WEBVTT

00:00:00.000 --> 00:00:02.096 Today's grand round speaker

00:00:02.096 --> 00:00:05.860 is Mina Shu or very own Mina.

00:00:05.860 --> 00:00:08.500 She needs no introduction.

00:00:08.500 --> 00:00:11.960 Actually, Mina has been here longer than I,

00:00:11.960 --> 00:00:15.212 but I'll introduce Mina for the

00:00:15.212 --> 00:00:19.684 benefit of the new folks Mina grew up

00:00:19.684 --> 00:00:22.972 in California and came to northeast

00:00:22.972 --> 00:00:26.798 for college at Harvard University,

00:00:26.800 --> 00:00:30.304 and then she went back for MD at.

00:00:30.310 --> 00:00:33.580 UCSF and she must have missed

00:00:33.580 --> 00:00:36.430 the seasons and the snow,

00:00:36.430 --> 00:00:39.106 so she came back to Yale

00:00:39.106 --> 00:00:40.890 to train in pathology.

00:00:40.890 --> 00:00:42.450 During her training,

NOTE Confidence: 0.694471460454545

00:00:42.450 --> 00:00:46.740 Mina rose to become chief resident and Mina

NOTE Confidence: 0.694471460454545

00:00:46.740 --> 00:00:50.064 showed an early interest in hematology.

NOTE Confidence: 0.694471460454545

00:00:50.070 --> 00:00:54.474 She spent a year doing research

NOTE Confidence: 0.694471460454545

00:00:54.474 --> 00:00:58.780 at Brigham and Women's Hospital.

NOTE Confidence: 0.694471460454545

00:00:58.780 --> 00:01:03.400 During her medical school and then after

NOTE Confidence: 0.694471460454545

00:01:03.400 --> 00:01:07.348 finishing her pathology residency at Yale,

NOTE Confidence: 0.694471460454545

00:01:07.350 --> 00:01:10.784 she went back to Brigham and Women's

NOTE Confidence: 0.694471460454545

00:01:10.784 --> 00:01:13.688 Hospital to do a clinical fellowship.

NOTE Confidence: 0.694471460454545

00:01:13.690 --> 00:01:16.270 And as minard's,

NOTE Confidence: 0.694471460454545

00:01:16.270 --> 00:01:19.498 if you logged in earlier you

NOTE Confidence: 0.694471460454545

00:01:19.498 --> 00:01:22.267 heard me say there was no room

NOTE Confidence: 0.694471460454545

00:01:22.267 --> 00:01:24.817 to do anything else but clinical

NOTE Confidence: 0.694471460454545

00:01:24.817 --> 00:01:27.460 work with voice extremely heavy.

NOTE Confidence: 0.857018006363636

00:01:29.990 --> 00:01:32.955 Fortuitously, you know was recruited

NOTE Confidence: 0.857018006363636

00:01:32.955 --> 00:01:36.190 right back at faculty position at

00:01:36.190 --> 00:01:39.304 Yale pathology, and we are very

00:01:39.304 --> 00:01:42.809 lucky to have Meena here with us.

00:01:42.810 --> 00:01:46.625 Mina has established a track record of

00:01:46.625 --> 00:01:49.767 pursuit of curiosity and excellence in

00:01:49.767 --> 00:01:54.221 all her endeavors and I would say all her

00:01:54.221 --> 00:01:57.407 endeavors because she won many grants,

00:01:57.410 --> 00:01:59.195 awards and scholarships.

00:01:59.195 --> 00:02:01.860 From early age, in fact,

00:02:01.860 --> 00:02:04.872 several in high school making it

00:02:04.872 --> 00:02:08.630 to Harvard University Dean's list.

00:02:08.630 --> 00:02:11.510 At Yale, an outstanding achievement

00:02:11.510 --> 00:02:15.420 in autopsy or world during residency.

00:02:15.420 --> 00:02:18.104 Several Chairmans challenge grant

00:02:18.104 --> 00:02:21.459 awards and a Gilleard foundation

00:02:21.459 --> 00:02:24.737 grant that is just to name a few.

00:02:24.740 --> 00:02:28.280 Mina is a consummate clinician and

NOTE Confidence: 0.857018006363636

00:02:28.280 --> 00:02:30.640 an excellent research collaborator.

NOTE Confidence: 0.857018006363636

00:02:30.640 --> 00:02:33.976 She has close to add publications

NOTE Confidence: 0.857018006363636

00:02:33.976 --> 00:02:36.624 to her credit. In addition,

NOTE Confidence: 0.857018006363636

00:02:36.624 --> 00:02:40.033 Mina is an outstanding teacher and mentor,

NOTE Confidence: 0.857018006363636

00:02:40.040 --> 00:02:43.868 and that's demonstrated by her various

NOTE Confidence: 0.857018006363636

00:02:43.868 --> 00:02:46.800 speaking engagements all over US,

NOTE Confidence: 0.857018006363636

00:02:46.800 --> 00:02:48.944 Canada, and also China.

NOTE Confidence: 0.857018006363636

00:02:48.944 --> 00:02:51.624 She has given short courses,

NOTE Confidence: 0.857018006363636

00:02:51.630 --> 00:02:54.702 interactive microscopy sessions and

NOTE Confidence: 0.857018006363636

00:02:54.702 --> 00:02:58.542 participated in workshops and symposia

NOTE Confidence: 0.857018006363636

00:02:58.542 --> 00:03:02.593 at annual meetings of the US and

NOTE Confidence: 0.857018006363636

00:03:02.593 --> 00:03:05.710 Canadian Academy of the Theology.

NOTE Confidence: 0.857018006363636

00:03:05.710 --> 00:03:09.290 And at other professional organizations.

NOTE Confidence: 0.857018006363636

00:03:09.290 --> 00:03:10.970 And her mentees,

NOTE Confidence: 0.857018006363636

00:03:10.970 --> 00:03:13.210 mostly residents and fellows,

00:03:13.210 --> 00:03:15.818 they have successfully presented

00:03:15.818 --> 00:03:19.078 abstracts at national and international

00:03:19.078 --> 00:03:22.211 meetings and published the manuscripts

00:03:22.211 --> 00:03:24.005 in impactful journals.

00:03:24.010 --> 00:03:27.050 So with no further ado,

00:03:27.050 --> 00:03:31.054 let me now present her work today.

00:03:31.060 --> 00:03:31.560 You know?

00:03:35.960 --> 00:03:39.488 Thank you so much mandjou for

00:03:39.488 --> 00:03:41.840 that really amazing introduction

00:03:41.942 --> 00:03:44.787 that I probably don't deserve,

00:03:44.790 --> 00:03:47.318 but I just wanted to say, you know,

00:03:47.318 --> 00:03:49.670 thank you also for asking me to do

00:03:49.738 --> 00:03:52.006 this talk when you first asked me,

00:03:52.010 --> 00:03:54.649 I wasn't sure which of the many

00:03:54.649 --> 00:03:56.670 cool stories that were involved

00:03:56.670 --> 00:03:59.484 in in heme path I should present,

NOTE Confidence: 0.857488426

00:03:59.490 --> 00:04:02.346 but I quickly decided to do this one

NOTE Confidence: 0.857488426

00:04:02.346 --> 00:04:05.480 because I think you would agree with me.

NOTE Confidence: 0.857488426

00:04:05.480 --> 00:04:07.865 And and probably malani as

NOTE Confidence: 0.857488426

00:04:07.865 --> 00:04:09.773 the current IHC director.

NOTE Confidence: 0.857488426

00:04:09.780 --> 00:04:12.628 That now is a good time to tell

NOTE Confidence: 0.857488426

00:04:12.628 --> 00:04:15.495 our trainees and students about the

NOTE Confidence: 0.857488426

00:04:15.495 --> 00:04:18.085 importance of discovering new markers

NOTE Confidence: 0.857488426

00:04:18.085 --> 00:04:21.376 and that we are not at the end of the

NOTE Confidence: 0.857488426

00:04:21.376 --> 00:04:24.774 IHC era but at the beginning and we

NOTE Confidence: 0.857488426

00:04:24.774 --> 00:04:28.930 will get even better during the next ten,

NOTE Confidence: 0.857488426

00:04:28.930 --> 00:04:31.780 20-30 years at investigating protein

NOTE Confidence: 0.857488426

00:04:31.780 --> 00:04:34.060 expression in human tissues.

NOTE Confidence: 0.857488426

00:04:34.060 --> 00:04:37.350 And then cancer in particular.

NOTE Confidence: 0.857488426

00:04:37.350 --> 00:04:40.026 So these are my COI disclosures.

NOTE Confidence: 0.857488426

00:04:40.030 --> 00:04:42.151 I don't think that any of this

00:04:42.151 --> 00:04:43.860 will impact our talk today.

00:04:43.860 --> 00:04:45.140 And this is my outline,

00:04:45.140 --> 00:04:49.860 so I wanted to do a case presentation of a

00:04:49.978 --> 00:04:53.480 patient recently seen this phantom menace,

00:04:53.480 --> 00:04:56.140 which is our counting of blast and

00:04:56.215 --> 00:04:58.360 blast equivalents on heme path.

00:04:58.360 --> 00:05:01.078 A New Hope or marker for AMOL,

00:05:01.078 --> 00:05:03.706 and then a few other projects

00:05:03.706 --> 00:05:06.740 I spun off the original one.

00:05:06.740 --> 00:05:08.120 And by the way,

00:05:08.120 --> 00:05:11.139 I am not actually a Star Wars geek.

00:05:11.140 --> 00:05:14.535 Some of my friends are and they.

00:05:14.540 --> 00:05:17.120 I have thought in their childhood

00:05:17.120 --> 00:05:20.352 that becoming a Jedi is a legitimate

00:05:20.352 --> 00:05:21.306 career choice,

00:05:21.310 --> 00:05:22.759 which I think is kind of funny

NOTE Confidence: 0.857488426

00:05:22.759 --> 00:05:24.010 because as a pathologist,

NOTE Confidence: 0.857488426

00:05:24.010 --> 00:05:27.028 sometimes I think we are living

NOTE Confidence: 0.857488426

00:05:27.028 --> 00:05:29.570 that dream because we're actually

NOTE Confidence: 0.857488426

00:05:29.570 --> 00:05:32.186 able to on a daily basis,

NOTE Confidence: 0.857488426

00:05:32.190 --> 00:05:34.675 force miniscule pieces of tissue

NOTE Confidence: 0.857488426

00:05:34.675 --> 00:05:38.505 to tell us their truth and that to

NOTE Confidence: 0.857488426

00:05:38.505 --> 00:05:41.417 me is amazing and quite Jedi like.

NOTE Confidence: 0.857488426

00:05:41.420 --> 00:05:45.038 So here's my books case presentation.

NOTE Confidence: 0.857488426

00:05:45.040 --> 00:05:47.176 This is a 58 year old woman with

NOTE Confidence: 0.857488426

00:05:47.176 --> 00:05:50.159 a 2 year history of chronic

NOTE Confidence: 0.857488426

00:05:50.159 --> 00:05:51.345 myelomonocytic leukemia,

NOTE Confidence: 0.857488426

00:05:51.350 --> 00:05:54.549 and I actually saw that initial CML

NOTE Confidence: 0.857488426

00:05:54.549 --> 00:05:57.104 diagnosis now with progressive cytopenias

NOTE Confidence: 0.857488426

00:05:57.104 --> 00:06:00.404 bone pain and circulating glass and

NOTE Confidence: 0.857488426

00:06:00.404 --> 00:06:03.790 she is admitted for the symptoms.

NOTE Confidence: 0.857488426

00:06:03.790 --> 00:06:07.198 So her peripheral blood showed 8% blasts.

NOTE Confidence: 0.857488426

00:06:07.198 --> 00:06:11.988 These are mono blastic cells.

NOTE Confidence: 0.857488426

00:06:11.990 --> 00:06:14.850 She also had degranulate poesis.

NOTE Confidence: 0.857488426

00:06:14.850 --> 00:06:16.995 So dysplasia of the granulocyte

NOTE Confidence: 0.857488426

00:06:16.995 --> 00:06:18.711 lineage with abnormal folding

NOTE Confidence: 0.857488426

00:06:18.711 --> 00:06:21.433 of the granulocytes and in other

NOTE Confidence: 0.857488426

00:06:21.433 --> 00:06:22.765 areas hypo granularity.

NOTE Confidence: 0.857488426

00:06:22.770 --> 00:06:25.360 She also had a monocytosis as is

NOTE Confidence: 0.857488426

00:06:25.360 --> 00:06:27.728 normally seen for her blood smear.

NOTE Confidence: 0.857488426

00:06:27.730 --> 00:06:29.998 These delicately folding cells

NOTE Confidence: 0.857488426

00:06:29.998 --> 00:06:32.266 with Gray blue cytoplasm.

NOTE Confidence: 0.857488426

00:06:32.270 --> 00:06:33.890 These are mature monos.

NOTE Confidence: 0.857488426

00:06:33.890 --> 00:06:35.915 They proceeded to do a

NOTE Confidence: 0.857488426

00:06:35.915 --> 00:06:37.840 bone marrow aspiration,

NOTE Confidence: 0.857488426

00:06:37.840 --> 00:06:39.460 but it was a dry tap,

NOTE Confidence: 0.857488426

00:06:39.460 --> 00:06:42.208 most likely because of the fibrosis

NOTE Confidence: 0.857488426

00:06:42.208 --> 00:06:44.040 in the core biopsy.

NOTE Confidence: 0.857488426

00:06:44.040 --> 00:06:46.496 This was the core biopsy in which you

NOTE Confidence: 0.857488426

00:06:46.496 --> 00:06:49.444 see it is hypercellular for her age and

NOTE Confidence: 0.857488426

00:06:49.444 --> 00:06:52.349 there is dysplasia in the megakaryocytes.

NOTE Confidence: 0.857488426

00:06:52.350 --> 00:06:55.381 You can also see a myeloid predominance

NOTE Confidence: 0.857488426

00:06:55.381 --> 00:06:58.578 with hardly any erythroid islands here.

NOTE Confidence: 0.857488426

00:06:58.580 --> 00:07:01.500 But at least there is maturation in the

NOTE Confidence: 0.857488426

00:07:01.500 --> 00:07:03.873 form of metamyelocytes granulocytes.

NOTE Confidence: 0.857488426

00:07:03.873 --> 00:07:06.711 So actually if you compare to

NOTE Confidence: 0.857488426

00:07:06.711 --> 00:07:09.319 her initial bone marrow biopsy,

NOTE Confidence: 0.857488426

00:07:09.320 --> 00:07:11.185 this area looks very similar

NOTE Confidence: 0.857488426

00:07:11.185 --> 00:07:12.677 to the initial one,

NOTE Confidence: 0.857488426

00:07:12.680 --> 00:07:15.360 but a little more hypercellular.

NOTE Confidence: 0.857488426

00:07:15.360 --> 00:07:15.841 However,

NOTE Confidence: 0.857488426

00:07:15.841 --> 00:07:18.727 about 30% of the bone marrow

NOTE Confidence: 0.857488426

00:07:18.727 --> 00:07:20.170 actually showed these

NOTE Confidence: 0.880798311538462

00:07:20.251 --> 00:07:21.799 foci of immaturity.

NOTE Confidence: 0.880798311538462

00:07:21.800 --> 00:07:24.481 So here I say immaturity because the

NOTE Confidence: 0.880798311538462

00:07:24.481 --> 00:07:27.180 cells have more dispersed chromatin,

NOTE Confidence: 0.880798311538462

00:07:27.180 --> 00:07:28.632 some distinct nucleoli.

NOTE Confidence: 0.880798311538462

00:07:28.632 --> 00:07:31.052 And you're having a lack

NOTE Confidence: 0.880798311538462

00:07:31.052 --> 00:07:33.869 of the mature granulocytes,

NOTE Confidence: 0.880798311538462

00:07:33.870 --> 00:07:35.370 so this is very worrisome,

NOTE Confidence: 0.880798311538462

00:07:35.370 --> 00:07:38.890 especially in this clinical context

NOTE Confidence: 0.880798311538462

00:07:38.890 --> 00:07:41.706 of transformation into AML.

NOTE Confidence: 0.880798311538462

00:07:41.710 --> 00:07:45.066 So can we treat this patient as AML now?

NOTE Confidence: 0.880798311538462

00:07:45.070 --> 00:07:47.500 Well, the definition of AML is

NOTE Confidence: 0.880798311538462

00:07:47.500 --> 00:07:49.908 20% loss in blood or bone marrow.

NOTE Confidence: 0.880798311538462

00:07:49.910 --> 00:07:51.800 So how can we reach that with

NOTE Confidence: 0.880798311538462

00:07:51.800 --> 00:07:53.370 our without our gold standard

NOTE Confidence: 0.880798311538462

00:07:53.370 --> 00:07:54.770 of the aspirin count?

NOTE Confidence: 0.8497792575

00:07:56.820 --> 00:07:59.460 If the AML expressed our most

NOTE Confidence: 0.8497792575

00:07:59.460 --> 00:08:01.750 utilized immunostain which is CD 34,

NOTE Confidence: 0.8497792575

00:08:01.750 --> 00:08:04.550 we could demonstrate that on core biopsy,

NOTE Confidence: 0.8497792575

00:08:04.550 --> 00:08:06.070 but without that marker.

NOTE Confidence: 0.8497792575

00:08:06.070 --> 00:08:08.894 It would be very difficult to substantiate

NOTE Confidence: 0.8497792575

00:08:08.894 --> 00:08:11.726 the cytologic blast count on core,

NOTE Confidence: 0.8497792575

00:08:11.730 --> 00:08:13.620 and this was actually negative,

NOTE Confidence: 0.8497792575

00:08:13.620 --> 00:08:16.990 as we knew from before.

NOTE Confidence: 0.8497792575

00:08:16.990 --> 00:08:19.640 So just taking a step back and L is a

NOTE Confidence: 0.8497792575

00:08:19.716 --> 00:08:22.800 genetically heterogeneous myeloid neoplasm,

NOTE Confidence: 0.8497792575

00:08:22.800 --> 00:08:25.452 and while the FAAB classification is

NOTE Confidence: 0.8497792575

00:08:25.452 --> 00:08:27.879 not employed in clinical use now,

NOTE Confidence: 0.8497792575

00:08:27.880 --> 00:08:30.974 it is still the most adherent to

NOTE Confidence: 0.8497792575

00:08:30.974 --> 00:08:32.300 myeloid differentiation status,

NOTE Confidence: 0.8497792575

00:08:32.300 --> 00:08:34.452 so you'll see that it still comes into

NOTE Confidence: 0.8497792575

00:08:34.452 --> 00:08:36.519 play in current research studies.

NOTE Confidence: 0.8497792575

00:08:36.520 --> 00:08:38.823 The overall poor 5 year old survival

NOTE Confidence: 0.8497792575

00:08:38.823 --> 00:08:41.173 for AML as well as the relapse

NOTE Confidence: 0.8497792575

00:08:41.173 --> 00:08:43.740 rate continue to be a huge problem.

