WEBVTT

NOTE duration: ”00:48:37.333”

NOTE Confidence: 0.8162174

00:00:02.480 --> 00:00:04.900 Good afternoon. Welcome to pathology

NOTE Confidence: 0.8162174

00:00:05.120 --> 00:00:05.940 ground runs.

NOTE Confidence: 0.916151

00:00:06.319 --> 00:00:06.819 And,

NOTE Confidence: 0.9559158

00:00:08.480 --> 00:00:10.580 we have today's speaker, doctor

NOTE Confidence: 0.96635044

00:00:11.360 --> 00:00:11.860 Joshua

NOTE Confidence: 0.7720872

00:00:12.320 --> 00:00:12.820 Warwick.

NOTE Confidence: 0.8595538

00:00:13.635 --> 00:00:14.135 And,

NOTE Confidence: 0.923213

00:00:15.075 --> 00:00:16.935 doctor Warwick graduated from

NOTE Confidence: 0.72671854

00:00:18.675 --> 00:00:21.015 the, West Wayne State University

NOTE Confidence: 0.9525562

00:00:21.315 --> 00:00:22.775 for her medical educations.

NOTE Confidence: 0.94743246

00:00:23.635 --> 00:00:25.395 After that, he he did

NOTE Confidence: 0.94743246

00:00:25.395 --> 00:00:26.295 his residency

NOTE Confidence: 0.72918695

00:00:27.330 --> 00:00:29.330 at initially, actually, it's a

NOTE Confidence: 0.72918695

00:00:29.330 --> 00:00:29.830 Lou,

NOTE Confidence: 0.8043071

00:00:31.810 --> 00:00:33.510 Saint Louis or Saint Louis

NOTE Confidence: 0.8043071

00:00:33.650 --> 00:00:35.350 University, Saint Litton,

NOTE Confidence: 0.68973094

00:00:35.729 --> 00:00:36.229 WashU,

NOTE Confidence: 0.80383885

00:00:37.010 --> 00:00:39.090 and complete his residency. And

NOTE Confidence: 0.80383885

00:00:39.090 --> 00:00:40.790 then which is followed by

NOTE Confidence: 0.8375368

00:00:41.185 --> 00:00:43.425 the fellowship training in Geo

NOTE Confidence: 0.8375368

00:00:43.425 --> 00:00:43.925 Passage

NOTE Confidence: 0.70315653

00:00:44.385 --> 00:00:46.325 as well as surgical massage

NOTE Confidence: 0.8572543

00:00:46.784 --> 00:00:48.245 at University of Michigan.

NOTE Confidence: 0.967669

00:00:49.185 --> 00:00:49.685 So,

NOTE Confidence: 0.94893384

00:00:50.785 --> 00:00:51.525 he joined,

NOTE Confidence: 0.99793136

00:00:52.625 --> 00:00:53.125 Pennsylvania

NOTE Confidence: 0.99546456

00:00:53.505 --> 00:00:54.325 State University

NOTE Confidence: 0.89813846

00:00:55.500 --> 00:00:58.140 and, starting his career and,

NOTE Confidence: 0.89813846

00:00:58.460 --> 00:00:59.679 risk his ranking

NOTE Confidence: 0.95919013

00:01:00.059 --> 00:01:01.760 for initial assistant professor

NOTE Confidence: 0.9873908

00:01:02.379 --> 00:01:03.359 to full professor.

NOTE Confidence: 0.98036134

00:01:03.980 --> 00:01:04.959 So he,

NOTE Confidence: 0.90486443

00:01:05.899 --> 00:01:06.799 was the

NOTE Confidence: 0.980286

00:01:08.325 --> 00:01:10.665 vice chair for clinical operation

NOTE Confidence: 0.9513092

00:01:12.244 --> 00:01:13.625 and director of

NOTE Confidence: 0.7706558

00:01:14.244 --> 00:01:15.625 the anatomic massage

NOTE Confidence: 0.8841187

00:01:16.485 --> 00:01:18.325 and also director of the

NOTE Confidence: 0.8841187

00:01:18.325 --> 00:01:19.625 GU Pathology Services

NOTE Confidence: 0.9828989

00:01:20.084 --> 00:01:20.584 there.

NOTE Confidence: 0.92884773

00:01:21.180 --> 00:01:21.920 We're fortunate

NOTE Confidence: 0.9852949

00:01:22.300 --> 00:01:23.280 to have him,

NOTE Confidence: 0.95276725

00:01:23.660 --> 00:01:25.280 you know, join the Yale

NOTE Confidence: 0.9291777

00:01:25.580 --> 00:01:27.340 and he just started his

NOTE Confidence: 0.9291777

00:01:27.340 --> 00:01:27.840 faculty

NOTE Confidence: 0.9639

00:01:28.540 --> 00:01:30.620 here as director of the

NOTE Confidence: 0.9639

00:01:30.620 --> 00:01:31.520 GU Passage.

NOTE Confidence: 0.98094857

00:01:32.380 --> 00:01:32.880 So

NOTE Confidence: 0.64828694

00:01:34.355 --> 00:01:36.215 Dodd Warrick did extensive

NOTE Confidence: 0.9973799

00:01:36.515 --> 00:01:37.655 research on

NOTE Confidence: 0.9738672

00:01:37.955 --> 00:01:39.095 the bladder cancers.

NOTE Confidence: 0.9404886

00:01:39.795 --> 00:01:41.555 His research funding was,

NOTE Confidence: 0.9724516

00:01:42.435 --> 00:01:44.375 supported by the NIH

NOTE Confidence: 0.69119453

00:01:45.315 --> 00:01:45.955 and cancer

NOTE Confidence: 0.86435336

00:01:46.354 --> 00:01:48.854 American Cancer Society and also

NOTE Confidence: 0.86435336

00:01:48.915 --> 00:01:49.415 DODs.

NOTE Confidence: 0.95731246

00:01:51.450 --> 00:01:51.770 He,

NOTE Confidence: 0.99749625

00:01:52.570 --> 00:01:54.010 has been invited to give

NOTE Confidence: 0.99749625

00:01:54.010 --> 00:01:54.909 many talks

NOTE Confidence: 0.92651474

00:01:55.530 --> 00:01:58.270 and, at national and international,

NOTE Confidence: 0.8934134

00:01:59.530 --> 00:02:00.030 conference.

NOTE Confidence: 0.77962565

00:02:00.650 --> 00:02:02.030 He path bridge extensively

NOTE Confidence: 0.92151046

00:02:03.049 --> 00:02:05.035 and has more than around

NOTE Confidence: 0.92151046

00:02:05.035 --> 00:02:06.815 the one hundred publications

NOTE Confidence: 0.7476066

00:02:07.835 --> 00:02:08.975 and peer reviewed,

NOTE Confidence: 0.970968

00:02:09.595 --> 00:02:10.575 journal articles,

NOTE Confidence: 0.9445422

00:02:11.115 --> 00:02:12.014 book chapters.

NOTE Confidence: 0.94372797

00:02:12.875 --> 00:02:13.355 And,

NOTE Confidence: 0.86340714

00:02:14.075 --> 00:02:15.835 so today he gonna share

NOTE Confidence: 0.86340714

00:02:15.835 --> 00:02:16.735 his experience

NOTE Confidence: 0.86691386

00:02:17.435 --> 00:02:19.195 in the breast cancer with

NOTE Confidence: 0.86691386

00:02:19.195 --> 00:02:21.590 us. His topic the the

NOTE Confidence: 0.86691386

00:02:21.590 --> 00:02:22.709 title of his talk is

NOTE Confidence: 0.86691386

00:02:22.709 --> 00:02:24.010 the lineage praxisity

NOTE Confidence: 0.9876508

00:02:24.389 --> 00:02:25.610 of the blood cancer.

NOTE Confidence: 0.96015805

00:02:26.230 --> 00:02:28.150 So without further ado, I

NOTE Confidence: 0.96015805

00:02:28.150 --> 00:02:29.830 will hand over to doctor

NOTE Confidence: 0.96015805

00:02:29.830 --> 00:02:31.209 Warrick. Thank you.

NOTE Confidence: 0.87207687

00:02:34.745 --> 00:02:36.525 Okay. Thank you, Doctor. Kai.

NOTE Confidence: 0.92103815

00:02:38.505 --> 00:02:39.225 So, yeah, so we're going

NOTE Confidence: 0.92103815

00:02:39.225 --> 00:02:40.764 to talk about bladder cancer.

NOTE Confidence: 0.9038643

00:02:42.264 --> 00:02:42.905 So I have I have

NOTE Confidence: 0.9038643

00:02:42.905 --> 00:02:44.105 no conflicts of interest right

NOTE Confidence: 0.9038643

00:02:44.105 --> 00:02:44.605 now.

NOTE Confidence: 0.9890051

00:02:47.600 --> 00:02:48.880 So there's there's two themes

NOTE Confidence: 0.9890051

00:02:48.880 --> 00:02:49.860 to the talk today.

NOTE Confidence: 0.97913665

00:02:50.320 --> 00:02:51.360 The first is gonna be

NOTE Confidence: 0.97913665

00:02:51.360 --> 00:02:53.680 that, bladder cancer demonstrates remarkable

NOTE Confidence: 0.97913665

00:02:53.680 --> 00:02:54.500 lineage plasticity,

NOTE Confidence: 0.98745257

00:02:55.280 --> 00:02:56.880 even without selective pressure from

NOTE Confidence: 0.98745257

00:02:56.880 --> 00:02:58.160 treatment. A lot of cancer

NOTE Confidence: 0.98745257

00:02:58.160 --> 00:02:59.505 types, you know, lung cancer,

NOTE Confidence: 0.98745257

00:02:59.585 --> 00:03:01.505 prostate cancer, they undergo lineage

NOTE Confidence: 0.98745257

00:03:01.505 --> 00:03:03.105 plasticity, but they generally require

NOTE Confidence: 0.98745257

00:03:03.105 --> 00:03:04.385 treatment pressure like prostate cancer

NOTE Confidence: 0.98745257

00:03:04.385 --> 00:03:06.065 and androgen deprivation therapy. Whereas

NOTE Confidence: 0.98745257

00:03:06.065 --> 00:03:07.605 bladder cancer is just plastic.

NOTE Confidence: 0.98745257

00:03:07.905 --> 00:03:08.785 It just does it on

NOTE Confidence: 0.98745257

00:03:08.785 --> 00:03:09.445 its own.

NOTE Confidence: 0.9486768

00:03:10.785 --> 00:03:12.419 And this is key, in

NOTE Confidence: 0.9486768

00:03:12.419 --> 00:03:13.540 in part driven by key

NOTE Confidence: 0.9486768

00:03:13.540 --> 00:03:15.780 transcription factors and interferon gamma

NOTE Confidence: 0.9486768

00:03:15.780 --> 00:03:16.280 signal.

NOTE Confidence: 0.9770849

00:03:16.580 --> 00:03:17.860 So these two statements are

NOTE Confidence: 0.9770849

00:03:17.860 --> 00:03:18.739 are gonna really, you know,

NOTE Confidence: 0.9770849

00:03:18.739 --> 00:03:19.780 like, be the frame from

NOTE Confidence: 0.9770849

00:03:19.780 --> 00:03:19.860 which

NOTE Confidence: 0.9763003

00:03:20.580 --> 00:03:21.080 yeah.

NOTE Confidence: 0.98398894

00:03:21.459 --> 00:03:22.660 So these are the these

NOTE Confidence: 0.98398894

00:03:22.660 --> 00:03:23.860 will be the the ideas

NOTE Confidence: 0.98398894

00:03:23.860 --> 00:03:25.080 that we frame the entire,

NOTE Confidence: 0.98398894

00:03:25.220 --> 00:03:26.040 talk through.

NOTE Confidence: 0.89512336

00:03:29.285 --> 00:03:30.004 Can you guys see the

NOTE Confidence: 0.89512336

00:03:30.004 --> 00:03:30.905 mouse? Good.

NOTE Confidence: 0.63659215

00:03:31.325 --> 00:03:31.825 So

NOTE Confidence: 0.87053585

00:03:32.245 --> 00:03:33.525 transcription factors, like so what

NOTE Confidence: 0.87053585

00:03:33.525 --> 00:03:35.125 are transcription factors? Let's all

NOTE Confidence: 0.87053585

00:03:35.125 --> 00:03:35.925 get on the same page

NOTE Confidence: 0.87053585

00:03:35.925 --> 00:03:36.584 here. So

NOTE Confidence: 0.947088

00:03:36.885 --> 00:03:38.724 transcription factors are proteins that

NOTE Confidence: 0.947088

00:03:38.724 --> 00:03:40.450 regulate gene expression. So we

NOTE Confidence: 0.947088

00:03:40.450 --> 00:03:41.810 have about fifteen hundred of

NOTE Confidence: 0.947088

00:03:41.810 --> 00:03:43.570 these named, in the human

NOTE Confidence: 0.947088

00:03:43.570 --> 00:03:44.690 genome. And what they do

NOTE Confidence: 0.947088

00:03:44.690 --> 00:03:46.130 is they're small proteins or

NOTE Confidence: 0.947088

00:03:46.130 --> 00:03:47.970 they're proteins that bind gene

NOTE Confidence: 0.947088

00:03:47.970 --> 00:03:48.470 promoters

NOTE Confidence: 0.95816386

00:03:49.250 --> 00:03:49.830 or enhancers

NOTE Confidence: 0.98383635

00:03:50.130 --> 00:03:50.950 or silencers

NOTE Confidence: 0.99734175

00:03:51.490 --> 00:03:52.710 to alter gene expression.

NOTE Confidence: 0.964362

00:03:53.105 --> 00:03:54.225 They they recruit, you know,

NOTE Confidence: 0.964362

00:03:54.225 --> 00:03:55.425 different proteins and stuff. But

NOTE Confidence: 0.964362

00:03:55.425 --> 00:03:56.225 by and large, what they

NOTE Confidence: 0.964362

00:03:56.225 --> 00:03:57.825 do is they bind what

NOTE Confidence: 0.964362

00:03:57.825 --> 00:03:59.445 we call cis regulatory elements

NOTE Confidence: 0.97468084

00:03:59.905 --> 00:04:00.405 to

NOTE Confidence: 0.9517339

00:04:00.785 --> 00:04:01.985 alter expression of a given

NOTE Confidence: 0.9517339

00:04:01.985 --> 00:04:02.485 gene.

NOTE Confidence: 0.8776003

00:04:03.905 --> 00:04:05.285 And these can be extremely

NOTE Confidence: 0.8776003

00:04:05.425 --> 00:04:07.550 powerful in in their So,

NOTE Confidence: 0.8823962

00:04:08.170 --> 00:04:08.330 this is Shinya,

NOTE Confidence: 0.93297577

00:04:09.770 --> 00:04:11.290 Yamanaka. He won the Nobel

NOTE Confidence: 0.93297577

00:04:11.290 --> 00:04:12.810 Prize in twenty twelve. He's

NOTE Confidence: 0.93297577

00:04:12.810 --> 00:04:13.610 kind of a hero to

NOTE Confidence: 0.93297577

00:04:13.610 --> 00:04:14.430 many of us.

NOTE Confidence: 0.9872197

00:04:14.810 --> 00:04:16.589 So he showed something really

NOTE Confidence: 0.97585607

00:04:16.890 --> 00:04:17.390 amazing,

NOTE Confidence: 0.9736813

00:04:18.010 --> 00:04:19.050 that he got the Nobel

NOTE Confidence: 0.9736813

00:04:19.050 --> 00:04:19.930 Prize for. He showed that

NOTE Confidence: 0.9736813

00:04:19.930 --> 00:04:20.890 you could take an adult

NOTE Confidence: 0.9736813

00:04:20.890 --> 00:04:21.710 dermal fibroblast,

NOTE Confidence: 0.9794099

00:04:22.295 --> 00:04:24.135 add four transcription factors, and

NOTE Confidence: 0.9794099

00:04:24.135 --> 00:04:25.255 turn it into an induced

NOTE Confidence: 0.9794099

00:04:25.255 --> 00:04:26.714 pluripotent stem cell.

NOTE Confidence: 0.9291465

00:04:27.095 --> 00:04:28.775 Those four transcription factors are

NOTE Confidence: 0.9291465

00:04:28.775 --> 00:04:30.315 SOX2, WAC4, KLF4,

NOTE Confidence: 0.9483969

00:04:31.175 --> 00:04:31.995 and and MYC.

NOTE Confidence: 0.9512753

00:04:33.255 --> 00:04:34.455 And so him and and

NOTE Confidence: 0.9512753

00:04:34.455 --> 00:04:35.520 others who worked in this

NOTE Confidence: 0.9512753

00:04:35.599 --> 00:04:37.360 space kinda bulldozer an old

NOTE Confidence: 0.9512753

00:04:37.360 --> 00:04:38.720 idea. The old idea was

NOTE Confidence: 0.9512753

00:04:38.720 --> 00:04:40.020 this this idea of Waddington's

NOTE Confidence: 0.9512753

00:04:40.080 --> 00:04:41.759 canals. This idea that that

NOTE Confidence: 0.9512753

00:04:41.759 --> 00:04:43.220 embryologic tissue was,

NOTE Confidence: 0.95827544

00:04:43.759 --> 00:04:45.599 was, destined to become one

NOTE Confidence: 0.95827544

00:04:45.599 --> 00:04:46.479 thing, and it couldn't really

NOTE Confidence: 0.95827544

00:04:46.479 --> 00:04:47.279 back up. It was like

NOTE Confidence: 0.95827544

00:04:47.279 --> 00:04:48.000 once you got to a

NOTE Confidence: 0.95827544

00:04:48.000 --> 00:04:49.599 certain degree of differentiation, you

NOTE Confidence: 0.95827544

00:04:49.599 --> 00:04:50.925 didn't reverse it. And he

NOTE Confidence: 0.95827544

00:04:50.925 --> 00:04:52.705 showed that four transcription factors

NOTE Confidence: 0.95827544

00:04:52.764 --> 00:04:53.805 can reverse it, which is

NOTE Confidence: 0.95827544

00:04:53.805 --> 00:04:54.845 kind of amazing. And that's

NOTE Confidence: 0.95827544

00:04:54.845 --> 00:04:55.565 why I won the Nobel

NOTE Confidence: 0.95827544

00:04:55.565 --> 00:04:57.085 Prize. And it it also

NOTE Confidence: 0.95827544

00:04:57.085 --> 00:04:58.125 goes to show the the

NOTE Confidence: 0.95827544

00:04:58.125 --> 00:04:59.264 incredible power

NOTE Confidence: 0.98258454

00:04:59.645 --> 00:05:00.705 of even a few,

NOTE Confidence: 0.9860237

00:05:01.565 --> 00:05:03.264 small proteins. A few transcription

NOTE Confidence: 0.9860237

00:05:03.325 --> 00:05:05.620 factors can drive tremendous phenotypic

NOTE Confidence: 0.9860237

00:05:05.680 --> 00:05:06.180 change,

NOTE Confidence: 0.91895294

00:05:06.640 --> 00:05:08.020 in in in a cell.

NOTE Confidence: 0.9641331

00:05:10.960 --> 00:05:12.480 And so one of the

NOTE Confidence: 0.9641331

00:05:12.480 --> 00:05:14.480 things that, makes some a

NOTE Confidence: 0.9641331

00:05:14.480 --> 00:05:16.080 subset of these transcription factors

NOTE Confidence: 0.9641331

00:05:16.080 --> 00:05:16.725 so powerful

NOTE Confidence: 0.92595404

00:05:17.685 --> 00:05:19.765 is they're called pioneer facts,

NOTE Confidence: 0.92595404

00:05:19.765 --> 00:05:21.845 pioneer transcription factors. And so

NOTE Confidence: 0.92595404

00:05:21.845 --> 00:05:23.445 as whereas many factors can

NOTE Confidence: 0.92595404

00:05:23.445 --> 00:05:24.885 only bind chromatin that's opened

NOTE Confidence: 0.92595404

00:05:24.885 --> 00:05:26.085 and has their their response

NOTE Confidence: 0.92595404

00:05:26.085 --> 00:05:27.125 elements or the areas they

NOTE Confidence: 0.92595404

00:05:27.125 --> 00:05:29.525 bind, open, pioneer factors can

NOTE Confidence: 0.92595404

00:05:29.525 --> 00:05:30.585 open close chromatin.

NOTE Confidence: 0.95622945

00:05:31.320 --> 00:05:32.760 And they can change the

NOTE Confidence: 0.95622945

00:05:32.760 --> 00:05:34.140 the the epigenomic landscape,

NOTE Confidence: 0.9994362

00:05:34.600 --> 00:05:35.100 truly

NOTE Confidence: 0.93650734

00:05:35.560 --> 00:05:37.320 of of, DNA that they're

NOTE Confidence: 0.93650734

00:05:37.320 --> 00:05:38.760 they're exposed to. And so

NOTE Confidence: 0.93650734

00:05:38.760 --> 00:05:39.880 three of these I've named

NOTE Confidence: 0.93650734

00:05:39.880 --> 00:05:41.080 because they're important in in

NOTE Confidence: 0.93650734

00:05:41.080 --> 00:05:42.360 bladder cancer. So one is

NOTE Confidence: 0.93650734

00:05:42.360 --> 00:05:43.154 Fox a one.

NOTE Confidence: 0.9729969

00:05:43.795 --> 00:05:45.075 That's a pioneer factor that's

NOTE Confidence: 0.9729969

00:05:45.075 --> 00:05:46.195 known to be important in

NOTE Confidence: 0.9729969

00:05:46.195 --> 00:05:47.475 in breast cancer, for example,

NOTE Confidence: 0.9729969

00:05:47.475 --> 00:05:48.855 in ER and AR binding.

NOTE Confidence: 0.95099115

00:05:49.395 --> 00:05:51.235 This one's particularly well studied.

NOTE Confidence: 0.95099115

00:05:51.235 --> 00:05:52.115 It it mimics a link

NOTE Confidence: 0.95099115

00:05:52.115 --> 00:05:53.154 or histone. That's how it's

NOTE Confidence: 0.95099115

00:05:53.154 --> 00:05:54.835 able to open up, close

NOTE Confidence: 0.95099115

00:05:54.835 --> 00:05:55.335 chromatin.

NOTE Confidence: 0.8483268

00:05:56.050 --> 00:05:57.490 Two other ones, GATA3 p,

NOTE Confidence: 0.8483268

00:05:57.490 --> 00:05:58.530 PAR gamma, these are probably

NOTE Confidence: 0.8483268

00:05:58.530 --> 00:05:59.990 also pioneer factors.

NOTE Confidence: 0.90681005

00:06:00.530 --> 00:06:01.830 So these these are,

NOTE Confidence: 0.9496293

00:06:02.450 --> 00:06:04.130 transcription factors, again, that can

NOTE Confidence: 0.9496293

00:06:04.130 --> 00:06:06.290 bind closed chromatin fundamentally on

NOTE Confidence: 0.9496293

00:06:06.290 --> 00:06:08.130 their own, change the the

NOTE Confidence: 0.9496293

00:06:08.130 --> 00:06:09.350 epigenomic landscape,

NOTE Confidence: 0.99323726

00:06:10.185 --> 00:06:11.145 is just a few a

NOTE Confidence: 0.99323726

00:06:11.145 --> 00:06:12.445 few of these these transcription

NOTE Confidence: 0.99323726

00:06:12.585 --> 00:06:13.085 factors.

NOTE Confidence: 0.98182553

00:06:15.865 --> 00:06:16.904 So let's talk about bladder

NOTE Confidence: 0.98182553

00:06:16.904 --> 00:06:18.985 cancer. So so bladder cancer

NOTE Confidence: 0.98182553

00:06:18.985 --> 00:06:20.745 has a very well well

NOTE Confidence: 0.98182553

00:06:20.745 --> 00:06:21.885 known progression.

NOTE Confidence: 0.9640744

00:06:22.699 --> 00:06:23.820 Those in the urology world

NOTE Confidence: 0.9640744

00:06:23.820 --> 00:06:25.339 and the the geopathology world

NOTE Confidence: 0.9640744

00:06:25.339 --> 00:06:26.080 know it well.

