:53:11.062 You know,

00:53:11.062 --> 00:53:12.399 there was an attempt to get something

00:53:12.399 --> 00:53:13.657 approved based on some real-world data.

00:53:13.660 --> 00:53:15.196 And I think they rightly looked at that

00:53:15.196 --> 00:53:16.523 and they said that this particular

00:53:16.523 --> 00:53:17.867 set of data is not trustworthy

00:53:17.915 --> 00:53:19.235 and we’re not going to go for it.

00:53:19.240 --> 00:53:21.095 But I don’t think that that should

00:53:21.095 --> 00:53:22.780 shut down the whole endeavor.
I think that they need, we need guidance from them and components should and should not be, you know, collected routinely. I think that might simplify things a lot. Attempt to put together criteria that this set of real world data is adequate to Brock inclusions from you know, in terms of how much it has to be cleaned up, how large the sample size has to be. It’s such an interesting question and I’m not aware of anything at this moment but I do you
NOTE Confidence: 0.90763503
00:54:02.934 --> 00:54:05.178 know we are there’s this great bias
NOTE Confidence: 0.90763503
00:54:05.178 --> 00:54:07.684 that I just learned about called the
NOTE Confidence: 0.90763503
00:54:07.684 --> 00:54:09.654 informed presence bias which I kind of
NOTE Confidence: 0.90763503
00:54:09.654 --> 00:54:12.197 knew I knew it but not by those words
NOTE Confidence: 0.90763503
00:54:12.197 --> 00:54:14.108 but that basically means that patients
NOTE Confidence: 0.90763503
00:54:14.108 --> 00:54:16.700 who spend a lot of time in the clinic
NOTE Confidence: 0.90763503
00:54:16.770 --> 00:54:19.362 or the medical system have a lot of data
NOTE Confidence: 0.90763503
00:54:19.362 --> 00:54:21.319 right whereas those that don’t don’t
NOTE Confidence: 0.90763503
00:54:21.319 --> 00:54:23.940 and and it’s and it’s actually
NOTE Confidence: 0.90763503
00:54:23.940 --> 00:54:25.640 an incredibly important source of.
NOTE Confidence: 0.90763503
00:54:25.640 --> 00:54:30.050 The bias? That. That.
NOTE Confidence: 0.90763503
00:54:30.050 --> 00:54:31.162 You know, can you?
NOTE Confidence: 0.90763503
00:54:31.162 --> 00:54:33.231 So if a patient doesn’t spend enough
NOTE Confidence: 0.90763503
00:54:33.231 --> 00:54:35.265 time to get enough data generated,
NOTE Confidence: 0.90763503
00:54:35.270 --> 00:54:36.600 that’s something we should know.
NOTE Confidence: 0.90763503

99
That's something we need to know, right?

But that's almost that kind of, descriptor is almost never available in any real world data study to my knowledge, so.

The online version.

Yeah.

What is?

COVID-19.

Yeah. Yeah. So the question is, it seems to be the case that the patients with the pre-existing cancer having worse outcomes during the COVID era than before and why might that be? I can say from our consortium now we
only look at patients who had COVID.

So that’s a subset, right?

Well, as time goes on, it’s going to be everybody maybe.

But what we do see is that you know at least in our registry 40% of patients have their treatment altered in some way and usually that’s a delay.

But sometimes they can’t get the same treatment that they were getting before a surgery gets cancelled.

And and we know from you know previous work, obviously the treatment delays don’t usually ever. Work out very well.
So we haven’t yet systematically evaluated that, but we have now several thousands of those patients. So we’re going to be looking at that probably in the upcoming year. As far as other patients, well, especially in China, I think, but also with sort of substituting oral medications whenever possible, even if they were sort of known to be inferior or not, you know, not quite as good so that patients didn’t have to come into the.
To the clinic.

So that’s been presented on in some settings, but you know I think what we think that those substitutions are generally OK, I know that.

You know a lot of people went on neoadjuvant hormone therapy and instead of going direct to surgery for early stage breast cancer and you know so that they could push this you know during periods of time when elective surgeries were shut down. So all those things probably add up right.
But there’s absolutely a factor of psychology and patients being afraid to come into the clinic and you know potentially again skipping a treatment or.

So, to answer your question is that it’s quite complex but I think we need to understand it better and of course new diagnosis coming in which we’re starting to get that information.

There’s clearly a stage migration and and you know to later stage more more advanced, more metastatic disease. Because of delays in screening and so forth.
So.
So I think we’re going to face a challenging decade and I think Ned Sharpless forecast that at the very beginning of the pandemic. I think in the first month or two he wrote a paper and nature of science modeling out what that might look like. Hopefully COVID ends really soon.

Seems like.
Yeah so we’re overtime and and I think you know I mean there’s there’s many strategies to try to mitigate but you can’t eliminate bias right. So you can understand it you can try to mitigate it there’s you know matching strategies to if you’re doing sort of a case and control style approach where you try to make the controls as similar to the cases you know and some of those been around for decades, some of those are kind of emerging at this point.
But I don’t think we can forget that there’s bias in perspective trials as well, right. So I mean I think either side of the coin. Yeah, it’s just, it’s just one more thing and it’s not the only, I mean it’s there’s also ascertainment, but I mean there’s a lot of biases, right and. You know, one thing we’ve worked on with our consortium is developing standardized language around limitations, which I think is critical because you know. I mean, the data are the plural, right? But.
But the way it’s presented really does influence the reader, right?

So. So that’s something we’re thinking about and might have some. You know, thought pieces or something coming out about how to handle that.