NOTE Confidence: 0.9457947

00:08:45.840 --> 00:08:47.868 You can see that some improvements

NOTE Confidence: 0.9457947

00:08:47.868 --> 00:08:50.302 have been made in the last couple

NOTE Confidence: 0.9457947

00:08:50.302 --> 00:08:53.830 of decades as seen here in Black is

NOTE Confidence: 0.9457947

00:08:53.830 --> 00:08:57.260 2000 to 2006 and yellow is until

NOTE Confidence: 0.9457947

00:08:57.260 --> 00:09:00.396 2011 and blue is the most current.

NOTE Confidence: 0.9457947

00:09:00.400 --> 00:09:02.352 This is from a Danish study that I'm

NOTE Confidence: 0.9457947

00:09:02.352 --> 00:09:04.260 using because it's one of the most recent,

NOTE Confidence: 0.9457947

00:09:04.260 --> 00:09:06.300 but those published from the

NOTE Confidence: 0.9457947

00:09:06.300 --> 00:09:07.932 US show similar statistics.

NOTE Confidence: 0.9457947

00:09:07.940 --> 00:09:10.109 You can see that there is still a long

NOTE Confidence: 0.9457947

00:09:10.109 --> 00:09:12.592 way to go for patients over the age of 60.

NOTE Confidence: 0.870314763684211

00:09:15.510 --> 00:09:17.634 In broad strokes, some of the

00:09:17.634 --> 00:09:19.742 major AML subtypes are classified

00:09:19.742 --> 00:09:22.222 according to cytogenetic findings

00:09:22.222 --> 00:09:24.702 that include balanced translocations.

00:09:24.710 --> 00:09:26.612 Molecular findings also

00:09:26.612 --> 00:09:29.148 help in risk stratification.

00:09:29.150 --> 00:09:31.173 Older age remains one of the most

00:09:31.173 --> 00:09:33.048 major risk factors for poor outcome.

00:09:36.100 --> 00:09:38.305 The foundation of treatment for

00:09:38.305 --> 00:09:40.510 new AML is induction chemotherapy

00:09:40.580 --> 00:09:42.820 followed by either consolidation,

00:09:42.820 --> 00:09:45.200 chemo or consideration toward

00:09:45.200 --> 00:09:47.580 allogeneic stem cell transplant.

00:09:47.580 --> 00:09:49.704 Newer therapeutic options include

00:09:49.704 --> 00:09:52.620 small molecule inhibitors, and in 2018,

00:09:52.620 --> 00:09:54.820 BCL 2 inhibitor venetoclax was

NOTE Confidence: 0.862296337142857

00:09:54.820 --> 00:09:57.058 approved as a combo regimen,

NOTE Confidence: 0.862296337142857

00:09:57.060 --> 00:09:58.816 typically with hypomethylating agents,

NOTE Confidence: 0.862296337142857

00:09:58.816 --> 00:10:01.450 such as a deciding that does

NOTE Confidence: 0.862296337142857

00:10:01.523 --> 00:10:04.079 show great effect in older AML

NOTE Confidence: 0.862296337142857

00:10:04.079 --> 00:10:05.783 patients though durable remission.

NOTE Confidence: 0.862296337142857

00:10:05.790 --> 00:10:09.250 Is still difficult to obtain.

NOTE Confidence: 0.862296337142857

00:10:09.250 --> 00:10:11.200 So going back to our case,

NOTE Confidence: 0.862296337142857

00:10:11.200 --> 00:10:13.120 the problem is whether we can

NOTE Confidence: 0.862296337142857

00:10:13.120 --> 00:10:14.855 diagnose AML in this particular

NOTE Confidence: 0.862296337142857

00:10:14.855 --> 00:10:17.195 biopsy where you have some areas

NOTE Confidence: 0.862296337142857

00:10:17.195 --> 00:10:19.010 of maturation and some not,

NOTE Confidence: 0.862296337142857

00:10:19.010 --> 00:10:21.694 and a absent aspirate,

NOTE Confidence: 0.862296337142857

00:10:21.694 --> 00:10:25.830 not just bad aspirate and just to show you

NOTE Confidence: 0.862296337142857

00:10:25.830 --> 00:10:28.947 in cases where you do get a good asper smear.

NOTE Confidence: 0.862296337142857

00:10:28.950 --> 00:10:30.110 This is the gold standard.

NOTE Confidence: 0.862296337142857

00:10:30.110 --> 00:10:32.378 The gold standard is counting of 500

NOTE Confidence: 0.862296337142857

00:10:32.378 --> 00:10:34.780 cells in each patient to enumerate

NOTE Confidence: 0.862296337142857

00:10:34.780 --> 00:10:37.050 not just myeloblasts and monoblast,

NOTE Confidence: 0.862296337142857

00:10:37.050 --> 00:10:39.409 but in the case of monocytic leukemias.

NOTE Confidence: 0.862296337142857

00:10:39.410 --> 00:10:40.312 Pro monocytes,

NOTE Confidence: 0.862296337142857

00:10:40.312 --> 00:10:42.567 which are considered blast equivalents

NOTE Confidence: 0.862296337142857

00:10:42.567 --> 00:10:45.760 but not to include mature monocytes.

NOTE Confidence: 0.862296337142857

00:10:45.760 --> 00:10:49.621 So in this study in which they had 14

NOTE Confidence: 0.862296337142857

00:10:49.621 --> 00:10:51.320 hematopathologist do consensus counting

NOTE Confidence: 0.862296337142857

00:10:51.320 --> 00:10:55.200 of a number of cases on blood and aspirate.

NOTE Confidence: 0.862296337142857

00:10:55.200 --> 00:10:59.416 These two are mono blasts so clearly blasts.

NOTE Confidence: 0.862296337142857

00:10:59.420 --> 00:11:01.616 This one is the pro monocyte.

NOTE Confidence: 0.862296337142857

00:11:01.620 --> 00:11:04.536 So just a step towards maturation,

NOTE Confidence: 0.862296337142857

00:11:04.540 --> 00:11:06.820 but still a blast equivalent.

NOTE Confidence: 0.862296337142857

00:11:06.820 --> 00:11:09.688 And here is a mature monocyte.

NOTE Confidence: 0.862296337142857

00:11:09.690 --> 00:11:11.712 And of course they use the

NOTE Confidence: 0.862296337142857

00:11:11.712 --> 00:11:12.723 best picture presentation.

NOTE Confidence: 0.862296337142857

00:11:12.730 --> 00:11:15.110 This is in a peripheral blood and

NOTE Confidence: 0.862296337142857

00:11:15.110 --> 00:11:17.688 just to make the situation worse,

NOTE Confidence: 0.862296337142857

00:11:17.690 --> 00:11:19.850 CML is further stratified.

NOTE Confidence: 0.862296337142857

00:11:19.850 --> 00:11:23.709 So this is the chronic counterpart to AML

NOTE Confidence: 0.862296337142857

00:11:23.710 --> 00:11:26.209 is stratified further by this last county.

NOTE Confidence: 0.863308785555556

00:11:28.770 --> 00:11:31.392 And concordance can be very difficult

NOTE Confidence: 0.863308785555556

00:11:31.392 --> 00:11:34.288 to achieve even among these expert

NOTE Confidence: 0.863308785555556

00:11:34.288 --> 00:11:36.436 hematopathologist only getting 2

NOTE Confidence: 0.863308785555556

00:11:36.436 --> 00:11:40.006 consensus at 74% which just to be clear,

NOTE Confidence: 0.863308785555556

00:11:40.010 --> 00:11:42.560 I don't think is good concordance.

NOTE Confidence: 0.863308785555556

00:11:42.560 --> 00:11:45.194 When you're trying to get a

NOTE Confidence: 0.863308785555556

00:11:45.194 --> 00:11:47.390 patient into chemo for AML.

NOTE Confidence: 0.863308785555556

00:11:47.390 --> 00:11:49.016 So the challenge is that even

NOTE Confidence: 0.863308785555556

00:11:49.016 --> 00:11:50.650 in the best possible scenario,

NOTE Confidence: 0.863308785555556

00:11:50.650 --> 00:11:52.234 like an excellent aspirant,

NOTE Confidence: 0.863308785555556

00:11:52.234 --> 00:11:55.215 the counting of Mono City lost equivalents

NOTE Confidence: 0.863308785555556

00:11:55.215 --> 00:11:57.890 is riddled with reliability issues,

NOTE Confidence: 0.863308785555556

00:11:57.890 --> 00:11:59.260 good as spirits are harder

NOTE Confidence: 0.863308785555556

00:11:59.260 --> 00:12:00.630 and harder to come by.

NOTE Confidence: 0.863308785555556

00:12:00.630 --> 00:12:03.336 This is something that when I

NOTE Confidence: 0.863308785555556

00:12:03.336 --> 00:12:05.655 talk to senior hematologist they

NOTE Confidence: 0.863308785555556

00:12:05.655 --> 00:12:07.585 really feel in their bones that

NOTE Confidence: 0.863308785555556

00:12:07.585 --> 00:12:09.749 it has become like a lost art,

NOTE Confidence: 0.863308785555556

00:12:09.750 --> 00:12:11.598 very difficult to get good aspirates.

NOTE Confidence: 0.863308785555556

00:12:11.600 --> 00:12:14.507 I'm on service this week and Cohen and I

NOTE Confidence: 0.863308785555556

00:12:14.507 --> 00:12:17.487 were guessing that about three of our 20.

NOTE Confidence: 0.863308785555556

00:12:17.490 --> 00:12:22.110 Last day or so we're good aspirates.

NOTE Confidence: 0.863308785555556

00:12:22.110 --> 00:12:23.825 Some of it is due to treatment.

NOTE Confidence: 0.863308785555556

00:12:23.830 --> 00:12:26.490 The newer treatments can lead to fibrosis.

NOTE Confidence: 0.863308785555556

00:12:26.490 --> 00:12:28.906 There are procedural issues.

NOTE Confidence: 0.863308785555556

00:12:28.906 --> 00:12:32.030 There's going towards IR which may not be.

NOTE Confidence: 0.863308785555556

00:12:32.030 --> 00:12:32.824 You know,

NOTE Confidence: 0.863308785555556

00:12:32.824 --> 00:12:35.603 as invested in looking at the aspirates

NOTE Confidence: 0.863308785555556

00:12:35.603 --> 00:12:38.284 later and there is no reliable

NOTE Confidence: 0.863308785555556

00:12:38.284 --> 00:12:40.489 monoblast marker on biopsy material.

NOTE Confidence: 0.863308785555556

00:12:40.490 --> 00:12:43.162 So just to keep in mind that aspirate

NOTE Confidence: 0.863308785555556

00:12:43.162 --> 00:12:45.298 where that material comes from is

NOTE Confidence: 0.863308785555556

00:12:45.298 --> 00:12:47.740 the same tube that the flow and.

NOTE Confidence: 0.863308785555556

00:12:47.740 --> 00:12:49.168 Heterogenetic S are deriving

NOTE Confidence: 0.863308785555556

00:12:49.168 --> 00:12:51.685 their specimen from so it kind of

NOTE Confidence: 0.863308785555556

00:12:51.685 --> 00:12:53.245 hurts us on multiple levels,

NOTE Confidence: 0.863308785555556

00:12:53.250 --> 00:12:55.038 but the core biopsy remains good.

NOTE Confidence: 0.863308785555556

00:12:55.040 --> 00:12:56.979 The core biopsy is still coming from

NOTE Confidence: 0.863308785555556

00:12:56.979 --> 00:12:59.204 that same jump shooting needle and

NOTE Confidence: 0.863308785555556

00:12:59.204 --> 00:13:01.774 it can add additional information

NOTE Confidence: 0.863308785555556

00:13:01.774 --> 00:13:05.262 beyond the aspirate in terms of

NOTE Confidence: 0.863308785555556

00:13:05.262 --> 00:13:07.269 architecture and localization.

NOTE Confidence: 0.863308785555556

00:13:07.270 --> 00:13:08.677 This is what I like to call

NOTE Confidence: 0.863308785555556

00:13:08.677 --> 00:13:10.010 the tree of myeloid life.

NOTE Confidence: 0.863308785555556

00:13:10.010 --> 00:13:12.584 So we start here with the

NOTE Confidence: 0.863308785555556

00:13:12.584 --> 00:13:14.883 hematopoietic stem cell going towards

NOTE Confidence: 0.863308785555556

00:13:14.883 --> 00:13:17.373 myeloid progenitors that then go

NOTE Confidence: 0.863308785555556

00:13:17.373 --> 00:13:20.050 toward GMP becoming granulocytes

NOTE Confidence: 0.863308785555556

00:13:20.050 --> 00:13:24.250 or monos and dendritic cells.

NOTE Confidence: 0.863308785555556

00:13:24.250 --> 00:13:26.470 So just in case you're wondering

NOTE Confidence: 0.863308785555556

00:13:26.470 --> 00:13:28.570 about mono markers in general,

NOTE Confidence: 0.863308785555556

00:13:28.570 --> 00:13:31.405 we do have a lot of sorry.

NOTE Confidence: 0.863308785555556

00:13:31.410 --> 00:13:34.152 A lot of immunostains and flow

NOTE Confidence: 0.863308785555556

00:13:34.152 --> 00:13:36.920 markers like these that will mark.

NOTE Confidence: 0.863308785555556

00:13:36.920 --> 00:13:41.636 All of these mono lineage cells,

NOTE Confidence: 0.863308785555556

00:13:41.640 --> 00:13:44.650 but they do not differentiate

NOTE Confidence: 0.863308785555556

00:13:44.650 --> 00:13:47.058 between blast versus mature.

NOTE Confidence: 0.863308785555556

00:13:47.060 --> 00:13:48.276 On the other hand,

NOTE Confidence: 0.863308785555556

00:13:48.276 --> 00:13:50.904 CD 34 is a great marker for glass

NOTE Confidence: 0.863308785555556

00:13:50.904 --> 00:13:52.714 that are positive for it,

NOTE Confidence: 0.863308785555556

00:13:52.720 --> 00:13:55.499 so the granular acidic glass are positive

NOTE Confidence: 0.863308785555556

00:13:55.499 --> 00:13:58.558 for CD34 whereas the granulocytes are not.

NOTE Confidence: 0.863308785555556

00:13:58.560 --> 00:14:01.248 So what we're looking for is something here.

NOTE Confidence: 0.9566488

00:14:04.920 --> 00:14:08.398 OK. Is there something with the sound

NOTE Confidence: 0.78706251

00:14:08.920 --> 00:14:10.468 ohh you're good now,

NOTE Confidence: 0.93971398375

00:14:10.640 --> 00:14:15.288 OK? So we went on the hunt for.

NOTE Confidence: 0.93971398375

00:14:15.290 --> 00:14:18.315 A phenotype. That is strongly

NOTE Confidence: 0.93971398375

00:14:18.315 --> 00:14:21.340 strongly expressed by mono precursors,

NOTE Confidence: 0.93971398375

00:14:21.340 --> 00:14:24.118 but not expressed in later stages,

NOTE Confidence: 0.93971398375

00:14:24.120 --> 00:14:26.878 and in this older study using human

NOTE Confidence: 0.93971398375

00:14:26.878 --> 00:14:29.258 umbilical cord blood and bone marrow,

NOTE Confidence: 0.93971398375

00:14:29.260 --> 00:14:32.390 they were able to fractionate

NOTE Confidence: 0.93971398375

00:14:32.390 --> 00:14:34.894 GMP into four subpopulations.

NOTE Confidence: 0.93971398375

00:14:34.900 --> 00:14:37.984 Human common monocyte progenitors are one

NOTE Confidence: 0.93971398375

00:14:37.984 --> 00:14:41.546 of the subpopulations here that do not

NOTE Confidence: 0.93971398375

00:14:41.546 --> 00:14:43.926 show any potential for differentiating

NOTE Confidence: 0.93971398375

00:14:43.926 --> 00:14:46.318 into myeloid or lymphoid cells,

NOTE Confidence: 0.93971398375

00:14:46.320 --> 00:14:47.562 and according to.

NOTE Confidence: 0.93971398375

00:14:47.562 --> 00:14:50.046 Gene expression profiling I of eight

NOTE Confidence: 0.93971398375

00:14:50.046 --> 00:14:52.725 here seems to show the features that

NOTE Confidence: 0.93971398375

00:14:52.725 --> 00:14:55.599 we're looking for in terms of being

NOTE Confidence: 0.93971398375

00:14:55.599 --> 00:14:57.834 expressed in early mono progenitors,

NOTE Confidence: 0.93971398375

00:14:57.840 --> 00:15:00.558 but not in their later stages.

NOTE Confidence: 0.93971398375

00:15:00.560 --> 00:15:03.720 We also considered an R481,

NOTE Confidence: 0.93971398375

00:15:03.720 --> 00:15:06.594 but didn't have as much supporting

NOTE Confidence: 0.93971398375

00:15:06.594 --> 00:15:08.510 data in the literature.

NOTE Confidence: 0.93971398375

00:15:08.510 --> 00:15:10.496 Fire Eight was also a great

NOTE Confidence: 0.93971398375

00:15:10.496 --> 00:15:12.770 candidate for us because there was

NOTE Confidence: 0.93971398375

00:15:12.770 --> 00:15:14.530 a commercially available antibody

NOTE Confidence: 0.93971398375

00:15:14.530 --> 00:15:16.290 for purchase and testing.

NOTE Confidence: 0.93971398375

00:15:16.290 --> 00:15:18.355 Some of you might say to yourself,

NOTE Confidence: 0.93971398375

00:15:18.360 --> 00:15:21.896 wait, I just heard about IRV for some

NOTE Confidence: 0.93971398375

00:15:21.896 --> 00:15:24.782 reason and you did last week when

NOTE Confidence: 0.93971398375

00:15:24.782 --> 00:15:26.842 we had Lee Grimes from Cincinnati.

NOTE Confidence: 0.93971398375

00:15:26.842 --> 00:15:29.693 Come and talk to us about his work

NOTE Confidence: 0.93971398375

00:15:29.693 --> 00:15:31.397 in severe congenital neutropenia.

NOTE Confidence: 0.93971398375

00:15:31.400 --> 00:15:34.600 He actually used IRF 8 in his recent

NOTE Confidence: 0.93971398375

00:15:34.600 --> 00:15:37.652 studies as a negative control in

NOTE Confidence: 0.93971398375

00:15:37.652 --> 00:15:40.140 the balance between granulocyte

NOTE Confidence: 0.93971398375

00:15:40.140 --> 00:15:42.006 and monocyte differentiation.

NOTE Confidence: 0.93971398375

00:15:42.010 --> 00:15:44.202 If I that paper actually came out later

NOTE Confidence: 0.93971398375

00:15:44.202 --> 00:15:46.547 than when we proceeded down this pathway.