NOTE Confidence: 0.8745842

00:06:27.020 --> 00:06:28.620 Starts off as noninvasive disease,

NOTE Confidence: 0.8745842

00:06:28.620 --> 00:06:29.760 like like all cancers

NOTE Confidence: 0.94087476

00:06:30.139 --> 00:06:32.300 do. Either t, TIS or

NOTE Confidence: 0.94087476

00:06:32.300 --> 00:06:33.900 flat carcinoma in situ or

NOTE Confidence: 0.94087476

00:06:33.900 --> 00:06:35.279 TA, which is this noninvasive

NOTE Confidence: 0.93909353

00:06:35.895 --> 00:06:37.255 papillary tumor. It's kinda like

NOTE Confidence: 0.93909353

00:06:37.255 --> 00:06:38.535 a like a bush growing

NOTE Confidence: 0.93909353

00:06:38.535 --> 00:06:39.415 on the surface or like

NOTE Confidence: 0.93909353

00:06:39.415 --> 00:06:39.995 a cauliflower.

NOTE Confidence: 0.97409886

00:06:41.014 --> 00:06:42.375 It invades the lamina propria.

NOTE Confidence: 0.97409886

00:06:42.375 --> 00:06:43.975 That's the superficial connective tissue

NOTE Confidence: 0.97409886

00:06:43.975 --> 00:06:44.955 underneath the urothelium,

NOTE Confidence: 0.95646507

00:06:45.735 --> 00:06:47.335 continues to progress into the

NOTE Confidence: 0.95646507

00:06:47.335 --> 00:06:48.535 the the muscular layer, the

NOTE Confidence: 0.95646507

00:06:48.535 --> 00:06:50.455 muscularis propria of the bladder

NOTE Confidence: 0.95646507

00:06:50.455 --> 00:06:52.020 extends outside of it, and

NOTE Confidence: 0.95646507

00:06:52.020 --> 00:06:53.380 then eventually extends into other

NOTE Confidence: 0.95646507

00:06:53.380 --> 00:06:54.900 organs. So we generally call

NOTE Confidence: 0.95646507

00:06:54.900 --> 00:06:56.900 this non invasive tumor. We

NOTE Confidence: 0.95646507

00:06:56.900 --> 00:06:58.100 call it non muscle invasive

NOTE Confidence: 0.95646507

00:06:58.100 --> 00:06:58.740 if it's up to a

NOTE Confidence: 0.95646507

00:06:58.740 --> 00:06:59.779 t one because it's not

NOTE Confidence: 0.95646507

00:06:59.779 --> 00:07:00.980 quite in muscle. And then

NOTE Confidence: 0.95646507

00:07:00.980 --> 00:07:02.260 we've got muscle invasive bladder

NOTE Confidence: 0.95646507

00:07:02.260 --> 00:07:03.795 cancer whenever it's beyond that.

NOTE Confidence: 0.95646507

00:07:03.795 --> 00:07:04.755 And this is used to

NOTE Confidence: 0.95646507

00:07:04.755 --> 00:07:05.335 to classify,

NOTE Confidence: 0.9481915

00:07:05.955 --> 00:07:06.995 you know, treatments and and

NOTE Confidence: 0.9481915

00:07:06.995 --> 00:07:07.575 and breakdown,

NOTE Confidence: 0.9859388

00:07:08.435 --> 00:07:10.595 you know, different prognostic tests

NOTE Confidence: 0.9859388

00:07:10.595 --> 00:07:11.795 and things. So let's keep

NOTE Confidence: 0.9859388

00:07:11.795 --> 00:07:12.595 this in mind as we

NOTE Confidence: 0.9859388

00:07:12.595 --> 00:07:13.555 as we keep chatting about

NOTE Confidence: 0.9859388

00:07:13.555 --> 00:07:14.355 the rest of the of

NOTE Confidence: 0.9859388

00:07:14.355 --> 00:07:15.095 the talk.

NOTE Confidence: 0.95021635

00:07:15.715 --> 00:07:16.510 And so this is the

NOTE Confidence: 0.95021635

00:07:16.510 --> 00:07:18.430 histology of of most bladder

NOTE Confidence: 0.95021635

00:07:18.430 --> 00:07:19.729 cancers. So this is urothelial

NOTE Confidence: 0.95021635

00:07:19.870 --> 00:07:21.229 carcinoma. This is the stage

NOTE Confidence: 0.95021635

00:07:21.229 --> 00:07:22.830 TA, the non invasive papillary

NOTE Confidence: 0.95021635

00:07:22.830 --> 00:07:24.110 tumor that we talked about.

NOTE Confidence: 0.95021635

00:07:24.110 --> 00:07:25.389 It's got these fibro vascular

NOTE Confidence: 0.95021635

00:07:25.389 --> 00:07:26.510 cores. It's got these this

NOTE Confidence: 0.95021635

00:07:26.510 --> 00:07:27.010 urothelial

NOTE Confidence: 0.9662154

00:07:27.389 --> 00:07:29.165 thickening. There's fusion. It's really

NOTE Confidence: 0.9662154

00:07:29.165 --> 00:07:31.005 just kinda confused cauliflower thing

NOTE Confidence: 0.9662154

00:07:31.005 --> 00:07:31.885 growing off the surface of

NOTE Confidence: 0.9662154

00:07:31.885 --> 00:07:32.545 the urothelium.

NOTE Confidence: 0.953309

00:07:33.565 --> 00:07:35.005 You've got stage TIS or

NOTE Confidence: 0.953309

00:07:35.005 --> 00:07:36.365 flat carcinoma in situ. It's

NOTE Confidence: 0.953309

00:07:36.365 --> 00:07:37.725 these malignant cells sitting on

NOTE Confidence: 0.953309

00:07:37.725 --> 00:07:38.385 the surface.

NOTE Confidence: 0.9824193

00:07:38.845 --> 00:07:40.380 Then you've got invasive urothelial

NOTE Confidence: 0.9824193

00:07:40.380 --> 00:07:40.880 carcinoma.

NOTE Confidence: 0.94069916

00:07:41.259 --> 00:07:42.699 Kinda looks like urothelial. It's

NOTE Confidence: 0.94069916

00:07:42.699 --> 00:07:43.919 not really as, you know,

NOTE Confidence: 0.94069916

00:07:43.979 --> 00:07:45.020 easy to describe as a

NOTE Confidence: 0.94069916

00:07:45.020 --> 00:07:45.979 lot of cancer types like

NOTE Confidence: 0.94069916

00:07:45.979 --> 00:07:47.500 colon cancer and stuff. But

NOTE Confidence: 0.94069916

00:07:47.500 --> 00:07:48.620 it's these jagged, you know,

NOTE Confidence: 0.94069916

00:07:48.620 --> 00:07:50.460 infiltrative nests of cancer that

NOTE Confidence: 0.94069916

00:07:50.460 --> 00:07:51.820 looks kinda like urothelial. And

NOTE Confidence: 0.94069916

00:07:51.820 --> 00:07:53.145 this is the astrology of

NOTE Confidence: 0.94069916

00:07:53.145 --> 00:07:54.345 t one. So the lamina

NOTE Confidence: 0.94069916

00:07:54.345 --> 00:07:55.545 appropriate invasive stuff, and then

NOTE Confidence: 0.94069916

00:07:55.545 --> 00:07:56.845 anything beyond that.

NOTE Confidence: 0.9953939

00:07:59.705 --> 00:08:01.805 So we can also classify

NOTE Confidence: 0.9813665

00:08:02.185 --> 00:08:03.465 bladder cancers into this, this

NOTE Confidence: 0.9813665

00:08:03.465 --> 00:08:05.085 luminal versus basal,

NOTE Confidence: 0.9756401

00:08:05.705 --> 00:08:06.205 dichotomy.

NOTE Confidence: 0.92276514

00:08:06.630 --> 00:08:07.350 And this got a lot

NOTE Confidence: 0.92276514

00:08:07.350 --> 00:08:09.350 of attention, about ten years

NOTE Confidence: 0.92276514

00:08:09.350 --> 00:08:10.870 ago. And so the luminal

NOTE Confidence: 0.92276514

00:08:10.870 --> 00:08:12.970 cancers tend to express, urothelial

NOTE Confidence: 0.92276514

00:08:13.190 --> 00:08:14.470 genes. So FOXA one, you

NOTE Confidence: 0.92276514

00:08:14.470 --> 00:08:15.590 know, get a three, PPAR

NOTE Confidence: 0.92276514

00:08:15.590 --> 00:08:16.410 gamma, uroplacants.

NOTE Confidence: 0.94529086

00:08:16.710 --> 00:08:18.150 They're enriched in FGFR three

NOTE Confidence: 0.94529086

00:08:18.150 --> 00:08:19.270 mutations. Then there's the basal

NOTE Confidence: 0.94529086

00:08:19.270 --> 00:08:21.290 cancers. Those express basal genes.

NOTE Confidence: 0.937006

00:08:21.784 --> 00:08:22.985 They're enriched in high molecular

NOTE Confidence: 0.937006

00:08:22.985 --> 00:08:24.824 weight keratins, TFAPs. They're also

NOTE Confidence: 0.937006

00:08:24.824 --> 00:08:26.104 enriched in t p TB

NOTE Confidence: 0.937006

00:08:26.104 --> 00:08:27.245 fifty three gene mutations.

NOTE Confidence: 0.9610542

00:08:28.185 --> 00:08:29.064 And so there was an

NOTE Confidence: 0.9610542

00:08:29.064 --> 00:08:30.824 idea about ten, eleven years

NOTE Confidence: 0.9610542

00:08:30.824 --> 00:08:31.865 ago when they this this,

NOTE Confidence: 0.9610542

00:08:31.865 --> 00:08:32.665 I think, first came out

NOTE Confidence: 0.9610542

00:08:32.665 --> 00:08:33.750 in bladder cancer, and this

NOTE Confidence: 0.9610542

00:08:33.910 --> 00:08:34.950 idea was that we have

NOTE Confidence: 0.9610542

00:08:34.950 --> 00:08:37.370 intrinsic subtypes. We've identified intrinsic

NOTE Confidence: 0.98745155

00:08:37.830 --> 00:08:39.350 molecular subtypes of bladder cancer,

NOTE Confidence: 0.98745155

00:08:39.350 --> 00:08:40.630 and we can start tailoring

NOTE Confidence: 0.98745155

00:08:40.630 --> 00:08:41.990 our treatments to these two

NOTE Confidence: 0.98745155

00:08:41.990 --> 00:08:42.490 different

NOTE Confidence: 0.9583521

00:08:43.030 --> 00:08:44.470 molecular subtypes. And a lot

NOTE Confidence: 0.9583521

00:08:44.470 --> 00:08:45.350 of attention, a lot of

NOTE Confidence: 0.9583521

00:08:45.350 --> 00:08:46.365 money, and a lot of

NOTE Confidence: 0.9583521

00:08:46.445 --> 00:08:47.964 effort went into coming up

NOTE Confidence: 0.9583521

00:08:47.964 --> 00:08:49.084 with ways to to treat

NOTE Confidence: 0.9583521

00:08:49.084 --> 00:08:51.505 these these different molecular subtypes.

NOTE Confidence: 0.9663916

00:08:52.524 --> 00:08:53.565 And I submit to you

NOTE Confidence: 0.9663916

00:08:53.565 --> 00:08:54.684 that that is not the

NOTE Confidence: 0.9663916

00:08:54.684 --> 00:08:56.545 case. They are not intrinsic.

NOTE Confidence: 0.9663916

00:08:56.605 --> 00:08:57.404 This is not a story

NOTE Confidence: 0.9663916

00:08:57.404 --> 00:08:59.005 of intrinsic molecular subtypes that

NOTE Confidence: 0.9663916

00:08:59.005 --> 00:09:00.125 are born basal or born

NOTE Confidence: 0.9663916

00:09:00.125 --> 00:09:00.625 luminal.

NOTE Confidence: 0.9410395

00:09:01.300 --> 00:09:02.580 The story of bladder cancer,

NOTE Confidence: 0.9410395

00:09:02.580 --> 00:09:03.540 the story of luminal and

NOTE Confidence: 0.9410395

00:09:03.540 --> 00:09:04.840 basal is a story of

NOTE Confidence: 0.9410395

00:09:05.059 --> 00:09:05.960 lineage plasticity.

NOTE Confidence: 0.9717077

00:09:07.140 --> 00:09:07.640 And

NOTE Confidence: 0.88194066

00:09:08.260 --> 00:09:09.700 the utility of the luminal

NOTE Confidence: 0.88194066

00:09:09.700 --> 00:09:11.220 and basal is really not

NOTE Confidence: 0.88194066

00:09:11.220 --> 00:09:12.260 in naming them a luminal

NOTE Confidence: 0.88194066

00:09:12.260 --> 00:09:13.615 cancer or basal cancer, but

NOTE Confidence: 0.88194066

00:09:13.615 --> 00:09:15.155 rather the utility is understanding

NOTE Confidence: 0.97859424

00:09:15.695 --> 00:09:17.715 the drivers of luminal differentiation,

NOTE Confidence: 0.97859424

00:09:17.855 --> 00:09:19.475 the drivers of basal differentiation,

NOTE Confidence: 0.97859424

00:09:19.615 --> 00:09:20.735 and how we can exploit

NOTE Confidence: 0.97859424

00:09:20.735 --> 00:09:21.795 those in the future

NOTE Confidence: 0.9122079

00:09:22.255 --> 00:09:23.775 to treat patients with bladder

NOTE Confidence: 0.9122079

00:09:23.775 --> 00:09:24.275 cancer.

NOTE Confidence: 0.9965873

00:09:27.780 --> 00:09:29.220 So so here's some relevant

NOTE Confidence: 0.9965873

00:09:29.220 --> 00:09:30.740 signatures whenever you break these

NOTE Confidence: 0.9965873

00:09:30.740 --> 00:09:32.260 these tumors down. So,

NOTE Confidence: 0.9705259

00:09:32.900 --> 00:09:34.179 what these data are are

NOTE Confidence: 0.9705259

00:09:34.179 --> 00:09:35.700 from the Cancer Genome Atlas,

NOTE Confidence: 0.9705259

00:09:35.860 --> 00:09:36.900 bladder cancer data, which is

NOTE Confidence: 0.9705259

00:09:36.900 --> 00:09:38.100 a nice repository if you

NOTE Confidence: 0.9705259

00:09:38.100 --> 00:09:39.480 wanna just look at stuff.

NOTE Confidence: 0.9400889

00:09:40.715 --> 00:09:41.915 And so what we did

NOTE Confidence: 0.9400889

00:09:41.915 --> 00:09:43.115 is we we took the

NOTE Confidence: 0.9400889

00:09:43.115 --> 00:09:44.335 cancer genome atlas,

NOTE Confidence: 0.97316754

00:09:44.715 --> 00:09:46.475 invasive bladder cancers, divided them

NOTE Confidence: 0.97316754

00:09:46.475 --> 00:09:48.075 into luminal versus basal based

NOTE Confidence: 0.97316754

00:09:48.075 --> 00:09:48.955 on, you know, just the

NOTE Confidence: 0.97316754

00:09:48.955 --> 00:09:50.554 standard, you know, dichotomous, you

NOTE Confidence: 0.97316754

00:09:50.554 --> 00:09:51.915 know, change. And then we

NOTE Confidence: 0.97316754

00:09:51.915 --> 00:09:53.115 looked at single sample gene

NOTE Confidence: 0.97316754

00:09:53.115 --> 00:09:54.735 set enrichment analysis scores,

NOTE Confidence: 0.96878624

00:09:55.355 --> 00:09:56.630 and then compared them, in

NOTE Confidence: 0.96878624

00:09:56.630 --> 00:09:58.149 these different scores. So as

NOTE Confidence: 0.96878624

00:09:58.149 --> 00:09:59.750 expected, luminal cancers tend to

NOTE Confidence: 0.96878624

00:09:59.750 --> 00:10:01.029 have, you know, high expression

NOTE Confidence: 0.96878624

00:10:01.029 --> 00:10:01.929 of luminal genes.

NOTE Confidence: 0.9712025

00:10:02.630 --> 00:10:03.990 Basal cancers tend to have

NOTE Confidence: 0.9712025

00:10:03.990 --> 00:10:05.269 higher expression of basal genes.

NOTE Confidence: 0.9712025

00:10:05.269 --> 00:10:06.709 This is obvious. But there's

NOTE Confidence: 0.9712025

00:10:06.709 --> 00:10:07.830 some things that that pop

NOTE Confidence: 0.9712025

00:10:07.830 --> 00:10:08.649 out that are

NOTE Confidence: 0.9597808

00:10:08.995 --> 00:10:10.515 also of of of value.

NOTE Confidence: 0.9597808

00:10:10.755 --> 00:10:12.135 One is cell cycle activity.

NOTE Confidence: 0.9597808

00:10:12.195 --> 00:10:12.995 It's a little bit higher

NOTE Confidence: 0.9597808

00:10:12.995 --> 00:10:14.675 in basal versus luminal. Another

NOTE Confidence: 0.9597808

00:10:14.675 --> 00:10:16.355 is inflammatory signature. So this

NOTE Confidence: 0.9597808

00:10:16.355 --> 00:10:17.155 is just, you know, our

NOTE Confidence: 0.9597808

00:10:17.155 --> 00:10:18.535 standard hallmark inflammation

NOTE Confidence: 0.73140216

00:10:18.995 --> 00:10:19.735 kinda signature.

NOTE Confidence: 0.9968168

00:10:20.115 --> 00:10:21.235 And it shows that the

NOTE Confidence: 0.9968168

00:10:21.235 --> 00:10:22.535 basal cancers are

NOTE Confidence: 0.9278592

00:10:22.980 --> 00:10:24.580 enriched largely in in an

NOTE Confidence: 0.9278592

00:10:24.580 --> 00:10:25.800 inflammatory signature.

NOTE Confidence: 0.98608416

00:10:26.660 --> 00:10:27.959 And perhaps more importantly,

NOTE Confidence: 0.98832417

00:10:28.899 --> 00:10:30.500 basal tumors are heavily enriched

NOTE Confidence: 0.98832417

00:10:30.500 --> 00:10:32.120 at interferon gamma activity.

NOTE Confidence: 0.93302214

00:10:32.820 --> 00:10:34.179 So we name them after

NOTE Confidence: 0.93302214

00:10:34.179 --> 00:10:35.540 the epithelial cell that they're

NOTE Confidence: 0.93302214

00:10:35.540 --> 00:10:37.134 differentiating toward more basal, more

NOTE Confidence: 0.93302214

00:10:37.134 --> 00:10:37.634 squamous.

NOTE Confidence: 0.9300864

00:10:38.334 --> 00:10:39.934 But whenever we break it

NOTE Confidence: 0.9300864

00:10:39.934 --> 00:10:40.574 down and look at the

NOTE Confidence: 0.9300864

00:10:40.574 --> 00:10:42.755 signatures, interferon gamma is extremely

NOTE Confidence: 0.9300864

00:10:42.815 --> 00:10:44.574 strong in the basal squamous

NOTE Confidence: 0.9300864

00:10:44.574 --> 00:10:46.095 or the basal type of

NOTE Confidence: 0.9300864

00:10:46.095 --> 00:10:46.915 bladder cancer.

NOTE Confidence: 0.88520473

00:10:50.559 --> 00:10:52.559 And molecular subtype also associates

NOTE Confidence: 0.88520473

00:10:52.559 --> 00:10:53.700 strongly with stage.

NOTE Confidence: 0.9213271

00:10:54.320 --> 00:10:55.679 And so to my mind,

NOTE Confidence: 0.9213271

00:10:55.679 --> 00:10:56.800 if these were intrinsic and

NOTE Confidence: 0.9213271

00:10:56.800 --> 00:10:58.080 they were either born basilar,

NOTE Confidence: 0.9213271

00:10:58.080 --> 00:10:59.220 they were born luminal,

NOTE Confidence: 0.93226904

00:11:00.400 --> 00:11:02.320 you would see precursors that

NOTE Confidence: 0.93226904

00:11:02.320 --> 00:11:03.945 are basal. You would see

NOTE Confidence: 0.93226904

00:11:03.945 --> 00:11:05.065 precursors that are luminal and

NOTE Confidence: 0.93226904

00:11:05.065 --> 00:11:06.045 they would be in roughly

NOTE Confidence: 0.93226904

00:11:06.265 --> 00:11:07.945 equal proportion, but that's not

NOTE Confidence: 0.93226904

00:11:07.945 --> 00:11:08.905 the case at all.

NOTE Confidence: 0.9672631

00:11:09.625 --> 00:11:10.505 It turns out that the

NOTE Confidence: 0.9672631

00:11:10.505 --> 00:11:12.265 vast majority of non invasive

NOTE Confidence: 0.9672631

00:11:12.265 --> 00:11:13.945 and even early stage invasive

NOTE Confidence: 0.9672631

00:11:13.945 --> 00:11:15.005 cancers are luminal.

NOTE Confidence: 0.9702113

00:11:15.305 --> 00:11:16.960 Whereas the basal nist, the

NOTE Confidence: 0.9702113

00:11:16.960 --> 00:11:18.480 basal phenotype doesn't really show

NOTE Confidence: 0.9702113

00:11:18.480 --> 00:11:19.280 up until you're in the

NOTE Confidence: 0.9702113

00:11:19.280 --> 00:11:20.580 muscle invasive stage.

NOTE Confidence: 0.90889996

00:11:21.440 --> 00:11:23.120 And so these data are,

NOTE Confidence: 0.90889996

00:11:23.440 --> 00:11:23.940 combined,

NOTE Confidence: 0.9114095

00:11:24.800 --> 00:11:25.920 cancer genome at least data

NOTE Confidence: 0.9114095

00:11:25.920 --> 00:11:27.520 for muscle invasive tumors. And

NOTE Confidence: 0.9114095

00:11:27.520 --> 00:11:28.960 then there's this large European

NOTE Confidence: 0.9114095

00:11:28.960 --> 00:11:29.460 study,

NOTE Confidence: 0.9016151

00:11:30.570 --> 00:11:31.807 Linsgrogg et al. They had

NOTE Confidence: 0.9016151

00:11:31.807 --> 00:11:33.045 the TA and t one

NOTE Confidence: 0.9016151

00:11:33.045 --> 00:11:34.530 cancers. So we the the

NOTE Confidence: 0.9016151

00:11:34.530 --> 00:11:35.767 analysis we're looking at here,

NOTE Confidence: 0.9016151

00:11:36.015 --> 00:11:37.252 was one of my group,

NOTE Confidence: 0.9016151

00:11:37.252 --> 00:11:38.490 we we lumped the cases,

NOTE Confidence: 0.9016151

00:11:38.490 --> 00:11:39.727 normalized them, and then used

NOTE Confidence: 0.9016151

00:11:39.727 --> 00:11:40.965 a UNC classifier that's published

NOTE Confidence: 0.9016151

00:11:40.965 --> 00:11:42.202 at University of North Carolina

NOTE Confidence: 0.9016151

00:11:42.202 --> 00:11:43.440 into either luminal or basal.

NOTE Confidence: 0.9016151

00:11:43.679 --> 00:11:44.660 And as expected,

NOTE Confidence: 0.9577621

00:11:45.040 --> 00:11:46.320 based on some prior studies,

NOTE Confidence: 0.9577621

00:11:46.320 --> 00:11:48.000 the TA were vast majority,

NOTE Confidence: 0.9577621

00:11:48.000 --> 00:11:49.280 ninety five percent plus for

NOTE Confidence: 0.9577621

00:11:49.280 --> 00:11:49.780 luminal.

NOTE Confidence: 0.9247971

00:11:50.640 --> 00:11:51.600 Most of the t ones,

NOTE Confidence: 0.9247971

00:11:51.600 --> 00:11:52.720 which is somewhat surprising, were

NOTE Confidence: 0.9247971

00:11:52.720 --> 00:11:54.179 also luminal, whereas the,

NOTE Confidence: 0.9233642

00:11:55.280 --> 00:11:56.640 the muscle invasive cancers, those

NOTE Confidence: 0.9233642

00:11:56.640 --> 00:11:57.600 that were in the muscular

NOTE Confidence: 0.9233642

00:11:57.600 --> 00:11:58.720 as appropriate or deeper were

NOTE Confidence: 0.9233642

00:11:58.720 --> 00:12:00.345 about half luminal, about half

NOTE Confidence: 0.9233642

00:12:00.345 --> 00:12:01.785 base. So this this to

NOTE Confidence: 0.9233642

00:12:01.785 --> 00:12:02.825 me even, like, looking at

NOTE Confidence: 0.9233642

00:12:02.825 --> 00:12:03.625 it says that this is

NOTE Confidence: 0.9233642

00:12:03.625 --> 00:12:04.665 a a story of these

NOTE Confidence: 0.9233642

00:12:04.665 --> 00:12:06.025 things changing as they develop

NOTE Confidence: 0.9233642

00:12:06.025 --> 00:12:07.085 higher stage disease.