NOTE Confidence: 0.93971398375

23

00:15:46.550 --> 00:15:48.512 But if we had seen it at that time,

NOTE Confidence: 0.93971398375

00:15:48.520 --> 00:15:50.736 I think it would have given us further

NOTE Confidence: 0.93971398375

00:15:50.736 --> 00:15:52.420 support to pursue this marker.

NOTE Confidence: 0.739135859

00:15:54.970 --> 00:15:57.646 So RV is a master transcriptional

NOTE Confidence: 0.739135859

00:15:57.646 --> 00:15:59.430 regulator of monocyte development,

NOTE Confidence: 0.739135859

00:15:59.430 --> 00:16:01.395 and it regulates monocyte differentiation

NOTE Confidence: 0.739135859

00:16:01.395 --> 00:16:04.107 genes that we know about is strongly

NOTE Confidence: 0.739135859

00:16:04.107 --> 00:16:05.807 induced by interferon gamma in

NOTE Confidence: 0.739135859

00:16:05.807 --> 00:16:08.073 the setting of infection and its

NOTE Confidence: 0.739135859

00:16:08.073 --> 00:16:10.048 first expressed after that comment.

NOTE Confidence: 0.739135859

00:16:10.050 --> 00:16:12.118 Granulocyte monocyte progenitor stage.

NOTE Confidence: 0.739135859

00:16:12.118 --> 00:16:15.691 Its expression is maintained at much lower

NOTE Confidence: 0.739135859

00:16:15.691 --> 00:16:18.463 levels in monos Max and dendritic cells,

NOTE Confidence: 0.739135859

00:16:18.470 --> 00:16:20.434 but not in neutrophils.

NOTE Confidence: 0.739135859

00:16:20.434 --> 00:16:22.889 It promotes apoptosis via activation

NOTE Confidence: 0.739135859

00:16:22.889 --> 00:16:25.338 of facts and repression of.

NOTE Confidence: 0.739135859

00:16:25.340 --> 00:16:28.550 CL2 and ECL Excel and loss of IRA in mice

NOTE Confidence: 0.739135859

00:16:28.637 --> 00:16:31.619 leads to an expansion of granulocytes,

NOTE Confidence: 0.739135859

00:16:31.620 --> 00:16:32.760 decreased monos,

NOTE Confidence: 0.739135859

00:16:32.760 --> 00:16:36.545 decreased's and a CML like picture and

NOTE Confidence: 0.739135859

00:16:36.545 --> 00:16:39.100 in fact overexpression of IR of eight

NOTE Confidence: 0.739135859

00:16:39.100 --> 00:16:41.859 inhibits BCR 8 ball driven leukemogenesis.

NOTE Confidence: 0.739135859

00:16:41.860 --> 00:16:44.165 It's transcripts are greatly reduced

NOTE Confidence: 0.739135859

00:16:44.165 --> 00:16:47.532 and CML patients and it's so far acts

NOTE Confidence: 0.739135859

00:16:47.532 --> 00:16:50.200 as a tumor suppressor in mouse a PML.

NOTE Confidence: 0.739135859

00:16:50.200 --> 00:16:52.671 So you might wonder what prompted me

NOTE Confidence: 0.739135859

00:16:52.671 --> 00:16:55.618 to look at this marker in an acute.

NOTE Confidence: 0.739135859

00:16:55.620 --> 00:16:59.679 Leukemia and I have to say at that time.

NOTE Confidence: 0.739135859

00:16:59.680 --> 00:17:01.376 I just really want to test it out.

NOTE Confidence: 0.739135859

00:17:01.380 --> 00:17:05.136 Given the earlier gene expression data,

NOTE Confidence: 0.739135859

00:17:05.140 --> 00:17:08.164 even though there was not much known

NOTE Confidence: 0.739135859

00:17:08.164 --> 00:17:11.380 about it acting as an oncogene in AML,

NOTE Confidence: 0.739135859

00:17:11.380 --> 00:17:13.200 and in fact it was the reverse,

NOTE Confidence: 0.739135859

00:17:13.200 --> 00:17:15.438 but later studies did show that

NOTE Confidence: 0.739135859

00:17:15.438 --> 00:17:17.520 it was a good hunch.

NOTE Confidence: 0.739135859

00:17:17.520 --> 00:17:20.913 So we started doing this validation

NOTE Confidence: 0.739135859

00:17:20.913 --> 00:17:24.078 on a cornucopia of tissues.

NOTE Confidence: 0.739135859

00:17:24.080 --> 00:17:26.450 This is susmita adapala who actually

NOTE Confidence: 0.739135859

00:17:26.450 --> 00:17:28.436 had done Hurricane Path Fellowship

NOTE Confidence: 0.739135859

00:17:28.436 --> 00:17:31.124 before she came to Yale to be a

NOTE Confidence: 0.739135859

00:17:31.124 --> 00:17:33.237 research fellow with us for a year,

NOTE Confidence: 0.739135859

00:17:33.240 --> 00:17:36.360 and she is now a hematopathologist at LJ,

NOTE Confidence: 0.739135859

00:17:36.360 --> 00:17:37.503 so she did.

NOTE Confidence: 0.739135859

00:17:37.503 --> 00:17:39.789 The scouring of literature for this

NOTE Confidence: 0.739135859

00:17:39.789 --> 00:17:42.123 gene expression profile and helped

NOTE Confidence: 0.739135859

00:17:42.123 --> 00:17:44.937 me get started on this validation.

NOTE Confidence: 0.739135859

00:17:44.940 --> 00:17:47.460 You can see that our of eight.

NOTE Confidence: 0.739135859

00:17:47.460 --> 00:17:49.693 Does in fact stain B cells in

NOTE Confidence: 0.739135859

00:17:49.693 --> 00:17:51.457 follicles in their mantle zone

NOTE Confidence: 0.739135859

00:17:51.457 --> 00:17:53.307 and in the germinal center.

NOTE Confidence: 0.739135859

00:17:53.310 --> 00:17:55.478 This is myeloid sarcoma.

NOTE Confidence: 0.739135859

00:17:55.478 --> 00:17:59.885 In soft tissue it stains the tumor cells

NOTE Confidence: 0.739135859

00:17:59.885 --> 00:18:03.840 and it is negative in this carcinoma,

NOTE Confidence: 0.739135859

00:18:03.840 --> 00:18:06.143 but you can see in the background

NOTE Confidence: 0.739135859

00:18:06.143 --> 00:18:08.389 stroma here that there are granular

NOTE Confidence: 0.739135859

00:18:08.389 --> 00:18:10.759 sites and there are histiocytes and

NOTE Confidence: 0.739135859

00:18:10.759 --> 00:18:13.135 those did not stand for our marker.

NOTE Confidence: 0.739135859

00:18:13.140 --> 00:18:16.173 So then I went ahead and pulled some of

NOTE Confidence: 0.739135859

00:18:16.173 --> 00:18:18.778 our decalcified core bone marrow because

NOTE Confidence: 0.739135859

00:18:18.778 --> 00:18:22.778 we want to use this on decalcified tissue.

NOTE Confidence: 0.739135859

00:18:22.780 --> 00:18:24.999 This is what we get most often

NOTE Confidence: 0.739135859

00:18:24.999 --> 00:18:27.703 and here the blast counting is by

NOTE Confidence: 0.739135859

00:18:27.703 --> 00:18:29.793 the aspirate or gold standard.

NOTE Confidence: 0.739135859

00:18:29.800 --> 00:18:32.236 So here is an initial diagnosis.

NOTE Confidence: 0.739135859

00:18:32.240 --> 00:18:34.440 Am OL monocytic leukemia at

NOTE Confidence: 0.739135859

00:18:34.440 --> 00:18:36.103 more than 90% blast.

NOTE Confidence: 0.739135859

00:18:36.103 --> 00:18:38.161 Here is a normal staging bone

NOTE Confidence: 0.739135859

00:18:38.161 --> 00:18:39.966 marrow for Hodgkin lymphoma that

NOTE Confidence: 0.739135859

00:18:39.966 --> 00:18:43.480 was not involved and a residual.

NOTE Confidence: 0.739135859

00:18:43.480 --> 00:18:46.567 Disease or residual for AML at 10%

NOTE Confidence: 0.739135859

00:18:46.570 --> 00:18:48.936 loss in the aspirate and here is

NOTE Confidence: 0.739135859

00:18:48.936 --> 00:18:50.788 1 at morphologic remission defined

NOTE Confidence: 0.739135859

00:18:50.788 --> 00:18:53.950 by less than 5% less.

NOTE Confidence: 0.739135859

00:18:53.950 --> 00:18:56.530 So then we pulled our whole

NOTE Confidence: 0.739135859

00:18:56.530 --> 00:18:58.650 cohort of 90 am OL.

NOTE Confidence: 0.739135859

00:18:58.650 --> 00:19:01.350 That included remission residual somewhere

NOTE Confidence: 0.739135859

00:19:01.350 --> 00:19:05.552 in between and also a smaller cohort

NOTE Confidence: 0.739135859

00:19:05.552 --> 00:19:08.368 of chronic myelomonocytic leukemia.

NOTE Confidence: 0.739135859

00:19:08.370 --> 00:19:09.714 Other AML.

NOTE Confidence: 0.739135859

00:19:09.714 --> 00:19:14.782 So ammo's not monocytic and normal for the

NOTE Confidence: 0.739135859

00:19:14.782 --> 00:19:17.706 normal control bone marrows we enriched.

NOTE Confidence: 0.739135859

00:19:17.706 --> 00:19:20.702 For the ones that had monocytosis in

NOTE Confidence: 0.739135859

00:19:20.702 --> 00:19:23.806 the peripheral blood from 10 to 30%.

NOTE Confidence: 0.739135859

00:19:23.810 --> 00:19:29.620 And you can see that. This.

NOTE Confidence: 0.739135859

00:19:29.620 --> 00:19:31.168 The different diagnosis they

NOTE Confidence: 0.739135859

00:19:31.168 --> 00:19:32.716 actually had the CBC,

NOTE Confidence: 0.8698511955

00:19:32.720 --> 00:19:34.552 a presentation, treatment protocols

NOTE Confidence: 0.8698511955

00:19:34.552 --> 00:19:36.842 and outcomes that were compatible

NOTE Confidence: 0.8698511955

00:19:36.842 --> 00:19:39.093 with what you would expect to

NOTE Confidence: 0.8698511955

00:19:39.093 --> 00:19:40.823 find for each disease category.

NOTE Confidence: 0.840351166

00:19:43.550 --> 00:19:47.114 The NGS showed that the tumors

NOTE Confidence: 0.840351166

00:19:47.114 --> 00:19:49.490 had typical molecular features,

NOTE Confidence: 0.840351166

00:19:49.490 --> 00:19:53.090 about half the leukemias had NPM 1 mutations

NOTE Confidence: 0.840351166

00:19:53.090 --> 00:19:56.236 and close to a third had FLIT 3 ITD.

NOTE Confidence: 0.840351166

00:19:56.240 --> 00:19:58.658 You can also see that for

NOTE Confidence: 0.840351166

00:19:58.658 --> 00:19:59.867 the monocytic leukemias,

NOTE Confidence: 0.840351166

00:19:59.870 --> 00:20:02.600 whether they're chronic or acute,

NOTE Confidence: 0.840351166

00:20:02.600 --> 00:20:04.826 that they were enriched for SRSF,

NOTE Confidence: 0.840351166

00:20:04.830 --> 00:20:06.330 2 pathogenic variants,

NOTE Confidence: 0.840351166

00:20:06.330 --> 00:20:08.400 and of course, tattoo.

NOTE Confidence: 0.8664532

00:20:11.140 --> 00:20:12.898 Two practicing hematopathologist counted

NOTE Confidence: 0.8664532

00:20:12.898 --> 00:20:16.300 the stain on core biopsies and these

NOTE Confidence: 0.8664532

00:20:16.367 --> 00:20:19.069 are plotted here for each biopsy with

NOTE Confidence: 0.8664532

00:20:19.069 --> 00:20:21.759 correlation to their aspirate blast counts.

NOTE Confidence: 0.8664532

00:20:21.760 --> 00:20:24.287 Sam Katz really gets all the credit

NOTE Confidence: 0.8664532

00:20:24.287 --> 00:20:26.566 here for prompting me to do this

NOTE Confidence: 0.8664532

00:20:26.566 --> 00:20:28.308 project in the 1st place because

NOTE Confidence: 0.8664532

00:20:28.308 --> 00:20:30.932 if you don't know him well by now,

NOTE Confidence: 0.8664532

00:20:30.940 --> 00:20:33.898 he is a very eloquent complainer.

NOTE Confidence: 0.8664532

00:20:33.900 --> 00:20:36.780 And so while some people might just say,

NOTE Confidence: 0.8664532

00:20:36.780 --> 00:20:38.996 oh, I don't like to count 500 cells

NOTE Confidence: 0.8664532

00:20:38.996 --> 00:20:41.040 or this aspirin is really bad.

NOTE Confidence: 0.8664532

00:20:41.040 --> 00:20:45.176 He really hones down on the problem here

NOTE Confidence: 0.8664532

00:20:45.176 --> 00:20:49.956 and compelled me to go upon this search.

NOTE Confidence: 0.8664532

00:20:49.960 --> 00:20:53.101 So as you might know about what they say

NOTE Confidence: 0.8664532

00:20:53.101 --> 00:20:55.960 about good deeds not going unpunished,

NOTE Confidence: 0.8664532

00:20:55.960 --> 00:20:57.976 he had to be roped into the

NOTE Confidence: 0.8664532

00:20:57.976 --> 00:20:58.840 validation as well.

NOTE Confidence: 0.8664532

00:20:58.840 --> 00:21:01.300 So this was done independently

NOTE Confidence: 0.8664532

00:21:01.300 --> 00:21:03.760 with disregard for their diagnosis,

NOTE Confidence: 0.8664532

00:21:03.760 --> 00:21:08.149 and we achieved a pretty good correlation.

NOTE Confidence: 0.8664532

00:21:08.150 --> 00:21:11.230 This was the diagnostic test

NOTE Confidence: 0.8664532

00:21:11.230 --> 00:21:13.116 characteristics using aspera count

NOTE Confidence: 0.8664532

00:21:13.116 --> 00:21:15.648 as the surrogate for disease status,

NOTE Confidence: 0.8664532

00:21:15.650 --> 00:21:18.772 so AML being 20% plus or higher

NOTE Confidence: 0.8664532

00:21:18.772 --> 00:21:21.540 residual disease being 5% plus or

NOTE Confidence: 0.8664532

00:21:21.540 --> 00:21:25.080 higher and negative or residual being

NOTE Confidence: 0.8664532

00:21:25.080 --> 00:21:29.710 less than 5% as compared to IR 8 IHC

NOTE Confidence: 0.8664532

00:21:29.710 --> 00:21:32.910 result due to a reviewer question.

NOTE Confidence: 0.8664532

00:21:32.910 --> 00:21:35.143 We actually went back and did the

NOTE Confidence: 0.8664532

00:21:35.143 --> 00:21:37.733 same with CD 34 because we actually

NOTE Confidence: 0.8664532

00:21:37.733 --> 00:21:40.067 didn't know how well we're doing.

NOTE Confidence: 0.8664532

00:21:40.070 --> 00:21:40.396 CD34,

NOTE Confidence: 0.8664532

00:21:40.396 --> 00:21:42.352 as opposed to our aspirate blast

NOTE Confidence: 0.8664532

00:21:42.352 --> 00:21:44.118 count in the granulocytic leukemia

NOTE Confidence: 0.8664532

00:21:44.118 --> 00:21:46.624 and we did not actually get to

NOTE Confidence: 0.8664532

00:21:46.624 --> 00:21:47.910 the same good correlation.

NOTE Confidence: 0.8664532

00:21:47.910 --> 00:21:49.110 It was still good,

NOTE Confidence: 0.8664532

00:21:49.110 --> 00:21:51.082 but it was not quite at .8

NOTE Confidence: 0.8664532

00:21:51.082 --> 00:21:53.194 which we had for IR 8.

NOTE Confidence: 0.734265515714286

00:21:55.750 --> 00:21:59.026 And this is the correlation for CML,

NOTE Confidence: 0.734265515714286

00:21:59.030 --> 00:22:00.480 which is not as strong.

NOTE Confidence: 0.734265515714286

00:22:00.480 --> 00:22:04.190 But we also had a smaller cohort for CML.

NOTE Confidence: 0.734265515714286

00:22:04.190 --> 00:22:07.710 One of the reasons that CML cases might

NOTE Confidence: 0.734265515714286

00:22:07.802 --> 00:22:10.806 be especially difficult I believe,

NOTE Confidence: 0.734265515714286

00:22:10.806 --> 00:22:12.150 is that occasionally,

NOTE Confidence: 0.734265515714286

00:22:12.150 --> 00:22:15.474 as with our first case that I showed there

NOTE Confidence: 0.734265515714286

00:22:15.474 --> 00:22:18.022 is focal elevation of glass which may

NOTE Confidence: 0.734265515714286

00:22:18.022 --> 00:22:21.310 not be well represented on aspirin smear,

NOTE Confidence: 0.734265515714286

00:22:21.310 --> 00:22:23.590 because, as you might know,

NOTE Confidence: 0.734265515714286

00:22:23.590 --> 00:22:25.846 for aspirus you're really kind of sucking it.

NOTE Confidence: 0.734265515714286

00:22:25.850 --> 00:22:28.080 Thought from one specific point.

NOTE Confidence: 0.734265515714286

00:22:28.080 --> 00:22:30.078 So here is an interesting biopsy.

NOTE Confidence: 0.734265515714286

00:22:30.080 --> 00:22:32.420 We had a few years ago where you can

NOTE Confidence: 0.734265515714286

00:22:32.420 --> 00:22:35.244 see even on low power that this corner

NOTE Confidence: 0.734265515714286

00:22:35.244 --> 00:22:37.360 here looks different from this part.

NOTE Confidence: 0.734265515714286

00:22:37.360 --> 00:22:39.817 So most of the bone marrow showed

NOTE Confidence: 0.734265515714286

00:22:39.820 --> 00:22:42.316 as in the upper part maturing

NOTE Confidence: 0.734265515714286

00:22:42.316 --> 00:22:43.980 trilineage amount of polices.

NOTE Confidence: 0.734265515714286

00:22:43.980 --> 00:22:45.900 Some increase in boss because

NOTE Confidence: 0.734265515714286

00:22:45.900 --> 00:22:47.820 this person also had CML.

NOTE Confidence: 0.734265515714286

00:22:47.820 --> 00:22:49.830 That was a little bit elevated

NOTE Confidence: 0.734265515714286

00:22:49.830 --> 00:22:51.679 like CML one or CM L2,

NOTE Confidence: 0.734265515714286

00:22:51.680 --> 00:22:54.242 but then the lower right hand corner

NOTE Confidence: 0.734265515714286

00:22:54.242 --> 00:22:56.490 actually had a sheet of glass.

NOTE Confidence: 0.734265515714286

00:22:56.490 --> 00:22:58.590 As represented in E here and when

NOTE Confidence: 0.734265515714286

00:22:58.590 --> 00:23:01.377 we did our of eight you can see

NOTE Confidence: 0.734265515714286

00:23:01.377 --> 00:23:03.187 how dramatic this transition is.

NOTE Confidence: 0.734265515714286

00:23:03.190 --> 00:23:05.866 Almost like a solid tumor malignancy.

NOTE Confidence: 0.912389138888889

00:23:08.960 --> 00:23:11.756 I also get asked whether the

NOTE Confidence: 0.912389138888889

00:23:11.756 --> 00:23:13.154 macrophages are positive,

34

NOTE Confidence: 0.912389138888889

00:23:13.160 --> 00:23:14.788 and I think not.

NOTE Confidence: 0.912389138888889

00:23:14.788 --> 00:23:17.970 This is a AML that is not

NOTE Confidence: 0.912389138888889

00:23:17.970 --> 00:23:21.095 monocytic with a federal flage.

NOTE Confidence: 0.912389138888889

00:23:21.100 --> 00:23:23.206 Here this is a monocytic leukemia

NOTE Confidence: 0.912389138888889

00:23:23.206 --> 00:23:25.343 at initial diagnosis and this is

NOTE Confidence: 0.912389138888889

00:23:25.343 --> 00:23:27.341 one of our staging bone marrow

NOTE Confidence: 0.912389138888889

00:23:27.341 --> 00:23:29.183 biopsies showing a Cidra page here

NOTE Confidence: 0.912389138888889

00:23:29.183 --> 00:23:33.260 and they were negative for a marker.

NOTE Confidence: 0.912389138888889

00:23:33.260 --> 00:23:35.440 There were discrepancies in

NOTE Confidence: 0.912389138888889

00:23:35.440 --> 00:23:37.075 assessing residual disease,

NOTE Confidence: 0.912389138888889

00:23:37.080 --> 00:23:40.804 so 10 cases showed a discrepancy defined

NOTE Confidence: 0.912389138888889

00:23:40.804 --> 00:23:44.360 at where aspirate had less than 5% loss.

NOTE Confidence: 0.912389138888889

00:23:44.360 --> 00:23:46.360 But IRA expression was

NOTE Confidence: 0.912389138888889

00:23:46.360 --> 00:23:48.860 just a little above 5%,

NOTE Confidence: 0.912389138888889

00:23:48.860 --> 00:23:51.434 so three of these actually had

NOTE Confidence: 0.912389138888889

00:23:51.434 --> 00:23:53.752 definitive evidence of disease by

NOTE Confidence: 0.912389138888889

00:23:53.752 --> 00:23:55.852 cytogenetics as unbalanced translocations

NOTE Confidence: 0.912389138888889

00:23:55.852 --> 00:23:59.520 flit 3 ITD or MPM 1 mutations,

NOTE Confidence: 0.912389138888889

00:23:59.520 --> 00:24:01.385 and three have clinical relapse

NOTE Confidence: 0.912389138888889

00:24:01.385 --> 00:24:03.790 within two months of the biopsy.

NOTE Confidence: 0.912389138888889

00:24:03.790 --> 00:24:05.566 So I just want to point out here

NOTE Confidence: 0.912389138888889

00:24:05.566 --> 00:24:06.995 that our whole correlation our

NOTE Confidence: 0.912389138888889

00:24:06.995 --> 00:24:08.849 ground truth in this study has

NOTE Confidence: 0.912389138888889

00:24:08.849 --> 00:24:10.570 been the aspirate blast count.

NOTE Confidence: 0.912389138888889

00:24:10.570 --> 00:24:12.530 But that as we know,

NOTE Confidence: 0.912389138888889

00:24:12.530 --> 00:24:14.786 as pathologist is just another sample.

NOTE Confidence: 0.912389138888889

00:24:14.790 --> 00:24:17.390 It's a different sample from the core biopsy.

NOTE Confidence: 0.912389138888889

00:24:17.390 --> 00:24:19.826 So what is really the truth?

NOTE Confidence: 0.912389138888889

00:24:19.830 --> 00:24:21.906 Maybe it is the clinical behavior.

NOTE Confidence: 0.912389138888889

00:24:21.910 --> 00:24:24.164 Maybe it is genetics or molecular and

NOTE Confidence: 0.912389138888889

00:24:24.164 --> 00:24:26.755 and I think that that correlation comes

NOTE Confidence: 0.912389138888889

00:24:26.755 --> 00:24:30.009 into play when we're looking at a new marker.

NOTE Confidence: 0.912389138888889

00:24:30.010 --> 00:24:31.880 One had flow elevation of

NOTE Confidence: 0.912389138888889

00:24:31.880 --> 00:24:33.376 human tacones above 10%.

NOTE Confidence: 0.912389138888889

00:24:33.380 --> 00:24:35.440 Which pumped in me to go on a search for

NOTE Confidence: 0.912389138888889

00:24:35.497 --> 00:24:37.814 all the biopsies that had increased humidity.

NOTE Confidence: 0.912389138888889

00:24:37.820 --> 00:24:39.548 Phones, hard to find,

NOTE Confidence: 0.912389138888889

00:24:39.548 --> 00:24:41.276 but they're they are.

NOTE Confidence: 0.912389138888889

00:24:41.280 --> 00:24:42.465 IRA dusting hematogenous,

NOTE Confidence: 0.912389138888889

00:24:42.465 --> 00:24:44.835 so that could be a pitfall.

NOTE Confidence: 0.912389138888889

00:24:44.840 --> 00:24:47.934 In the rare case where you had

NOTE Confidence: 0.912389138888889

00:24:47.934 --> 00:24:49.598 really significant elevation by

NOTE Confidence: 0.912389138888889

00:24:49.598 --> 00:24:52.272 flow and then we had two remaining

NOTE Confidence: 0.912389138888889

00:24:52.272 --> 00:24:54.160 discrepancies of overcount by IR.

NOTE Confidence: 0.912389138888889

00:24:54.160 --> 00:24:56.440 RF eight as compared to aspirate

NOTE Confidence: 0.912389138888889

00:24:56.440 --> 00:24:58.780 at a low percentage blast,

NOTE Confidence: 0.912389138888889

37

00:24:58.780 --> 00:25:01.132 one did show RA expression that was

NOTE Confidence: 0.912389138888889

00:25:01.132 --> 00:25:03.490 lower than the aspire blast count.

NOTE Confidence: 0.912389138888889

00:25:03.490 --> 00:25:05.041 But upon evaluation,

NOTE Confidence: 0.912389138888889

00:25:05.041 --> 00:25:07.109 the core biopsy showed

NOTE Confidence: 0.912389138888889

00:25:07.109 --> 00:25:08.660 substantial aspiration artifact,

NOTE Confidence: 0.912389138888889

00:25:08.660 --> 00:25:10.610 so perhaps it should have been

NOTE Confidence: 0.912389138888889

00:25:10.610 --> 00:25:12.350 excluded in the first place.

NOTE Confidence: 0.912389138888889

00:25:12.350 --> 00:25:13.810 So, excluding the above cases,

NOTE Confidence: 0.912389138888889

00:25:13.810 --> 00:25:15.420 where disease was still present,

NOTE Confidence: 0.912389138888889

00:25:15.420 --> 00:25:18.698 the overall discrepancy was 3% with

NOTE Confidence: 0.912389138888889

00:25:18.698 --> 00:25:21.938 regard to residual disease assessment.

NOTE Confidence: 0.912389138888889

00:25:21.940 --> 00:25:23.044 So in conclusion,

NOTE Confidence: 0.912389138888889

00:25:23.044 --> 00:25:26.090 in Almal there is high correlation of IRV

NOTE Confidence: 0.912389138888889

00:25:26.090 --> 00:25:28.496 positive cells to aspirate last count.

NOTE Confidence: 0.912389138888889

00:25:28.500 --> 00:25:31.507 The comparison of IRV staining to

NOTE Confidence: 0.912389138888889

00:25:31.507 --> 00:25:33.109 blast count and see mammal also

NOTE Confidence: 0.912389138888889

00:25:33.109 --> 00:25:34.880 showed a pretty good correlation,

NOTE Confidence: 0.912389138888889

00:25:34.880 --> 00:25:37.958 though that requires more study and

NOTE Confidence: 0.912389138888889

00:25:37.958 --> 00:25:40.606 in contrast reactive monocytosis and

NOTE Confidence: 0.912389138888889

00:25:40.606 --> 00:25:42.658 AML without monocytic differentiation

NOTE Confidence: 0.912389138888889

00:25:42.658 --> 00:25:46.550 did not show IRA elevation when it was

NOTE Confidence: 0.912389138888889

00:25:46.550 --> 00:25:49.455 used to categorize cases as acute leukemia,

NOTE Confidence: 0.912389138888889

00:25:49.460 --> 00:25:51.890 positive or residual leukemia or negative.

NOTE Confidence: 0.912389138888889

00:25:51.890 --> 00:25:53.186 Sensitivity and specificity

NOTE Confidence: 0.912389138888889

00:25:53.186 --> 00:25:56.210 was high and this marker can be

NOTE Confidence: 0.912389138888889

00:25:56.284 --> 00:25:59.092 clinically useful as IHC to possibly

NOTE Confidence: 0.912389138888889

00:25:59.092 --> 00:26:00.964 diagnose and track disease.

NOTE Confidence: 0.912389138888889

00:26:00.970 --> 00:26:03.785 Particularly in cases of poor

NOTE Confidence: 0.912389138888889

00:26:03.785 --> 00:26:06.600 aspiration or focal blast increase.

NOTE Confidence: 0.912389138888889

00:26:06.600 --> 00:26:09.050 So shortly after this manuscript

NOTE Confidence: 0.912389138888889

00:26:09.050 --> 00:26:11.010 was accepted for publication,

NOTE Confidence: 0.912389138888889

00:26:11.010 --> 00:26:12.888 actually a great study came out

NOTE Confidence: 0.912389138888889

00:26:12.888 --> 00:26:14.570 in molecular cell that actually

NOTE Confidence: 0.912389138888889

00:26:14.570 --> 00:26:16.054 really helped me understand

NOTE Confidence: 0.912389138888889

00:26:16.054 --> 00:26:17.909 what we were seeing better.

NOTE Confidence: 0.912389138888889

00:26:17.910 --> 00:26:19.878 This is a summary of transcription

NOTE Confidence: 0.912389138888889

00:26:19.878 --> 00:26:20.862 factor domain focus.

NOTE Confidence: 0.912389138888889

00:26:20.870 --> 00:26:23.545 CRISPER screens genes were ranked

NOTE Confidence: 0.912389138888889

00:26:23.545 --> 00:26:26.220 by AML biased essentiality scores

NOTE Confidence: 0.912389138888889

00:26:26.301 --> 00:26:28.576 defined by the difference in

NOTE Confidence: 0.912389138888889

00:26:28.576 --> 00:26:30.851 a particular domain score in

NOTE Confidence: 0.912389138888889

00:26:30.934 --> 00:26:33.328 AML versus non AML cell lines.

NOTE Confidence: 0.912389138888889

00:26:33.330 --> 00:26:34.842 And I should point out that

NOTE Confidence: 0.912389138888889

00:26:34.842 --> 00:26:35.850 in the cell lines

NOTE Confidence: 0.8651197875

00:26:35.908 --> 00:26:38.812 that showed. Particularly high IRF

NOTE Confidence: 0.8651197875

00:26:38.812 --> 00:26:41.725 8 dependency, those were monocytic,

NOTE Confidence: 0.8651197875

00:26:41.725 --> 00:26:44.575 leukemias, and the others are not.

NOTE Confidence: 0.05407837

00:26:47.630 --> 00:26:51.155 Umm? Competition based proliferation

NOTE Confidence: 0.05407837

00:26:51.155 --> 00:26:54.180 assays performed in Castine positive

NOTE Confidence: 0.05407837

00:26:54.180 --> 00:26:57.027 cell lines show that AML cells

NOTE Confidence: 0.05407837

00:26:57.027 --> 00:26:59.367 that were transduced with IRF 8

NOTE Confidence: 0.05407837

00:26:59.449 --> 00:27:02.014 guided RNA were rapidly depleted

NOTE Confidence: 0.05407837

00:27:02.014 --> 00:27:04.579 and outcompeted by parental cells.

NOTE Confidence: 0.05407837

00:27:04.580 --> 00:27:08.820 In separate studies showing

NOTE Confidence: 0.05407837

00:27:08.820 --> 00:27:10.316 173 AML patient samples,

NOTE Confidence: 0.05407837

00:27:10.316 --> 00:27:13.664 High R of eight expression was seen in

NOTE Confidence: 0.05407837

00:27:13.664 --> 00:27:15.732 association with diverse cytogenetic

NOTE Confidence: 0.05407837

00:27:15.732 --> 00:27:17.800 and molecular driver mutations,

NOTE Confidence: 0.05407837

00:27:17.800 --> 00:27:20.452 so there's genetic and molecular features

NOTE Confidence: 0.05407837

00:27:20.452 --> 00:27:23.250 actually did not define this behavior.

NOTE Confidence: 0.762178523333333

00:27:27.520 --> 00:27:29.410 They also found that RFA is

NOTE Confidence: 0.762178523333333

00:27:29.410 --> 00:27:31.339 enriched at the MEF 2D locus.

NOTE Confidence: 0.762178523333333

00:27:31.340 --> 00:27:33.550 That is another transcription factor,

NOTE Confidence: 0.762178523333333

00:27:33.550 --> 00:27:38.118 and it is known to be important in

NOTE Confidence: 0.762178523333333

00:27:38.118 --> 00:27:40.648 some Bal in several cell lines,

NOTE Confidence: 0.762178523333333

00:27:40.648 --> 00:27:42.036 such as month 13,

NOTE Confidence: 0.762178523333333

00:27:42.040 --> 00:27:43.798 which is a monocytic cell line,

NOTE Confidence: 0.762178523333333

00:27:43.800 --> 00:27:45.380 RNA seek of gene expression.

NOTE Confidence: 0.762178523333333

00:27:45.380 --> 00:27:47.076 Changes indicate that cell

NOTE Confidence: 0.762178523333333

00:27:47.076 --> 00:27:48.772 lines transduced with guided

NOTE Confidence: 0.762178523333333

00:27:48.772 --> 00:27:52.145 RNA to IF8 revealed MEF 2D to

NOTE Confidence: 0.762178523333333

00:27:52.145 --> 00:27:53.660 be significantly downregulated.

NOTE Confidence: 0.85399628875

00:27:56.350 --> 00:27:58.610 So transcription factors are

NOTE Confidence: 0.85399628875

00:27:58.610 --> 00:28:00.870 difficult to therapeutically target,

NOTE Confidence: 0.85399628875

00:28:00.870 --> 00:28:03.210 so they looked for a chromatin

NOTE Confidence: 0.85399628875

00:28:03.210 --> 00:28:05.212 regulator upstream that would be

NOTE Confidence: 0.85399628875

00:28:05.212 --> 00:28:07.062 more druggable in a separate crisper

NOTE Confidence: 0.85399628875

00:28:07.062 --> 00:28:08.452 dropout screen that was focused

NOTE Confidence: 0.85399628875

00:28:08.452 --> 00:28:10.230 on chromatin regulatory domains.

NOTE Confidence: 0.85399628875

00:28:10.230 --> 00:28:13.966 They uncover CMU and eight as AML specific,

NOTE Confidence: 0.85399628875

00:28:13.970 --> 00:28:16.834 and here you can see that in certain

NOTE Confidence: 0.85399628875

00:28:16.834 --> 00:28:19.618 cell lines they are hypersensitive to

NOTE Confidence: 0.85399628875

00:28:19.618 --> 00:28:22.203 depletion of this chromatin reader,

NOTE Confidence: 0.85399628875

00:28:22.210 --> 00:28:25.020 and others are less so.

NOTE Confidence: 0.85399628875

00:28:25.020 --> 00:28:27.358 The ones that are non AML are

NOTE Confidence: 0.85399628875

00:28:27.358 --> 00:28:29.497 insensitive to it and by the way,

NOTE Confidence: 0.85399628875

00:28:29.500 --> 00:28:31.220 cmda is ubiquitously expressed

NOTE Confidence: 0.85399628875

00:28:31.220 --> 00:28:32.940 in all cell lines,

NOTE Confidence: 0.85399628875

00:28:32.940 --> 00:28:34.662 so it was not because of how

NOTE Confidence: 0.85399628875

00:28:34.662 --> 00:28:36.328 much the YD ate there was.

NOTE Confidence: 0.49053782

00:28:39.100 --> 00:28:41.015 They further found that all the

NOTE Confidence: 0.49053782

00:28:41.015 --> 00:28:43.806 AML cell lines are IR 8 high are

NOTE Confidence: 0.49053782

00:28:43.806 --> 00:28:46.982 hypersensitive to depletion of CMY D8

NOTE Confidence: 0.49053782

00:28:46.982 --> 00:28:49.510 and loss of CMD 8 resulted in decrease

00:28:49.586 --> 00:28:51.890 in ire of eight as well as Mick

00:28:51.890 --> 00:28:55.130 over time and an increase in Miller

00:28:55.130 --> 00:28:56.684 differentiation associated genes.

00:28:56.690 --> 00:28:58.795 Genetic depletion CMND in normal

00:28:58.795 --> 00:29:00.479 hematopoietic stem cells did

00:29:00.479 --> 00:29:02.389 not impact cells in vitro.

00:29:02.390 --> 00:29:05.180 So just what you want for a druggable target.

00:29:09.780 --> 00:29:11.418 Altogether and with other data that I'm

00:29:11.418 --> 00:29:13.030 not presenting in the interest of time,

00:29:13.030 --> 00:29:15.970 they show that IR 8 helps form

00:29:15.970 --> 00:29:17.848 a transcriptional circuit to

00:29:17.848 --> 00:29:19.477 support AML proliferation.

00:29:19.480 --> 00:29:22.735 They also showed that a targetable chromatin

00:29:22.735 --> 00:29:26.069 reader CMI and eight regulates IRF 8

00:29:26.069 --> 00:29:28.859 by lineage specific enhancers in AML.

NOTE Confidence: 0.862529079285714

00:29:28.860 --> 00:29:30.764 So at this point we were quite

NOTE Confidence: 0.862529079285714

00:29:30.764 --> 00:29:32.759 convinced that I of eight might

NOTE Confidence: 0.862529079285714

00:29:32.759 --> 00:29:34.614 serve as a transcriptional addiction

NOTE Confidence: 0.862529079285714

00:29:34.614 --> 00:29:36.000 in monocytic leukemias,

NOTE Confidence: 0.862529079285714

00:29:36.000 --> 00:29:38.817 and we were curious as to how else we

NOTE Confidence: 0.862529079285714

00:29:38.817 --> 00:29:41.969 can use this in daily clinical practice.