NOTE Confidence: 0.54236466

00:12:11.870 --> 00:12:12.370 Okay.

NOTE Confidence: 0.9206568

00:12:13.149 --> 00:12:14.029 Did I break it? There

NOTE Confidence: 0.9206568

00:12:14.029 --> 00:12:14.850 we go. Okay.

NOTE Confidence: 0.9233445

00:12:15.470 --> 00:12:17.149 And so, there's another piece

NOTE Confidence: 0.9233445

00:12:17.149 --> 00:12:18.110 to the story in the

NOTE Confidence: 0.9233445

00:12:18.110 --> 00:12:19.550 histology that really starts to

NOTE Confidence: 0.9233445

00:12:19.550 --> 00:12:21.949 argue for lineage plasticity playing

NOTE Confidence: 0.9233445

00:12:21.949 --> 00:12:23.709 an important role in this

NOTE Confidence: 0.9233445

00:12:23.709 --> 00:12:25.490 phenotypic evolution. So,

NOTE Confidence: 0.98161584

00:12:26.145 --> 00:12:26.645 in

NOTE Confidence: 0.9102148

00:12:27.025 --> 00:12:28.145 bladder cancer world and the

NOTE Confidence: 0.9102148

00:12:28.145 --> 00:12:29.184 residents, we talked about these

NOTE Confidence: 0.9102148

00:12:29.184 --> 00:12:30.785 this morning and Tuesday morning,

NOTE Confidence: 0.9102148

00:12:30.785 --> 00:12:31.825 they're probably tired of me

NOTE Confidence: 0.9102148

00:12:31.825 --> 00:12:32.385 at this point.

NOTE Confidence: 0.88936424

00:12:34.705 --> 00:12:35.745 So the bladder cancer has

NOTE Confidence: 0.88936424

00:12:35.745 --> 00:12:36.145 many,

NOTE Confidence: 0.82643914

00:12:36.545 --> 00:12:38.085 histologic variants or

NOTE Confidence: 0.9148137

00:12:38.529 --> 00:12:40.210 divergent differentiation or histologic subtypes.

NOTE Confidence: 0.9148137

00:12:40.210 --> 00:12:41.330 There's a bunch of ways

NOTE Confidence: 0.9148137

00:12:41.330 --> 00:12:42.610 to describe these, but they're

NOTE Confidence: 0.9148137

00:12:42.610 --> 00:12:43.670 named histomorphologies

NOTE Confidence: 0.99420714

00:12:44.130 --> 00:12:45.350 that have specific,

NOTE Confidence: 0.96060354

00:12:45.890 --> 00:12:47.890 clinical correlations and complete and

NOTE Confidence: 0.96060354

00:12:47.890 --> 00:12:49.910 specific prognostic, you know, implications.

NOTE Confidence: 0.9369464

00:12:50.450 --> 00:12:51.089 You know, one of those

NOTE Confidence: 0.9369464

00:12:51.089 --> 00:12:52.690 is micropapillary. That's these tiny

NOTE Confidence: 0.9369464

00:12:52.690 --> 00:12:54.554 little, you know, micropapillary nest

NOTE Confidence: 0.9369464

00:12:54.554 --> 00:12:55.834 with attraction clefts. We've got

NOTE Confidence: 0.9369464

00:12:55.834 --> 00:12:57.834 plasmacytoid that's infiltrative single cells.

NOTE Confidence: 0.9369464

00:12:57.834 --> 00:12:59.115 We've got glandular, that means

NOTE Confidence: 0.9369464

00:12:59.115 --> 00:13:00.254 it's it's making glands.

NOTE Confidence: 0.9541435

00:13:00.634 --> 00:13:01.675 Nested, that means it's little

NOTE Confidence: 0.9541435

00:13:01.675 --> 00:13:02.795 tiny blend nest that are

NOTE Confidence: 0.9541435

00:13:02.795 --> 00:13:04.154 easy to to miss. Got

NOTE Confidence: 0.9541435

00:13:04.154 --> 00:13:05.194 small cell that looks like

NOTE Confidence: 0.9541435

00:13:05.194 --> 00:13:06.235 small cell lung cancer. You've

NOTE Confidence: 0.9541435

00:13:06.235 --> 00:13:08.074 got squamous carcinoma that's making

NOTE Confidence: 0.9541435

00:13:08.074 --> 00:13:09.540 keratin, not to be confused

NOTE Confidence: 0.9541435

00:13:09.540 --> 00:13:11.059 with with basal or basal

NOTE Confidence: 0.9541435

00:13:11.059 --> 00:13:12.260 squamous, which is usually what

NOTE Confidence: 0.9541435

00:13:12.260 --> 00:13:13.140 we use to describe, you

NOTE Confidence: 0.9541435

00:13:13.140 --> 00:13:14.660 know, the molecular subtypes. But

NOTE Confidence: 0.9541435

00:13:14.660 --> 00:13:16.679 rather, it's histologic squamous differentiation

NOTE Confidence: 0.9541435

00:13:16.740 --> 00:13:18.360 where it's making making keratin.

NOTE Confidence: 0.93217814

00:13:18.900 --> 00:13:20.595 You have lymphopodeal leoma like,

NOTE Confidence: 0.93217814

00:13:21.154 --> 00:13:22.995 that looks like nasopharyngeal carcinoma,

NOTE Confidence: 0.93217814

00:13:22.995 --> 00:13:24.454 which is an EBV mediated

NOTE Confidence: 0.93217814

00:13:24.514 --> 00:13:26.134 phenomenon with an intense inflammatory

NOTE Confidence: 0.93217814

00:13:26.194 --> 00:13:26.694 infiltrate.

NOTE Confidence: 0.9620597

00:13:27.235 --> 00:13:29.074 This actually isn't EBV mediated.

NOTE Confidence: 0.9620597

00:13:29.074 --> 00:13:30.115 It just looks like a

NOTE Confidence: 0.9620597

00:13:30.115 --> 00:13:32.754 nasopharyngeal tumor that, that is.

NOTE Confidence: 0.9620597

00:13:32.754 --> 00:13:33.735 Then there's sarcomatoid,

NOTE Confidence: 0.9768306

00:13:34.355 --> 00:13:36.110 which is relatively common, but

NOTE Confidence: 0.9768306

00:13:36.110 --> 00:13:38.050 it's differentiating towards a sarcoma.

NOTE Confidence: 0.9927418

00:13:38.429 --> 00:13:39.570 And so this is the

NOTE Confidence: 0.9927418

00:13:39.790 --> 00:13:41.309 the the diversity of, you

NOTE Confidence: 0.9927418

00:13:41.309 --> 00:13:43.070 know, of of bladder cancer

NOTE Confidence: 0.9927418

00:13:43.070 --> 00:13:44.210 for the large part.

NOTE Confidence: 0.9989066

00:13:45.630 --> 00:13:46.830 And these things tend to

NOTE Confidence: 0.9989066

00:13:46.830 --> 00:13:48.050 have, consistent

NOTE Confidence: 0.6784177

00:13:49.150 --> 00:13:50.210 molecular subtypes.

NOTE Confidence: 0.94653237

00:13:50.915 --> 00:13:52.515 Not perfect, but there's a

NOTE Confidence: 0.94653237

00:13:52.515 --> 00:13:54.115 strong tendency here. So, the

NOTE Confidence: 0.94653237

00:13:54.115 --> 00:13:56.195 plasmacytoid, the micropapillary, the nested,

NOTE Confidence: 0.94653237

00:13:56.195 --> 00:13:57.255 they tend to be luminal.

NOTE Confidence: 0.77426624

00:13:58.835 --> 00:13:59.655 The lymphopithelium

NOTE Confidence: 0.9345267

00:14:00.035 --> 00:14:01.955 alike, the squamous, histologically squamous

NOTE Confidence: 0.9345267

00:14:01.955 --> 00:14:02.934 tend to be basal.

NOTE Confidence: 0.9381133

00:14:03.459 --> 00:14:05.059 The sarcomatoid kinda do whatever

NOTE Confidence: 0.9381133

00:14:05.059 --> 00:14:05.940 they wanna do. They're turning

NOTE Confidence: 0.9381133

00:14:05.940 --> 00:14:07.220 into sarcomas, so they're a

NOTE Confidence: 0.9381133

00:14:07.220 --> 00:14:07.959 little wild.

NOTE Confidence: 0.99418676

00:14:08.580 --> 00:14:09.240 The glandular,

NOTE Confidence: 0.9740543

00:14:09.700 --> 00:14:11.000 you know, they make glands.

NOTE Confidence: 0.9740543

00:14:11.059 --> 00:14:12.100 They can be variable as

NOTE Confidence: 0.9740543

00:14:12.100 --> 00:14:12.600 well.

NOTE Confidence: 0.84076715

00:14:13.220 --> 00:14:14.200 You know, in neuroendocrine,

NOTE Confidence: 0.90104026

00:14:14.820 --> 00:14:15.860 the small cell, they have

NOTE Confidence: 0.90104026

00:14:15.860 --> 00:14:17.300 neuroendocrine phenotype, you know, they're

NOTE Confidence: 0.90104026

00:14:17.300 --> 00:14:18.440 not really getting, you know,

NOTE Confidence: 0.90104026

00:14:18.465 --> 00:14:19.685 you're the only one anymore.

NOTE Confidence: 0.9761339

00:14:20.305 --> 00:14:21.665 And so there's, you know,

NOTE Confidence: 0.9761339

00:14:21.665 --> 00:14:22.865 not only and my phone

NOTE Confidence: 0.9761339

00:14:22.865 --> 00:14:24.325 is just buzzing. Hold on.

NOTE Confidence: 0.96725273

00:14:24.785 --> 00:14:25.745 Spam. Do you guys get

NOTE Confidence: 0.96725273

00:14:25.745 --> 00:14:27.105 spammed constantly? It's making me

NOTE Confidence: 0.96725273

00:14:27.105 --> 00:14:28.865 crazy. It's, like, half ninety

NOTE Confidence: 0.96725273

00:14:28.865 --> 00:14:29.925 percent of my calls.

NOTE Confidence: 0.82336366

00:14:30.990 --> 00:14:32.350 Okay. So, so back to

NOTE Confidence: 0.82336366

00:14:32.350 --> 00:14:33.170 this. So,

NOTE Confidence: 0.6818592

00:14:34.830 --> 00:14:35.970 these histologic variants

NOTE Confidence: 0.8476024

00:14:36.510 --> 00:14:38.990 strongly associate with these specific

NOTE Confidence: 0.8476024

00:14:38.990 --> 00:14:40.050 molecular subtypes.

NOTE Confidence: 0.909075

00:14:42.975 --> 00:14:44.654 And so, you know, back

NOTE Confidence: 0.909075

00:14:44.654 --> 00:14:46.274 in twenty nineteen, we had

NOTE Confidence: 0.909075

00:14:46.334 --> 00:14:47.615 a study published in European

NOTE Confidence: 0.909075

00:14:47.615 --> 00:14:48.574 urology that got a lot

NOTE Confidence: 0.909075

00:14:48.574 --> 00:14:49.154 of attention.

NOTE Confidence: 0.9768763

00:14:49.694 --> 00:14:50.194 Because

NOTE Confidence: 0.8497105

00:14:50.574 --> 00:14:51.694 before the study came out,

NOTE Confidence: 0.8497105

00:14:51.694 --> 00:14:52.574 there was this, like I

NOTE Confidence: 0.8497105

00:14:52.574 --> 00:14:53.555 said, there was this

NOTE Confidence: 0.8429552

00:14:54.014 --> 00:14:56.035 intense interest in intrinsicness

NOTE Confidence: 0.93762565

00:14:57.150 --> 00:14:58.910 of of these molecular subtypes.

NOTE Confidence: 0.93762565

00:14:58.910 --> 00:14:59.630 And there have been clinical

NOTE Confidence: 0.93762565

00:14:59.630 --> 00:15:00.910 trials that were being developed,

NOTE Confidence: 0.93762565

00:15:00.910 --> 00:15:01.950 putting people in these different

NOTE Confidence: 0.93762565

00:15:01.950 --> 00:15:03.310 subtypes and then treating them

NOTE Confidence: 0.93762565

00:15:03.310 --> 00:15:05.150 differently based on the the

NOTE Confidence: 0.93762565

00:15:05.150 --> 00:15:05.810 the classifications.

NOTE Confidence: 0.96554124

00:15:06.590 --> 00:15:07.470 And this study was one

NOTE Confidence: 0.96554124

00:15:07.470 --> 00:15:08.270 of the first to really

NOTE Confidence: 0.96554124

00:15:08.270 --> 00:15:09.070 kind of, you know, shoot

NOTE Confidence: 0.96554124

00:15:09.070 --> 00:15:09.975 a hole on that idea.

NOTE Confidence: 0.96554124

00:15:10.134 --> 00:15:11.095 And so what we did

NOTE Confidence: 0.96554124

00:15:11.095 --> 00:15:12.295 is we took about three

NOTE Confidence: 0.96554124

00:15:12.295 --> 00:15:12.795 hundred,

NOTE Confidence: 0.9852567

00:15:13.815 --> 00:15:14.315 consecutive,

NOTE Confidence: 0.9628844

00:15:14.694 --> 00:15:16.454 cystectomy cases. We mapped them

NOTE Confidence: 0.9628844

00:15:16.454 --> 00:15:16.954 out.

NOTE Confidence: 0.9920251

00:15:17.334 --> 00:15:18.694 We identified all the different

NOTE Confidence: 0.9920251

00:15:18.694 --> 00:15:20.454 areas of histologically distinct invasive

NOTE Confidence: 0.9920251

00:15:20.454 --> 00:15:21.334 carcinoma. We,

NOTE Confidence: 0.9384578

00:15:21.975 --> 00:15:23.495 named them. We identified areas

NOTE Confidence: 0.9384578

00:15:23.495 --> 00:15:24.714 of non invasive carcinoma,

NOTE Confidence: 0.92837167

00:15:25.490 --> 00:15:27.270 and we performed molecular subtyping

NOTE Confidence: 0.92837167

00:15:27.410 --> 00:15:29.110 on them using, the,

NOTE Confidence: 0.9371734

00:15:29.570 --> 00:15:30.770 a group or a a

NOTE Confidence: 0.9371734

00:15:30.770 --> 00:15:32.290 schema developed by the Lund

NOTE Confidence: 0.9371734

00:15:32.290 --> 00:15:32.790 University,

NOTE Confidence: 0.87237453

00:15:34.690 --> 00:15:35.190 in,

NOTE Confidence: 0.91618794

00:15:35.570 --> 00:15:37.970 in in Switzerland. No. Sweden.

NOTE Confidence: 0.91618794

00:15:37.970 --> 00:15:39.105 In Sweden. They would make

NOTE Confidence: 0.91618794

00:15:39.345 --> 00:15:40.065 they would be angry if

NOTE Confidence: 0.91618794

00:15:40.065 --> 00:15:41.045 I said they were Swiss.

NOTE Confidence: 0.87248456

00:15:41.425 --> 00:15:43.605 But they're, they developed this,

NOTE Confidence: 0.9802457

00:15:44.145 --> 00:15:46.245 system for for molecular classification.

NOTE Confidence: 0.9375

00:15:47.025 --> 00:15:48.065 And so they have a,

NOTE Confidence: 0.9375

00:15:48.065 --> 00:15:48.865 you know, this kind of

NOTE Confidence: 0.9375

00:15:48.865 --> 00:15:49.665 type where they call them

NOTE Confidence: 0.9375

00:15:49.665 --> 00:15:51.425 urothelial like and genomically unstable,

NOTE Confidence: 0.9375

00:15:51.425 --> 00:15:53.025 but really practically speaking, those

NOTE Confidence: 0.9375

00:15:53.025 --> 00:15:54.400 are those are luminal. They

NOTE Confidence: 0.9375

00:15:54.400 --> 00:15:55.680 have a basal squamous equivalent

NOTE Confidence: 0.9375

00:15:55.680 --> 00:15:56.400 to a basal on the

NOTE Confidence: 0.9375

00:15:56.400 --> 00:15:58.020 other systems. They have mesenchymal

NOTE Confidence: 0.9375

00:15:58.080 --> 00:15:58.960 like that is really rare,

NOTE Confidence: 0.9375

00:15:58.960 --> 00:15:59.840 kind of like sarcoma, and

NOTE Confidence: 0.9375

00:15:59.840 --> 00:16:00.980 then they have non type.

NOTE Confidence: 0.96854216

00:16:01.280 --> 00:16:02.080 What we did is we

NOTE Confidence: 0.96854216

00:16:02.080 --> 00:16:03.760 performed molecular subtyping on all

NOTE Confidence: 0.96854216

00:16:03.760 --> 00:16:05.120 the different areas from these

NOTE Confidence: 0.96854216

00:16:05.120 --> 00:16:06.405 bladders that we mapped out.

NOTE Confidence: 0.96854216

00:16:06.805 --> 00:16:07.525 And this is how we

NOTE Confidence: 0.96854216

00:16:07.525 --> 00:16:09.225 demonstrated those that had,

NOTE Confidence: 0.976852

00:16:09.725 --> 00:16:11.545 you know, histologic diversity.

NOTE Confidence: 0.9425763

00:16:12.165 --> 00:16:13.605 And so each column is

NOTE Confidence: 0.9425763

00:16:13.605 --> 00:16:15.125 a histology, we've got conventional

NOTE Confidence: 0.9425763

00:16:15.125 --> 00:16:18.105 urothelial, squamous, micropapillary, glandular, etcetera.

NOTE Confidence: 0.9425763

00:16:18.325 --> 00:16:19.465 Each row is a patient,

NOTE Confidence: 0.98074776

00:16:20.210 --> 00:16:21.810 and then each color is

NOTE Confidence: 0.98074776

00:16:21.810 --> 00:16:23.350 a a molecular subtype.

NOTE Confidence: 0.95377934

00:16:23.890 --> 00:16:25.090 So what we we see

NOTE Confidence: 0.95377934

00:16:25.090 --> 00:16:26.530 here is that if we

NOTE Confidence: 0.95377934

00:16:26.530 --> 00:16:27.650 go along each row, we

NOTE Confidence: 0.95377934

00:16:27.650 --> 00:16:29.030 can see the different histologies

NOTE Confidence: 0.95377934

00:16:29.170 --> 00:16:30.690 each patient had. Gray means

NOTE Confidence: 0.95377934

00:16:30.690 --> 00:16:31.650 they didn't have it. Then

NOTE Confidence: 0.95377934

00:16:31.650 --> 00:16:32.690 we can see what molecular

NOTE Confidence: 0.95377934

00:16:32.690 --> 00:16:34.230 subtype they were assigned to.

NOTE Confidence: 0.99721336

00:16:34.545 --> 00:16:35.345 And what we can see

NOTE Confidence: 0.99721336

00:16:35.345 --> 00:16:36.645 here is that there's diversity.

NOTE Confidence: 0.9964238

00:16:37.425 --> 00:16:38.945 They're not all the same.

NOTE Confidence: 0.9964238

00:16:38.945 --> 00:16:39.845 They're not intrinsic.

NOTE Confidence: 0.9161839

00:16:40.464 --> 00:16:41.745 They differ. So for example,

NOTE Confidence: 0.9161839

00:16:41.745 --> 00:16:42.625 this first row of the

NOTE Confidence: 0.9161839

00:16:42.785 --> 00:16:44.545 conventional urothelial was a luminal

NOTE Confidence: 0.9161839

00:16:44.545 --> 00:16:46.625 subtype and associated histologically squamous

NOTE Confidence: 0.9161839

00:16:46.625 --> 00:16:48.019 was basal squamous.

NOTE Confidence: 0.98393047

00:16:48.560 --> 00:16:49.940 Same thing with these guys.

NOTE Confidence: 0.9709802

00:16:50.720 --> 00:16:52.079 Here, this was also luminal.

NOTE Confidence: 0.9709802

00:16:52.079 --> 00:16:53.279 These are basal squamous. The

NOTE Confidence: 0.9709802

00:16:53.279 --> 00:16:55.459 conventional was urothelial. The histologically

NOTE Confidence: 0.9709802

00:16:55.680 --> 00:16:57.220 squamous was a basal subtype.

NOTE Confidence: 0.9709802

00:16:57.519 --> 00:16:58.399 And then it gets even

NOTE Confidence: 0.9709802

00:16:58.399 --> 00:16:59.839 more interesting. Some have, you

NOTE Confidence: 0.9709802

00:16:59.839 --> 00:17:00.420 know, like

NOTE Confidence: 0.92140436

00:17:01.225 --> 00:17:02.665 a, you know, basal conventional

NOTE Confidence: 0.92140436

00:17:02.665 --> 00:17:04.425 urothelial, basal squamous, then there's

NOTE Confidence: 0.92140436

00:17:04.425 --> 00:17:05.465 a micropapillary in a different

NOTE Confidence: 0.92140436

00:17:05.465 --> 00:17:06.525 area that was luminal.

NOTE Confidence: 0.99811673

00:17:07.145 --> 00:17:07.885 So this

NOTE Confidence: 0.9553363

00:17:08.185 --> 00:17:09.065 really is one of the

NOTE Confidence: 0.9553363

00:17:09.065 --> 00:17:10.425 first indications that, like, no.

NOTE Confidence: 0.9553363

00:17:10.425 --> 00:17:11.385 These things are not just

NOTE Confidence: 0.9553363

00:17:11.385 --> 00:17:12.825 born one way and they

NOTE Confidence: 0.9553363

00:17:12.825 --> 00:17:14.285 stay that way. There's plasticity

NOTE Confidence: 0.9553363

00:17:14.345 --> 00:17:15.465 going on. These are changing

NOTE Confidence: 0.9553363

00:17:15.465 --> 00:17:16.560 as they evolve from different

NOTE Confidence: 0.9553363

00:17:16.960 --> 00:17:17.520 to different,

NOTE Confidence: 0.9747021

00:17:18.000 --> 00:17:18.500 histologies.

NOTE Confidence: 0.96463275

00:17:19.200 --> 00:17:20.320 And in fact, thirty nine

NOTE Confidence: 0.96463275

00:17:20.320 --> 00:17:21.220 percent of cases

NOTE Confidence: 0.9576434

00:17:21.760 --> 00:17:23.220 in which there was histologic

NOTE Confidence: 0.9576434

00:17:23.360 --> 00:17:25.280 diversity also demonstrated a difference

NOTE Confidence: 0.9576434

00:17:25.280 --> 00:17:26.720 in molecular subtype, and it's

NOTE Confidence: 0.9576434

00:17:26.720 --> 00:17:28.080 extremely common in those that

NOTE Confidence: 0.9576434

00:17:28.080 --> 00:17:29.635 had a basal squamous component.

NOTE Confidence: 0.9576434

00:17:29.774 --> 00:17:30.894 There was even one basal

NOTE Confidence: 0.9576434

00:17:30.894 --> 00:17:32.755 squamous component. Nearly eighty percent

NOTE Confidence: 0.9576434

00:17:32.975 --> 00:17:34.255 had another area that was

NOTE Confidence: 0.9576434

00:17:34.255 --> 00:17:34.755 luminal.

NOTE Confidence: 0.89624697

00:17:35.455 --> 00:17:36.095 It could have been the

NOTE Confidence: 0.89624697

00:17:36.095 --> 00:17:37.215 non invasive component, could have

NOTE Confidence: 0.89624697

00:17:37.215 --> 00:17:38.255 been another, but it really

NOTE Confidence: 0.89624697

00:17:38.255 --> 00:17:39.455 demonstrated that there's a a

NOTE Confidence: 0.89624697

00:17:39.455 --> 00:17:40.674 tremendous amount of,

NOTE Confidence: 0.9629556

00:17:41.450 --> 00:17:42.410 diversity in terms of the

NOTE Confidence: 0.9629556

00:17:42.410 --> 00:17:43.609 luminal versus basal,

NOTE Confidence: 0.9818024

00:17:44.090 --> 00:17:45.470 dichotomy in these things.

NOTE Confidence: 0.9548248

00:17:46.250 --> 00:17:47.290 And so that led to

NOTE Confidence: 0.9548248

00:17:47.290 --> 00:17:48.410 a different framework than they're

NOTE Confidence: 0.9548248

00:17:48.410 --> 00:17:49.609 born luminal or they're born

NOTE Confidence: 0.9548248

00:17:49.609 --> 00:17:51.130 basal, but rather they're mostly,

NOTE Confidence: 0.9548248

00:17:51.130 --> 00:17:52.890 if not all born, luminal.