NOTE Confidence: 0.862529079285714

00:29:41.970 --> 00:29:44.214 What I'm presenting here is work

NOTE Confidence: 0.862529079285714

00:29:44.214 --> 00:29:45.710 done by Dan Mcquade,

NOTE Confidence: 0.862529079285714

00:29:45.710 --> 00:29:48.069 who is the 2nd year Yale MD,

NOTE Confidence: 0.862529079285714

00:29:48.070 --> 00:29:50.690 PhD candidate who really learned

NOTE Confidence: 0.862529079285714

00:29:50.690 --> 00:29:52.786 all of heme path.

NOTE Confidence: 0.862529079285714

00:29:52.790 --> 00:29:56.798 It seems within a year and this was

NOTE Confidence: 0.862529079285714

00:29:56.798 --> 00:29:59.908 just published a couple months ago.

NOTE Confidence: 0.862529079285714

00:29:59.910 --> 00:30:02.922 We showed that RF-8 specifically stains

NOTE Confidence: 0.862529079285714

00:30:02.922 --> 00:30:05.470 moneyglass and these extramedullary tumors,

NOTE Confidence: 0.862529079285714

00:30:05.470 --> 00:30:08.190 so this is a myeloid sarcoma in a lymph node.

NOTE Confidence: 0.862529079285714

00:30:08.190 --> 00:30:09.406 Follicles are still intact,

NOTE Confidence: 0.862529079285714

00:30:09.406 --> 00:30:11.640 but you just can see the blast.

NOTE Confidence: 0.862529079285714

00:30:11.640 --> 00:30:14.080 In the uh, Paracortical area,

NOTE Confidence: 0.862529079285714

00:30:14.080 --> 00:30:17.192 some of the blocks are more towards medullary

NOTE Confidence: 0.862529079285714

00:30:17.192 --> 00:30:20.349 area and they were actually MPO positive.

NOTE Confidence: 0.862529079285714

00:30:20.350 --> 00:30:21.173 Seen here,

NOTE Confidence: 0.862529079285714

00:30:21.173 --> 00:30:24.717 but the areas of the boss without MPO

NOTE Confidence: 0.862529079285714

00:30:24.717 --> 00:30:27.059 positivity were expressing IRF 8,

NOTE Confidence: 0.862529079285714

00:30:27.060 --> 00:30:28.550 so this is in tumor.

NOTE Confidence: 0.862529079285714

00:30:28.550 --> 00:30:31.490 This is a little dimmer in the

NOTE Confidence: 0.862529079285714

00:30:31.490 --> 00:30:34.660 mantle zone and when we plotted the

NOTE Confidence: 0.862529079285714

00:30:34.660 --> 00:30:37.396 relative expression of CD 34 MPO

NOTE Confidence: 0.862529079285714

00:30:37.396 --> 00:30:39.918 and RF-8 for all of these cases,

NOTE Confidence: 0.862529079285714

00:30:39.920 --> 00:30:42.440 you see an almost inverse relationship.

NOTE Confidence: 0.38732213

00:30:44.880 --> 00:30:50.152 Another recent I think that we did was

NOTE Confidence: 0.38732213

00:30:50.152 --> 00:30:53.926 looking at BPDCN, so BPDCN is another

NOTE Confidence: 0.38732213

00:30:53.926 --> 00:30:56.128 extramedullary hematopoietic tumor.

NOTE Confidence: 0.38732213

00:30:56.130 --> 00:30:58.415 It's often difficult to diagnose

NOTE Confidence: 0.38732213

00:30:58.415 --> 00:31:01.202 as it presents first in the

NOTE Confidence: 0.38732213

00:31:01.202 --> 00:31:04.114 skin or soft tissue and the most

NOTE Confidence: 0.38732213

00:31:04.114 --> 00:31:06.680 helpful marker to date is CD 123,

NOTE Confidence: 0.38732213

00:31:06.680 --> 00:31:09.170 which is also a druggable target.

NOTE Confidence: 0.38732213

00:31:09.170 --> 00:31:10.880 This can be very dimly staining.

NOTE Confidence: 0.38732213

00:31:10.880 --> 00:31:12.385 This is not just in our lab,

NOTE Confidence: 0.38732213

00:31:12.390 --> 00:31:15.758 it's universally known that city 123

NOTE Confidence: 0.38732213

00:31:15.758 --> 00:31:18.194 can be somewhat dim in this tumor.

NOTE Confidence: 0.38732213

00:31:18.200 --> 00:31:20.818 That really, really relies on the marker,

NOTE Confidence: 0.38732213

00:31:20.820 --> 00:31:22.930 so we look to see if IRF 8 can be

NOTE Confidence: 0.38732213

00:31:23.002 --> 00:31:25.438 helpful in these instances and it was.

NOTE Confidence: 0.38732213

00:31:25.440 --> 00:31:27.750 This was done in collaboration with Doctor

NOTE Confidence: 0.38732213

00:31:27.750 --> 00:31:29.990 Gallery Pansy from Dermatopathology here.

NOTE Confidence: 0.702619746

00:31:33.640 --> 00:31:35.176 Doctor Jacqueline Pinkus,

NOTE Confidence: 0.702619746

00:31:35.176 --> 00:31:38.004 who was the health director at

NOTE Confidence: 0.702619746

00:31:38.004 --> 00:31:40.259 Brigham when I was training.

NOTE Confidence: 0.702619746

00:31:40.260 --> 00:31:44.089 She is just a guru in immunohistochemistry.

NOTE Confidence: 0.702619746

00:31:44.090 --> 00:31:45.475 I think she actually discovered

NOTE Confidence: 0.702619746

00:31:45.475 --> 00:31:46.583 how disdain for Kappa,

NOTE Confidence: 0.702619746

00:31:46.590 --> 00:31:48.558 Lambda and tissue back in the

NOTE Confidence: 0.702619746

00:31:48.558 --> 00:31:50.938 day and when she saw our paper,

NOTE Confidence: 0.702619746

00:31:50.940 --> 00:31:52.775 she immediately started doing some

NOTE Confidence: 0.702619746

00:31:52.775 --> 00:31:55.590 double stains and this is leukemia cutis.

NOTE Confidence: 0.702619746

00:31:55.590 --> 00:31:57.500 Double stain with RV in

NOTE Confidence: 0.702619746

00:31:57.500 --> 00:31:59.410 brown and lysozyme in red.

NOTE Confidence: 0.702619746

00:31:59.410 --> 00:32:00.410 So as you might remember,

NOTE Confidence: 0.702619746

00:32:00.410 --> 00:32:03.638 lysozyme stains all of the different

NOTE Confidence: 0.702619746

00:32:03.638 --> 00:32:06.580 maturation stages of monos and histiocytes.

NOTE Confidence: 0.702619746

00:32:06.580 --> 00:32:08.950 And you can see it staining

NOTE Confidence: 0.702619746

00:32:08.950 --> 00:32:10.379 the history of site.

NOTE Confidence: 0.702619746

00:32:10.380 --> 00:32:11.082 Like Sweets,

NOTE Confidence: 0.702619746

00:32:11.082 --> 00:32:13.539 but there are eight is not staining

NOTE Confidence: 0.702619746

00:32:13.539 --> 00:32:15.648 because there are no glass in here.

NOTE Confidence: 0.702619746

00:32:15.650 --> 00:32:18.142 Other potentially helpful double

NOTE Confidence: 0.702619746

00:32:18.142 --> 00:32:20.710 stains are CD34 with RF-8.

NOTE Confidence: 0.702619746

00:32:20.710 --> 00:32:24.411 I think in terms of what if we

NOTE Confidence: 0.702619746

00:32:24.411 --> 00:32:27.483 have a Milo monocytic leukemia and

NOTE Confidence: 0.702619746

00:32:27.483 --> 00:32:29.854 I think Doctor Pinkus is already

NOTE Confidence: 0.702619746

00:32:29.854 --> 00:32:31.870 doing the double stain with City

NOTE Confidence: 0.702619746

00:32:31.870 --> 00:32:34.187 123 to kind of take out the

NOTE Confidence: 0.702619746

00:32:34.187 --> 00:32:36.260 dendritic cells in a bone marrow.

NOTE Confidence: 0.876580608333333

00:32:38.290 --> 00:32:40.006 We also looked at the TCG,

NOTE Confidence: 0.876580608333333

00:32:40.010 --> 00:32:42.964 a pattern of expression for IRF 8.

NOTE Confidence: 0.876580608333333

00:32:42.970 --> 00:32:45.190 The red block boxes are tumor.

NOTE Confidence: 0.876580608333333

00:32:45.190 --> 00:32:47.726 The Gray is normal, and you can see

NOTE Confidence: 0.876580608333333

00:32:47.726 --> 00:32:51.218 for AML and DLBCL you have this very

NOTE Confidence: 0.876580608333333

00:32:51.218 --> 00:32:53.074 dramatic difference in expression,

NOTE Confidence: 0.876580608333333

00:32:53.080 --> 00:32:54.850 whereas in the other cancers,

NOTE Confidence: 0.876580608333333

00:32:54.850 --> 00:32:56.638 not as much in the ones

NOTE Confidence: 0.876580608333333

00:32:56.638 --> 00:32:58.554 here like this is, I think,

NOTE Confidence: 0.876580608333333

00:32:58.554 --> 00:33:00.726 stomach and testicular germ cell tumor.

NOTE Confidence: 0.876580608333333

00:33:00.730 --> 00:33:02.571 We're kind of curious as to whether

NOTE Confidence: 0.876580608333333

00:33:02.571 --> 00:33:04.548 it really did show that difference.

NOTE Confidence: 0.876580608333333

00:33:04.550 --> 00:33:07.567 We had a tissue microarray composed of.

NOTE Confidence: 0.876580608333333

00:33:07.570 --> 00:33:09.736 All these different types of carcinomas

NOTE Confidence: 0.876580608333333

00:33:09.736 --> 00:33:12.795 and it really did not stain for any of

NOTE Confidence: 0.876580608333333

00:33:12.795 --> 00:33:15.298 them except for one lymphoma that snuck in.

NOTE Confidence: 0.876580608333333

00:33:15.300 --> 00:33:17.466 This was actually diagnosed by Doctor

NOTE Confidence: 0.876580608333333

00:33:17.466 --> 00:33:19.978 Jose Costa really back in the day

NOTE Confidence: 0.876580608333333

00:33:19.978 --> 00:33:21.982 where it was called malignant lymphoma.

NOTE Confidence: 0.876580608333333

00:33:21.990 --> 00:33:24.620 So of course that prompted me to do a CD

NOTE Confidence: 0.876580608333333

00:33:24.686 --> 00:33:27.580 20 just to make sure it was in fact a DLBCL.

NOTE Confidence: 0.876580608333333

00:33:27.580 --> 00:33:29.218 So for the rest of the tumors you can

NOTE Confidence: 0.876580608333333

00:33:29.218 --> 00:33:30.920 see here that there is some staining,

NOTE Confidence: 0.876580608333333

00:33:30.920 --> 00:33:32.558 but that is not in tumor,

NOTE Confidence: 0.876580608333333

00:33:32.560 --> 00:33:35.010 so that may explain the TCGA data.

NOTE Confidence: 0.870332921818182

00:33:37.630 --> 00:33:39.622 We also looked at the other

NOTE Confidence: 0.870332921818182

00:33:39.622 --> 00:33:41.410 differential diagnosis in soft tissue,

NOTE Confidence: 0.870332921818182

00:33:41.410 --> 00:33:43.685 which is actual sarcomas as

NOTE Confidence: 0.870332921818182

00:33:43.685 --> 00:33:45.505 opposed to myeloid sarcomas,

NOTE Confidence: 0.870332921818182

00:33:45.510 --> 00:33:47.598 so this is done in collaboration

NOTE Confidence: 0.870332921818182

00:33:47.598 --> 00:33:48.990 with Doctor William Wong,

NOTE Confidence: 0.870332921818182

00:33:48.990 --> 00:33:51.678 who had been a mentor of Doctor Gary

NOTE Confidence: 0.870332921818182

00:33:51.678 --> 00:33:53.787 Pansies when she was in training,

NOTE Confidence: 0.870332921818182

00:33:53.790 --> 00:33:56.150 and you can see that for the sarcomas,

NOTE Confidence: 0.870332921818182

00:33:56.150 --> 00:33:57.480 including the ones that are

NOTE Confidence: 0.870332921818182

00:33:57.480 --> 00:33:58.810 small round blue cell tumors.

NOTE Confidence: 0.870332921818182

00:33:58.810 --> 00:34:01.696 They're negative for higher of eight.

NOTE Confidence: 0.870332921818182

00:34:01.700 --> 00:34:04.372 So so far we've been talking about all

NOTE Confidence: 0.870332921818182

00:34:04.372 --> 00:34:06.978 the myeloid and monocytic differentials.

NOTE Confidence: 0.870332921818182

00:34:06.980 --> 00:34:08.440 What about the lymphoid?

NOTE Confidence: 0.870332921818182

00:34:08.440 --> 00:34:11.500 Because we know it also stains for B cells.

NOTE Confidence: 0.870332921818182

00:34:11.500 --> 00:34:13.675 Well, here is another common

NOTE Confidence: 0.870332921818182

00:34:13.675 --> 00:34:15.415 problem in hematopathology classic

NOTE Confidence: 0.870332921818182

00:34:15.415 --> 00:34:17.261 country and lymphoma versus

NOTE Confidence: 0.870332921818182

00:34:17.261 --> 00:34:19.049 anaplastic large cell lymphoma,

NOTE Confidence: 0.870332921818182

00:34:19.050 --> 00:34:21.442 and these have overlapping

NOTE Confidence: 0.870332921818182

00:34:21.442 --> 00:34:22.638 morphologic features.

NOTE Confidence: 0.870332921818182

00:34:22.640 --> 00:34:25.052 They also have overlapping

NOTE Confidence: 0.870332921818182

00:34:25.052 --> 00:34:26.258 immunophenotypic features,

NOTE Confidence: 0.870332921818182

00:34:26.260 --> 00:34:30.260 and we sometimes have to rely only on PAX 5,

NOTE Confidence: 0.870332921818182

00:34:30.260 --> 00:34:31.812 which is not always.

NOTE Confidence: 0.870332921818182

00:34:31.812 --> 00:34:33.752 Positive and classic caution lymphomas

NOTE Confidence: 0.870332921818182

00:34:33.752 --> 00:34:36.289 and can also be amplified in some alcl's.

NOTE Confidence: 0.870332921818182

00:34:36.289 --> 00:34:39.367 So we took 74 cases of Hodgkin and 15 cases

NOTE Confidence: 0.870332921818182

00:34:39.367 --> 00:34:42.450 of ALK negative LCL to see how they would do.

NOTE Confidence: 0.870332921818182

00:34:42.450 --> 00:34:44.345 Obviously all positive ACL we

NOTE Confidence: 0.870332921818182

00:34:44.345 --> 00:34:46.670 would not have a problem with.

NOTE Confidence: 0.870332921818182

00:34:46.670 --> 00:34:48.605 And you can see here that even in the

NOTE Confidence: 0.870332921818182

00:34:48.605 --> 00:34:50.548 PAX five negative Hodgkin lymphomas,

NOTE Confidence: 0.870332921818182

00:34:50.550 --> 00:34:51.930 you can have dim staining.

NOTE Confidence: 0.870332921818182

00:34:51.930 --> 00:34:52.980 For IRF 8,

NOTE Confidence: 0.870332921818182

00:34:52.980 --> 00:34:55.430 we shouldn't be using this in isolation,

NOTE Confidence: 0.870332921818182

00:34:55.430 --> 00:34:56.078 of course,

NOTE Confidence: 0.870332921818182

00:34:56.078 --> 00:34:58.022 but in the context of the

NOTE Confidence: 0.870332921818182

00:34:58.022 --> 00:34:59.629 morphology and other markers,

NOTE Confidence: 0.870332921818182

00:34:59.630 --> 00:35:02.360 I think it can be helpful since

NOTE Confidence: 0.870332921818182

00:35:02.360 --> 00:35:05.490 it is dead negative in all ACL.

NOTE Confidence: 0.870332921818182

00:35:05.490 --> 00:35:07.656 And this is the kind of

NOTE Confidence: 0.870332921818182

00:35:07.656 --> 00:35:09.890 composite of cases are pacified,

NOTE Confidence: 0.870332921818182

00:35:09.890 --> 00:35:12.130 negative I of eight positive,

NOTE Confidence: 0.870332921818182

00:35:12.130 --> 00:35:14.050 some of course are double negative,

NOTE Confidence: 0.870332921818182

00:35:14.050 --> 00:35:16.073 and here we really have to look

NOTE Confidence: 0.870332921818182

00:35:16.073 --> 00:35:18.279 at all the different stains and

NOTE Confidence: 0.870332921818182

00:35:18.279 --> 00:35:20.389 other features that we have.

NOTE Confidence: 0.870332921818182

00:35:20.390 --> 00:35:22.588 This was also a first author paper

NOTE Confidence: 0.870332921818182

00:35:22.588 --> 00:35:25.307 for Dan who just got this accepted

NOTE Confidence: 0.870332921818182

00:35:25.307 --> 00:35:27.432 for publication couple weeks ago.

NOTE Confidence: 0.870332921818182

00:35:27.440 --> 00:35:28.604 So in conclusion,

NOTE Confidence: 0.870332921818182

00:35:28.604 --> 00:35:31.320 IFA can be used to detect extramedullary

NOTE Confidence: 0.870332921818182

00:35:31.396 --> 00:35:33.340 hematopoietic tumors as well.

NOTE Confidence: 0.870332921818182

00:35:33.340 --> 00:35:36.028 That can be a diagnostic challenge

NOTE Confidence: 0.870332921818182

00:35:36.028 --> 00:35:39.062 such as leukemia cutis myeloid sarcomas

NOTE Confidence: 0.870332921818182

00:35:39.062 --> 00:35:41.004 BPDCN its expression is essentially

NOTE Confidence: 0.870332921818182

00:35:41.004 --> 00:35:43.050 absent in all other solid tumor

NOTE Confidence: 0.870332921818182

00:35:43.107 --> 00:35:45.321 malignancies that can present as a

NOTE Confidence: 0.870332921818182

00:35:45.321 --> 00:35:47.171 differential diagnosis here and as

NOTE Confidence: 0.870332921818182

00:35:47.171 --> 00:35:48.761 a transcription factor that's also

NOTE Confidence: 0.870332921818182

00:35:48.761 --> 00:35:50.818 important in B cell lineage commitment.

NOTE Confidence: 0.870332921818182

00:35:50.818 --> 00:35:53.541 It can show some promise in the

NOTE Confidence: 0.870332921818182

00:35:53.541 --> 00:35:55.789 detection between Hodgkin versus ALCL,

NOTE Confidence: 0.870332921818182

00:35:55.790 --> 00:35:57.968 which is a real clinical dilemma.

NOTE Confidence: 0.858756120714286

00:36:00.560 --> 00:36:02.755 Our findings were just recently

NOTE Confidence: 0.858756120714286

00:36:02.755 --> 00:36:05.493 replicated by a couple labs in

NOTE Confidence: 0.858756120714286

00:36:05.493 --> 00:36:07.916 Switzerland and Italy, showing that yes,

NOTE Confidence: 0.858756120714286

00:36:07.916 --> 00:36:09.968 it is a reliable monoblast marker,

NOTE Confidence: 0.858756120714286

00:36:09.970 --> 00:36:12.946 but they also show it staining BPDCN well.

NOTE Confidence: 0.662321272

00:36:15.920 --> 00:36:19.317 And thanks to Anoj Verma, our resident here,

NOTE Confidence: 0.662321272

00:36:19.317 --> 00:36:22.250 this has been reviewed in the context

NOTE Confidence: 0.662321272

00:36:22.331 --> 00:36:24.987 of other emerging immunohistochemical

NOTE Confidence: 0.662321272

00:36:24.987 --> 00:36:27.643 biomarkers for myeloid neoplasms.

NOTE Confidence: 0.893188766

00:36:29.770 --> 00:36:31.270 So what about our case?

NOTE Confidence: 0.893188766

00:36:31.270 --> 00:36:32.810 Or a patient with CML?

NOTE Confidence: 0.893188766

00:36:32.810 --> 00:36:34.868 How do I diagnose this as our

NOTE Confidence: 0.893188766

00:36:34.868 --> 00:36:36.511 final diagnosis after showing this

NOTE Confidence: 0.893188766

00:36:36.511 --> 00:36:38.593 case around to multiple other heme

NOTE Confidence: 0.893188766

00:36:38.593 --> 00:36:40.574 path faculty members was myeloid

NOTE Confidence: 0.893188766

00:36:40.574 --> 00:36:42.624 neoplasm with increased blasts most

NOTE Confidence: 0.893188766

00:36:42.624 --> 00:36:44.773 compatible with progression to AML?

NOTE Confidence: 0.893188766

00:36:44.773 --> 00:36:47.860 And our patient was started on treatment

NOTE Confidence: 0.893188766

00:36:47.940 --> 00:36:51.928 with PIXIUS which is a liposomal 7 + 3.

NOTE Confidence: 0.893188766

00:36:51.930 --> 00:36:54.110 It's Donna Robinson was cytarabine

NOTE Confidence: 0.893188766

00:36:54.110 --> 00:36:55.854 with a consideration toward

NOTE Confidence: 0.893188766

00:36:55.854 --> 00:36:57.548 associated Gene and venetoclax.

NOTE Confidence: 0.893188766

00:36:57.550 --> 00:37:00.756 She would have gotten that instead if.

NOTE Confidence: 0.893188766

00:37:00.760 --> 00:37:02.284 The age was older and she

NOTE Confidence: 0.893188766

00:37:02.284 --> 00:37:03.300 didn't have the symptoms.

NOTE Confidence: 0.91975849

00:37:05.470 --> 00:37:06.950 So here is our case.

NOTE Confidence: 0.91975849

00:37:06.950 --> 00:37:09.630 When I went back to stain it with our eight,

NOTE Confidence: 0.91975849

00:37:09.630 --> 00:37:11.429 you can see that in fact the

NOTE Confidence: 0.91975849

00:37:11.429 --> 00:37:13.044 areas where we suspected increased

NOTE Confidence: 0.91975849

00:37:13.044 --> 00:37:15.411 loss there was increase in RF-8

NOTE Confidence: 0.91975849

00:37:15.411 --> 00:37:17.817 and in the areas of maturing

NOTE Confidence: 0.91975849

00:37:17.817 --> 00:37:19.650 Trilineage Marquis there was not,

NOTE Confidence: 0.91975849

00:37:19.650 --> 00:37:21.939 so this certainly made me feel better

NOTE Confidence: 0.91975849

00:37:21.939 --> 00:37:24.180 about calling her as evolution to AML.

NOTE Confidence: 0.692884770142857

00:37:26.270 --> 00:37:28.926 Another recent study also showed I of a

NOTE Confidence: 0.692884770142857

00:37:28.926 --> 00:37:32.107 as an AML specific susceptibility gene.

NOTE Confidence: 0.692884770142857

00:37:32.110 --> 00:37:34.860 So here using publicly available

NOTE Confidence: 0.692884770142857

00:37:34.860 --> 00:37:38.919 databases they show that these red dots

NOTE Confidence: 0.692884770142857

00:37:38.919 --> 00:37:41.222 representing genes that were essential

NOTE Confidence: 0.692884770142857

00:37:41.222 --> 00:37:45.208 to AML but not in non AML cell lines.

NOTE Confidence: 0.692884770142857

00:37:45.210 --> 00:37:47.821 And here what I really want to

NOTE Confidence: 0.692884770142857

00:37:47.821 --> 00:37:50.569 highlight is that IFA expression is

NOTE Confidence: 0.692884770142857

00:37:50.569 --> 00:37:53.480 also correlated with poor prognosis and

NOTE Confidence: 0.692884770142857

00:37:53.480 --> 00:37:56.120 I think for those of us who remember.

NOTE Confidence: 0.692884770142857

00:37:56.120 --> 00:37:58.170 The FAB classification and little

NOTE Confidence: 0.692884770142857

00:37:58.170 --> 00:38:00.220 period of time after that,

NOTE Confidence: 0.692884770142857

00:38:00.220 --> 00:38:03.160 many times when we first diagnosed AML,

NOTE Confidence: 0.692884770142857

00:38:03.160 --> 00:38:04.816 clinicians will come down and say,

NOTE Confidence: 0.692884770142857

00:38:04.820 --> 00:38:06.024 but is it monocytic?

NOTE Confidence: 0.692884770142857

00:38:06.024 --> 00:38:07.830 Does it look monocytic to you?

NOTE Confidence: 0.692884770142857

00:38:07.830 --> 00:38:09.675 Because then I will consider

NOTE Confidence: 0.692884770142857

00:38:09.675 --> 00:38:11.520 this as a worse prognosis.

NOTE Confidence: 0.692884770142857

00:38:11.520 --> 00:38:13.732 And here we have if we consider

NOTE Confidence: 0.692884770142857

00:38:13.732 --> 00:38:16.380 RFA to be a marker of mono bus,

NOTE Confidence: 0.692884770142857

00:38:16.380 --> 00:38:19.220 some substantiation of that suspicion.

NOTE Confidence: 0.692884770142857

00:38:19.220 --> 00:38:20.954 We're no longer asked that because

NOTE Confidence: 0.692884770142857

00:38:20.954 --> 00:38:22.942 there's more of a focus right

NOTE Confidence: 0.692884770142857

00:38:22.942 --> 00:38:24.862 now on exactly what mutations

NOTE Confidence: 0.692884770142857

00:38:24.862 --> 00:38:26.014 and genetic translocations?

NOTE Confidence: 0.692884770142857

00:38:26.020 --> 00:38:26.824 They have,

NOTE Confidence: 0.692884770142857

00:38:26.824 --> 00:38:29.638 but I think that that older clinician

NOTE Confidence: 0.692884770142857

00:38:29.638 --> 00:38:31.788 perspective of when we say monocytic,

NOTE Confidence: 0.692884770142857

00:38:31.790 --> 00:38:33.570 it's usually worse for them.

NOTE Confidence: 0.692884770142857

00:38:33.570 --> 00:38:35.430 Still holds true in some way.

NOTE Confidence: 0.915611486428571

00:38:37.900 --> 00:38:40.652 This also made me think of a prior

NOTE Confidence: 0.915611486428571

00:38:40.652 --> 00:38:42.699 observation made a couple years ago,

NOTE Confidence: 0.915611486428571

00:38:42.700 --> 00:38:45.285 which I think is experientially

NOTE Confidence: 0.915611486428571

00:38:45.285 --> 00:38:47.499 many hematopathologist feel that we

NOTE Confidence: 0.915611486428571

00:38:47.499 --> 00:38:49.542 have seen certain very prominent

NOTE Confidence: 0.915611486428571

00:38:49.542 --> 00:38:52.128 instances of which is monoblast elk

NOTE Confidence: 0.915611486428571

00:38:52.128 --> 00:38:54.500 growth after venetoclax treatment.

NOTE Confidence: 0.915611486428571

00:38:54.500 --> 00:38:57.223 So in this study they also segregated

NOTE Confidence: 0.915611486428571

00:38:57.223 --> 00:38:59.342 their patients based on fab

NOTE Confidence: 0.915611486428571

00:38:59.342 --> 00:39:01.994 classification and found that only the

NOTE Confidence: 0.915611486428571

00:39:01.994 --> 00:39:03.773 monocytic classifier was predictive

NOTE Confidence: 0.915611486428571

00:39:03.773 --> 00:39:06.233 of refractory response to Aza Ven.

NOTE Confidence: 0.915611486428571

00:39:06.240 --> 00:39:07.170 So here.

NOTE Confidence: 0.915611486428571

00:39:07.170 --> 00:39:09.960 This is a non monocytic leukemia

NOTE Confidence: 0.915611486428571

00:39:09.960 --> 00:39:13.218 and this is a monocytic leukemia.

NOTE Confidence: 0.915611486428571

00:39:13.220 --> 00:39:16.237 They talk primary human AML cells from

NOTE Confidence: 0.915611486428571

00:39:16.237 --> 00:39:19.135 both what they term primitive and

NOTE Confidence: 0.915611486428571

00:39:19.135 --> 00:39:22.165 AMOLED and in vitro demonstrated lower

NOTE Confidence: 0.915611486428571

00:39:22.165 --> 00:39:25.586 kill with both phonetic clocks and a

NOTE Confidence: 0.915611486428571

00:39:25.586 --> 00:39:29.330 combo phonetic clocks with acidity.

NOTE Confidence: 0.915611486428571

00:39:29.330 --> 00:39:31.843 They also showed this in a violin

NOTE Confidence: 0.915611486428571

00:39:31.843 --> 00:39:34.016 plot how monocytic disease arising

NOTE Confidence: 0.915611486428571

00:39:34.016 --> 00:39:36.571 after treatment can be derived

NOTE Confidence: 0.915611486428571

00:39:36.571 --> 00:39:38.104 from preexisting subclones.

NOTE Confidence: 0.915611486428571

00:39:38.110 --> 00:39:40.210 In this other patient at relapse.

NOTE Confidence: 0.742571882857143

00:39:42.960 --> 00:39:45.235 So our future directions include

NOTE Confidence: 0.742571882857143

00:39:45.235 --> 00:39:48.050 something Poe hands working on with

NOTE Confidence: 0.742571882857143

00:39:48.050 --> 00:39:50.360 flow cytometric detection of R8

NOTE Confidence: 0.742571882857143

00:39:50.360 --> 00:39:52.650 and refining that monoblast gate.

NOTE Confidence: 0.742571882857143

00:39:52.650 --> 00:39:55.728 Doing that in collaboration with OHSU,

NOTE Confidence: 0.742571882857143

00:39:55.730 --> 00:39:57.378 a multi institutional validation

NOTE Confidence: 0.742571882857143

00:39:57.378 --> 00:40:00.390 using AI tools that suit your parent.

NOTE Confidence: 0.742571882857143

00:40:00.390 --> 00:40:03.333 Cherry is leading and I got a lot of

NOTE Confidence: 0.742571882857143

00:40:03.333 --> 00:40:05.863 helpful consultation from Doctor David Rim

NOTE Confidence: 0.742571882857143

00:40:05.863 --> 00:40:09.107 and this is being done in collaboration

NOTE Confidence: 0.742571882857143

00:40:09.107 --> 00:40:12.690 with MGH BWH Upenn, New Mexico.

NOTE Confidence: 0.742571882857143

00:40:12.690 --> 00:40:15.024 OHSU Cornell and Stanford and there

NOTE Confidence: 0.742571882857143

00:40:15.024 --> 00:40:18.193 is a focus in this group on wanting

NOTE Confidence: 0.742571882857143

00:40:18.193 --> 00:40:21.076 to further look at CML and this

NOTE Confidence: 0.742571882857143

00:40:21.076 --> 00:40:23.621 whole subclassification of CML which

NOTE Confidence: 0.742571882857143

00:40:23.621 --> 00:40:26.779 is a bit controversial in The Who.

NOTE Confidence: 0.742571882857143

00:40:26.779 --> 00:40:28.644 Whether this marker can help

NOTE Confidence: 0.742571882857143

00:40:28.644 --> 00:40:31.180 us hone it down a little more.

NOTE Confidence: 0.742571882857143

00:40:31.180 --> 00:40:33.788 And I do hope to identify IRF 8

NOTE Confidence: 0.742571882857143

00:40:33.788 --> 00:40:36.564 target genes in actual am OL samples

NOTE Confidence: 0.742571882857143

00:40:36.564 --> 00:40:38.604 and in primary human monoblast.

NOTE Confidence: 0.742571882857143

00:40:38.610 --> 00:40:40.780 And since I have a regulates BCL,

NOTE Confidence: 0.742571882857143

00:40:40.780 --> 00:40:43.720 two family members maybe 1 pathway.

NOTE Confidence: 0.742571882857143

00:40:43.720 --> 00:40:47.690 Of venetoclax resistance in AML.

NOTE Confidence: 0.742571882857143

00:40:47.690 --> 00:40:50.336 So thank you very much for

NOTE Confidence: 0.742571882857143

00:40:50.336 --> 00:40:52.630 your attention and your time.

NOTE Confidence: 0.742571882857143

00:40:52.630 --> 00:40:55.486 Thank you so much for the many people

NOTE Confidence: 0.742571882857143

00:40:55.486 --> 00:40:57.762 who contributed and really helped

NOTE Confidence: 0.742571882857143

00:40:57.762 --> 00:41:00.630 move this forward to our external

NOTE Confidence: 0.742571882857143

00:41:00.707 --> 00:41:02.907 collaborators for the project that

NOTE Confidence: 0.742571882857143

00:41:02.907 --> 00:41:06.048 our that is ongoing and to our

NOTE Confidence: 0.742571882857143

00:41:06.048 --> 00:41:08.640 colleagues in derm path soft tissue

NOTE Confidence: 0.742571882857143

00:41:08.640 --> 00:41:11.037 path pathology tissue services this

NOTE Confidence: 0.742571882857143

00:41:11.037 --> 00:41:14.600 could not have been done without Amos

NOTE Confidence: 0.742571882857143

00:41:14.690 --> 00:41:17.786 and Laurie and are flow hematology.

NOTE Confidence: 0.742571882857143

00:41:17.786 --> 00:41:20.060 And biostats colleagues.

NOTE Confidence: 0.742571882857143

00:41:20.060 --> 00:41:21.008 Thank you so much.

NOTE Confidence: 0.945264442

00:41:30.230 --> 00:41:33.485 We are open for questions that

NOTE Confidence: 0.945264442

00:41:33.485 --> 00:41:35.660 was excellent by the way.

NOTE Confidence: 0.945264442

00:41:35.660 --> 00:41:38.900 From a non humanoid pathologist,

NOTE Confidence: 0.945264442

00:41:38.900 --> 00:41:41.510 I thought the story is riveting.

NOTE Confidence: 0.98421958

00:41:43.070 --> 00:41:43.680 Thank you.

NOTE Confidence: 0.864354593333333

00:41:45.240 --> 00:41:45.618 May I ask

NOTE Confidence: 0.766595401166667

00:41:45.630 --> 00:41:47.400 a question Mina that was fantastic,

NOTE Confidence: 0.837881986111111

00:41:47.670 --> 00:41:50.901 lot of work and you know you have carried

NOTE Confidence: 0.837881986111111

00:41:50.901 --> 00:41:53.080 through something that you found and

NOTE Confidence: 0.837881986111111

00:41:53.080 --> 00:41:55.418 it is now evolving into something far

NOTE Confidence: 0.837881986111111

00:41:55.418 --> 00:41:57.350 bigger than you may have imagined.

NOTE Confidence: 0.837881986111111

00:41:57.350 --> 00:42:01.136 Initially from the stain that you

NOTE Confidence: 0.837881986111111

00:42:01.136 --> 00:42:04.598 showed you in the recent case of the

NOTE Confidence: 0.837881986111111

00:42:04.598 --> 00:42:07.934 case that you're diagnosed with acute

NOTE Confidence: 0.837881986111111

00:42:07.934 --> 00:42:11.690 or progression to acute leukemia.

NOTE Confidence: 0.837881986111111

00:42:11.690 --> 00:42:15.570 It looks like the staining.

NOTE Confidence: 0.837881986111111

00:42:15.570 --> 00:42:18.470 Is was probably more than 20% and

NOTE Confidence: 0.837881986111111

00:42:18.470 --> 00:42:20.076 there is a graduation of stating

NOTE Confidence: 0.837881986111111

00:42:20.076 --> 00:42:22.074 there are many nuclei which are

NOTE Confidence: 0.837881986111111

00:42:22.074 --> 00:42:26.890 dimmer in their expression of ifit so.

NOTE Confidence: 0.837881986111111

00:42:26.890 --> 00:42:30.054 Do you think as the last mature,

NOTE Confidence: 0.837881986111111

00:42:30.060 --> 00:42:32.190 the expression level slowly decreases?

NOTE Confidence: 0.837881986111111

00:42:32.190 --> 00:42:35.010 Is not an all in non phenomena and

NOTE Confidence: 0.837881986111111

00:42:35.010 --> 00:42:37.185 second question is this is a surface

NOTE Confidence: 0.837881986111111

00:42:37.185 --> 00:42:40.620 you know marker in some ways right so?

NOTE Confidence: 0.854028683333333

00:42:41.650 --> 00:42:43.168 It's a it's a nuclear marker

NOTE Confidence: 0.617058726

00:42:43.210 --> 00:42:46.060 nuclear marker, so is it? So can

NOTE Confidence: 0.858715913

00:42:46.070 --> 00:42:47.275 it be targeted for therapies

NOTE Confidence: 0.858715913

00:42:47.275 --> 00:42:48.480 in some ways or no?

NOTE Confidence: 0.72757639

00:42:50.920 --> 00:42:53.560 OK, so great questions Dan Pat.

NOTE Confidence: 0.72757639

00:42:53.560 --> 00:42:55.852 I think for the first one

NOTE Confidence: 0.72757639

00:42:55.852 --> 00:42:58.099 you know in terms of the.

NOTE Confidence: 0.72757639

00:42:58.100 --> 00:43:01.680 Some lighter or some darker that is

NOTE Confidence: 0.72757639

00:43:01.680 --> 00:43:05.070 very important and I think that.

NOTE Confidence: 0.72757639

00:43:05.070 --> 00:43:07.218 In the validation, what was helpful

NOTE Confidence: 0.72757639

00:43:07.218 --> 00:43:09.369 was its correlation with last count.

NOTE Confidence: 0.72757639

00:43:09.370 --> 00:43:12.037 So we were counting all the ones

NOTE Confidence: 0.72757639

00:43:12.037 --> 00:43:15.093 that had any staining and you know

NOTE Confidence: 0.72757639

00:43:15.093 --> 00:43:17.379 obviously this is going to be.