NOTE Confidence: 0.9548248

00:17:52.890 --> 00:17:54.010 And certainly we can't be

NOTE Confidence: 0.9548248

00:17:54.010 --> 00:17:55.309 absolute here. This is

NOTE Confidence: 0.9348496

00:17:55.625 --> 00:17:56.345 this is cancer. It kind

NOTE Confidence: 0.9348496

00:17:56.345 --> 00:17:57.225 of does what it wants.

NOTE Confidence: 0.9348496

00:17:57.225 --> 00:17:58.665 We've seen squamous displays in

NOTE Confidence: 0.9348496

00:17:58.665 --> 00:18:00.025 the bladder, but by and

NOTE Confidence: 0.9348496

00:18:00.025 --> 00:18:00.525 large,

NOTE Confidence: 0.89617544

00:18:00.905 --> 00:18:02.025 most of these things start

NOTE Confidence: 0.89617544

00:18:02.025 --> 00:18:03.145 off, we think is not

NOTE Confidence: 0.89617544

00:18:03.145 --> 00:18:04.185 invasive. You're of the ileal

NOTE Confidence: 0.89617544

00:18:04.185 --> 00:18:06.285 carcinoma that's luminal. It invades

NOTE Confidence: 0.89617544

00:18:06.345 --> 00:18:07.145 like we see with the

NOTE Confidence: 0.89617544

00:18:07.145 --> 00:18:08.025 t one cancers that are

NOTE Confidence: 0.89617544

00:18:08.025 --> 00:18:09.580 luminal And early on, it's

NOTE Confidence: 0.89617544

00:18:09.580 --> 00:18:11.260 the invasive cancers also luminal.

NOTE Confidence: 0.89617544

00:18:11.260 --> 00:18:12.559 And then from there, it

NOTE Confidence: 0.9098628

00:18:12.859 --> 00:18:14.320 it undergoes lineage plasticity

NOTE Confidence: 0.9792777

00:18:14.700 --> 00:18:15.840 to a basal subtype.

NOTE Confidence: 0.99331474

00:18:16.380 --> 00:18:17.419 And those can turn into

NOTE Confidence: 0.99331474

00:18:17.419 --> 00:18:17.919 histologic,

NOTE Confidence: 0.92866504

00:18:18.779 --> 00:18:20.059 basal variance. And then the

NOTE Confidence: 0.92866504

00:18:20.059 --> 00:18:21.740 urothelial conventional can turn into

NOTE Confidence: 0.92866504

00:18:21.740 --> 00:18:23.200 invasive histologic luminal,

NOTE Confidence: 0.8636782

00:18:23.845 --> 00:18:24.345 variance.

NOTE Confidence: 0.9922096

00:18:24.725 --> 00:18:25.605 So this is the framework

NOTE Confidence: 0.9922096

00:18:25.605 --> 00:18:27.044 that we're working from now.

NOTE Confidence: 0.9922096

00:18:27.044 --> 00:18:27.784 And so,

NOTE Confidence: 0.9370829

00:18:28.965 --> 00:18:29.845 you know, the one of

NOTE Confidence: 0.9370829

00:18:29.845 --> 00:18:30.804 the questions as well, how

NOTE Confidence: 0.9370829

00:18:30.804 --> 00:18:31.765 do you know that it's

NOTE Confidence: 0.9370829

00:18:31.765 --> 00:18:32.725 not just, like, you know,

NOTE Confidence: 0.9370829

00:18:32.725 --> 00:18:34.404 collision tumors? Why aren't the

NOTE Confidence: 0.9370829

00:18:34.484 --> 00:18:35.784 why were the luminal micropapularies

NOTE Confidence: 0.96593875

00:18:36.085 --> 00:18:37.684 and the histologically squamous basal

NOTE Confidence: 0.96593875

00:18:37.684 --> 00:18:39.210 ones? Are they two separate

NOTE Confidence: 0.96593875

00:18:39.210 --> 00:18:39.710 tumors

NOTE Confidence: 0.92993367

00:18:40.090 --> 00:18:41.609 that just collided? And it's

NOTE Confidence: 0.92993367

00:18:41.609 --> 00:18:42.650 just a coincidence, and I

NOTE Confidence: 0.92993367

00:18:42.650 --> 00:18:43.950 think the answer is no.

NOTE Confidence: 0.9363896

00:18:44.330 --> 00:18:45.530 And we we answered that

NOTE Confidence: 0.9363896

00:18:45.530 --> 00:18:47.369 with, the paper, in nature

NOTE Confidence: 0.9363896

00:18:47.369 --> 00:18:48.990 communications a few years back.

NOTE Confidence: 0.8799877

00:18:49.290 --> 00:18:50.570 This was a collaboration with,

NOTE Confidence: 0.79209554

00:18:51.565 --> 00:18:52.925 Memorial Sloan Kettering, Hikma Del

NOTE Confidence: 0.79209554

00:18:52.925 --> 00:18:53.805 Amadi, and,

NOTE Confidence: 0.6190146

00:18:54.445 --> 00:18:54.945 Wenohu,

NOTE Confidence: 0.99469215

00:18:55.405 --> 00:18:56.205 were two of the main

NOTE Confidence: 0.99469215

00:18:56.205 --> 00:18:57.965 collaborators there. And so what

NOTE Confidence: 0.99469215

00:18:57.965 --> 00:18:58.925 we did in in this

NOTE Confidence: 0.99469215

00:18:58.925 --> 00:19:00.065 study is we,

NOTE Confidence: 0.99569833

00:19:01.005 --> 00:19:01.505 gathered

NOTE Confidence: 0.9649106

00:19:02.445 --> 00:19:03.725 a number of patients, twelve

NOTE Confidence: 0.9649106

00:19:03.725 --> 00:19:05.600 in total, who had invasive

NOTE Confidence: 0.9649106

00:19:05.600 --> 00:19:08.159 urothelial carcinomas with a clearly

NOTE Confidence: 0.9649106

00:19:08.159 --> 00:19:10.179 conventional urothelial carcinoma component

NOTE Confidence: 0.8951326

00:19:10.480 --> 00:19:12.480 and a clearly squamous invasive

NOTE Confidence: 0.8951326

00:19:12.480 --> 00:19:14.399 squamous carcinoma component. And we

NOTE Confidence: 0.8951326

00:19:14.399 --> 00:19:14.799 did,

NOTE Confidence: 0.9611508

00:19:16.159 --> 00:19:18.080 you know, comprehensive genomic evaluation

NOTE Confidence: 0.9611508

00:19:18.080 --> 00:19:18.799 on them or at least

NOTE Confidence: 0.9611508

00:19:18.799 --> 00:19:20.024 what was called comprehensive at

NOTE Confidence: 0.9611508

00:19:20.024 --> 00:19:20.904 the time. So we did,

NOTE Confidence: 0.9611508

00:19:21.384 --> 00:19:23.144 whole exome sequencing. We did

NOTE Confidence: 0.9611508

00:19:23.144 --> 00:19:24.044 RNA sequencing.

NOTE Confidence: 0.98043007

00:19:24.664 --> 00:19:25.304 We did this on a

NOTE Confidence: 0.98043007

00:19:25.304 --> 00:19:26.424 lot more than twelve, but

NOTE Confidence: 0.98043007

00:19:26.424 --> 00:19:27.544 the we only kept the

NOTE Confidence: 0.98043007

00:19:27.544 --> 00:19:28.744 twelve that had high quality

NOTE Confidence: 0.98043007

00:19:28.744 --> 00:19:30.184 RNA. It's difficult to get

NOTE Confidence: 0.98043007

00:19:30.184 --> 00:19:31.304 high quality RNA out of

NOTE Confidence: 0.98043007

00:19:31.304 --> 00:19:32.125 tissue blocks.

NOTE Confidence: 0.9269225

00:19:33.059 --> 00:19:34.500 So we we performed RNA

NOTE Confidence: 0.9269225

00:19:34.500 --> 00:19:35.000 sequencing,

NOTE Confidence: 0.34325778

00:19:35.380 --> 00:19:35.880 sequencing.

NOTE Confidence: 0.9876019

00:19:37.220 --> 00:19:38.340 And then we we, you

NOTE Confidence: 0.9876019

00:19:38.340 --> 00:19:39.460 know, saw the results. And

NOTE Confidence: 0.9876019

00:19:39.460 --> 00:19:40.340 this is the first thing

NOTE Confidence: 0.9876019

00:19:40.340 --> 00:19:41.080 we saw

NOTE Confidence: 0.8535427

00:19:41.700 --> 00:19:43.059 was the the the pair

NOTE Confidence: 0.8535427

00:19:43.059 --> 00:19:45.400 urothelial carcinomas and squamous carcinomas,

NOTE Confidence: 0.92998296

00:19:46.285 --> 00:19:48.305 were clonally related, but subclonally

NOTE Confidence: 0.92998296

00:19:48.445 --> 00:19:48.945 distinct.

NOTE Confidence: 0.9637529

00:19:49.325 --> 00:19:50.205 And so they were all,

NOTE Confidence: 0.9637529

00:19:50.205 --> 00:19:51.725 all twelve of them had

NOTE Confidence: 0.9637529

00:19:51.725 --> 00:19:52.225 multiple,

NOTE Confidence: 0.9673283

00:19:53.645 --> 00:19:54.765 cancer driver genes that were

NOTE Confidence: 0.9673283

00:19:54.765 --> 00:19:56.045 identical between the two different

NOTE Confidence: 0.9673283

00:19:56.045 --> 00:19:58.045 histologies. So for example, we've

NOTE Confidence: 0.9673283

00:19:58.045 --> 00:19:59.325 got, you know, we're demonstrating

NOTE Confidence: 0.9673283

00:19:59.325 --> 00:20:00.365 here, we've got the urothelial

NOTE Confidence: 0.9673283

00:20:00.365 --> 00:20:01.619 component, the squamous component

NOTE Confidence: 0.93696874

00:20:02.100 --> 00:20:03.160 Here, we've got,

NOTE Confidence: 0.97471017

00:20:04.660 --> 00:20:05.859 you know, like, the common

NOTE Confidence: 0.97471017

00:20:05.859 --> 00:20:07.720 precursor presumed common precursor.

NOTE Confidence: 0.97641814

00:20:08.180 --> 00:20:09.780 Here's the common mutations between

NOTE Confidence: 0.97641814

00:20:09.780 --> 00:20:11.619 the two. Here's common or

NOTE Confidence: 0.97641814

00:20:11.619 --> 00:20:13.059 here's mutations exclusive to the

NOTE Confidence: 0.97641814

00:20:13.059 --> 00:20:15.619 squamous component. Here's, mutations unique

NOTE Confidence: 0.97641814

00:20:15.619 --> 00:20:17.145 to the erythema component. And

NOTE Confidence: 0.97641814

00:20:17.145 --> 00:20:18.025 so these are just three

NOTE Confidence: 0.97641814

00:20:18.025 --> 00:20:18.925 example cases.

NOTE Confidence: 0.8113766

00:20:20.345 --> 00:20:21.705 So in this one, they're

NOTE Confidence: 0.8113766

00:20:21.705 --> 00:20:22.205 identical.

NOTE Confidence: 0.90764326

00:20:23.065 --> 00:20:24.825 You know, cancer driver mutations

NOTE Confidence: 0.90764326

00:20:24.825 --> 00:20:27.145 in Fgfr3, TP53, PIK3CA, and

NOTE Confidence: 0.90764326

00:20:27.145 --> 00:20:28.025 then thirty one more that

NOTE Confidence: 0.90764326

00:20:28.025 --> 00:20:29.305 were common to both. They

NOTE Confidence: 0.90764326

00:20:29.305 --> 00:20:30.585 were unique mutations in both

NOTE Confidence: 0.90764326

00:20:30.585 --> 00:20:32.285 the squamous and urothelial components.

NOTE Confidence: 0.93582636

00:20:32.770 --> 00:20:33.809 Same with this one, also

NOTE Confidence: 0.93582636

00:20:33.809 --> 00:20:34.530 f g f r three

NOTE Confidence: 0.93582636

00:20:34.530 --> 00:20:36.050 mutations. And remember, f g

NOTE Confidence: 0.93582636

00:20:36.050 --> 00:20:37.170 f r three is more

NOTE Confidence: 0.93582636

00:20:37.170 --> 00:20:38.369 associated with luminal cancer, and

NOTE Confidence: 0.93582636

00:20:38.369 --> 00:20:40.369 these developed histologically squamous disease.

NOTE Confidence: 0.93582636

00:20:40.369 --> 00:20:40.869 So

NOTE Confidence: 0.93379605

00:20:41.330 --> 00:20:42.850 this is really screaming lineage

NOTE Confidence: 0.93379605

00:20:42.850 --> 00:20:44.290 plasticity to my mind. So

NOTE Confidence: 0.93379605

00:20:44.290 --> 00:20:45.170 you've got f g f

NOTE Confidence: 0.93379605

00:20:45.170 --> 00:20:46.309 r three, you've got ATM,

NOTE Confidence: 0.8557341

00:20:46.855 --> 00:20:47.595 we've got PIK3CA.

NOTE Confidence: 0.8218598

00:20:47.975 --> 00:20:50.215 Again, there's some unique mutations

NOTE Confidence: 0.8218598

00:20:50.215 --> 00:20:51.414 in the squamous component including

NOTE Confidence: 0.8218598

00:20:51.414 --> 00:20:51.914 TP53.

NOTE Confidence: 0.92154795

00:20:52.534 --> 00:20:53.255 And then the same with

NOTE Confidence: 0.92154795

00:20:53.255 --> 00:20:54.135 this one, it's not an

NOTE Confidence: 0.92154795

00:20:54.135 --> 00:20:56.695 FGFR3 mutant cancer, but it's

NOTE Confidence: 0.92154795

00:20:56.695 --> 00:20:57.195 got,

NOTE Confidence: 0.72007966

00:20:58.215 --> 00:20:58.715 multiple

NOTE Confidence: 0.88203615

00:20:59.290 --> 00:21:00.890 known cancer driver genes between

NOTE Confidence: 0.88203615

00:21:00.890 --> 00:21:03.050 both the urothelial component and

NOTE Confidence: 0.88203615

00:21:03.050 --> 00:21:05.290 the paired histologically squamous component.

NOTE Confidence: 0.88203615

00:21:05.290 --> 00:21:06.510 Really, I think

NOTE Confidence: 0.82477456

00:21:06.890 --> 00:21:08.590 proving that these things iterize

NOTE Confidence: 0.82477456

00:21:08.650 --> 00:21:10.170 from a common precursor despite

NOTE Confidence: 0.82477456

00:21:10.170 --> 00:21:10.990 their distinct

NOTE Confidence: 0.9296661

00:21:11.369 --> 00:21:11.869 histology.

NOTE Confidence: 0.926686

00:21:15.494 --> 00:21:17.335 So what about, your molecular

NOTE Confidence: 0.926686

00:21:17.335 --> 00:21:19.355 subtype, this luminal versus bathel

NOTE Confidence: 0.926686

00:21:19.575 --> 00:21:20.695 dichotomy? So we have the

NOTE Confidence: 0.926686

00:21:20.695 --> 00:21:22.135 RNA Seq data. We only

NOTE Confidence: 0.926686

00:21:22.135 --> 00:21:23.734 selected cases that had, you

NOTE Confidence: 0.926686

00:21:23.734 --> 00:21:25.255 know, high quality RNA sequencing

NOTE Confidence: 0.926686

00:21:25.255 --> 00:21:25.755 data.

NOTE Confidence: 0.95347804

00:21:26.419 --> 00:21:27.460 Anew did a few things.

NOTE Confidence: 0.95347804

00:21:27.780 --> 00:21:29.299 First, we put them into

NOTE Confidence: 0.95347804

00:21:29.299 --> 00:21:29.799 categorical,

NOTE Confidence: 0.98085093

00:21:30.340 --> 00:21:31.960 luminal versus basal subtypes

NOTE Confidence: 0.98491246

00:21:32.260 --> 00:21:33.859 based on the TCGA system

NOTE Confidence: 0.98491246

00:21:33.859 --> 00:21:35.380 and and centroid analysis. So

NOTE Confidence: 0.98491246

00:21:35.380 --> 00:21:36.440 that's shown here.

NOTE Confidence: 0.926997

00:21:36.820 --> 00:21:38.119 Each column is a patient.

NOTE Confidence: 0.95897174

00:21:39.045 --> 00:21:40.244 Each row is a histology.

NOTE Confidence: 0.95897174

00:21:40.244 --> 00:21:41.225 So this is the urothelial

NOTE Confidence: 0.95897174

00:21:41.445 --> 00:21:42.744 part. This is the squamous

NOTE Confidence: 0.95897174

00:21:42.805 --> 00:21:44.405 part. The color is the

NOTE Confidence: 0.95897174

00:21:44.405 --> 00:21:44.905 subtype.

NOTE Confidence: 0.83558387

00:21:45.285 --> 00:21:46.885 So that's kinda orange salmon

NOTE Confidence: 0.83558387

00:21:46.885 --> 00:21:47.865 color is basal.

NOTE Confidence: 0.9498706

00:21:48.244 --> 00:21:49.125 Then the blue and the

NOTE Confidence: 0.9498706

00:21:49.125 --> 00:21:50.744 green are both luminol subtypes.

NOTE Confidence: 0.9498706

00:21:50.885 --> 00:21:51.445 There are a lot of

NOTE Confidence: 0.9498706

00:21:51.445 --> 00:21:52.885 different systems. The TCGA has

NOTE Confidence: 0.9498706

00:21:52.885 --> 00:21:54.165 one that's subclassified as liminal,

NOTE Confidence: 0.9498706

00:21:54.165 --> 00:21:55.660 but we'll pull them, for

NOTE Confidence: 0.9498706

00:21:55.660 --> 00:21:56.460 the sake of, you know,

NOTE Confidence: 0.9498706

00:21:56.460 --> 00:21:57.760 simplicity in the discussion.

NOTE Confidence: 0.89695835

00:21:58.460 --> 00:21:59.760 And four of the twelve,

NOTE Confidence: 0.7618834

00:22:00.700 --> 00:22:01.680 switched subtype,

NOTE Confidence: 0.9631149

00:22:02.300 --> 00:22:03.420 whenever we use the centroid

NOTE Confidence: 0.9631149

00:22:03.420 --> 00:22:03.920 analysis.

NOTE Confidence: 0.94697696

00:22:04.300 --> 00:22:05.820 So using the subtype as

NOTE Confidence: 0.94697696

00:22:05.820 --> 00:22:08.320 a categorical variable centroid analysis,

NOTE Confidence: 0.9924932

00:22:08.780 --> 00:22:09.900 we saw that, you know,

NOTE Confidence: 0.9924932

00:22:09.900 --> 00:22:10.994 a third of them were

NOTE Confidence: 0.9924932

00:22:10.994 --> 00:22:12.195 different between the two. This

NOTE Confidence: 0.9924932

00:22:12.195 --> 00:22:13.155 is consistent with what we

NOTE Confidence: 0.9924932

00:22:13.155 --> 00:22:13.895 found earlier.

NOTE Confidence: 0.8990756

00:22:14.755 --> 00:22:15.415 And and

NOTE Confidence: 0.91560644

00:22:15.955 --> 00:22:17.395 I think more interestingly, we

NOTE Confidence: 0.91560644

00:22:17.395 --> 00:22:19.155 found that it it it

NOTE Confidence: 0.91560644

00:22:19.155 --> 00:22:20.855 was went beyond that. So,

NOTE Confidence: 0.8844683

00:22:22.115 --> 00:22:23.550 we performed, you know, single

NOTE Confidence: 0.8844683

00:22:23.550 --> 00:22:24.750 sample gene set of enrichment

NOTE Confidence: 0.8844683

00:22:24.750 --> 00:22:26.190 analysis with gene lists of

NOTE Confidence: 0.8844683

00:22:26.190 --> 00:22:28.030 basal genes and and luminal

NOTE Confidence: 0.8844683

00:22:28.030 --> 00:22:29.330 genes to give a quantified

NOTE Confidence: 0.8844683

00:22:29.470 --> 00:22:31.790 or quantitative score of baseness

NOTE Confidence: 0.8844683

00:22:31.790 --> 00:22:32.450 and luminous.

NOTE Confidence: 0.9151498

00:22:33.630 --> 00:22:35.445 In every single case, the

NOTE Confidence: 0.9151498

00:22:35.445 --> 00:22:37.445 squamous component had a higher

NOTE Confidence: 0.9151498

00:22:37.445 --> 00:22:38.725 basal score than the luminal

NOTE Confidence: 0.9151498

00:22:38.884 --> 00:22:40.264 than the urothelial component.

NOTE Confidence: 0.97905767

00:22:40.804 --> 00:22:41.924 And in every single case,

NOTE Confidence: 0.97905767

00:22:41.924 --> 00:22:43.205 the squamous component had a

NOTE Confidence: 0.97905767

00:22:43.205 --> 00:22:45.284 lower luminal score than the

NOTE Confidence: 0.97905767

00:22:45.284 --> 00:22:46.505 urothelial component.

NOTE Confidence: 0.93710303

00:22:47.445 --> 00:22:48.884 Really showing that this it

NOTE Confidence: 0.93710303

00:22:48.965 --> 00:22:50.160 it's really, I think, putting

NOTE Confidence: 0.93710303

00:22:50.160 --> 00:22:50.960 more and more cracks in

NOTE Confidence: 0.93710303

00:22:50.960 --> 00:22:52.240 this idea of luminal versus

NOTE Confidence: 0.93710303

00:22:52.240 --> 00:22:53.920 basal dichotomy. That that we

NOTE Confidence: 0.93710303

00:22:53.920 --> 00:22:55.440 we have not only that

NOTE Confidence: 0.93710303

00:22:55.440 --> 00:22:56.880 a third of them change

NOTE Confidence: 0.93710303

00:22:56.880 --> 00:22:57.380 subtype,

NOTE Confidence: 0.9628545

00:22:57.920 --> 00:22:59.200 but that all of them

NOTE Confidence: 0.9628545

00:22:59.200 --> 00:23:00.480 are more basal, and all

NOTE Confidence: 0.9628545

00:23:00.480 --> 00:23:01.700 of them are less liminal.

NOTE Confidence: 0.9628545

00:23:01.840 --> 00:23:02.815 So this is looking more

NOTE Confidence: 0.9628545

00:23:02.815 --> 00:23:04.055 like a continuous variable than

NOTE Confidence: 0.9628545

00:23:04.055 --> 00:23:05.075 it is like a categorical

NOTE Confidence: 0.9628545

00:23:05.215 --> 00:23:05.715 variable.

NOTE Confidence: 0.94661635

00:23:08.095 --> 00:23:09.055 How about, you know, we

NOTE Confidence: 0.94661635

00:23:09.055 --> 00:23:09.955 talked about that,

NOTE Confidence: 0.94382894

00:23:10.895 --> 00:23:11.395 immunity,

NOTE Confidence: 0.88718605

00:23:12.095 --> 00:23:12.595 before.

NOTE Confidence: 0.8623554

00:23:13.135 --> 00:23:14.255 We talked about how they're

NOTE Confidence: 0.8623554

00:23:14.255 --> 00:23:15.475 the interferon gamma,

NOTE Confidence: 0.94041115

00:23:16.619 --> 00:23:17.580 and just looking at these

NOTE Confidence: 0.94041115

00:23:17.580 --> 00:23:18.859 subtypes is higher in the

NOTE Confidence: 0.94041115

00:23:18.859 --> 00:23:20.460 basal subtype, and it's pretty

NOTE Confidence: 0.94041115

00:23:20.460 --> 00:23:22.380 significantly higher. So what about

NOTE Confidence: 0.94041115

00:23:22.380 --> 00:23:22.880 immune

NOTE Confidence: 0.98501855

00:23:23.660 --> 00:23:24.160 subtype,

NOTE Confidence: 0.9803649

00:23:24.619 --> 00:23:26.300 between the urothelial and the

NOTE Confidence: 0.9803649

00:23:26.300 --> 00:23:27.920 histologically squamous components?

NOTE Confidence: 0.9618599

00:23:28.460 --> 00:23:29.900 So, we handle this in

NOTE Confidence: 0.9618599

00:23:29.900 --> 00:23:30.700 a few ways. One of

NOTE Confidence: 0.9618599

00:23:30.700 --> 00:23:32.240 them is we assign them

NOTE Confidence: 0.8551704

00:23:32.615 --> 00:23:33.734 what was called an immune

NOTE Confidence: 0.8551704

00:23:33.734 --> 00:23:34.855 subtype. So this group, you

NOTE Confidence: 0.8551704

00:23:34.855 --> 00:23:36.395 know, Thorson et al published

NOTE Confidence: 0.8551704

00:23:36.535 --> 00:23:37.655 a nice paper in immunity

NOTE Confidence: 0.8551704

00:23:37.655 --> 00:23:38.555 in twenty eighteen,

NOTE Confidence: 0.91080135

00:23:39.015 --> 00:23:39.895 that I found is really

NOTE Confidence: 0.91080135

00:23:39.895 --> 00:23:41.494 useful where they assigned six

NOTE Confidence: 0.91080135

00:23:41.494 --> 00:23:42.475 different inflammatory

NOTE Confidence: 0.9893243

00:23:42.775 --> 00:23:43.275 subtypes,

NOTE Confidence: 0.99526405

00:23:44.055 --> 00:23:45.575 to cancers, you know, based

NOTE Confidence: 0.99526405

00:23:45.575 --> 00:23:46.535 on on, you know, the

NOTE Confidence: 0.99526405

00:23:46.535 --> 00:23:47.755 TCGA data.

NOTE Confidence: 0.9635202

00:23:48.140 --> 00:23:49.180 They named them c one

NOTE Confidence: 0.9635202

00:23:49.180 --> 00:23:50.080 to c six.

NOTE Confidence: 0.9911696

00:23:50.860 --> 00:23:52.000 C two is an interferon

NOTE Confidence: 0.9911696

00:23:52.060 --> 00:23:52.880 gamma dominant

NOTE Confidence: 0.9256486

00:23:53.420 --> 00:23:55.500 in, inflammatory subtype. And then

NOTE Confidence: 0.9256486

00:23:55.500 --> 00:23:56.300 there's a number of other

NOTE Confidence: 0.9256486

00:23:56.300 --> 00:23:57.580 ones. C one's wound healing.

NOTE Confidence: 0.9256486

00:23:57.580 --> 00:23:58.640 C three is inflamed.

NOTE Confidence: 0.9819069

00:23:58.940 --> 00:23:59.660 They have a number of

NOTE Confidence: 0.9819069

00:23:59.660 --> 00:24:00.640 other named ones.

NOTE Confidence: 0.9951016

00:24:01.405 --> 00:24:02.525 And so we used our

NOTE Confidence: 0.9951016

00:24:02.525 --> 00:24:04.285 RNA sequencing data to put

NOTE Confidence: 0.9951016

00:24:04.285 --> 00:24:05.905 the the tumors into,

NOTE Confidence: 0.86441875

00:24:06.525 --> 00:24:08.225 these thorasin immune subtypes.

NOTE Confidence: 0.9431179

00:24:08.765 --> 00:24:10.205 And not surprisingly, we found

NOTE Confidence: 0.9431179

00:24:10.205 --> 00:24:12.305 all the histologically squamous areas,

NOTE Confidence: 0.9392852

00:24:13.085 --> 00:24:14.705 where the c two interferon

NOTE Confidence: 0.9392852

00:24:14.925 --> 00:24:15.825 gamma dominant

NOTE Confidence: 0.99035513

00:24:17.050 --> 00:24:19.050 subtype. We similarly found that,

NOTE Confidence: 0.9936639

00:24:20.010 --> 00:24:21.130 nine of the twelve,

NOTE Confidence: 0.956124

00:24:21.450 --> 00:24:23.050 urothelials were also, you know,

NOTE Confidence: 0.956124

00:24:23.050 --> 00:24:24.030 the c two interferon,

NOTE Confidence: 0.96839064

00:24:24.650 --> 00:24:25.930 dominant, but three of them

NOTE Confidence: 0.96839064

00:24:25.930 --> 00:24:27.210 were not. So there was

NOTE Confidence: 0.96839064

00:24:27.210 --> 00:24:27.869 some heterogeneity,

NOTE Confidence: 0.99821454

00:24:28.650 --> 00:24:30.190 in the immune subtype

NOTE Confidence: 0.93538207

00:24:30.685 --> 00:24:31.825 in in these tumors.

NOTE Confidence: 0.9237314

00:24:32.525 --> 00:24:34.445 PDL one also differed. And

NOTE Confidence: 0.9237314

00:24:34.445 --> 00:24:34.945 so,

NOTE Confidence: 0.9684282

00:24:35.565 --> 00:24:37.005 PDL one is a a

NOTE Confidence: 0.9684282

00:24:37.005 --> 00:24:38.685 target of interferon gamma. So

NOTE Confidence: 0.9684282

00:24:38.685 --> 00:24:39.185 interferon

NOTE Confidence: 0.95245945

00:24:39.725 --> 00:24:41.645 gamma signaling induces higher PDL

NOTE Confidence: 0.95245945

00:24:41.645 --> 00:24:42.765 one expression. This is pretty

NOTE Confidence: 0.95245945

00:24:42.765 --> 00:24:44.179 well well known. And the

NOTE Confidence: 0.95245945

00:24:44.179 --> 00:24:45.859 squamous component on average had

NOTE Confidence: 0.95245945

00:24:45.859 --> 00:24:47.299 higher PDL1 expression of the

NOTE Confidence: 0.95245945

00:24:47.299 --> 00:24:47.799 urothelial.

NOTE Confidence: 0.9942515

00:24:49.140 --> 00:24:49.640 So

NOTE Confidence: 0.9907394

00:24:50.020 --> 00:24:51.400 not only are they histologically

NOTE Confidence: 0.9907394

00:24:51.540 --> 00:24:51.940 different,

NOTE Confidence: 0.92028755

00:24:52.500 --> 00:24:53.619 and they're different in their

NOTE Confidence: 0.92028755

00:24:53.619 --> 00:24:54.900 immune sub their their molecular

NOTE Confidence: 0.92028755

00:24:54.900 --> 00:24:56.420 subject, their immune subtype seems

NOTE Confidence: 0.92028755

00:24:56.420 --> 00:24:57.540 to be different as well.

NOTE Confidence: 0.92028755

00:24:57.540 --> 00:24:58.815 So So this lineage plasticity

NOTE Confidence: 0.92028755

00:24:58.955 --> 00:25:00.075 is taking on a kind

NOTE Confidence: 0.92028755

00:25:00.075 --> 00:25:00.875 of a life of its

NOTE Confidence: 0.92028755

00:25:00.875 --> 00:25:01.375 own.

NOTE Confidence: 0.91946816

00:25:03.994 --> 00:25:05.275 And so what does it

NOTE Confidence: 0.91946816

00:25:05.275 --> 00:25:06.655 matter at this point? Right?

NOTE Confidence: 0.91946816

00:25:06.715 --> 00:25:08.235 That's always the question I

NOTE Confidence: 0.91946816

00:25:08.235 --> 00:25:09.115 like to ask myself. Why

NOTE Confidence: 0.91946816

00:25:09.115 --> 00:25:09.840 is this important?

NOTE Confidence: 0.99605054

00:25:10.320 --> 00:25:11.039 And so,

NOTE Confidence: 0.5981457

00:25:11.520 --> 00:25:12.580 Hikmat Elhamdi,

NOTE Confidence: 0.9674483

00:25:12.880 --> 00:25:14.080 from Sloan Kettering, he's a

NOTE Confidence: 0.9674483

00:25:14.080 --> 00:25:15.600 pathologist out there. So he

NOTE Confidence: 0.9674483

00:25:15.600 --> 00:25:17.039 was part of, one of

NOTE Confidence: 0.9674483

00:25:17.039 --> 00:25:18.559 the clinical trials that looked

NOTE Confidence: 0.9674483

00:25:18.559 --> 00:25:19.220 at at atezolizumab

NOTE Confidence: 0.8978408

00:25:20.000 --> 00:25:21.840 in metastatic and locally invasive

NOTE Confidence: 0.8978408

00:25:21.840 --> 00:25:22.659 bladder cancer.

NOTE Confidence: 0.9631831

00:25:23.279 --> 00:25:24.240 And so he was one

NOTE Confidence: 0.9631831

00:25:24.240 --> 00:25:25.039 of the guys who reviewed

NOTE Confidence: 0.9631831

00:25:25.039 --> 00:25:26.294 the slides and confirmed its

NOTE Confidence: 0.9631831

00:25:26.294 --> 00:25:27.174 bladder cancer and all that

NOTE Confidence: 0.9631831

00:25:27.174 --> 00:25:28.534 kind of stuff. And so

NOTE Confidence: 0.9631831

00:25:28.534 --> 00:25:29.654 he he he had an

NOTE Confidence: 0.9631831

00:25:29.654 --> 00:25:30.774 idea. He's like, alright. So

NOTE Confidence: 0.9631831

00:25:30.774 --> 00:25:32.394 we see this immune heterogeneity

NOTE Confidence: 0.9958877

00:25:33.014 --> 00:25:34.695 in our tumors. So I'm

NOTE Confidence: 0.9958877

00:25:34.695 --> 00:25:35.195 gonna

NOTE Confidence: 0.9022553

00:25:35.575 --> 00:25:36.774 grab the the tumors from

NOTE Confidence: 0.9022553

00:25:36.774 --> 00:25:38.375 Sloan Kettering that were part

NOTE Confidence: 0.9022553

00:25:38.375 --> 00:25:39.770 of this this clinical trial.

NOTE Confidence: 0.9022553

00:25:39.910 --> 00:25:40.630 I'm just gonna look at

NOTE Confidence: 0.9022553

00:25:40.630 --> 00:25:42.090 them blinded, and I'm gonna

NOTE Confidence: 0.9022553

00:25:42.150 --> 00:25:43.830 break down, is there histologic

NOTE Confidence: 0.9022553

00:25:43.830 --> 00:25:45.670 heterogeneity or not? Or is

NOTE Confidence: 0.9022553

00:25:45.670 --> 00:25:46.890 there morphologic heterogeneity?

NOTE Confidence: 0.9493991

00:25:47.270 --> 00:25:48.650 And he defined this precisely.

NOTE Confidence: 0.9493991

00:25:48.710 --> 00:25:49.510 He said, is it a

NOTE Confidence: 0.9493991

00:25:49.510 --> 00:25:51.030 named are there more than

NOTE Confidence: 0.9493991

00:25:51.030 --> 00:25:52.490 one named histology

NOTE Confidence: 0.9272292

00:25:53.225 --> 00:25:55.065 in this in this tumor?

NOTE Confidence: 0.9272292

00:25:55.065 --> 00:25:56.265 Yes or no? Just kinda,

NOTE Confidence: 0.9272292

00:25:56.265 --> 00:25:57.305 you know, made us hash

NOTE Confidence: 0.9272292

00:25:57.305 --> 00:25:58.345 marks. And then we did

NOTE Confidence: 0.9272292

00:25:58.345 --> 00:25:59.785 the statistics in terms of,

NOTE Confidence: 0.9862828

00:26:00.505 --> 00:26:01.645 response or no response.

NOTE Confidence: 0.963713

00:26:02.825 --> 00:26:03.865 And it turned out those

NOTE Confidence: 0.963713

00:26:03.865 --> 00:26:04.365 with,

NOTE Confidence: 0.93791854

00:26:05.305 --> 00:26:06.445 morphologic heterogeneity

NOTE Confidence: 0.92326874

00:26:08.279 --> 00:26:09.399 were enriched in the non

NOTE Confidence: 0.92326874

00:26:09.399 --> 00:26:10.299 responder group.

NOTE Confidence: 0.9478052

00:26:11.240 --> 00:26:12.700 Whereas those who

NOTE Confidence: 0.97011757

00:26:13.000 --> 00:26:14.619 lacked morphologic heterogeneity

NOTE Confidence: 0.9165654

00:26:15.320 --> 00:26:16.519 were enriched in the responder

NOTE Confidence: 0.9165654

00:26:16.519 --> 00:26:18.139 group. Certainly a small n,

NOTE Confidence: 0.9165654

00:26:18.359 --> 00:26:19.320 but it was significant and

NOTE Confidence: 0.9165654

00:26:19.320 --> 00:26:20.460 it was it was impressive.

NOTE Confidence: 0.9521741

00:26:20.984 --> 00:26:22.025 And so one of the

NOTE Confidence: 0.9521741

00:26:22.025 --> 00:26:23.725 thoughts here is that maybe

NOTE Confidence: 0.9521741

00:26:23.945 --> 00:26:25.325 we know there's this immune

NOTE Confidence: 0.8800481

00:26:26.185 --> 00:26:27.385 heterogeneity or we've seen this

NOTE Confidence: 0.8800481

00:26:27.385 --> 00:26:28.125 immune heterogeneity.

NOTE Confidence: 0.9743477

00:26:28.665 --> 00:26:30.105 Are these tumors with immune

NOTE Confidence: 0.9743477

00:26:30.105 --> 00:26:32.025 heterogeneity in spatially distinct areas

NOTE Confidence: 0.9743477

00:26:32.025 --> 00:26:33.165 better able to adapt

NOTE Confidence: 0.90001374

00:26:33.630 --> 00:26:35.310 to immune checkpoint inhibitor because

NOTE Confidence: 0.90001374

00:26:35.310 --> 00:26:35.970 they have

NOTE Confidence: 0.8900799

00:26:36.830 --> 00:26:38.369 this greater diversity to

NOTE Confidence: 0.88235646

00:26:38.830 --> 00:26:40.609 get around it. And so

NOTE Confidence: 0.9098152

00:26:41.070 --> 00:26:43.010 this is likely clinically important.

NOTE Confidence: 0.9789176

00:26:44.270 --> 00:26:45.490 So what about the experimental

NOTE Confidence: 0.9789176

00:26:45.550 --> 00:26:46.050 data?

NOTE Confidence: 0.9508917

00:26:46.414 --> 00:26:47.294 You know, this is all

NOTE Confidence: 0.9508917

00:26:47.294 --> 00:26:48.575 observational. You know, we've we're

NOTE Confidence: 0.9508917

00:26:48.575 --> 00:26:49.855 looking at human tumors. This

NOTE Confidence: 0.9508917

00:26:49.855 --> 00:26:51.154 is really pointing at,

NOTE Confidence: 0.9238439

00:26:51.774 --> 00:26:53.375 lineage plasticity as being being

NOTE Confidence: 0.9238439

00:26:53.375 --> 00:26:54.355 important here.

NOTE Confidence: 0.9254286

00:26:56.895 --> 00:26:57.774 Being the driver of, you

NOTE Confidence: 0.9254286

00:26:57.774 --> 00:26:59.395 know, the luminal versus basal

NOTE Confidence: 0.9254286

00:26:59.534 --> 00:27:00.034 dichotomy.

NOTE Confidence: 0.87772435

00:27:01.190 --> 00:27:03.609 What about experimental data? So

NOTE Confidence: 0.89148504

00:27:04.230 --> 00:27:05.190 I'll give it away, the

NOTE Confidence: 0.89148504

00:27:05.190 --> 00:27:06.950 experimental data is pretty good

NOTE Confidence: 0.89148504

00:27:06.950 --> 00:27:08.230 and we I think we've

NOTE Confidence: 0.89148504

00:27:08.230 --> 00:27:09.850 identified some main drivers

NOTE Confidence: 0.9601622

00:27:10.310 --> 00:27:11.690 of both luminal differentiation

NOTE Confidence: 0.9126239

00:27:12.150 --> 00:27:14.375 and of basal differentiation. And

NOTE Confidence: 0.9126239

00:27:14.375 --> 00:27:15.595 I think the luminal differentiation

NOTE Confidence: 0.9126239

00:27:15.655 --> 00:27:16.615 is driven by a few

NOTE Confidence: 0.9126239

00:27:16.615 --> 00:27:18.395 transcription factors and basal

NOTE Confidence: 0.9273867

00:27:18.695 --> 00:27:20.775 differentiation appears driven heavily by

NOTE Confidence: 0.9273867

00:27:20.775 --> 00:27:22.615 interferon gamma signaling. So I'll

NOTE Confidence: 0.9273867

00:27:22.615 --> 00:27:23.575 tell you the evidence we've

NOTE Confidence: 0.9273867

00:27:23.575 --> 00:27:25.175 got right now. So this

NOTE Confidence: 0.9273867

00:27:25.175 --> 00:27:26.375 is an older paper, we

NOTE Confidence: 0.9273867

00:27:26.375 --> 00:27:27.595 published twenty sixteen,

NOTE Confidence: 0.918766

00:27:28.590 --> 00:27:29.490 where we,

NOTE Confidence: 0.96908164

00:27:30.910 --> 00:27:31.950 asked the question, can we

NOTE Confidence: 0.96908164

00:27:31.950 --> 00:27:33.570 change the molecular subtype

NOTE Confidence: 0.99307203

00:27:33.869 --> 00:27:35.809 of bladder cancer cell lines?

NOTE Confidence: 0.98751205

00:27:36.109 --> 00:27:37.390 So what we did is

NOTE Confidence: 0.98751205

00:27:37.390 --> 00:27:37.790 we,

NOTE Confidence: 0.97573704

00:27:38.590 --> 00:27:39.630 took the cancer cell line

NOTE Confidence: 0.97573704

00:27:39.630 --> 00:27:40.990 encyclopedia data, which is, you

NOTE Confidence: 0.97573704

00:27:40.990 --> 00:27:42.670 know, publicly available expression data

NOTE Confidence: 0.97573704

00:27:42.670 --> 00:27:43.895 for cell lines. We put

NOTE Confidence: 0.97573704

00:27:43.895 --> 00:27:45.335 them into two categories, either

NOTE Confidence: 0.97573704

00:27:45.335 --> 00:27:46.855 basal cell lines, luminous or

NOTE Confidence: 0.97573704

00:27:46.855 --> 00:27:47.895 luminal cell lines. We threw

NOTE Confidence: 0.97573704

00:27:47.895 --> 00:27:48.534 away a bunch of them

NOTE Confidence: 0.97573704

00:27:48.534 --> 00:27:49.575 because they didn't really, you

NOTE Confidence: 0.97573704

00:27:49.575 --> 00:27:50.855 know, have the expression pattern

NOTE Confidence: 0.97573704

00:27:50.855 --> 00:27:51.515 of either.

NOTE Confidence: 0.96113557

00:27:52.534 --> 00:27:53.494 Then we picked one of

NOTE Confidence: 0.96113557

00:27:53.494 --> 00:27:55.095 the basal cell lines, five

NOTE Confidence: 0.96113557

00:27:55.095 --> 00:27:56.534 six three seven. This is

NOTE Confidence: 0.96113557

00:27:56.534 --> 00:27:57.815 the CCLE one. This is

NOTE Confidence: 0.96113557

00:27:57.815 --> 00:27:58.315 ours.

NOTE Confidence: 0.9931778

00:27:58.800 --> 00:27:59.540 And we

NOTE Confidence: 0.9672109

00:28:00.720 --> 00:28:01.680 saw if we could push

NOTE Confidence: 0.9672109

00:28:01.680 --> 00:28:03.140 it from basal to luminal

NOTE Confidence: 0.9672109

00:28:03.280 --> 00:28:05.380 using transient transfection with,

NOTE Confidence: 0.7492238

00:28:06.880 --> 00:28:08.320 Foxy one, get a three,

NOTE Confidence: 0.7492238

00:28:08.320 --> 00:28:09.620 and then use rosaglitazone

NOTE Confidence: 0.9630458

00:28:10.400 --> 00:28:11.680 to is a PPAR gamma

NOTE Confidence: 0.9630458

00:28:11.680 --> 00:28:12.984 agonist to see if activation

NOTE Confidence: 0.9630458

00:28:12.984 --> 00:28:14.544 of these three transcription factors

NOTE Confidence: 0.9630458

00:28:14.544 --> 00:28:15.205 could push

NOTE Confidence: 0.91692144

00:28:15.505 --> 00:28:16.725 it. And and they did,

NOTE Confidence: 0.9831677

00:28:17.105 --> 00:28:19.125 and they impressively so. So

NOTE Confidence: 0.9831677

00:28:19.265 --> 00:28:20.244 here's our,

NOTE Confidence: 0.93369323

00:28:20.705 --> 00:28:22.645 five six three seven controls.

NOTE Confidence: 0.8593761

00:28:23.265 --> 00:28:24.544 This is FOXA one alone.

NOTE Confidence: 0.8593761

00:28:24.544 --> 00:28:25.265 This is got a three

NOTE Confidence: 0.8593761

00:28:25.265 --> 00:28:26.385 alone. This is FOXA one

NOTE Confidence: 0.8593761

00:28:26.385 --> 00:28:27.470 and got a three. Together

NOTE Confidence: 0.8593761

00:28:27.470 --> 00:28:28.609 you kinda get the picture.

NOTE Confidence: 0.960444

00:28:29.150 --> 00:28:30.270 This is a centroid plot,

NOTE Confidence: 0.960444

00:28:30.270 --> 00:28:31.070 so this is a basal

NOTE Confidence: 0.960444

00:28:31.070 --> 00:28:31.970 centroid correlation.

NOTE Confidence: 0.97416764

00:28:32.670 --> 00:28:33.630 The higher it is, the

NOTE Confidence: 0.97416764

00:28:33.630 --> 00:28:34.450 more basal,

NOTE Confidence: 0.9575697

00:28:35.150 --> 00:28:36.510 the cell line is. Here's

NOTE Confidence: 0.9575697

00:28:36.510 --> 00:28:38.190 the luminal centroid correlation, the

NOTE Confidence: 0.9575697

00:28:38.190 --> 00:28:39.230 higher it is, the more

NOTE Confidence: 0.9575697

00:28:39.230 --> 00:28:39.730 luminal,

NOTE Confidence: 0.9478269

00:28:40.270 --> 00:28:41.945 the cell line is. And

NOTE Confidence: 0.9478269

00:28:41.945 --> 00:28:43.405 as we add more transcription

NOTE Confidence: 0.9478269

00:28:43.465 --> 00:28:44.745 factors, we we push them

NOTE Confidence: 0.9478269

00:28:44.745 --> 00:28:46.285 more in the liminal direction.

NOTE Confidence: 0.9478269

00:28:46.505 --> 00:28:47.385 To the point where when

NOTE Confidence: 0.9478269

00:28:47.385 --> 00:28:48.685 we've added all three transcription

NOTE Confidence: 0.9478269

00:28:48.745 --> 00:28:49.245 factors,

NOTE Confidence: 0.88993067

00:28:49.545 --> 00:28:50.905 we consistently, and at least

NOTE Confidence: 0.88993067

00:28:50.905 --> 00:28:51.985 two replicates, and this is

NOTE Confidence: 0.88993067

00:28:52.025 --> 00:28:53.625 we've seen beyond this, we

NOTE Confidence: 0.88993067

00:28:53.625 --> 00:28:54.505 push them to a a

NOTE Confidence: 0.88993067

00:28:54.505 --> 00:28:55.485 luminal phenotype.

NOTE Confidence: 0.9523347

00:28:56.490 --> 00:28:56.990 And

NOTE Confidence: 0.88669264

00:28:57.929 --> 00:28:58.990 so, go back to Yamanaka

NOTE Confidence: 0.88669264

00:28:59.130 --> 00:29:00.490 factors, we can turn a

NOTE Confidence: 0.88669264

00:29:00.490 --> 00:29:00.990 fibroblast

NOTE Confidence: 0.9489727

00:29:01.450 --> 00:29:02.970 into an induced pluripotent stem

NOTE Confidence: 0.9489727

00:29:02.970 --> 00:29:04.590 cell with four transcription factors.

NOTE Confidence: 0.9489727

00:29:04.809 --> 00:29:05.690 It looks like we can

NOTE Confidence: 0.9489727

00:29:05.690 --> 00:29:06.970 turn a bladder cancer cell

NOTE Confidence: 0.9489727

00:29:06.970 --> 00:29:07.929 line from a basal type

NOTE Confidence: 0.9489727

00:29:07.929 --> 00:29:08.590 to a luminal

NOTE Confidence: 0.8284437

00:29:10.010 --> 00:29:11.150 type with three.

NOTE Confidence: 0.8721833

00:29:16.065 --> 00:29:16.865 And so what are the

NOTE Confidence: 0.8721833

00:29:16.865 --> 00:29:17.765 opposite direction?