NOTE Confidence: 0.851914538636364

00:43:19.810 --> 00:43:21.150 You know, if you.

NOTE Confidence: 0.851914538636364

00:43:21.150 --> 00:43:23.160 Had a stronger dilution you might

NOTE Confidence: 0.851914538636364

00:43:23.231 --> 00:43:25.007 be seeing more of the background

NOTE Confidence: 0.851914538636364

00:43:25.007 --> 00:43:27.309 if you had a lesser dilution.

NOTE Confidence: 0.851914538636364

00:43:27.310 --> 00:43:31.014 So what we titrated to was that point

NOTE Confidence: 0.851914538636364

00:43:31.014 --> 00:43:34.602 at which we were seeing a percentage

NOTE Confidence: 0.851914538636364

00:43:34.602 --> 00:43:38.058 blast that were reflective of the

NOTE Confidence: 0.851914538636364

00:43:38.058 --> 00:43:40.369 actual morphologic blast count.

NOTE Confidence: 0.851914538636364

00:43:40.370 --> 00:43:44.388 So it is interesting in that a

NOTE Confidence: 0.851914538636364

00:43:44.388 --> 00:43:45.740 lot of hematopathologist ask,

NOTE Confidence: 0.851914538636364

00:43:45.740 --> 00:43:47.966 well, does it stain Pro monocytes,

NOTE Confidence: 0.851914538636364

00:43:47.970 --> 00:43:50.616 and it's such a good question.

NOTE Confidence: 0.851914538636364

00:43:50.620 --> 00:43:52.964 I don't know how to answer it because.

NOTE Confidence: 0.851914538636364

00:43:52.970 --> 00:43:55.255 Homicide is a cytologic definition

NOTE Confidence: 0.851914538636364

00:43:55.255 --> 00:43:58.455 when we see it in the aspirate

NOTE Confidence: 0.851914538636364

00:43:58.455 --> 00:44:01.171 and there is no great marker that

NOTE Confidence: 0.851914538636364

00:44:01.171 --> 00:44:03.313 just gets at the Pomona sites.

NOTE Confidence: 0.851914538636364

00:44:03.320 --> 00:44:05.152 So I wish that I could just stay

NOTE Confidence: 0.851914538636364

00:44:05.152 --> 00:44:07.464 in and aspirate that had a ton of

NOTE Confidence: 0.851914538636364

00:44:07.464 --> 00:44:09.900 promyelocytes and see if it did pick them up.

NOTE Confidence: 0.851914538636364

00:44:09.900 --> 00:44:12.852 The only consoling part of this

NOTE Confidence: 0.851914538636364

00:44:12.852 --> 00:44:15.559 whole dimmer staining is that what

NOTE Confidence: 0.851914538636364

00:44:15.559 --> 00:44:18.293 we got it to is in correlation

NOTE Confidence: 0.851914538636364

00:44:18.293 --> 00:44:20.217 with that gold standard,

NOTE Confidence: 0.851914538636364

00:44:20.220 --> 00:44:23.100 so we are counting them and I do think that.

NOTE Confidence: 0.851914538636364

00:44:23.100 --> 00:44:26.406 At some point it is not

NOTE Confidence: 0.851914538636364

00:44:26.406 --> 00:44:28.610 seeable by light microscopy,

NOTE Confidence: 0.851914538636364

00:44:28.610 --> 00:44:33.538 but is probably still baseline there by RNA,

NOTE Confidence: 0.851914538636364

00:44:33.540 --> 00:44:33.850 right?

NOTE Confidence: 0.851914538636364

00:44:33.850 --> 00:44:36.020 Like if you look at the really

NOTE Confidence: 0.851914538636364

00:44:36.020 --> 00:44:37.900 mature macrophage you can see in

NOTE Confidence: 0.851914538636364

00:44:37.900 --> 00:44:39.395 the gene expression profiles that

NOTE Confidence: 0.851914538636364

00:44:39.395 --> 00:44:41.110 they do have some expression,

NOTE Confidence: 0.851914538636364

00:44:41.110 --> 00:44:43.540 but we're not seeing it by by our IHC now.

NOTE Confidence: 0.669145725

00:44:45.090 --> 00:44:47.940 That particular case, if you use that state,

NOTE Confidence: 0.82695271

00:44:47.940 --> 00:44:49.977 your counts for the blast would have

NOTE Confidence: 0.82695271

00:44:49.977 --> 00:44:51.590 been much higher than 30%. Then

NOTE Confidence: 0.874354805

00:44:52.290 --> 00:44:53.850 is that right? Or I'm just?

NOTE Confidence: 0.816597968333333

00:44:54.020 --> 00:44:55.934 Yeah, I think what I showed

NOTE Confidence: 0.816597968333333

00:44:55.934 --> 00:44:58.050 you though was one foci right?

NOTE Confidence: 0.816597968333333

00:44:58.050 --> 00:45:00.338 One area where it seemed a little higher,

NOTE Confidence: 0.816597968333333

00:45:00.340 --> 00:45:02.690 but then just in practice,

NOTE Confidence: 0.816597968333333

00:45:02.690 --> 00:45:04.377 and I'm not sure this is the

NOTE Confidence: 0.816597968333333

00:45:04.377 --> 00:45:05.998 right thing to do in practice.

NOTE Confidence: 0.816597968333333

00:45:06.000 --> 00:45:08.562 By consensus we we typically have to

NOTE Confidence: 0.816597968333333

00:45:08.562 --> 00:45:11.350 do it through the whole entire core.

NOTE Confidence: 0.816597968333333

00:45:11.350 --> 00:45:13.348 Yeah, and in terms of whether

NOTE Confidence: 0.816597968333333

00:45:13.348 --> 00:45:14.347 it's therapeutically targetable,

NOTE Confidence: 0.816597968333333

00:45:14.350 --> 00:45:15.440 you know it may be,

NOTE Confidence: 0.816597968333333

00:45:15.440 --> 00:45:18.302 but it is a transcription factor and it is,

NOTE Confidence: 0.816597968333333

00:45:18.310 --> 00:45:20.065 you know, also important in

NOTE Confidence: 0.816597968333333

00:45:20.065 --> 00:45:21.469 B cell lineage development,

NOTE Confidence: 0.816597968333333

00:45:21.470 --> 00:45:23.325 so I think it would be hard

NOTE Confidence: 0.816597968333333

00:45:23.325 --> 00:45:25.750 to just try to focus on that.

NOTE Confidence: 0.816597968333333

00:45:25.750 --> 00:45:28.599 You could end up causing a lot

NOTE Confidence: 0.816597968333333

00:45:28.599 --> 00:45:29.820 of the problems.

NOTE Confidence: 0.816597968333333

00:45:29.820 --> 00:45:32.187 David, I think you were next with the hand.

NOTE Confidence: 0.784033972666667

00:45:33.070 --> 00:45:34.743 Yeah, that my question is similar to

NOTE Confidence: 0.784033972666667

00:45:34.743 --> 00:45:36.680 Dan Potts in a little bit in a little

NOTE Confidence: 0.784033972666667

00:45:36.680 --> 00:45:38.163 ways I see that you're progressing

NOTE Confidence: 0.784033972666667

00:45:38.163 --> 00:45:39.793 toward a multi institutional study

NOTE Confidence: 0.784033972666667

00:45:39.793 --> 00:45:41.749 which will be really interesting to

NOTE Confidence: 0.784033972666667

00:45:41.749 --> 00:45:44.445 see if this can be carried out by

NOTE Confidence: 0.784033972666667

00:45:44.445 --> 00:45:46.305 many pathologists at many places,

NOTE Confidence: 0.784033972666667

00:45:46.310 --> 00:45:48.431 but it worries me that the intensity

NOTE Confidence: 0.784033972666667

00:45:48.431 --> 00:45:50.495 at which excel becomes a positive

NOTE Confidence: 0.784033972666667

00:45:50.495 --> 00:45:52.310 cell because someone were pretty

NOTE Confidence: 0.784033972666667

00:45:52.310 --> 00:45:54.792 light and some of them are pretty

NOTE Confidence: 0.784033972666667

00:45:54.792 --> 00:45:56.896 dark and that probably represents a

NOTE Confidence: 0.784033972666667

00:45:56.896 --> 00:45:58.926 difference in RF-8 expression levels.

NOTE Confidence: 0.784033972666667

00:45:58.930 --> 00:46:00.386 Do you have any way to standardize that?

NOTE Confidence: 0.784033972666667

00:46:00.390 --> 00:46:02.217 Or how are you going to check that the

00:46:02.217 --> 00:46:03.616 results here at Yale are the same?

00:46:03.620 --> 00:46:04.970 As your other institutions that

00:46:04.970 --> 00:46:05.780 you're collaborating with,

00:46:06.560 --> 00:46:08.546 yeah, that's that's a great question,

00:46:08.550 --> 00:46:12.708 and we are. You know, as you know,

00:46:12.708 --> 00:46:15.270 we're trying to do this with some

00:46:15.351 --> 00:46:18.357 quantitative imaging analysis to see out

00:46:18.357 --> 00:46:21.851 what cutoff point does it actually show.

00:46:21.851 --> 00:46:25.037 Kind of a consensus with regard

00:46:25.037 --> 00:46:28.260 to not just the diagnosis,

00:46:28.260 --> 00:46:33.186 but a consensus across all 7 institutions.

00:46:33.186 --> 00:46:35.515 And you know, I,

00:46:35.515 --> 00:46:37.635 I think that this is I wish we

00:46:37.635 --> 00:46:40.048 had done this earlier with CD 34.

00:46:40.050 --> 00:46:41.838 In fact, because all these labs.

00:46:41.840 --> 00:46:44.465 Doing CD 34 and using that day-to-day

NOTE Confidence: 0.82646443

00:46:44.465 --> 00:46:47.542 to tell you whether the AML still there

NOTE Confidence: 0.82646443

00:46:47.542 --> 00:46:50.757 but we don't know how compatible we are

NOTE Confidence: 0.82646443

00:46:50.757 --> 00:46:53.416 with each other and whether you know

NOTE Confidence: 0.82646443

00:46:53.416 --> 00:46:55.510 if we did some quantitative imaging

NOTE Confidence: 0.82646443

00:46:55.577 --> 00:46:57.671 whether it would actually bring us

NOTE Confidence: 0.82646443

00:46:57.671 --> 00:47:00.431 to a better consensus and tell us the

NOTE Confidence: 0.82646443

00:47:00.431 --> 00:47:02.793 truth that we're not reporting right now.

NOTE Confidence: 0.82646443

00:47:02.793 --> 00:47:04.858 So I and you know,

NOTE Confidence: 0.82646443

00:47:04.860 --> 00:47:07.296 nobody really wants to do the bus

NOTE Confidence: 0.82646443

00:47:07.296 --> 00:47:08.510 quantification themselves by I,

NOTE Confidence: 0.82646443

00:47:08.510 --> 00:47:10.830 so I think it's it's really moving us

NOTE Confidence: 0.82646443

00:47:10.830 --> 00:47:12.916 forward to a point where we can be.

NOTE Confidence: 0.82646443

00:47:12.920 --> 00:47:14.860 More standardized across the board.

NOTE Confidence: 0.806298309375

00:47:14.970 --> 00:47:16.330 Yeah, I'm not worried about

NOTE Confidence: 0.806298309375

00:47:16.330 --> 00:47:18.338 standardized accounting as much as I am

NOTE Confidence: 0.806298309375

00:47:18.338 --> 00:47:19.538 standardizing the biochemistry part,

NOTE Confidence: 0.806298309375

00:47:19.540 --> 00:47:21.745 that is the tighter and the stain.

NOTE Confidence: 0.806298309375

00:47:21.750 --> 00:47:22.860 That is, how do you know

NOTE Confidence: 0.806298309375

00:47:22.860 --> 00:47:24.688 if it's if it's too light,

NOTE Confidence: 0.806298309375

00:47:24.688 --> 00:47:26.476 then whether you count it by

NOTE Confidence: 0.806298309375

00:47:26.476 --> 00:47:28.628 eye or by an imaging system,

NOTE Confidence: 0.806298309375

00:47:28.630 --> 00:47:30.550 it will just not be counted,

NOTE Confidence: 0.806298309375

00:47:30.550 --> 00:47:32.542 and that's what I would guess that there

NOTE Confidence: 0.806298309375

00:47:32.542 --> 00:47:34.943 will be some institutions that will be

NOTE Confidence: 0.806298309375

00:47:34.943 --> 00:47:36.788 lighter than other institutions overall,

NOTE Confidence: 0.806298309375

00:47:36.790 --> 00:47:40.358 and then that could throw off the result.

NOTE Confidence: 0.806298309375

00:47:40.360 --> 00:47:41.620 Absolutely yeah.

NOTE Confidence: 0.806298309375

00:47:41.620 --> 00:47:42.302 Transit control,

NOTE Confidence: 0.806298309375

00:47:42.302 --> 00:47:44.007 like you know with estrogen

NOTE Confidence: 0.806298309375

00:47:44.007 --> 00:47:45.790 receptor we have intrinsic the

NOTE Confidence: 0.806298309375

00:47:45.790 --> 00:47:47.545 ducts inside the normal breast

NOTE Confidence: 0.768800545714286

00:47:48.360 --> 00:47:49.720 and we absolutely have

NOTE Confidence: 0.768800545714286

00:47:49.720 --> 00:47:50.740 those internal controls.

NOTE Confidence: 0.768800545714286

00:47:50.740 --> 00:47:52.560 That's the good thing with him is

NOTE Confidence: 0.768800545714286

00:47:52.560 --> 00:47:54.018 we almost always have internal

NOTE Confidence: 0.768800545714286

00:47:54.018 --> 00:47:55.578 control because there's so many

NOTE Confidence: 0.768800545714286

00:47:55.578 --> 00:47:57.349 other cells in the background.

NOTE Confidence: 0.768800545714286

00:47:57.350 --> 00:48:00.260 So we're using B cells as the

NOTE Confidence: 0.768800545714286

00:48:00.260 --> 00:48:02.360 control and also dendritic cells.

NOTE Confidence: 0.768800545714286

00:48:02.360 --> 00:48:05.448 So I've actually seen

NOTE Confidence: 0.768800545714286

00:48:05.450 --> 00:48:07.278 brighams immunostain for it,

NOTE Confidence: 0.768800545714286

00:48:07.278 --> 00:48:10.840 which you're using on the Ventana I believe.

NOTE Confidence: 0.768800545714286

00:48:10.840 --> 00:48:15.780 And also cornells and also.

NOTE Confidence: 0.768800545714286

00:48:15.780 --> 00:48:20.060 OHSU UM and and then of course the

NOTE Confidence: 0.768800545714286

00:48:20.060 --> 00:48:22.987 two international groups so so far,

NOTE Confidence: 0.768800545714286

00:48:22.990 --> 00:48:26.002 seven groups in the US large

NOTE Confidence: 0.768800545714286

00:48:26.002 --> 00:48:28.919 academic centers have brought it on

NOTE Confidence: 0.768800545714286

00:48:28.919 --> 00:48:31.361 board for optimization and I have

NOTE Confidence: 0.768800545714286

00:48:31.361 --> 00:48:34.149 not yet seen one that was very,

NOTE Confidence: 0.768800545714286

00:48:34.149 --> 00:48:35.785 you know, significantly different

NOTE Confidence: 0.768800545714286

00:48:35.785 --> 00:48:38.360 in terms of staining a tissue.

NOTE Confidence: 0.768800545714286

00:48:38.360 --> 00:48:40.580 They've also sent me their tissues

NOTE Confidence: 0.768800545714286

00:48:40.580 --> 00:48:42.624 to stain to compare side by

NOTE Confidence: 0.768800545714286

00:48:42.624 --> 00:48:44.580 side so that has been helpful.

NOTE Confidence: 0.768800545714286

00:48:44.580 --> 00:48:47.004 It takes a lot of work to see.

NOTE Confidence: 0.768800545714286

00:48:47.010 --> 00:48:48.218 Whether that question and

NOTE Confidence: 0.768800545714286

00:48:48.218 --> 00:48:49.426 that answer holds out,

NOTE Confidence: 0.768800545714286

00:48:49.430 --> 00:48:52.210 though it's a great question.

NOTE Confidence: 0.768800545714286

00:48:52.210 --> 00:48:52.820 Amarie

NOTE Confidence: 0.868036462105263

00:48:54.080 --> 00:48:56.992 thank you, just a superb talk and

NOTE Confidence: 0.868036462105263

00:48:56.992 --> 00:48:59.996 such an elegant presentation of your

NOTE Confidence: 0.868036462105263

00:48:59.996 --> 00:49:03.332 thought process and the steps through.

NOTE Confidence: 0.868036462105263

00:49:03.340 --> 00:49:06.960 And so I congratulate you as a

NOTE Confidence: 0.868036462105263

00:49:06.960 --> 00:49:08.600 busy surgical pathologist for

NOTE Confidence: 0.868036462105263

00:49:08.600 --> 00:49:10.697 thinking for the thought process

NOTE Confidence: 0.868036462105263

00:49:10.697 --> 00:49:13.019 and for getting this work done.

NOTE Confidence: 0.868036462105263

00:49:13.020 --> 00:49:14.121 So many congratulations.

NOTE Confidence: 0.868036462105263

00:49:14.121 --> 00:49:17.168 I I'm I think a lot about inflammation

NOTE Confidence: 0.868036462105263

00:49:17.168 --> 00:49:19.947 these days and I notice that I

NOTE Confidence: 0.868036462105263

00:49:19.947 --> 00:49:22.169 don't know anything about RF 8

NOTE Confidence: 0.868036462105263

00:49:22.169 --> 00:49:24.600 except I do notice that it is.

NOTE Confidence: 0.868036462105263

00:49:24.600 --> 00:49:26.200 Important in battling infection

NOTE Confidence: 0.868036462105263

00:49:26.200 --> 00:49:29.034 and that if you if you're deficient

NOTE Confidence: 0.868036462105263

00:49:29.034 --> 00:49:32.058 in IRF 8 you have a severe primary

NOTE Confidence: 0.868036462105263

00:49:32.134 --> 00:49:34.806 immunodeficiency and that it's

NOTE Confidence: 0.868036462105263

00:49:34.806 --> 00:49:37.521 also now in GW studies,

NOTE Confidence: 0.868036462105263

00:49:37.521 --> 00:49:41.028 they find variance of IRA or a

NOTE Confidence: 0.868036462105263

00:49:41.028 --> 00:49:44.280 significant risk for autoimmune diseases,

NOTE Confidence: 0.868036462105263

00:49:44.280 --> 00:49:46.086 and I just wondered if you had

NOTE Confidence: 0.868036462105263

00:49:46.086 --> 00:49:47.520 any any thoughts about that?

NOTE Confidence: 0.868036462105263

00:49:47.520 --> 00:49:49.956 Does that manifest at all in your

NOTE Confidence: 0.868036462105263

00:49:49.956 --> 00:49:51.860 world and pathology and and I'm?