NOTE Confidence: 0.963308

00:29:18.225 --> 00:29:18.725 So

NOTE Confidence: 0.9588564

00:29:19.184 --> 00:29:20.304 the next thought is we

NOTE Confidence: 0.9588564

00:29:20.385 --> 00:29:22.065 FOXA1 seems like the best

NOTE Confidence: 0.9588564

00:29:22.065 --> 00:29:23.345 established. We knew more about

NOTE Confidence: 0.9588564

00:29:23.345 --> 00:29:23.845 FOXA1

NOTE Confidence: 0.98631936

00:29:24.385 --> 00:29:25.345 than any of these other

NOTE Confidence: 0.98631936

00:29:25.345 --> 00:29:25.845 factors.

NOTE Confidence: 0.85906345

00:29:26.779 --> 00:29:27.899 So we're like, what happens

NOTE Confidence: 0.85906345

00:29:27.899 --> 00:29:28.960 if we knock out FOXA1?

NOTE Confidence: 0.9081375

00:29:29.419 --> 00:29:30.559 So we knocked out FOXA1

NOTE Confidence: 0.9081375

00:29:30.620 --> 00:29:31.419 in a couple of luminal

NOTE Confidence: 0.9081375

00:29:31.419 --> 00:29:32.080 cell lines,

NOTE Confidence: 0.95570916

00:29:32.860 --> 00:29:34.059 and it doesn't just turn

NOTE Confidence: 0.95570916

00:29:34.059 --> 00:29:34.799 into basal.

NOTE Confidence: 0.9612611

00:29:35.100 --> 00:29:35.899 It doesn't just you know,

NOTE Confidence: 0.9612611

00:29:35.899 --> 00:29:37.019 you knock out FOXA1, they

NOTE Confidence: 0.9612611

00:29:37.019 --> 00:29:38.139 become basal. That doesn't happen

NOTE Confidence: 0.9612611

00:29:38.139 --> 00:29:39.500 at all. There's buffering in

NOTE Confidence: 0.9612611

00:29:39.500 --> 00:29:40.000 there.

NOTE Confidence: 0.8547602

00:29:40.675 --> 00:29:41.555 Just kinda like they're not

NOTE Confidence: 0.8547602

00:29:41.555 --> 00:29:43.315 even that much more more

NOTE Confidence: 0.8547602

00:29:43.315 --> 00:29:44.435 basal really when you knock

NOTE Confidence: 0.8547602

00:29:44.435 --> 00:29:45.475 out Fox a one. And

NOTE Confidence: 0.8547602

00:29:45.475 --> 00:29:46.435 we've done this with visa

NOTE Confidence: 0.8547602

00:29:46.435 --> 00:29:46.935 lines,

NOTE Confidence: 0.8895922

00:29:47.475 --> 00:29:48.755 but something else does happen.

NOTE Confidence: 0.8895922

00:29:48.755 --> 00:29:50.855 That's kinda telling, kinda fascinating

NOTE Confidence: 0.9217432

00:29:51.235 --> 00:29:52.455 and probably important.

NOTE Confidence: 0.9472205

00:29:52.890 --> 00:29:54.090 And I think it comes

NOTE Confidence: 0.9472205

00:29:54.090 --> 00:29:55.210 to, you know, what I

NOTE Confidence: 0.9472205

00:29:55.210 --> 00:29:56.510 was saying earlier about,

NOTE Confidence: 0.95756507

00:29:57.370 --> 00:29:59.610 molecular subtypes being not as

NOTE Confidence: 0.95756507

00:29:59.610 --> 00:30:01.050 important as a categorical things.

NOTE Confidence: 0.95756507

00:30:01.050 --> 00:30:01.930 We put things in and

NOTE Confidence: 0.95756507

00:30:01.930 --> 00:30:04.170 treat people differently, but giving

NOTE Confidence: 0.95756507

00:30:04.170 --> 00:30:05.530 us an understanding and insight

NOTE Confidence: 0.95756507

00:30:05.530 --> 00:30:06.830 into where the Achilles

NOTE Confidence: 0.5851877

00:30:07.290 --> 00:30:07.790 heels

NOTE Confidence: 0.929478

00:30:08.294 --> 00:30:09.654 in bladder cancer. What are

NOTE Confidence: 0.929478

00:30:09.654 --> 00:30:10.634 the super important

NOTE Confidence: 0.95153254

00:30:11.014 --> 00:30:12.294 little triggers that we can

NOTE Confidence: 0.95153254

00:30:12.294 --> 00:30:13.495 we can work with? And

NOTE Confidence: 0.95153254

00:30:13.495 --> 00:30:14.375 I think Fox a one

NOTE Confidence: 0.95153254

00:30:14.375 --> 00:30:15.095 is one of them. And

NOTE Confidence: 0.95153254

00:30:15.095 --> 00:30:15.674 I think

NOTE Confidence: 0.93283397

00:30:16.455 --> 00:30:17.654 that one of the pieces

NOTE Confidence: 0.93283397

00:30:17.654 --> 00:30:18.455 of data we have that

NOTE Confidence: 0.93283397

00:30:18.455 --> 00:30:19.254 is if you knock out

NOTE Confidence: 0.93283397

00:30:19.254 --> 00:30:20.774 Fox a one in a

NOTE Confidence: 0.93283397

00:30:20.774 --> 00:30:22.215 luminal cell line, it doesn't

NOTE Confidence: 0.93283397

00:30:22.215 --> 00:30:23.034 become basal,

NOTE Confidence: 0.88198173

00:30:23.600 --> 00:30:26.260 but it turns up interfering

NOTE Confidence: 0.88198173

00:30:26.320 --> 00:30:27.140 gamma signal,

NOTE Confidence: 0.90178007

00:30:27.920 --> 00:30:29.600 which is kinda weird. So

NOTE Confidence: 0.90178007

00:30:29.600 --> 00:30:30.720 like these are cell lines,

NOTE Confidence: 0.90178007

00:30:30.720 --> 00:30:31.760 these are not CD eight

NOTE Confidence: 0.90178007

00:30:31.760 --> 00:30:32.260 cells.

NOTE Confidence: 0.9399889

00:30:32.800 --> 00:30:34.260 These these are just epithelial

NOTE Confidence: 0.9399889

00:30:34.400 --> 00:30:34.900 cells,

NOTE Confidence: 0.86961174

00:30:35.615 --> 00:30:36.895 but the the basal cell

NOTE Confidence: 0.86961174

00:30:36.895 --> 00:30:38.595 lines tend to over express,

NOTE Confidence: 0.9335593

00:30:39.615 --> 00:30:41.055 interferon gammas even though they're

NOTE Confidence: 0.9335593

00:30:41.055 --> 00:30:42.095 just cell lines, whereas the

NOTE Confidence: 0.9335593

00:30:42.095 --> 00:30:43.555 luminal ones have lower expression.

NOTE Confidence: 0.9335593

00:30:43.615 --> 00:30:44.415 But if you take a

NOTE Confidence: 0.9335593

00:30:44.415 --> 00:30:46.095 luminal one, you knock out

NOTE Confidence: 0.9335593

00:30:46.095 --> 00:30:47.855 FOXA1, you turn up interferon

NOTE Confidence: 0.9335593

00:30:47.855 --> 00:30:49.135 gamma signaling, you don't do

NOTE Confidence: 0.9335593

00:30:49.135 --> 00:30:49.795 it subtly.

NOTE Confidence: 0.9950532

00:30:50.570 --> 00:30:51.530 So here's the here's the

NOTE Confidence: 0.9950532

00:30:51.530 --> 00:30:52.750 data for that. So,

NOTE Confidence: 0.7770917

00:30:53.450 --> 00:30:54.670 here we used the UMEC

NOTE Confidence: 0.7770917

00:30:54.730 --> 00:30:55.230 one,

NOTE Confidence: 0.9808864

00:30:55.690 --> 00:30:56.830 luminal cell line.

NOTE Confidence: 0.8474238

00:30:58.010 --> 00:30:59.130 There's this is our expression

NOTE Confidence: 0.8474238

00:30:59.130 --> 00:31:00.510 data from RNA sequencing,

NOTE Confidence: 0.9194729

00:31:01.050 --> 00:31:02.250 ROSA genes. These are some,

NOTE Confidence: 0.9194729

00:31:02.410 --> 00:31:03.470 what are called the interferon

NOTE Confidence: 0.9194729

00:31:03.530 --> 00:31:04.430 response genes.

NOTE Confidence: 0.90168977

00:31:04.924 --> 00:31:06.044 Blue is higher, red is

NOTE Confidence: 0.90168977

00:31:06.044 --> 00:31:07.165 lower. Wen Ho did that.

NOTE Confidence: 0.90168977

00:31:07.165 --> 00:31:08.285 Blame him. He's one of

NOTE Confidence: 0.90168977

00:31:08.285 --> 00:31:09.245 our collaborators. I wish we

NOTE Confidence: 0.90168977

00:31:09.245 --> 00:31:10.225 did on the opposite.

NOTE Confidence: 0.980032

00:31:10.605 --> 00:31:11.645 But what it showed is

NOTE Confidence: 0.980032

00:31:11.645 --> 00:31:12.765 that on our knockouts, we

NOTE Confidence: 0.980032

00:31:12.765 --> 00:31:14.705 see this substantial increase in,

NOTE Confidence: 0.99760646

00:31:15.804 --> 00:31:17.345 expression of interferon

NOTE Confidence: 0.98098075

00:31:18.040 --> 00:31:19.660 responsive genes in our knockouts.

NOTE Confidence: 0.9739577

00:31:20.040 --> 00:31:20.840 And and we saw the

NOTE Confidence: 0.9739577

00:31:20.840 --> 00:31:22.440 same with interferon alpha signaling,

NOTE Confidence: 0.9739577

00:31:22.440 --> 00:31:23.960 interferon gamma signaling using, you

NOTE Confidence: 0.9739577

00:31:23.960 --> 00:31:25.260 know, standard GSEA.

NOTE Confidence: 0.9318127

00:31:26.040 --> 00:31:27.080 We also saw that when

NOTE Confidence: 0.9318127

00:31:27.080 --> 00:31:28.540 we knocked out FOXA1 PDL1

NOTE Confidence: 0.9318127

00:31:28.600 --> 00:31:30.115 expression went up, which we

NOTE Confidence: 0.9318127

00:31:30.115 --> 00:31:31.414 know is a a downstream,

NOTE Confidence: 0.9318127

00:31:31.475 --> 00:31:32.755 you know, product of interferon

NOTE Confidence: 0.9318127

00:31:32.755 --> 00:31:33.575 gamma signaling.

NOTE Confidence: 0.97035927

00:31:34.275 --> 00:31:35.395 So so this is, I

NOTE Confidence: 0.97035927

00:31:35.395 --> 00:31:36.755 I think, a potentially important

NOTE Confidence: 0.97035927

00:31:36.755 --> 00:31:37.635 thing, and we're digging into

NOTE Confidence: 0.97035927

00:31:37.635 --> 00:31:38.434 this a lot. We talked

NOTE Confidence: 0.97035927

00:31:38.434 --> 00:31:39.235 a little bit about this

NOTE Confidence: 0.97035927

00:31:39.235 --> 00:31:40.355 on on Tuesday at the,

NOTE Confidence: 0.9438708

00:31:41.395 --> 00:31:42.355 the the rip talk. But,

NOTE Confidence: 0.9438708

00:31:42.515 --> 00:31:43.635 this is, I think, an

NOTE Confidence: 0.9438708

00:31:43.635 --> 00:31:44.370 important thing

NOTE Confidence: 0.95535874

00:31:44.850 --> 00:31:46.370 in developing, you know, customized

NOTE Confidence: 0.95535874

00:31:46.370 --> 00:31:48.690 treatments for for, for bladder

NOTE Confidence: 0.95535874

00:31:48.690 --> 00:31:50.130 cancer. And we're we're continuing

NOTE Confidence: 0.95535874

00:31:50.130 --> 00:31:51.010 to work on on what

NOTE Confidence: 0.95535874

00:31:51.010 --> 00:31:51.750 this means.

NOTE Confidence: 0.8948211

00:31:53.570 --> 00:31:54.850 And it, you know, raises

NOTE Confidence: 0.8948211

00:31:54.850 --> 00:31:56.050 another question too. So, okay,

NOTE Confidence: 0.8948211

00:31:56.050 --> 00:31:56.930 we this is this is

NOTE Confidence: 0.8948211

00:31:56.930 --> 00:31:57.890 kind of strange. We knock

NOTE Confidence: 0.8948211

00:31:57.890 --> 00:31:58.550 out FOXA1

NOTE Confidence: 0.97629005

00:31:59.465 --> 00:32:01.485 in epithelial cancer cell lines.

NOTE Confidence: 0.97629005

00:32:01.705 --> 00:32:03.725 We drive interferon gamma signaling

NOTE Confidence: 0.9539013

00:32:04.025 --> 00:32:05.305 even though there's no inflammatory

NOTE Confidence: 0.9539013

00:32:05.305 --> 00:32:06.365 cells to be found.

NOTE Confidence: 0.9985111

00:32:06.905 --> 00:32:08.045 And we know that

NOTE Confidence: 0.9376976

00:32:08.425 --> 00:32:09.465 if through through some other

NOTE Confidence: 0.9376976

00:32:09.465 --> 00:32:11.065 data that, you know, basal

NOTE Confidence: 0.9376976

00:32:11.065 --> 00:32:12.425 squamous bladder cancers not only

NOTE Confidence: 0.9376976

00:32:12.425 --> 00:32:13.785 have higher interferon gamma signaling,

NOTE Confidence: 0.9376976

00:32:13.785 --> 00:32:15.010 but they're inflamed. There are

NOTE Confidence: 0.9376976

00:32:15.010 --> 00:32:16.170 more, you know, immune cells

NOTE Confidence: 0.9376976

00:32:16.170 --> 00:32:16.750 in them.

NOTE Confidence: 0.96103585

00:32:17.929 --> 00:32:19.050 How's it getting there? And

NOTE Confidence: 0.96103585

00:32:19.050 --> 00:32:20.410 the question arose, like, does

NOTE Confidence: 0.96103585

00:32:20.490 --> 00:32:22.429 what does interferon gamma do

NOTE Confidence: 0.9443425

00:32:22.730 --> 00:32:24.570 to luminal cell lines? So

NOTE Confidence: 0.9443425

00:32:24.570 --> 00:32:25.370 we know if we knock

NOTE Confidence: 0.9443425

00:32:25.370 --> 00:32:26.730 out FOXA1 in the luminal

NOTE Confidence: 0.9443425

00:32:26.730 --> 00:32:28.090 cell line, we turn into

NOTE Confidence: 0.9443425

00:32:28.090 --> 00:32:29.095 a basal cell line. What

NOTE Confidence: 0.9443425

00:32:29.095 --> 00:32:29.894 if we take a liminal

NOTE Confidence: 0.9443425

00:32:29.894 --> 00:32:30.615 cell line, we treat it

NOTE Confidence: 0.9443425

00:32:30.615 --> 00:32:32.154 with interferon gamma, what happens?

NOTE Confidence: 0.92996985

00:32:32.774 --> 00:32:33.995 And it turns out they

NOTE Confidence: 0.92996985

00:32:34.294 --> 00:32:35.115 turn basal

NOTE Confidence: 0.9050054

00:32:36.134 --> 00:32:37.495 or they get more basal

NOTE Confidence: 0.9050054

00:32:37.495 --> 00:32:38.294 at least. So what we

NOTE Confidence: 0.9050054

00:32:38.294 --> 00:32:40.215 did, here's three, liminal cell

NOTE Confidence: 0.9050054

00:32:40.215 --> 00:32:41.095 lines, r t one one

NOTE Confidence: 0.9050054

00:32:41.095 --> 00:32:41.595 two,

NOTE Confidence: 0.8929637

00:32:43.530 --> 00:32:44.750 SW seven eighty.

NOTE Confidence: 0.9786834

00:32:45.850 --> 00:32:47.290 These are our genes. These

NOTE Confidence: 0.9786834

00:32:47.290 --> 00:32:48.970 are our luminal genes. These

NOTE Confidence: 0.9786834

00:32:48.970 --> 00:32:50.110 are our basal genes.

NOTE Confidence: 0.9763096

00:32:51.290 --> 00:32:52.410 And so you can see

NOTE Confidence: 0.9763096

00:32:52.410 --> 00:32:53.370 here that, you know, with

NOTE Confidence: 0.9763096

00:32:53.370 --> 00:32:54.330 the knockouts, these are the

NOTE Confidence: 0.9763096

00:32:54.330 --> 00:32:55.210 knockouts here, these are the

NOTE Confidence: 0.9763096

00:32:55.210 --> 00:32:56.650 wild types. We see this

NOTE Confidence: 0.9763096

00:32:56.650 --> 00:32:57.550 increased expression

NOTE Confidence: 0.96683055

00:32:57.995 --> 00:32:59.835 in basal genes consistently. I

NOTE Confidence: 0.96683055

00:32:59.835 --> 00:33:00.635 mean, sorry. These are the,

NOTE Confidence: 0.96683055

00:33:00.875 --> 00:33:02.495 these are interferon gamma treated.

NOTE Confidence: 0.96683055

00:33:02.635 --> 00:33:04.895 I apologize. So control interferon

NOTE Confidence: 0.96683055

00:33:05.035 --> 00:33:06.395 gamma treated. You see this

NOTE Confidence: 0.96683055

00:33:06.395 --> 00:33:07.375 increased expression

NOTE Confidence: 0.95621806

00:33:08.155 --> 00:33:09.935 of the the basal genes,

NOTE Confidence: 0.94141114

00:33:10.300 --> 00:33:11.660 including the molecular the, you

NOTE Confidence: 0.94141114

00:33:11.660 --> 00:33:13.340 know, keratin six, you know,

NOTE Confidence: 0.94141114

00:33:13.340 --> 00:33:14.860 keratin fourteen, these high molecular

NOTE Confidence: 0.94141114

00:33:14.860 --> 00:33:15.820 weight keratin. It's not just

NOTE Confidence: 0.94141114

00:33:15.820 --> 00:33:17.420 the inflammatory things. It's the

NOTE Confidence: 0.94141114

00:33:17.420 --> 00:33:18.700 epithelial things as well that

NOTE Confidence: 0.94141114

00:33:18.700 --> 00:33:19.520 are going up.

NOTE Confidence: 0.9730642

00:33:21.260 --> 00:33:22.620 And so we also, you

NOTE Confidence: 0.9730642

00:33:22.620 --> 00:33:24.080 know, looked at centroid analysis

NOTE Confidence: 0.9730642

00:33:24.140 --> 00:33:25.100 similar to we did in

NOTE Confidence: 0.9730642

00:33:25.100 --> 00:33:25.580 that that,

NOTE Confidence: 0.90918833

00:33:26.325 --> 00:33:27.784 study where we turned luminal

NOTE Confidence: 0.90918833

00:33:27.924 --> 00:33:29.205 cell lines into basal cell

NOTE Confidence: 0.90918833

00:33:29.205 --> 00:33:29.705 lines.

NOTE Confidence: 0.92327976

00:33:30.245 --> 00:33:31.845 So here's control, here's interferon

NOTE Confidence: 0.92327976

00:33:31.845 --> 00:33:32.664 gamma treatment.

NOTE Confidence: 0.94706625

00:33:33.044 --> 00:33:34.325 This is showing the correlation

NOTE Confidence: 0.94706625

00:33:34.325 --> 00:33:35.765 of the basal centroid. So

NOTE Confidence: 0.94706625

00:33:35.765 --> 00:33:37.625 that means with centroid analysis,

NOTE Confidence: 0.94706625

00:33:37.684 --> 00:33:39.445 our sequencing data, the higher

NOTE Confidence: 0.94706625

00:33:39.445 --> 00:33:40.565 it is, the the more

NOTE Confidence: 0.94706625

00:33:40.565 --> 00:33:41.990 the more basalts becoming, the

NOTE Confidence: 0.94706625

00:33:41.990 --> 00:33:43.110 closer it's getting to that

NOTE Confidence: 0.94706625

00:33:43.110 --> 00:33:43.930 basal centroid.

NOTE Confidence: 0.93340045

00:33:45.830 --> 00:33:46.710 And so with each one

NOTE Confidence: 0.93340045

00:33:46.710 --> 00:33:47.350 of them, they got a

NOTE Confidence: 0.93340045

00:33:47.350 --> 00:33:48.230 little they got closer to

NOTE Confidence: 0.93340045

00:33:48.230 --> 00:33:49.350 that basal centroid and two

NOTE Confidence: 0.93340045

00:33:49.350 --> 00:33:50.970 of the threes flipped flipped.

NOTE Confidence: 0.93340045

00:33:51.110 --> 00:33:52.550 Meaning, they got closer to

NOTE Confidence: 0.93340045

00:33:52.550 --> 00:33:53.830 the basal centroid than the

NOTE Confidence: 0.93340045

00:33:53.990 --> 00:33:54.950 they were to the luminal

NOTE Confidence: 0.93340045

00:33:54.950 --> 00:33:56.325 centroid. And those two were,

NOTE Confidence: 0.93340045

00:33:56.565 --> 00:33:58.565 UMBC one and RT one

NOTE Confidence: 0.93340045

00:33:58.565 --> 00:33:59.845 one two, whereas the SW

NOTE Confidence: 0.93340045

00:33:59.845 --> 00:34:01.285 seven eighty cell line didn't

NOTE Confidence: 0.93340045

00:34:01.285 --> 00:34:02.085 flip, but it just got

NOTE Confidence: 0.93340045

00:34:02.085 --> 00:34:02.585 closer.

NOTE Confidence: 0.92820126

00:34:03.845 --> 00:34:04.585 And similarly,

NOTE Confidence: 0.9760315

00:34:05.525 --> 00:34:07.045 you know, the interferon dominant,

NOTE Confidence: 0.9760315

00:34:07.045 --> 00:34:07.925 we also put these in

NOTE Confidence: 0.9760315

00:34:07.925 --> 00:34:08.585 the inflammatory

NOTE Confidence: 0.8844807

00:34:08.885 --> 00:34:10.320 thoresen subtypes. And, you know,

NOTE Confidence: 0.8844807

00:34:10.320 --> 00:34:11.520 totally as you'd expect they'd

NOTE Confidence: 0.8844807

00:34:11.520 --> 00:34:12.560 be. They got much much

NOTE Confidence: 0.8844807

00:34:12.560 --> 00:34:14.239 more of this interferon gamma

NOTE Confidence: 0.8844807

00:34:14.239 --> 00:34:14.739 dominant,

NOTE Confidence: 0.99234265

00:34:15.280 --> 00:34:15.780 subtype.

NOTE Confidence: 0.9568415

00:34:16.320 --> 00:34:17.360 So that was interesting. So

NOTE Confidence: 0.9568415

00:34:17.360 --> 00:34:18.560 interferon gamma appeared to be

NOTE Confidence: 0.9568415

00:34:18.560 --> 00:34:19.840 driving the basal. It wasn't

NOTE Confidence: 0.9568415

00:34:19.840 --> 00:34:20.800 just that if you knock

NOTE Confidence: 0.9568415

00:34:20.800 --> 00:34:22.080 out FOXA1, it becomes more

NOTE Confidence: 0.9568415

00:34:22.080 --> 00:34:24.000 interferon gamma dominant. There's there's

NOTE Confidence: 0.9568415

00:34:24.000 --> 00:34:25.035 a loop here. There's some

NOTE Confidence: 0.9568415

00:34:25.035 --> 00:34:26.714 kind of a feedback mechanism

NOTE Confidence: 0.9568415

00:34:26.714 --> 00:34:27.614 going on.

NOTE Confidence: 0.91075945

00:34:29.434 --> 00:34:30.474 Then we thought, well, maybe

NOTE Confidence: 0.91075945

00:34:30.474 --> 00:34:31.454 we could do the opposite.

NOTE Confidence: 0.9796807

00:34:31.755 --> 00:34:32.255 So,

NOTE Confidence: 0.95477784

00:34:33.194 --> 00:34:34.315 what if we take basal

NOTE Confidence: 0.95477784

00:34:34.315 --> 00:34:35.835 cell lines and we inhibit

NOTE Confidence: 0.95477784

00:34:35.835 --> 00:34:37.214 interferon gamma signaling?

NOTE Confidence: 0.94685173

00:34:38.049 --> 00:34:39.890 So we did, we took,

NOTE Confidence: 0.9286532

00:34:40.369 --> 00:34:41.989 the basal cell line stabber,

NOTE Confidence: 0.9286532

00:34:42.049 --> 00:34:43.269 which is a well established

NOTE Confidence: 0.9286532

00:34:43.329 --> 00:34:45.029 bladder cancer basal cell line,

NOTE Confidence: 0.9286532

00:34:45.089 --> 00:34:46.130 and we treated it with

NOTE Confidence: 0.9286532

00:34:46.130 --> 00:34:47.910 the the JAK inhibitor ruxolitinib.

NOTE Confidence: 0.9754675

00:34:48.369 --> 00:34:50.309 Ruxolitinib is it's a relatively

NOTE Confidence: 0.9754675

00:34:50.369 --> 00:34:51.329 new drug. It's used to

NOTE Confidence: 0.9754675

00:34:51.329 --> 00:34:51.989 treat myelofibrosis,

NOTE Confidence: 0.96278703

00:34:52.369 --> 00:34:53.750 a couple other heme diseases.

NOTE Confidence: 0.8924507

00:34:54.335 --> 00:34:55.535 It's a pan JAK inhibitor

NOTE Confidence: 0.8924507

00:34:55.535 --> 00:34:56.414 and it's JAK one and

NOTE Confidence: 0.8924507

00:34:56.414 --> 00:34:57.535 JAK two, and those are

NOTE Confidence: 0.8924507

00:34:57.535 --> 00:34:59.295 the receptor tyrosine kinases that

NOTE Confidence: 0.8924507

00:34:59.295 --> 00:35:00.914 carry out interfering gamma signaling.

NOTE Confidence: 0.96550524

00:35:01.855 --> 00:35:02.575 So we can treat it

NOTE Confidence: 0.96550524

00:35:02.575 --> 00:35:04.434 as an interfering gamma inhibitor.

NOTE Confidence: 0.8823363

00:35:05.055 --> 00:35:06.335 And so whenever we treated

NOTE Confidence: 0.8823363

00:35:06.335 --> 00:35:07.454 the basal cell lines GABA

NOTE Confidence: 0.8823363

00:35:07.454 --> 00:35:08.434 with the JAK inhibitor,

NOTE Confidence: 0.96145225

00:35:09.200 --> 00:35:10.400 it didn't flip all the

NOTE Confidence: 0.96145225

00:35:10.400 --> 00:35:11.680 way to luminol, but it

NOTE Confidence: 0.96145225

00:35:11.680 --> 00:35:12.739 became more luminol.

NOTE Confidence: 0.9475346

00:35:13.200 --> 00:35:14.719 So it it lowered expression

NOTE Confidence: 0.9475346

00:35:14.719 --> 00:35:15.839 of basal genes and it

NOTE Confidence: 0.9475346

00:35:15.839 --> 00:35:18.319 increased expression of of, luminal

NOTE Confidence: 0.9475346

00:35:18.319 --> 00:35:19.440 genes. So we've got here

NOTE Confidence: 0.9475346

00:35:19.440 --> 00:35:21.859 is our ruxolitinib treated group,

NOTE Confidence: 0.84148234

00:35:22.164 --> 00:35:22.664 our,

NOTE Confidence: 0.9585079

00:35:23.444 --> 00:35:24.884 control group. Here are our

NOTE Confidence: 0.9585079

00:35:24.884 --> 00:35:26.325 genes. Here are our basal

NOTE Confidence: 0.9585079

00:35:26.325 --> 00:35:27.364 genes. Here are our luminal

NOTE Confidence: 0.9585079

00:35:27.364 --> 00:35:28.644 genes. And you can see

NOTE Confidence: 0.9585079

00:35:28.644 --> 00:35:29.924 that whenever you're treated with

NOTE Confidence: 0.9585079

00:35:29.924 --> 00:35:30.424 ruxolitinib,

NOTE Confidence: 0.7403642

00:35:31.684 --> 00:35:32.505 the ex

NOTE Confidence: 0.8160252

00:35:33.045 --> 00:35:34.184 expression of the

NOTE Confidence: 0.9761661

00:35:34.630 --> 00:35:36.150 the the luminal genes went

NOTE Confidence: 0.9761661

00:35:36.150 --> 00:35:37.530 up pretty substantially.

NOTE Confidence: 0.9269419

00:35:38.469 --> 00:35:39.430 Not only to flip it

NOTE Confidence: 0.9269419

00:35:39.430 --> 00:35:40.550 because these SCABER cell lines,

NOTE Confidence: 0.9269419

00:35:40.550 --> 00:35:41.670 they're whenever you grow these

NOTE Confidence: 0.9269419

00:35:41.670 --> 00:35:43.030 things in xenografts, they're making

NOTE Confidence: 0.9269419

00:35:43.030 --> 00:35:44.869 keratin. They are very, very

NOTE Confidence: 0.9269419

00:35:44.869 --> 00:35:47.349 basal bladder cancers. Even those,

NOTE Confidence: 0.9269419

00:35:47.349 --> 00:35:48.390 we are able to to

NOTE Confidence: 0.9269419

00:35:48.390 --> 00:35:49.545 push more in in the

NOTE Confidence: 0.9269419

00:35:49.545 --> 00:35:50.925 luminal direction with ruxolitinib.

NOTE Confidence: 0.96016186

00:35:52.984 --> 00:35:54.105 And you'll notice among these

NOTE Confidence: 0.96016186

00:35:54.105 --> 00:35:56.364 luminal genes, FOXA1 went up,

NOTE Confidence: 0.94140726

00:35:56.665 --> 00:35:58.265 GATA3 went up, and PPAR

NOTE Confidence: 0.94140726

00:35:58.265 --> 00:36:00.344 gamma largely went up. And

NOTE Confidence: 0.94140726

00:36:00.344 --> 00:36:01.464 you'll recall those are the

NOTE Confidence: 0.94140726

00:36:01.464 --> 00:36:02.744 three that we used to

NOTE Confidence: 0.94140726

00:36:02.744 --> 00:36:04.364 drive the basal cell line

NOTE Confidence: 0.899007

00:36:04.730 --> 00:36:06.589 to a liminal liminal type.

NOTE Confidence: 0.9842496

00:36:07.849 --> 00:36:09.230 And, you know, as expected,

NOTE Confidence: 0.9842496

00:36:09.289 --> 00:36:10.809 we we also looked at

NOTE Confidence: 0.9842496

00:36:10.809 --> 00:36:12.510 this, these these inflammatory

NOTE Confidence: 0.9171978

00:36:12.890 --> 00:36:14.410 subtypes, the thoras and ones,

NOTE Confidence: 0.9171978

00:36:14.410 --> 00:36:15.930 and we really diminished the

NOTE Confidence: 0.9171978

00:36:15.930 --> 00:36:17.770 the the, probability of a

NOTE Confidence: 0.9171978

00:36:17.770 --> 00:36:19.469 interferon gamma, you know, inflammatory

NOTE Confidence: 0.9171978

00:36:19.609 --> 00:36:20.109 subtype.

NOTE Confidence: 0.77783054

00:36:25.114 --> 00:36:26.095 So, so in summary,

NOTE Confidence: 0.9490078

00:36:27.195 --> 00:36:28.715 you know, I think that

NOTE Confidence: 0.9490078

00:36:28.715 --> 00:36:30.155 with the evidence we've collected,

NOTE Confidence: 0.9490078

00:36:30.235 --> 00:36:31.515 you know, bladder cancer is

NOTE Confidence: 0.9490078

00:36:31.515 --> 00:36:33.275 phenotypically diverse, we can know

NOTE Confidence: 0.9490078

00:36:33.275 --> 00:36:34.680 this, and it's likely a

NOTE Confidence: 0.9490078

00:36:34.680 --> 00:36:36.280 result of lineage plasticity. It's

NOTE Confidence: 0.9490078

00:36:36.280 --> 00:36:37.160 not that they're just born

NOTE Confidence: 0.9490078

00:36:37.160 --> 00:36:37.960 one way or the other.

NOTE Confidence: 0.9490078

00:36:37.960 --> 00:36:39.400 It's a plastic process that

NOTE Confidence: 0.9490078

00:36:39.400 --> 00:36:41.000 starts off probably from stuff

NOTE Confidence: 0.9490078

00:36:41.000 --> 00:36:42.460 that's differentiated toward urothelium.

NOTE Confidence: 0.94675267

00:36:43.560 --> 00:36:44.940 And then that lineage plasticity

NOTE Confidence: 0.94675267

00:36:45.080 --> 00:36:46.440 toward the basal phenotype appears

NOTE Confidence: 0.94675267

00:36:46.440 --> 00:36:47.420 driven by interferons

NOTE Confidence: 0.751865

00:36:47.800 --> 00:36:49.420 or interferon gamma, whereas,

NOTE Confidence: 0.98380196

00:36:50.484 --> 00:36:52.165 differentiation toward the liminal phenotype

NOTE Confidence: 0.98380196

00:36:52.165 --> 00:36:53.445 appears to be driven by

NOTE Confidence: 0.98380196

00:36:53.445 --> 00:36:55.065 by these these key transcription

NOTE Confidence: 0.98380196

00:36:55.285 --> 00:36:55.785 factors.

NOTE Confidence: 0.998281

00:36:56.805 --> 00:36:57.925 And that is all I

NOTE Confidence: 0.998281

00:36:57.925 --> 00:36:58.744 have to say.

NOTE Confidence: 0.9636124

00:36:59.125 --> 00:37:00.565 Thank you. Happy to take

NOTE Confidence: 0.9636124

00:37:00.565 --> 00:37:01.065 questions.

NOTE Confidence: 0.8600798

00:37:08.700 --> 00:37:10.619 Yeah. Go ahead. I have

NOTE Confidence: 0.8600798

00:37:10.619 --> 00:37:11.839 two questions. Yes.

NOTE Confidence: 0.8702503

00:37:29.335 --> 00:37:30.455 Yes. No. So it was

NOTE Confidence: 0.8702503

00:37:30.614 --> 00:37:31.415 it's just kind of a

NOTE Confidence: 0.8702503

00:37:31.415 --> 00:37:31.915 theoretical,

NOTE Confidence: 0.95278513

00:37:32.295 --> 00:37:33.734 you know, precursor, so I

NOTE Confidence: 0.95278513

00:37:33.734 --> 00:37:35.035 can I can go back?

NOTE Confidence: 0.95857984

00:37:37.969 --> 00:37:39.190 Yeah. So it was like

NOTE Confidence: 0.94341594

00:37:40.690 --> 00:37:41.890 Yes. Yeah. So this one.

NOTE Confidence: 0.94341594

00:37:41.890 --> 00:37:42.390 So,

NOTE Confidence: 0.92282736

00:37:43.170 --> 00:37:44.370 you know, we we sequence

NOTE Confidence: 0.92282736

00:37:44.370 --> 00:37:45.330 both. These are part of

NOTE Confidence: 0.92282736

00:37:45.330 --> 00:37:46.210 the same tumor. So think

NOTE Confidence: 0.92282736

00:37:46.210 --> 00:37:47.170 of this as a tumor.

NOTE Confidence: 0.92282736

00:37:47.170 --> 00:37:48.370 You know, one area squamous,

NOTE Confidence: 0.92282736

00:37:48.370 --> 00:37:49.350 one area is epithelial.

NOTE Confidence: 0.97827786

00:37:49.695 --> 00:37:51.455 And so spatially distinct parts

NOTE Confidence: 0.97827786

00:37:51.455 --> 00:37:53.235 of the same physical mass,

NOTE Confidence: 0.94556445

00:37:53.535 --> 00:37:54.815 and we sequenced them. And

NOTE Confidence: 0.94556445

00:37:54.815 --> 00:37:56.835 so this dot here indicates,

NOTE Confidence: 0.98149395

00:37:58.335 --> 00:37:59.855 the the common precursor. You

NOTE Confidence: 0.98149395

00:37:59.855 --> 00:38:00.575 know, think of this like

NOTE Confidence: 0.98149395

00:38:00.575 --> 00:38:01.875 an evolutionary phylogeny.

NOTE Confidence: 0.9763937

00:38:02.580 --> 00:38:03.620 This would be the the

NOTE Confidence: 0.9763937

00:38:03.620 --> 00:38:04.739 the common ancestor of the

NOTE Confidence: 0.9763937

00:38:04.739 --> 00:38:05.540 two, and we can say

NOTE Confidence: 0.9763937

00:38:05.540 --> 00:38:07.060 it's the common ancestor because

NOTE Confidence: 0.9763937

00:38:07.060 --> 00:38:08.180 it shares the key driver

NOTE Confidence: 0.9763937

00:38:08.180 --> 00:38:09.700 mutations. And then this thing

NOTE Confidence: 0.9763937

00:38:09.700 --> 00:38:11.380 is, we just added that

NOTE Confidence: 0.9763937

00:38:11.380 --> 00:38:12.260 so you'd have, like, you

NOTE Confidence: 0.9763937

00:38:12.260 --> 00:38:13.380 know, some idea of, like,

NOTE Confidence: 0.9763937

00:38:13.380 --> 00:38:14.180 you know, the cell from

NOTE Confidence: 0.9763937

00:38:14.180 --> 00:38:15.460 which they both arose. It's

NOTE Confidence: 0.9763937

00:38:15.460 --> 00:38:16.420 more like eye candy. It

NOTE Confidence: 0.9763937

00:38:16.420 --> 00:38:17.895 really doesn't, you know, add

NOTE Confidence: 0.9763937

00:38:17.895 --> 00:38:18.775 much to the meaning of

NOTE Confidence: 0.9763937

00:38:18.775 --> 00:38:19.435 the figure.

NOTE Confidence: 0.98110443

00:38:33.410 --> 00:38:34.370 So this this was the

NOTE Confidence: 0.98110443

00:38:34.370 --> 00:38:36.210 biopsy. So those were, either

NOTE Confidence: 0.98110443

00:38:36.210 --> 00:38:38.469 metastatic or locally advanced, urothelial

NOTE Confidence: 0.98110443

00:38:38.690 --> 00:38:40.130 carcinoma that that we were

NOTE Confidence: 0.98110443

00:38:40.130 --> 00:38:41.170 looking at. So these would

NOTE Confidence: 0.98110443

00:38:41.170 --> 00:38:42.790 have been biopsies from

NOTE Confidence: 0.9409097

00:38:43.170 --> 00:38:44.850 it it they weren't super

NOTE Confidence: 0.9409097

00:38:44.850 --> 00:38:45.984 strict in terms of the

NOTE Confidence: 0.9409097

00:38:45.984 --> 00:38:47.265 histology that was required,

NOTE Confidence: 0.91985685

00:38:47.825 --> 00:38:48.864 but it was just some

NOTE Confidence: 0.91985685

00:38:48.864 --> 00:38:50.385 kind of biopsy demonstrating that

NOTE Confidence: 0.91985685

00:38:50.385 --> 00:38:52.465 was either locally advanced or

NOTE Confidence: 0.91985685

00:38:52.465 --> 00:38:53.925 or a metastatic disease.

NOTE Confidence: 0.6593489

00:38:54.305 --> 00:38:55.344 And you can't file with

NOTE Confidence: 0.6593489

00:38:55.344 --> 00:38:57.025 the GHAH and E even

NOTE Confidence: 0.6593489

00:38:57.025 --> 00:38:58.225 for our own Even from

NOTE Confidence: 0.6593489

00:38:58.225 --> 00:38:58.965 that. Yep.

NOTE Confidence: 0.90082693

00:39:03.560 --> 00:39:04.460 Anyone else?

NOTE Confidence: 0.72464305

00:39:05.880 --> 00:39:06.380 Excellent.

NOTE Confidence: 0.9473354

00:39:06.680 --> 00:39:07.180 Okay.

NOTE Confidence: 0.7814873

00:39:08.600 --> 00:39:09.480 So I have a question

NOTE Confidence: 0.7814873

00:39:09.480 --> 00:39:10.380 about your diagram.

NOTE Confidence: 0.9387647

00:39:19.265 --> 00:39:20.145 There is, but you you

NOTE Confidence: 0.9387647

00:39:20.145 --> 00:39:21.684 gotta draw the line somewhere.

NOTE Confidence: 0.89753884

00:39:22.704 --> 00:39:23.684 Yeah. So it's

NOTE Confidence: 0.8591853

00:39:23.984 --> 00:39:24.944 we we just pick these

NOTE Confidence: 0.8591853

00:39:24.944 --> 00:39:26.145 as kinda like to illustrate

NOTE Confidence: 0.8591853

00:39:26.145 --> 00:39:27.424 because their genes that that

NOTE Confidence: 0.8591853

00:39:27.424 --> 00:39:28.785 are important or are well

NOTE Confidence: 0.8591853

00:39:28.785 --> 00:39:29.285 known.

NOTE Confidence: 0.96061254

00:39:30.110 --> 00:39:31.230 But it was it's kind

NOTE Confidence: 0.96061254

00:39:31.230 --> 00:39:32.110 of amazing. Like, some of

NOTE Confidence: 0.96061254

00:39:32.110 --> 00:39:33.310 these cases, they were they

NOTE Confidence: 0.96061254

00:39:33.310 --> 00:39:34.270 were more different than they

NOTE Confidence: 0.96061254

00:39:34.270 --> 00:39:35.010 were similar.

NOTE Confidence: 0.84394544

00:39:35.710 --> 00:39:36.590 In some cases, they were

NOTE Confidence: 0.84394544

00:39:36.590 --> 00:39:37.469 more similar than they were

NOTE Confidence: 0.84394544

00:39:37.469 --> 00:39:38.590 different. But, yeah, we just

NOTE Confidence: 0.84394544

00:39:38.590 --> 00:39:39.469 kinda had to, you know,

NOTE Confidence: 0.84394544

00:39:39.469 --> 00:39:40.670 start somewhere, so that's why

NOTE Confidence: 0.84394544

00:39:40.670 --> 00:39:42.114 we we limited it. It's

NOTE Confidence: 0.84394544

00:39:42.114 --> 00:39:43.395 easy to find the current

NOTE Confidence: 0.84394544

00:39:43.795 --> 00:39:45.155 Mhmm. And then being on

NOTE Confidence: 0.84394544

00:39:45.155 --> 00:39:46.055 as one week.

NOTE Confidence: 0.8542314

00:39:50.515 --> 00:39:51.475 Yeah. Yeah. I mean and,

NOTE Confidence: 0.8542314

00:39:51.475 --> 00:39:52.355 well, I think, you know,

NOTE Confidence: 0.8542314

00:39:52.355 --> 00:39:52.935 it it

NOTE Confidence: 0.8644766

00:39:53.315 --> 00:39:54.935 possibly informing new biology.

NOTE Confidence: 0.9549264

00:39:55.590 --> 00:39:56.790 Because, you know, like, for

NOTE Confidence: 0.9549264

00:39:56.790 --> 00:39:57.910 example, this one, the TP

NOTE Confidence: 0.9549264

00:39:57.910 --> 00:39:59.830 fifty three, gene mutation was

NOTE Confidence: 0.9549264

00:39:59.830 --> 00:40:01.210 was private to the squamous

NOTE Confidence: 0.9549264

00:40:01.350 --> 00:40:02.630 part. And, you know, squamous

NOTE Confidence: 0.9549264

00:40:02.630 --> 00:40:03.350 is thought to be more

NOTE Confidence: 0.9549264

00:40:03.350 --> 00:40:04.310 aggressive, and I guess that

NOTE Confidence: 0.9549264

00:40:04.310 --> 00:40:04.970 makes sense.

NOTE Confidence: 0.97520643

00:40:05.510 --> 00:40:06.230 But, you know, in this

NOTE Confidence: 0.97520643

00:40:06.230 --> 00:40:07.965 one, the TP fifty three

NOTE Confidence: 0.97520643

00:40:08.285 --> 00:40:09.165 gene mutation and in this

NOTE Confidence: 0.97520643

00:40:09.165 --> 00:40:09.885 one, it was it was

NOTE Confidence: 0.97520643

00:40:09.885 --> 00:40:11.245 common to both. So it's

NOTE Confidence: 0.97520643

00:40:11.245 --> 00:40:12.364 it's really hard. I I

NOTE Confidence: 0.97520643

00:40:12.364 --> 00:40:13.165 think one of the things

NOTE Confidence: 0.97520643

00:40:13.165 --> 00:40:14.445 we've learned from the past

NOTE Confidence: 0.97520643

00:40:14.445 --> 00:40:15.325 ten years is that it's

NOTE Confidence: 0.97520643

00:40:15.325 --> 00:40:17.085 very hard to identify, you

NOTE Confidence: 0.97520643

00:40:17.085 --> 00:40:18.625 know, key driver mutations

NOTE Confidence: 0.9960327

00:40:19.085 --> 00:40:19.985 that are responsible

NOTE Confidence: 0.97095567

00:40:20.285 --> 00:40:21.825 or relate to squamous histology.

NOTE Confidence: 0.9572509

00:40:22.150 --> 00:40:22.950 It really seems to be

NOTE Confidence: 0.9572509

00:40:22.950 --> 00:40:23.989 more of a, you know,

NOTE Confidence: 0.9572509

00:40:23.989 --> 00:40:24.650 a transcriptional

NOTE Confidence: 0.9119984

00:40:24.950 --> 00:40:26.390 process than it is a

NOTE Confidence: 0.9119984

00:40:26.390 --> 00:40:28.150 mutation driven process, if you

NOTE Confidence: 0.9119984

00:40:28.150 --> 00:40:28.650 will.

NOTE Confidence: 0.74136555

00:40:30.869 --> 00:40:32.810 So I have a question.

NOTE Confidence: 0.4918609

00:40:33.110 --> 00:40:34.869 You know, why we we

NOTE Confidence: 0.4918609

00:40:34.869 --> 00:40:35.369 validate

NOTE Confidence: 0.65323

00:40:36.070 --> 00:40:36.570 that

NOTE Confidence: 0.8973319

00:41:31.090 --> 00:41:31.969 Yeah. So it's it's a

NOTE Confidence: 0.8973319

00:41:31.969 --> 00:41:33.170 great question and much,

NOTE Confidence: 0.92311865

00:41:33.730 --> 00:41:34.450 there's been a lot of

NOTE Confidence: 0.92311865

00:41:34.450 --> 00:41:35.424 conversation about this in the

NOTE Confidence: 0.92311865

00:41:35.424 --> 00:41:36.785 bladder cancer world, a lot

NOTE Confidence: 0.92311865

00:41:36.785 --> 00:41:37.904 of lot of ink spilled

NOTE Confidence: 0.92311865

00:41:37.904 --> 00:41:39.265 or, you know, virtual ink

NOTE Confidence: 0.92311865

00:41:39.265 --> 00:41:40.385 spilled out on the topic.

NOTE Confidence: 0.92311865

00:41:40.385 --> 00:41:41.045 And so,

NOTE Confidence: 0.9982101

00:41:41.585 --> 00:41:42.625 one of the things that's

NOTE Confidence: 0.9982101

00:41:42.625 --> 00:41:44.085 popped out is that

NOTE Confidence: 0.9939579

00:41:44.785 --> 00:41:46.724 it's very difficult to create

NOTE Confidence: 0.9988501

00:41:47.184 --> 00:41:47.684 reliable

NOTE Confidence: 0.9858962

00:41:48.065 --> 00:41:48.565 categorical

NOTE Confidence: 0.9980574

00:41:48.864 --> 00:41:49.364 tests

NOTE Confidence: 0.9111288

00:41:49.950 --> 00:41:51.489 for basal versus luminal.

NOTE Confidence: 0.95722514

00:41:52.030 --> 00:41:52.910 And I think it relates

NOTE Confidence: 0.95722514

00:41:52.910 --> 00:41:53.869 to, you know, us showing

NOTE Confidence: 0.95722514

00:41:53.869 --> 00:41:55.550 this as a, a it's

NOTE Confidence: 0.95722514

00:41:55.550 --> 00:41:57.150 not a categorical variable. Truly,

NOTE Confidence: 0.95722514

00:41:57.150 --> 00:41:58.450 it's a it's a continuous

NOTE Confidence: 0.95722514

00:41:58.510 --> 00:41:59.950 variable. And so I think

NOTE Confidence: 0.95722514

00:41:59.950 --> 00:42:00.910 one of the the best

NOTE Confidence: 0.95722514

00:42:00.910 --> 00:42:02.109 stories well, not best stories,

NOTE Confidence: 0.95722514

00:42:02.109 --> 00:42:02.750 but one of the most

NOTE Confidence: 0.95722514

00:42:02.750 --> 00:42:03.570 telling stories,

NOTE Confidence: 0.9627402

00:42:04.270 --> 00:42:05.685 is with the DECIPHER bladder

NOTE Confidence: 0.9627402

00:42:05.685 --> 00:42:07.685 cancer test. So decipher bladder

NOTE Confidence: 0.9627402

00:42:07.685 --> 00:42:09.045 cancer test was something that

NOTE Confidence: 0.9627402

00:42:09.045 --> 00:42:10.344 was, marketed,

NOTE Confidence: 0.9530465

00:42:12.005 --> 00:42:12.885 I believe it was even

NOTE Confidence: 0.9530465

00:42:12.885 --> 00:42:13.705 FDA approved.