NOTE Confidence: 0.868036462105263

00:49:51.860 --> 00:49:53.738 I'm wondering if we can use

NOTE Confidence: 0.868036462105263

00:49:53.738 --> 00:49:54.990 this antibody as well.

NOTE Confidence: 0.868036462105263

00:49:54.990 --> 00:49:58.193 As we think about these autoimmune

NOTE Confidence: 0.868036462105263

00:49:58.193 --> 00:50:00.159 inflammatory conditions.

NOTE Confidence: 0.81544541125

00:50:01.290 --> 00:50:04.466 Yeah, I that is such a fantastic question.

NOTE Confidence: 0.81544541125

00:50:04.470 --> 00:50:07.830 I really don't know that much about its

NOTE Confidence: 0.81544541125

00:50:07.830 --> 00:50:11.554 role in autoimmunity except to say that you

NOTE Confidence: 0.81544541125

00:50:11.554 --> 00:50:15.828 know if you take out the monocytic lineage,

NOTE Confidence: 0.81544541125

00:50:15.830 --> 00:50:18.576 there will be kind of hell to pay, you know.

NOTE Confidence: 0.81544541125

00:50:18.576 --> 00:50:21.200 So I think that it it absolutely plays

NOTE Confidence: 0.81544541125

00:50:21.278 --> 00:50:23.948 an important role when it's functional.

00:50:23.950 --> 00:50:26.603 When it's doing its normal job in

00:50:26.603 --> 00:50:29.168 terms of infection and inflammation.

00:50:29.170 --> 00:50:30.766 So we cannot.

00:50:30.766 --> 00:50:33.958 Completely take it out of function,

00:50:33.960 --> 00:50:39.198 but only in when it is upregulated in tumor.

00:50:39.200 --> 00:50:40.540 And I think that's it.

00:50:40.540 --> 00:50:43.609 Also is confusing to me and I think something

00:50:43.609 --> 00:50:46.543 that I really want to work on is why in in

00:50:46.618 --> 00:50:48.976 its normal function it is proapoptotic.

00:50:48.976 --> 00:50:50.688 But then in tumor,

00:50:50.690 --> 00:50:52.795 obviously they are continuing to

00:50:52.795 --> 00:50:57.120 proliferate and live on, so it must be.

00:50:57.120 --> 00:50:59.689 Maybe it's binding differently in some way.

00:50:59.690 --> 00:51:01.910 When it's tumor,

00:51:01.910 --> 00:51:04.928 you know there there have been

NOTE Confidence: 0.81544541125

00:51:04.928 --> 00:51:07.398 studies showing its deficiency and

NOTE Confidence: 0.81544541125

00:51:07.398 --> 00:51:09.107 DLBCL that I have to read more about,

NOTE Confidence: 0.81544541125

00:51:09.110 --> 00:51:12.074 but you know it has manifested

NOTE Confidence: 0.81544541125

00:51:12.074 --> 00:51:14.050 different kinds of phenotype,

NOTE Confidence: 0.81544541125

00:51:14.050 --> 00:51:16.100 whether it's tumor versus normal.

NOTE Confidence: 0.81544541125

00:51:16.100 --> 00:51:18.494 So I hope that others will be

NOTE Confidence: 0.81544541125

00:51:18.494 --> 00:51:20.562 interested in working on this because

NOTE Confidence: 0.81544541125

00:51:20.562 --> 00:51:22.816 I cannot do all of the different

NOTE Confidence: 0.81544541125

00:51:22.889 --> 00:51:24.569 types of studies and IRA.

NOTE Confidence: 0.81544541125

00:51:24.570 --> 00:51:27.188 I think it's just really cool and.

NOTE Confidence: 0.81544541125

00:51:27.190 --> 00:51:29.690 Complicated.

NOTE Confidence: 0.81544541125

00:51:29.690 --> 00:51:30.180 Won't you?

NOTE Confidence: 0.957642576666667

00:51:31.850 --> 00:51:35.126 I've got two questions. One is,

NOTE Confidence: 0.957642576666667

00:51:35.130 --> 00:51:38.210 do you think that bone marrow aspirates

NOTE Confidence: 0.957642576666667

00:51:38.210 --> 00:51:41.140 are going to fall out of favor?

NOTE Confidence: 0.886626861666667

00:51:45.330 --> 00:51:48.210 So, so I don't think so.

NOTE Confidence: 0.886626861666667

00:51:48.210 --> 00:51:50.676 I you know it's hard for them to do

NOTE Confidence: 0.886626861666667

00:51:50.676 --> 00:51:53.282 a good aspirate, but a good aspirate

NOTE Confidence: 0.886626861666667

00:51:53.282 --> 00:51:55.490 is just worth its weight in gold.

NOTE Confidence: 0.886626861666667

00:51:55.490 --> 00:51:57.905 It is so important to get that

NOTE Confidence: 0.886626861666667

00:51:57.905 --> 00:52:00.650 fluid sample that we can use for

NOTE Confidence: 0.886626861666667

00:52:00.650 --> 00:52:02.690 cytogenetics and molecular and flow.

NOTE Confidence: 0.886626861666667

00:52:02.690 --> 00:52:04.322 I don't think it would ever

NOTE Confidence: 0.886626861666667

00:52:04.322 --> 00:52:05.830 really fall out of favor.

NOTE Confidence: 0.886626861666667

00:52:05.830 --> 00:52:06.954 I do think that.

NOTE Confidence: 0.886626861666667

00:52:06.954 --> 00:52:09.342 We need a better way to obtain it

NOTE Confidence: 0.886626861666667

00:52:09.342 --> 00:52:12.283 because it is not just like at Yale or

NOTE Confidence: 0.886626861666667

00:52:12.283 --> 00:52:14.677 you know this clinic or that clinic.

NOTE Confidence: 0.886626861666667

00:52:14.680 --> 00:52:17.518 When I've talked to other institutions,

NOTE Confidence: 0.886626861666667

00:52:17.520 --> 00:52:21.426 this is a major problem in the US and

NOTE Confidence: 0.886626861666667

00:52:21.426 --> 00:52:24.856 folks coming from outside of the US

NOTE Confidence: 0.886626861666667

00:52:24.856 --> 00:52:27.076 hematologist trained at other countries

NOTE Confidence: 0.886626861666667

00:52:27.076 --> 00:52:29.575 usually have been really trained at

NOTE Confidence: 0.886626861666667

00:52:29.575 --> 00:52:32.013 looking at their own aspirates and

NOTE Confidence: 0.886626861666667

00:52:32.013 --> 00:52:34.299 seeing whether they're good or not.

NOTE Confidence: 0.886626861666667

00:52:34.300 --> 00:52:35.828 They're much better at

NOTE Confidence: 0.886626861666667

00:52:35.828 --> 00:52:37.356 getting an aspirate right,

NOTE Confidence: 0.886626861666667

00:52:37.360 --> 00:52:38.848 so I think it's partly that

NOTE Confidence: 0.886626861666667

00:52:38.848 --> 00:52:40.050 the training and the US.

NOTE Confidence: 0.886626861666667

00:52:40.050 --> 00:52:43.635 Focus more on treatment versus

NOTE Confidence: 0.886626861666667

00:52:43.635 --> 00:52:45.786 the diagnostic procedure,

NOTE Confidence: 0.886626861666667

00:52:45.790 --> 00:52:47.876 so there might be a swing in

NOTE Confidence: 0.886626861666667

00:52:47.876 --> 00:52:49.773 the other direction as we see

NOTE Confidence: 0.886626861666667

00:52:49.773 --> 00:52:51.328 how important the aspirate is.

NOTE Confidence: 0.907322532727273

00:52:52.920 --> 00:52:56.142 The other question I have is

NOTE Confidence: 0.907322532727273

00:52:56.142 --> 00:52:59.060 this drug that works again.

NOTE Confidence: 0.907322532727273

00:52:59.060 --> 00:53:00.581 That targets BCL.

NOTE Confidence: 0.907322532727273

00:53:00.581 --> 00:53:03.623 Two BCL two is expressed on

NOTE Confidence: 0.907322532727273

00:53:03.623 --> 00:53:06.230 other lymphocytes as well.

NOTE Confidence: 0.907322532727273

00:53:06.230 --> 00:53:09.524 So are there what happens to

NOTE Confidence: 0.907322532727273

00:53:09.524 --> 00:53:11.720 those lymphocytes in patients

NOTE Confidence: 0.907322532727273

00:53:11.815 --> 00:53:14.560 that are receiving this drug?

NOTE Confidence: 0.834722404

00:53:15.760 --> 00:53:18.190 Yeah, you know no drug is

NOTE Confidence: 0.834722404

00:53:18.190 --> 00:53:19.810 without its side effects,

NOTE Confidence: 0.834722404

00:53:19.810 --> 00:53:22.274 but I I have to say that venetoclax

NOTE Confidence: 0.834722404

00:53:22.274 --> 00:53:25.245 has reportedly done pretty well in

NOTE Confidence: 0.834722404

00:53:25.245 --> 00:53:28.454 these patients because so much of

NOTE Confidence: 0.834722404

00:53:28.454 --> 00:53:31.134 their lymphocytes are actually really

NOTE Confidence: 0.834722404

00:53:31.134 --> 00:53:33.774 abnormal or myeloid cells are so

NOTE Confidence: 0.834722404

00:53:33.774 --> 00:53:36.554 abundant that they have a depression

NOTE Confidence: 0.834722404

00:53:36.554 --> 00:53:39.258 in normal lymphocytes already.

NOTE Confidence: 0.834722404

00:53:39.260 --> 00:53:42.644 So venetoclax has been shown to

NOTE Confidence: 0.834722404

00:53:42.644 --> 00:53:45.980 really induce that initial remission.

NOTE Confidence: 0.834722404

00:53:45.980 --> 00:53:48.676 The duration of that remission is not long,

NOTE Confidence: 0.834722404

00:53:48.680 --> 00:53:50.000 so that is a problem.

NOTE Confidence: 0.834722404

00:53:50.000 --> 00:53:53.915 And these breakthroughs and relapses

NOTE Confidence: 0.834722404

00:53:53.915 --> 00:53:55.690 happen pretty quickly thereafter.

NOTE Confidence: 0.834722404

00:53:55.690 --> 00:53:58.000 So so that is a real issue.

NOTE Confidence: 0.834722404

00:53:58.000 --> 00:54:02.480 But, you know, I think also we,

NOTE Confidence: 0.834722404

00:54:02.480 --> 00:54:05.296 we think of OK, this stain is high,

NOTE Confidence: 0.834722404

00:54:05.296 --> 00:54:08.100 and so this this drug must work, you know.

NOTE Confidence: 0.834722404

00:54:08.100 --> 00:54:09.260 Well in the one.

NOTE Confidence: 0.834722404

00:54:09.260 --> 00:54:09.974 Sustained highly,

NOTE Confidence: 0.834722404

00:54:09.974 --> 00:54:13.150 but it actually has not worked out that way.

NOTE Confidence: 0.834722404

00:54:13.150 --> 00:54:17.632 So in terms of CLL it's worked really well,

NOTE Confidence: 0.834722404

00:54:17.640 --> 00:54:18.606 but you know,

NOTE Confidence: 0.834722404

00:54:18.606 --> 00:54:21.328 full of your lymphoma is BCL 2 positive

NOTE Confidence: 0.834722404

00:54:21.328 --> 00:54:23.796 and yet it's not as it's not doing

NOTE Confidence: 0.834722404

00:54:23.796 --> 00:54:25.841 as well in follicular so it's not

NOTE Confidence: 0.834722404

00:54:25.841 --> 00:54:27.850 like a one to one correlation either.

NOTE Confidence: 0.759111265

00:54:31.460 --> 00:54:33.808 Thank you Mina. The venetoclax

NOTE Confidence: 0.759111265

00:54:33.808 --> 00:54:35.356 is very interesting.

NOTE Confidence: 0.724115359333334

00:54:35.360 --> 00:54:37.608 Manju, because this is a drug where you

NOTE Confidence: 0.724115359333334

00:54:37.608 --> 00:54:39.336 actually have to titrate up in CLL,

NOTE Confidence: 0.724115359333334

00:54:39.340 --> 00:54:41.764 you give it all at once and patients

NOTE Confidence: 0.724115359333334

00:54:41.764 --> 00:54:44.399 will get extreme tumor lysis syndrome.

NOTE Confidence: 0.724115359333334

00:54:44.400 --> 00:54:46.108 The problem with these drugs as well,

NOTE Confidence: 0.724115359333334

00:54:46.110 --> 00:54:48.630 based on their structure

NOTE Confidence: 0.724115359333334

00:54:48.630 --> 00:54:50.520 is they're extravascular.

NOTE Confidence: 0.724115359333334

00:54:50.520 --> 00:54:51.816 Extrusion is very limited,

NOTE Confidence: 0.724115359333334

00:54:51.816 --> 00:54:54.629 so there are many tumors where within the

NOTE Confidence: 0.724115359333334

00:54:54.629 --> 00:54:56.659 circulating system it's very effective,

NOTE Confidence: 0.724115359333334

00:54:56.660 --> 00:54:59.428 but on tissues it's just a drug property.

NOTE Confidence: 0.724115359333334

00:54:59.430 --> 00:55:00.642 That drug is very,

NOTE Confidence: 0.724115359333334

00:55:00.642 --> 00:55:02.157 very tightly albumin bound and

NOTE Confidence: 0.724115359333334

00:55:02.157 --> 00:55:03.895 very poorly able to actually

NOTE Confidence: 0.724115359333334

00:55:03.895 --> 00:55:05.275 egress from the bloodstream.

NOTE Confidence: 0.91433855

00:55:07.000 --> 00:55:08.290 Thank you, thank

NOTE Confidence: 0.921617997142857

00:55:08.300 --> 00:55:09.679 you so much. That's a great point.

NOTE Confidence: 0.86452940125

00:55:11.130 --> 00:55:15.026 Hi Mina, I have a question for you.

NOTE Confidence: 0.86452940125

00:55:15.030 --> 00:55:17.572 So this is more of an

NOTE Confidence: 0.86452940125

00:55:17.572 --> 00:55:18.840 immunohistochemistry question.

NOTE Confidence: 0.86452940125

00:55:18.840 --> 00:55:21.588 Are you really looking into multiplexing?

NOTE Confidence: 0.86452940125

00:55:21.590 --> 00:55:23.935 And since this monoblast count

NOTE Confidence: 0.86452940125

00:55:23.935 --> 00:55:26.950 is so critical in the 20% count,

NOTE Confidence: 0.86452940125

00:55:26.950 --> 00:55:28.150 so I was wondering,

NOTE Confidence: 0.86452940125

00:55:28.150 --> 00:55:32.358 are you relying only on IR F8 and would

NOTE Confidence: 0.86452940125

00:55:32.358 --> 00:55:35.240 you also consider multiplexing with CD 34?

NOTE Confidence: 0.86452940125

00:55:35.240 --> 00:55:38.240 But then we no CD 34 doesn't pick

NOTE Confidence: 0.86452940125

00:55:38.240 --> 00:55:40.271 up all monoblast monocytic leukemia,

NOTE Confidence: 0.86452940125

00:55:40.271 --> 00:55:43.890 so is there any other marker for example,

NOTE Confidence: 0.86452940125

00:55:43.890 --> 00:55:46.658 which is cytoplasmic localization?

NOTE Confidence: 0.86452940125

00:55:46.658 --> 00:55:49.426 Like CD 117 would be more helpful

NOTE Confidence: 0.86452940125

00:55:49.426 --> 00:55:51.939 for you versus CD 34, which also I

NOTE Confidence: 0.86452940125

00:55:51.939 --> 00:55:53.743 believe goes to the nucleus, right?

NOTE Confidence: 0.86452940125

00:55:53.743 --> 00:55:57.207 So having a Multiplex stay in that is.

NOTE Confidence: 0.86452940125

00:55:57.210 --> 00:55:57.778 You know,

NOTE Confidence: 0.86452940125

00:55:57.778 --> 00:55:59.198 picks up two different localizations

NOTE Confidence: 0.86452940125

00:55:59.198 --> 00:56:01.050 would be more helpful than having.

NOTE Confidence: 0.86452940125

00:56:01.050 --> 00:56:02.380 Absolutely yeah,

NOTE Confidence: 0.839677546

00:56:02.650 --> 00:56:04.594 I'm I'm so glad you brought it up

NOTE Confidence: 0.839677546

00:56:04.594 --> 00:56:07.062 and I really hope to get your buy in

NOTE Confidence: 0.839677546

00:56:07.062 --> 00:56:09.570 and doing the multiplexing. In fact,

NOTE Confidence: 0.839677546

00:56:09.570 --> 00:56:12.810 I think CD34 with RA would be perfect.

NOTE Confidence: 0.839677546

00:56:12.810 --> 00:56:16.023 In fact, CD 34 is going to be membranous,

NOTE Confidence: 0.839677546

00:56:16.030 --> 00:56:17.166 and this is nuclear.

NOTE Confidence: 0.839677546

00:56:17.166 --> 00:56:20.612 Then we would capture all of them, you know.

NOTE Confidence: 0.839677546

00:56:20.612 --> 00:56:26.104 And at MGB they're already doing 123 with RH,

NOTE Confidence: 0.839677546

00:56:26.104 --> 00:56:28.294 just to show its double.

NOTE Confidence: 0.839677546

00:56:28.300 --> 00:56:32.330 Expression in the dendritic cells,

NOTE Confidence: 0.839677546

00:56:32.330 --> 00:56:34.450 so so that's another possibility.

NOTE Confidence: 0.839677546

00:56:34.450 --> 00:56:37.393 But I I do think that in cases where

NOTE Confidence: 0.839677546

00:56:37.393 --> 00:56:40.850 we really are relying on this kind of

NOTE Confidence: 0.839677546

00:56:40.850 --> 00:56:43.289 getting to 20% the the multiplexing

NOTE Confidence: 0.839677546

00:56:43.289 --> 00:56:45.970 with 34 would be super super helpful.

NOTE Confidence: 0.839677546

00:56:45.970 --> 00:56:47.506 So I'd be happy to work on it

NOTE Confidence: 0.839677546

00:56:47.506 --> 00:56:48.240 with your staff.

NOTE Confidence: 0.97088134

00:56:53.380 --> 00:56:56.600 Thank you so much for all of your time.

NOTE Confidence: 0.97088134

00:56:56.600 --> 00:56:58.616 Please feel free to ask me any other

NOTE Confidence: 0.97088134

00:56:58.616 --> 00:57:00.348 questions as you might see me in

NOTE Confidence: 0.97088134

00:57:00.348 --> 00:57:03.660 the hallway. Thank you, thank you,

NOTE Confidence: 0.90936305

00:57:03.660 --> 00:57:05.390 thank you all for coming.

NOTE Confidence: 0.90198743

00:57:06.800 --> 00:57:07.560 Great talk.