NOTE Confidence: 0.97345406

00:42:14.165 --> 00:42:14.965 I don't remember. I have

NOTE Confidence: 0.97345406

00:42:14.965 --> 00:42:15.605 to look that up, but

NOTE Confidence: 0.97345406

00:42:15.605 --> 00:42:16.325 it was marketed,

NOTE Confidence: 0.989375

00:42:17.285 --> 00:42:19.385 to to assign molecular subtypes

NOTE Confidence: 0.989375

00:42:19.445 --> 00:42:21.090 to muscle invasive bladder cancer

NOTE Confidence: 0.989375

00:42:21.330 --> 00:42:23.090 to to decide if it's

NOTE Confidence: 0.989375

00:42:23.090 --> 00:42:23.969 going to be,

NOTE Confidence: 0.98217374

00:42:24.290 --> 00:42:26.290 responsive to neoadjuvant cisplatin based

NOTE Confidence: 0.98217374

00:42:26.290 --> 00:42:27.830 chemotherapy, which is the standard.

NOTE Confidence: 0.9678627

00:42:28.130 --> 00:42:29.350 And they showed that,

NOTE Confidence: 0.9513018

00:42:30.850 --> 00:42:33.110 the their their basal subtype

NOTE Confidence: 0.9513018

00:42:33.170 --> 00:42:34.450 had better response than their

NOTE Confidence: 0.9513018

00:42:34.450 --> 00:42:35.545 non basal sub subtype. So

NOTE Confidence: 0.9513018

00:42:35.545 --> 00:42:36.985 they were they were advocating

NOTE Confidence: 0.9513018

00:42:36.985 --> 00:42:38.205 using this to make this

NOTE Confidence: 0.9513018

00:42:38.265 --> 00:42:39.705 key clinical decision, and that

NOTE Confidence: 0.9513018

00:42:39.705 --> 00:42:41.085 was the decipher group.

NOTE Confidence: 0.966773

00:42:42.025 --> 00:42:43.145 Then the the Lund group

NOTE Confidence: 0.966773

00:42:43.145 --> 00:42:44.105 I told you about came

NOTE Confidence: 0.966773

00:42:44.105 --> 00:42:45.545 out with another project that

NOTE Confidence: 0.966773

00:42:45.545 --> 00:42:46.905 was very large and very

NOTE Confidence: 0.966773

00:42:46.905 --> 00:42:47.565 well done.

NOTE Confidence: 0.92485964

00:42:49.299 --> 00:42:50.420 It showed the opposite. They

NOTE Confidence: 0.92485964

00:42:50.420 --> 00:42:51.719 said that the basal group

NOTE Confidence: 0.9671372

00:42:52.339 --> 00:42:54.260 was resistant to neoadjuvant chemotherapy

NOTE Confidence: 0.9671372

00:42:54.260 --> 00:42:56.099 and their genomically unstable group

NOTE Confidence: 0.9671372

00:42:56.099 --> 00:42:57.000 was more sensitive.

NOTE Confidence: 0.80709726

00:42:57.779 --> 00:42:59.480 And so then there's another,

NOTE Confidence: 0.8686775

00:43:00.019 --> 00:43:01.059 then someone's like, what is

NOTE Confidence: 0.8686775

00:43:01.059 --> 00:43:02.200 going on here? So,

NOTE Confidence: 0.927462

00:43:02.825 --> 00:43:03.785 forget what the what group

NOTE Confidence: 0.927462

00:43:03.785 --> 00:43:04.985 it was, but they basically,

NOTE Confidence: 0.927462

00:43:04.985 --> 00:43:05.865 they took some cancers and

NOTE Confidence: 0.927462

00:43:05.865 --> 00:43:06.585 they sent them out for

NOTE Confidence: 0.927462

00:43:06.585 --> 00:43:08.125 decipher and got them profiled.

NOTE Confidence: 0.94975215

00:43:08.505 --> 00:43:10.105 Then they did the lung

NOTE Confidence: 0.94975215

00:43:10.105 --> 00:43:10.605 classification,

NOTE Confidence: 0.9597922

00:43:11.225 --> 00:43:12.025 and they were all over

NOTE Confidence: 0.9597922

00:43:12.025 --> 00:43:13.465 the place. So there was

NOTE Confidence: 0.9597922

00:43:13.465 --> 00:43:14.445 there was an overlap.

NOTE Confidence: 0.95540863

00:43:14.825 --> 00:43:16.105 The basils from one didn't

NOTE Confidence: 0.95540863

00:43:16.105 --> 00:43:17.385 overlap with the the basils

NOTE Confidence: 0.95540863

00:43:17.385 --> 00:43:18.205 from the other.

NOTE Confidence: 0.9215385

00:43:19.200 --> 00:43:21.040 And so the I think

NOTE Confidence: 0.9215385

00:43:21.040 --> 00:43:22.080 that goes to the tell

NOTE Confidence: 0.9215385

00:43:22.080 --> 00:43:23.119 the story, like, whenever we

NOTE Confidence: 0.9215385

00:43:23.119 --> 00:43:24.480 say basilar, we say luminal,

NOTE Confidence: 0.9215385

00:43:24.480 --> 00:43:25.680 we're saying something that's somewhat

NOTE Confidence: 0.9215385

00:43:25.680 --> 00:43:26.180 arbitrary.

NOTE Confidence: 0.9271245

00:43:26.719 --> 00:43:28.420 Who's basal? Who's luminal?

NOTE Confidence: 0.97603863

00:43:29.119 --> 00:43:29.940 There's there's

NOTE Confidence: 0.8992005

00:43:30.575 --> 00:43:31.615 there really, I think that

NOTE Confidence: 0.8992005

00:43:31.615 --> 00:43:32.495 the way to do this

NOTE Confidence: 0.8992005

00:43:32.495 --> 00:43:33.295 isn't to say this is

NOTE Confidence: 0.8992005

00:43:33.295 --> 00:43:34.335 a luminal cancer or basal

NOTE Confidence: 0.8992005

00:43:34.335 --> 00:43:35.855 cancer, but rather, what are

NOTE Confidence: 0.8992005

00:43:35.855 --> 00:43:36.515 the processes?

NOTE Confidence: 0.95425403

00:43:36.895 --> 00:43:37.935 What are the signatures that

NOTE Confidence: 0.95425403

00:43:37.935 --> 00:43:39.055 are active and how can

NOTE Confidence: 0.95425403

00:43:39.055 --> 00:43:40.575 we use those to inform

NOTE Confidence: 0.95425403

00:43:40.575 --> 00:43:41.075 therapy?

NOTE Confidence: 0.86897266

00:43:42.095 --> 00:43:42.975 So at this point, I'm

NOTE Confidence: 0.86897266

00:43:43.055 --> 00:43:44.015 I really am not an

NOTE Confidence: 0.86897266

00:43:44.015 --> 00:43:44.975 advocate at all of the

NOTE Confidence: 0.86897266

00:43:44.975 --> 00:43:46.219 descending molecular subtypes,

NOTE Confidence: 0.9889423

00:43:46.599 --> 00:43:47.480 in the clinical setting. I

NOTE Confidence: 0.9889423

00:43:47.480 --> 00:43:48.920 think there's no we don't

NOTE Confidence: 0.9889423

00:43:48.920 --> 00:43:49.719 know how to do it,

NOTE Confidence: 0.9889423

00:43:49.880 --> 00:43:50.760 basically, and we don't know

NOTE Confidence: 0.9889423

00:43:50.760 --> 00:43:51.239 what to do with the

NOTE Confidence: 0.9889423

00:43:51.239 --> 00:43:52.700 information once we get it.

NOTE Confidence: 0.6296114

00:44:03.585 --> 00:44:04.085 Yeah.

NOTE Confidence: 0.72238946

00:44:06.225 --> 00:44:07.685 So with those

NOTE Confidence: 0.33082885

00:44:08.225 --> 00:44:09.445 with the base of our

NOTE Confidence: 0.7003598

00:44:22.670 --> 00:44:23.170 Yeah.

NOTE Confidence: 0.9615175

00:44:30.984 --> 00:44:31.705 So I don't know if

NOTE Confidence: 0.9615175

00:44:31.705 --> 00:44:32.585 anyone who's looked at the

NOTE Confidence: 0.9615175

00:44:32.585 --> 00:44:35.145 basal phenotype of noninvasive papillary

NOTE Confidence: 0.9615175

00:44:35.145 --> 00:44:36.185 cancers. I would assume they're

NOTE Confidence: 0.9615175

00:44:36.185 --> 00:44:36.984 high grade, but I I

NOTE Confidence: 0.9615175

00:44:36.984 --> 00:44:37.805 don't know that.

NOTE Confidence: 0.96239656

00:44:38.425 --> 00:44:39.785 But people have looked at

NOTE Confidence: 0.96239656

00:44:39.785 --> 00:44:40.905 the subtype of these, the

NOTE Confidence: 0.96239656

00:44:40.905 --> 00:44:42.344 flat carcinoma in situ, and

NOTE Confidence: 0.96239656

00:44:42.344 --> 00:44:43.145 there is a subset of

NOTE Confidence: 0.96239656

00:44:43.145 --> 00:44:44.219 those. There's a small subset

NOTE Confidence: 0.96239656

00:44:44.219 --> 00:44:45.180 of flat carcinoma in situ

NOTE Confidence: 0.96239656

00:44:45.180 --> 00:44:46.480 that has a basal phenotype,

NOTE Confidence: 0.96239656

00:44:46.540 --> 00:44:47.739 and that's more aggressive. That's

NOTE Confidence: 0.96239656

00:44:47.739 --> 00:44:49.180 associated with higher risk of

NOTE Confidence: 0.96239656

00:44:49.180 --> 00:44:51.040 progression to muscle invasion, etcetera.

NOTE Confidence: 0.96239656

00:44:51.099 --> 00:44:52.700 So, so it's not completely

NOTE Confidence: 0.96239656

00:44:52.700 --> 00:44:53.900 false that there's like this

NOTE Confidence: 0.96239656

00:44:53.900 --> 00:44:55.099 subset that start off basal.

NOTE Confidence: 0.96239656

00:44:55.099 --> 00:44:55.739 I just think it's a

NOTE Confidence: 0.96239656

00:44:55.739 --> 00:44:57.359 minority of them that do.

NOTE Confidence: 0.98791206

00:44:59.965 --> 00:45:00.864 Anyone else?

NOTE Confidence: 0.80559623

00:45:01.405 --> 00:45:03.085 Oh, yes. So the, a

NOTE Confidence: 0.80559623

00:45:03.085 --> 00:45:04.285 lot of us working on,

NOTE Confidence: 0.8784168

00:45:04.765 --> 00:45:06.364 cell lines. Yes. And and

NOTE Confidence: 0.8784168

00:45:06.364 --> 00:45:06.864 the,

NOTE Confidence: 0.6260448

00:45:07.405 --> 00:45:09.565 the prototypical aluminum cell lines

NOTE Confidence: 0.6260448

00:45:09.565 --> 00:45:10.705 and for physical

NOTE Confidence: 0.8232107

00:45:11.645 --> 00:45:12.385 cell lines,

NOTE Confidence: 0.9075588

00:45:22.480 --> 00:45:24.080 Yeah. They do. It it's

NOTE Confidence: 0.9075588

00:45:24.080 --> 00:45:25.280 kind of amazing, actually. Oh,

NOTE Confidence: 0.9075588

00:45:25.280 --> 00:45:26.080 did you have more? Go

NOTE Confidence: 0.9075588

00:45:26.080 --> 00:45:26.640 ahead. Go ahead. I can

NOTE Confidence: 0.9075588

00:45:26.640 --> 00:45:27.140 explain.

NOTE Confidence: 0.8981229

00:45:39.195 --> 00:45:40.235 So we haven't done the

NOTE Confidence: 0.8981229

00:45:40.235 --> 00:45:41.515 latter yet, but but the

NOTE Confidence: 0.8981229

00:45:41.515 --> 00:45:43.114 the former question, yes. So

NOTE Confidence: 0.8981229

00:45:43.114 --> 00:45:43.770 some of these

NOTE Confidence: 0.9795281

00:45:44.250 --> 00:45:45.630 do have similar histologies.

NOTE Confidence: 0.93065786

00:45:46.730 --> 00:45:48.410 It's it's difficult to to

NOTE Confidence: 0.93065786

00:45:48.410 --> 00:45:49.770 really compare them. And the

NOTE Confidence: 0.93065786

00:45:49.770 --> 00:45:50.650 way that we've done it

NOTE Confidence: 0.93065786

00:45:50.650 --> 00:45:52.670 historically is is with xenograft.

NOTE Confidence: 0.93065786

00:45:52.730 --> 00:45:53.610 So if you grow, like,

NOTE Confidence: 0.93065786

00:45:53.610 --> 00:45:54.489 the the cell in r

NOTE Confidence: 0.93065786

00:45:54.489 --> 00:45:55.450 t four, for example, which

NOTE Confidence: 0.93065786

00:45:55.450 --> 00:45:56.730 is a liminal cell line

NOTE Confidence: 0.93065786

00:45:56.730 --> 00:45:58.030 in a subcapsular,

NOTE Confidence: 0.9610967

00:45:58.844 --> 00:46:00.224 you know, kidney xenograft

NOTE Confidence: 0.92183065

00:46:00.605 --> 00:46:01.885 in skin mice. It looks

NOTE Confidence: 0.92183065

00:46:01.885 --> 00:46:03.744 like a papillary carcinoma, classic,

NOTE Confidence: 0.91623896

00:46:04.125 --> 00:46:05.645 you know, papillary or theeloid

NOTE Confidence: 0.91623896

00:46:05.645 --> 00:46:06.925 carcinoma. You grow a SCABER

NOTE Confidence: 0.91623896

00:46:06.925 --> 00:46:07.885 cell line. It's a basal

NOTE Confidence: 0.91623896

00:46:07.885 --> 00:46:09.005 one in the same model.

NOTE Confidence: 0.91623896

00:46:09.005 --> 00:46:10.525 Even a subcutaneous xenograft, it's

NOTE Confidence: 0.91623896

00:46:10.525 --> 00:46:12.190 keratinizing squamous cell cancer. So

NOTE Confidence: 0.91623896

00:46:12.190 --> 00:46:14.050 the the histology does mirror

NOTE Confidence: 0.91623896

00:46:14.110 --> 00:46:16.050 the molecular subtype very well.

NOTE Confidence: 0.9495036

00:46:17.150 --> 00:46:18.110 But they're they're hard to

NOTE Confidence: 0.9495036

00:46:18.110 --> 00:46:19.390 grow. Like, not every all

NOTE Confidence: 0.9495036

00:46:19.390 --> 00:46:20.270 all these cell lines grow

NOTE Confidence: 0.9495036

00:46:20.270 --> 00:46:21.710 easily in xenograft, some just

NOTE Confidence: 0.9495036

00:46:21.710 --> 00:46:22.110 don't.

NOTE Confidence: 0.9221141

00:46:22.910 --> 00:46:23.950 And so we've we've not

NOTE Confidence: 0.9221141

00:46:23.950 --> 00:46:25.150 done that experiment, but that's

NOTE Confidence: 0.9221141

00:46:25.150 --> 00:46:25.560 it's a

NOTE Confidence: 0.9406257

00:46:26.525 --> 00:46:27.645 yeah, that's it's something I

NOTE Confidence: 0.9406257

00:46:27.645 --> 00:46:28.525 thought about, but I've not

NOTE Confidence: 0.9406257

00:46:28.525 --> 00:46:30.045 done it. They don't have

NOTE Confidence: 0.9406257

00:46:30.045 --> 00:46:31.645 the state. It it's not

NOTE Confidence: 0.9406257

00:46:31.645 --> 00:46:32.925 that impressive. So in culture,

NOTE Confidence: 0.9406257

00:46:32.925 --> 00:46:33.805 yeah, like, the the r

NOTE Confidence: 0.9406257

00:46:33.805 --> 00:46:34.844 t fours are kinda like

NOTE Confidence: 0.9406257

00:46:34.844 --> 00:46:36.285 little little dots. They're little

NOTE Confidence: 0.9406257

00:46:36.285 --> 00:46:38.045 papillary looking things, but nothing

NOTE Confidence: 0.9406257

00:46:38.045 --> 00:46:39.344 is impressive as the xenografts.

NOTE Confidence: 0.9406257

00:46:39.485 --> 00:46:40.605 But it really doesn't change

NOTE Confidence: 0.9406257

00:46:40.605 --> 00:46:42.000 the just, like, the

NOTE Confidence: 0.99456024

00:46:42.400 --> 00:46:43.460 the, you know,

NOTE Confidence: 0.8491456

00:46:43.760 --> 00:46:44.560 the look of the cell

NOTE Confidence: 0.8491456

00:46:44.560 --> 00:46:45.600 lines. So it suggests that

NOTE Confidence: 0.8491456

00:46:45.600 --> 00:46:46.500 maybe some

NOTE Confidence: 0.9926554

00:46:46.880 --> 00:46:47.380 of

NOTE Confidence: 0.71949065

00:46:47.760 --> 00:46:48.500 the morphologic,

NOTE Confidence: 0.85978293

00:46:48.800 --> 00:46:49.239 histologic

NOTE Confidence: 0.58568627

00:46:49.680 --> 00:46:50.340 Mhmm. Is

NOTE Confidence: 0.6885501

00:46:51.280 --> 00:46:53.040 derived from interactions from the

NOTE Confidence: 0.6885501

00:46:53.040 --> 00:46:54.100 others. Yeah.

NOTE Confidence: 0.7387666

00:46:54.560 --> 00:46:55.540 Yes. Yeah.

NOTE Confidence: 0.94171935

00:46:56.424 --> 00:46:57.244 For sure.

NOTE Confidence: 0.80148125

00:46:58.825 --> 00:46:59.644 Yeah. Go ahead.

NOTE Confidence: 0.8633055

00:47:15.870 --> 00:47:16.430 Yes. So,

NOTE Confidence: 0.9985114

00:47:17.070 --> 00:47:17.550 we

NOTE Confidence: 0.95042443

00:47:17.870 --> 00:47:19.310 actually, I've I Andrew, I

NOTE Confidence: 0.95042443

00:47:19.310 --> 00:47:20.430 just analyzed your data he

NOTE Confidence: 0.95042443

00:47:20.430 --> 00:47:21.150 gave me, and so we

NOTE Confidence: 0.95042443

00:47:21.150 --> 00:47:21.950 actually have some of this

NOTE Confidence: 0.95042443

00:47:21.950 --> 00:47:23.070 we're looking at right now.

NOTE Confidence: 0.91617197

00:47:23.630 --> 00:47:24.945 They're they appear to be

NOTE Confidence: 0.91617197

00:47:25.025 --> 00:47:26.225 more basal in our hands

NOTE Confidence: 0.91617197

00:47:26.225 --> 00:47:26.625 at least.

NOTE Confidence: 0.9923878

00:47:27.185 --> 00:47:27.985 But in the hands of

NOTE Confidence: 0.9923878

00:47:27.985 --> 00:47:28.945 others who have published on

NOTE Confidence: 0.9923878

00:47:28.945 --> 00:47:29.445 this,

NOTE Confidence: 0.9981405

00:47:30.465 --> 00:47:31.445 it it's it's

NOTE Confidence: 0.94514954

00:47:31.745 --> 00:47:33.105 inconsistent. And it's it's a

NOTE Confidence: 0.94514954

00:47:33.105 --> 00:47:33.985 similar kind of story that

NOTE Confidence: 0.94514954

00:47:33.985 --> 00:47:34.785 if you look at spatially

NOTE Confidence: 0.94514954

00:47:34.785 --> 00:47:36.085 distinct parts of a tumor,

NOTE Confidence: 0.94514954

00:47:36.145 --> 00:47:37.585 you get different subtypes. If

NOTE Confidence: 0.94514954

00:47:37.585 --> 00:47:38.305 you also look at the

NOTE Confidence: 0.94514954

00:47:38.305 --> 00:47:39.745 lymph node metastasis or distant

NOTE Confidence: 0.94514954

00:47:39.745 --> 00:47:41.309 metastasis, it it can differ,

NOTE Confidence: 0.9784097

00:47:41.690 --> 00:47:43.049 from the primary as well.

NOTE Confidence: 0.9784097

00:47:43.049 --> 00:47:44.010 So it really it's what

NOTE Confidence: 0.9784097

00:47:44.010 --> 00:47:45.049 part of the main tumor,

NOTE Confidence: 0.9784097

00:47:45.049 --> 00:47:46.489 you know, gave rise to

NOTE Confidence: 0.9784097

00:47:46.489 --> 00:47:47.230 the MET.

NOTE Confidence: 0.9517762

00:47:51.770 --> 00:47:53.069 Alright. No one else?

NOTE Confidence: 0.9589621

00:47:53.770 --> 00:47:54.829 Oh oh, yeah. Go ahead.

NOTE Confidence: 0.63840806

00:47:56.155 --> 00:47:57.755 Just in general, you found

NOTE Confidence: 0.63840806

00:47:57.755 --> 00:47:59.615 lung classification that was reproducible.

NOTE Confidence: 0.9593348

00:48:00.955 --> 00:48:02.075 I I don't think any

NOTE Confidence: 0.9593348

00:48:02.075 --> 00:48:03.135 of them are that reproducible.

NOTE Confidence: 0.9593348

00:48:03.195 --> 00:48:04.075 I think that it just

NOTE Confidence: 0.9593348

00:48:04.235 --> 00:48:05.675 I mean, they're reproducible on

NOTE Confidence: 0.9593348

00:48:05.675 --> 00:48:06.415 their own.

NOTE Confidence: 0.85040575

00:48:06.875 --> 00:48:08.315 In the lung classification is

NOTE Confidence: 0.85040575

00:48:08.315 --> 00:48:09.355 nice because they have got

NOTE Confidence: 0.85040575

00:48:09.355 --> 00:48:10.655 some some biological,

NOTE Confidence: 0.99886096

00:48:11.115 --> 00:48:11.730 you know

NOTE Confidence: 0.9424151

00:48:12.930 --> 00:48:14.050 you know, consistency to it.

NOTE Confidence: 0.9424151

00:48:14.050 --> 00:48:14.690 So, you know, like, their

NOTE Confidence: 0.9424151

00:48:14.690 --> 00:48:15.890 lumenal types, there's two of

NOTE Confidence: 0.9424151

00:48:15.890 --> 00:48:17.170 them and they're they classify

NOTE Confidence: 0.9424151

00:48:17.170 --> 00:48:18.130 them based on the cell

NOTE Confidence: 0.9424151

00:48:18.130 --> 00:48:19.250 cycle gene that's been knocked

NOTE Confidence: 0.9424151

00:48:19.250 --> 00:48:19.750 out.

NOTE Confidence: 0.9715816

00:48:20.850 --> 00:48:21.570 But I don't I don't

NOTE Confidence: 0.9715816

00:48:21.570 --> 00:48:22.609 wanna use the word consistent.

NOTE Confidence: 0.9715816

00:48:22.609 --> 00:48:23.489 I think they're all consistent

NOTE Confidence: 0.9715816

00:48:23.489 --> 00:48:24.369 with themselves, but they're just

NOTE Confidence: 0.9715816

00:48:24.369 --> 00:48:25.410 not consistent with each other

NOTE Confidence: 0.9715816

00:48:25.410 --> 00:48:26.290 because it depends on the

NOTE Confidence: 0.9715816

00:48:26.290 --> 00:48:27.555 genes you pick to put

NOTE Confidence: 0.9715816

00:48:27.555 --> 00:48:28.675 them in the different groups,

NOTE Confidence: 0.9715816

00:48:28.675 --> 00:48:29.875 and they can be, a

NOTE Confidence: 0.9715816

00:48:29.875 --> 00:48:31.575 little inconsistent based on that.

NOTE Confidence: 0.9946853

00:48:34.915 --> 00:48:36.614 Alright. Well, thank you all.